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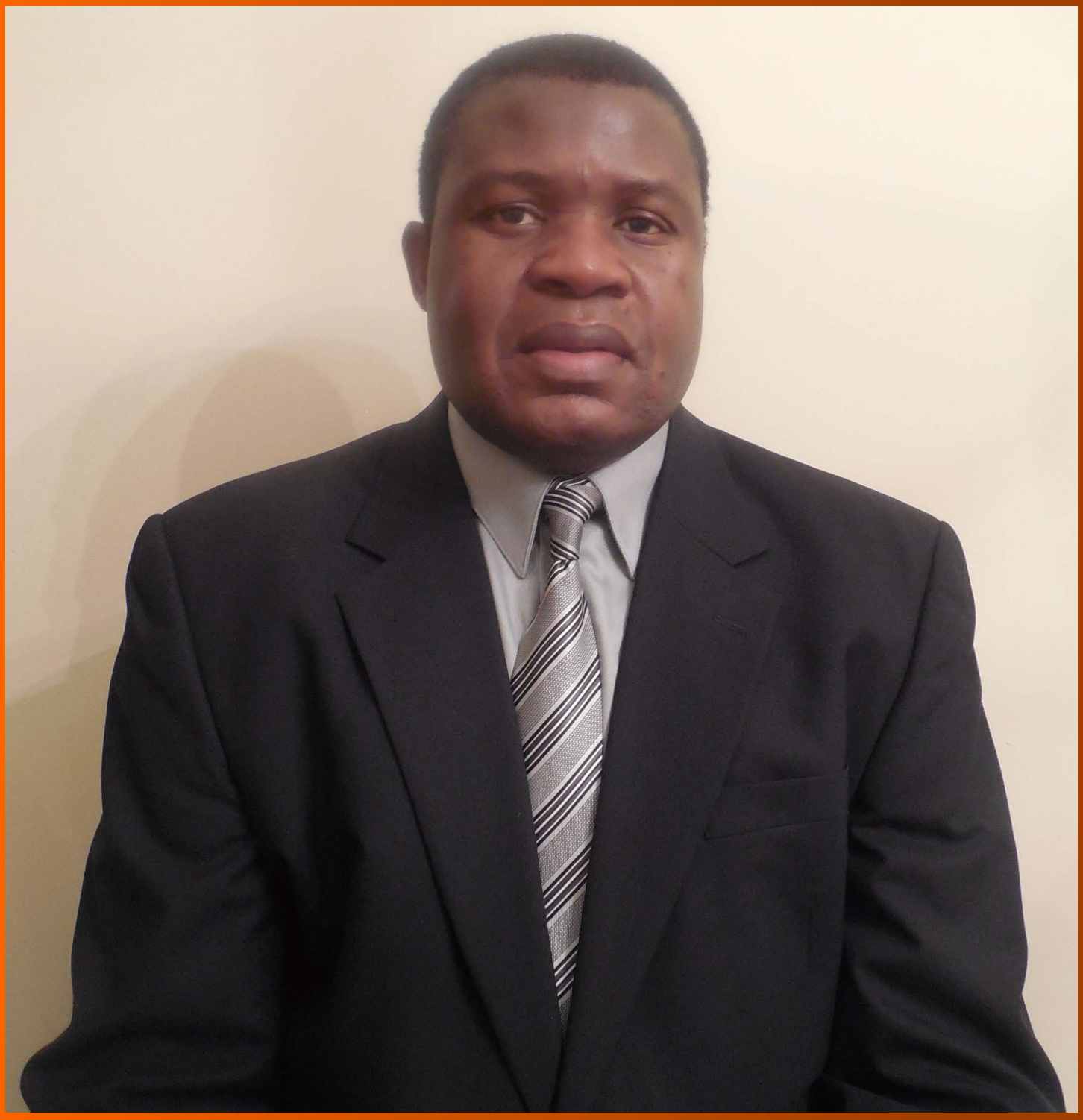

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REVIEW

Impact of technology on indications and limitations for transanal surgical removal of rectal neoplasms

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Abstract

Transanal surgery has and continues to be well accepted for local excision of benign rectal disease not amenable to endoscopic resection. More recently, there has been increasing interest in applying transanal surgery to local resection of early malignant disease. In addition, some groups have started utilizing a transanal route in order to accomplish total mesorectal excision (TME) for more advanced rectal malignancies. We aim to review the role of various transanal and endoscopic techniques in the local resection of benign and malignant rectal disease based on published trial data. Preliminary data on the use of transanal platforms to accomplish TME will also be highlighted. For endoscopically unresectable rectal adenomas, transanal surgery remains a widely accepted method with minimal morbidity that avoids the downsides of a major abdomino-pelvic operation. Transanal endoscopic microsurgery and transanal minimally invasive surgery offer improved visualization and magnification, allowing for finer and more precise dissection of more proximal and larger rectal lesions without compromising patient outcome. Some studies have demonstrated efficacy in utilizing transanal platforms in the surgical management of early rectal malignancies in selected patients. There is an overall higher recurrence rate with transanal surgery with the concern that neither chemoradiation nor salvage surgery may compensate for previous approach and correct the inferior outcome. Application of transanal platforms to accomplish transanal TME in a natural orifice fashion are still in their infancy and currently should be considered experimental. The current data demonstrate that transanal surgery remains an excellent option in the surgical management of benign rectal disease. However, care should be used when selecting patients with malignant disease. The application of transanal platforms continues to evolve. While the new uses of transanal platforms in TME for more advanced rectal malignancy are exciting, it is important to remain cognizant and not sacrifice long term survival for short term decrease in morbidity and improved cosmesis.

Key words: Transanal surgery; Transanal endoscopic microsurgery; Endoscopic mucosal resection; Transanal total mesorectal excision; Transanal minimally invasive surgery; Robotic transanal surgery; Local excision rectal neoplasms

Core tip: The review summarizes the technology advances and analyzes their impact on the validity of local transanal management of benign *vs* malignant rectal neoplasms. Current data demonstrate that transanal surgery remains an excellent option for benign disease. As transanal platforms continue to evolve, caution should be used when selecting patients with malignant disease. In view of the fact that the alternative of abdominal oncological procedures (laparoscopic, robotic, open) provide high cure rates, it is important to remain cognizant and not sacrifice long term survival for short term benefits (decrease in morbidity and improved cosmesis).

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INTRODUCTION

Rectal neoplasms are frequent and range from simple to highly complex conditions. Decision factors for their optimal management among others include the size and true axial and radial location of the lesion, the level of rectal wall and adjacent organ involvement, but most importantly, whether a definitively non-malignant (*e.g.*, lipoma), a potentially malignant (adenomatous polyp, carcinoid), or a malignant process is suspected or confirmed. Particularly for more advanced and malignant lesions, the standard approach consists of an abdominal low anterior resection; depending on the proximity to the pelvic floor and sphincter complex, it includes a resection of the anus (abdomino-perineal resection) or allows for restoration of the intestinal continuity[1,2]. The advantage of the abdominal total mesorectal excision (TME) is that it assures a lymphadenectomy and-if done correctly-the removal of an intact mesorectal envelope (fascia propria) as the two most relevant factors to reduce the risk of local recurrences. The disadvantages, however, include the magnitude of the surgery as such, the length of recovery, the risk for an anastomotic leak, a not negligible probability to require a temporary or permanent ostomy, and a marked negative functional impact.

As communicated by Parks *et al*[3], conventional transanal excision (TAE) became a widely adopted surgical technique with minimal morbidity for the management of low rectal lesions. Criteria were defined to characterize lesions best suited for TAE: it should be < 3-4 cm in size/diameter, encompass less than 25%-40% of the circumference, be mobile, and be in reach of the finger/anoscope (*i.e.*, no more than 6-8 cm from the anal verge)[1]. This latter aspect represented the biggest technical limitations of conventional transanal surgery, as mid to upper rectal tumors were out of reach secondary to inadequate exposure.

In more recent years, a number of technical developments have evolved to overcome these limitations. Transanal endoscopic microsurgery (TEMS) and later transanal minimally invasive surgery (TAMIS) have allowed for local excision of tumors anywhere in the entire rectum. The improved reach and visualization allows for a finer and controlled dissection which made it possible for surgeons to push the limits of what can be accomplished *via* a transanal route. Resection of larger, more proximal adenomas encompassing more than 40% of the circumference have been carried out with low morbidity and acceptable recurrence rates for benign neoplasms[4-6].

Whether transanal surgery should be applied to malignant disease remains a matter of considerable debate. Even when limiting local excision to early tumors with favorable histology, as described by Willett *et al*[7], a significant rate of local recurrence has been reported[8-10]. Two factors are thought to contribute to this unfavorable outcome: (1) direct implantation of cancer cells into the surgical wound as a result of the direct instrumentation of the tumor; and (2) the lack of a lymphadenectomy even though 7%-10% of T1 tumors are found to have lymph node metastases[1,2]. This latter aspect not only leaves behind nodal tumor tissue, but results in understaging and hence undertreatment of stage Ⅲ disease. Furthermore, salvage therapy after failure of local excision may involve more than what would have been needed initially and potentially require multivisceral resection with increased morbidity and lower overall survival[11,12].

Advances in endoscopy techniques have led to the introduction of endoscopic mucosal resection (EMR). This procedure has demonstrated some efficacy in the resection of larger (> 2 cm) and sessile lesions, characteristics that would have in the past ruled out the possibility of an endoscopic resection[13-16]. Similar to transanal surgery, EMR is not suited to perform a lymphadenectomy and carries a risk of bowel perforation with intraperitoneal bowel segments.

In recent years, some groups have extended the use of TEMS and TAMIS platforms in order to accomplish transanal natural orifice transluminal endoscopic surgery (NOTES) TME[17,18]. In addition, a combination of the da Vinci robotic system (Intuitive Surgical Inc., Sunnyvale, CA, United States) with the TAMIS platform was used to carry out the first series of robotic-assisted transanal surgery for TME[19]. Experience with these approaches remain confined to specialty groups and limited to feasibility case reports[19-22].

The goal of this article is to highlight the various transanal surgical techniques and analyze the available evidence on the validity of local excision of benign and

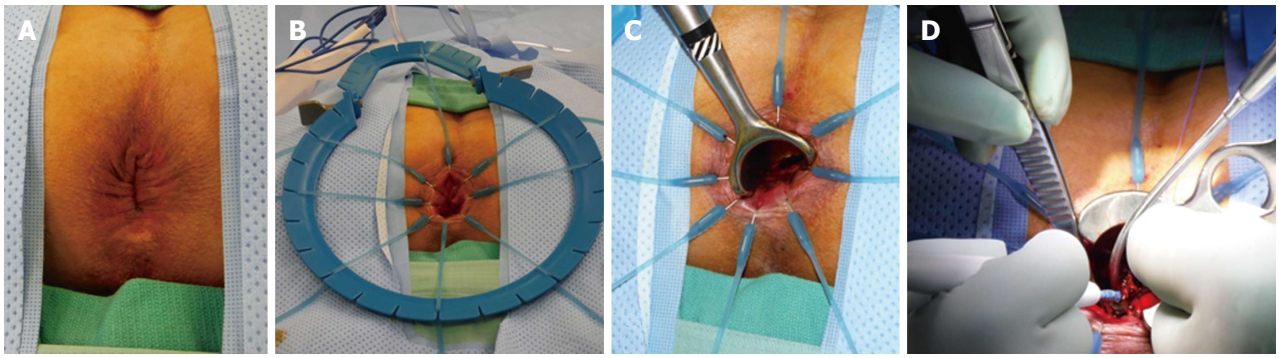

Figure 1 Conventional transanal excision with the patient in prone-jackknife position. A: Anus at beginning of the surgery; B: Placement of Lone Star retractor; C: Additional hand-held retractor optimizes exposure; D: Direct transanal instrumentation under regular view.

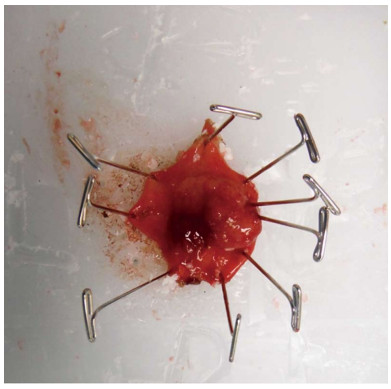

Figure 2 Fixation and orientation of the specimen on a wax board. The tissue is pinned down with needles. L(eft), R(ight), D(istal), and P(roximal) are carved into the wax. The specimen is subsequently placed in formalin for at least 24 h before processing and sectioning it onto slides.

malignant rectal neoplasms.

TAE

TAE can be performed with minimal specialty equipment, but depends on an optimized exposure of the target lesion as well as good hemostasis throughout the procedure. A variety of retractors are available, but in our hands, a Lone Star retractor (Coopersurgical, Inc. Trumbull, Connecticut, United States) to retract/evert the dentate line in combination with a handheld anal retractor has been the most reliable set-up (Figure 1). A circumferential margin of about 1cm is marked out by diathermy around the lesion. A full thickness excision using energy devices is then carried out whereby fragmentation of the specimen should be avoided. Fixation and orientation of the excised lesion on a wax board should then be carefully performed to prevent the tissue from rolling up and allow for proper pathological assessment of the resection margins (Figure 2). The defect should be washed out and either closed transversely with interrupted absorbable stitches or left open.

TAE overall is well tolerated and associated with only minor morbidity. However, there appears to be a significant variability in regards to recurrence rates after local excision of rectal adenomas ranging from 3%-40% in published series[23-26]. In a 10 year single institution review of 26 transanally excised adenomas, Hoth *et al*[27] reported a 38% recurrence rate over an average follow-up period of 25 mo. In a larger series of 117 patients with an average follow-up of 55 mo, Sakamoto *et al*[28] demonstrated an overall 30% recurrence rate for rectal adenomas. The authors postulated that the high recurrence rate was the result of inadequate exposure leading to incomplete excision[28]. A more recent and even larger study by Pigot *et al*[29] on a cohort of 207 patients undergoing TAE for rectal villous adenomata yielded better outcomes. The authors claimed to obtain improved intra-operative visualization by creating a cutaneo-mucus flap handle to allow for gentle traction, hence allowing for complete excision of the rectal adenoma with a recurrence rate of only 3.6%. Overall, the data on conventional TAE demonstrate higher than expected recurrence rates even for benign rectal adenomas; nonetheless, this surgical approach remains widely accepted for management of benign rectal pathologies in very distal location and close proximity to the sphincter structures.

Unquestionably, similarly high local recurrence rates would seem much more concerning in the management of malignant rectal tumors. Some 20 years ago, Willett *et al*[7] completed one of the earlier comparisons of standard resection with transanal local excision for low T1/T2 rectal cancer. This study was one of the first to suggest that in patients with favorable cancer histology (well differentiated, no venous or lymphovascular involvement), transanal surgery might be an acceptable alternative to standard resection. Fifty-six patients who had undergone transanal surgery were compared to 69 patients subjected to an abdomino-perineal resection (APR). Transanal surgery in 28 patients with favorable cancer histology resulted in a 5 year disease-free survival of 87% and a local control rate of 96%, whereas the other 28 patients with unfavorable cancer histology only achieved a 57% and 68%, respectively. In contrast, APR in 49 patients with favorable tumor histology resulted in 5 year disease-free survival and local control rates of 91%

Table 1 Single center comparison of transanal excision and standard resection for T1 rectal cancer

Ref.	Year	Follow-up (yr)	*n*		5 yr local recurrence		5 yr overall survival	
			TAE	SR	TAE	SR	TAE	SR
Mellgren *et al*[31]	2000	4.4-4.8	69	30	18%[1]	0[1]	72%	80%[1]
Nascimbeni *et al*[32]	2004	9.2	70	74	6.6%	2.8%	72%[1]	90%[1]
Bentrem *et al*[30]	2005	4.3	151	168	15%[1]	3%[1]	89%	93%
Nash *et al*[33]	2009	5.6	137	145	13.2%[1]	2.7%[1]	87%[1]	96%[1]

[1]Statistically significant. TAE: Transanal excision; SR: Standard resection.

Table 2 National cancer registries comparison of transanal excision and standard resection for T1 rectal cancer

Ref.	Year	Follow-up (yr)	*n*		5 yr local recurrence		5 yr overall survival	
			TAE	SR	TAE	SR	TAE	SR
Endreseth *et al*[37]	2005	2-8.1	35	256	12%	6%[1]	70%[1]	80%[1]
You *et al*[42]	2007	6.3	601	493	12.5%	6.9%[1]	77%	82%
Ptok *et al*[40]	2007	3.5	85	359	5.1%[1]	1.4%[1]	84%	92%
[2]Folkesson *et al*[38]	2007	NA	256	1141	7%	2%[1]	87%	93%
Hazard *et al*[39]	2009	3.9	573	3040	NA	NA	71%	84%
[2]Saraste *et al*[41]	2013	NA	448	3246	11.2%	2.9%	81%	92%

[1]Statistically significant; [2]Mix of T1 and T2 tumors. SR: Standard resection; TAE: Transanal excision; NA: Not available.

and 91%, compared to 79% and 89%, respectively, in 20 patients with unfavorable tumor histology.

Since then, several single institution case series have been published that compared transanal local excision to standard resection in T1 rectal cancers[30-33]. These results are summarized in Table 1. Overall, there is a significantly increased 5 year local recurrence rate with transanal surgery (7%-18%) compared to standard resection (0%-3%). The 5 year overall survival in the transanal local excision group was also noted to be substantially lower (72%-87%) than in the standard resection groups (80%-96%). The most recent of these studies by Nash *et al*[33] found a 20% incidence of lymph node metastasis in the standard resection group despite the tumor histological profile being similar between the 2 groups. This high prevalence of lymph node metastasis for early T tumors is about double the expected number from previously published reports[34-36]. At 7 years, cancer related deaths were 17% in the TAE group compared to 6% in patients undergoing a standard oncological resection. The differences in both local recurrence and 5 year overall survival were not only statistically significant but clinically alarming enough for the authors to conclude that transanal surgery even in early rectal cancer offered inferior oncological outcomes and should be restricted to patients that are unable to undergo standard resection[33].

In addition to single institution case series, national cancer registries have recently reported results comparing transanal surgery to standard resection[37-42]. These results are summarized in Table 2. Such registries have the benefit of a much larger sample size at the expense of a lack of detail and standardization (surgical techniques, data incorporation and surveillance protocols). Even though two of the studies included a mix of T1 and T2 rectal tumors in their analysis[38,41], there still appear to be higher than expected local recurrence rates for transanal surgery (5.1%-12.5%) compared to standard resection (1.4%-6.9%). Though not reaching statistical significance, there was a clear trend towards improved overall survival in patients undergoing standard resection (80%-93%) *vs* transanal surgery (70%-87%). An insufficiently analyzed factor contributing to the lower survival in the transanal excision group could be the inherent selection bias prevalent in registry data whereby patients might have been directed towards local excision if they had relevant comorbidities and limited operability.

While there is little doubt about the substantially increased local recurrence rates after transanal surgery compared to standard resection, a key question is whether these recurrences are salvageable with further surgical or adjuvant chemoradiation. Data on this topic are limited to single institution reviews[43]. Data from Memorial Sloan Kettering Cancer Center suggested that a substantial fraction of patients with local recurrences only could be managed with salvage surgery, but that only 30% of these were alive at 6 years[43]. In the most recent data analysis from MD Anderson Cancer Center over an 18 year period, You *et al*[44] demonstrated that recurrent rectal cancer (initial T1-T3 disease) appeared at a median interval of 1.9 years. The majority of patients (87%) were candidates to undergo salvage therapy with an R0 resection being attained in 80% of these patients. However, salvage therapy was associated significant morbidity: sphincter preservation was possible in only a third; a third underwent multi-visceral resection with a perioperative morbidity of 50%. In addition, 5 year

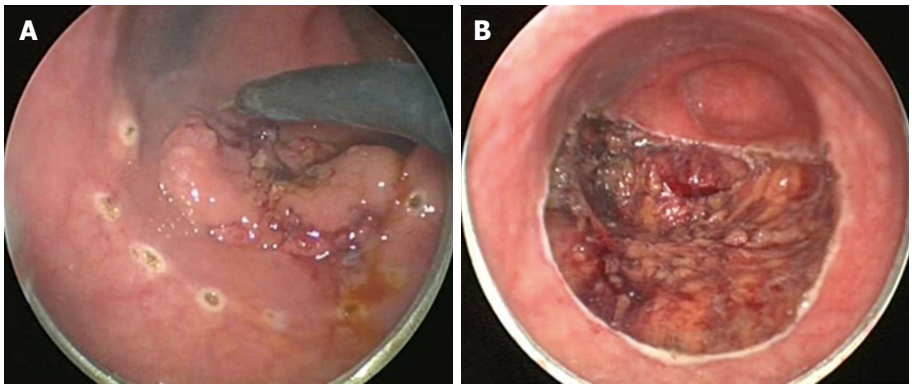

Figure 3 Transanal endoscopic microsurgery-internal view demonstrating an excellent exposure of the lesion. A: Sessile lesion being marked with a dotted line at about 1 cm around the border of the lesion; B: View after full thickness excision with exposed mesorectal fat.

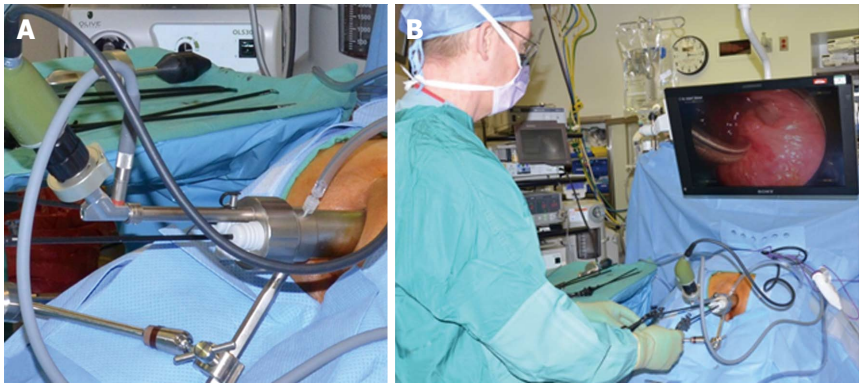

Figure 4 Transanal endoscopic microsurgery-external view. A: Close-up to working anoscope with air insufflation, camera port, and 3 working ports; B: Surgeon and monitor position during procedure with a patient in prone-jackknife position.

overall survival after salvage therapy was significantly lower at 68% compared to the reported 80%-90% survival rate that should be expected in stage 1-2 rectal cancers. Earlier data from other institutions mirror the MD Anderson experience: all demonstrating lower 5 year overall survival in salvage therapy (53%-59%) despite attaining an R0 resection in most cases (79%-97%)[11,12,45].

TEMS

TEMS was originally developed by Buess *et al*[46] in Germany in the early 1980s. This transanal platform which is offered by different vendors includes video optics and an improved visibility due to creation of a pneumorectum (Figure 3). It consists of a 4 cm diameter proctoscope with a variable length of 7.5 to 20 cm allowing for visualization of the entire rectum. An airtight seal is maintained between the proctoscope and the anus allowing for pressure-controlled rectal insufflation with CO_2. The faceplate of the proctoscope has 4 ports allowing for the insertion of the camera and three other working instruments (Figure 4). The ends of the operating instruments are angulated to improve their range of motion in the tight rectal space. The entire unit is fixed to the operating table and stabilized *via* an articulating arm. The procedure is facilitated by positioning the patient such that the target lesion is in the dependent position. Obstacles of this technology are its substantial initial cost to purchase the specialty equipment as well as a steep learning curve[47,48].

As with TAE, there is overall minimal perioperative morbidity associated with TEMS[49-51]. However, given the larger size of the operating proctoscope in relation to traditional handheld anal retractors, a negative impact (stretch injury) on the sphincter would not come as a surprise. In fact, some studies analyzed the effect of TEMS on anorectal function[52-57]; lower sphincter pressures were observed but the squeeze pressures ultimately improved by 1 year after TEMS[57]. Similarly, in study with a 5 year follow up after TEMS, Allaix *et al*[52] demonstrated a return of manometric values to pre-operative levels after 1 year. Utilizing sequential Fecal Incontinence Severity Index (FISI) and Fecal Incontinence Quality of Life scores, Cataldo *et al*[53] and Doornebosch *et al*[54] did not note a decrease in either one after TEMS. The current evidence suggests that TEMS does not have any long lasting deleterious effect on anorectal function.

With the introduction of TEMS, larger and more proximal rectal adenomas are now amenable to local surgical excision. Local recurrence rates after adenoma

Table 3 Recurrence after transanal endoscopic microsurgery resection of benign rectal adenoma

Ref.	Year	Follow-up (yr)	*n*	Recurrence
Said *et al*[67]	1995	3.2	260	6.5%
Platell *et al*[65]	2004	1.5	62	2.4%
Endreseth *et al*[60]	2005	2	64	13%
Whitehouse *et al*[71]	2006	3.3	143	4.8%
McCloud *et al*[63]	2006	2.6	75	16%
Guerrieri *et al*[86]	2008	3.7	588	4.3%
Speake *et al*[68]	2008	1	80	12.5%
Moore *et al*[64]	2008	1.7	40	3%
de Graaf *et al*[59]	2009	2.3	309	6.6%
Ramirez *et al*[66]	2009	3.6	149	5.4%
van den Broek *et al*[70]	2009	1.1	248	9.3%
Guerrieri *et al*[61]	2010	7	402	4%
Tsai *et al*[69]	2010	2	156	5%
de Graaf *et al*[58]	2011	2.7	208	6.1%

excision by TEMS have been reported by numerous largely single institution studies (2.4%-16%)[58-71]. The results are summarized in Table 3. Even though the majority of studies did not strictly compare the two approaches, there appeared overall to be a lower recurrence rate of rectal adenomas excised *via* TEMS compared to TAE (3%-40%) as mentioned earlier. In addition, 2 other studies designed to pitch TEMS against conventional transanal surgery have also demonstrated lower recurrence rates with TEMS[58,64]. De Graaf *et al*[58] resected 216 adenomas *via* TEMS and 43 *via* TAE and found more frequent negative margins (88% *vs* 50%, $P < 0.001$) and lower recurrence rates (6.1% *vs* 28.7%, $P < 0.001$) in the TEMS group. Similarly, Moore *et al*[64] demonstrated a lesser degree of specimen fragmentation (94% *vs* 65%, $P < 0.001$) in addition to increased negative margins (90% *vs* 71%, $P = 0.001$) and lower recurrence rates (5% *vs* 27%, $P = 0.004$) with TEMS. Numerous factors come together and contribute to the better quality and outcomes parameters achieved with TEMS, such as improved operative visualization and magnification, increased stability and decreased need for specimen traction, optimized hemostasis, as well as improved instrumentation, all of which lead to increased completeness of the excision and decreased fragmentation of the specimen. Technical challenges are encountered with either higher lesions or very low lesions. In the upper rectum, the risk of perforation into the peritoneum is higher and particularly true for anterior lesions in female patients. On the other hand, very distal rectal polyps may represent a challenge insofar as the pneumorectum may be difficult to entertain. Furthermore, there is a risk of creating a rectovaginal fistula. Nonetheless, reported complication rates for TEMS are comparably low and range between 3%-15% and includes among others bleeding, infection, urinary retention; retroperitoneal tracking of air can frequently be seen but typically does not require any intervention. Even the majority of perforations into the peritoneum can be managed directly through the transanal approach, hence without a need for an abdominal intervention[62,71-74]. The available evidence suggests that TEMS for rectal adenomas not only avoids major abdominal procedures, but also is safe and achieves acceptable recurrence rates that are favorable compared to TAE.

Given the improved success with management of adenomas with TEMS compared to TAE, the next natural progression would be to ascertain if these results extended to malignant disease. Comparing TEMS to TAE in early rectal cancers (T1, T2), Christoforidis *et al*[75] noted significantly higher rates of negative margins with TEMS (98% *vs* 75%, $P = 0.017$). Although not reaching statistical significance, they also estimated 5 year recurrence rates to be lower (15.4% *vs* 29.1%, $P = 0.108$) and 5 year overall survival rates to be higher (79.9% *vs* 66%, $P = 0.119$) with TEMS. Similarly, Langer *et al*[76] also found lower recurrence rates with TEMS compared to TAE (10% *vs* 15%). The authors surmised that this was likely due to the overall lower rates of R1 resections that resulted from TEMS excision (19% *vs* 37%, $P = 0.001$).

Head to head comparisons of TEMS against standard resection for T1 rectal cancers have also been reported by various single institutions (Table 4)[77-81]. In general, the risk of recurrence after TEMS, although lower than after TAE, remains substantially higher compared to standard oncological resection. Results of data regarding salvage therapy for recurrent disease after TEMS are similar to that reported for TAE[82,83]. Sphincter preservation was improved (50%-70%) compared to TAE (33%)[44]; however, this difference might simply be accounted for by the more proximal location of the lesions excised in the TEMS group thus allowing for more salvage low anterior resections to be performed. Comparable to salvage therapy after TAE, perioperative morbidity was high at 50% and overall 3 year survival after salvage surgery was decreased[82].

For more advanced rectal cancer (T2 and above), significant local recurrence rates have been reported after either TAE or TEMS likewise[84-92]. Lee *et al*[79] reported a 5 year recurrence rate of 20% with TEMS compared to only 9% recurrence with standard resection of T2 rectal cancer. Similarly, the Minnesota experience on utilizing TEMS for T2 and T3 rectal cancers found recurrence rates of 23.5% and 100%, respectively[69]. As a result, some groups have incorporated the use of neoadjuvant chemo and radiation therapy (CRT) prior to TEMS excision in hopes of reducing the unacceptably high local recurrence rates in T2 rectal cancers. Lezoche *et al*[93] reported a substantially decreased local recurrence rate of 5.7% after neoadjuvant CRT and TEMS for T2 cancers. However, the recurrence rate was still double that of standard resection (2.8%). More recently, Marks *et al*[94] demonstrated a recurrence rate of 6.8% with TEMS compared to 0% in the standard resection arm after neoadjuvant CRT. The ACOSOG Z6041 trial, a prospective, multi-center phase-2 trial of neoadjuvant CRT and local excision for T2 rectal

Table 4 Single center comparison of transanal endoscopic microsurgery and standard resection for T1 rectal cancer

Ref.	Year	Follow-up (yr)	*n*		5 yr local recurrence		5 yr overall survival	
			TEMS	SR	TEMS (%)	SR (%)	TEMS (%)	SR (%)
Winde *et al*[81]	1996	3.8[TEMS]/3.4[SR]	24	26	4.2	0	96	96
Heintz *et al*[78]	1998	4.3	46	34	4.3	2.9	79	81
Lee *et al*[79]	2003	2.6[TEMS]/2.9[SR]	52	22	4.1	0	100	92.9
Palma *et al*[80]	2009	7.2[TEMS]/7.8[SR]	34	17	5.9	0	88.23	82.35
De Graaf *et al*[77]	2009	3.5[TEMS]/7[SR]	80	75	24[1]	0[1]	75	77

[1]Statistically significant. SR: Standard resection; TEMS: Transanal endoscopic microsurgery.

cancers recently reported its preliminary results[95]. The neoadjuvant protocol included treatment with capecitabine and oxaliplatin in addition to 50.4 Gy of external beam radiotherapy. Local excision *via* TAE or TEMS was performed 4 wk after completion of neoadjuvant CRT. At the price of substantial toxicity, 34 out of 77 patients completing the protocol (44%) showed a complete pathological response with overall 49 (64%) patient's tumors being downstaged (ypT0-1). Four patients (5%) did progress to ypT3 tumors. Long term follow up on recurrence and overall survival rates are still pending. Furthermore, neoadjuvant CRT protocols will likely further undergo optimization to improve the adverse event profile. The current evidence suggests that local excision for more advanced rectal cancers (T2 and above) risks treatment understaging and leads to significant local recurrence. It should therefore be restricted to palliation of patients that are otherwise not able to undergo standard resection.

A different target for which TEMS has been increasingly used are rectal carcinoids. With growing numbers of colonoscopies being performed, a 10 fold increase in the incidence of rectal carcinoids has been noted in the Surveillance, Epidemiology and end results registry[96]. As a result, there has also been a substantial increase in the number of transanal surgical excisions of the incidental rectal carcinoids. General consensus guidelines for rectal carcinoids consider them amenable to transanal excision include if they are well differentiated, no more than 2 cm in size, are confined to the submucosa and show no lymphovascular invasion[97]. The majority of published data on rectal carcinoids have utilized the TEMS platform as the approach to carry out the transanal excision[98-103]. Kumar *et al*[102] in a review of 24 patients who underwent TEMS excision of rectal carcinoids demonstrated no recurrence. Kinoshita *et al*[100] reported no recurrence or carcinoid-specific mortality after TEMS excision in 27 patients over a follow-up period of 70.6 mo. Likewise, Ishikawa *et al*[99] found no recurrence when rectal carcinoids were excised by either TEMS or conventional transanal surgery after a mean follow-up of 2 years. However, the analysis of 202 patients with rectal carcinoids surprisingly found that up to 30% of carcinoid tumors > 1 cm harbored nodal disease (OR = 32.7, P = 0.006), with lymphovascular invasion being an additional independent risk factor for nodal disease (OR = 19.6, $P < 0.001$)[104]. Despite the limitations of the data and generally rather small cohorts, it appears that transanal excision either by conventional approach or TEMS is appropriate to tumor sizes up to 1 cm.

TAMIS

TAMIS was "accidentally" reported in 2009 and quickly gained attention as a cheap and easily available alternative to the TEMS[105]. A SILS port (Covidien, Mansfield, MA, United States) was used in the beginning. Subsequently, specifically designed single-use transanal port systems (GelPOINT Path, Applied Medical, Rancho Santa Margarita, CA, United States) were developed and made commercially available. The GELPOINT path platform is about 44 mm long with a diameter of 34 mm and was specifically designed for TAMIS. The TAMIS port should sit on the levator ani muscles just above the puborectalis. The port is then optionally secured in place with sutures. Usually, 3 working ports are placed into the GelPOINT path: 2 working instruments and a laparoscopic 5 mm camera. As in TEMS, a seal is created between the anus and the TAMIS port allowing for distention of the rectum with CO_2 insufflation. Unlike TEMS, the camera position is not fixed and the TAMIS port is shorter and not angled at the end: this enables an increased working angle allowing for potentially near/circumferential excision without having to re-position the patient. No specialty laparoscopic instruments are required. However, there some potential drawbacks: The stability of the transanal platform is overall reduced given that there is no stabilizing arm to dock onto. In addition, the laparoscopic camera generally has to be removed quite often and cleaned. To combat this, the use of an endoscope has been employed[106].

Like for TAE and TEMS, morbidity associated with TAMIS has been minimal[105,107-109]. Schiphorst *et al*[109], over a median short term follow-up of 11 mo, recently reported comparable anorectal function based on FISI scores to TEMS after TAMIS.

Given the relatively short interval since TAMIS inception, the majority of data on TAMIS - related the excision of rectal neoplasms is limited to small cohort single institution studies and case reports. A

comprehensive review of the TAMIS experience from 2010-2013 was recently published by Martin-Perez *et al*[5]. The authors reported an overall margin positivity rate of 4.36% (12/275). Local recurrence was 2.7% (7/259) on short term follow-up (mean 7.1 mo). Conversion was only 2.3% (9/390) with a 1.025% (4/390) rate of unintended entry to the peritoneal cavity. In the largest published single institution series, Albert *et al*[107] resected 25 rectal adenomas, 23 malignancies (1 TIS, 16 T1, 3 T2, 3 T3) and 2 neuroendocrine tumors. The authors reported a 94% negative margin rate (47/50) with 4% (2/50) specimen fragmentation. Over a median of 20 mo follow-up, a local recurrence rate of 4% (2/50) was reported. Overall, the preliminary data showed that TAMIS achieved results comparable to TEMS in terms of recurrence rates and morbidity. Head to head comparisons in prospective studies with more long term follow up data are needed before any final recommendation can be made on the preferred transanal platform for local excision.

EMR

In recent years, application of EMR has led to more aggressive endoscopic resection of rectal adenomas and even early rectal cancers in specialized centers. The technique involves circumferentially marking the resection margin as done in transanal surgery. A submucosal injection of mixture of dye, saline and diluted epinephrine is performed to accomplish lifting of the lesion away from the underlying tissue. In some instances, magnification or chromoendoscopy can help further elucidate the true edges of a rectal lesion. Snare excision with cautery is performed whereby lesions < 2 cm are usually resected en bloc, while larger lesions may require several separate excisions. Reported complications include bleeding, post polypectomy syndrome and perforation, the vast majority of which resolve conservatively or require application of endoscopic clips for resolution[110-112].

In an earlier prospective study on use of EMR in resection of rectal adenomas, Hurlstone *et al*[113] resected 62 rectal adenomas (4 T1 cancers, 58 adenomas). The 3 mo local recurrence rate was 8% (5/62): 4 patients underwent repeat EMR and 1 patient had a low anterior resection. After a median follow-up of 14 mo, they noted that 98% (61/62) of the cohort remained free of recurrence. Main complication was bleeding (8%) that was managed with an endoclip placement. Based on this, the authors suggested that EMR for rectal adenomas and early rectal cancers is safe and effective.

More recently, Arezzo *et al*[114] completed a meta-analysis comparing EMR to TEMS in the resection of large rectal lesions. Eleven EMR and 10 TEMS studies involving 2077 patients were included for review. *En bloc* resection rates were 87.8% (CI: 84.3-90.6) for EMR compared to 98.7% (CI: 97.4-99.3) for TEMS. This corresponded to a substantially reduced R0 resection percentage for EMR *vs* TEMS (74.6% *vs* 88.5%, $P < 0.001$). Interestingly, recurrence rates were lower in the EMR group (2.6% *vs* 5.2%, $P < 0.001$). However, this difference could be explained by the significantly longer length of follow-up in the TEMS arm (mean 58.9 mo *vs* 6-12 mo). Even though there was a lower recurrence rate in the EMR group, a larger percentage of EMR patients eventually required standard resection (8.4% *vs* 1.8%, $P < 0.001$). Morbidity was similar at 8% in both groups.

In summary, the available data demonstrate that while feasible, EMR for rectal lesions appears to have poorer results compared to TEMS. No data comparing TAMIS to EMR is available at present, but it seems reasonable to expect similar results given the overall comparability of results obtained between TEMS and TAMIS thus far.

FUTURE APPLICATION OF TRANSANAL SURGERY

Expanding on the principles of NOTES, preliminary case series reported utilizing the transanal route to accomplish TME. An updated assessment of the transanal NOTES experience by Emhoff *et al*[18] included a total of 72 cases where a complete TME excision with largely negative circumferential margins could be obtained. The overall intraoperative and postoperative complication rate was 8.3% and 27.8%, respectively. There was a 2.8% incidence of conversion to open surgery with no 30 d mortality. No recurrence was reported but follow-up periods were generally limited to a few months only. Furthermore, there was an inherent patient selection bias with the majority of patients having early rectal cancer (T1, T2), low body mass indexs (BMIs), non-recurrent tumors and no previous history of pelvic surgery. Of the 10 case series reviewed, only 1 study by Rouanet *et al*[115] included higher risk patients (BMI > 30, narrow pelvis, T3/T4, recurrent and large tumors) with longer follow-up (median 21 mo). Not surprisingly, the results were less favorable: negative margin rates were lower (87% *vs* 95%) compared to lower risk patients in the other studies. Distant disease was noted in 8 patients (26.7%) and local recurrence occurred in 4 patients (13.3%). Overall survival was only 80.5% at 2 years. A 20 patient experience utilizing the TAMIS platform to achieve a TME were comparable to those by Emhoff *et al*[18]: 90% negative margin, 85% complete/near complete TME, and a 5% recurrence rate over median follow-up of 6 mo[17].

Transanal/TAMIS TME are techniques still in their infancy. The current data are limited to single institution cases series and lack a control arm. In addition, functional data are extremely limited with regard to the colo-anal anastomoses that generally ensues from the transanal/TAMIS TME. Data from randomized controlled studies with long term follow-up will ultimately be needed to determine if this new approach to TME

Table 5 Appropriate indications for the use of transanal excision/transanal endoscopic microsurgery/transanal minimally invasive surgery or endoscopic mucosal resection

Category	Primary approach	Secondary or individualized approach
Benign pathology	Low rectum: TAE or TEMS Middle to high rectum: TEMS/TAMIS/EMR or LAR Proximal to rectum: EMR or L/O CR	Very large lesion: LAR
Borderline pathology	Carcinoid < 1 cm with favorable features: TEMS/TAMIS Scar after colonoscopic removal of cancerous polyp: TEMS/TAMIS Uncertain dignity: TEMS/TAMIS mucosal resection as excisional biopsy	Excisional biopsy with TEMS/TAMIS/TAE → LAR if malignant?
Malignant (Rectum)	u/pT1: LAR u/pT2: LAR u/pT3: CRT + LAR Recurrence: CRT + LAR Carcinoid > 1 cm: LAR	u/pT1 + morbidity: TAE/TEMS/TAMIS u/pT2: TAE/TEMS/TAMIS + CRT
Malignant (Colon)	pTis: EMR/polypectomy pT1: L/O CR (unless free stalk > 2 mm) > T1: L/O CR	pTis (large): L/O CR pT1 + morbidity: EMR + observation

LAR: Low anterior resection (laparoscopic, robotic, open); L/O CR: Laparoscopic *vs* open colon resection; TAE: Transanal excision; TAMIS: Transanal minimally invasive surgery; TEMS: Transanal endoscopic microsurgery; TME: Total mesorectal excision; EMR: Endoscopic mucosal resection.

is truly needed and should be adopted on a more universal level.

SYNOPSIS

Transanal surgery has undergone significant technical advances in the last 25 years. The onset of improved video and computer technology and the onset of laparoscopic surgery in general have undoubtedly contributed to the evolution of this field. Conventional TAE remains a widely accepted approach in the management of low rectal adenomas. However, the transanal platforms of TEMS and TAMIS offer improved visualization, reach and allow for a finer and better controlled dissection in the limited rectal space. This likely explains the overall lower recurrence rates observed in the TEMS-/TAMIS-assisted local resection of benign rectal tumors. EMR for rectal lesions, while feasible, requires considerable technical expertise and more importantly offers inferior results compared to transanal or laparoscopic resective surgery. Based on the available evidence, local excision of rectal adenomas (which by definition are limited to the mucosa) is safe technique affording low morbidity without compromising patient outcome.

Data surrounding transanal excision of rectal malignancies remain more of a mixed baggage because the local excision does not achieve a lymphadenectomy and risk implanting malignant cells into the surgical wound. Small size (1 cm or less) rectal carcinoids appear to be amenable to local resection without any long term increase risks of recurrence. However, local recurrence rates of even early rectal adenocarcinoma unquestionably are higher than with a standard oncological resection and cannot reliably be improved with (neo-)adjuvant chemoradiation without substantial morbidity. Salvage therapy after local failure is not always possible but is usually associated with high perioperative morbidity and lower overall long term survival.

The true philosophical question a surgeon should not only ask the patient but also him-/herself is whether vanity and fear from an abdominal surgery, its scars, or a potential stoma are sufficient reason to jeopardize the chances to cure an early cancer (stage Ⅰ) which by all means should have a > 90% of disease-free survival. A wealth of data in the literature has supported the use of laparoscopic surgery in particular for mid and high rectal tumors, not to speak of any colon tumors. Intermediate and long term outcomes from various randomized controlled trials from Europe and Asia (CLASICC, COLOR Ⅱ, COREAN) have demonstrated non-inferiority of laparoscopic surgery compared to traditional open surgery for rectal cancer in regards to completeness of the resection, lymph node harvest, local recurrence rates, and overall survival. In addition, the laparoscopic approach has consistently been associated with shorter length of stay and reduced time to bowel function recovery[116-118]. Even for low tumors, the laparoscopic or robotic approach allows for a sphincter-preserving complete mesorectal excision and colo-anal anastomosis in the overwhelming majority of cases with excellent oncological and acceptable functional outcomes, and with no local recurrence noted for early rectal cancers[119-121]. It therefore seems not justifiable to risk an incomplete excision or seeding the operative field with cancer cells, which in the case of a TAMIS/TME would come to be located right on the freed presacral fascia, pelvic side wall, or the free peritoneal cavity. An unbiased discussion highlighting the risks and benefits of transanal surgery with the patient should assure to make the best informed decision in the setting of rectal adenocarcinoma. Appropriate use of an excellent technology should include self-restriction to define the best selection of pathologies and patients (Table 5). In cases where the diagnosis and/or stage are uncertain, the transanal local excision can be used as excisional biopsies (potentially limited to the mucosa

only to avoid distortion of the mesorectum), but final judgment on the appropriateness of the transanal approach as opposed to the ultimate best treatment should be reserved until the definitive pathology report has been obtained. If more treatment should be needed, it might-for concerns of postsurgical tissue changes-be desirable to postpone it for 4-6 wk.

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REVIEW

Techniques that accurately identify the sentinel lymph node in cancer

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Abstract

Sentinel lymph node (SLN) biopsy has become the gold standard for patients with melanoma and breast cancer but it's clinical application in other solid tumor types such as cancers of the esophagus, stomach, colon and rectum, head and neck, penis, uterine cervix and endometrium has been somewhat limited. Commonly used mapping techniques utilizing the combination of radiocolloid and blue dye may result in reduced SLN detection and increased false negative rates when applied to cancers with more complex lymphatic drainage patterns. Novel localization techniques including near infrared fluorescence, high resolution imaging and molecular targeted agents have been developed to address the limitations of conventional SLN detection practices in many solid tumor types. This article reviews the indications, techniques and detection rates for SLN biopsy in several different solid tumor types as well as the promising novel techniques created to address the contemporary limitations of this procedure.

Key words: Sentinel lymph node biopsy; Carcinoma; Radionucleotide; Blue dye; Techniques; Imaging

Core tip: Novel localization techniques including near infrared fluorescence, high resolution imaging and molecular targeted agents have been developed to address the limitations of conventional sentinel lymph node (SLN) detection practices in many solid tumor types. This article reviews the indications, techniques and detection rates for SLN biopsy in several different solid tumor types as well as the promising novel techniques created to address the contemporary limitations of this procedure.

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THE SENTINEL LYMPH NODE: PAST AND PRESENT

The modern understanding of cancer metastasis from primary tumors to regional lymph nodes originated from the observations of anatomists and pathologists. In the mid-19th century, Sappey illustrated breast

lymphatics travelling in the subareolar plexus towards the axilla *via* lymph collecting vessels[1] forming the theoretical basis of the subareolar injection of dye and isotope in the contemporary sentinel lymph node biopsy (SLNB). In 1860, Virchow[2] observed that an axillary node in breast cancer can be diseased for a long period of time without affecting adjacent nodes or distant organs. He postulated that node functioned as a filter that did not permit harmful particles to travel systemically until the node's barrier function had become insufficient or the node itself had become a new source of independent metastases[2].

One of the first operations based on knowledge of the lymphatics and importance of regional lymph node status was the radical mastectomy, thought to effectively control the orderly, translymphatic contiguous extension of tumor[3,4]. Radical operations for rectal, uterine, pancreatic, colon, stomach, and lung cancers adopted the same principle of removing the primary tumor, the organ from which it arose and regional lymph nodes en bloc[5-8]. Even early operations for melanoma described removal of the primary tumor, the regional lymph nodes and a long strip of contiguous skin and subcutaneous tissue thought to contain the lymphatics[9]. The morbidity of these resections drove surgeons to consider less invasive operations based on increasing knowledge of lymphatics and cancer metastasis[10].

Cabanas, an American-trained urologist, recognized the devastating complications of inguinofemoral lymphadenectomy for the treatment of penile cancer and devised an operation based on the identification and evaluation of the first echelon node draining the penis. By injecting contrast material *via* the dorsal lymphatics of the penis[11], he was able to reliably identify the first lymph node to drain the primary tumor, which he termed the "sentinel lymph node (SLN)". If the SLN was negative for cancer, it followed that cancer had not metastasized to the locoregional nodal basin and the patient would not benefit from inguinofemoral iliac dissection.

The sentinel node era continued to move forward by animal and human studies designed to explore the mechanisms of metastasis. The function of lymph nodes in the spread of cancer was investigated by injection of small particles into afferent lymphatics of animal models[12-15]. Observations from these experiments contradicted both the "filter function" postulated by Virchow and the Halstedian model of contiguous cancer spread, giving rise to new understandings and differing hypotheses of SLN function[16]. Fisher and Fisher observed that the node was not a "filter" that prevented dissemination of tumor cells but that metastatic disease in the lymph node was a "marker" for the presence of systemic disease[13-15]. Hellman proposed locoregional metastasis to be on a "spectrum" of the disease process that was relative to growth and progression of the primary tumor[17]. The subsequent "incubator" hypothesis described by Morton considered the unique immunologic interrelationship between the tumor and host, suggesting immunosuppressive factors released by the primary tumor allow for the growth and cloning of tumor cells in the SLN until the tumor reaches a critical mass, allowing it's movement to upper eschelon nodes or systemic dissemination[18]. By the 1990's, the SLNB had become a valid technique in staging malignant tumors of the skin and breast[19-23].

Accurate identification of the SLN documenting presence of occult regional node metastasis has helped to avoid complete lymphadenectomy in certain patients and may allow upstaging in others. The ideal tracer for SLN identification and lymphatic mapping should be standardized, easily acquired, require minimal preparation, nontoxic, have prompt translocation into the peritumoral lymphatics with reliable rate of travel, be taken up into the first encountered lymph node (SLN) in high amounts with high retention without lingering of radioactive signal in the primary injection site, creating a high signal to noise ratio and minimal "shine through"[24,25].

This ideal tracer does not yet exist, but knowledge of the size and chemical characteristics of clinically available agents can be used to optimize intraoperative, preoperative or postoperative use. Small sized contrast agents (< 5-10 nm) have fast uptake into the lymphatics, leaving only a brief window of SLN visualization before diffusion into upper eschelon nodes occurs. Medium sized agents (50-200 nm) have a slower transport rate through lymphatics but provide a longer imaging window. Larger particles (> 500 nm) tend to migrate very slowly after having been taken up by macrophages and dendritic cells[26] (Table 1).

This article will review the indications, techniques and detection rates for SLN biopsy in several different solid tumor types as well as the promising novel techniques created to address the contemporary limitations of this procedure.

MELANOMA

Indications for lymphatic mapping and subsequent SLNB in melanoma continue to evolve based on the recent results of landmark trials. The Multicenter Selective Lymphadenectomy Trial-Ⅰ was the largest trial to address the role of lymphatic mapping with SLNB in determining prognosis and survival[27]. Ten year follow-up results confirmed the role of lymphatic mapping and SLNB guided lymphadenectomy as a prognostic tool that improves disease specific survival compared to observation in intermediate thickness (1.20 to 3.50 mm) and thick (> 3.50 mm) melanomas[28]. Current National Comprehensive Cancer Network (NCCN) Guidelines recommend SLN biopsy for melanoma > 1 mm thick or those ≤ 1 mm thick with high risk features including ulceration or mitotic rate ≥ 1 per square millimeter[29] (Table 2). The American Joint Committee on Cancer (AJCC) guidelines emphasize lymphoscintigraphy followed by lymphatic mapping and SLNB as important components of melanoma staging that should be used to identify occult stage Ⅲ regional

Table 1 Characteristics of common tracers

Blue dyes	Inherent low molecular weight of blue dyes translates into a very rapid migration into and subsequently out of the lymphatics with fairly low SLN retention, relying on surgeon expertize to identify, locate and remove the SLN before the dye spreads to other nodes[111] Better for localization of superficial lymph nodes Methylene blue (tetramethylthionine chloride, C16H18ClN3S) is a heterocyclic aromatic dye, a member of thiazine dyes[112] First line of treatment in methemoglobinemias, is used frequently in the treatment of ifosfamide-induced encephalopathy and has applications in the treatment of memory loss[112]. Has risk of skin necrosis observed with intradermal injection[113]. Excreted primarily in the urine and causes a green-blue discoloration of the urine which can also be observed in saliva and bile that disappears within a few days. Better safety profile when compared to Isosulfan Blue[114] Patent blue (Isosulfan Blue, Lymphazurin) has a vivid affinity for the lymphatics, with particle size small enough to travel through the lymph vessel but large to be trapped in the lymph nodes[115]
Radiolabelled colloid	Variable size, from 100-400 nm[24] Sulphide-based nanoparticles conjugated with Tc-99m are the most commonly used and available[116] Half life is approximately 6 h[116] As the radiocolloid emits high energy gamma radiation (140 keV) which is highly penetrating, allowing for its use in variable tissue depth, density and coloration[116] Gamma detection instruments are needed to localize tracer (hand held gamma probes, gamma cameras, SPECT)
Indocyanine green	ICG is a negatively charged ion tricarbocyanine dye belonging to the large family of cyanine dyes ICG fluoresces at about 800 nm and longer wavelengths, confines to the vascular compartment through binding with plasma proteins, has low toxicity and rapid excretion, almost exclusively into the bile[117] ICG is a low molecular weight contrast agent, and is both rapidly taken up into the lymphatics but also can diffuse from the lymphatics, reducing the local concentrations and contributing to background signal[116] and needs to be readministered
Tilmanocept (99mTc, Lymphoseek)	Radiopharmaceutical that accumulates in lymphatic tissues by binding to a mannose-binding protein on the surface of macrophages[101] The molecule, 99mTc-DTPA-mannosyl-dextran, is composed of a dextran backbone to which multiple units of mannose and DTPA are synthetically attached[101]

DTPA: Diethylenetriamine pentaacetic acid; SLN: Sentinel lymph node; ICG: Indocyanine green; SPECT: Single-photon emission computerized tomography.

nodal disease among patients with clinical stage Ⅰ B or Ⅱ melanoma[30].

Blue dye

Morton's landmark research validated the clinical use of intraoperative lymphatic mapping for early stage melanoma[22]. In his study, patent V blue or isosulfan blue (0.5-1 mL) was injected intradermally with a 25 gauge needle at the site of melanoma, gently massaged and repeated every 20 min throughout the duration of the case. The rate of SLN identification with this technique was 81.8% (194 of 237 subjects) with a false negative rate (FNR) of less than 1% (non-SLNs were the sole site of metastasis in only 2 of 3079 nodes).

Radiolabelled colloid

Lymphatic mapping was first described with radio-labelled colloidal gold (198-Au) to predict the often ambiguous lymphatic drainage in truncal melanomas. In a pilot study of 57 patients with truncal melanoma, 0.1 mCi of radiolabelled colloid was injected into the dermis of the primary melanoma site and followed by radionucleotide scanning a day later. The authors reported no lymph node metastases were found at sites other than those taking up the radiolabeled colloid, providing a promising technique to accurately identify the draining nodal basin of the primary tumor[10].

A recent meta-analysis including 71 studies and 25240 patients demonstrated the proportion of successfully mapped SLN to be 98.1% (95%CI: 97.3%-98.6%) using scintigraphy with radiolabeled colloid[31]. The average dose of radiocolloid was 0.98 mCi.

Near infrared fluorescence

Recent clinical trials have used near-infrared (NIR) imaging with indocyanine green (ICG) to identify the SLN in melanoma. NIR imaging has high tissue penetration allowing for transcutaneous visualization of the tracer as it migrates from the peritumoral injection site to the regional lymph node basin in real time. Fluorescent lymphangiography using ICG has proven to be an effective method of SLN identification in patients with cutaneous melanoma and when used in combination with radiolabelled colloid, may replace the use of blue dye. In a recent study examining 52 consecutive patients with cutaneous melanoma of the trunk or extremities, rates of SLN detection were 96.2% for technetium-99m sulfur colloid, 59.6% for isosulfan blue, and 88.5% for ICG[32].

Imaging

Ultrasound relies upon the detection of anatomic changes in nodes with metastatic disease that may not always be apparent until a large nodal tumor burden is present. Loss of the normal fatty hilum and peripheral hypervascularity may indicate presence of nodal metastasis. Ultrasound guided fine needle aspiration performed in the presence of these concerning imaging characteristics increases the sensitivity of ultrasound for the diagnosis of nodal metastasis to approximately 82% with a positive predictive value of 52%[33]. In a

Table 2 National Comprehensive Cancer Network Guidelines for sentinel lymph node biopsy by cancer type

Melanoma (version 4.2014)	In general, SLN biopsy is not recommended for primary melanomas ≤ 0.75 mm thick, unless there is significant uncertainty about the adequacy of microstaging For melanomas 0.76-1.0 mm thick, SLN biopsy may be considered in the appropriate clinical context In patients with thin melanomas (≤ 1.0 mm), apart from primary tumor thickness, there is little consensus as to what should be considered "high-risk features" for a positive SLN. Conventional risk factors for a positive SLN, such as ulceration, high mitotic rate, and LVI, are very uncommon in melanomas ≤ 0.75 mm thick; when present, SLN biopsy may be considered on an individual basis For melanomas > 1 mm thick, discuss and offer SLN biopsy
Breast (version 3.2014)	Performance of SLN mapping and resection in the surgical staging of the clinically negative axilla is recommended for assessment of the pathologic status of the axillary lymph nodes in patients with clinical stage Ⅰ or Ⅱ breast cancer. This recommendation is supported by results of randomized clinical trials showing decreased arm and shoulder morbidity (pain, lymphedema, sensory loss) in patients with breast cancer undergoing SLN biopsy compared with patients undergoing standard axillary lymph node dissection. The patient must be a candidate for SLN biopsy and an experienced SLN team is mandatory for the use of SLN mapping and excision Axillary staging following preoperative systemic therapy may include SLN biopsy or level Ⅰ/Ⅱ dissection SLN mapping injections may be peritumoral, subareolar, or subdermal. However, only peritumoral injections map to the internal mammary lymph node(s) The performance of a SLN procedure should be strongly considered if the patient with apparent pure DCIS is to be treated with mastectomy or with excision in an anatomic location compromising the performance of a future SLN procedure In women with a local breast recurrence after breast conserving surgery who had a prior SNB, a repeat SNB may be technically possible. The accuracy of repeat SNB is unproven and the prognostic significance of repeat SNB after mastectomy is unknown and its use is discouraged The use of blue dye is contraindicated in pregnancy; radiolabelled sulfur colloid appears to be safe for SNB in pregnancy
Esophagus and Esophagogastric Junction (version 1.2014)	No guidelines for SLN biopsy exist
Stomach (version 1.2014)	No guidelines for SLN biopsy exist
Colon (version 3.2014)	Examination of the SLN allows an intense histologic and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. At the present time the use of SLNs should be considered investigational, and results should be used with caution in clinical management decisions
Rectum (version 3.2014)	Examination of the SLN allows an intense histologic and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. At the present time the use of SLNs should be considered investigational, and results should be used with caution in clinical management decisions
Head and Neck (version 2.2014)	SLN biopsy is an alternative to elective neck dissections for identifying occult cervical metastasis in patients with early (T1 or T2) oral cavity carcinoma in centers where expertise for this procedure is available. Patients with metastatic disease in their sentinel nodes must undergo a completion neck dissection while those without may be observed
Penis (version 1.2014)	Dynamic SLN biopsies are recommended only in patients with nonpalpable inguinal lymph nodes treated at tertiary care centers that perform greater than 20 per year
Cervix (version 1.2015)	Consider SLN mapping in stage ⅠA1 (with LVSI), ⅠA2 and ⅠB1 Consider SLN mapping for positive margins or dysplasia or carcinoma on cone biopsy for stage ⅠA1 without LVSI
Endometrium (version 1.2015)	SLN mapping can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration Cervical injection with dye has emerged as a useful and validated technique for identification of LNs that are at high risk for metastasis The combination of a superficial (1-3 mm) and deep (1-2 cm) cervical injection leads to dye delivery to the main layers of the lymphatic channel origins in the cervix and corpus

SLN: Sentinel lymph node; SNB: Sentinel node biopsy; LVSI: Lymphovascular space invasion; LVI: Lymphovascular invasion; DCIS: Ductal carcinoma *in situ*; LN: Lymph node.

feasibility study examining non-invasive staging of melanoma by ultrasound, 325 patients with melanoma underwent preoperative SLN ultrasound before SLN biopsy. Overall, sensitivity of ultrasound was 33.8%, specificity 85.7%, positive predictive value 36.5%, and negative predictive value 84.2%[33]. Variable lymphatic drainage patterns and low sensitivity make the routine clinical application of preoperative ultrasound without lymphoscintigraphic localization impractical.

Single-photon emission computerized tomography (SPECT)/computed tomography (CT) is a multimodal imaging technique that combines single photon emission computed tomography with CT. In melanoma, SPECT may allow for greater sensitivity, resolution, and anatomical localization than conventional lymphoscintigraphy alone, leading to a larger number of metastatic nodes excised (2.40 *vs* 1.87; 95%CI: 1.93-2.18; $P < 0.001$), decreased local recurrence rates (6.8% *vs* 23.8%, $P = 0.03$) and prolonged 4-year disease-free survival (93.9% *vs* 79.2%; $P = 0.02$) in a recent prospective randomized trial[34]. SPECT/CT may be of particular value in melanomas of the trunk and head and neck region, where lymphatic drainage is variable[35].

Failure of SLN detection and false negative rates

Factors that lead to failure of SLN localization in melanoma include inexperience of the surgeon, poor

tracer injection technique or injection away from the biopsy scar, timing of tracer injection, imaging the wrong nodal basin, not imaging all possible nodal basins, and complete replacement of the SLN with neoplastic disease causing the injected tracer to completely bypass the infiltrated node[22,36,37].

The FNR (calculated as number of patients with negative SLN biopsy who recur divided by the number of patients with positive SLN regardless of recurrence combined with the number patient with negative SLN who recur) in a meta-analysis that included data from about 25240 patients in 71 studies was 12.5%[31]. Likewise, collaborative groups worldwide have sited relatively high FNR ranging between 5.6% and 21%[37]. FNR increased with the length of follow-up (P = 0.002) but decreased with greater number of lymph nodes sampled (P = 0.001).

Gold standard

In the meta-analysis mentioned above that included data from about 25000 patients in 71 studies, at least one SLN was extracted in 14481 of 14818 patients, making SLN detection rate approximately 97.5%. All studies in the meta-analysis used scintigraphy, and 89% (63 studies) used blue dye[31]. Successful intraoperative SLN identification rates are generally reported to range between 97% and 100%[38], but this number is vastly discordant from the identification rates of the "true" SLN given the high false positive rates reported with melanoma. Most surgeons have adopted the preoperative use of radiolabeled colloid to detect the location of the SLN *via* lymphoscintigraphy and intraoperative use of a hand held gamma probe in conjunction with blue dye for visualization. The combination of techniques may increase the SLN identification rate when compared to a single technique alone but the lack of international guidelines and consensus for preoperative lymphoscintigraphy and intraoperative identification may contribute to the relatively high FNR continued to be reported in melanoma management[39].

BREAST CANCER

The SLNB has become invaluable in the staging of breast cancer. Although techniques for SLN identification may differ by clinician and institution, the American Society of Clinical Oncology 2014 practice guidelines[40] and NCCN guidelines[29] be viewed as the evidence based standard of care (Table 2). The SLN biopsy can be offered to women with operable breast cancer who have multicentric tumors, ductal carcinoma *in situ* (DCIS) with simultaneous mastectomy, history prior breast or axillary surgery and to those who will undergo preoperative or neoadjuvant systemic therapy. There continues to be insufficient evidence to recommend SLNB in large or locally advanced breast cancer (T3/T4), inflammatory breast cancer, DCIS when breast conserving surgery is planned and in pregnancy[40].

Blue dye

The SLNB in breast cancer was pioneered by Guiliano at John Wayne Cancer Institute[24]. Applying contemporary techniques used for intraoperative lymphatic mapping of cutaneous melanoma, his landmark paper described using isosulfan blue vital dye (Lymphazurin, Hirsch Industries, Inc., Richmond, VA) to accurately identify the SLN in breast cancer. His technique became standardized to the use of 3 to 5 mL injected in and around the breast tumor with interval wait time of 5 min from injection to exploration. Although a learning curve was observed, the SLN was identified 65.5% of the time (114 of 174 cases) and accurately predicted axillary nodal status in 95.6% (109 of 114 cases). Since its inception, the SLN identification rates with the use of blue dye alone have been reported to be 70%-98%[41-45]. Blue dye (methylene blue or isosulfan blue vital dye) is readily available and inexpensive, but the risk anaphylaxis remains a concern. Allergic reaction to the dyes isosulfan blue and patent blue V is rare and the reported incidence varies between 0.07% and 2.7%[46].

Radiolabelled colloid

The use of radiolabelled colloid in SLN identification was applied to the staging of breast cancer from its use in melanoma. Krag *et al*[47] first described the injection of 0.4 mCi technetium sulfur colloid in 0.5 mL saline around the breast lesion and the intraoperative use of a hand-held gamma probe to locate the nodes receiving drainage from the breast. A SLN was identified in 81.8% of consecutive patients (18 of 22) in this pilot study. The availability of radiolabeled colloid has been limited by the cost and departmental infrastructure needed to accommodate its parent isotope. A meta-analysis including over 8000 patients sited overall identification rate of 96% and false negative rate of 7.3% with the use of radiolabeled colloid[42].

NIR

NIR using ICG creates a real time image penetrable through tissue up to 2 cm, allowing percutaneous visualization of lymphatic channels and has been suggested for SLN mapping and identification. Based on a recent meta-analysis, ICG was shown to be better than blue dye alone but had no difference when compared to radiocolloid alone in terms of improved SLN identification[48]. Phase Ⅱ trials evaluating the accuracy of ICG have demonstrated an increased rate of SLN localization with the combination of ICG and conventional techniques *vs* blue dye alone. Using both NIR fluorescence and radioactivity, the FNR for SLN mapping was only 1% and the sensitivity of NIR fluorescence for initial localization of SLNs was 98%[49]. A multimodal approach of ICG, blue dye and radioisotope *vs* radioisotope alone demonstrated a significant increase in the average number of SLNs

identified in the multimodal approach group (3.4 ± 1.37 *vs* 2.3 ± 1.04, respectively; $P < 0.001$). Identification of SLNs occurred in all patients (100%) and there were no complications, leading the authors to consider the use of ICG in combination with blue dye and radioisotope safe[50]. The use of NIR may compliment the standard of care in SLN detection but head to head randomized control trials and cost analyses are needed.

Imaging

Imaging modalities including ultrasound (US), US guided SLNB, positron emission tomography (PET)/CT and MRI can identify structural and anatomic atypia in the regional lymph nodes and accurately predict the presence of metastasis in the SLN in breast cancer.

High resolution US is used to identify patients with clinically negative axillae who harbor nodal metastasis and may be candidates for preoperative chemotherapy. Eccentric cortical enlargement, thickening or lobulation, displacement or absence of the fatty hilum, hypoechoic echotexture or round or ovoid nodes are ultrasonographic findings suggestive of nodal metastasis[51-54]. In a meta-analysis of 21 studies using axillary US to identify metastasis (4313 patients), mean sensitivity and specificity were 61.4% (51.2% to 79.4%) and 82% (76.9% to 89.0%), respectively[52]. The addition of US guided biopsy improved both sensitivity and specificity to 79.4% (68.3% to 89%) and 100%, respectively[52]. Pooled data from a 31 study meta-analysis observed a FNR of axillary US with or without image guided biopsy to be 25% (95%CI: 24%-27%)[55]. Despite the high FNR, US guided biopsy has become a useful adjunct to the surgical SLN biopsy in the preoperative staging of patients with breast cancer.

A meta-analysis of 26 studies (2591 patients) evaluating diagnostic accuracy of PET or PET/CT in the axillary nodal metastasis, the mean sensitivity was 63% (95%CI: 52%-74%; range 20%-100%) and mean specificity 94% (95%CI: 91%-96%; range 75%-100%). Of 7 studies evaluating PET/CT (862 patients), the mean sensitivity in SLN identification was 56% (95%CI: 44%-67%) and mean specificity was 96% (95%CI: 90%-99%)[56]. Despite the application of PET/CT imaging in the evaluation of distant metastasis, evidence suggests that PET-based staging of the axilla in breast cancer is not recommended.

The use of MRI in the evaluation of axillary metastasis is also not supported by current evidence. In a meta-analysis, based on the highest sensitivity and specificity reported in each of the nine studies evaluating magnetic resonance imaging (MRI) (307 patients), mean sensitivity was 90% (95%CI: 78%-96%; range 65%-100%) and mean specificity was 90% (95%CI: 75%-96%; range 54%-100%). Estimates of sensitivity and specificity do not support replacement of SLN biopsy with any current MRI technology in this patient group[57].

Intraoperative assessment

Measuring intranodal pressure of the SLN and clinical suspicion based on intraoperative palpation has correlated well with the prediction of SLN macro- and micrometastasis in breast cancer[58]. The "true SLN" may be firmer and larger than other non-SLNs and highly suspicious for metastasis if it is more round than kidney-bean shaped, larger than usual, firm or matted.

Failure of SLN detection and false negative rates

Factors leading to the failure of SLN identification include the presence of altered lymphatic dynamics secondary to increased tumor burden in the nodal basin[59] and the receipt of preoperative chemotherapy (reported detection rates were 80.1% following chemotherapy)[60]. In the ACOSOG Z1071 study, in patients who received neoadjuvant chemotherapy, the use of blue dye alone increased the likelihood of failure to identify the SLN comparted to using radiolabeled colloid alone or with blue dye ($P = 0.006$; OR = 3.82; 95%CI: 1.47-9.92). The SLN identification rate in this study cohort was 78.6% with blue dye alone; 91.4% with radiolabeled colloid and 93.8% with dual mapping agents[61].

Gold standard

The gold standard of SLN identification in breast cancer remains the dual technique of blue dye and radioisotope injection[48]. The randomized EORTC AMAROS trial reported a SLN identification rate of 97% (1888 of 1953 patients) for which the majority (1744 patients) had the combined blue dye and isotope technique[62]. In the SENTINA trial, the SLN detection rate was 99.1% (95%CI: 98.3-99.6; 1013 of 1022 patients) in patients prior to receiving neoadjuvant chemotherapy[60].

ESOPHAGEAL CANCER

Minimally invasive esophageal resections for cancer have recently been shown to decrease the rate of comorbidities associated with open esophagectomy[63]. Prognosis however, remains dependent on extent of lymphatic spread and nodal metastasis[64]. The application of the SLNB to esophageal resection might be useful for accurate intraoperative decision making in determining the extent of lymphadenectomy in patients with early stage adenocarcinoma who are high surgical risk or in consideration for endoscopic resection[65].

Accurate identification of SLNs in esophageal cancer is most important in a cancer where direction of metastases is somewhat unpredictable[66,67]. The use of radiolabelled colloid (technetium 99m), blue dye and CT lymphoscintigraphy have provided individual detection rates of approximately 97%[65]. These tracers are most commonly injected around the tumor with endoscopic guidance. Increased detection rates are seen with smaller, thinner tumors, and adenocarcinoma (when compared to squamous cell carcinoma)[68].

Advocates of the widespread application of SLNB in esophageal cancer site increased ability to tailor and individualize cancer resection. "Ultrastaging" the most important lymph nodes by serial sectioning, immunohistochemistry and/or reverse transcriptase chain reaction, enables the identification of micro-metastatic disease that may guide decision-making in the administration of chemotherapy[69,70].

GASTRIC CANCER

The widespread application and clinical value of SLNB in gastric cancer is not well established. Gastrectomy with D2 lymphadenectomy remains the standard surgical treatment for gastric cancer worldwide[29,71] and a minimum of 15 lymph nodes submitted for pathological analysis has been shown to improve the prognostic ability if the AJCC guidelines to more accurately predict 5 year disease specific and overall survival[72]. This resection is not without morbidity, including bleeding, pancreatitis, subdiaphragmatic abscess, lymphorrhea and chylous ascites[73], leading to the application of the sentinel node theory in the management of early stage gastric cancer with the possibility that patients with small primary tumors (T1 or T2, less than or equal to 4 cm), clinically undetectable perigastric nodes (by imaging and endoscopy) with true pN0 gastric cancer may avoid extensive resections.

In a meta-analysis of 26 articles evaluating the FNR of different tracer methods in SLN biopsy in gastric cancer, FNR (defined as number of false negatives divided by number of true positives) were found to be 34.7% (95%CI: 21.2-48.1), 18.5% (95%CI: 9.1-28.0) and 13.1% (95%CI: 0.9-27.2) for blue dye, radiolabelled colloid and a combination of the two techniques, respectively[74]. A recent meta-analysis of 38 articles (2128 patients) reported a pooled identification rate of 93.7% (95%CI: 91.1-95.6) with combined tracer methods. Early T stage and submucosal injection resulted in a higher sensitivity but stressed the need for further studies to standardize the procedure and selection criteria[75].

Prospective trials have also demonstrated promising results in SLNB in gastric cancer. A prospective multicenter trial in Japan that included 397 patients with clinical T1N0M0 or T2N0M0 adenocarcinoma of the stomach used a dual tracer method (Technitium 99m labeled colloid and 1% isosulfan blue) to perform SLN mapping[76]. On the day prior to surgery, 20 mL of technetium 99m colloid (0.3 mCi) was injected into four quadrants of the submucosal layer of the lesion utilizing endoscopy. Intraoperatively, the gastrocolic ligament was divided to visualize lymphatic flow around the stomach. Isosulfan blue was then injected with the use of intraoperative endoscopy and a hand-held gamma probe was used. SLN detection rate was 97.5%. Pathology revealed four cases of false SLNs that were negative for carcinoma and nonSLN were positive, three of which were pT2 tumors (> 4 cm). SLNB using ICG has also been described with good detection rates (99.6%)[77] but real limitations of this method include the need for multiplanes of visualization, use of imprint cytology and open surgery by experienced surgeons. The JCOG0302 study concluded that the proportion of false negatives (46%) remains too high for the intraoperative "real time" evaluation of SLNs and further improvement on the application of the SLN concept in gastric cancer is needed[78].

COLORECTAL CANCER

Intraoperative SLN identification techniques have been described in the staging of colorectal cancer but there is no consensus on the application or validity of such practice. Regional lymph-node metastasis represents one of the most important indications for adjuvant chemotherapy in colorectal cancer. The use of blue dye to identify pericolonic lymph nodes that would have otherwise been overlooked intraoperatively can provide surgeons with a practical means to improve the staging of node negative patients. Early investigative studies defined SLNs as being those nodes closest to and receiving the most direct drainage from the tumor. When 1 mL of Lymphazurin 1% was injected in the subserosa of the primary tumor circumferentially, the SLN was correctly identified in 98.8% of cases (85 of 86 patients) and may have upstaged 18% of patients from stage Ⅰ/Ⅱ to stage Ⅲ disease[79].

There is no gold standard for this technique, which has been described using different tracers (methylene blue, isosulfan blue, patent blue, technetium 99m, ICG), modes of injection (four quadrant, peritumoral) and stages of surgery (*in situ, ex vivo*)[80]. A meta-analysis of 1168 patients (912 with colon cancer, 256 with rectal cancer) observed a SLN detection rate of 94% (95%CI: 92-95) with a mean weighted sensitivity of 76% (95%CI: 72-80; range 25-100) and rate of upstaging of 11% (95%CI: 6-22). Because of the potential to improve staging in colorectal cancer and based on the results of this study, the authors suggested that for every patient diagnosed with colon or rectal cancer without clinical evidence of lymph node involvement or metastatic disease, a SLN procedure, in addition to conventional resection, should be considered[80].

CANCER OF THE HEAD AND NECK

Lymph node status is an important prognostic factor in cancer of the upper aerodigestive tract. It is universally accepted that head and neck squamous cell cancer (HNSCC) with regional metastasis has to be addressed by either surgery with or without adjuvant chemoradiation or by primary chemoradiation, but the management of the clinically node negative neck remains controversial. In 2014, the NCCN guidelines were updated to include the use of SLNB in early (T1/T2) cancers (Table 2)[29]. Implementation of SLNB

in clinically node negative disease can potentially spare the morbidity of elective neck dissections and chemotherapy in three-quarters of patients[81,82]. In HNSCC, a clinically negative neck must have a negative physical examination and imaging including CT, MRI, ultrasound guided fine needle aspiration, and/or PET or PET/CT according to recent practice guidelines[83]. In these guidelines, the SLNB is performed with preoperative lymphoscintigraphy using planar or SPECT/CT followed by intraoperative detection with a portable gamma probe with or without the addition of blue dye. Two recent meta-analyses (1753 patients) examining the diagnostic value of the SLN concluded that SLNB is a valid diagnostic technique with sensitivity of over 90% and detection rates of over 95%[82,84]. Lower detection rates and sensitivity, however have been reported in cancers of the floor of the mouth[85,86]. SLN should be successfully located in greater than 90% of patients, positive SLN should match that of the observed rate of positive nodes in a formal neck dissections (20%-30%) and rate of false negatives should be < 5%[81-83]. Evidence favoring SLNB in T1/T2 HNSCC as a staging tool continues to grow with promising results of trials with longer term follow-up[85].

PENILE CANCER

Since the landmark work of lymphatic mapping and SLN identification by Cabanas[11], the routine implementation of SLN biopsy in penile cancer still remains in its infancy. NCCN guidelines no longer recommend lymphangiograms due to high reported FNR (over 20%)[87,88]. Dynamic SLN biopsies are recommended only in patients with nonpalpable inguinal lymph nodes treated at tertiary care centers that perform greater than 20 of these cases per year[29]. This method involves preoperative lymphoscintigraphy by intradermal injection of technetium 99m around the primary tumor and intraoperative use of gamma probe and intradermal blue dye injection. The addition of groin ultrasonography with or without fine needle aspiration preoperatively can potentially identify occult nodal metastases in patients with clinical N0 penile cancer. SLN biopsy alone might miss between 5%-10% of metastases[89]. Despite the advent of SLN biopsy in penile cancer leading to decreased inguinal dissection, 5 year disease specific mortality has decreased in clinical N0 disease[90]. A recent literature review examining management of inguinal nodes in penile cancer from 1977-2010 concluded that in order to obtain the lowest possible FNRs, performing a SLN biopsy in penile cancer requires urologists, radiologists and pathologists working together as a multidisciplinary team in a high volume center[91].

CERVICAL CANCER

NCCN guidelines recommend SLN mapping in cervical cancer for in stage Ⅰ A1 [with lymphovascular space invasion (LVSI)], Ⅰ A2 and IB1 and for positive margins, dysplasia or carcinoma on cone biopsy for stage Ⅰ A1 without LVSI[29]. SLN mapping studies have reported greater than 80% of identified SLNs are peri-iliac, contained in the common, external and internal iliac regions[92,93].

Precise detection of the SLN may allow for accurate prediction of pelvic lymph node status[94] which is a crucial factor for optimized treatment of cervical cancer. Initial studies using both radiocolloid (technitium 99m injected one day preoperatively in the 3, 6, 9 and 12 o'clock position into the cervix) and blue dye (injected into the same locations intraoperatively) reported SLN detection rates of 78% and established currently used injection protocols[95]. SLN detection with ICG seems to have similar detection rates to that of radiocolloid and blue dye[96].

Preoperative SPECT/CT in addition to radiolabeled colloid and intraoperative blue dye has demonstrated better anatomic correlation and improved rates of SLN detection (approaching 100%) compared to planar lymphoscintigraphy[97].

The SENTICOL Study is the largest multi-institutional trial in women with early stage cervical cancer (Ⅰ A1 and Ⅰ B1) who underwent dual tracer guided SLN biopsy (radiocolloid and blue dye) followed by pelvic lymphadenectomy. Detection rates of 97.8% were reported, leading the authors to conclude that SLN biopsy is a highly sensitive and important technique in women with early stage cervical cancer[98].

ENDOMETRIAL CANCER

Prognosis for endometrial cancer is correlated with lymph node status but complete pelvic lymphadenectomy for all patients regardless of risk is a subject of debate. In a recent multicenter study, SLN biopsy was associated with "ultrastaging" that was helpful in guiding adjuvant therapies[99]. Four quadrant cervical injection of technetium sulfur colloid (around the 3, 6, 9 and 12 o'clock) was performed on the day prior to surgery and patent blue dye was injected intraoperatively with a SLN detection rate of 86.4%. In this study, complete pelvic lymphadenectomy was performed in all patients and results recommended the routine use of SLNB in low- and medium-risk patients to guide chemotherapy. The SENTI-ENDO prospective multicenter study also reported the upstaging of 10% of low risk patients and 15% of intermediate risk patients[100]. Although it is not the standard of care, implementation of SLNB and subsequent "ultrastaging" in endometrial cancer may lead to more individualized treatment options for these patients.

DISCUSSION

The SLN biopsy created a paradigm shift away from

invasive, morbid surgical resections and towards more individualized care. Despite the increased use of SLNB in different solid tumor types and improvement in techniques, failure or false detection of the true SLN can still result in poor locoregional control and decreased survival. Further understanding of the molecular mechanisms of lymphatic metastasis has led to the creation of novel tracers and mapping techniques.

Protein receptors on the surface of lymphoid cells have become promising targets in SLN identification. Tilmanocept (99mTc, Lymphoseek) is a synthetic radiotracer that relies on carbohydrate moieties to target the CD206 receptor on the surface of macrophages and reticuloendothelial cells in lymphatics. It has demonstrated highly concordant SLN detection rates compared to traditional tracers[101-103] and was recently approved by the Food and Drug Administration for SLNB[104,105]. Gold nanoparticles bioconjugated anti-CD45 antibodies demonstrate high affinity for CD45 expressing cells in the lymph node, have rapid lymphatic uptake and significant retention in the nodes after 6 and 24 h[106]. The increased binding, uptake and retention of these new immunotracers may allow for their use in solid tumors that are in close anatomical proximity to their SLN or in those tumors with unpredictable or multiple nodal drainage patterns.

Novel maging techniques have been studied to increase the *in vivo* detection rates of the SLN as well. The use of intradermally injected microbubbles containing sulphur hexafluoride gas and high resolution contrast enhanced US have allowed for real time identification of lymphatic channels that can be traced up to the draining nodal basin. This technique has been shown to facilitate accurate SLN identification and targeted SLNB in pre-operative breast cancer patients[107]. The use of MRI with peripherally injected iron oxide nanoparticles has been shown to successfully identify the SLN but has failed to gain wide exceptance in clinical practice[108,109].

US-guided spectroscopic photoacoustic imaging of molecularly activated plasmonic nanosensors can detect lymph node metastasis as small as 50 microns with high sensitivity in animal models, suggesting promising clinical applications for the detection of SLN micrometastasis in the future[110].

As more is known about the unique molecular identity of the SLN itself, the peritumoral and intervening lymphatics, and the cells involved in lymphatic metastasis, tracers can be formulated to identify and irreversibly bind those unique biochemical targets, allowing for more accurate identification of the SLN and ultimately, patient individualized SLN guided lymphadenectomy in more solid tumor types.

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REVIEW

Mesorectal excision: Surgical anatomy of the rectum, mesorectum, and pelvic fascia and nerves and clinical relevance

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Abstract

Biologic behavior and management of rectal cancer differ significantly from that of colon cancer. The surgical treatment is challenging since the rectum has dual arterial blood supply and venous drainage, extensive lymphatic drainage and is located in a bony pelvic in close proximity to urogenital and neurovascular structures that are invested with intricate fascial covering. The rectum is encased by fatty lymphovascular tissue (mesorectum) that is surrounded by perirectal fascia that act as barrier to the spread of the cancer and constitute the surgical circumferential margin. Locoregional recurrence after rectal cancer surgery is influenced by tumor-related factors and adequacy of the resection. Local recurrence is associated with incomplete excision of circumferential margin, violation of perirectal fascia, transmesorectal dissection, presence of isolated deposits in the mesorectum and tumor in regional lymph nodes and incomplete lymph node clearance. Hence to eradicate the primary rectal tumor and control regional disease, the rectum, first area of lymph node drainage and surrounding tissue must be completely excised while maintaining an intact fascial envelope around the rectum and preserving surrounding structures. This is achieved with extrafascial dissection and removal of the entire mesorectum including the portion distal to the tumor (total mesorectal excision) within its enveloping fascia as an intact unit. Total mesorectal excision is the standard of care surgical treatment of mid and low rectal cancer and can be performed in conjunction with low anterior resection, abdominoperineal resection, extralevator abdominoperineal resection, and extraregional dissection. To accomplish such a resection, thorough knowledge of the surgical anatomy of the rectum and pelvic structures and fascial planes is paramount.

Key words: Mesorectum; Pelvic fascia; Mesorectal excision

Core tip: Radical resection of rectal cancer entails removal of the rectum with its fascia as an intact unit while preserving surrounding vital structures. The procedure is technically challenging because of the complex multilayered pelvic fascia and intimate

relationship between the rectum and vital surrounding structures. Despite the clear-cut "text book" description of surgical technique and straightforward manner of handling different structures in the pelvis, there are many variations and contradictory accounts reported in the literature as to the nature, anatomy and significance of some of the structures, proper plane of dissection, and the optimal technique to achieve oncological resection while decreasing urogenital and bowel dysfunction.

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INTRODUCTION

Colorectal cancer is the most common gastrointestinal malignancy in the United States and the second leading cause of death in the western countries. About 30% of the cancers are located in the rectum and 40000-42500 new cases of rectal cancer are diagnosed in the United States every year. The biologic behaviour and management of rectal cancer differ from colon cancer since it arises from an organ that has dual arterial supply and venous drainage and complex and extensive lymphatic drainage and is located in the pelvic in close proximity to the anal sphincter complex, surrounded by major neurovascular structures and constrained by the bony pelvis. Surgery remains the mainstay treatment modality. The primary goals of treatment are to cure the cancer, reduce local recurrence, maximize disease-free survival, maintain function, and optimize quality of life (Qol). Mortality of rectal cancer is related to metastatic spread prior to resection and local recurrence after resection. About 50%-75% of local recurrences are confined to the pelvis (locoreginal)[1]. The 5-year survival with local recurrence is < 5% and Qol is severely impaired by symptoms associated with local recurrence[2,3]. Locoregional recurrence is influenced by surgery-related factors and tumor-related factors and one of the most important surgery-related factors is adequacy of the resection.

Treatment of rectal cancer continues to evolve and change is brought about by improved preoperative staging of the cancer, better understanding of the biologic behavior of the cancer, development of new instruments and the introduction of new and effective chemotherapeutic agents. The surgical resection has also become a more refined and accurate procedure as a result of better understanding of the surgical anatomy of the rectum and endopelvic fascia, topographic relationship between the rectum and surrounding structures and adherence to the principles of oncologic surgery. As a result, there has been a reduction in the number of locoregional recurrences, increased utility of reconstructive surgery and minimally invasive laparoscopic and robotic surgery, and decreased bowel, urinary and sexual dysfunction.

DISCUSSION

The rectum

Surgical anatomy: The rectum resides in the pelvis and extends from the rectosigmoid junction to the anal canal. It commences where the tenia coli of the sigmoid colon fuse to form a single continuous longitudinal muscle coat around the rectum. According to anatomists, it begins at third sacral vertebra (S3) and according to surgeons at the sacral promontory[4]. The junction of the rectum with the anal canal is demarcated by anorectal ring where the puborectalis muscle blends with the deep external anal sphincter (EAS). Although often described to measure 13-18 cm in length, the rectum is situated within the true pelvis (the part of the pelvis located distal to a line drawn from the sacral promontory to the symphysis pubis) is rarely 15 cm long[5]. The rectum has intraperitoneal and extraperitoneal components and is divided into upper, middle and lower parts. The upper rectum is intraperitoneal surrounded by peritoneum except for a small segment posteriorly where the superior hemorrhoidal vessels descend through the mesorectum to supply the rectum. It is situated 10-15 cm from the anal verge. The middle rectum is covered by peritoneum only anteriorly and is situated 6-10 cm from the anal verge. The lower rectum is extraperitoneal and situated 5 cm from the anal verge[5]. The peritoneum covering the upper third of the rectum is reflected onto the pelvic sidewalls to form the pararectal fossa and onto the seminal vesicles in the male and vagina in the female to form the rectovesical and rectovaginal pouch respectively.

The rectum possesses an outer longitudinal and inner circular smooth muscle layer. The outer surface lacks the appendices epiploica and the inner surface lacks the haustra found in the sigmoid colon. The outer longitudinal layer mixes with some of the fibers of the levator ani and forms the conjoint longitudinal muscle. This muscle extends in the intersphincteric plane between the internal anal sphincter (IAS) and EAS and sends fibers that traverse the EAS, ischioanal space, and the IAS. The EAS is a striated muscle that surrounds the IAS. The deepest portion of the EAS is intimately related to the puborectalis muscle and the superficial part is attached to the anococcygeal ligament posteriorly and perineal body anteriorly. The outer surface of the rectum has three lateral curves and the luminal surface has three folds that constitute the valves of Houston. The middle valve (Kohlrasch's valve) is the most consistent and marks the anterior peritoneal reflection that is about 7-9 cm above the anal verge in men and 5-7.5 cm in women.

The rectum is surrounded with the mesorectum

that is in turn wrapped by the perirectal fascia. The intraperitoneal part of the rectum is related to the uterine appendages laterally and the upper part of the vagina in females anteriorly. Loops of small bowel, sigmoid colon and the ovaries and fallopian tubes often reside in the rectovesical or rectouterine recess. The lower two thirds of the rectum follow the curve of the sacral hollow. The extra-peritoneal part of the rectum is related to the sacrum and the coccyx posteriorly, pararectal space laterally, and the urogenital organs anteriorly.

The rectum is surrounded with potential spaces: pararectal, retrorectal and supralevator. The pararectal space is an extraperitoneal space on the lateral side of the rectum and composed of loose and partly dense connective tissue. It is bound superiorly by the peritoneum, rectum medially, pelvic side wall and obturator internus laterally, and the levator ani inferiorly. The supralevator space is located between the peritoneum superiorly, levator inferiorly, rectum medially and obturator fascia laterally. The retrorectal space is located between the fascia propria of the rectum anteriorly, presacral fascia posteriorly, rectosacral ligament inferiorly, and lateral rectal ligaments laterally. The retrorectal space is continuous with the retroperitoneum superiorly.

Clinical relevance: Treatment of rectal cancer depends on its location in the rectum and extent of involvement of rectal wall and regional lymph nodes (LN) by primary tumor.

The level of the tumor in the rectum can be determined clinically in relation to the anorectal ring and endoscopically in relation to the rectal valves. The anorectal ring is felt on rectal examination as a muscular band that corresponds to the proximal shelf of the anal canal[5]. Kohlrasch's valve marks the anterior peritoneal reflection that is 7-9 cm above the anal verge in men and 5-7.5 cm in women. Cancers of the intraperitoneal rectum (upper third) behave like cancers of the colon with regards to recurrence patterns and prognosis but cancers of the extraperitoneal rectum constitute the rectum from the oncologic standpoint. Cancers of the upper and proximal part of the middle rectum are treated with an anterior resection and a straight colorectal anastomosis. Cancers of the distal middle and lower rectum are treated with abdominoperineal resection (APR) and end colostomy, sphincter sparing procedure or intersphincteric resection. For distal rectal cancer, sphincter sparing is possible if the lower edge of the tumor is at least 3 cm from the anorectal ring so as to allow a 2 cm distal magin. A 2 cm is considered adequate since any distal intramural spread is almost always within 1.5 cm of the primary and only 4%-10% have spread > 1 cm and any spread beyond 1.5 cm is associated with high grade or widely metastatic tumors[6-9]. A 1 cm margin is considered adequate for tumors < 5 cm from the anal verge especially when neoadjuvant chemoradiotherapy is used[10]. With sphincter-sparing procedure, an extended or ultralow anterior resection with a straight colo- or colonic-pouch-low rectal/anal anastomosis is performed. The coloanal anastomosis may be performed hand sewn transanally at the dendate line after excision of the mucosa from the dentate line to the anorectal junction or stapled at the anorectal junction. With intersphincteric resection, dissection is performed in the intersphincteric plane starting at the intersphincteric groove with partial or complete removal of the internal sphincter and a hand-sewn anastomosis performed transanally.

Select cases of early stage rectal cancer (Stage Ⅰ) may be treated with conservative resection, *i.e.*, local excison, either through a posterior approach (Kraske posterior proctotomy and York-Mason trans-sphincteric excision) or per anal approach (Park's per anal excision)[11-13]. The posterior approach is an established procedure but not frequently practiced because of associated morbidity and the advent of newer, less invasive and refined transanal procedures, *i.e.*, transanal endoscopic microresection (TEM), transanal minimally invasive surgery (TAMIS) and Robotic-TEM. With peranal excision (Parks' transanal local excision) the tumor is excised under direct visualization through the anal orifice. The procedure is limited to T1 or T2 small tumors (< 3-4 cm or < 30% of the circumference of rectal lumen), 8-10 cm from the anal verge and not fixed to the levator muscle. With TEM, TAMIS and Robotic-TEM, more proximal, larger or advanced lesions can be excised.

PELVIC FASCIA AND MESORECTUM

Surgical anatomy

Pelvic fascia: The pelvic fascia is associated with the pelvic wall and viscera and fills spaces between pelvic viscera and is continuous at the pelvic brim with the extraperitoneal abdominal fascia.

In pelvic dissection for low rectal cancer, Takahashi *et al*[14] described the "visceral and parietal endopelvic fasciae" as downward extension from the fascia in retroperitoneal space in the abdomen. In the abdomen, the visceral fascia runs under the peritoneum anterior to the aorta and cava, extends into the pelvis and envelops the rectum and mesorectum as the visceral endopelvic fascia. The parietal fascia runs posterior to the aorta and cava and extends into the pelvis along the entire pelvic wall as the parietal endopelvic fascia. In the true pelvis posteriorly, there is a potenial space between the two fasciae filled with loose areolar tissue and devoid of vessels and nerves[14]. Anteriorly at the level of the peritoneal reflection, the visceral endopelvic fascia envelops Denonvilliers' fascia on the anterior side of the rectum. Below the peritoneal reflection the circular continuity of the visceral endopelvic fascia is interrupted laterally by the presence of the lateral rectal ligaments and pelvic nerve fibers that arise from S3 and S4 foramina. At the distal side of the lateral

ligaments is a free space that extends between the endopelvic fasciae to the levator ani muscles[14].

Others divide the pelvic fascial arrangement into thin connective tissue layers covering surfaces of organs and connective tissue condensations of varying thickness that separate compartments. The parietal endopelvic fascia is described as a multilayered fascial tissue condensation that contain the hypogastric nerves together with the pelvic splanchnic nerves (PSN)[15-17]. Posteriorly, the fascia and embedded nerves can be easily separated as a compact structure from the anterior surface of the sacrum to uncover another thin fascia in front of the sacrum[16]. The fascia fuses with mesorectal fascia in the mid line posteriorly at the level of S4 creating a connective tissue bridge that can be quite dense and corresponds to the rectosacral ligament[17,18]. Antero-laterally, thin connective tissue continuations spread out medially from the fascia to interweave with the lateral extension of Denonvilliers' fascia that separates the rectum from the prostate and vagina[16]. The parietal endopelvic fascia exhibits an inner and outer lamella[15,19]. The continuity of the 2 lamellae varies, as does the thickness of tissue between them. The inner lamella envelops the mesorectal fascia posteriorly and laterally, thus confining the retrorectal space. Laterally the inner lamella and mesorectal fascia fuse thus the retrorectal space does not extend anterolateral[14,16]. The outer lamella extends between the iliac vessels on both sides and borders the presacral fascia posteriorly creating another plane that could be mistaken for the retrorectal space[19]. Laterally, the outer lamella cannot be delineated as distinctly as posteriorly since it is pierced by the PSN and blood vessels. The PSN emerging from the sacral roots and the hypogastric nerves originating from the superior hypogastric plexus, join the inferior pelvic plexus within the parietal pelvic fascia from and send several fine branches that diverge in a fan-like pattern towards the distal ureter, vas deferens, seminal vesicles, urinary bladder, prostate and the rectum[16]. The autonomic nerve fibers innervating the rectum pierce the lateral aspect of the fascia and enter the rectal wall (T-junction)[16,20].

Presacral fascia: On the posterior abdominal wall, a connective tissue sheath associated with the kidneys, ureters and genital vessels (urogenital fascia) descends into the pelvis below the promontory of the sacrum for few cm in front of S1, rarely S2, where it ends anterior to presacral fascia sometimes as a conspicuous border arched between the hypogastric nerves[21,22]. The urogenital fascia invests the ureters always lateral to the hypogastric nerves on the pelvic wall under the peritoneum of the pararectal fossa[21,22].

The presacral fascia (retrorectal fascia, Waldeyer's fascia) originates from S2 and S3 as thickened part of the parietal endopelvic fascia[23,24]. In the mid line posteriorly it descends in front of the sacrum, coccyx, the middle sacral artery and presacral veins, fuses with the periosteum of the sacrum and coccyx and covers the piriformis muscle. At the sacral foramina it ensheathes the nervi erigentes. The presacral fascia and the interface with the backside of the parietal pelvic fascia mimic the retrorectal space and the posterior aspect of the mesorectum[16]. The lateral margin of the fascia is connected with loose tissue to the sheath around the PSN[25]. At the level of S3-S4, the fascia sends extensions, the rectosacral ligament (posterior rectal ligament), in an anterior inferior direction or may become adherent to the fascia propria of the rectum 3-5 cm above the anorectal ring[16,18,21,25-27]. Sato *et al*[26] noted that the rectosacral ligament varies from several layers of parietal fascia passing forward and attaching to fascia propria as a "ligament" to a diffuse adherence between the two fasciae. It separates the retrorectal space from the subfascial space[21]. The composition of the rectosacral ligament is not well studied. Although few vessels and nerves are identified in cadavers, the rectosacral fascia does not contain any significant vessels. Distal to the rectosacral ligament between the fascia propria of the rectum and presacral fascia, lays the horizontal last 2-3 cm of the rectum[21]. The presacral fascia in that area becomes thinner and fascia propria thicker and may be composed of two layers.

Perirectal fascia: The rectum is "cocooned" within the mesorectum that is surrounded by perirectal fascia (or fascia propria) that fixes it in the pelvis and isolates it from the other adjacent pelvic organs. Fascia propria is an extension of the abdominal retroperitoneal visceral fascia or represents an upward capsular extension from the superior fascia of the pelvic floor that reflects off the pelvic sidewalls to become continuous with the subperitoneal loose connective tissues of the pelvis covering the pelvic floor musculature[14,28].

Thomas Jonnesco[29] (1901) was the first to describe the perirectal fascia as a strong, nonyielding, no more than 2-3 mm thick serofibrous sheath that encapsulated the rectum, fat, and the superior hemorrhoidal vessels and its branches and tributaries.

Bisset *et al*[27] likened fascia propria to a "sock", a shiny continuous sheath that completely surrounded the rectum and the surrounding mesorectum fusing with the peritoneum where the peritoneum reflects off the rectum. The sheath extended cranially around the rectum as far as the upper limit of the ampulla and continued into the retroperitoneum in a plane posterior to the inferior mesenteric vessels. Caudally it adhered to the presacral fascia opposite the S4 as the rectosacral ligament. Most distally as the mesorectum thinned out to the point where the fascia propria adhered intimately to the longitudinal muscle layer of the rectum at the anorectal junction. Anteriorly the fascia did not extend as high but rather merged with the peritoneum reflection (rectovesical or rectovaginal pouch). Below the peritoneal reflection, the fascia lied immediately posterior to the fascia of Denonvilliers' and could not be demonstrated as a separate layer.

At the lateral border of the pouch it fused with the submesothelial fibrous layer of the peritoneum lateral to the rectum and thin connective tissue continuation spread out medially to interweave with lateral extensions of the Denonvilliers' fascia. On histologic and electron microscopy examination, fascia propria appeared as a multilayered structure (in 80% of cases) of variable thickness ranging from 20 to 1000 um with an average thickness (measured *in vitro*) of about 150 um made up of multiple bundles of collagen fibers. It appeared thicker posteriorly than anteriorly. Anteriorly the fascia could not be demonstrated as a separate layer.

Mesorectum: The mesentery of the rectum, *i.e.*, mesorectum, is the perirectal fatty lymphovascular tissue extending the length of the rectum[5]. The mesorectum encases the rectum as a thick cushion mainly posteriorly and laterally. Posteriorly it has a characteristic bilobed appearance[21,27,28,30]. Inferiorly it thins out and tapers down to the anorectal junction. The mesorectum is enclosed with the perirectal fascia[27].

The superior, middle and inferior hemorrhoidal arteries (SHA, MHA and IHA respectively) provide blood supply to the rectum and anal canal. The SHA is a direct continuation of the inferior mesenteric artery (IMA) that arises from the anterior surface of the aorta at the undersurface of the third part of the duodenum. It descends in the mesosigmoid colon to the level of S3 where it bifurcates into right and left branches then further divides into anterior and posterior branches. These branches penetrate rectal wall into the submucosa and descend in that plane to the level of columns of Morgagni. The MHA shows great variability in its origin, presence, size and number. The artery may arise from the anterior division of the internal iliac artery (IIA) or have an anomalous origin from the inferior vesicle, inferior gluteal, or internal pudendal artery[26,31,32]. The MHA is identified in 12% to 100% of cases depending on size of vessel described[26,31,32]. The artery is bilaterally present in 14%-48% of cases and unilateral in 24%-31%[26,33]. When present bilaterally the origin is not always identical on both sides[32]. The artery is long and tortuous, passes down and medially below the peritoneal reflection on top the levator muscle, pierces the pelvic plexus during its course, enters the anterolateral aspect of the rectum between the superior and inferior rectal branches of the pelvic plexus, and gives several branches to the muscular coat of the lower rectum and submucosal plexus[25,32,33]. The size of the artery is variable and the point of insertion in rectum is 5-6 cm from the anus[25,32,33]. Immediately at the insertion, it is anterolateral to the rectum related anteriorly to the prostate and seminal vesicle or upper vagina. It then passes obliquely and medially traversing Denonvilliers' fascia[25,31,33,34]. The branching PSN arise posterior to the origin of the MHA and run in an anteromedial direction and reach the rectum at a similar height above the pelvic floor as the MHA. The MHA is closer to the pelvic floor and crosses the mesorectum independent of any structure. The vessel does not go through the lateral rectal ligaments and only accessory branches are found in 25% of cases and pass through the lateral ligaments[31,35]. By injection technique, the superior rectal field is filled by virtue of anastomotic connections with branches of MHA, the anastomosis between the SHA and MHA occurs both in the wall and extramurally, and connections between the SHA and MHA with the IHA are not demonstrable[31]. Since the presence of the MHA is variable and mostly is absent and its blood goes mainly to the muscle of the rectum and mostly to the prostate, its contribution to the viability of the rectum is considered insignificant[32]. The IHA is a branch of the anterior division of the internal pudendal artery that is a branch of the IIA and is mainly extrapelvic. The endopelvic fascia invests it as it passes out of the pelvis below the piriformis muscle through the greater sciatic foramina. It courses for a short distance in the buttocks then reenters the pelvis after passing over the sacrospinous ligament to enter Alcock's canal in the lateral wall of the ischioanal fossa. The vessel crosses the ischioanal fossa, traverses the EAS to reach the submucosa of the anal canal and ascends in that plane. Its main significance is to supply the sphincter complex[31]. The venous drainage of the rectum is partly hepatic and partly systemic: through the inferior mesenteric vein to the portal vein or through middle and inferior hemorrhoidal veins that drain into the iliac vein then the inferior vena cava. Information on the middle rectal vein is sparse but its rate of appearance is similar to that of the artery and drains into the internal iliac vein[26].

The lymphatic drainage of the rectum follows the vascular supply. Drainage occurs to mesorectal (perirectal) lymph nodes (LN) then upward along the SHA toward the mesenteric LN along the IMA to lateral aortic and para-aortocaval LN[36,37]. The mesenteric LN stations include central intermediate LN (from origin of last sigmoid artery to the origin of the left colic artery) and central LN (from the left colic artery to origin of IMA). Drainage into paracolic LN is unusual. The lower rectum however has a cloacal origin and its lymphatic channels are part of the pedicles draining to lateral LN[38]. From the middle and lower rectum lymphatic drainage is mainly up wards along SHA and lateral to pelvic LN; downward spread is uncommon. Lateral drainage occurs to intermediate lateral LN (LN along the MHA outside fascia propria) and lateral main LN (along IIA and obturator artery) to para-aortic LN[36]. The number of LN found in the mesorectum ranges from 14-28 depending on the method of preparation of specimens[39,40]. The majority of the mesorectal LN are located posteriorly with few on each side. There are relatively few LN in the mesorectum of the lower rectum.

Clinical relevance

At presentation, about 70%-80% of rectal cancers are advanced either due to direct extension or lymphatic invasion. The mesorectum and outermost perirectal fascia act as barrier to the spread of the cancer and constitute the surgical "circumferential margin". Rectal cancer can spread outside the rectal wall in a continuous fashion or as discontinuous tumor extensions or deposits into the mesorectum up to 5 cm distal to the tumor margin[30,41-46]. Discrete nodules found in the extramural adipose tissue may represent LN replaced by tumor. In the absence of residual nodal tissue, nodules > 3 mm are classified as pN disease and ⩽ 3 mm are classified in the pT3 category as discontinuous extramural tumor[47]. Involvement of circumferential margin by tumor is the main cause of local recurrence after rectal cancer surgery[46,48]. Circumferential margin is the nonperitonealized surface of the rectal specimen created by mesorectal dissection at surgery. Circumferential margin is considered positive if the distance between the deepest extent of the tumor and closest surgical clearance around the tumor, *i.e.*, circumferential resection margin (CRM), is 0 to 1 mm. CRM is an independent predictor of outcome in patients with rectal cancer[49-51]. When CRM is < 1 mm, local recurrence rate is 22% and when > 1 mm, the rate drops to 5%. Furthermore, CRM < 1mm is predictive of an increased risk of distant metastases (37% *vs* 15% for those with CRM > 1 mm) and shorter survival (70% *vs* 90% at 2 years for those with CRM > 1 mm). However, other investigators have considered 2 mm as the cutoff point. Nagtegaal *et al*[52] reported that the local recurrence was 16% for CRM < 2 mm *vs* 6% for patients with radial margins > 2 mm. Although the ideal CRM has not been universally accepted, resection with as wide of a CRM margin as possible must be accomplished. Circumferential margin for distal tumors is problematic since the mesorectum encases the rectum as a thick cushion mainly posteriorly and laterally proximally and inferiorly it thins out and tapers down to the anorectal junction making it impossible to obtain a 2 cm cuff of marginal tissue circumferentially. Lymph node involvement is the most important prognostic factor and a major determining factor whether a patient is candidate for adjuvant therapy. The overall survival is determined by number of LN involved. Violation of the perirectal fascia and transmesorectal dissection is associated with high local recurrence rate[24]. Local recurrence after rectal cancer surgery is associated with incomplete excision of circumferential margin, presence of isolated deposits in the mesorectum and tumor in regional LN and incomplete LN clearance[43,53,54]. To eradicate the primary rectal tumor and control regional disease, the rectum, first area of LN drainage (mesorectal LN) and surrounding tissue must be completely excised while maintaining an intact fascial envelope around the rectum and protecting and preserving surrounding structures, including the ureters, gonado iliac vessels, sacral venous plexus and pelvic autonomic nerves. To achieve such a radical resection, thorough knowledge of the pelvic structures and fascial planes is paramount.

Total mesorectal excision (TME), originally described by Abel[55] in 1931 and later adopted by other surgeon, implies removal of the entire mesorectum including portion distal to the tumor within its enveloping fascia as an intact unit[27,30,45,53,56,57]. TME is performed in conjunction with low anterior resection (LAR), abdominoperineal resection (APR), extralevator APR (ELAPR), and extraregional dissection (extended lymphadenectomy; lateral clearance). For mid- to low-rectal cancer, LAR with TME has been demonstrated to minimize locoregional recurrences[30,56-61]. For upper rectal cancer, or tumors > 10 cm from the anal verge, where a distal margin of 5 cm can be achieved, tumor specific mesorectal excision (TSMRE), *i.e.*, dividing the rectum and the mesorectum at the same level, is sufficient and is associated with results similar to that achieved with TME[53,62-64]. With, APR, the operative plane follows the mesorectum to the muscular tube of the rectal wall stopping at the puborectalis sling. The anus is removed by perineal approach and dissection is performed outside the edge of the EAS and leaving the ischioanal fat. With ELAPR, abdominal dissection stops at the rectosacral ligament and the anus, coccyx and most of the levator muscle are removed by perineal approach[19]. Lateral LN dissection may be performed with TME as part of an extraregional dissection (lateral clearance) for lower rectal cancer but the reported outcome is no different than that with TME[40,57,65]. Whether TME or TSMRE is performed, the technique of the excision is key: precise, sharp dissection is performed under vision outside the fascia propria of the rectum in the plane between the fascia propria and parietal pelvic fascia, *i.e.*, extrafascial dissection so as to remove the rectum with the enveloping fascia, as an intact package, without violating the fascial envelop of the rectum[16,27,30,45,58-60]. Sharp dissection facilitates identification and preservation of the autonomic nerves, allows adequate hemostasis and avoids tearing of the fascial envelope around the mesorectum. The inferior mesenteric vessels are divided and retracted with the rectosigmoid junction anteriorly, and extrafascial dissection is commenced.

Identification and preservation of the hypogastric nerves is discussed later. Dissection is performed between the fascia propria of the rectum and the presacral fascia posteriorly in the retrorectal space that contains loose areolar tissue and is devoid of vessels and nerves and pelvic wall laterally. Sharp dissection is performed under vision down to the rectosacral ligament posteriorly and lateral rectal ligaments laterally. The rectosacral ligament is divided so as to gain access and mobilize the last 2-3 cm of the rectum and the anorectal junction[21]. However with ELAPR, dissection stops at the rectosacral ligament. The mesorectal fascia is not detached from the parietal pelvic fascia and the levator muscle is not separated

from the sacrococcygeal junction[19]. The sacrococcygeal junction is disconnected through the perineal phase to detach the coccyx that is the insertion of the midline raphe of the levator muscle. The parietal pelvic fascia is divided in the midline through the disconnected sacrococcygeal junction and the levator is divided laterally at both sides[19]. The anterior plane of dissection to separate the rectum from the prostate gland and vagina is controversial and is discussed later. However, dissection is performed inside the pelvic autonomic nerves down to the top of the anorectal junction where the rectum has little mesorectal fat and appears as a bare tube[25,31,32]. Laterally the lateral rectal ligaments are divided (detailed discussion to follow). Damage to the accessory branches rather than the main of the MHA may occur MHA during division of the lateral ligaments. The point of insertion of the MHA into the rectum is 5-6 cm from the anus. Damage to the main MHA occurs during dissection of the rectum anteriorly and anterolaterally on the pelvic floor, when it is being dissected off the seminal vesicle and prostate gland or vagina (vide infra). With extrafascial mesorectal excision, regional LN's (mesorectal LN) are removed. In surgical terms, the lymphatic spread of cancer occurs to perirectal (mesorectal LN) and upwards to intermediate central and central LN along the SHA and IMA. Down ward spread is uncommon. Lateral spread to lateral pelvic LN is more clinically important in tumors with lower margin below 5 cm from the dendate line and the incidence becomes significantly higher with lower margin below 3 cm above the dendate line[14,36,40]. Superior LN metastasis occurs in more than 30%-40% of rectal cancer patients and has great clinical significance[66]. Lateral spread from the lower rectum to the iliac LN occurs in about 15% of cases[14]. Lateral spread occurs to LN's along the MHA that lie outside fascia propria. With extended resection, *i.e.*, mesorectal excision with extraregional lymphadenectomy, lateral pelvic and or lumboaortic LN are removed. The number of LN removed with extrafascial mesorectal excision depends on level of the tumor. Canessa *et al*[39] in a study in formalin-fixed cadavers noted that the mean number of LN was 8.4 per specimen. The LN ranged in size from 2 to 10 mm. Most of the LN's (71.4%) were found around the branches of the SHA proximal to the peritoneal reflection and 28.6% were found distal to the peritoneal reflection. Topor *et al*[67] using LN clearing solution identified 25 LN per patient (average 14/mesorectum and about 5 for each pelvic side wall). The majority of LN's (> 80%) were small (≤ 3 mm) and majority (56%) located posteriorly and most (92%) located within the mesentery of the proximal two thirds of the posterior mesorectum. The lower third of the rectum contained the fewest nodes (8% of LN) and most of LN's on the sidewall were located in the area of the middle rectum. It is shown that 12-15 LN must be examined to accurately determine node negativity and any less limits the predictive value of the pathologic examination[68,69]. The role of extended resections is controversial since randomized studies on survival benefits from the procedure are still missing. Opponents of lateral pelvic lymphadenectomy question the benefit of the procedure since only small percentage of patients have lateral LN involvement. The operative time with extended resections is prolonged and morbidity is high. Furthermore, their presence is indicative of systemic disease and hence patient's prognosis is poor. In addition some studies have shown lateral pelvic lymphadenectomy is not necessary in terms of curability for patients with advanced lower rectal cancer who undergo preoperative radiotherapy[70]. Several other studies reported the outcome with TME to be no different from the data on extended lymphadenectomy. Hence many surgeons in the Western World, Europe, to some extent in Japan favored the mesorectal excision only. The number of regional LN removed varies with location of the tumor and surgical technique.

LATERAL RECTAL LIGAMENTS

Considerable anatomical, surgical and physiological importance has been attached to the lateral ligaments of the rectum. Anatomists consider the ligaments as fascial bridge that act as a pathway for nerve fibers, small vessels and lymphatics from and to the rectum[28,50]. Surgeons recognize the ligaments as extraperitoneal thick bundle of dense connective tissue that provide pathway to lymphatic channels and contribute to the support of the rectum and in which the MHA and plexuses are embedded[71,72]. Proper handling of the ligaments during surgery has an important bearing on colonic, anorectal, sexual and urinary function as well as the prevention of local recurrence of the cancer[56,61,73-75]. To gain access to the depths of the lateral pelvis, full mobilization of the mid-lower rectum requires identification of the lateral rectal ligaments that are then clamped, divided and ligated to avoid intra- and post-operative hemorrhage since the MHA are large and do not respond to electro cautery[61]. Despite this clear-cut description and straightforward handling of the ligaments, there are many variations and contradictory accounts reported in the literature as to the nature, anatomy, and contents of the lateral rectal ligaments.

Surgical anatomy

Thomas Jonnesco[29] (1901) was the first to describe the lateral rectal ligaments as a continuation of the parietal fascia predominantly surrounding the origin of MHA from the IIA. Miles[76] (1910) in describing his technique with the APR stated that the dissection is carried downward on either side of the rectum until "the lateral ligaments can be realized as firm vertical bands of fascia requiring division with scissors". Goligher *et al*[61] (1984) described the ligaments, as seen from above, as having a triangular shape with the base on the pelvic sidewall and the apex joining the side of the rectum. Hojo[77] (1986) considered the ligaments as

rectal structures that should be removed completely. Heald in original and subsequent articles (1980s)[30,45] and Reynolds *et al*[78] did not mention the lateral ligaments in their description of TME. Enker[75] (1992) recognized the ligament as an important landmark during autonomic nerve sparing sidewall dissection for rectal cancer. Takahashi *et al*[14] described the ligament as a bundle of dense connective tissue in the pararectal space with variable thickness and length that extends from the peripheral part of the IIA to the sidewall of the midrectum between the peritoneum and levator muscle. The hypogastric nerve fibers reach the center of the ligament where they unite with the PSN as they emerge from the sacral roots and form the inferior hypogastric nerve plexus inside the ligament[14]. Thus the ligament is divided into a lateral part that contains the MHA and inferior vesicle arteries and the medial part that holds nerve fibers to the rectum together with branches of MHA. In addition to branches of IIA and autonomic nerves, the lateral ligament provides a route for lymph vessels that penetrate the inferior hypogastric plexus and reach LN around the origin of the MHA.

Jones *et al*[34] in a study performed on cadavers embalmed in formalin found very insubstantial connective tissue strands and at times no definite connective tissue structure crossing from the pelvic sidewall to the rectum. The strands of fibrous tissue were inconsistent in direction, variable in height above the pelvic floor and often absent all together or present unilaterally. The MHA was present in 50% of pelves mostly as a unilateral structure, was closer to the pelvic floor and crossed the mesorectum independent of any structure. The branching PSN arose posterior to the origin of the MHA, ran in an anteromedial direction and reached the rectum at a similar height above the pelvic floor as the MHA. Boxall *et al*[31] described similar findings during anterior resections and found only accessory branches of the MHA crossing to the rectum in condensations of fascia in 25% of cases. Nano *et al*[33] in a study on fresh cadavers and embalmed pelves viewed the lateral ligaments as extensions of the lateral aspect of the mesorectum as approximately trapezoid structures with their apex towards the rectum. The ligaments ran caudally and distally and anchored to the endopelvic fascia. The ligaments contained fatty tissue in communication with mesorectal fat but did not contain any significant vascular structures. When present, in some cases unilaterally, the MHA crossed together with the nervi recti that arose from the inferior hypogastric plexus transverse almost perpendicular to the inferior aspect of the ligament at its distal end before entering the anteromedial aspect of the rectal wall. The urogenital bundle ran just above the lateral ligament at its insertion of the endopelvic fascia. Sato *et al*[26] visualized the ligaments in human as composed of three components, the MHA, middle rectal vein and the pelvic plexus. The most constant component was the PSN as the middle rectal vessels were often absent, identified in 22% of cases, and when present occurred unilaterally. When present the artery was long and tortuous and pierced the pelvic plexus. The MHA divided the ligament into medial and lateral segments. The artery entered the rectum mid-way between the superior and inferior branches of the pelvic plexus. The PSN arose somewhere posterior and inferior to the MHA. The lateral segment consists of two sheaths one surrounding the MHA and one around the PSN. The medial segment share a common sheath with the nerves and follow the same course as that of the rectal branches of the pelvic plexus. Pak-art *et al*[35] during sharp dissection on "soft cadavers" (cadavers freshly embalmed with CU-formula I solution, a preservative that renders muscles soft) recognized the lateral ligaments as white, opaque bands of connective tissue distinct from surrounding areolar tissue traversing the space between the posterolateral aspect of the rectum and mesorectum and the lateral aspect of the anterior surface of the third and fourth sacral vertebrae. These ligaments were closer to the coccyx than the promontory of the sacrum. Components of the ligaments were loose connective tissue containing multiple small nerves. Small arterioles and venules were present in the ligament in 11% of cases. Muntean[22] described the rectal stalks as the paraproctium that arise from the pelvic fascia and run medially and dorsally to reach the anterolateral wall of the rectal wall at 10 and 2 o'clock. The paraproctium houses the rectal nerves and middle rectal vessels when present.

Clinical relevance

The lateral rectal ligaments vary from insubstantial connective tissue strands to no definite connective tissue structure crossing from the pelvic sidewall to the rectum. The incidence of the vessels occupying the ligament varies from 22% to 100% depending on the caliber of the vessel present and exact relationship of the vessels to the ligament. The main MHA does not traverse the lateral ligament but rather send minor branches through them, unilateral or bilateral in only 25% of cases. Hence the ligaments can be divided with diathermy. The nervi erigentes lie in and under the endopelvic fascia and are close to the lateral margin of the ligament and together with the MHA do not run below them. The ligaments contain mesorectal fat and must be divided close to the pelvic wall to ensure optimal oncologic clearance. Leaving behind remnants of the ligaments implies inadequate adequate lateral clearance of the mesorectum[45]. Traction on the rectum may tent the endopelvic fascia with its enclosed nerves and puts the nerve at jeopardy during division of the ligament[22].

DENONVILLIERS' FASCIA

Separating the rectum from the anterior urogenital structures is a layer of tissue that is an important anatomical structure to the colorectal and urology surgeons

for oncologic and functional reasons, particularly in males. Denonvilliers[79] was the first to describe in 1836 the "prostatoperitoneal membranous layer" as a thin layer of tissue that separates the rectum from the urinary bladder, seminal vesicles and prostate gland in men. A similar structure consisting of essentially the same tissues was found in female pelves separating the rectum from the vagina often referred to as the "rectovaginal septum"[80]. Denonvilliers' fascia and the rectovaginal septum are also referred to as the "rectogenital septum". There is controversy as to origin, morphology, function and anatomical relationship to the fascia propria and urogenital structures and whether it can be identified during surgery and the precise plan of anterior rectal dissection for rectal cancer.

Surgical anatomy

Earlier studies have suggested that the septum is formed either as a result of incomplete partition between the rectum and urogenital organs or represents peritoneal fusion or condensation of loose areolar tissue after peritoneal fusion[80-82]. Aigner *et al*[83] on the other hand noted that local condensation of collagenous fibers is present between the rectum and urogenital organs from the beginning of fetal development and subsequent increase in dense collagen fibers and longitudinal smooth muscle cells produced the anatomical partition.

Kourambas *et al*[20] found in autopsies of adult males that Denonvilliers' fascia was easily seen as a sheet of fibrous tissue lying between the prostate and the rectum that had no defined layers or lateral edges. The fascia widened laterally and became continuous with the perirectal fascia posteriorly and the lateral pelvic fascia between the levator ani and prostate anteriorly. Stelzner *et al*[16] noted in human cadaver pelvises thin connective tissue continuations spread out medially from the parietal pelvic fascia to interweave with lateral extensions of the Denonvilliers' fascia that separates the rectum from the vagina and prostate capsule. The fascia splits into a number of laminae laterally[16,19-21]. Prominent nerves are seen intermingled with the lateral aspects of Denonvilliers' fascia and its fascial continuations and extended medially almost to the midline. Others identified Denonvilliers' fascia as it ran almost vertically between the peritoneal reflection of the rectovesical pouch and the pelvic floor anterior and separate from fascia propria of the extraperitoneal rectum[18,27,84]. The septum forms an anatomical incomplete partition between the middle and posterior compartments in the female and the anterior and posterior compartments in the male that is completed by the perineal body distally[83]. Immediately anterior to the lateral borders of the fascia, the parasympathetic cavernous nerves run to supply the corpora and govern erectile function and are in jeopardy during deep anterior dissection of the rectum and are jeopardy[85].

Histologically, the rectogenital septum is predominantly made of connective tissue and contains smooth muscle fibers and sensory neurons[18,20,27,79,80,83]. The connective tissue consists mainly of dense collagenous fibers and few course elastic fibers derived from mesenchymal condensation[27,80,83]. The origin of the smooth muscle bundles may be traced to the external longitudinal muscle sheath of the ventral wall of the rectum at the level of the middle transverse fold of the rectum (Kohlrausch's valve) where the muscle layer appears thicker[83]. Similar muscle fibers are also noted within the anal sphincter musculature[83]. The smooth muscle fibers in the ventral rectal wall give origin to the longitudinal muscle of the anal canal and also bend caudally to traverse the rectogenital septum terminating in the perineal body that is a dense connective tissue that separates the urogenital hiatus from the anal hiatus. The longitudinal smooth muscle fibers are accompanied by small nerve bundles attached to the connective tissue of the perineal body. Neurovascular bundles coming from the autonomic inferior hypogastic plexus intermingle with the lateral margin of the septum and cross the midline between the septum and the rectum[83].

The precise function of the rectogenital septum is not clear but there is evidence to suggest an important role in urinary and fecal continence. In one study, intrinsic innervation was confirmed by the presence of parasympathetic nerves innervating the septum and sensory neurons present within the septum was demonstrated[83]. Neurovascular bundles coming from the autonomic inferior hypogastric plexus intermingled with the lateral margin of the septum and crossed the midline between the septum and the rectum. The rectogenital septum and its smooth muscle component share the same innervation as the longitudinal muscle layer of the rectum. The longitudinal muscle fibers in the septum terminate in the perineal body and act as anchors and when the muscle contracts it results foreshortening and opening of the anal canal[83].

Clinical relevance

To mobilize the midrectum, anterior dissection is performed to separate the anterior wall of the rectum from the urogenital structures. From the surgical point, there is controversy as to the appearance of the septum and whether it can be identified during surgery and plane of dissection during proctectomy.

Many surgeons believe the fascia is more closely applied to the prostate gland and seminal vesicles than the rectum[28,86]. Others describe the fascia as more closely adherent to the rectum than the prostate[87]. The operative appearance of the fascia varies considerably from a fragile translucent layer to a tough leathery dense membrane but overall it is more obvious and substantial than fascia propria which is a thin membrane enveloping the mesorectum[28,87]. It is often more prominent in the young and becomes less prominent with increasing age and women and becomes more prominent after preoperative radiotherapy or if there is transmural rectal inflammation as in Crohn's disease[37,65]. Heald *et al*[30] noted the fascia on the anterior surface of

the mesorectum with a distinct plane separating this shiny fascia and the seminal vesicles. Thus during TME dissection takes the surgeon anterior to the fascia and thus resecting the fascia. Nano *et al*[88] suggested that the fascia "represented a plane of cleavage both with the rectum and between the two leaves that made it up" and that "the anterior leaf of the fascia is closely applied to the seminal vesicles." They believed dissection splits the fascia into two. Northover[89] and Bisset *et al*[27] on the other hand described dissection anterior to the fascia cranially then breaching it distally by dividing it transversely 1 cm below the base of the prostate in the male and opposite the vault of the vagina in the female to dissect posterior to it caudally. Others have maintained that excision of the fascia depends on location of the tumor in the rectum[59,64,84]. Lindsey *et al*[84] found Denonvilliers' fascia is left on the prostate and seminal vesicles during the usual anterior dissection in TME. For anterior and circumferential tumors in which the anterior margin is threatened, it is often taken with the specimen to gain maximal margin control[18]. In these cases the dissection is considered extramesorectal resulting in excision of the fascia[18,84]. With cancers sparing the anterior rectum, extramesorectal excision is not performed and in approximately half of anterior cancers dissection is extramesorectal and Denonvilliers' fascia is excised[18]. The risk of impotence is higher when tumors involve the anterior quadrant of the rectum because of the relationship of the cavernous nerves to Denonvilliers' fascia. In cases where the anterior circumferential margin is not threatened resection that does not jeopardize erectile dysfunction must be employed. To these cases the caudal portion of the ventral rectal wall including the septum must be left undissected[83]. Staying anterior to the septum behind the bladder and then posterior to it more caudally will prevent injury to the cavernous nerves and in consequence prevent erectile dysfunction[28,86]. Hence, in the male the peritoneum on the seminal vesicles is incised and dissection is carried anterior to Denonvilliers' fascia to the base of the prostate gland. In the female the peritoneum is incised in the pouch of Douglas. If the layers of the fascia are defined, the fascia propria and Denonvilliers' equivalent are excised with the specimen and if not defined stay close to posterior vagina. Dissection plane may be kept close to the rectum leaving the facia on the back of the vagina or prostate gland or between fascia propria and part of or all layers of Denonvilliers' fascia and equivalent fascia in the female[27,86].

The parasympathetic cavernous nerves run anteriorly, in close proximity to the lateral borders of the fascia to supply the corpora and govern erectile function[90]. These nerves are in jeopardy during deep anterior dissection of the rectum[85]. When disrupted during dissection of the distal aspect of ventral wall of the rectum during restorative proctectomy, the anchoring mechanism of the septum is interfered with and incontinence may result[90]. On the other hand when the caudal portion of the ventral rectal wall including the septum are left undisturbed during sphincter preserving procedure potency and continence are preserved[90].

PELVIC NERVES

Surgical anatomy

Parasympathetic innervation to the proximal colon down to the transverse colon runs *via* the vagus nerve and sympathetic innervation *via* postganglionic fibers from the paravertebral sympathetic chain. The left colon and rectum receive sympathetic innervation from the preaortic plexus and presaral nerves and retrograde parasympathetic innervation from neural efferents running through the lateral ligaments.

The sympathetic nerves arise from the thoracolumbar center T11-L2. Preganglionic fibers synapse in the pre-aortic plexus and postganglionic fibers follow the branches of the IMA and SHA to the left colon and upper rectum. The presacral nerves formed by fusion of aortic plexus and lumbar splanchnic nerves form the superior hypogastric plexus that gives rise to the right and left hypogastric nerves that innervate the lower rectum. The hypogastric nerves run between the presacral fascia and fascia propria and send nerves to the pelvic plexus (also termed inferior hypogastric plexus)[65]. The retroperitoneal fascia covers the lumbar sympathetic nerves and superior hypogastric plexus and the plexus is situated directly in the visceral fascia above the bifurcation of the aorta[65]. The hypogastric nerves separate from the plexus and descend caudad and laterally passing for a short distance through the visceral endopelvic fascia. The right and left hypogastric nerves run distally about 1 cm lateral to the midline and 1-2 cm medial to the ureters[27]. Thereafter the hypogastric nerve fibers are situated close to the visceral endopelvic fascia[14].

The parasympathetic nerves are formed largely by visceral efferent preganglionic fibers that arise from sacral nerves (mainly S3-S4, at times S2) and contain sensory nerves (PSN)[26,71]. The PSN are identified as two bundles on either side that emerge from the sacral roots, travel over the piriformis muscle covered by the endopelvic fascia[26,65]. The largest branch is S3 that runs caudal to the middle rectal artery and vein. The PSN pass laterally, forward and upwards and join the parietal pelvic fascia and the pelvic plexus within it very close to the anterolateral aspect of the lower rectum and the upper lateral wall of the vagina or posterolateral aspect of the prostate[16,65]. The inferior pelvic plexus is a complex network of sympathetic and parasympathetic nerves, located between the internal iliac vessels and the rectum on the pelvic sidewall amid the parietal pelvic fascia well outside the fascia propria of the rectum and is divides the MHA into a lateral and medial segments[16,26-28,91]. It is the center of autonomic innervation of the pelvic visceral. Branches from the inferior pelvic plexus diverge in fanlike pattern and innervate the urinary bladder, distal ureters, seminal

vesicles, prostate, membranous urethra, corpora cavernosa, uterus and vagina, rectum and the perineal body[16,26,65,71]. The nerve to the rectum diverge directly from the plexus into the rectal wall (T-junctions) and the remaining nervous network form the neurovascular bundles[16]. The nerves to the rectum arise from the pelvic plexus as a 1 cm long band course towards the rectum accompanied by small vessels along fascial fibers (lateral ligaments) and reach the rectal wall 6 cm above the anus or similar height above pelvic floor as the MHA[25,34].

Clinical relevance

Damage to the pelvic nerves results in sexual and urinary dysfunction[92]. In conventional surgery for rectal cancer as well as TME as initially described and extraregional dissection (lateral clearance) performed by the Japanese in the 1970's and 1980's, the autonomic nerves are sacrificed to achieve radical surgery[30,83,92]. In the mid 80's and thereafter, autonomic nerve preservation (ANP) was adopted by the Japanese and European surgeons and applied by the Western surgeons to preserve urologic and sexual function while maintaining oncological principles[14,27,58,91-93]. Surgical procedures for treatment of rectal cancer have changed to TME, and TME and extraregional dissection (lateral clearance) with ANP. ANP may be total where major components of the pelvic nerves are identified and preserved or partial where one or more component is sacrificed unilaterally or bilaterally[65].

During TME, the superior hypogastric plexus and nerves, PSN and the pelvic plexus are encountered and adequate mobilization of the mesorectum can be achieved while preserving these nerves. The superior hypogastric plexus can be identified on the front of the aorta at the level of the aortic bifurcation[94]. The right and left hypogastric nerves are identified about 1 cm lateral to the midline and 1-2 cm medial to the ureters[27]. Thereafter the hypogastric nerve fibers are situated close to the visceral endopelvic fascia. Extrafascial dissection is performed along a plane medial to the hypogastric nerves that are followed laterally and caudally[27]. The ureters invested in the urogenital fascia pass over the iliac vessels normally at the bifurcation of the iliac vessels then run laterally always lateral to the hypogastric nerves on the pelvic wall under the peritoneum of the pararectal fossa[22,23]. In females, the ureter crosses dorsal to the ovary and underneath the broad ligament within 2 cm of the uterine vessels. In males, the vas deferens crosses ventral to the ureter as it courses from the midline prostate to join the gonadal vessels laterally near the internal inguinal ring. The lateral rectal ligaments are divided sharply and in the process the nerves to the rectum arising from the pelvic plexus (T-junction) are sharply transected thus separating the mesorectum from the pelvic autonomic nerves undamaged on the lateral pelvic wall. The inferior hypogastric plexus and pelvic nerves lie on the pelvic sidewalls amid the parietal pelvic fascia well outside the fascia propria of the rectum[27,28,91].

Preservation of the urinary bladder nerves requires identification of the vesicorectal interspace[65]. The vesicorectal interspace emerges when the anterior rectal wall is mobilized. Branch to the urinary sphincter is found in a groove between the rectum and levator muscle beneath the levator fascia. From its origin in the inferior hypogastric plexus the pelvic nerve to the urinary bladder sphincter courses in a groove inferomedial to the rectum. At the level of prostatic apex it courses around the rectum en route to the urinary sphincter and there it susceptible to injury when the levator muscles are divided during APR. As the plans between the rectum and prostate is developed, if Denonvilliers' fascia is violated the continence nerve near the apex of the prostate can be injured.

CONCLUSION

Extrafascial dissection describes removal of the rectum, regional LN and mesorectum as a package with an intact envelope while protecting and preserving surrounding structures.

Sharp dissection is performed under vision in the plane between fascia propria of the rectum and parietal pelvic fascia posteriorly and pelvic wall laterally. The superior hypogastric plexus is identified on the front of the aorta at the level of the aortic bifurcation. The right and left hypogastric nerves are identified about 1 cm lateral to the midline and 1-2 cm medial to the ureters. Thereafter the hypogastric nerve fibers are situated close to the visceral endopelvic fascia. The ureters pass over the iliac vessels normally at the bifurcation of the iliac vessels then run laterally always lateral to the hypogastric nerves on the pelvic wall under the peritoneum of the pararectal fossa. In females, the ureter crosses dorsal to the ovary and underneath the broad ligament within 2 cm of the uterine vessels. In males, the vas deferens crosses ventral to the ureter as it courses from the midline prostate to join the gonadal vessels laterally near the internal inguinal ring. The recto-scaral ligament is divided to gain access and mobilize the last 2-3 cm of the rectum and the anorectal junction when an APR is performed or not divided when ELAPR is performed. The lateral rectal ligaments are divided close to the pelvic wall with diathermy close to the pelvic wall since the main MHA does not traverse the lateral ligament but rather sends minor branches through them. The nerves to the rectum arising from the pelvic plexus (T-junction) along the ligament are sharply transected in the process thus separating the mesorectum from the pelvic autonomic nerves undamaged on the lateral pelvic wall. The inferior hypogastric plexus and pelvic nerves lie on the pelvic sidewalls amid the parietal pelvic fascia well outside the fascia propria of the rectum. Denonvilliers' fascia is left anteriorly on the seminal vesicles and prostate gland or dissection is carried anterior to the fascia cranially

then the fascia is breached distally by dividing it transversely 1 cm below the base of the prostate in the male and opposite the vault of the vagina in the female. However, for anterior and circumferential tumors in which the anterior margin is threatened, the fascia is taken (extrafascial dissection) with the specimen to gain maximal margin control. Extrafascial dissection is performed along a plane medial to the hypogastric nerves that are followed laterally and caudally.

Extrafascial dissection is a safe and oncologically sound radical resection associated with low locoregional recurrence and satisfactory urogenital and intestinal functional results. The treatment can be achieved only with thorough knowledge of the surgical anatomy and topographic relationship of the rectum to the surrounding structures and adherence to sound oncologic principles.

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REVIEW

Caval reconstruction techniques in orthotopic liver transplantation

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Abstract

There are several caval reconstruction techniques currently in use for orthotopic liver transplantation. These include caval replacement or the conventional technique, performed with or without venovenous bypass, piggyback technique with anastomosis with two or three hepatic veins with or without cavotomy and modifications of the piggyback technique including end-to-side and side-to-side cavocaval anastomosis. There are few randomized controlled trials comparing the use of these techniques and our knowledge of their comparability is based on a few multi- and many single-center retrospective and prospective reviews. Although there are advantages and disadvantages for each technique, it is advisable that the surgeon perform the technique with which they have the most the experience and at which they are the most skilled as excellent outcomes can be obtained with any of the caval reconstruction options discussed.

Key words: Caval replacement; Piggyback technique; Conventional liver transplant; Standard liver transplant; Venovenous bypass; Portocaval shunt

Core tip: There are multiple options available for caval reconstruction currently in use for orthotopic liver transplantation. Those options include caval replacement or the conventional technique, performed with or without venovenous bypass, piggyback technique with anastomosis with two or three hepatic veins with or without cavotomy and modifications of the piggyback technique including end-to-side and side-to-side cavocaval anastomosis. There is currently no consensus in regards to the best technique although

there are advantages and disadvantages for each. Excellent outcomes can be obtained with any of the described techniques and the surgeon's comfort and skill with the technique is likely the most important factor.

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INTRODUCTION

Conventional liver transplantation includes total hepatectomy and resection of the recipient retrohepatic inferior vena cava (IVC) with interposition and anastomosis of the donor IVC as first described by Starzl *et al*[1] in 1963. In the conventional orthotopic liver transplantation (OLT) the recipient retrohepatic IVC is removed above the renal veins to the hepatic vein confluence at the diaphragm and replaced with the segment of donor retrohepatic IVC in an end-to-end fashion. The conventional technique reduces cardiac preload secondary to IVC clamping which can present hemodynamic challenges during the anhepatic phase of the operation. Venovenous bypass (VVB) was first utilized to increase cardiac preload and reduce venous and portal congestion thereby improving hemodynamic stability during the transplant procedure at the cost of increasing complexity.

The piggyback technique was first described by Calne *et al*[2] in 1968 and further developed by Tzakis *et al*[3]. The piggyback technique seeks to simplify the liver transplant by generally obviating the need for VVB by allowing venous return through the IVC. This technique involves full preservation of the recipient IVC with anastomosis of the donor IVC directly to the hepatic veins of the recipient[2,3]. The middle hepatic vein (MHV) and left hepatic vein (LHV) are frequently used as a common orifice for the anastomosis. It is also possible to use the MHV, LHV and right hepatic vein (RHV) or to use the MHV and RHV. Additionally some authors make further modification by adding a 1 to 3 centimeter cavotomy, in order to enlarge the anastomosis[4,5], or make a triangular cavotomy at the level of the RHV[6].

Belghiti *et al*[7,8] introduced a modified version of the piggyback technique in 1992, with a side-to-side cavocaval anastomosis (STSCCA) with partial clamping of the IVC. A temporary portocaval shunt (TPCS) was used during the procedure to preserve the portal venous flow thereby reducing intestinal congestion during the anhepatic phase[7,8]. Tzakis *et al*[9] also introduced the use of a TPCS in patients with intraoperative hemodynamic compromise.

Although these techniques have been compared in single-center prospective and retrospective studies there are only two randomized controlled trials comparing techniques and they have differing conclusions[10,11].

The issue of whether or not to use VVB with the conventional or piggyback technique or its' modifications or whether to use a TPCS are explored as a separate issue.

CONVENTIONAL OLT WITH VVB

OLT begins with a bilateral subcostal incision with or without a vertical midline extension. Left and right triangular ligaments are divided. If VVB is to be used, it is introduced at this point[12].

To establish VVB, catheters may be placed by percutaneous puncture of the femoral vein and internal jugular vein or alternatively by open exposure of the axillary vein and femoral vein. A catheter is placed in the portal vein after it is divided during the native hepatectomy[12]. Vascular clamps are placed on the infra- and suprahepatic vena cava and VVB is initiated[13]. Other authors describe cannulation of the left axillary vein and left iliac vein by way of the left greater saphenous vein[12].

The portal vein, infrahepatic and suprahepatic IVC are sequentially clamped. The recipient hepatectomy is completed. A running monofilament suture is used for completion of the suprahepatic and infrahepatic venous anastomosis. The portal vein, hepatic artery and common bile duct anastomosis are performed in the standard fashion as described elsewhere[12].

The conventional technique requires cross-clamping of the IVC and the portal vein during the anhepatic phase[14], and end-to-end interposition of the donor vena cava to the recipient vena cava[15].

THE PIGGYBACK TECHNIQUE

The piggyback technique is begun with mobilization of the native liver by division of the left and right triangular, coronary, and gastrohepatic ligaments. After dissection of the porta hepatis, the cystic duct, common hepatic duct, right hepatic artery and left hepatic arteries are ligated and divided. The portal vein is skeletonized with selective ligation and division of the anterior pancreatoduodenal vein[12].

The right lobe of the liver is reflected to the left exposing the retrohepatic IVC and the IVC ligament is divided. Several authors describe this division as the key to dissecting the retrohepatic vena cava[16]. The small hepatic veins draining the caudate lobe and right accessory vein(s) are ligated[12,14,16]. Some authors also describe the isolation and division of the RHV to prevent bleeding from the parenchymal side while mobilizing the liver[14,16], this vein is then oversewn[12]. The portal vein is clamped. The MHV and LHV are isolated and clamped[14,16]. In the piggyback technique the orifices of the LHV and MHV are joined into a common orifice[12,16]. Some authors also include

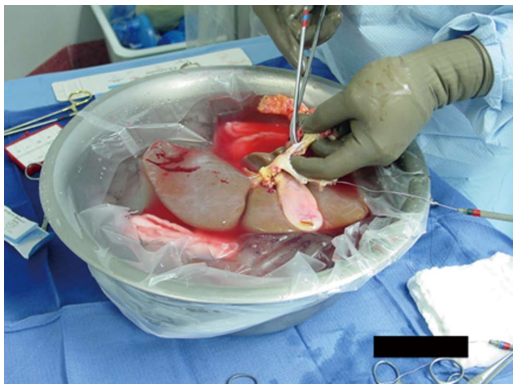

Figure 1 Liver back bench with clearing of tissue and flushing from donor inferior vena cava.

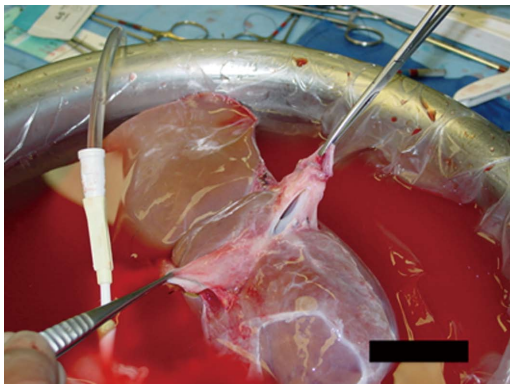

Figure 2 Longitudinal cavotomy is made in the donor inferior vena cava in preparation for the side to side caval anastomosis.

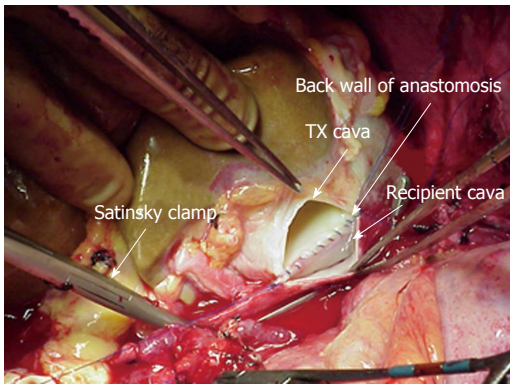

Figure 3 Side to side cavocaval anastomosis.

the RHV or an additional cavotomy of 1 to 3 cm[4,5]. An alternative approach is suggested by Gerber *et al*[6] who make a triangular cavotomy at the level of the RHV. If the donor and recipient are of similar weights and size the donor suprahepatic caval opening will fit the ostium created from the recipient hepatic veins. If not, it may be necessary to enlarge the anastomotic orifice[16]. Some authors suggest that in this case it may be necessary to cross-clamp the IVC. If this is poorly tolerated, VVB may be required[16].

Robles *et al*[17] report differing approach to the piggyback technique depending on whether they are completing the anastomosis with two or three suprahepatic veins. When they are using the MHV and LHV they dissect and suture the RHV, clamp the portal vein, complete the piggyback on the left until the common patch between the MHV and LHV is isolated and then transversely clamp the patch without occluding the retrohepatic IVC. When they use all three veins they dissect the retrohepatic vena cava on both sides, delaying portal venous clamping as long as possible and reaching the posterior face of the three veins without separating them. They then dissect the retrohepatic vena cava above the exit of the suprahepatic veins and free them from the diaphragm. They fit a transverse clamp. An end-to-end anastomosis is then performed between the two or three suprahepatic veins and the donor vena cava[17]. There are several detailed descriptions available in the literature of how to achieve a three-vein anastomosis in the piggyback technique. Tayar *et al*[18] recommend creating a common ostium from the three hepatic veins to provide a wide channel that is unlikely to obstruct or lead to symptoms of blocked outflow, positioning the anastomosis on the anterior and right aspect of the vena cava and shortening the graft suprahepatic IVC to avoid redundancy and kinking[18]. The portal vein, hepatic artery and biliary anastomosis are then completed in standard fashion.

STSCCA (PIGGYBACK VARIANT)

The donor hepatectomy is performed in the standard fashion. The upper cava cuff of the donor IVC is shortened flush to the hepatic veins. Both ends of the donor IVC are closed with running sutures, usually 4-0[16] or 5-0[19] polypropylene suture, or using a vascular stapler or EndoGIA stapler[20]. The IVC is flushed (Figure 1) to explore for and repair any leaks[20].

The porta hepatis is dissected and hepatic artery and common bile duct are transected. The portal vein is prepared and dissected. The hepatocaval ligament is dissected and RHV is oversewn or divided with an EndoGIA stapler. The MHV and LHV are then stapled. The recipient liver is removed[20].

A 3-4[15] or 6[16,20] centimeter long cavotomy is made on the posterior side of the donor IVC (Figure 2) encompassing the orifices of the major hepatic veins. This will allow future transjugular biopsy or transjugular intrahepatic portosystemic stent shunting placement if necessary. The donor liver is then implanted using one large anastomosis between the recipient IVC anteriorly and the posterior wall of the donor IVC (Figure 3). The anastomosis is performed from the left side using two running 4-0 polypropylene[15,16].

Akbulut *et al*[21] report an additional modification of this technique in which they use a linear stapler to complete this anastomosis. The upper and lower orifices of the donor IVC are closed on the back table

Table 1 Randomized controlled trial comparing conventional technique with venovenous bypass and piggyback technique

Variable	Conventional	Piggyback	*P*-value
n	34	33	
Age	46.5 (24-73)	48 (18-66)	0.831
Child-Pugh Score			0.931
A	5	5	
B	21	19	
C	8	9	
Anesthesia time (min) median (range)	795 (540-1115)	690 (510-1140)	0.162
Operative time (min) median (range)	647 (420-925)	600 (370-960)	0.270
Graft cold ischemia time (min) median (range)	536 (261-900)	497 (330-930)	0.205
Duration of mechanical ventilation (min) median (range)	712 (200-8070)	650 (0-26555)	0.429
Length of hospital stay (d) median (range)	15.5 (6-72)	17.0 (10-45)	0.846
Operative mortality (30 d)	0	1.3%	1.000
Red blood cells (units) median (range)	5.5 (0-34)	5.0 (0-35)	0.940
Fresh frozen plasma (units) median (range)	22.5 (0-84)	19.0 (0-82)	0.890
Platelet concentrate (units) median (range)	9.5 (0-40)	0.0 (0-30)	0.209
Aferesis platelet concentrate (units) median (range)	0.0 (0-3)	1.0 (1-10)	0.486
Crystalloid solution	1.5 (0-7.5)	1.5 (0-10)	0.985

Adapted from Isern *et al*[10], 2004.

with running 5-0 polypropylene suture. Three stay sutures are placed in the caudal parts of recipient and donor cava with 5-millimeter venotomies. An endoscopic linear stapler is placed upward through the orifice and fired. A second stapler is placed more cranially and also fired. This creates an 8-9 cm long cavocavostomy. This anastomosis was performed in 4 min. The insertion points are then closed with running 4-0 polypropylene suture[21]. The portal vein, hepatic artery and biliary anastomosis are then completed in standard fashion.

END-TO-SIDE CAVOCAVAL ANASTOMOSIS (PIGGYBACK VARIANT)

Polak *et al*[22] describe the end-to-side cavocaval anastomosis. First, recipient hepatectomy is performed in a standard manner. The hepatoduodenal ligament is dissected and the common bile duct is ligated and transected. After mobilization of the liver, the RHV is oversewn, or stapled. On the back table the caudal end of the donor IVC is shortened and closed over a silastic tube with a purse string suture around it. The opening of the suprahepatic IVC is extended by longitudinal midline incision on the posterior wall. Next, the native hepatic artery and portal vein, are ligated and transected. The MHV and LHV are oversewn and the liver is removed. TPCS is only used in selective cases, by most authors, to minimize the risk of splanchnic congestion in patients without portal hypertension or in the case of a very large caudate lobe that encircled the IVC[22,23]. After tangential clamping of recipient IVC, occluding approximately a third[22] to one-half[23] of its lumen, the anterior wall of the IVC is incised longitudinally and the graft is placed orthotopically. End-to-side anastomosis is performed between donor and recipient IVC using two running sutures[22,23]. The portal vein, hepatic artery and biliary anastomosis are then completed in standard fashion.

TECHNIQUES COMPARED

There are two randomized controlled trials (RCTs) comparing techniques for caval reconstruction in liver transplantation. There are a multitude of prospective and retrospective multi- and single-center reviews. The results of these will now be discussed.

RANDOMIZED CONTROLLED TRIALS AND COCHRANE REVIEW

Isern *et al*[10] in 2004 in Brazil performed a RCT in which 33 patients were randomized to the piggyback technique with no TPCS and 34 patients were randomized to the standard technique with VVB. There were no differences between the two groups noted in their primary outcomes, which included post-operative mortality, chest complications, transfusion requirements and hospital stay. There was no difference reported in anesthesia time ($P = 0.162$), operative time ($P = 0.270$), cold ischemia time ($P = 0.205$), duration of mechanical ventilation ($P = 0.429$), length of hospital stay ($P = 0.846$) or operative mortality ($P = 1.000$) (Table 1). There was also no difference reported in red blood cell use ($P = 0.940$), fresh frozen plasma use ($P = 0.890$), platelet concentrate use ($P = 0.209$), apheresis platelet concentrate use ($P = 0.486$) or use of crystalloid solution ($P = 0.985$) (Table 1)[10].

Jovine *et al*[11] in 1997 in Italy performed a RCT in which 20 patients were randomized to the piggyback technique with no TPCS and 19 patients were randomized to the standard technique with VVB. The

primary outcomes examined included primary graft nonfunction, renal failure, transfusion requirements, intensive therapy unit stay and hospital stay. They determined that there was a decrease in warm ischemia time (48.5 ± 13 min for piggy-back *vs* 60 ± 12 min for the conventional method) and in postoperative renal failure (zero cases in piggyback group *vs* four cases in conventional group) in the piggyback technique group. These results are conflicting with the RCT reported above in which there was no difference in these and other variables[11].

Additionally, a Cochrane Review published in 2011 performed a systematic review which included both of these studies[24]. They considered three trials in their review, the randomized controlled trials mentioned above: Isern *et al*[10] and Jovine *et al*[11] which both compared the standard technique with VVB to the piggyback technique without TPCS, and a randomized controlled trial by Figueras *et al*[25] which compared piggyback technique with and without TPCS.

For the Cochrane Review the following primary outcomes were chosen: post-operative mortality, graft failure and retransplantation. Post-operative mortality was only reported in one of the two studies, Isern *et al*[10], and there was no difference between the two groups (P = 0.49). Graft failure due to primary nonfunction was only reported in one study, Jovine *et al*[11] and there was no difference between the groups (P = 0.96). Long-term graft function and retransplantation were not reported in either trial[24].

The secondary outcomes included: adverse events, vascular morbidity, renal failure, transfusion requirements, intensive therapy unit stay, hospital stay, operating time, warm ischemia time. Specific adverse events were reported in both trials. Vascular morbidity was reported only in Jovine *et al*[11] and there were none. There was no difference in post-operative renal failure as defined by the need for hemodialysis (P = 0.50), transfusion of blood or platelets (P = 0.65), intensive care unit (ICU) stay (P = 0.37), hospital length of stay (P = 0.10) or operating time (P = 0.05). Warm ischemia time was only reported in Jovine *et al*[11] and it was lower in the piggyback group (P < 0.01). A higher proportion of chest complications were reported in the piggyback group (P = 0.01). This includes chest infections and pleural effusions[24].

These two RCTs and the associated Cochrane Review do not provide sufficient information on which to base a decision regarding which procedure to use in practice, and in fact provide conflicting information.

PROSPECTIVE AND RETROSPECTIVE STUDIES

There are a plethora of prospective and retrospective studies available in the literature comparing the different caval reconstruction techniques.

PROSPECTIVE AND RETROSPECTIVE STUDIES: THE PIGGYBACK TECHNIQUE

Several authors report exclusively on their experience with the piggyback technique (Table 2). Anastomosis using the LHV and MHV is abbreviated LM. Anastomosis using the LHV, MHV and RHV is abbreviated LMR. Anastomosis using LHV and MHV and an added cavotomy is abbreviated LM+.

In 1994 Fleitas *et al*[26] report a series of 39 patients who underwent 44 transplants with the piggyback technique and concluded that the piggyback operation could be performed in most patients undergoing OLT and should not be restricted based on anatomic considerations. They did a complex analysis of hemodynamic parameters including mean arterial pressure, IVC pressure, renal perfusion pressure, cardiac index and systemic vascular index and concluded that hemodynamic parameters were maintained throughout the procedures. They concluded that lateral IVC clamping and unclamping resulted in good hemodynamic stability. Vascular complications, retransplantation, blood requirements and overall survival were similar to that reported in the literature for the conventional technique[26].

Belghiti *et al*[8] in 1995 report the use of the piggyback technique with TPCS in 51 consecutive patients. They concluded that portocaval anastomosis was minimally time consuming with a mean time to perform of 9 min, and a range of 5 to 17 min, and that they were able to perform satisfactory portal venous anastomosis. They also conclude that the preservation of portal and caval flows as achieved with the piggyback operation with TPCS may have special importance in transplantation of partial livers[8].

Levi *et al*[27] performed a retrospective study comparing two different eras of their own experience. Era Ⅰ was from 1994 to 2002 and era Ⅱ from 2002 to 2010. They noted that they increasingly used the piggyback technique over time (P < 0.0002). Over time had shorter warm ischemia time (P = 0.0004) and less frequent need for VVB (P = 0.001). From era Ⅰ to era Ⅱ they noticed that their median operative time (P = 0.0000) and hospital length of stay (P = 0.0000) improved. Hepatic venous outflow obstruction was rarely encountered in their series. There were nine reported cases of hepatic venous outflow, six in era Ⅰ and three in era Ⅱ. The authors report that, "twice, it was recognized and corrected intraoperatively. Seven patients presented with refractory ascites. Six were successfully treated (4 balloon dilatation, 2 surgical revision), one patient died after attempted dilatation[27]".

Several authors in this series and others report on hepatic venous outflow obstructions, which do appear to be common with the piggyback technique[5,28]. There are a multitude of potential solutions to this problem, including the ones reported above: angioplasty with

Table 2 The piggyback technique

Ref.	*n*	Anastomosis	VVB	TPCS	Complications reported	Conclusion
Fleitas *et al*[26] single center	44 OLTs 39 patients	LM	No	No	Hepatic artery thrombosis (1), suprahepatic stricture (1), retransplant (5 - hepatic artery thrombosis, suprahepatic stricture, primary nonfunction, rejection), relaparotomy for bleeding (2), splenic steal (1)	Piggyback operation could be done in most OLTs, not restricted to certain anatomic situations. Lateral IVC clamping and unclamping results in good hemodynamic stability. Vascular complications, blood requirements, retransplantation, overall survival similar to that reported with standard technique
Belghiti *et al*[8] single center	51	LM	No	Yes, 100%	Four postoperative deaths (sepsis and primary nonfunction - 2, nosocomial pneumonitis at 3 and 5 mo - 2), no pulmonary embolism, NO IVC stump thrombosis	Piggyback technique was always technically feasible irrespective of graft size, VVB not required
Levi *et al*[27] single center	Era Ⅰ: 945 of 1080 (87.5%)	LMR when possible	177 (18.7%)	No	Outflow obstruction (6)	Increasingly used piggyback technique over time ($P < 0.0002$). Over time had shorter warm ischemia time ($P = 0.0004$), less frequent need for VVB ($P = 0.001$). Hepatic venous outflow obstruction rarely encountered
	Era Ⅱ: 851 of 920 (92.5%)	LMR when possible	97 (11.4%)	No	Outflow obstruction (3)	
Ducerf *et al*[5]	88 OLTs, 81 patients	LM *vs* LM+ 3-cm cavotomy	No	No	No outflow obstruction (0)	Preservation of the IVC with recipient caval anastomosis with MHV and LHV is reliable. Associated cavotomy is not necessary
Parrilla *et al*[13] multi-center	1112	440 LM 672 LMR	No	6 at one center	Abdominal bleeding (2), acute outflow obstruction (9), ascites (3), intraoperative complications (28 - 2 venous tears, 26 congestion), graft failure (11)	Complications inherent to the piggyback technique including intraoperative venous congestion and acute and chronic Budd Chiari syndrome were more common when patients underwent anastomosis with two suprahepatic veins *vs* three ($P < 0.001$)
Cescon *et al*[4]	431	LM, LMR, LM+ 1 cm cavotomy	No	No	Complications related to anastomosis (20, 4.6%)	Increase in complications related to caval anastomosis in patients with two-vein anastomosis (LM *vs* LM+ $P < 0.0001$, LM *vs* LMR $P = 0.065$, LM+ *vs* LMR $P = 0.4$). Orifice formed with two veins is not sufficient. Advocate balloon angiography for dilation of anastomotic narrowing in most cases
Robles *et al*[17]	171	87 LM 84 LMR	No	No	Hepatic venous outflow obstruction in 7 patients with LM (8%) and in 1 patient with LMR (1.2%)	Increase in hepatic venous outflow obstruction in patients with two-vein anastomosis ($P < 0.05$)

LM: Anastomosis with left hepatic vein and middle hepatic vein; LMR: Anastomosis with left, middle and right hepatic veins; VVB: Venovenous bypass; TPCS: Temporary portocaval shunt; OLT: Orthotopic liver transplant; MHV: Middle hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava.

or without stent placement[19,20,27,29,30], surgical revision of the anastomosis[13,20,27,30] creation of a, "neo-bed," or suturing the peritoneum covering Gerota's fascia of the right kidney to the diaphragm, which reduces the size of the recipients' hepatic fossa[13,17] and retransplantation[19,20,30].

There have been many studies published on possible rescue techniques for hepatic venous outflow obstruction. These include the use of venous patches[19], lifting and suspending the liver the the diaphragm[19], conversion to termino-terminal cavo-cavostomy[31], end-to-side anastomosis[4,28,32] and side-to-side cavo-cavostomy[16], and side-to-side cavocavostomy with an endovascular stapler[30].

Several authors have undertaken studies comparing the piggyback operation with two-vein anastomosis *vs* three-vein anastomosis to analyze feasibility of these techniques and the rates of complications with somewhat conflicting results.

Ducerf *et al*[5] compared a group of patients who had undergone suprahepatic caval anastomosis between the graft suprahepatic IVC and the recipient left and MHVs to a group of patients that had an associated 3 centimeter vertical cavotomy with partial clamping of the recipient vena cava. Twenty patients from each group had pressure and gradient measurements done 20 mo post-operatively to assess the hepatic veins, right atria and retrohepatic vena cava. The authors concluded that preservation of the IVC with recipient caval anastomosis at the ostia of the

middle and LHVs is a reliable technique. Furthermore they concluded that there is no alteration in hepatic venous outflow and that associated cavotomy is not necessary[5].

In contrast, Parilla *et al*[13] compare anastomosis with two hepatic veins to anastomosis with three hepatic veins and conclude that venous congestion and acute or chronic Budd Chiari syndrome are more common with anastomosis performed with two veins than when it is performed with three ($P < 0.001$)[13].

Cescon *et al*[4] compare three types of piggyback anastomosis: (1) anastomosis incorporating a cuff of the recipient LM; (2) anastomosis with the MHV and LHV plus one-centimeter cavoplasty (LM+); and (3) anastomosis with the LMR. They found an increased rate of complications with the group undergoing anastomosis with the MHV and LHV in comparison to those undergoing anastomosis with the MHV and LHV with associated cavotomy ($P < 0.0001$). They report their complications including four cases of thrombosis all of which required early retransplantation. For patients with anastomotic stricture, two were offered retransplantation and this was successful. The remaining cases were treated with balloon dilation during cavography (13, 65%) or anastomotic revision with end-to-side cavo-caval anastomosis between the distal stump of the donor vena cava and the recipient vena cava. Balloon dilation was successful in one session in eight patients and in two sessions in two patients. One patient in this group died from unrelated causes. In one patient balloon dilation was only partially successful and they were retransplanted. In another patient anastomotic kinking was demonstrated and cavo-caval anastomosis was attempted, but the patient required retransplant and then died soon after. Another patient had partial benefit from one session of balloon dilation and total recovery after cavo-caval anastomosis, but died of independent causes[4]. In contrast to the findings of Ducerf *et al*[5], they conclude that the caval anastomosis can be performed using the orifice formed by the MHV and LHV with associated cavotomy greater than one-centimeter and that the orifice formed by the two veins alone is not sufficient. Additionally, they advocate angiographic balloon dilation for anastomotic narrowing in most cases[4].

Robles *et al*[17] also compare the use of two-vein *vs* three-vein anastomosis, reporting that hepatic venous outflow complications were more common, and more serious, when two suprahepatic veins were used compared to the use of three ($P < 0.05$). There were six patients who presented with severe venous congestion of the graft intraoperatively which was attributed to suprahepatic vein kinking, which was treated with neo-bed creation. Five of these cases were in patients with two-vein anastomosis and one in a patient with three-vein anastomosis. Additionally, there were two patients who presented with post-operative hepatic venous outflow complications. One presented with acute Budd-Chiari syndrome due to stenosis of the anastomosis and required immediate retransplantation. A second presented with chronic Budd-Chiari syndrome with ascites and moderate graft dysfunction and was treated with diuretics. Both of these patients had two-vein anastomosis. There were no postoperative hepatic venous outflow complications in patients with three-vein anastomosis[17].

PROSPECTIVE AND RETROSPECTIVE STUDIES: PIGGYBACK *VS* CONVENTIONAL TECHNIQUE

There are several retrospective and prospective studies that compare the use of the piggyback technique to the conventional technique (Table 3).

Tzakis *et al*[3] compared 24 patients who had undergone piggyback operations to 24 matched controls who had undergone the standard operation (Table 3). They reported no difference in blood loss, retransplantation rate, portal vein or hepatic artery thrombosis or biliary tract complications (no *P*-values reported). They asserted that favorable anatomic conditions are required for use of the piggyback technique[3]. The least favorable circumstances tend to be with small cirrhotic livers and that the most favorable are patients with primary sclerosing cholangitis or primary biliary cirrhosis as patients with these conditions have hepatic veins which are relatively normal and accessible[3]. Tzakis *et al*[9] later report the use of the piggyback technique with TPCS in four hemodynamically unstable children with no established portosystemic collateral circulation[9].

Busque *et al*[33] report their experience with attempting the piggyback technique in 131 patients (Table 3). They were successful at performing the piggyback technique in 75% of their patients. The authors report, "reasons for conversion to the standard technique were: anatomical (22 transplants), severe portal hypertension requiring VB (8 transplants), tumor (1 transplant), and other reasons (2 transplants)[33]". They reported that piggyback technique without caval occlusion is possible, safe and reduced the need for VVB. Additionally, the authors report that it, "avoids retrocaval dissection, facilitates retransplantation, and is associated with a short anhepatic phase, low blood product usage, and short intensive care unit stay[33]". They report that partial outflow obstruction caused by the rotation of a small donor liver in large abdominal cavity at the hepatic vein anastomosis can be prevented by sewing the graft in counterclockwise[33].

Reddy *et al*[14] report their single center experience and compare the standard technique with VVB and the piggyback technique with selective VVB (Table 3). They report that the piggyback technique is safe, can be performed in the majority of patients, reduced the use of VVB (94% *vs* 22%), is associated with shorter anhepatic phase ($P < 0.0001$) and total operating time ($P = 0.002$), lower blood product use ($P = 0.023$) and

Table 3 Comparison of standard and piggyback technique with and without venovenous bypass

Ref.	Comparison	Results
Tzakis *et al*[3]	24 piggyback, selective VVB 24 standard, selective VVB	No difference in blood loss, retransplantation rate, portal vein or hepatic artery thrombosis or biliary tract complications
Busque *et al*[33]	98 piggyback 33 standard, 15% VVB	Attempted piggyback in 131 patients. Were able to complete in 98
Reddy *et al*[14]	40 standard, routine VVB 36 piggyback, selective VVB	Piggyback associated with shorter anhepatic phase, shorter total operating time, less red blood cell use, trend towards shorter hospital stay, reduced hospital charges
Gerber *et al*[6]	75 piggyback 127 standard	Piggyback here done with triangular vagotomy at level of right hepatic vein. Decreased operative time, use of blood products, caval complications in piggyback group
Hosein Shokouh-Amiri *et al*[34]	34 piggyback 56 standard, routine VVB	Piggyback with 60% reduction in anhepatic phase, decreased operative time, higher core body temperature, decrease in fluid, plasma, platelets, RBC volume, 30% shorter ICU stay, hospital stay. Significant reduction in hospital costs
Barshes *et al*[12]	122 piggyback 98 standard, 76% VVB	Trend towards shorter operating time and ischemia time in piggyback group. Similar amount of blood products transfused. No hepatic vein thrombosis or strictures, no IVC strictures or thrombosis, no hepatic vein obstruction, no anastomotic strictures, no hemorrhagic complications
Nishida *et al*[35]	918 piggyback, 19.7% VVB 149 standard, 79.2% VVB	Blood transfusion, warm ischemia time, use of VVB were less in piggyback group. Liver, renal function similar
Sakai *et al*[36]	104 standard, with VVB 148 piggyback, with VVB 174 piggyback, without VVB	Piggyback without VVB required less RBCs, FFP, cryoprecipitate, cell-saver return, less acute renal failure, better patient and graft survival. The piggyback with VVB group had shorter operative time, warm ischemia time, and less acute renal failure than the standard with VVB group
Vieira de Melo *et al*[37]	125 standard, without VVB 70 piggyback, without VVB	Piggyback group had reduced surgical time, warm ischemia time, red blood cell use, FFP use, mortality at 30 d. No difference in cold ischemia time, length of stay, use of vasoactive drugs in ICU, period of intubation, duration of hospital stay, renal or graft function, need for reoperation, incidence of sepsis, biliary complications, vascular complications, need for retransplantation, 1-yr mortality. Cumulative survival at 1 yr significantly better in PB patients
Cabezuelo *et al*[38]	84 standard 20 standard with VVB 80 piggyback	Standard technique in comparison to piggyback technique is an independent risk factor for post-operative renal failure. VVB does not ameliorate this effect

VVB: Venovenous bypass; IVC: Inferior vena cava; ICU: Intensive care unit; RBC: Red blood cell; FFP: Fresh frozen plasma; PB: Piggyback.

a trend towards shorter hospital stay (17 d *vs* 11 d) and reduced hospital charges ($105439 *vs* $91779) when compared with the standard technique with VVB. With the piggyback technique they reduced their rate of VVB use to 20%. In their patient population 34 of 36 patients were able to undergo the piggyback operation. In 8 of these patients VVB was used. For three of these patients VVB use was elective and in the remaining 5 it was used when the patient became hemodynamically unstable during the hepatectomy[14].

Gerber *et al*[6] introduced a further modification of the piggyback technique in which they make a triangular venotomy at the level of the RHV of the recipient (Table 3). The LHV and MHV are oversewn. A triangular venotomy is created on the posterior wall of the donor IVC. The cavo-caval anastomosis is completed with 3 running sutures. This incision allows the liver to settle into a dependent position in the right subdiaphragmatic space. They report significantly reduced operative time ($P < 0.05$), use of blood products ($P < 0.05$) and decreased caval complications in their piggyback group (3.9% *vs* 1.3%)[6].

Hosein Shokouh-Amiri *et al*[34] performed a prospective study comparing patients undergoing standard OLT with VVB to those undergoing the piggyback technique (Table 3). They concluded that the piggyback procedure resulted in a 60% reduction of the anhepatic phase ($P < 0.001$), reduction in operative time ($P < 0.003$), higher core body temperature ($P < 0.002$) and associated decrease in the requirements for fluid ($P \leqslant 0.03$), plasma ($P \leqslant 0.06$), platelets (< 0.009) and red blood cells ($P = 0.18$), 30% shorter ICU stays ($P < 0.008$) and similar reduction in overall hospital stay ($P \leqslant 0.05$). A reduction in hospital charges was also seen in the piggyback group ($P \leqslant 0.002$). The authors assert that what time is added in dissection in the piggyback group is eliminated because you do not have to place bypass catheters or spend as long achieving retroperitoneal hemostasis. There is also one less anastomosis in the piggyback technique providing significant time savings[34].

Barshes *et al*[12] report that operative time [5:20 *vs* 5:47, P = non-significant (NS)] and ischemia time (5:32 *vs* 6:06, P = NS) were shorter in the piggyback group (Table 3). There was no significant survival difference between the two groups ($P = 0.65$). Two patients in the piggyback group developed graft congestion after requiring massive fluid volumes to maintain hemodynamic stability and were rescued with end-to-side donor infrahepatic IVC to recipient vena-cava cavostomy. There were no hepatic vein thrombosis or strictures, IVC strictures or thrombosis or hemorrhagic complications. Similar amounts of blood were transfused. Eight patients in each group

had post-operative ascites without evidence of hepatic vein obstruction or anastomotic stricture. All of these resolved without further intervention[12].

Nishida *et al*[35] performed a retrospective study looking at 1067 transplants in 965 patients. Nine hundred and eighteen underwent the piggyback technique with two or three hepatic vein anastomosis *vs* 149 patients who underwent the conventional technique. Blood transfusions (P = 0.000202), warm ischemia time (P = 0.000000) and the use of VVB (P = 0.000000) were less with the piggyback group. Liver and renal function between the two groups in the postoperative period was similar. On univariate analysis cava reconstruction method, cold ischemia time, warm ischemia time, amount of transfusion, length of hospital stay, donor age and tumor presence were significant factors influencing graft survival (P < 0.05). On multivariate analysis cold ischemia time, donor age, amount of transfusion, and hospital stay were independent prognostic factors for graft survival (P < 0.05). Importantly caval reconstruction method as an independent marker did not show prognostic impact on graft and patient survival[35]. The authors report undertaking the conventional techniques for, "presence of tumor close to the IVC, presence of the intrahepatic cava, Budd-Chiari syndrome, or technical difficulties including the presence of the large caudate lobe or severe inflammation and adhesion between the caudate lobe and the retrohepatic IVC[35]". Additionally, they report that, "the reasons for using VVB were as follows: hypotension due to intolerance of IVC clamping, previous TIPS procedure, previous abdominal surgery making dissection in the portal hilum difficult, anatomic reasons including fulminant liver failure without the collateral veins, or intrahepatic inferior IVC or large caudate lobes[35]".

Sakai *et al*[36] compared the standard technique with VVB to the piggyback technique with and without VVB (Table 3). The choice of procedure was based on surgeon preference. The piggyback without VVB group required less intraoperative red blood cells (P = 0.006), fresh frozen plasma (P = 0.005), cryoprecipitate and cell-saver return (P = 0.007), had less acute renal failure (P = 0.001), better patient (P = 0.039) and graft survival (P = 0.003). The piggyback with VVB group had shorter operative time (P = 0.0001), warm ischemia time (P = 0.0001) and less acute renal failure (P = 0.001) than the conventional with VVB group[36].

Vieira de Melo *et al*[37] compared the conventional technique and piggyback technique, both without VVB or TPCS. The piggyback group had reduced surgical time, warm ischemia time, the use of red blood cells and fresh frozen plasma, and mortality at 30 d (P < 0.05). There was no difference demonstrated in cold ischemia time, length of stay or use of vasoactive drugs in ICU, period of intubation, duration of hospital stay, renal function, graft function, need for reoperation, incidence of sepsis, biliary complications, vascular complications, need for retransplantation or 1-year mortality (P-value not reported). The piggyback group had higher cumulative survival at one year (P = 0.03). There were similar rates of postoperative complications between groups[37].

Cabezuelo *et al*[38] compared the conventional technique, the conventional technique with VVB and the piggyback technique. They concluded that the conventional technique, in comparison with the piggyback technique, appears to be an independent risk factor for postoperative renal failure. They specifically looked at renal function in the first week after transplant and defined acute renal failure as serum creatinine > 1.5 mg/dL, an increase of 50% in the baseline creatinine or oliguria requiring renal replacement therapy. They analyzed which factors were associated with postoperative renal failure and demonstrated that intraoperative fresh frozen plasma and cryoprecipitate transfusion, intraoperative complications, postreperfusion syndrome, need for noradrenaline or dopamine, standard surgical technique verses piggyback and conventional technique with VVB *vs* piggyback were associated with postoperative renal failure (P < 0.01). In logistic regression analysis they demonstrated that conventional technique *vs* piggyback (P < 0.01), conventional technique with VVB *vs* piggyback (P = 0.02) and > 20 U of cryoprecipitate (P = 0.01) had independent prognostic value for the development of postoperative renal failure. They concluded that the conventional technique was an independent risk factor for postoperative renal failure and that the use of VVB did not ameliorate this effect[38].

RETROSPECTIVE AND PROSPECTIVE STUDIES: STSCCA

Durand *et al*[39] presents their experience with s STSCCA with a specific focus on post-operative renal function (Table 4). They report that STSCCA results in low rates of postoperative renal failure in their small prospective study. STSCCA is associated with preserved renal perfusion pressure throughout the procedure and preserved cardiac index and mean arterial pressure in the anhepatic phase[39].

Hesse *et al*[40] compared patients undergoing STSCCA with IVC preservation, STSCCA with VVB and STSCCA with TPCS (Table 4). In contrast to what is reported by other authors they reported the lowest perioperative blood loss in their VVB group and the highest rate of red blood cell and fresh frozen plasma transfusion in the group without VVB or TPCS (P = 0.002). Post-operative ICU stay and ventilation days did not differ between groups (no P-value reported). The changes in pre-operative and post-operative creatinine levels were most pronounced in patients that had construction of a temporary portacaval shunt (not significant, no P-value reported)[40].

Mehrabi *et al*[20] explored their single center

Table 4 Side-to-side cavocaval anastomosis

Ref.	Anastomosis	Conclusion
Durand *et al*[39]	STSCCA	Low rates of postoperative renal failure. Maintained postoperative creatinine clearance. Preserved renal perfusion pressure, mean arterial pressure, cardiac index throughout procedure
Hesse *et al*[40]	STSCCA *vs* STSCCA with VVB *vs* STSCCA with TPCS	Lowest blood loss in group with VVB (no *P*-value reported). Highest red blood cell and fresh-frozen plasma transfusion in group without VVB or TPCS ($P = 0.002$). Changes in pre- and post-operative creatinine most pronounced in group with TPCS (not significant, no *P*-value reported)
Mehrabi *et al*[20]	STSCCA	Technique feasible in all patients, no anatomic limitations. Minimizes need for VVB or TPCS. Some patients with hepatic venous outflow obstruction managed with stenting, early revision or retransplant. Can apply technique in retransplants
Pisaniello *et al*[19]	STSCCA	Safe technique. Can be performed in most patients. Recommend post-anastomotic doppler ultrasonography

STSCCA: Side-to-side cavocaval anastomosis; VVB: Venovenous bypass; TPCS: Temporary portocaval shunt.

Table 5 Comparing standard technique with venovenous bypass to side-to-side cavocaval anastomosis

Ref.	Anastomosis	Conclusion
Zieniewicz *et al*[42]	STSCCA *vs* conventional with VVB	Reduction in warm ischemia time ($P < 0.001$) and blood loss in the STSCCA group ($P < 0.001$)
Remiszewski *et al*[43]	STSCCA *vs* conventional with VVB	Reduced complication rate (36% *vs* 30%) and reduced cost (*P*-value not reported) in STSCCA group
Khan *et al*[44]	STSCCA *vs* conventional with VVB	Reduced FFP ($P = 0.03$) and platelets ($P = 0.04$) transfused, shorter ICU stay ($P = 0.005$), less patients requiring ventilation after POD1 ($P = 0.03$) and less total days on the ventilator ($P = 0.04$) in STSCCA group. Comparable operating time, warm ischemia time, length of stay (*P*-value not reported). Outflow obstruction in 1.2% of STSCCA patients. Report hematoma formation as complication associated with VVB
Schmitz *et al*[45]	STSCCA *vs* conventional with VVB	Shorter warm ischemia times, reduced red blood cell ($P = 0.000$) and platelet transfusion ($P = 0.002$) in STSCCA group. Increased risk of hepatic artery stenosis ($P = 0.045$) and biliary leaks ($P = 0.042$) in the STSCCA group

STSCCA: Side-to-side cavocaval anastomosis; VVB: Venovenous bypass; ICU: Intensive care unit; FFP: Fresh frozen plasma.

experience with 500 OLTs performed with STSCCA (Table 4). They determined that the technique was feasible in all patients without anatomic limitations. At the beginning of their experience there were 7 cases of Budd-Chiari like syndrome due to compression of the liver on the IVC or kinking of the hepatic veins. They attributed these to long donor suprahepatic IVC or misplacement of the caval incision. These cases were managed with stenting, early revision or retransplantation. They also assert that this technique can be applied in retransplants[20].

Pisaniello *et al*[19] report a single center series of patients who underwent liver transplant with STSCCA, concluding that it is safe technique that can be performed in most patients even in the retransplant setting with low incidence of hepatic venous outflow obstruction (Table 4). They recommend routine postanastomotic Doppler ultrasonography[19].

Several authors report that retransplantation is easy and can performed without interfering with caval flow in patients who have undergone a STSCCA. Lerut *et al*[16] discuss that this is one reason that they prefer a side-to-side anastomosis to an end-to-side anastomosis, it allows removal of the failed allograft without interfering with caval flow. They also advocate for the use of a side-to-side anastomosis in delayed retransplantation because it allows the surgeon to access the most accessible and least hemorrhagic plane[16]. Mosimann *et al*[41] reported that patients who underwent procedures with side-to-side anastomosis could easily undergo retransplantation in a quick and safe procedure. This finding has been confirmed by other authors as well[16,33].

PROSPECTIVE AND RETROSPECTIVE STUDIES: COMPARING STANDARD AND STSCCA

Zieniewicz *et al*[42] report their experience with the first 79 transplants in their program (Table 5). Sixty-eight of these were done with standard technique with VVB and the remaining 11 with the STSCCA. They report reduced warm ischemia time ($P < 0.001$) and blood loss in the STSCCA group ($P < 0.001$)[42].

Remiszewski *et al*[43] compared the conventional technique with VVB to the STSCCA in a retrospective study (Table 5). They concluded that individualization is important in choosing which procedure to use for a particular patient. Their survival ($P = 0.473$) and lengths of stay ($P = 0.63$) were similar between groups. They do report a reduced complication rate (36% *vs* 30%, *P*-value not reported) and cost (*P*-value not reported) in the STSCCA group, although they do

Table 6 End-to-side cavocaval anastomosis

Ref.	Anastomosis	Conclusion
Polak *et al*[22]	ETSCCA	Simple and safe procedure. Allows wide anastomosis and eliminates risk of venous outflow tract obstruction. Can be performed without routine TPCS. Minimal intraoperative blood products used. Can be used in first and second retransplantations
Wojcicki *et al*[23]	ETSCCA	Low risk of vascular outflow obstruction complications with ETSCCA. Partial portal and mesenteric vein thrombosis not a contraindication for OLT, can treat with eversion thrombectomy
Belghiti *et al*[47]	STSCCA, ETSCCA	Caval preservation possible in most patients. Patients tolerate transient cross-clamping of the IVC prior to reperfusion when necessary to create wide anastomosis

STSCCA: Side-to-side cavocaval anastomosis; TPCS: Temporary portocaval shunt; ETSCCA: End-to-side cavocavostomy; IVC: Inferior vena cava; OLT: Orthotopic liver transplant.

not provide specifics regarding cost[43].

Khan *et al*[44] in prospective study compared patients undergoing conventional technique with VVB to patients undergoing STSCCA (Table 5). The STSCCA group patients required less fresh frozen plasma (P = 0.03) and platelets (P = 0.04), had decreased cold ischemia time (P = 0.01), shorter ICU stays (P = 0.005), less patients requiring ventilation after post-operative day 1 (POD1) (P = 0.03) and less total days on the ventilator (P = 0.04). The two groups had comparable operating time, warm ischemia time, red cell usage, requirement for renal support and POD3 creatinine, and total hospital stay length (P = NS, value not reported). Three patients in the piggyback group developed outflow obstruction (1.2%), which the authors refer to as, "piggyback syndrome." They also reported complications related to VVB in the conventional technique group which included 16 patients who developed hematomas at the VVB site in the axilla[44].

Schmitz *et al*[45] performed a retrospective study comparing patients undergoing the standard technique with VVB to patients undergoing STSCCA. The STSCCA group had shorter warm ischemia times (P = 0.000), reduced transfusion of red blood cell (P = 0.002) and fresh frozen plasma (FFP) (P = 0.004). They also demonstrated an increased risk of hepatic artery stenosis (P = 0.045) and biliary leaks in the STSCCA group (P = 0.042)[45].

PROSPECTIVE AND RETROSPECTIVE STUDIES: END-TO-SIDE ANASTOMOSIS

Polak *et al*[22] demonstrated that end-to-side cavo-cavostomy (ETSCCA), as originally described by Cherqui *et al*[46], between the end of the donor suprahepatic IVC and a longitudinal incision on the anterior wall of the recipient IVC can be used successfully (Table 6). They obtained consistent patient and graft survival rates with few anastomosis related complications, performed this technique for patients who had previously had this or another type of liver transplant and had minimal intraoperative blood product requirements[22].

Wojcicki *et al*[23] also report a retrospective single center study of ETSCCA (Table 6). They determined that there was a low rate of vascular complications with ETSCCA and that partial portal or mesenteric vein thrombosis is no longer a contraindication to OLT and can be managed with eversion thrombovenectomy[23].

Belghiti *et al*[47] present their experience with ETSCCA. They conclude that IVC preservation is feasible in almost all candidates, as it was in 90% of the patients in their series. They initial performed STSCCA, but transitioned to ETSCCA after 1993 to provide improved exposure with larger grafts and allow for post-operative transjugular biopsies when necessary. They report that they were able to perform most of their procedures with preservation of caval flow, but in cases where they were not, transient IVC cross-clamping prior to reperfusion was well tolerated. When done after reperfusion it results in a high rate of early graft failure[47].

PROSPECTIVE AND RETROSPECTIVE STUDIES: COMPARING MULTIPLE TECHNIQUES

In a single-center retrospective study Lerut *et al*[16] compared patients undergoing conventional technique with VVB, patients undergoing piggyback technique with VVB and patients undergoing STSCCA without VVB or TPCS (Table 7). The piggyback and STSCCA groups had reduced warm ischemia time (P < 0.001), reduced need for intraoperative blood products (P < 0.01) and lower rates of reoperation for bleeding (P < 0.01). Additionally, the STSCCA group had a significantly higher frequency of immediate extubation (P < 0.001) compared to the other two groups. The authors suggest that partial clamping of the IVC leads to reduced requirement for fluid administration which may contribute to the higher rate of immediate extubation. They assert that STSCCA preserves the advantages of piggyback OLT including reduced implantation time and need for blood products while also eliminating VVB and reducing ventilation time[16].

Navarro *et al*[48] report a retrospective multi-center study involving 17 centers in France (Table 7). They compare three groups of patients: piggyback technique, STSCCA and ETSCCA. They report an increase in the

Table 7 Comparing standard, piggyback and side-to-side cavocaval anastomosis

Ref.	Anastomosis	Conclusion
Lerut *et al*[16]	Conventional with routine VVB, piggyback with selective VVB, STSCCA	Piggyback and STSCCA groups had reduced warm ischemia time ($P < 0.001$), reduced need for intraoperative blood products ($P < 0.01$), lower rates of reoperation for bleeding ($P < 0.01$). STSCCA had higher frequency of immediate extubation ($P < 0.001$). STSCCA preserves advantages of piggyback technique including reduced implantation time and need for blood products while also eliminating VVB and reducing ventilation time
Navarro *et al*[48]	Piggyback, STSCCA, ETSCCA	Reduced vascular complication in STSCCA compared to piggyback group with less cases of Budd Chiari syndrome and fewer releases of the cavocaval running suture (no *P*-value reported)
Hesse *et al*[15]	Conventional with selective VVB, piggyback with selective VVB, STSCCA	Use of packed red blood cells higher in piggyback group than standard group ($P = 0.01$). Use of packed red blood cells ($P = 0.01$), number of patients operated on for hemorrhage (0.002) and use of VVB ($P = 0.02$) lower in STSCCA than other two groups. Perioperative FFP, time in ICU, postoperative graft function and survival similar between the three groups (P = NS, values not reported)
Lai *et al*[49]	Conventional with VVB, piggyback, STSCCA	STSCCA group with lowest median cold ($P = 0.001$) and warm ischemia times ($P < 0.0001$), best immediate postoperative graft function ($P < 0.0001$), lowest transaminase peak ($P = 0.007$) and best bile output ($P = 0.003$). No complications reported
González *et al*[50]	Conventional with VVB, conventional without VVB, IVC preservation	Total operating time ($P = 0.004$), packed red blood cell ($P = 0.009$), fresh frozen plasma ($P = 0.005$) transfusion lower in the IVC preservation group. Postoperative kidney and renal function did not differ between groups. Incidence of complications similar between groups

STSCCA: Side-to-side cavocaval anastomosis; ETSCCA: End-to-side cavocavostomy; IVC: Inferior vena cava; VVB: Venovenous bypass; ICU: Intensive care unit; NS: Non-significant.

vascular complication rate in the piggyback group *vs* the STSCCA group with an increase in Budd Chiari syndrome and release of the cavocaval running suture (*P*-value not reported). They report a 1.5% rate of venous obstruction complications, which were treated with rotation of the graft, reconstruction of the caval anastomosis, placement of a Blakemore catheter, omentoplasty, placement of a second caval anastomosis, endoluminal anastomotic dilation, conversion to conventional technique with caval replacement and retransplantation. They do report some anatomical limitations to the vena cava preservation techniques including inadequate graft size. They report performing conventional OLT for a patient with fibrous stenosis of the IVC and the death of a patient with IVC agenesis[48].

Hesse *et al*[15] compare three groups: conventional technique with selective VVB, piggyback technique with selective VVB and STSCCA with selective VVB (Table 7). They concluded that the use of packed red blood cells was higher in the piggyback group than the conventional group, which conflicts the results of many other studies. The use of packed red blood cells post-operatively ($P = 0.02$), postoperative hemorrhage and the number of patients operated on for hemorrhage ($P = 0.002$) were lower in the STSCCA group than the other two groups. Perioperative FFP time in the ICU, postoperative graft function and survival rates were similar between the three groups (P = NS, values not reported). The STSCCA had significantly reduced use of VVB ($P = 0.02$). The authors concluded that preservation of the vena cava can reduce, but not avoid the use of VVB[15].

Lai *et al*[49] did a retrospective single-center study comparing conventional technique with VVB, piggyback and STSCCA (Table 7). They determined that STSCCA had lowest median cold ischemia time ($P = 0.001$), lowest warm ischemia time ($P < 0.0001$), best immediate postoperative graft function ($P < 0.0001$), lowest transaminase peak ($P = 0.007$) and best bile output ($P = 0.003$). They did not report or discuss complications[49].

González *et al*[50] compared the conventional technique with VVB, the conventional technique without VVB and IVC preservation (Table 7). The total operating time ($P = 0.004$), packed red blood cell ($P = 0.009$) and fresh frozen plasma ($P = 0.005$) requirements were all significantly lower in the IVC preservation group. Postoperative liver and renal function did not differ between the three groups. The incidence of complications was similar between the three groups[50].

CHOICE OF TECHNIQUE IN THE PRESENCE OF HEPATOCELLULAR CARCINOMA

One retrospective study, Mangus *et al*[51], published in 2008 evaluated outcomes for patients with hepatocellular carcinoma (HCC) who underwent conventional and piggyback liver transplantation (Table 8). The study does not demonstrate a difference in HCC recurrence ($P = 0.47$) or patient survival (1-year $P = 0.49$, 2-year $P = 0.55$) between groups, although their piggyback group did have higher median tumor size ($P = 0.09$) and a higher percentage of patients with bilateral tumors (24.40% *vs* 15.80%) (Table 8). They concluded that the

Table 8 Comparison of piggyback and conventional in patients with hepatocellular carcinoma

	Conventional	Piggyback	*P*-value
n	19, 14%	119, 86%	
Age (yr) (mean, median, range)	52, 52, 41-66	57, 57, 21-73	0.09
MELD at transplant (mean, median, range)	21, 22, 8-30	20, 22, 6-36	0.02
Total cold ischemia time (h) (mean, median, range)	8, 8, 4-13	7, 7, 3-17	0.03
Total warm ischemia time (min) (mean, median, range)	56, 59, 29-78	38, 29, 18-103	< 0.001
Outside milan criteria	15.80%	33.60%	0.18
Tumor number (mean, median, range)	2, 1, 1-4+	2, 1, 1-4+	0.6
Maximum tumor size (mean, median, range)	2.6, 2.7, 0.4-8.0	3.2, 3.0, 0.4-8.2	0.09
Tumor location bilateral	15.80%	24.40%	0.41
Lymphovascular invasion	21.10%	14.30%	0.49
Chemoembolization	10.50%	37.80%	0.02
1-yr overall survival	89.50%	83.20%	0.49
2-yr overall survival	84.20%	75.90%	0.55
Any HCC recurrence	5.30%	14.30%	0.47

Adapted from Mangus *et al*[51]. HCC: Hepatocellular carcinoma; MELD: Model for end stage liver disease.

two groups did not differ in survival within or outside of Milan criteria and that the presence of HCC should not preclude the use of the piggyback technique[51].

COST

Several authors assert that the piggyback technique is cheaper, especially in comparison to the conventional technique with VVB. Specific information about costs, however, is not plentiful in the literature.

Reddy *et al*[14] compare the median hospital charges between patients undergoing conventional OLT and those undergoing piggyback technique with anastomosis with three suprahepatic veins. They report that the median hospital charges for patients undergoing conventional OLT was $105439 and the median hospital charges for patients undergoing the piggyback technique was $91779 ($P$ = NS, P-value not reported)[14].

Hesse *et al*[15] report that the avoidance of VVB saves time and reduces cost, but do not provide specific values. Lerut *et al*[16] reports that the side-to-side anastomosis represents another means of reducing the cost of liver transplantation, but do not provide specific values. Zieniewicz *et al*[42] assert that the piggyback technique is less expensive, but do not provide specific values. Remiszewski also reports reduced cost of the piggyback technique, but does not provide specific values[43].

Hosein Shokouh-Amiri *et al*[34] in 2000 reported a statistically significant difference in the cost of liver transplantation. They report the mean cost for patients undergoing the piggyback technique to be $90412 ± 5753 and the cost of the conventional technique $113838 ± 4483 ($P \leqslant 0.002$). The authors suggest that the added cost of the standard technique is accounted for by the added cost of machines, catheters and personnel for VVB[34].

VVB

In 1984 Shaw *et al*[52] published a study in which they compared outcomes in patients who underwent liver transplantation with and without VVB. They determined that patients with VVB had better postoperative renal function ($P < 0.001$), required less blood during surgery ($P < 0.01$) and had improved 30-d survival (no P-value reported)[52]. Several of the previously mentioned studies offer a comparison of the standard technique with and without VVB in addition to comparisons with one or another type of caval preservation. It has been suggested that in patients without significant collateral circulation, excessive hemorrhage and major portal hypertension VVB or TPCS must be used to maintain hemodynamic stability[40].

Fonouni *et al*[53] published a review paper on the use of VVB in liver transplantation in 2008. They concluded that the piggyback technique with preservation of the IVC can be used in most cases of primary transplant and retransplant without VVB. They do recommend that VVB be used in selective cases including in patients with a intraoperative hemodynamic instability and those who fail a test of transient IVC occlusion[53]. Other authors agree with the assertion that the piggyback technique with IVC preservation obviates the need for VVB in many cases[26,40].

Proposed advantages of VVB that are reported in the literature include: maintaining cerebral, pulmonary and cardiovascular flow[51], reduced need for fluid resuscitation[34], maintaining kidney perfusion[54], maintaining hemodynamic stability during the anhepatic phase[16,34,52,55-57], providing longer anhepatic phase[24], better maintenance of core body temperature[34], reduction of intraoperative blood loss[24,56] and improving the clinical outcome[24,56].

Regarding maintaining blood flow and hemodynamic stability, Lerut *et al*[16] did detailed hemodynamic comparisons between patients undergoing classical OLT with VVB and those undergoing STSCCA and report that there are no significant differences in hemodynamic parameters. They suggest that this means that partial IVC clamping fulfills the function of VVB. This group determines the need for VVB based on a decrease in mean arterial pressure of more than

50% or decrease in cardiac index (> 50%) during the occlusion test[16].

Most authors agree that in patients without preoperative renal failure who tolerate a clamping trial well VVB is not required to maintain post-operative renal function and should be used selectively[54-56]. In a randomized controlled trial VVB was shown not to be associated with any clear benefit in renal function and the authors of the trial concluded that its use is not justified on this basis[54].

Complications related to VVB that have been reported in the literature include: access site problems including delayed healing of bypass access site, seroma, nerve injury[15,16,34], as well as intraoperative pulmonary or air embolism[16,52,55,58], longer operating and warm ischemia times, hypothermia[57] thrombosis of axillary and femoral veins[16] and higher cost associated with machine, catheters and personnel[34,59,60]. Many authors assert that VVB increases intraoperative blood loss. Lerut *et al*[16] report that there is an additional 500-1000 mL of blood loss when VVB is used.

Most authors of recent publications assert that it is most appropriate to use VVB selectively, although the criteria for its use are not always agreed upon. Hesse *et al*[15] in 2000 report that their decision about whether to use VVB is made based on recipient intraoperative hemodynamics, using it when the mean arterial pressure decreases by more than 30% or the cardiac index decreases by more than 50% or both during a trial clamping of the portal vein and IVC[29]. They also use VVB when excessive hemorrhage occurs due to portal hypertension and a small size recipient is preventing sufficient venous return to the heart during lateral vena cava clamping[15].

Steib *et al*[61] compared the conventional technique with VVB to the piggyback technique with TPCS in a small prospective study. They determined that two important intraoperative parameters, cardiac output and systemic oxygen delivery, were improved in the piggyback group with TPCS. They also determined that that graft function between the two groups was adequate and comparable[61].

It was originally asserted that the piggyback technique without VVB resulted in significant hemodynamic compromise that was not tolerated well by patients. Lázaro *et al*[62] completed a prospective study of the hemodynamics of a small group of patients undergoing the piggyback technique and concluded that there was a minimal hemodynamic disturbance and that this was well tolerated by patients[26].

TPCS

It has been suggested that portacaval shunting helps avoid splanchnic congestion and the sequestration of third spaced fluids. An additional proposed advantage of TPCS is improved hemodynamic stability secondary to increased venous return[5].

Cherqui *et al*[46] proposed using TPCS systematically to achieve hemodynamic instability. Contrarily, Busque *et al*[33] report that they used TPCS in only 3 of 98 patients who underwent OLT with the piggyback technique. Reddy *et al*[14] completed 34 transplants using the piggyback technique and only performed a TPCS in one patient with severe portal hypertension, to decrease the risk of bleeding.

Belghiti *et al*[8] in 1995 report the use of the piggyback technique with 51 consecutive patients. The primary purpose of this paper was to report the use of a TPCS in 51 consecutive patients undergoing the piggyback technique. The mean time to perform the temporary portocaval anastomosis was 9 min with a range of 5 min to 17 min. They concluded that portocaval anastomosis was minimally time consuming and that they were able to perform satisfactory portal venous anastomosis. They also conclude that the preservation of portal and caval flows as achieved with the piggyback operation with ETSCCA and TPCS may have special importance in transplantation of partial livers[8].

Tzakis *et al*[9] in 1995 report the successful use of a TPCS in 4 pediatric patients experiencing hemodynamic instability in whom VVB was difficult or impossible to use.

Belghiti *et al*[47] in 2001 reported that they routinely use a TPCS in patients who do not have prior surgical portosystemic shunts or large spontaneous porto-systemic shunts. In their series a TPCS was performed in 218 (79%) of cases. There were 57 cases in which a shunt was not performed: 45 with large spontaneous portosystemic shunt, 4 with previous portosystemic shunt, and 8 with portal vein thrombosis[47].

There is one randomized controlled trial comparing patients undergoing OLT with the piggyback technique with (n = 40) and without (n = 40) TPCS. They report that the decrease in cardiac output during the anhepatic phase is lower the TPCS group (P = 0.005). There was reduced transfusion of red blood cells in the TPCS group with 45% of patients not requiring transfusions *vs* 22% in the non-TPCS group (P = 0.05). The groups received similar quantities of of red blood cells (P = 0.09), fresh-frozen plasma (P = 0.76) and platelets (P = 0.88). The TPCS had greater diuresis during the anhepatic phase (P = 0.005). The authors report that patients undergoing OLT with TPCS have improved hemodynamic status, reduced intraoperative transfusion requirements and preservation of renal function[25].

DISCUSSION

There are advantages and disadvantages to each caval reconstruction technique in OLT. Although many authors conclude that there is lower operative and warm ischemia time, and decreased transfusion of blood products including red blood cells and fresh frozen plasma, with the piggyback technique and its' modifications, especially when compared with

conventional technique with VVB, there are centers where this has not been the case. The conventional technique certainly maintains a position in the surgical repertoire and is practiced by many surgeons at many centers with excellent results. Improvements in anesthesia management, ICU care, improved immunosuppression, and complication management have played at least as large a role in the excellent outcomes obtained with modern liver transplantation as the techniques described in this review. Having familiarity with the variety of options available for reconstruction of the IVC and tailoring these techniques to the individual patient when needed is advantageous. However, surgeons should utilize the techniques that they are most comfortable with and perform well as the quality of the operation is more important than the specific technique employed in achieving excellent outcomes.

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REVIEW

New approaches in laparoscopic surgery for colorectal diseases: The totally laparoscopic and single-incision approaches

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Abstract

More than 20 years have passed since the first report of laparoscopic colectomy in 1991. Thereafter, laparoscopic surgery for the management of colorectal diseases has been widely accepted as a prevailing option because of improved cosmetic outcomes, less postoperative pain, and shorter hospital stay in comparison with open surgery. To further the principle of minimally invasive surgery, two new approaches have been developed in this rapidly evolving field. The first is the totally laparoscopic approach. Currently most of standard techniques inevitably involve an abdominal incision for retrieval of the specimen and preparation for anastomosis, which might compromise the benefits of laparoscopic surgery. The totally laparoscopic approach dispenses with this incision by combining completely intraperitoneal anastomosis with retrieval of the specimen *via* a natural orifice, such as the anus or the vagina. Our new and reliable technique for intraperitoneal anastomosis is also described in detail in this article. The second is the single-incision approach. While three to six ports are needed in standard laparoscopic surgery, the single-incision approach uses the umbilicus as the sole access to the abdominal cavity. All of the laparoscopic procedures are performed entirely through the umbilicus, in which the surgical scar eventually becomes hidden, achieving virtually scarless surgery. This article reviews the current status of these two approaches and discusses the future of minimally invasive surgery for colorectal diseases.

Key words: Totally laparoscopic surgery; Minimally invasive surgery; Single-incision laparoscopic surgery; Natural orifice transluminal endoscopic surgery; Natural orifice specimen extraction

Core tip: We reviewed the current status of two new approaches in laparoscopic surgery for colorectal diseases: the totally laparoscopic and single-incision approaches, and showed our own data concerning these two approaches. We also discussed the future of minimally invasive surgery.

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INTRODUCTION

There is a famous maxim in the surgical community: "the greater the surgeon, the bigger the incision", meaning that great surgeons make big incisions and perform complex and challenging operations. However, now we are in the era of "the greater the surgeon, the smaller the incision". Surgical treatment has been constantly evolving over the last 30 years in the quest for minimal invasiveness irrespective of the complexity and difficulty of the procedure. In 1986, the German surgeon Eric Mühe reported the first cases of laparoscopic cholecystectomy at the Congress of the German Surgical Society, but his concept did not attract much attention. Although his pioneering work was not properly recognized at first, this event represents a epochal paradigm shift from conventional open surgery to minimally invasive surgery. Thereafter, the trend that began with laparoscopic cholecystectomy progressed to include other more technically challenging abdominal procedures[1-5]. Improvements in techniques and instruments now make it feasible to perform complicated surgical procedures in a minimally invasive fashion. Moreover, the principle of minimally invasive surgery eventually reached the next stage in surgical access, natural orifice transluminal endoscopic surgery (NOTES), which does not require any anterior abdominal wall incision.

In the field of colorectal surgery, more than 20 years have passed since the first report of laparoscopic colectomy by Jacobs *et al*[6] in 1991. Since then, laparoscopic surgery for the management of colorectal diseases has been widely accepted as a prevailing option because of improved short-term outcomes in comparison with open surgery, as prospective randomized trials have demonstrated its safe clinical application for malignant diseases[7-10].

At present, to further the principle of minimally invasive surgery, two new approaches have been developed in the field of colorectal surgery, namely the totally laparoscopic approach and the single-incision approach.

Currently standard procedures of laparoscopic colectomy inevitably involve an additional abdominal incision for delivery of the specimen and preparation for anastomosis. The totally laparoscopic approach dispenses with this incision by combining completely intraperitoneal anastomosis with delivery of the specimen *via* a natural orifice, which is the anus or the vagina.

The single-incision laparoscopic surgery uses the umbilicus as the sole access to the abdominal cavity, whereas three to six ports are needed in standard laparoscopic surgery. All of the laparoscopic procedures are performed entirely through the umbilicus, in which the surgical scar becomes hidden, achieving virtually scarless surgery.

Undoubtedly, incisionless surgery using the NOTES technique is the most minimally invasive treatment method up to the present. However, NOTES, which faces obvious safety hurdles, is still far from being widely accepted in the standard surgical practice. This article reviews the current status of these two alternative approaches to enhance the advantages of laparoscopic surgery, *i.e.*, the totally laparoscopic and single-incision approaches, and discusses the future of minimally invasive surgery for colorectal diseases.

TOTALLY LAPAROSCOPIC APPROACH

The advent of laparoscopic surgery has brought great changes in the surgical management of colorectal diseases because it involves less postoperative pain, improved cosmetic outcomes, earlier return of bowel function, and shorter hospital stay in comparison with open surgery. Currently most laparoscopic colectomies are performed in a "laparoscopy-assisted" fashion including extracorporeal procedures, such as bowel division and preparation for anastomosis, following laparoscopic mobilization of the bowel and lymph nodes dissection. Therefore, these procedures ineluctably necessitate an additional abdominal incision to the trocar placement sites. There have been many reports of completely intraperitoneal anastomosis combined with delivery of the specimen *via* a natural orifice, such as the anus or the vagina, which dispenses with a larger abdominal incision other than trocar placement sites[11-15]. Natural orifice specimen extraction (NOSE) has been postulated as an alternative approach to extracting the resected specimen out of the peritoneal cavity through an anatomic passage rather than an additional abdominal incision. Moreover, in the transition period from conventional laparoscopic surgery to true "scarless surgery", hybrid techniques combining laparoscopic resection and NOSE technique is a convincing alternative in minimally invasive surgery to circumvent the safety hurdles which NOTES faces.

Obviously, extraction of a left-side colon specimen *via* the anus is not particularly difficult. However, the ensuing completely intraperitoneal anastomosis poses the major challenge in laparoscopic colectomy. In completely intraperitoneal anastomosis using a circular stapling device, in particular, placement and fixation of the anvil are the most difficult steps. For fixation of the anvil in the proximal end of the colon, a procedure using an Endo-loop and a procedure involving a hand-sewn purse-string suture have been two major options[11,13]. These two techniques have their strong and weak points. On the one hand, ligation using an Endo-loop is a very simple technique in itself, whereas it may be less reliable in comparison with a hand-sewn purse-string suture mainly due to difficulty in stabilizing the colonic stump while putting the ligature in place and

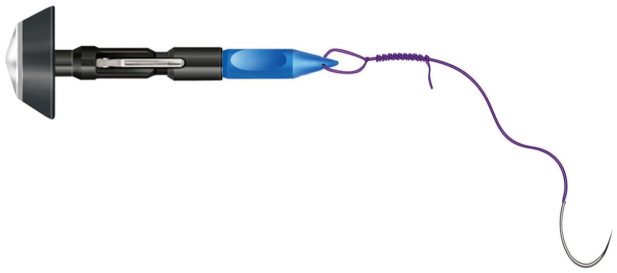

Figure 1 The anvil of a circular stapling device with its center rod secured with a 2-0 monofilament suture at the hole of the tip, is shown. The suture is tied over 10 times so that the thread that is pulled completely out of the colon does not slip into the intraluminal cavity.

tightening the loop around the center rod of the anvil. On the other hand, the technique using a hand-sewn purse-string suture is naturally more time-consuming and involves extensive skills in laparoscopic suturing. We have developed a simple and reliable technique for placement of the anvil in the esophageal stump in laparoscopic total gastrectomy using a linear stapling device[16,17]. We have also reported application of this technique to totally laparoscopic sigmoid colectomy[18] and totally laparoscopic low anterior resection[19]. Our technique, named the "efficient purse-string stapling technique", achieves transection of the colon and placement of the anvil of a circular stapling device on the colonic stump at the same time using a linear stapling device. Our totally laparoscopic procedure using this technique is described in Figures 1-3[18-22].

Specimen extraction *via* the anorectal canal is applicable to both male and female patients. However, the application of the transvaginal route is limited only to female patients, whereas it is more complicated due to the necessity of colpotomy in comparison with the transanal route. Moreover, Franklin *et al*[23] reported that one characteristic complication of transvaginal extraction was accidental damage of the sigmoid colon and rectum, at a rate of 7.7%, because of the narrowness of Douglas's pouch. On the other hand, regarding the transanal route, there are concerns over intra-abdominal fecal contamination and infectious complications. Leroy *et al*[24] reported that there was no infectious complications in 16 patients who underwent laparoscopic colectomy with transanal specimen extraction for sigmoid diverticulitis, whereas all peritoneal cultures were positive for polybacterial growth. However, inherent limitations of the transanal route have been pointed out; namely, this route is not applicable to patients with large tumor or narrow anorectal canal[25].

Bernstein *et al*[26] compared a complete laparoscopic procedure with a conventional laparoscopic procedure and found no statistically significant differences in terms of the hospitalization period or the duration of postoperative ileus. Moreover, a recent systematic review of the current literature concerning left-sided laparoscopic colectomy with transanal specimen extraction pointed out a lack of standardization of techniques and concluded that the level of the evidence supporting laparoscopic colectomy with transanal specimen extraction is low[27].

SINGLE-INCISION APPROACH

Recently, the endeavor to enhance the advantages of laparoscopic surgery has led minimally invasive surgeons to seek to minimize the number and the size of incisions. Especially, the development of single-incision laparoscopic surgery has been attracting increasing attention in the field of minimally invasive surgery. While three to six ports are needed in standard laparoscopic surgery, the single-incision approach uses the umbilicus as the sole access to the abdominal cavity.

The technique of single-incision surgery was first applied to appendectomy, thereafter to cholecystectomy[28]. Pelosi *et al*[29] reported single-puncture laparoscopic appendectomy in 1992, and in 1997, Navarra *et al*[30] performed laparoscopic cholecystectomy using only transumbilical trocars. Recently, the single-incision approach has been applied to more complicated procedures including inguinal hernia repair, colectomy, and gastrectomy[31-37]. The authors utilized the umbilicus, which some researchers call an embryologic natural orifice, as the sole access to the abdominal cavity to perform a surgical procedure that will leave a concealed surgical scar, thus achieving an essentially scarless surgical procedure. Unlike NOTES, which requires further development of techinique and the instrument, single-incision transumbilical laparoscopic surgery is ready for widespread implementation. This is because single-incision procedures can be performed using standard laparoscopic instruments, which would enable surgeons to conform to standard surgical principles and techniques. However, conflicts between laparoscopic instruments when used through a narrow single incision often make it infeasible to get adequate retraction and exposure, which necessitates surgeons to have extensive skills in standard laparoscopic surgery.

In the field of colorectal surgery, the first single-access laparoscopic colectomies were reported in 2008. Bucher *et al*[33,34] have described single-port access laparoscopic right hemicolectomy and left colectomy. They placed two standard laparoscopic ports, a 12-mm umbilical port and a 5-mm port, in a 2-cm umbilical incision, and used a 10-mm laparoscope with a 6-mm working channel. To facilitate dissection, suspension and exposition of the colon was achieved by placing transparietal stitches anchored on the mesentery or the colon wall. Only standard straight laparoscopic instruments were used. The authors pointed out that a low possibility of triangulation and the absence of off-axis vision would make the procedure complex. Remzi *et al*[35] performed laparoscopic right hemicolectomy using a

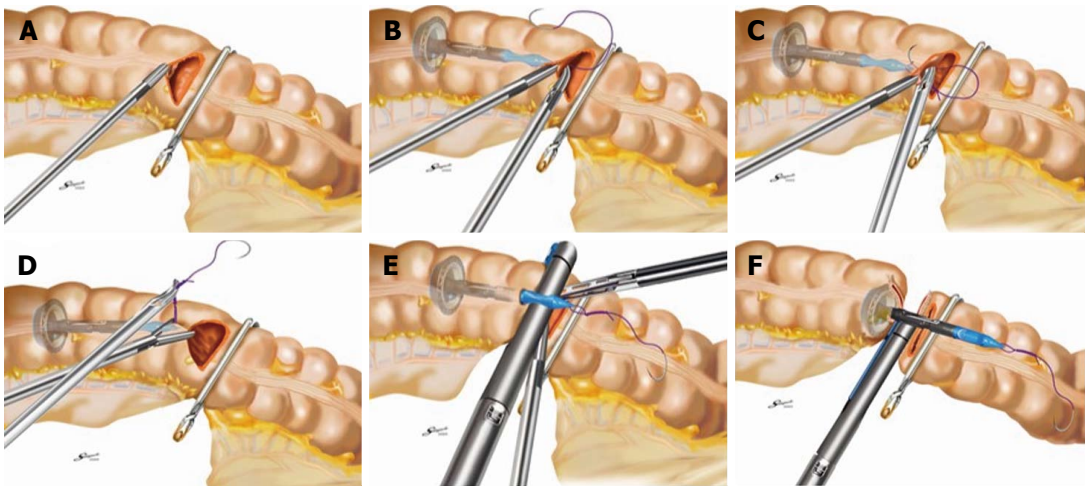

Figure 2 Efficient purse-string stapling technique. A: A semi-circumferential colotomy is performed at the colonic wall just proximal to the forceps; B: Anvil insertion into the colon *via* a semi-circumferential colotomy: An anvil with suture is held by a grasper and fully inserted into the proximal colon; C: The accompanying needle is advanced through the anterior colonic wall; D: The suture is pulled out of the colon until all knots are completely exposed; E: While pulling the suture to the right side horizontally, the colon is clamped using a linear stapling device with disposable gastrointestinal cartridge; F: The colon is then transected by firing the instrument to secure the anvil on the colonic stump.

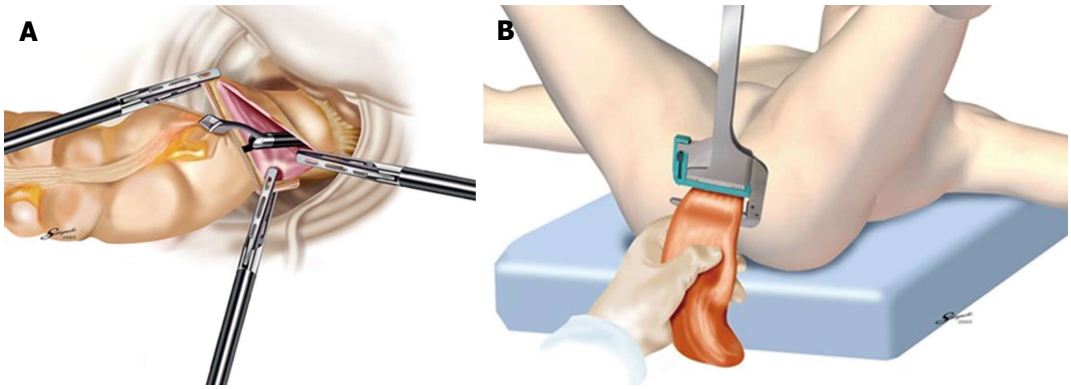

Figure 3 Transanal specimen extraction. A: In sigmoid colectomy, a grasping forceps is brought through the rectum, and the specimen is extracted through the colotomy made at the distal staple line; B: In low anterior resection, a grasping forceps is inserted under laparoscopic vision from the anus to grasp the staple in the stump, and the distal rectum is everted and pulled transanally outside the body.

special multichannel umbilical port and specially designed curved instruments. They emphasized that the flexible steerable laparoscope and instruments helped to reduce the difficulties of dissection due to loss of triangulation. Leroy *et al*[38] performed sigmoidectomy in a patient with diverticulitis using a multichannel umbilical port that allows the insertion of three laparoscopic instruments concurrently. To facilitate dissection of the mesentery, they used a sigmoidoscope to supplement retraction by means of tip angulation and instrument torque. For placement of the anvil of the circular stapler in the proximal end of the colon, they used an extracorporeal magnet to lock the metal anvil in position. They pointed out that the use of different curved or straight instruments of varying caliber allowed triangulation of the working instruments. They also mentioned the possibility of direct translation of their procedure into a NOTES format. At the same time, they emphasized that their procedure did not allow full mesenteric dissection and therefore was not suitable in its current format for oncological resections. Recently, Takemasa *et al*[39] reported the technical feasibility and safety of laparoscopic complete mesocolic excision with central vascular ligation for colon cancer.

We introduced single-incision laparoscopic colectomy in our institute in 2009. Gradually expanding the indication to include advanced colorectal cancer, single-incision laparoscopic colectomy is now a standard procedure for colorectal cancer from the cecum to the rectosigmoid in our institute. Our typical setting for single-incision laparoscopic colectomy is shown (Figure 4). A 10-mm flexible laparoscope and standard straight laparoscopic instruments are used, of which, in particular, the flexible laparoscope that allows off-axis vision is extremely useful for single-incision laparoscopic surgery. We studied 429 consecutive patients who underwent single-incision laparoscopic colectomy in our institute from 2009 to 2013. The conversion rate to conventional multi-port laparoscopic colectomy was 3.3%. None of the patients was converted to open surgery. The rate

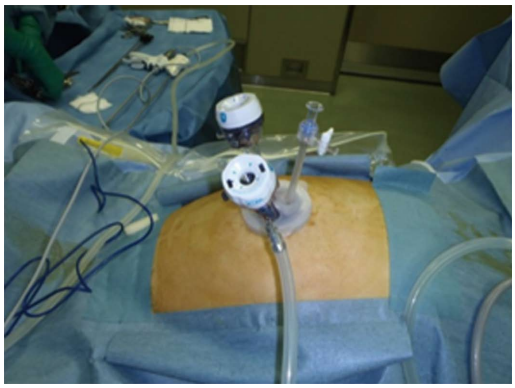

Figure 4 Intra-operative view of single-incision laparoscopic colectomy. We make an 2.5-cm long vertical incision in the umbilicus, and typically use E-Z Access (Hakko Co. Ltd., Nagano, Japan) on the Lap Protector™ (Hakko Co. Ltd., Nagano, Japan) for the insertion of two 5-mm trocars and one 12-mm trocar for a right colectomy, and one 5-mm trocar and two 12-mm trocars for a left colectomy, sigmoidectomy or rectal resection.

of postoperative complications was comparable with those in other reports of multi-port laparoscopic surgery. We also compared two groups of patients: patients with previous abdominal surgery and those with no previous abdominal surgery. There were no significant differences between the two groups in terms of blood loss, operative time, and short-term postoperative outcomes. Therefore, we concluded that single-incision colectomy is safe and feasible even in patients with previous abdominal surgery. Moreover, patients with advanced colorectal cancer were included in this series. Complete mesocolic excision with central vascular ligation can now be performed with our single-incision procedure, corresponding to the standard surgical procedures for advenced colorectal cancer in Japan. This study also showed that the single-incision method was comparable with the multi-port method in terms of resection margin and the number of harvested lymph nodes[40].

After single-incision laparoscopic colectomy for colon cancer was introduced by Remzi *et al*[35] and Bucher *et al*[33] in 2008, the feasibility of the procedure was examined in several case-control studies and two randomized controlled trials, which compared short-term outcomes between patients who underwent single-incision laparoscopic colectomy and those who underwent multi-port laparoscopic colectomy. Although single-incision laparoscopic colectomy provides a better cosmetic result and reduces postoperative pain, its impact on the length of hospital stay remains controversial[39,41-45].

DISCUSSION

Totally laparoscopic colectomy with natural orifice specimen extraction has been safely introduced to general surgical practice. Diana *et al*[46] reviewed 19 studies that reported transanal extraction of the specimen, and they concluded that transanal extraction is a feasible option to minimize incisions in colorectal surgery. At the same time, the concept of single-incision laparoscopic surgery is appealing to surgeons performing minimally invasive procedures and is evolving at a surprisingly rapid rate[29-37].

Undoubtedly, incisionless surgery using the NOTES technique is the final and ultimate goal for minimally invasive surgeons. Furthermore, a survey has shown that patients would prefer NOTES to standard laparoscopic surgery if the risks associated with the two approaches were comparable[47]. However, in spite of the initial enthusiasm after the first advent, NOTES currently remains in the area of experimental surgery mainly due to concerns over the surgical platform, accidental organ injury, and viscerotomy closure.

What is necessary for safe introduction of NOTES in clinical practice, while it takes time for the development of a new surgical platform or reliable techniques for viscerotomy-closure? The optimal transluminal access route for NOTES is now an area of active investigation. Initial work rather focused on transgastric and transvaginal NOTES, and transcolonic NOTES has been the least explored approach because of concerns related to fecal contamination and intra-abdominal infectious complications. Over time, however, transrectal accesss has in fact proved more practical than the former routes[48]. The benefits of transcolonic access include in-line endoscopic visualization, which dispenses with the need for scope retroflection for visualization of upper abdominal organs, more compliance of the anorectum than the esophagus, and suitability for both male and female patients[49]. Moreover, the transanal route has two major advantages over other routes. Firstly, there are reliable surgical platforms: Transanal Endoscopic Microsurgery (TEM) and Transanal Endoscopic Operation (TEO). Since Buess *et al*[50] introduced TEM in the 1980s, there has been accumulation of extensive human clinical experience with complex transanal surgery. TEO is a modification of TEM. Incorporated with an ordinary laparoscopic imaging system and readily available laparoscopic instruments, TEO allows precice dissection under magnified and high-definition view that is as effective as TEM. Secondly, in the case of rectosigmoid resection, viscerotomy can be removed as part of the specimen or incorporated into the anastomosis. Zhang *et al*[51] reported the first clinical case of pure transanal NOTES with total mesorectal excision (TME) in 2013. They used a three-channel single-port laparoscopic cannula placed in the procedure of prolapse and hemorrhoids anoscope as the surgical platform, and after removal of the specimen, they made a colorectal anastomosis at the site of the viscerotomy using a circular stapling device. Approximately at the same time, Leroy *et al*[52] also reported a clinical case of pure transanal NOTES with TME. They used the TEO device as the surgical platform. After the specimen was delivered transanally, a hand-sewn coloanal anastomosis was fashioned so that the viscerotomy was incorporated into the anastomosis. They emphasized the advantages of the

transanal route, which include easy accessibility to the anus, reliable surgical platforms like the TEO system, the possibility to eliminate viscerotomy-closure, and the use of currently available laparoscopic instrumentation.

Although two clinical cases of transanal NOTES were successfully carried out, it is unlikely for their procedure to be widely accepted in general practice in the near future. At present, the hybrid NOTES technique seems to be the most pragmatic way to enhance the concept of minimal invasiveness. There are several reports of hybrid NOTES procedures in humans. In all cases, a hybrid laparoscopic technique with one to three transabdominal trocars was used[53-55]. Techniques for totally laparoscopic colectomy with NOSE and single-incision colectomy are well established. Therefore, some of these techniques seem to be feasible and useful even in the hybrid NOTES setting. For example, our technique, *i.e.*, the "efficient purse-string stapling technique", could be performed in the hybrid NOTES format using standard laparoscopic instruments and stapling devices brought into the peritoneal cavity *via* the transvaginal port, followed by extraction of the specimen through the vagina[18,19].

The totally laparoscopic approach with NOSE and single-incision approach have been enhanced by both innovative port technology and technical expertise learned by developing NOTES. Conversely, new techniques and technology gained in clinical experience of totally laparoscopic colectomy and single-incision surgery may be ultimately used for NOTES procedures. Therefore, it is of utmost importance that all minimally invasive surgeons constantly keep up with new developments in these two approaches in this rapidly evolving field.

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REVIEW

How would we deal with hypothalamic hamartomas?

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Abstract

Hypothalamic hamartoma (HH) is usually associated with refractory epilepsy, cognitive impairment, and behavioral disturbance. There is now increasing evidence that HH can be treated effectively with a variety of neurosurgical approaches. Treatment options for intractable gelastic seizure in HH patients include direct open surgery with craniotomy, endoscopic surgery, radiosurgery with gamma knife and stereotactic radiofrequency thermocoagulation. Selection of treatment modalities depends on type and size of the HH and the surgeon's preference. Two surgical techniques, resection and disconnection, had been described with favorable outcomes. Pretreatment evaluation, patient selection, surgical techniques, complications, and possible selection of treatment are discussed.

Key words: Hypothalamic hamartoma; Epilepsy; Gelastic seizure; Transcallosal resection; Endoscopic surgery; Radiosurgery; Stereotactic radiofrequency ablation

Core tip: Neuronavigation-assisted neuroendoscopic surgery has been remarkably advancing. Furthermore high definition video recording system becomes its basic visualization system to facilitate the differentiation between normal tissue and abnormal tissue of hypothalamic hamartomas. Neuroendoscopic disconnection has been suggested to reduce the Gelastic seizure by the isolation of hypothalamic hamartomas (HHs) from surrounding structures. We are getting more powerful tools for performing sophisticated endoscopic disconnection surgery. Neuroendoscopic disconnection surgery used to be an optional surgery, but it becomes the first choice of surgery for HH with Gelastic seizure.

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INTRODUCTION

The compulsive bursts of laughter were first introduced at 1873. Since Gumpert *et al*[1] described the feature of gelastic seizure (GS) Gascon *et al*[2] suggested the diagnostic criteria of gelastic epilepsy. Gelastic seizures represent the most common clinical expression of epilepsy and cause the patient to present sudden,

brief, uncontrollable attacks of laughter. These gelastic attacks progress as the patient ages, and other types of seizure, cognitive deterioration, and behavioral problems appear, frequently developing late in first decade of life, together with drop attacks and other secondary generalized epilepsy symptoms[3]. It has been demonstrated that epileptic focus originates from the hamartoma and from neocortical foci strictly related to Hypothalamic hamartomas (HHs)[4,5]. HHs are rare non-neoplastic congenital lesions of the inferior hypothalamus and consist of an abnormal mixture of neuronal and glial tissue. They issue from the floor of the third ventricle, tuber cinereum, or mammillary bodies. Hypothalamic hamartoma can be classified as sessile or pedunculated, depending on the width of their attachment to hypothalamus. Various symptoms have been associated with the sessile type of HH, including refractory epilepsy, central precocious puberty, intellectual impairment, and behavioral problems[6]. On the other hand, HHs causing isosexual precocious puberty are more likely to be pedunculated lesions that "hang" below the tuber cinereum. Close anatomic connections between HH and diencephalic hypothalamic structures also explain the autonomic, mainly sympathetic, symptoms and hormonal changes that accompanying GS[7-9]. GS appears in early childhood and quickly becomes refractory to medical treatment. The severity of the syndrome might depend, at least in part, on the size (small *vs* large), localization (tuber cinereum *vs* mamillary bodies), type of attachment (pedunculate *vs* sessile) and degree of hypothalamic displacement of the HH (lacking *vs* marked)[10-13]. Since Paillas *et al*[14] reported successful seizure outcome after resection of HHs in some patients in 1969, surgical intervention for these lesions has been attempted with variable seizure outcome[14]. Since 2000 the understanding and management of HH has increased dramatically especially in terms of intractable epilepsy. The state of the art of magnetic resonance imaging (MRI) and neuronavigation have developed synchronously by the turn of the millennium. Eventually we can have the tools for the safe and effective treatment of lesions in critical areas of the brain and without physically demonstrable borders between the offending lesion and critical areas of the brain such as the hypothalamus[15].

Focal (frontal or temporal) resections have never resolved GS, even when associated with depth electrode studies[16-19], whereas surgical and gamma-knife ablation, and radiofrequency coagulation of HH resulted in good seizure control[4,18-25]. Four surgical treatments have been introduced to treat HH: direct open surgery with craniotomy, endoscopic surgery, radiosurgery with gamma knife (GKS), and stereotactic radiofrequency thermocoagulation. Two techniques for HH surgery are used: resection or disconnection of hamartoma. The concept of disconnection had been introduced by Delalande *et al*[26] and it showed dramatic improvement in the patient. The technique disconnects the connecting tract between the hamartoma and the surrounding normal tissue.

Between 1990 and 2000, case reports on the successful surgical management of HH began to surface. These reports presumably reflected the increasing availability of contemporary imaging techniques. The first computed tomography (CT) scanner was installed in the United States in 1973[15]. A neurosurgeon removing or disconnecting an HH sees tissue that looks just like normal brain. The ability to identify the HH-brain interface depends on the subtle differences in signal intensity seen on MRI and shown by the navigation system. The surgical view is through the microscope, utilizing the endoscope or stereotactic equipment for Gamma Knife or the implantation of radiofrequency electrodes. The surgical approach to the lesion should be tailored to each case. No single approach is best for every patient.

Presurgical evaluation includes routine electro-encephalographic (EEG) monitoring and video-EEG monitoring with scalp electrodes, interictal and ictal 99m-Tc hexamethylprophyleneamine oxime single photon emission CT, MRI, neuropsychological evaluation, ophthalmological assessments with perimetry, and endocrinological investigations. The dimensions of the HHs and the anatomy surrounding the tuber cinereum can be seen clearly by high-resolution coronal and sagittal T1-weighted MRI. Endocrine assessment includes measurement of basal gonadotrophin and growth hormone levels, thyroid function, prolactin level, and cortisol reserve with glucagon stimulation. Deep electrode insertion into the HH with EEG monitoring may be necessary in some cases. Intractable seizure of the predominant gelastic type is an indication for surgical treatment. Gelastic seizures refractory to medication, neurobehavioral deterioration and direct or indirect evidence of hypothalamic seizure origin, and the absence of a cortical lesion on MRI are recommended for surgical treatment. The potential risks to memory, endocrine function, behavior, and vision have to be explained to the parents[25,27,28].

Endoscopic surgery

In patients with gelastic epilepsy-HH syndrome, the hamartoma is usually sessile; pedunculated HH is an occasional finding or may be related to endocrinological disturbances and/or to visual impairment[13,29]. Choi *et al*[27] suggested the modified classification of sessile HH, which was introduced by Delalande *et al*[26] (Figure 1). Small HHs (< 20 mm) were classified as midline (Type Ⅰ), lateral (Type Ⅱ), or intraventricular (Type Ⅲ) according to the location of the HH relative to the hypothalamus and third ventricle. A large hamartoma (> 20 mm) was de fined as giant HH (Type Ⅳ). Delalande *et al*[26] first reported on the use of endoscopic disconnection only for intraventricular

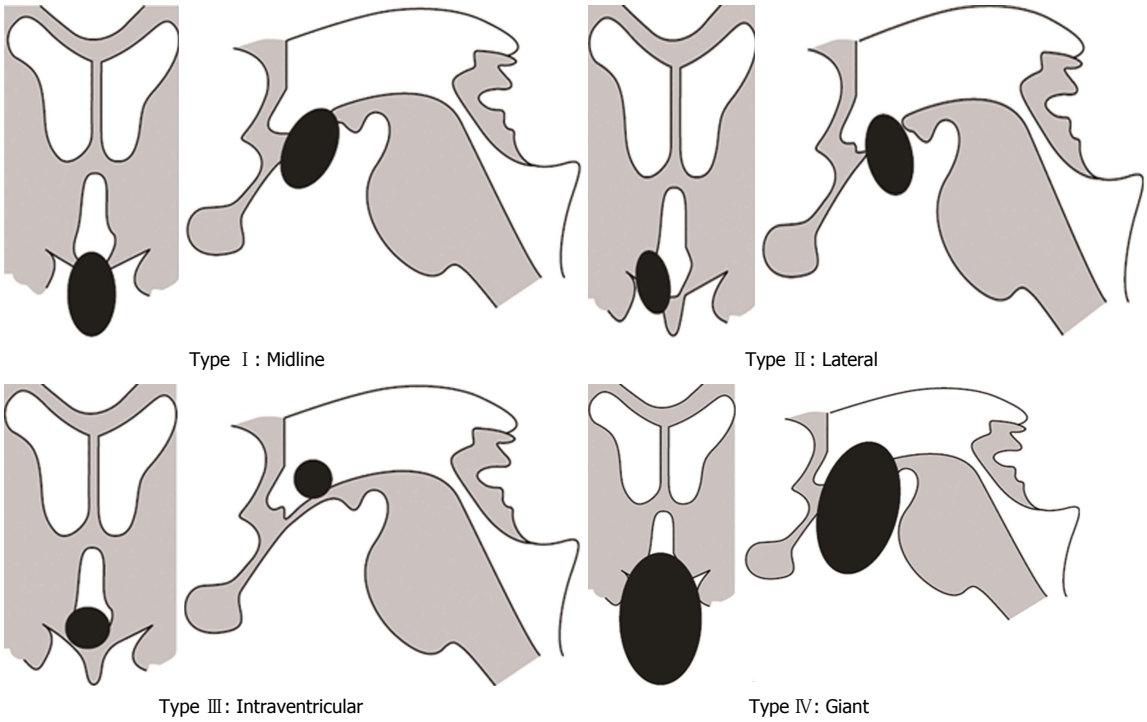


Figure 1 Classification of sessile hypothalamic hamartoma. (Modified by Choi *et al*[27] from that proposed by Delalande *et al*[26]). The hypothalamic hamartomas (HHs) were divided into four categories based on MRI findings demonstrating the relationship between the hamartoma and hypothalamus or the third ventricle. A large hamartoma (> 20 mm) was defined as a giant HH (Type Ⅳ). Small HHs (< 20 mm) were classified as midline (Type Ⅰ), lateral (Type Ⅱ), and intraventricular (Type Ⅲ) according to their relative location to the third ventricle. MRI: Magnetic resonance imaging.

type of hamartoma (Type Ⅲ) in 2003[3]. They also did endoscopic procedures in addition to conventional open surgery to treat other types of hamartoma. However, Choi *et al*[27] had tried endoscopic disconnection for Type Ⅰ, Type Ⅱ, and Type Ⅲ as the primary option of treatment and also used endoscopic surgery as an additional procedure for Type Ⅳ HH. Since Choi *et al*[27] suggested this approach Rekate *et al*[30] have found that most HHs within the third ventricle are excellent candidates for this type of excision[27,31]. Even the seizure returns redo endoscopic disconnection can be an effective rescue. Pati *et al*[32] reported their experience of repeat HHs surgery that they did re-endoscopic surgery for 8 of 21 patients and 50% of success rate.

Shim *et al*[25] (the authors' group) reported their experience with endoscopic disconnection in 11 patients in 2008. Six of 11 patients were seizure-free (Engel's class 1) immediately after surgery. Improvement in behavior was also noted in these patients after 2 mo. Outcome in three patients was class 2. In two other complicated cases which were treated with gamma knife surgery previously, seizure control was not satisfactory (class 3 or 4), but most cases showed complete resolution or a reduction of gelastic seizures. Procaccini *et al*[33] (the Delalande group) reported the results of 13 patients treated with frameless stereotactic endoscopic surgery in 2006[33]. Seizure-free recovery (Engel class 1) was achieved in 54% of the patients, and 46% of the patients showed improvement (Engel class 3). For the intraventricular type of HH, 90% of patients became seizure-free postoperatively. Ng *et al*[31] reported their experience with endoscopic removal in 44 patients based on early results. Ideal candidates for this surgery have been those with a lesion smaller than 1.5 cm in diameter. Patients with larger lesions also may be candidates as long as 6 mm of clearance is present to the top of the third ventricle. By the advance of high resolution of neuroimaging and technology of neuronavigation system the size of HHs might not be a critical point of decision for endoscopic surgery any more even though most of HHs patients have small ventricle[25,34]. In the Ng *et al*[31]'s report among 37 patients who underwent endoscopic resection 18 patients (48.6%) were seizure free at last follow-up (median 21 mo, range 13-28 mo). Seizures were reduced in 34 of 37 patients (91.9%)[30]. For giant HHs staged endoscopic disconnection becomes a one of the choice of treatment by the advent of neuronavigational neuroendoscope with high definition visualization system. The entry point, trajectory, and entry for small ventricle can be guided perfectly by this system. High definition visualization system can show a distinct cleft or indentation, the border of the HH attachment to the hypothalamus[25].

In Rekate's series, early complications occurred in 11 (25%) of 44 patients but resolved within 3 mo in all but three patients (6.8%), including one patient with postoperative hemiparesis and two patients with

short-term memory loss. Early complications included transient short-term memory loss, weight gain, thalamic infarction with memory loss, and hemiparesis[31,35]. Five of the 37 patients (13.5%) treated endoscopically experienced immediate short-term memory loss and permanent short term memory loss in 3 patients (8.2%) in endoscopic surgery group in Ng *et al*[31]'s series[30]. Choi *et al*[27] observed postoperative disconnection-like syndrome in three patients, which included mental dullness, verbal anomia, unilateral tactile anomia, and lack of somesthetic transfer. This disconnection-like syndrome disappeared spontaneously within 10 d. Even with multiple staging endoscopic disconnection the morbidity has been acceptable[25,32,36]. For minimizing complications proper trajectory directly to HHs, no anterior wiping motion of endoscope, not breaching arachnoid or pia mater keeping within third ventricle, and keep disconnection margin straight are very essential instructions. If the piarachnoid membrane was breached unilateral thalamic infarction can be resulted in about 30%[30]. However, many of these patients are so clinically and socially impaired that clinically significant damage to a mammillary body or fornix would not be evident. For this reason, it is reasonable to be more aggressive in pursuing resection or disconnection and in tolerating damage to relieve epilepsy in severely affected patients[36].

Although not all lesions are possibly deal with the endoscopic disconnection the feasibility of successful disconnection depends on a number of factors, including the plane and extent of attachment of the HH to the hypothalamus[37]. Some large lesions may require a multistep approach in which several disconnective procedures are used, or a combination of microsurgical resection and endoscopic disconnection. Larger lesion (> 15 mm) has been reported as an invincible with endoscopic disconnection. If you want to remove the HH completely, it will be nearly impossible with an HH that is over 1.5 cm. However, as we have reported, disconnection of the lesion from the brain is possible. The size of the lesion is not a major problem in disconnecting the lesion from the brain[25].

Open surgery with craniotomy

Multiple surgical approaches to the resection of HH have been described. Transbasal approaches with variations, such as the standard pterional approach, extended pterional approach with orbitotomy, and subfrontal approach, were reported but unfortunately many of these techniques were associated with high complication rates, including infarction of the internal capsule and thalamus, cranial nerve palsy (third nerve, olfactory nerve, and optic nerve), endocrinopathy, and memory loss. There also were difficulties in completely excising the lesion which extended into third ventricle[15,25,28]. Through these approaches, it was difficult or impossible to remove or disconnect the part of the mass that lay within the third ventricle, even after the lamina terminalis was opened[15]. The exposure is usually inadequate, and critical tissue borders are not readily apparent. Seizures were cured or reduced in 52% of patients undergoing approaches from below[6]. Delalande *et al*[26] introduced disconnecting surgical treatment for extraventricular HH in 2003. Dramatic improvement in 53% of those who underwent the procedure using pterional approach was reported. Two of 14 disconnection surgeries showed ischemic complications.

Rosenfeld *et al*[38] reported their experience with the transcallosal interforniceal approach in 2000[38,39]. Complete or nearly complete resection of HHs can be safely achieved *via* this approach with the possibility of seizure freedom and neurobehavioral improvement[39-41]. This approach can be used alone to treat large type Ⅱ and Ⅲ lesions. Many type Ⅳ lesions require a staged approach. If the lesion is entirely medial to the line of sight down the wall of each hypothalamus, then a large type Ⅲ or Ⅳ lesion can be disconnected during 1 operation[28,36]. Wait *et al*[36] described this approach at length.

Rosenfeld *et al*[21] reported complete or near total resection (> 95%) of HH in about 62% of the patients and 75%-95% resection was possible in about 24% of the patients. Harvey *et al*[42] reported that transcallosal resection of HH was effective treatment for intractable epilepsy, with 54%-76% of the patients being seizure-free or having a > 90% reduction in seizures. There also were improvements in behavior and cognition in 65%-88%. With univariate analysis, the likelihood of a seizure-free outcome correlated with younger age, shorter lifetime duration of epilepsy, smaller volume of HH, and total HH resection[42]. Postoperative complications were stroke, short-term memory disturbance, weight gain, diabetes insipidus, and other endocrine disturbances. Stroke is probably the result of injury of perforating vessels surrounding HH and short-term memory disturbance is due to surgical trauma of the septal, forniceal, or mammillary body. Five of the 37 patients (13.5%) treated endoscopically experienced immediate short-term memory loss, compared with 15 of 26 transcallosal patients (57.7%; $P = 0.7281$, Fishers exact test) in Ng *et al*[31]'s series[30] and permanent short term memory loss in 3 patients (8.2%) in endoscopic surgery group. Endocrinological morbidity is likely due to injury of neurovascular structure or pituitary stalk. Injuries to the optic tract and cranial nerve were rare with the transcallosal approach, but these injuries have been reported more with the traditional pterional and subfrontal approaches[43]. If the laterobasal approach is desired the orbitozygomatic approach should be preferred. Orbitozygomatic approach provides minimal brain retraction, maximum working space and light, and more favorable approach angle to HHs[44,45]. For lesions with ipsilateral attachment, the supraorbital eyebrow

approach may be sufficient[36]. Transcallosal anterior interforniceal approach used to resect HHs seems to be associated with a higher risk of postoperative memory difficulty than are approaches from below. The risk of endocrinological and hypothalamic damage may be higher, evidenced by diabetes insipidus, hypothyroidism, changes in appetite, decreased energy, and lethargy. This risk may reflect the potential for bilateral hypothalamic damage when approaching from above and midline compared with laterobasal access[40]. Potential long-term endocrinological deficits consist of permanent diabetes insipidus and hypothyroidism, which reported exclusively in patients after transcallosal anterior interforniceal approach approaches[40]. It is tremendously important to identify and follow the piarachnoid membrane 360° to disconnect HHs completely and avoid injury to critical structures, optic tract and perforating arteries of the basilar and posterior cerebral arteries. The overall rate of major permanent hypothalamic complications appeared to be slightly lower for the orbitozygomatic osteotomy group[40]. However there is a report for good cognitive outcomes with proper surgical resection for HHs of younger patients with relatively normal intelligence prior to surgery and shorter duration of epilepsy in case of no surgical complication[46].

Radiosurgery

Destruction of the HH lesion using focused ionizing radiation (gamma knife) is an attractive approach that does not require invasive surgery. Although a delayed (4-6 mo) response to gamma knife treatment is expected, early results suggest variable outcomes. Régis *et al*[47] reported excellent early seizure response. However, results in terms of long-term seizure freedom are not clear. The treatment goal of radiosurgery for HH is to deliver doses high enough to affect epileptogenesis without exceeding the tolerance of nearby critical structures. Modern radiosurgical devices such as Gamma Knife (Elekta AG), Cyber Knife (Accuray Inc.), and Novalis (BrainLab AG) can deliver conformal high-dose radiation with steep gradients providing a chance to achieve seizure freedom without hypothalamic or cranial nerve damage. Achievement of an excellent outcome following radiosurgery is related to the dose delivered. Régis *et al*[47] observed that four patients who received a peripheral dose of 18 Gy with the Gamma Knife became seizure free. Careful treatment planning and very tight dose distribution are essential to delivering similar doses without injuring the optic chiasm, optic tracts, pituitary stalk, fornices, mammillary bodies, and hypothalamic nuclei. The mean size of HH in a large series of radiosurgery was 19 mm in diameter, but radiosurgery can be accomplished in lesions smaller than 30 mm by using steep dose gradients around the target[47], while the size for ideal surgical candidate was reported less than 16 mm[48]. No serious complication has been reported with radiosurgery but temporary worsening of seizures can be seen as early as 2 mo after the procedure. Successful radiosurgical treatment of epileptogenic HHs was first reported in 1998 by Arita *et al*[22]. Régis *et al*[47] found a clear correlation between dose and efficacy; the marginal dose was > 17 Gy in all patients in whom seizure freedom was achieved and all patients who received < 13 Gy showed incomplete seizure control. Updated outcome of a large series (over 60 patients) by Régis *et al*[47] reported that thirty-one patients were evaluated for at least 3 years after radiosurgery; of these, satisfactory follow-up was available in 27. Only 10 (37%) of these 27 patients achieved seizure freedom; 6 others (22%) experienced a significant decrease in frequency of seizures[47]. The median prescribed marginal dose was 17 Gy (range 13-26 Gy). The authors judiciously used a beam blocking strategy to reduce the dose delivered to critical surrounding structures. However, in the other series in which doses ranging from 12 to 14 Gy were used, outcome of seizure control was variable[25,49].

Several other groups have reported their experience with GKS for treating intractable epilepsy related to HHs[25,50-56]. These studies demonstrate that GKS is an effective treatment modality for selected patients with HH-associated epilepsy. However, it is important to remember that, similar to the complications of microsurgical resection of the HH, radiosurgery can result in permanent neurological sequelae[57,58]. Also, there seems to be a dose-dependent response in which improved seizure control rates are attained with marginal doses > 16 Gy[59]. However, one of the main disadvantages is that clinical response can be very slow; the patient remains exposed to the risks of persistent seizures for up to 2 years after the radiosurgical procedure[60].

Stereotactic radiofrequency ablation

In 1999 Fukuda *et al*[61] reported on a single patient with HH treated by stereotactic radiofrequency thermocoagulation in the course of exploration with a depth electrode implanted within the lesion. Gelastic seizures ceased postoperatively and tonic seizures disappeared 4 mo later. Finally, this patient became seizure free within 14 mo. Kameyama *et al*[62] and Homma *et al*[63] reviewed results from 25 consecutive patients with HH and gelastic seizures who were treated with radiofrequency thermocoagulation. They divided HHs into 3 types based on coronal MRI findings: intrahypothalamic, parahypothalamic, and mixed type. Complete seizure freedom was seen in 19 (76%) of 25 patients over a mean follow-up of 2.3 years. Transient postoperative complications included hyperthermia, hyperphagia, hyponatremia, Horner syndrome, and short-term memory problems. Complications included low-grade fever (4 patients) and hyperphagia (2 patients) and occurred transiently as local hypothalamic symptoms. These transient symptoms resolved within

Table 1 Advantages and disadvantages between modalities

Treatment modality	Advantages	Disadvantages
Endoscopic surgery	Minimally invasive Low possibility to injure adjacent critical structures Critical tissue borders are readily apparent Relatively low complication even with Re-do surgery Relatively easy approach to the intrathird ventricular lesion	Multiple approaches for large HHs Dependent on surgeon's experience
Open surgery with craniotomy		
The standard pterional approach	The risk of endocrinological and hypothalamic damage may be lower than transcallosal approach	High complication rates Difficulties in completely excising the lesion which extended into third ventricle Inadequate exposure is usual Critical tissue borders are not readily apparent
Transcallosal interforniceal approach	Complete or nearly complete resection of HHs can be safely achieved *via* this approach Can be used alone to treat large HHs Injuries to the optic tract and cranial nerve were rare	Surgical trauma to the septal, forniceal, or mammillary body The risk of endocrinological and hypothalamic damage may be higher
Radiosurgery	Does not require invasive surgery Provide a chance to achieve seizure freedom without hypothalamic or cranial nerve damage	Delayed (4-6 mo) response Long-term seizure freedom are not clear Lesions smaller than 30 mm Dose-dependent response
Stereotactic radiofrequency ablation	Effective for a small hamartoma Immediate response	Effective for a small hamartoma Inexact volume of tissue ablation Multiple trajectories to treat larger hamartomas
Neuromodulation	No behavioral, endocrinological, or neurological side effects has been reported	No definite change in overall seizure frequency

HHs: Hypothalamic hamartomas.

1 wk after surgery after perifocal edema disappeared; no permanent complications were noted. All 10 patients who had behavior disturbances preoperatively showed complete resolution of their behavioral abnormalities following radiofrequency ablation.

This procedure seems to be effective for a small hamartoma but a long-term study of a large series will be necessary to con firm the efficacy and safety of this treatment[63-65]. The results with stereotactic radiofrequency ablation, unlike with stereotactic radiosurgery, can be seen immediately following the procedure. However, drawbacks of the technique include inexact volume of tissue ablation and the need for multiple trajectories to treat larger hamartomas, thereby adding to the risk of injury to the surrounding neurovascular structures compared with a single pass[25].

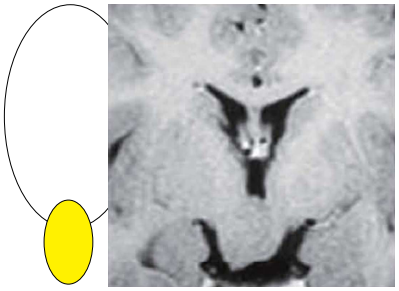
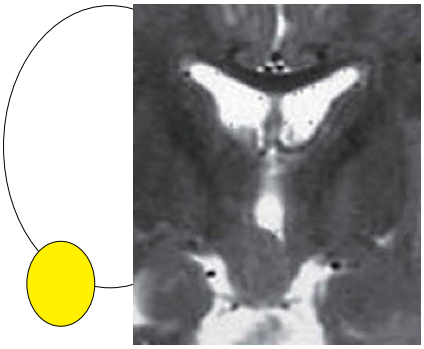
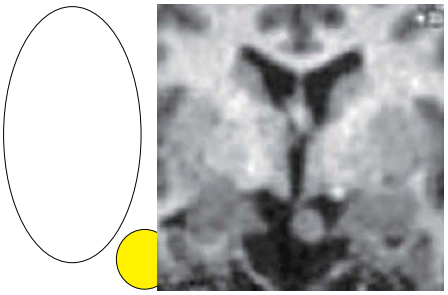
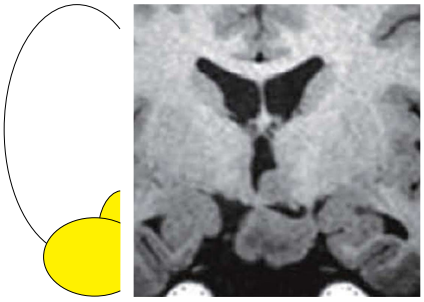
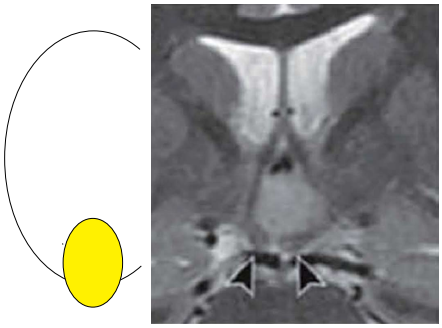
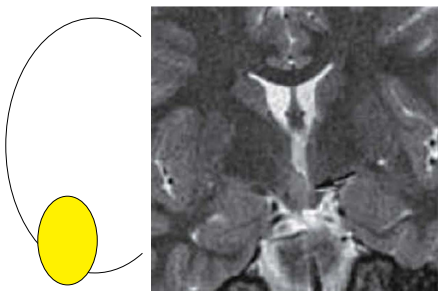
Neuromodulation

Deep brain stimulation and vagal nerve stimulation have tried to override epileptogenic activity from HHs[40,66-69]. No definite change in her overall seizure frequency (complex partial and gelastic seizures) as well as no behavioral, endocrinological, or neurological side effects has been reported. These palliative techniques are not effective in controlling gelastic seizures, and therefore have a very limited role in the treatment of patients with HH-associated gelastic seizures. Certainly, further work needs to be done to determine the role of these techniques in the treatment of epilepsy related to HHs.

Selection of the neurosurgical procedure to perform depends on the surgeon's preference and experience, but reasonable approaches can be selected according to the location, shape, and size of the HH. Possible treatment selections according to subdivided types of hypothalamic hamartoma are given in Figure 2, although treatment options can be different depending on the viewpoint of the surgeon[28].

No single approach is the best approach or is appropriate in all cases (Table 1). Adequate treatment requires individualization of the approach based on a patient's age and condition, on the anatomy of the HH, and on the surgeon's experience. It is becoming increasingly clear that a 1-stage approach to all HHs is probably inappropriate[36]. About 16% of patients required more than one procedure. By the nature and pathophysiology of HHs the complete disconnection from the surrounding structure and tracts which spread out its epileptogenic discharge to frontotemporal region will be enough to achieve the appropriate control of accompanying problems. If an HH can be disconnected completely from the hypothalamus, resection may not be necessary to eliminate seizures[4,30].

It is important to remember that a HH cannot be distinguished from normal hypothalamus under microsurgical view. Only the abnormal anatomy that it forms allows the surgeon to determine where to stop resection. Careful evaluation of the patient's preoperative MRI study and use of intraoperative stereotactic guidance

Type of hamartoma		Possible selection of treatment
Type Ⅰ midline		1 Radiosurgery 2 Endoscopic surgery 3 Stereotactic radiofrequency ablation
Type Ⅱ lateral Type ⅡA partially intraventricular		1 Radiosurgery 2 Endoscopic surgery 3 Stereotactic radiofrequency ablation
Type ⅡB totally extraventricular		1 Radiosurgery 2 Stereotaqctic radiolrequency ablation 3 Open craniotomy; pterional approach
Type ⅡC mixed		1 Endoscopic surgery + open craniotomy pterional 2 Staged radiosurgery
Type Ⅲ intraventricular Type ⅢA midline intraventricular		1 Endoscopic surgery 2 Open craniotomy; transcallosal approach
Type ⅢB lateral intraventricular		1 Endoscopic surgery 2 Open craniotomy; transcallosal approach

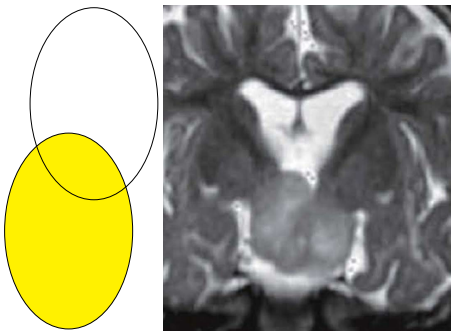


Figure 2 Possible treatments for subdivided types of hypothalamic hamartoma[28]. (Modification from Delalande *et al*[26]'s and Choi *et al*[27]'s classification).

help clarify the aforementioned limits of resection[36].

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REVIEW

Impact of circulating tumor cells in colorectal cancer patients undergoing laparoscopic surgery

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Abstract

Laparoscopic surgery has recently been widely used for various benign colorectal diseases as well as colorectal cancer. Although laparoscopic surgery has been shown to be with similar prognostic results for certain groups of colorectal cancer patients. The influence of laparoscopic procedures on the oncologist results, especially free tumor cell spreading is still a concern for some surgeons. Tumor cells found in the peripheral blood of patients with cancer are termed circulating tumor cells (CTCs). Presence of CTCs in the peripheral blood of patients with colorectal cancer has been reported to be associated with disease stage, poor prognosis, tumor progression, response to therapy, and drug resistance. Whether laparoscopic procedure enhances tumor spreading during operation remains unknown. Significantly less CTC detected during laparoscopic surgery than open surgery for colorectal cancer has been reported. In our previous experience, no significant elevation in CTC level was found in most patients during laparoscopic resection of colorectal cancer. We have shown that laparoscopic surgery had no significantly deleterious effect on CTCs in colorectal cancer patients. In this review, we aim at the impact of CTCs in patients with colorectal cancer undergoing laparoscopic surgery. The prognostic significance of CTCs in patients with colorectal cancer will also be addressed.

Key words: Laparoscopic surgery; Circulating tumor cell; Prognosis; Colorectal cancer

Core tip: Although laparoscopic surgery has been widely used for various benign colorectal diseases as well as colorectal cancer, the influence of this procedure on the tumor cell spreading is still unknown. The level of circulating tumor cells (CTCs) in patients with cancer has been reported to be significant prognostic and predictive factors. Whether laparoscopic procedure enhances tumor spreading during operation remains unknown. Significantly less CTC detected during laparoscopic surgery than open surgery for colorectal cancer has been reported. In our previous experience, we have shown that laparoscopic surgery had no significantly deleterious effect on CTCs in colorectal cancer patients.

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INTRODUCTION

Laparoscopic surgery has been widely adapted for various benign colorectal conditions[1,2] and now increasingly for colorectal cancer[3] since the first series of laparoscopic colectomy was reported in 1991[4]. Laparoscopic colorectal surgery has the benefits of less postoperative pain, early return of bowel function, improved cosmetic results and equivalent oncologic outcome as compared with open surgery. Therefore, laparoscopic techniques for colorectal cancer surgery are increasingly widespread use and have been regarded as therapeutic option for colorectal cancer. Port site recurrence[5-8], which was considered to be a drawback of laparoscopic cancer surgery, is no more a great concern after the use of protection device; however, the free tumor cell spreading either through the homogenous route or intra-peritoneal cavity during the pneumoperitoneal procedure is still a concern of laparoscopic surgery in cancer patient. Tumor cells found in the peripheral blood of patients diagnosed with cancer are termed circulating tumor cells (CTCs). CTCs were first identified by Ashworth[9] in 1869. Presence of CTCs in the peripheral blood of patients with colorectal cancer has been reported to be associated with poor prognosis, tumor progression and drug resistance[10-12]. This review aims at the prognostic significance of CTCs in patients with colorectal cancer. The impact of CTCs in laparoscopic surgery for patients with colorectal cancer will also be addressed.

LAPAROSCOPIC SURGERY FOR COLORECTAL CANCER

Although the aforementioned clinical benefits of laparoscopic surgery, long-term survival and the disease-free interval after surgery are the main concerns adapting the techniques for colorectal cancer. Equivalent intermediate and long-term outcomes of patient survival and tumor recurrence after laparoscopic surgery as compared to open surgery in colorectal cancer have been reported in the literature[13-16], including randomized controlled clinical trials[3,17-21]. The Clinical Outcomes of Surgical Therapy Group[3,20], the report by Leung *et al*[19] and MRC CLASSICC[21] showed that overall survival rate and cancer recurrent rate were similar between laparoscopic surgery and open surgery. In the study by Lacy *et al*[18], cancer-related mortality was lower in patients with stage Ⅲ disease who underwent laparoscopic surgery. There was no significant difference identified in patients with Stage Ⅰ and Ⅱ disease between laparoscopic surgery and open surgery in this trial[18]. Meta-analysis of these randomized controlled trials showed no significant difference in recurrence-free survival and long-term survival between laparoscopic and open surgery[22,23]. For rectal cancer, similar long-term local control and cancer-free survival between laparoscopic surgery and open surgery have been reported in a retrospective comparative study[24]. Long-term outcomes after resection of rectal cancer in CLASICC trail showed that there was no difference in survival, disease-free survival, and local and distant recurrence between laparoscopic surgery and open surgery groups[21,25,26].

CIRCULATING TUMOR CELLS

CTCs are rare in blood and bone marrow. Although CTCs have been identified more than a century[9], CTC-related research did not proceed rapidly until recently due to the lack of sensitive methods to detect these rare cells. CTCs are occurring approximately at the frequency of 1 CTC per 10^5-10^7 peripheral blood mononuclear cells[27-30]. Recent advances in technology make the detection of CTCs from a simple blood test possible[31], including quantitative reverse transcriptase-polymerase chain reaction (RT-PCR), flow cytometry, immunomagnetic techniques, assays based on molecular phenotyping, *etc*.[32-36]. In principle, these methods can be divided into nucleic-acid-based (*i.e.,* mRNA transcripts evaluated by RT-PCR) and cytometric (*i.e.,* immunocytochemistry, immunofluorescence and flow cytometry) approaches[33,37,38]. The nucleic-acid-based approach is highly sensitive, and quantitative RT-PCR permits relative quantification[33,37]. However, the disadvantage is that cells cannot be visualized directly for enumeration or morphology determination[33,37]. The advantage of cytometric approach is that cells can be directly visualized by immunocytochemistry or immunofluorescence[33,37]. Therefore, CTCs enumeration and morphology evaluation are possible. The disadvantage is that the sensitivity is moderate and epithelial-cell adhesion molecule negative cells may be missed[33,37]. The comparison between the two main approaches for detecting CTCs was listed in Table 1. For RT-PCR approach, both single marker and multiple markers have been used. Due to tumor heterogeneity, the use of multiple marker assay may have higher CTC yield as compared with single marker assay[33,37]. Targeting CTCs directly in vivo and the development of leukapheresis and elutriation for subsequent *ex vivo* CTC analyses are alternative approaches to improve CTC yield[33,37].

The prognostic significance of CTC enumeration has been reported in breast cancer[39,40], prostate cancer[41], lung cancer[42], and colorectal cancer[43,44]. CTC number has also been reported to be associated with radiological outcome in breast cancer[45] and colorectal cancer[46]. Furthermore, the application of CTC number is now extending beyond prognostication. Due to the progress in characterization of molecular profiles in CTCs, the

Table 1 Comparisons of the two main approaches for detection of circulating tumor cells

Approaches	Cell viability	Sensitivity	Specificity	Disadvantages
Nucleic-acid-based approach (*i.e.*, RT-PCR)	No	High	Low	Cytological analysis is not possible Cells cannot be visualized
Cytometric approach (*i.e.*, immunocytochemistry, immunofluorescence and flow cytometry)	Yes	Low	High	EpCAM dependent

RT-PCR: Reverse transcriptase-polymerase chain reaction; EpCAM: Epithelial-cell adhesion molecule.

predictive value of response to therapy and drug resistance has been demonstrated. Expression of HER2 in CTCs may be used as a biomarker for treatment of HER2-receptor antagonists in patients with breast cancer[47]. Epidermal growth factor receptor (EGFR) mutations can also be detected from CTCs in patients with lung cancer[48-50], and can be used as a predictive biomarker for treatment with EGFR tyrosine kinase inhibitors[49]. The convenience of real-time biopsy of CTCs contributes a lot to the development of CTC-guided anticancer therapies and personalized medicine.

PROGNOSTIC IMPACT OF CTC IN COLORECTAL CANCER

Prognostic significance of CTC detection in stage Ⅰ-Ⅲ colorectal cancer

Detection of CTCs has been shown to correlate with the stage of colorectal cancer[11,51,52]. Sastre *et al*[52] showed that stage was the only clinicopathological factor significantly associated with CTC level. The presence of CTCs in the peripheral blood of patients with stage Ⅰ-Ⅳ colorectal cancer has been reported to be associated with poor relapse-free survival and overall survival in a meta-analysis[12]. Several studies have demonstrated the prognostic significance of CTCs in patients with staged Ⅰ-Ⅲ colorectal cancer[53-60]. In a review article, Peach *et al*[58] evaluated the effect of sampling time on prognostic value of CTCs in patients with early stage colorectal cancer. There was no significant difference in detection rate at different sampling time (peri-/early or late postoperative). The presence of CTCs in peripheral blood at least 24 h after resection was a significant prognostic factor for recurrence and poor cancer-specific survival[58]. However, perioperative CTC level was not a significant predictor of recurrence[58].

Prognostic significance of CTC detection in metastatic colorectal cancer

The presence of CTCs in blood has been reported to be associated with worse progression-free survival and overall survival in colorectal cancer patients with metastatic disease[43,44,46,61-64]. Cohen *et al*[43] first demonstrated the predictive significance of CTCs in 430 patients with metastatic colorectal cancer receiving first, second and third lines of chemotherapy. CTC levels correlated not only with worse progression-free survival and overall survival, but with worse outcome for all treatment types. Their study showed that CTCs level can be used as both prognostic and predictive biomarkers[43,44]. In a multicenter phase Ⅲ trial (CAIRO2 trial) of patients with metastatic colorectal cancer who received first-line treatment with capecitabine, oxaliplatin, and bevacizumab ± weekly cetuximab, the CTC count before and during treatment independently predicts progression-free survival and overall survival[46]. In a study of 64 patients receiving oxaliplatin-based chemotherapy for metastatic colorectal cancer, patients with ⩾ 3 CTC at baseline and at 2 and 8-12 wk had a shorter median progression-free survival and overall survival than those with < 3 CTC[64]. No rise in early CTC level was observed among responders to chemotherapy[64]. In a prospective study of 180 metastatic colorectal cancer patients who received first line XELOX (capecitabine and oxaliplatin) with or without bevacizumab, the CTC count is a strong prognostic factor for progression-free survival and overall survival[63].

IMPACT OF CTC IN LAPAROSCOPIC SURGERY FOR COLORECTAL CANCER

CTC in laparoscopic surgery for primary colorectal cancer

Animal studies have shown that tumor cells shed into the circulation during resection of primary tumor, thus may increase the possibility of metastases[65]. Ito *et al*[66] demonstrated a significantly higher mean CEA mRNA value in postoperative blood than in preoperative blood by using real-time RT-PCR to detect CTC in peripheral blood of colorectal cancer patients. Their results suggest that tumor cells could be shed into the bloodstream during surgical procedures, and these free tumor cells are accompanied by a poor patient outcome[66]. Weitz *et al*[67] reported that increased intraoperative levels of CTCs were significantly associated with tumor recurrence in colorectal cancer patients. Clearance of CTCs within 24 h of colorectal cancer resection occurred in tumors with the best prognosis[68,69]. Whether laparoscopic surgery inadvertently facilitates tumor spread in colorectal cancer patients remains unknown. Several animal experiments have shown that pneumoperitoneum may enhance tumor growth or tumor cells dissemination[70-72]. However, Lécuru *et al*[73] demonstrated that CO_2 laparoscopy had no deleterious effect on circulating tumor DNA in xenograft ovarian cancer model. To evaluate the potential for tumor cell dissemination at time of curative

Table 2 Relationship between postoperative circulating free tumor cells and status of freedom from recurrence in patients of colorectal cancer undergoing laparoscopic surgery (n = 42)

	No recurrence	With recurrence	*P* value
Post-operative free CTC levels			
≤ 100/10^6 NBCs	28 (82.4%)	2 (25.0%)	0.001
> 100/10^6 NBCs	6 (17.6%)	6 (75.0%)	

CTC: Circulating tumor cell; NBC: Nucleated blood cell.

surgery, Wind *et al*[74] detected and quantified CTCs in peripheral and portal blood of patients who had open or laparoscopic surgery for primary colonic cancer. The detection rate and quantity of CTC were significantly increased intra-operatively and were significantly higher in portal blood compared to peripheral blood[74]. Significantly less CTC were detected during laparoscopic surgery than open surgery[74]. In our previous study[75], we examined the impact of laparoscopic manipulation on circulating CTCs by detecting the guanylyl cyclase C mRNA using real-time RT-PCR in 42 colorectal cancer patients undergoing laparoscopic resections. Quantitation of CTCs was performed preoperatively, intra-operatively, and 14 d after operation. Although there was a trend toward increased CTC level in patients of advanced stage, there was no significant difference in the preoperative CTC level by disease stage. No elevation in CTC level was found during the laparoscopic procedure in most patients, as compared with their preoperative CTC values. We also detected a marginal decrease in CTC level after removing the tumor during laparoscopy, which was sustained at 14 d after surgery. Among the 42 patients, elevated CTC level during the operation was identified in 6 patients. The CTC level concentration returned to undetectable levels or fewer than 100 CTCs/10^6 nucleated blood cells within 14 d after surgery in all the 6 patients. The return of CTC levels was similar to other studies that clearance of CTCs most commonly occurred within 24 h after operation[68,69,76]. Twelve of the 42 patients with persistently high CTC levels (> 100 CTCs/10^6 nucleated blood cells) 2 wk after surgery had significantly poor cancer-related survival when compared with those with undetectable or low CTC levels (≤ 100 CTCs/10^6 nucleated blood cells). Tumor recurrence or metastasis developed in eight patients during follow-up. Persistent high CTC levels at 14 d postoperatively were found in six of these eight patients. The percentage of recurrence in patients with high CTC levels was significantly higher that that in those with low or undetectable CTC levels (P = 0.001) (Table 2). According to our previous published report[75], laparoscopic procedure itself had no significantly deleterious effect on CTCs in colorectal cancer patients.

CTC in laparoscopic surgery for liver metastasis of colorectal cancer

Patients undergoing resection of hepatic metastases of colorectal cancer have a higher risk for extrahepatic tumor recurrence. Weitz *et al*[67] reported that resection of liver metastasis of colorectal cancer carries an increased risk for intraoperative tumor cell dissemination as compared with resection of primary colorectal cancer by detecting CTCs in blood and bone marrow samples[67]. One possible reason is that extensive manipulation of the liver and liver metastases was usually performed before venous drainage ligation[67]. Koch *et al*[69] demonstrated the prognostic value of CTCs in pre-, intra-, and postoperative blood and bone marrow samples of patients who underwent curative resection of liver metastasis of colorectal cancer. Multivariate analysis demonstrated that tumor cell detection in intraoperative blood and in bone marrow samples were significant prognostic factors of tumor relapse[69]. Jiao *et al*[77] determined the CTC level before and immediately after open surgery, laparoscopic resection, open/percutaneous radiofrequency ablation (RFA), in 29 patients with liver metastasis of colorectal cancer. Open liver resection was performed in 11 patients, laparoscopic liver resection in 4, open RFA in 5, and percutaneous RFA in 9. CTCs were localized to the hepatic portosystemic macrocirculation with significantly greater numbers than in the systemic circulation. Surgical procedures led to a statistically significant fall in CTCs at multiple sites measured. Conversely, RFA, either open or percutaneous, was associated with a significant increase in CTCs. Only 4 patients underwent laparoscopic resection in their study. Therefore, the difference between open and laparoscopic surgery was not conclusive. Several other reports also demonstrated that open surgery was superior to RFA for patients of liver metastasis of colorectal cancer[78,79]. Whether CTC was enhanced during laparoscopic surgical procedure for liver metastasis of colorectal cancer and lead to tumor growth and tumor cell dissemination needs further investigation.

CONCLUSION

The level of CTCs in the peripheral blood of patients with colorectal cancer is significantly associated with disease stage, poor prognosis, response to therapy, and drug resistance. It can be used as both prognostic and predictive factors. We have shown that laparoscopic surgery had no significantly deleterious effect on CTCs in colorectal cancer patients. Due to the limited references in the literature, the impact of laparoscopic procedure for colorectal cancer in CTC level and tumor spreading needs further investigation.

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REVIEW

Prevention and management of fractured instruments in endodontic treatment

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Abstract

Intracanal instrument fracture is an unpredictable and problematic occurrence that can prevent adequate cleaning and shaping procedures and influence the prognosis of endodontic treatment. The prevalence of instrument fracture is reported to range between 0.28% and 16.2%. This article presents an overview of the prevention and management of instruments fractured during endodontic therapy on the basis of literature retrieved from PubMed and selected journal searches. Instrument fracture occurs because of reduced metal fatigue and/or torsional resistance. The reasons include canal morphology and curvature, manufacturing processes and instrument design, instrument use times and technique, rotational speeds and operator experience. With the development of various equipment and techniques, most of the retained instrument separations can be removed safely. However, in canals without associated periapical disease not every fractured separation should be removed from difficult locations because of the increased risk for root perforation and fracture. In difficult cases, either retain or bypass the fragment in the root canal and ensure regular follow-up reviews. Fractured instruments retained in the presence of periapical disease reduce significantly the prognosis of endodontically treated teeth, indicating a greater need to attempt the removal or bypass of the file separations. Apical surgery might be required in some instances, emphasizing the importance of preventing instrument fracture.

Key words: Endodontics; Instrument fracture; Root canal preparation; Prevention; Management

Core tip: It is important to prevent the potential adverse consequences that may follow the fracture of endodontic instruments during root canal preparation. Nickel-titanium engine-driven rotary instruments are more prone to fracture than stainless steel hand

instruments, but the risks may be reduced by avoiding multiple use of instruments, by careful operative techniques, in particular with small-sized instruments used in sharply curved root canals, by employing reciprocating hand-pieces and by selecting instruments having high torsional and fatigue resistance.

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INTRODUCTION

Intracanal instrument fracture with separation is often an unpredictable and problematic occurrence that can prevent adequate root canal cleaning and shaping and adversely affect the prognosis of endodontic treatment. The prevalence and incidence of such fractures vary widely among different studies, and fracture not uncommon in the mesiobuccal root canals of molar teeth. Decisions to remove or bypass fractured instrument separations from root canals should be weighed against the necessity to do so, the time involved and the possible adverse iatrogenic complications that might occur. Care taken in the prevention of instrument fracture is preferable to managing the consequences of fracture.

Publications in PubMed were initially searched for by using the key words "instrument separation", "instrument broken", "removal" and "prevention". Further articles were obtained from references listed in the publications and related articles and from hand searching selected journals.

PREVALENCE AND INCIDENCE OF INSTRUMENT FRACTURE

The occurrence of intracanal instrument fracture is reported to range widely between 0.28% and 16.20%[1-8]. In a 5-year retrospective study involving postgraduate students the overall prevalence of instrument fracture among 1367 patients (2180 endodontic cases, 4897 root canals) during root canal preparation was found to be 1.83% (40/2180 cases)[1]. Among 1682 instruments collected over 16 mo, the prevalence of fracture was 5% with the lowest fracture rate being 3% for K3 (SybronEndo, Orange, CA, United States) stainless steel (SS) hand instruments[2]. In a student clinic, during a 10-year period (1997-2006) the overall incidence of instrument fracture in 3854 root-filled teeth was 1.0% at the tooth level[3]. Over 1 year, among 1235 patients (1403 teeth, 3181 canals) from a clinical practice, the incidence of fracture for ProFile (Dentsply-Maillefer, Ballaigues, Switzerland), ProTaper (Dentsply Maillefer), GTRotary (Dentsply Tulsa Dental Specialities, Tulsa, OK, United States) and K3Endo (SybronEndo) nickel-titanium (NiTi) rotary files was 0.28%, 0.41%, 0.39% and 0.52%, respectively[4]. A 4-year retrospective study of 3706 ProFile instruments reported a fracture rate of 0.3%[5]. In a large retrospective study, the incidence of Mtwo (VDW GmbH, Munich, Germany) NiTi rotary instrument separation was 2.2% according to the number of teeth (11306), and 1.0% according to the number of root canals (24108)[6]. In another 1-year study, the fracture incidence was 16.02% among 593 discarded Mtwo instruments after clinical use[7]. Over a 2-year period, 3543 canals were treated during which 46 LightSpeed (LightSpeed Technology, Inc., San Antonio, TX, United States) NiTi rotary instruments separated and were found to be non-retrievable, resulting in a separation rate of 1.30%[8]. A survey from Tehran reported that the most prevalent NiTi instrument failure fault was "intra-canal file fracture" (88.5%) among all procedural faults[9].

The prevalence and incidence of intracanal instrument fractures is difficult to determine, being reported variously (Table 1) at the tooth and/or canal level in disparate studies having very different designs and populations. The determination is compounded by such factors as differences in tooth location and operative difficulties and experience of the operators. Hence, the very wide range reported in literature for the occurrence of intracanal instrument fracture.

PREVENTION OF INSTRUMENT FRACTURE

The endodontic management of intracanal instrument fracture is often difficult and risky, and not all canals and teeth can be managed successfully. Hence, prevention of such fractures is important, requiring an understanding of factors contributing to instrument fracture to reduce the likelihood of file separation within the root canal. Iatrogenic mishaps have been associated with factors such as canal curvature and patency, instrument design and manufacturing process, instrument use times and metal alloy fatigue, hand-piece torque and rotational speed, and operator technique and experience[21]. Prevention of instrument fracture will be investigated as follows.

Canal morphology

It is important to assess the many variations in root and root-canal morphology before initiating any endodontic treatment[22]. Plotino *et al*[23] stated that the shape of an artificial root canal influenced the trajectory of the intracanal instrument. Differences in shape were reflected by the number of cycles to failure (NCF) measured for the same instrument in different artificial root canals, and by the impact of the type of

Table 1 The prevalence and incidence of files separation at different studies

Year	Ref.	Instrument	*n*	Level	Location	Separation
1997	Ramirez-Salomon *et al*[10]	LightSpeed	162	Canals	Molars	3.7%
			52	Teeth	Molars	11.5%
2000	Sattapan *et al*[11]	Quantec Series 2000	378	Files	Tooth	21%
2003	Al-Fouzan *et al*[12]	Profile	1457	Canals	Molars	1.4%
			419	Teeth	Molars	5%
2003	Hülsmann *et al*[13]	Quantec Sc	50	Canals	Molars	6%
			25	Teeth	Molars	12%
		LightSpeed	50	Canals	Molars	10%
			25	Teeth	Molars	20%
2004	Ankrum *et al*[14]	Profile	59	Files	Molars	1.7%
		Protaper	84	Files	Molars	6.0%
		K3 Endo	48	Files	Molars	2.1%
2006	Troian *et al*[15]	RaCe	50	Canals	Artificial	12%
		K3	50	Canals	Artificial	0%
2006	Iqbal *et al*[16]	Hand and rotary instrument	10237	Canals	Tooth	0.09%
			4116	Teeth	Tooth	0.22%
		Hand only	1801	Canals	Tooth	0.17%
			749	Teeth	Tooth	0.40%
		Rotary instrument	10237	Canals	Tooth	0.67%
			4116	Teeth	Tooth	1.68%
2006	Di Fiore *et al*[4]	Profile	2476	Files	Tooth	0.28%
		Protaper	1689	Files	Tooth	0.41%
		GTRotary	771	Files	Tooth	0.39%
		K3Endo	1725	Files	Tooth	0.52%
2006	Knowles *et al*[8]	LightSpeed	3543	Canals	Tooth	1.30%
2009	Inan *et al*[7]	Mtwo	593	Files	Tooth	16.2%
2009	Shen *et al*[2,5]	Profile	3706	Files	Tooth	0.3%
		Protaper	1895	Files	Tooth	0.26%
		Protaper for hand use	280	Files	Tooth	2.9%
		K3	294	Files	Tooth	3%
2011	Wu *et al*[17]	Protaper	6154	Canals	Tooth	1.1%
			2654	Teeth	Tooth	2.6%
2013	Gu *et al*[18]	Protaper	2061	Files	Tooth	28.2%
2014	Plotino *et al*[19]	Reciproc	3780	Canals	Tooth	0.21%
			1696	Files	Tooth	0.47%
2014	Labaf *et al*[20]	Hero642	233	Canals	Simulated	4.75%
		FlexMaster	92	Canals	Simulated	3.92%
		Mtwo	152	Canals	Simulated	6.33%
2014	Wang *et al*[6]	Mtwo	24108	Canals	Tooth	1.0%
			11036	Teeth	Tooth	2.2%
2014	Ungerechts *et al*[3]	Hand instruments	3854	Teeth	Tooth	1.0%

canal on both the NCF and fragment length. Lopes *et al*[24] indicated that significantly lower NCF values were observed for instruments tested in canals with the smallest root curvature radius, the longest arc and the arc located in the middle portion of the canal. Tzanetakis *et al*[1] reported that the prevalence of instruments fractured in the apical third (52.5%) was significantly higher when compared with the middle (27.5%) and coronal (12.5%) thirds of the canals. Instrument fracture occurred significantly more often in molars and in teeth rated as difficult preoperatively[3,25]. Di Fiore *et al*[4] found that instruments fractured in anterior teeth was 0.28%, in premolars 1.56% and in molars 2.74%, which appeared to be related to the increasingly complexity of canal morphology. Some 39.5% of fractured instruments were located in the mesiobuccal canals of molars and 76.5% of the fragments were located apically, while a significantly high percentage of instruments of small apical diameters (sizes 006-015) fractured in relatively straight root canals[3].

In conclusion, premolar and molar teeth, and the apical third of small-diameter and curved canals in particular are prone to cause instrument fracture separation.

Root canal curvature angle: The *in vitro* time to failure significantly decreased and the cyclic fatigue life increased as the angles of root canal curvature increased[26,27]. The abruptness of root canal curvature negatively influenced the failure rate of ProFile rotary instruments[28]. Rotary FlexMaster instruments, with a cross-section similar to a triangle with convex sides, are suitable for preparing curved root canals with the balanced-force technique[29]. These instruments provided results similar to LightSpeed rotary instruments, featured a noncutting pilot tip, a small cutting head and a smooth non-tapering shaft with a minimal risk

of instrument fracture, but an increased risk of root-canal transportation[29,30]. Kim *et al*[31] found that the "minimally invasive instrumentation" design of the Self-Adjusting File (ReDent-Nova, Ra'anana, Israel) may produce minimal stress concentrations in the apical root dentin during shaping of the curved canal. The calculated stress values from the ProTaper Universal F1 (Dentsply-Maillefer) and ProFile size 20/0.06 files were approximately 8 to 10 times larger than that of the Self-Adjusting File. Kitchens *et al*[32] reported that increasing the angle (25°, 28° and 33.5°) at which the ProFile instrument was rotated, decreased the number of rotations to fracture for the 0.04- and 0.06-tapers. The 0.04-taper ProFile was more affected by an increase in the angle than the 0.06-taper. Kramkowski *et al*[30] compared the torsional stress and cyclic fatigue characteristics of ProFile GT (Dentsply Tulsa Dental Specialities) and ProFile GT Series X (Dentsply Tulsa Dental Specialities) for root canals of 45° and 60° degree curvatures. For the 60° canal curvatures, ProFile GT was found to be significantly more resistant to cyclic fatigue fracture than ProFile GT Series X for file sizes 30/0.06, 20/0.06 and 30/0.04 ($P \leqslant 0.005$).

The greater the degree of root canal curvature, then the easier the instrument will fracture. Apart from possible root canal transportation, Rotary FlexMaster, LightSpeed and Self-Adjusting File instruments are suitable to prepare curved root canals. However, the risk of any instrument fracturing increases with the severity of canal curvature.

Root canal curvature radius: Haïkel *et al*[33] tested three engine-driven NiTi rotary instruments, using ProFile, Hero (Micro-Mega, Besancon, France) and Quantec (McSpadden, NT Co., Inc., Chattanooga, TN), in root canals with 5- and 10-mm radii of curvature. Radius of canal curvature was considered as the most significant factor in determining the fatigue resistance of the files. As the radius decreased, then the time to fracture also decreased. One other study compared the cyclic fatigue resistance of each size (S1, S2, F1, F2 and F3) of ProTaper NiTi rotary files in artificial canals also with 5- and 10-mm radii of curvature. The 5-mm radius group had significantly fewer cycles to fracture than the 10-mm radius group for all file sizes[34]. Azimi *et al*[35] investigated the fatigue and fracture modes of RaCe (FKG Dentaire, La-Chaux de Fonds, Switzerland) rotary instruments, which are designed to constantly switch the helix angles of the blades as they rotate inside root canals, and ProTaper instruments used by rotating the files 30° or 60°. Again, both file types exhibited significantly less resistance to fracture when the radius of canal curvature was reduced from 5 mm to 2 mm.

These *in vitro* studies all demonstrated that the risk of instrument fracture increases as the radius of canal curvature decreases.

Preparation instruments

The prevalence of SS hand and NiTi rotary instrument fractures by postgraduate students was reported as 0.55% and 1.33%, respectively[1]. SS instruments usually deform before they fracture, unlike NiTi instruments that do not show visual signs of deformation before fracture[36]. It was observed that SS files had a significantly greater occurrence of failure in clockwise rotation, whereas NiTi files had a significantly greater occurrence of failure in counterclockwise rotation[37]. Many studies have suggested that fatigue fracture and torsional fracture are two major reasons for instrument separation. Plotino *et al*[38] attributed the fracture of NiTi rotary instruments to cyclic flexural fatigue or torsional failure, or a combination.

Fatigue fracture: Instrument fractures often result from their cyclic fatigue. Plotino *et al*[39] evaluated the cyclic fatigue resistance of five NiTi rotary systems in an apical abrupt curvature using SS artificial canals with a 2-mm radius of curvature and a 90° angle of curvature. Ten each of FlexMaster, Mtwo, ProFile (Dentsply -Maillefer) and ProFile (Dentsply Tulsa Dental Specialities), all with tip size 25, taper 0.06, and 10 ProTaper Universal F2 (Dentsply-Maillefer) instruments were rotated passively at 300 rpm until fracture occurred. The survival times for the instruments tested in an apical abrupt curvature were Mtwo > ProFile (from Maillefer) > ProFile (from Tulsa) > FlexMaster > ProTaper. Bahia *et al*[40] found that the mechanical behavior of the NiTi wires was modified slightly by cyclic tensile loading in the superelastic plateau. Because the changes tended towards stabilization, the clinical use of ProFile rotary instruments did not compromise their superelastic properties until they fractured by fatigue or torsional overload, or were otherwise discarded. Lee *et al*[41] studied the cyclic fatigue resistance of various NiTi rotary files, using three root canal curvatures (25°, 35° and 45°), by correlating cyclic fatigue fracture test results with finite-element analysis. The NiTi rotary files investigated were ProTaper, ProFile (Dentsply-Maillefer), HeroShaper (Micro-Mega) and Mtwo. ProTaper showed the least cyclic fatigue resistance and the highest stress concentration for all tested curvatures, whereas Mtwo showed the most cyclic fatigue resistance. When the stresses increased, the number of instrument rotations to fracture decreased. Shen *et al*[42] found that most of the NiTi rotary instruments (78% of K3 and 66% of ProTaper) among 79 fractured instruments failed because of fatigue fracture, whereas 91% of NiTi hand instruments failed from shear fracture. In another (clinical) study, Shen *et al*[5] reported that 10 of 12 ProFile instruments failed because of shear stress, whereas only two failed because of fatigue fracture.

From these studies, most of the NiTi rotary instruments failed *in vitro* from fatigue fracture, but with different rates for different brands. However, the main

reason for NiTi hand instrument failures *in vitro* was from shear fracture.

Torsional fracture: Haïkel *et al*[43] assessed the torsional moment (torque at failure) of four brands of NiTi endodontic files: Brasseler (triangular cross-section; Cms-dental, Paris, France), JS Dental (triangular cross-section; JS Dental, Inc., Ridgefield, CT, United States), McSpadden (H-file types 0.8 to 20, Unifile or S-file cross-section sizes 25 to 40), and Maillefer (concave triangular cross-section). The results suggested that JS Dental and McSpadden NiTi files were the most resistant to torsional fracture, but all NiTi files were inferior when compared with SS files from a previous study. A relationship was proposed between fatigue fracture and torsional fracture[44]. When the torsional resistance of ProFile 25/0.06 and ProTaper F1 were investigated, it was found that approximately 75% cyclic fatigue reduced the torsional resistance of the NiTi rotary instruments significantly. A repeated clinical "locking effect" was considered in a study that evaluated the torsional resistance of five brands of NiTi rotary instruments: Twisted File (TF; SybronEndo), RaCe systems, ProTaper, Helix (DiaDent, Chongju, South Korea) and FlexMaster[45]. TF had the lowest and FlexMaster the highest torsional resistance among the five brands. Braga *et al*[46] also found that TF had similar (TF 25/0.08 taper and RaCe 25/0.06 taper) or significantly higher (TF 25/0.06 taper and RaCe 25/0.04 taper) torsional resistance. Setzer *et al*[47] tested three rotary NiTi systems at 30° curvature under cyclic fatigue only or in combination with torsional stress (with an added 1-Ncm torsional load): Revo-S (Micro-Mega), ProFile Vortex (Dentsply, York, PA, United States) and ProFile with tip sizes 25 and 35. Regardless of fatigue alone or in combination with torsional stress, all fractures occurred within the area of the file curvature. But, with the addition of a torsional load the location of the fracture moved in the direction of the additionally applied torsional stress. One other study found that torsional resistance and angular deflection of instruments were reduced following clinical use when compared with new instruments[48]. Stock NiTi instruments had a torsional fracture resistance up to 10.3%, 8.0% and 7.4% lower for the Small, Primary and Large files, respectively than did M-Wire (Dentsply Tulsa Dental Specialities) instruments, when using finite element analysis simulations based on micro-computed tomography scans at 10 μm resolution[49]. Shen *et al*[50] suggested that the torque at fracture values of K3 and K3XF (SybronEndo) instruments increased significantly with increased diameter.

The torsional resistance of SS files was certified many years ago to be higher than NiTi instruments. The higher the torsional resistance is, the less an instrument is prone to fracture, but clinical use reduces such resistance. There is a relationship between torsional and fatigue resistance, which are two significant factors associated with file separation. Any instrument may fracture in root canals if the curvatures are severe, regardless of how much torsional or fatigue resistance it has.

Manufacturing methods: Intracanal instruments produced by twisting had significantly lower Vickers microhardness values, but presented greater resistance to cyclic fatigue and were more flexible than instruments produced by a grinding process[46,51]. Larsen *et al*[52] reported that the twisted TF was significantly more resistant to cyclic fatigue than traditionally ground EndoSequence (Brasseler, Savannah, GA, United States) instruments, but not significantly different from ProFile. Recently, thermal treatments of NiTi alloys, *e.g.,* Controlled Memory Wire (CM Wire; DS Dental, Johnson City, TN, United States), M-Wire, and R-phase wire (SybronEndo) have been used to modify their mechanical properties[53]. M-Wire has been thermomechanically processed to have greater flexibility at body temperature. The GT Series X (Dentsply Tulsa Dental Specialities) instruments made from M-Wire are more flexible and capable of stress relief than ProFile GT at the most critical curved canal sections[54]. M-Wire is nearly 400% more resistant to cyclic fatigue than stock ProFile 25/0.04 taper instruments[55]. Thermal treatment improved the resistance of NiTi rotary instruments against fatigue fracture. Treatment resulted in significant changes in the instrument bulk with the appearance of an R-phase and an improved fatigue resistance. Indeed, after treatment at 500 ℃, the number of revolutions to failure increased up to 829 and 474 for electropolished and non-electropolished instruments, respectively[56]. The shape-memory CM-wire manufacturing process produced NiTi rotary instruments more flexible and more resistant to cyclic fatigue than instruments produced by a traditional manufacturing process or by a thermally treated NiTi alloy (M-wire)[57]. CM Wire files also showed a high angle of rotation before fracture, but the results were not significantly different from some other files[58]. CM Wire files may have a combined advantage of greater torsional strength and high deformation before fracture[59]. In various environments, the CM Wire instruments yielded an improvement of more than 4 to 9 times for the number of revolutions before fracture than conventional NiTi files with the same design[60]. Electropolished instruments performed significantly better than non-electropolished instruments in cyclic fatigue testing. The benefits of electropolishing were possibly from a reduction in surface irregularities that served as points for stress concentration and crack initiation[61]. Although surface smoothness was enhanced by electropolishing, this did not protect the instruments from low-cycle fatigue failure. No electropolished instrument showed more than one crack origin, significantly fewer than for the non-electropolished instruments[62]. Gutmann *et*

al[63] have reviewed the inherent metallic and surface properties of NiTi root canal instruments.

Many manufacturers have sought ways to enhance the performance, durability and safety of the many root canal instrument designs presently available, such as by modification of the alloy surface or the alloy microstructure with post-machining or post-twisting heat treatment.

Cross-section design: The resistance of NiTi rotary instruments to cyclic failure increased significantly with decreasing cross-sectional area[64]. The bending fatigue behavior was affected by the properties of the material and the cross-sectional configuration of the instrument. NiTi and triangular geometry profiles were associated with better fatigue resistance than SS and square cross-sections[65]. Yum *et al*[66] compared torsional strength, distortion angle and toughness of various NiTi rotary files with different cross-sectional geometries - TF and RaCe, ProTaper, ProFile, Mtwo (equilateral triangle, convex triangle, U-shape, and S-shape). TF and RaCe had significantly lowest yield strengths. TF had a significantly lowest ultimate strength, whereas Mtwo showed the highest. ProFile showed the highest distortion angle at break, followed by TF. ProFile also showed the highest toughness value, whereas TF and RaCe both showed a lowest toughness value[66]. Baek *et al*[67] also evaluated the effect of cross-sectional geometry on the torsional stiffness of NiTi instruments. Triangle, slender rectangle, rectangle and square were tested. The models with the rectangular cross section had higher torsional stiffness than models with the triangular cross section.

A larger cross-sectional area, a rectangular geometry and the S-shape of Mtwo instruments favored a higher fracture resistance.

Retreatment instruments: Inan *et al*[68] compared the cyclic fatigue resistance of three different rotary NiTi instruments designed for endodontic retreatments. The results showed that the R-Endo R3 (Micro-Mega) instruments were more resistant to fatigue failure than the ProTaper D3 and Mtwo R 25/0.05[68]. Hand and rotary instruments were compared for removing gutta-percha from previously treated curved root canals, where the NITi rotary FlexMaster, ProTaper Universal and D-RaCe (FKG Dentaire) retreatment files were associated with a higher risk of instrument fracture. No fractures occurred with the Hedström (Dentsply Maillefer) SS hand files[69,70].

Endodontic retreatments with NiTi rotary instruments resulted in a higher occurrence of instrument fracture than when using SS hand instruments.

Operator

In a 5-year retrospective study, the prevalence of fractured instruments was 7.41% for 2180 endodontic cases treated by postgraduate students[1]. A recent British survey showed that the main reasons for not adopting NiTi use included cost, a lack of training and the perceived risk of instrument fracture[71]. In another study, 88.8% of the respondents had experienced fractured endodontic instruments, with a significantly higher proportion of endodontists (94.8%) compared with general dental practitioners (85.1%)[72]. For ProTaper instruments used at two different clinics, defect rates (fracture and distortion combined) were observed of 7% (Clinic A) *vs* 13% (Clinic B) for shaping files, and 4% *vs* 10% for finishing files[2].

Dentists require more training and more comprehensive education regarding different endodontic instruments and techniques.

Use times: The main operator factors associated with the instrument fracture are "over-use" and "excessive pressure". Factors related to clinician experience, technique and competence have been shown to influence use times. In one study, 54.3% of the respondents re-used NiTi files more than 10 times[73]. The majority of defects (34/48) occurred in small (size 20) instruments, which should be considered as single-use, disposable instruments because of the higher possibility of torsional deformation[5]. The fracture rate of a single ProTaper rotary instrument was significantly increased after the number of prepared root canals exceeded 20 times[74]. Single-use of endodontic NiTi instruments has been recommended to reduce instrument fatigue and the possibility of cross-contamination[19]. The risk of NiTi rotary instrument fracture in the canal was low when a new instrument is used by experienced endodontists. A total of 1071 ProFile 0.04, 432 ProFile Series 29.04, and 1895 ProTaper files were discarded after single use. No fractures occurred in the ProFile, there were no fractures or deformations in the ProFile Series 29, and instrument separation was 0.26% in the ProTaper instruments[75]. Shen *et al*[53] reported that the risk of ProFile Vortex fracture is very low when the files were used once only by undergraduate students. Although multiple clinical use caused significant changes in the microstructural properties of HyFlex CM (Coltène Whaledent, Cuyahoga Falls, OH, United States) instruments, the risk of fracture in the root canal was very low when the instruments were discarded after three cases of clinical use[76]. ProTaper Universal rotary instruments used by an experienced endodontist allowed the cleaning and shaping of the root canal systems of five molar teeth without fracture[48]. The size of the rotary file, among other factors, will determine how many times a particular file should be used[77]. Root canal instrumentation following the manufacturer's instructions was performed with Reciproc (VDW GmbH) with a very low occurrence of instrument fracture and deformation[19].

The recommended use times for different files and for differently experienced operators, varied widely (Table 2). In narrow and/or sharply curved root canals

Table 2 The recommended use times of different studies

Year	Ref.	Instruments (rotary)	*n*	Used times	Operator	Deformation (files)	Separation (files)
2006	Wolcott *et al*[77]	ProTaper	4652 canals	1 tooth	Experienced		20
				2 teeth	Experienced		12
				3 teeth	Experienced		23
				4 teeth	Experienced		19
				5 teeth	Experienced		39
2009	Shen *et al*[75]	ProFile 0.04,	1071 files	1 visit	Experienced	8 (0.75%)	0
		ProFile Series 29 0.04	432 files	1 visit	Experienced	0	0
		ProTaper	1895 files	1 visit	Experienced	55 (2.9%)	5 (0.26%)
2009	Inan *et al*[7]	Mtwo	593 files	4 molar teeth or 2 molar teeth with curved canals	10 trained	58 (9.78%) (unwinding and curve/bend)	95 (16.02%)
2009	Vieira *et al*[48]	ProTaper Universal	10 sets files	5 molar teeth	Experienced	0	0
2010	Ma *et al*[74]	ProTaper	432 case	20 canals			27
2012	Shen *et al*[53]	ProFile Vortex	2023 files	1 visit	Undergraduate students	0	1 (0.04)
2013	Shen *et al*[76]	HyFlex CM	468 files	3 teeth	9 residents	16 (3.4%)	0
2015	Plotino *et al*[19]	Reciproc	1696 files	1 tooth		6 (0.35%)	8 (0.47%)

the number of times that an instrument is used should be as few as possible.

Rotational movements: Different rotational movements of endodontic instruments resulted in different cyclic fatigue survivals, and reciprocating movements were shown to increase the cyclic fatigue resistance of NiTi instruments[78]. When using the reciprocating Reciproc R25 (VDW GmbH) system, only 8 of 1580 instruments fractured during treatment, which represented 0.47% of the total number of instruments used and 0.21% of the root canals treated[19]. Compared with continuous rotation, the probability of a longer instrument survival was greater when using reciprocating motion for all file types tested (100% for K3, 87% for K3XF and 99% for Twisted File)[79]. Fatigue life was shown to increase with decreasing reciprocating amplitude in stationary reciprocation[80], and reciprocating movements resulted in a significantly longer cyclic fatigue life when compared with continuous rotation[81]. Kim *et al*[82] tested the cyclic fatigue of Reciproc and WaveOne (Dentsply-Maillefer) instruments using a simultaneous pecking motion performed with the instruments operating in the recommended reciprocation motion until fracture. Reciproc showed higher cycles to fracture and WaveOne higher torsional resistance. These two reciprocating files demonstrated significantly higher cyclic fatigue and torsional resistances than ProTaper. To simulate clinical conditions, Kiefner *et al*[78] employed a continuous up-and-down pecking motion along the vertical axes of Reciproc (R25 and R40) and Mtwo (M25 and M40) instruments when comparing reciprocating and continuous rotary motions. Reciproc files in reciprocating motion had a significantly higher number of cycles to fracture than Mtwo files used in continuous rotation[78]. Reciproc R25 instruments were associated with a significant increase in mean time to fracture when compared with primary (tip size 25 with a taper of 0.08) WaveOne instruments[83]. WaveOne Large (tip size 40 with a taper of 0.08) instruments presented significantly higher bending resistance than the Reciproc instruments, but Reciproc R40 resisted dynamic and static cyclic fatigue significantly better than WaveOne Large instruments[84]. [WaveOne NiTi files are available in three sizes: small (tip size 21 with a taper of 0.06), primary (tip size 25 with a taper of 0.08) and large (tip size 40 with a taper of 0.08)].

The likelihood of NiTi instrument fracture in root canals appeared to be reduced when using reciprocating rather than rotational motion with engine-driven instruments.

Rotational speeds: The time-to-failure for NiTi instruments decreased significantly as rotational speeds increased (200, 300 and 400 rpm), but the time-to-failure increased with increased pecking distances[26]. Pérez-Higueras *et al*[79] found that TF instruments were more resistant to cyclic fatigue when rotated at 300 rpm instead of 500 rpm. This result was supported by another study where ProTaper F2 instruments failed more rapidly at a rotational speed of 400 rpm (approximately 95 s) than those used at 250 rpm (approximately 25 s)[81]. Also, approximately a 30% reduction in the observed number of cycles to fracture occurred as rotational speeds were increased from 300 to 600 rmp[85]. By contrast, one study reported that the number of rotations to fracture was not related to the speed (350 or 600 rmp) at which the NiTi files were operated[32].

Appropriate rotational speeds and continuous pecking motions within the root canals are recommended. The rotational speed employed for any instrument should be considered in accordance with the manufacturer's recommendations, the clinical situation and the experience of the operator.

Lubricants: During root treatment, lubricants are mostly used to reduce the frictional resistance between the rotating instruments and float debris produced

after mechanical instrumentation. Boessler *et al*[86] used ProFile 30/0.06 instruments in milled artificial root canals in human dentin and gauged the effects of sodium hypochlorite (1% NaOCl) and a chelator (18% etidronic acid) on maximum torque, full torsional load, and maximum force values using a torque testing platform. They found that the aqueous lubricants significantly reduced all outcome variables compared to dry conditions ($P < 0.05$), and that an aqueous lubricant was more beneficial than a gel-type counterpart. The findings were similar to those reported by Shantiaee *et al*[87] who investigated the rates of fracture, deformity and metal slivering of ProTaper rotary instrument with three different lubricants [1% NaOCl (Gorang, Pakshoo Co.,Tehran, Iran), RC-Prep (Premier Dental Produce, Philadelphia, PA, United States) and 17% EDTA (Asia Chemi Teb Co., Tehran, Iran)] in the root canals of extracted molars. The fracture rate of instruments in the RC-Prep group was significant higher compared with the other two groups, with the lowest fracture rate in the EDTA group.

Different forms of lubricant influence the fracture rates of endodontic instruments. Aqueous lubricants are better than dry conditions, and paste-like lubricants can mix with dentin debris in the canal to create increased friction between the instrument and dentin walls.

Hypochlorite solutions: Reciprocating dynamic immersion in NaOCl solution for 1 or 5 min did not reduce significantly the cyclic fatigue resistance of NiTi files[88]. For all properties tested (torsional moment, maximum angular deflection, maximum bending moment and permanent angular deflection), NaOCI immersion had no statistically significant effect[43]. While instruments completely immersed in 5% NaOCl at 50 ℃ for 5 min had a significantly lower resistance to fracture from cyclic fatigue than instruments not immersed or only partially immersed, SEM observations revealed evident signs of corrosion of the fractured instruments[89]. Galvanic corrosion may be induced when different metals are immersed in an electrolyte, where one metal acts as the cathode and one as the anode of a galvanic couple.

The prolonged use of NaOCl as an intracanal irrigating solution might result in the corrosion and enhanced fracture of NiTi instruments.

Other factors: The use of small size SS K-files in a reciprocating manner might be a rational choice for the creation of a mechanical endodontic glide path in curved root canals[90]. The fatigue life of NiTi rotary instruments of larger size could be increased by using them with a lateral brushing or pressing movement[91]. The most frequently fractured file was 10/0.04 (30.39%) among 597 Mtwo rotary instruments[7]. Although more instruments with visible signs of plastic deformation were identified for the novice operator, the novice operator did not significantly affect the cyclic fatigue resistance when compared with the experienced operator[92]. Autoclave cycles had no significant overall effect on file performance for the tested instrument systems, including Profile Vortex made from M-Wire, Twisted File, and 10 Series files made from CM Wire[59]. Unused and sterilized used Profile GTX (Dentsply, Tulsa Dental Specialities) files lasted significantly longer than similar ProFile GT files with a probability of 75% and 65%, respectively; while mean life was significantly longer for GT than for GTX used files with a probability of 68%. Sterilized GT files lasted longer than unused files with a probability of 66%[93].

MANAGEMENT OF INSTRUMENT FRACTURE

When a file fractures during root-canal therapy, there are several treatment options available to the clinician. The management of the problem should be based on the effect of the fractured instrument on immediate treatment outcome and its potential influence on the endodontic prognosis[94]. Before clinical decision-making on the management, some factors should be considered as follows: (1) the stage of endodontic treatment at which the instrument fractured; (2) the armamentaria available; (3) the potential complications of the treatment approach adopted; (4) the presence or absence of periapical pathosis; and (5) the location and the length of the fractured fragment in the canal[95]. It is important that the patient is informed (accompanied by appropriate record keeping) when instrument fracture occurs during treatment or if a fractured file is discovered during a routine radiographic examination[96].

With no apical disease

Retain in the canal as a metal obstruction: Endodontists and general dental practitioners both reported a conservative approach when the management of fractured instruments failed[97]. In certain clinical situations it may be better to leave the fractured file in the root canal. After 5 years, in 12 instances of irretrievable instrument separation (from 3216 endodontically treated root canals), attempts were made to contact the patients to assess healing and tooth retention. Eight contacted patients confirmed the presence of the root canal-treated tooth in question. Among 5 attending patients, 2 teeth were classified as having complete healing, 2 uncertain healing, and 1 no healing according to radiographic assessments (Figure 1)[98]. Retained, fractured endodontic instruments did not reduce the prognosis of endodontically treated teeth when apical disease was absent and any treatment was well-managed[96,99]. Leaving fractured instruments in the apical one-third of the canal also

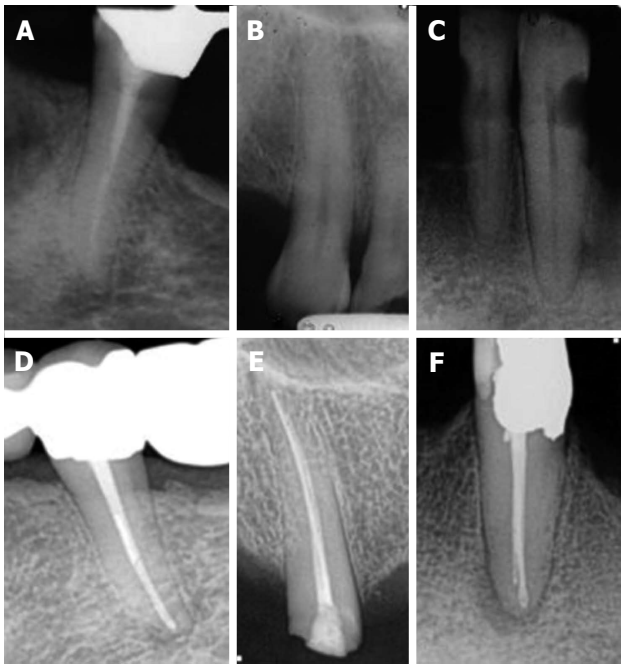

Figure 1 (A-C) preoperative and (D-E) 5-year follow-up radiographs: (D) complete healing, (E) uncertain healing, and (F) no healing.

did not appear to affect adversely the resistance of the root to vertical fracture[100].

Long-term tooth retention and functionality can occur after irretrievable instrument separation. However, clinicians are required to evaluate whether additional treatment is necessary.

Bypass: Bypassing a fractured instrument is often considered an acceptable treatment option to achieve clinical success. However, once bypassed, recent studies consider that the instrument could then be removed. Also, attempting to bypass a fractured instrument may result in perforation of the root canal wall[25].

With apical disease

If apical disease is present, healing is significantly reduced. Therefore, the treatment stage at which an instrument fractures in infected cases appears likely to be significant, as canal disinfection may be compromised[94]. At the earlier treatment stages, attempts must always be made to retrieve separated instruments and, if retrieval is not possible, a bypass should be attempted[101]. Ungerechts *et al*[3] reported that the success rate of removing fractured instruments was 72.7% for vital teeth, 58.3% for primary infected teeth and 42.9% in retreatment cases. The retrieval or bypass of fractured instruments was most successful in the coronal (100%) and middle (45.4%) thirds when compared with the apical third (37.5%) of the root canals[1]. Creating straight-line access and a ditched groove around the fractured instrument are two key steps for removal of fractured instruments. Then use ultrasonic files and/or bypass it with K-Files. Many fractured instruments can be vibrated ultrasonically and flushed out of the root canal. If not, the Tube-and-Hedström file-Method or similar techniques, such as a microdebrider, a Hedström file, a Masserann Kit trephine or with fine narrow-nosed pliers, can be used to remove the loosened instruments or bypass the instruments. When using these methods, 84 instruments (87%) were removed successfully[25]. Failure reasons might include ledge formation, excessive canal enlargement, perforation, limited visibility, dislocation, secondary fracture and incomplete removal, and apical extrusion of the fractured fragment. Several of these reasons may result in weakened root structure and predispose to vertical root fracture[99]. When used as canal filling materials, Resilon (Resilon Research, Madison, CT, United States) and mineral trioxide aggregate appeared to compensate for the root dentin loss that occurred as a result of attempts at retrieval of fractured instruments[100].

Microtube or trephine: When an attempt to bypass an instrument fragment becomes difficult, it should be retrieved by mechanical devices. A microtube or trephine creates a ditched groove around the coronal aspect of the retained instrument fragment. The Masserann Kit (Micro-Mega) is one such device, along with Gates-Glidden (Dentsply-Maillefer) drills, for the orthograde removal of intracanal fractured instruments[77,102]. The Masserann Kit is made up of hollow cutting-end trephine burs (ranging in diameter from 1.1-2.4 mm) and extractors (tubes into which a plunger can be advanced). The trephines are used to prepare a groove or trough around the coronal portion of the fragment. Then the extractor is inserted into the groove and locked the end of the fragment by the screw tightened between the plunger and the internal embossment (Figure 2)[95]. However, in the severely and moderately curved mesial root of mandibular molars, the Masserann Kit increased the risk of creating thin or perforated walls. Additionally, after 7.5 mm depth of drilling, the percentage of perforations increased[103].

Ultrasonics: The use of ultrasonic vibration is a favorite technique for the removal of fractured instruments, although it may result in some complications. The technique demonstrated a success rate of 80% in removing broken Hero 30/0.04 taper files within 70 extracted maxillary premolars[104]. Ultrasound, like above methods, creates a groove around the fractured instrument, but the used instruments are different. Diamond-coated zirconium ultrasonic tips (CPR 1-CPR 5; Obtura Spartan, Earth City, MO, United States) and titanium cutting tips (CPR 6-CPR 8; Obtura Spartan) were reported as the instruments. The former are selected according to the anatomy of the root canal to creat the groove. The later are placed in close contact with the fragment and worked in a circular counterclockwise motion to dislodge the fractured

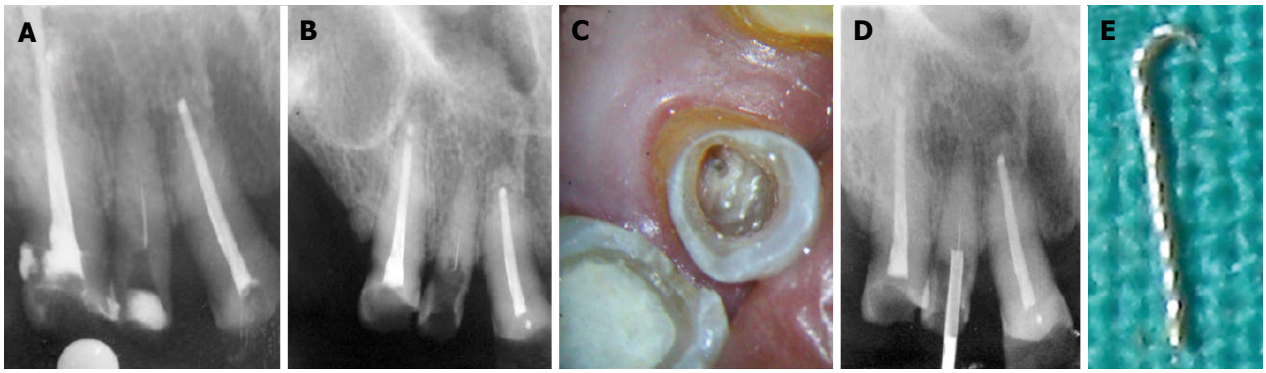

Figure 2 The extractor is inserted into the groove and locked the end of the fragment by the screw tightened between the plunger and the internal embossment. A: Periapical radiograph: Separated instrument is visible in middle 3rd of calcified root canal in maxillary right lateral incisor; B and C: Making a channel around the separated instrument to keep the broken instrument in the center of the tube of Masserann Kit; D and E: Engaging tube of Masserann Kit with the separated instrument and removal of the fragment from root canal.

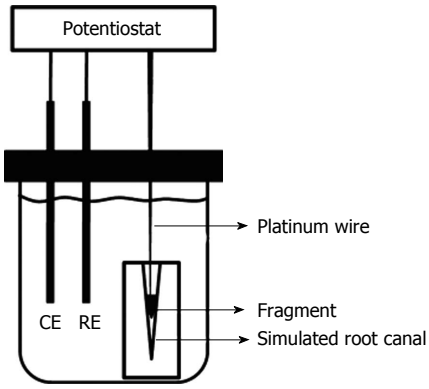

Figure 3 Schematic diagram of the intracanal fragment dissolution test. CE: Counter electrode; RE: Reference electrode.

instrument. All procedures are performed dry to ensure constant visualization, with the ultrasonic unit set at low power (20% to 30%)[96,105]. An ultrasonic technique was used to remove fractured NiTi rotary instruments from narrow, curved canals in both simulated (resin blocks) and mesiolingual canals of extracted mandibular first molars. However, when the fractured instrument segment was located entirely beyond the canal curvature, the success rate was significantly decreased and major canal wall damage often occurred[106]. Gencoglu *et al*[107] used ultrasonics with an operating microscope and reported that the success rate in removing fractured files in curved canals was 93.3%. This was significantly higher than the success rate of 66.6% when only conventional methods were used. The success rate was highest with ultrasonics (95.2%) in straight canals, followed by the conventional method (80.9%) and use of the Masserann Kit (47.6%)[107]. Visualization of fractured instruments with the aid of an operating microscope plays an important role in the success rates when removing or bypassing the fractured instruments. The success rate for the visible group was 85.3% (n = 58), and for the nonvisible group was 47.7% (n = 21)[105].

Electrochemical dissolution: Electrochemical dissolution has been proposed as a novel method to retrieve fractured instruments, especially for NiTi endodontic files. However, using NaF resulted in solutions that were cytotoxic to periodontal ligament fibroblasts, and artificial saliva may be a less toxic alternative for dissolving NiTi files[108]. A progressive consumption of K3 NiTi file tips was observed up to 30 min[109]. The anodic polarization of file fragments in simulated root canals for 60 min resulted in their partial dissolution and enabled the recovery of the original canal pathway with size 10 K-files[109]. The time taken by this procedure is clinically acceptable. K3 and ProTaper instruments had significantly greater weight loss than Mtwo instruments after 30 min of polarization in chloride- and fluoride-containing solutions, and 60 min anodic polarization of various NiTi instrument fragments in simulated root canals resulted in their partial dissolution (Figure 3) [110].

File removal system: Many different devices and techniques have been developed to retrieve fractured instruments from root canals, but iatrogenic accidents such as perforation, ledge formation, zipping, canal transportation or destruction, and fragments extruded beyond the root apex also occured during the removal procedures. The file removal process turns out to be more difficult when the fracture occurs in the apical third of the canal or in a sharply curved canal. Four separated files from the apical third of curved canals were successfully treated using the file removal system (FRS) (Figure 4)[111]. When compared with the Masserann Kit and an ultrasonic file-removal method, the FRS minimized both the root canal dentin removal and the time required to remove the fractured instruments[21].

Laser: Yu *et al*[112] found that a Nd:YAG laser successfully removed broken endodontic instruments from root canals in more than 55% of instances.

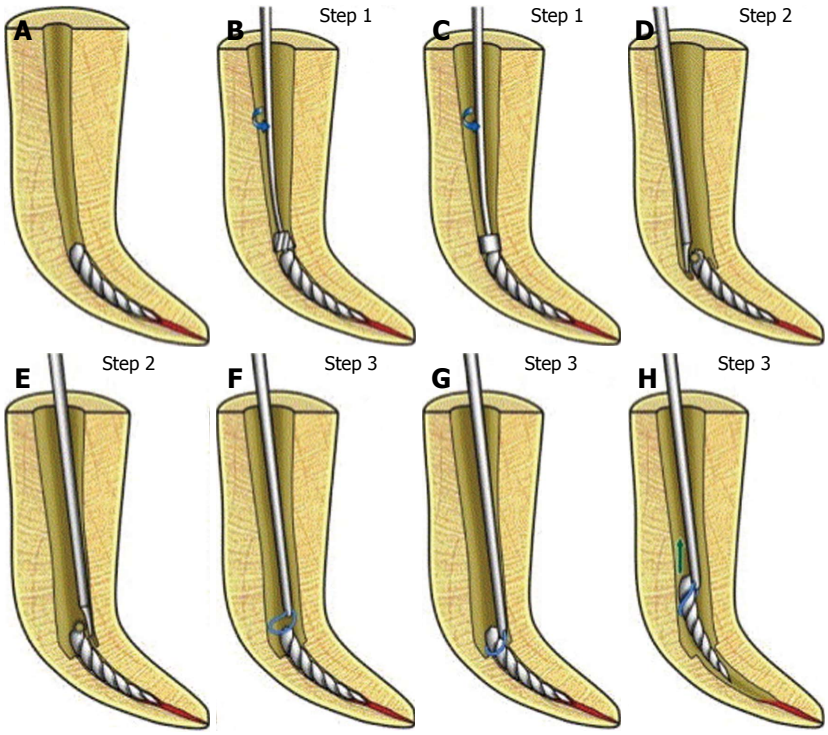

Figure 4 Procedures for removing a separated file from a root canal using the new file removal system. A: Initial canal with a separated file; B: Canal enlarged with CBA; C: Dentin removal around the separated file with CBB; D: Ultrasonic tip troughed semicircularly around the separated file to create space for the file-removal device; E: troughing semicircularly on the remaining half of the separated file for complete exposure; F: Placement of the loop over the separated file; G: Fastening the loop to grab the separated file; H: Removal of the separated file from the root canal.

However, temperature rises on root surfaces ranging from 17 ℃ to 27 ℃ might lead to periodontal tissue damage. Cvikl *et al*[113] also evaluated a Nd:YAG laser for the removal of fractured SS instruments. A narrow brass tube charged with solder was placed at the exposed coronal end of the fractured instrument and laser energy then used to melt the solder, fusing the fractured instrument to the brass tube. The laser technique requires the removal of a minimum amount of dentin, reducing the risk of root fracture.

Some other uncommon methods: Mini-forceps, broaches and cotton, and wire loops were historical methods used for the removal of instruments fractured and loosened in the more coronal portion of the root canal[114-116]. When the fractured instrument is positioned more deeply in the canal and is not visible or loose, and cannot be retrieved with other methods, then a Hedström or K-type file(s) can be inserted into the root canal where the clinician relies on tactile sense to withdraw the fractured instrument[25,116]. During the procedure, caution should be taken to avoid endodontic file separation. A modified 18-gauge needle and cyanoacrylate glue were used to retrieve a separated NiTi instrument from the mesiolingual canal of a mandibular first molar (Figure 5)[101]. As a safety feature during use, Gates-Glidden drills are designed to separate near the hub of the drill to allow for easier retrieval[117]. With the assistance of SS hand files and a chloroform-dipped gutta-percha cone, a fractured rotary NiTi instrument was successfully removed from the severely curved apical portion of the distobuccal canal of a mandibular molar[118]. However, chloroform is toxic and carcinogenic, and its extrusion through an existing root perforation resulted in subsequent necrosis in the supporting bone and periodontal tissues[119]. Chloroform used in the apical part of the root canal may also leak through the apical foramen and damage periapical tissues.

Factors influencing fractured instrument retrieval: Favorable factors for the removal of separated NiTi fragments are anterior teeth, straight root canals, localization before the canal curve, fragments longer than 5 mm, and NiTi hand K-files[116]. The success rate in roots with file fracture before the curve was 11.5 times more than that for file fracture beyond the curve[104]. Removal of a fractured instrument from the middle-third of the root canal decreased the force required to fracture the root vertically, regardless of the technique used for instrument removal[120]. There were statistically significant differences between experienced and less-experienced operators for the file-removal times and the root dentin removal rates[21].

Beyond the apical foramen

When the fractured instrument fragment is beyond the apical foramen, it is very difficult to retrieve the

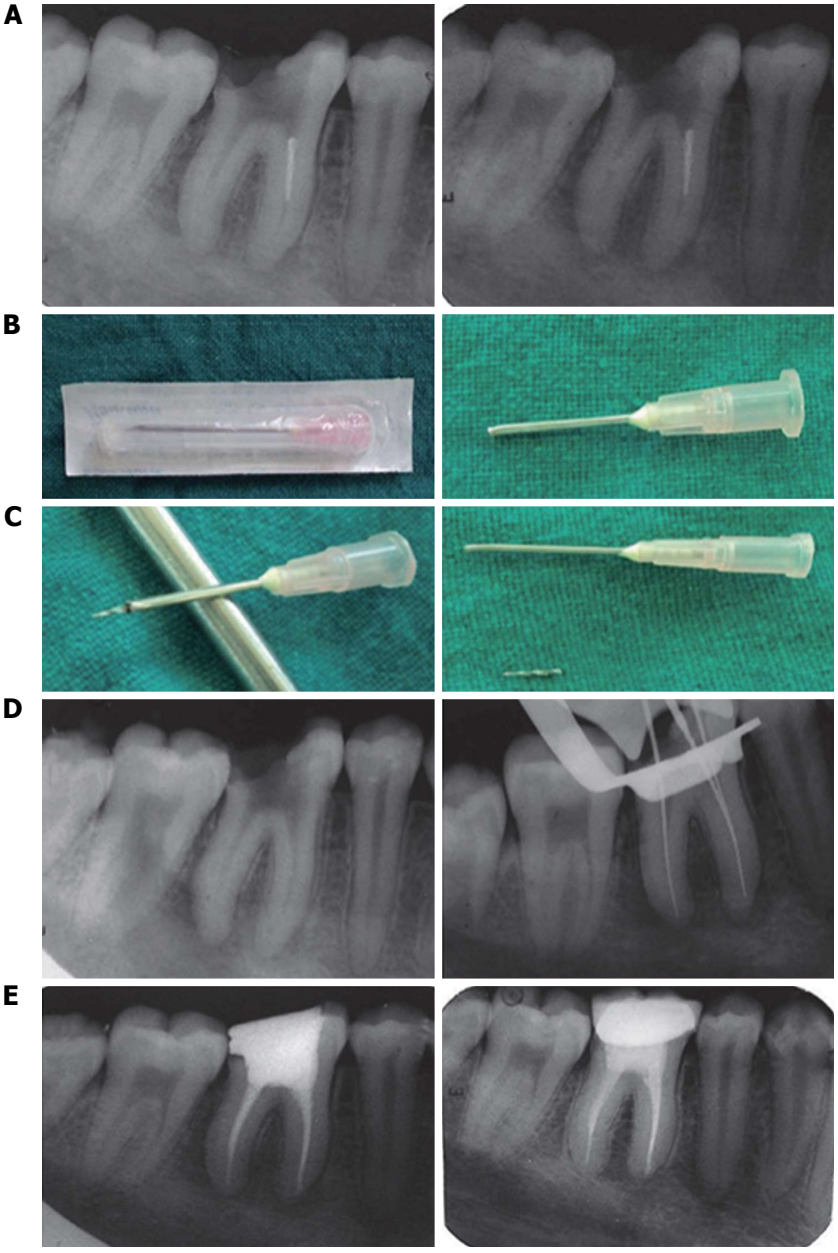

Figure 5 A modified 18-gauge needle and cyanoacrylate glue were used to retrieve a separated nickel-titanium instrument from the mesiolingual canal of a mandibular first molar. A: Radiograph showing separated instrument; Radiograph showing dentine surrounding the coronalend of the separated fragment removed with GG drill; B: An 18-guage needle, modified by cutting with a carborundum disc from the tip to transform it into a microtube; C: Separated instrument fragment removed adhered to the microtube; D: Radiograph confirming instrument removal; Working length reconfirmed; Post-obturation radiograph; E: Two-year follow up radiograph.

fragment using the previous approaches. In one report, two fragments beyond the apical foramen were removed by non-surgical approaches. A 3-mm fragment was pushed out of the root apex while the removal of a 7-mm fragment resulted in root perforation[25]. Surgical approaches may be better for these cases. However, the microsurgical procedure relies on considerable surgical skill and may reduce the crown-root ratio[96]. A separated hand instrument in a second molar was retrieved from the mesiobuccal root, which was close to the mandibular canal, using tooth replantation (Figure 6). After atraumatic tooth extraction, the separated instrument protruding 3 mm beyond the root apex was removed and the entrance to the mesiobuccal canal was cleaned, shaped and obturated. The tooth was re-implanted and orthodontic bands placed on both first and second molars. Periodic evaluations over 1 year showed progressive reductions in periapical radiolucency[121].

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We are very sad to declare that Professor Roger J Smales, as the second author of this article, was

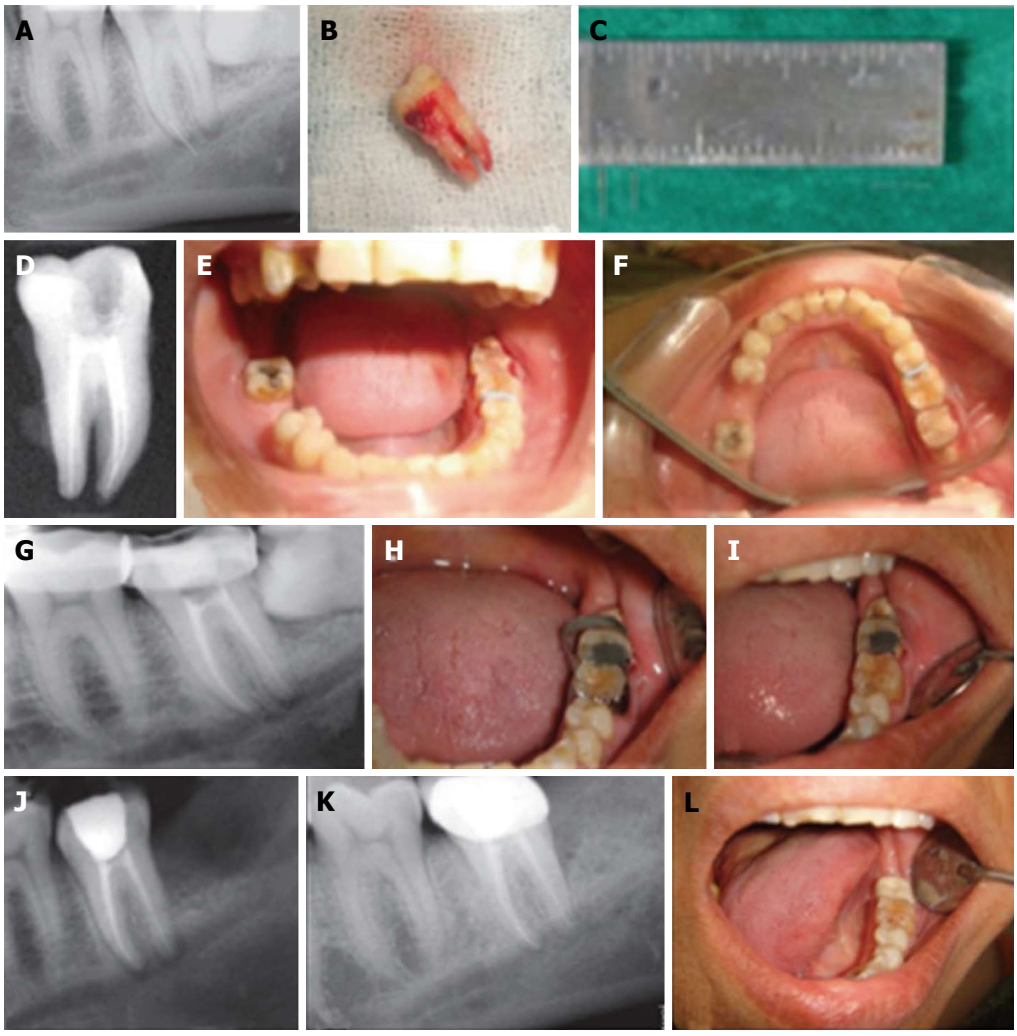

Figure 6 A separated hand instrument in a second molar was retrieved from the mesiobuccal root, which was close to the mandibular canal, using tooth replantation. A: Broken instrument near to the mandibular canal; B: After extraction; C: Measured broken instrument of 7 mm; D: After obturation; E: After separators were placed; F: Extra coronal splinting with orthodontic wires were prepared; G: Post operative Radiograph; H and I: Four weeks after Band removal; J: Three months follow-up Radiograph; K: One year follow-up radiograph; L: One year clinical radiograph.

sudden to die on Sunday November 9th. We dedicate this article to commemorate him.

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Surgical management of rectal prolapse: The role of robotic surgery

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Abstract

The robotic technique as a safe approach in treatment of rectal prolapse has been widely reported during the last decade. Although there is limited clinical data regarding the benefits of robotic surgery, the safety of robotic surgery in rectal prolapse treatment has been cited by several authors. Also, the robotic approach helps overcome some of the laparoscopic approach challenges with purported advantages including improved visualization, more precise dissection, easier suturing, accurate identification of anatomic structures and fewer conversions to open surgery which can facilitate the conduct of technically challenging cases. These advantages can make robotic surgery ideally suited for minimally invasive ventral rectopexy. Currently, with greater surgeon experience in robotic surgery, the length of the procedure and the recurrence rate with the robotic approach are decreasing and short term outcomes for robotic rectal prolapse seem on par with laparoscopic and open techniques in recent studies. However, the high cost of robotic procedures is still an important issue. The benefits of a robotic approach must be weighed against the higher cost. More research is needed to better understand if the increased cost is justified by an improvement in outcomes. Also, published articles comparing long term outcomes of the robotic approach with other approaches are very limited at this time and further clinical trials are indicated to affirm the role of robotic surgery in the treatment of rectal prolapse.

Key words: Rectal prolapse; Robotic surgery

Core tip: Robotic rectopexy is a safe and feasible technique for the treatment of rectal prolapse with improved visualization and ease of suturing. The robotic approach can provide functional results and short term outcomes similar to laparoscopic surgery. However, increased operative time and higher cost are challenges. Further prospective clinical trials assessing the role of robotic surgery in the treatment of rectal

prolapse are needed.

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INTRODUCTION

Rectal prolapse was first described in the Ebers Papyrus around 1500 BC. In 1899, Edmond Delorme reported the first successful surgical treatment of rectal prolapse[1,2]. Since 1899, more than 100 procedures have been described for the treatment of rectal prolapse[3]. However, there has been ongoing controversy regarding the ideal procedure for the treatment of prolapse with the lowest rates of recurrence, complications, and mortality.

Practically speaking, the numerous rectal prolapse procedures are categorized into trans-abdominal and perineal approaches. Trans-abdominal operations can be performed with open, laparoscopic, and robotic techniques. The perineal and abdominal approaches each have their own advantages and disadvantages. While the trans-abdominal approaches are reported to have longer operative times, higher costs, and lower recurrence rates, perineal approaches tends to be safer but with a greater recurrence rate[4]. The trans-abdominal approach is more commonly performed, and is a popular choice for patients without significant comorbidities[5] fit for a major abdominal operation. Also, trans-abdominal approaches can be combined with other abdominal/pelvic procedures such as uteropexy, colpopexy, or sigmoidectomy[6,7], whereas, the perineal approach can be done under regional anesthesia and is often favored for elderly and/or high-risk patients[2,5]. Treatment should be individualized for each patient with the aim of achieving the better outcome[2].

MINIMALLY INVASIVE APPROACHES IN TRANS-ABDOMINAL RECTAL PROLAPSE REPAIR

Trans-abdominal operations can be performed with open, laparoscopic, and robotic techniques. Since the introduction of minimally invasive techniques for rectal prolapse in 1993[7], the use of laparoscopy in the treatment of rectal prolapse has expanded. Lower morbidity, faster recovery time, shorter hospital stay, and less blood loss have been reported as the advantages of laparoscopic surgery over the open approach[8-10]. The laparoscopic approach as the preferred approach in the treatment of rectal prolapse has been recommended by several studies[8,9,11].

Since the introduction of robotic surgery in 1998, it has been widely applied in a variety of procedures across many surgical specialties[12]. The aims of robotic surgery are to facilitate minimally invasive surgery and overcome some of the challenges of laparoscopic surgery[13]. Features such as high-quality, three-dimensional vision, restoration of the eye-hand-target axis, better depth perception, tremor elimination, more precise dissection, and a better definition of tissue planes lead to precise dissection, especially in the pelvis[13]. Published articles have reported advantages of robotic surgery (*e.g.*, faster recovery time, and less postoperative pain compared to open surgery) including less blood loss and a lower conversion rate (compared to laparoscopic surgery)[13-15]. However, the high cost and prolonged operative time of robotic procedures are disadvantages of this approach[16]. As surgeons become more experienced in robotic techniques, the length of the procedure decreases significantly; however, the higher cost of robotic procedures is still an important issue[17]. More research is needed to better understand if the increased cost is justified by an improvement in outcomes.

OPERATIVE INDICATIONS AND PATIENT SELECTION

The first step in choosing the appropriate approach to treat rectal prolapse is to evaluate the patient's operative and anesthesia risk as well as their baseline bowel function and continence. It is commonly accepted that patients with low operative and anesthesia risk should be offered an abdominal approach. A robotic approach also has the additional advantage of allowing easier technical access to other pelvic pathologies including enterocele, rectocele and vaginal vault prolapse, should they exist. In patients who have failed a prior repair and have a recurrence of their rectal prolapse a laparoscopic or robotic-assisted abdominal repair is a good choice[18].

Contraindications to a laparoscopic or robotic approach are similar and can be subdivided into physiologic contraindications and anatomic/technical contraindications. Physiologic contraindications precluding laparoscopic/robotic surgery include: pregnancy, coagulopathy, increased intracranial pressure, low cardiac output, severe pulmonary disease and chronic liver disease. The above mentioned conditions are not an absolute contraindication for surgery and the risk of a laparoscopic/robotic surgery should be assessed for each case separately. Anatomic contraindications to robotic surgery are rare but mostly pertain to patients with an extensive prior history of abdominal operations with a hostile abdomen and thick adhesions which preclude good visualization and safe dissection with the surgical robot. These patients rarely suffer from rectal prolapse, but when they do, they are usually best served with an open surgical approach.

PREOPERATIVE WORKUP

Evaluation of patients always starts with a thorough and complete history and physical examination. The most common presentation of rectal prolapse is that of a large prolapsing rectal mass and patients usually provide a history of a mass protruding from the anus on defecation or with walking. However it is also not uncommon for patients to present with chief complaints of fecal incontinence or hemorrhoids as opposed to a large prolapsing rectal mass. Other less common presenting symptoms of rectal prolapse include: soiling of the undergarments, mucus discharge, feeling of incomplete evacuation, constipation, fecal urgency, change in bowel habits, and poor anal control. This constellation of symptoms underscores why a comprehensive history of anal function and bowel habits should be recorded as a baseline reference for future evaluations.

Physical examination of rectal prolapse requires a specific approach. In the lateral or prone position, it is sometimes very hard for patients to reproduce rectal prolapse. Frequently, the only abnormality identified in these positions is a patulous anus. To reproduce the prolapse in the office, it is sometimes required that the patient sits on a toilet and perform a Valsalva maneuver. If the examiner is unable to replicate the prolapse on examination then a defecography may be helpful. Defecography may also be helpful in patients suspected of internal prolapse or intussusception as a cause of obstructive defecation syndrome.

Once the diagnosis of rectal prolapse is established, the examiner is required to differentiate between mucosal prolapse and full-thickness rectal prolapse. This usually can be achieved during gross evaluation and digital rectal examination. Furthermore the patient's anal sphincter function and integrity may be evaluated subjectively with digital exam, or objectively with anorectal manometry. Patients with a concurrent history of constipation may also require a motility (Sitzmarks®) study to evaluate their symptoms. Finally, there exists a slightly increased risk for cancer in patients with rectal prolapse and thus all patients with prolapse should undergo colorectal cancer screening *via* a recent colonoscopy, barium enema, or alternative.

In terms of preoperative preparation, patients are commonly instructed to adhere to a clear liquid diet on the day prior to their surgery. Moreover, some surgeons advocate a limited bowel preparation and evacuation of the rectum with an enema before surgery. Single dose broad spectrum antibiotic should be administrated within an hour before the incision. Thrombosis prophylaxis should start prior to the operation and should be continued during hospitalization.

POSTOPERATIVE CARE

Patients ideally are treated in a clinical pathway (such as an enhanced recovery after surgery pathway) to expedite and optimize their recovery. These usually include prompt mobilization of the patient the day of or the first day after operation. The patient's diet should be advanced as tolerated and their urinary catheter removed as soon as the patient is adequately mobile. Patient's length of stay after laparoscopic/robotic rectal rectopexy repair is usually short, with most patients being discharged on the second or third post-operative day. In the first 6 wk of recovery, patients are reminded to abstain from any heavy lifting greater than 15lbs that might strain their fresh repair. Patients are also prescribed stool softeners liberally to try and limit any postoperative constipation or straining.

OPERATIVE DETAILS

Place the patient in modified lithotomy position with Allen stirrups. Soft foam or egg crates should be fixed to the surgical table and placed directly under the patient to prevent slipping during the steep Trendelenberg positioning required for the safe conduct of the operation. The arms are tucked at the sides with adequate padding to minimize injuries along pressure points. Place a padded strap across the patient's chest to prevent lateral movement. Intraoperative hypothermia can be minimized with Bair Hugger® blanket. The abdomen and perineum are prepped and draped in the usual sterile fashion.

Port placement and robotic docking

The robotic camera should be placed first, as placement of all other ports depends on the location of this particular port. A Veress needle is placed at Palmer's point and the abdomen is insufflated. The 12 mm camera port is placed about 15 cm cephalad to the pubis. Placing this port too far superiorly will result in difficulty in reaching the deep pelvis during the procedure. A line is drawn from the camera port to the anterior superior iliac spine on each side. Two additional robotic ports are placed about 8-10 cm from the camera port along this line. A third robotic port is placed 6 cm lateral to the left lower quadrant port (designated robotic arm number 3). Assistant ports consist of a 12 mm port in the right upper quadrant and 5 mm port in the epigastric area. The patient is then placed in steep Trendelenberg position. The small bowel is swept superiorly out of the pelvis.

Next, the robot is docked, with the robot cart positioned along the patient's left side. Arm 1 is placed in the right lower quadrant, Arm 2 in the left quadrant, and Arm 3 in left lateral abdomen. Instrument placement is as follows: Arm 1 with monopolar scissors, Arm 2 with fenestrated bipolar grasper, Arm 3 with atraumatic graspers. The beginning of the case proceeds with use of the 0-degree robotic camera.

Rectal mobilization

Inspect the abdomen and pelvis for any abnormalities.

Consideration may be given to lysis of adhesions if involved organs have adhesions. For female patients with an intact uterus, a 0-Prolene suture is inserted into the abdominal cavity on a straight Keith needle, passed once through the uterus and back through the abdominal wall to elevate the uterus during the surgery and provide gentle traction. The rectosigmoid is grasped and elevated anteriorly by the assistant using the epigastric port. Sharp dissection is used to open the peritoneum along the base of the rectosigmoid mesentery. Dissection along the sacral promontory is developed along the avascular areolar plane. While dissecting along the sacral promontory, care should be taken to identify and preserve the hypogastric nerve plexus and ureters. The peritoneum along the right side of the rectum is opened up to the rectovaginal septum, in females. A vaginal manipulator can be used to elevate the posterior vagina and aid dissection along the anterior rectum. While the vagina is elevated, the assistant uses an atraumatic grasper to lift the rectum up and out of the pelvis. Electrocautery is used to incise the peritoneum to enter the rectovaginal plane at this level. The dissection along this plane may be difficult in patients with chronic rectal prolapse as this layer may be especially thinned out. Dissection is carried along the right side of the sacral promontory towards the left lower rectum. Next, separate the rectum and vagina in females, and prostate in males, all the way down almost to the perineal body. Continue the dissection down laterally until the pelvic floor is visualized. Fully mobilize the rectum anteriorly and posteriorly, while leaving the lateral stalks intact. Perform a digital rectal exam during the dissection.

Mesh placement

Guidelines on appropriate choice of mesh are limited in the literature. In our practice, we routinely use lightweight, macroporous polypropylene mesh. Biologic mesh may also be considered in cases of gross fecal contamination or if the surgeon has high concern for infection. For the purposes of this review, we will discuss use of synthetic mesh. A slightly tapered mesh is used. The mesh is trimmed to 18 cm long, 3 cm wide along the portion that will be fixed to the anterior rectum, and tapered to 2 cm on the side that will attach to the sacral promontory. The mesh can be rolled up and introduced into the abdominal cavity through the 12 mm assistant port. Using a 2-0 Ethibond suture, about 6 sutures are used to fix the mesh along the anterior extraperitoneal surface of the rectum. The mesh is positioned along the right side of the rectum and brought to the sacral promontory. Care must be taken to ensure that both the rectal and vaginal walls are spared. The overlying presacral fascia is opened to expose the bare periosteum of the sacral promontory. Two 0-Ethibond sutures are placed in a mattress fashion to anchor the mesh to the sacral promontory. Before suture placement, care should be taken to avoid presacral veins, the right ureter, and iliac vessels. The peritoneum is then closed over the mesh with 3-0 absorbable sutures and Lapra-Ty suture clips. Check for hemostasis.

POSSIBLE COMPLICATIONS

Recurrent prolapse

Long term recurrence of rectal prolapse after robotic surgery is about 11%-13%[19,20] and is similar to recurrence rates after laparoscopic surgery[10,21]. Recurrent rectal prolapse after standard perineal surgery is reported around 25%[22]. Should the patient develop recurrent prolapse after robotic surgery, the surgeon may again consider reattempting robotic rectopexy. Intraoperatively, the surgeon can assess why the prolapse recurred (detachment of mesh from the sacrum or rectum) and take a tailored approach in correcting it.

Mesh complications

Use of mesh rectopexy has been shown to decrease recurrence of rectal prolapse[23]. However, as with use of any foreign body, use of mesh is not completely without consequence. The literature reports an increase in mesh-related complications when synthetic mesh is used in the presence of a rectal anastomosis[24,25]. Rates of pelvic sepsis have been reported in 2%-16% cases, however these rates were observed with use of polyvinyl alcohol sponge - a type of mesh that is no longer used[26,27]. Other mesh-associated complications include mesh erosion observed in 0%-1%[27-31], fistulas, and dyspareunia[32,33].

Management of mesh complications can be difficult. Mesh erosion involving the vagina or rectum have been successfully treated with simple transvaginal or transanal excision[28,29]. Other case reports also describe laparoscopic excision and primary repair for mesh erosion involving the rectum, vagina and bladder.

Several studies have analyzed the used of biologic mesh for pelvic organ prolapse. However, there is no strong evidence favoring the use of biologic mesh *vs* synthetic mesh. Indeed, some limited reports describe higher rates of recurrence with biologic mesh[34]. When comparing synthetic *vs* biologic mesh, mesh-related complications are similar. The use of mesh rectopexy in the absence of colon resection is associated with an acceptable rate of morbidity and mortality.

Constipation

Constipation is a very common pre-existing condition among patients with rectal prolapse[35]. Constipation after rectopexy surgery can be due to kinking of the redundant rectosigmoid in patients with suture rectopexy[36] or denervation of the rectum if the lateral stalks are divided[37]. Several studies have shown decreased rates of postoperative constipation with limited rectal dissection and preservation of the lateral

rectal ligaments[28,38]. Other studies have reported decreased rates of constipation with limited posterior rectal mobilization[39]. These maneuvers may be considered for patients with a history of constipation.

Fecal incontinence

Fecal incontinence is extremely common in patients with rectal prolapse[26,40]. This may be due to sphincter injury, pudendal neuropathy, or impaired rectal adaptation to distention in patients with chronic rectal prolapse[26,41]. In patients with fecal incontinence, the abdominal approach has been shown to be more effective than the perineal approach, and has been reported to improve incontinence in more than 62% of patients in short-term follow up[42,43].

OUTCOMES OF ROBOTIC SURGERY FOR RECTAL PROLAPSE

There are limited published articles regarding robotic rectal prolapse surgery. However, in this section the available literature is reviewed.

Although published studies are consistently small, available published case-series, case-control studies, and a recently published clinical trial study reveal that robotic-assisted rectal prolapse surgery has equivalent safety compared to laparoscopic surgery[12,13,44].

The safety of the robotic approach in the treatment of rectal prolapse has been cited numerous times in the literature, even in elderly patients. Munz *et al*[15] in 2002 reported treatment of six rectal prolapse patients with robotic assisted suture rectopexy. The study reported mean procedure time of 127 min with no major complications and without any recurrence in six months[15]. In 2007, a larger case control study with 14 consecutive patients who underwent robotic treatment of pelvic organ prolapse was published[17]. The authors noted that postoperative complication rates were similar in the robotic and laparoscopic groups. However, they reported longer operative time and greater hospitalization cost for the robotic group[17]. Both studies reported robotic surgery as a feasible, safe and effective technique in the treatment of rectal prolapse[15,17]. Later Germain *et al*[19], in a study of 77 rectal prolapse patients, reported robotic-assisted rectopexy as a safe approach in patients aged over 75 years with similar results in younger patients. The authors reported a morbidity rate of 1.7% for patients older than 75 years of age[19]. A published systematic review by Rondelli and a recently published clinical trial by Mehmood *et al*[44] confirmed safety of the robotic approach in treatment of rectal prolapse[44,45].

Short term outcomes for robotic rectal prolapse seem on par with the laparoscopic and open technique. Ayav *et al*[13], with one year follow up of eighteen female patients operated on by the robotic assisted technique, reported they all remained free of rectal prolapse. Zero short term recurrence rate was also reported by Munz *et al*[15] and Germain *et al*[19]. In a recently published systematic review of 340 patients in six observed studies by Rondelli a meta-analysis showed that the robotic approach does not influence the recurrence rate of rectal prolapse[45]. However, the only available clinical trial with 12 mo follow-up reported a better functional outcome and quality of life in patients undergoing robotic surgery compared to laparoscopic surgery[44].

Although published studies are low volume studies, some major postoperative complications have been reported. Overall, a 10.4% morbidity rate has been reported for rectal prolapse patients undergoing robotic surgery[20]. Heemskerk, with a case control study, reported similar rates of postoperative constipation and incontinence in robotic and laparoscopic techniques[17]. However, the complications of urinary tract infections, pre-sacral fluid collections, rectal injuries, and post-operative hemorrhage have been reported for robotic surgery[19,20,46]. Rondelli, in a systematic review, reported a decrease in intra-operative blood loss and post-operative complications in patients who underwent robotic surgery compared to laparoscopic surgery[45]. However, Mehmood *et al*[44], in a recent clinical trial did not find any significant difference in blood loss between robotic and laparoscopic approaches[44]. Further randomized clinical trials are needed to evaluate if the robotic approach will decrease complications compared to the laparoscopic approach.

Functional outcomes for robotic rectal prolapse seem on par with laparoscopic and open techniques. de Hoog *et al*[21], with a case control study comparing the functional results among three patient groups of robotic, laparoscopic, and open approaches, found no differences in either Wexner incontinence score or IDL score (impact on daily life-score as judged by patients) between the three operation types. Similar results were reported previously by Ayav *et al*[13], Munz *et al*[15], and Heemskerk *et al*[17]. However, a recent clinical trial by Mehmood *et al*[44] reported that postoperative Wexner fecal incontinence severity index scoring were significantly lower in the robotic approach compared to the laparoscopic approach[44]. Also, they reported the SF-36 questionnaires regarding physical and emotional component had better scoring with the robotic approach compared to the laparoscopic approach[44]. Considering the limited number of published studies regarding functional outcomes, further studies should be planned to evaluate functional outcomes of patients undergoing robotic treatment of rectal prolapse.

The long-term outcomes of robotic rectal prolapse repair remain relatively unknown and there is limited published data on this topic. The only published clinical trial did not find any relapse in 12 mo follow-up of patients[44]. Other case-control and case series studies reported equal long-term rate of recurrence of rectal prolapse in robotic technique compared to laparoscopic surgery[21,47]. de Hoog *et al*[21] with a study on long-term outcomes of 20 patients who underwent robotic

and laparoscopic rectal prolapse procedures reported respectively 20% and 27% recurrence rates for robotic and laparoscopic approaches, which were significantly higher than open abdominal procedure recurrence rate in his study (2%)[21]. However, in more recent studies relapse rates of 12.8% and 11% have been reported for robotic approach[20,47]. Further studies are indicated to discover long term outcomes of robotic approach rectal prolapse surgery compared to laparoscopic and open approaches.

Robotic surgery is associated with higher hospital costs compared to laparoscopic and open techniques. Higher cost of robotic rectal prolapse surgery has been reported by multiple studies[17,20]. However, a recent study shows that after adjusting the cost with hospitalization length, the cost of robotic technique is lower than laparoscopic or open surgeries in general surgery procedures except for cholecystectomy and esophagogastric procedures[48]. Further studies comparing robotic and laparoscopic approaches regarding cost-effectiveness in rectal prolapse surgery are needed.

The length of the robotic rectopexy procedure decreases with increased experience of surgeons. Increased operative time for robot rectopexy has been reported multiple times[15,17,21,44]. A portion of this increase in time is caused by robotic instruments set-up[15]. de Hoog *et al*[21] reported the mean operation time of 157 min for robotic rectopexy, which was more than two times longer than open rectopexy. However, in a more recent study, a significant decrease in operative time with improving experience of surgeons was reported[19].

CONCLUSION

Robotic surgery is a safe, effective, and feasible approach for the treatment of rectal prolapse that does not result in any difference in recurrence and function compared to laparoscopic rectopexy. However, the benefits of a robotic approach must be weighed against its higher cost and longer operative time. Further randomized clinical trials are needed to report functional outcomes and long term outcomes of robotic surgical treatment of rectal prolapse.

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Role of ablation in the treatment of breast cancer: A review

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Abstract

Breast cancer surgical treatment has evolved from the days of the radical mastectomy to breast conservation surgery. In recent years, there has been much interest in percutaneous treatment modalities for breast cancer, instead of surgery. There are several different methods of percutaneous treatment of breast cancer. These include cryoablation, radiofrequency ablation, microwave ablation, laser ablation, and ultrasound ablation. The advantages of these techniques include an outpatient or office procedure, with local anaesthesia; minimal scarring, which is only from introducing the percutaneous instrument into the breast, instead of a surgical incision; and minimal recovery time, as the procedure does not involve surgery or general anaesthesia. Disadvantages relate mainly to pathologic evaluation, in that the true size of the breast cancer has to be estimated from the pre-procedure imaging, and all molecular profiling must be obtained from the biopsy specimen. In addition, long term patient satisfaction with cosmesis after adjuvant radiotherapy has not been studied. We review these percutaneous ablation modalities in this paper, as well as their individual techniques, associated advantages, and disadvantages. We also review current clinical trials, exploring these methods of breast cancer treatment.

Key words: Breast cancer; Cryoablation; Radiofrequency ablation; High frequency ultrasound ablation

Core tip: This paper seeks to provide updated literature on percutaneous ablation modalities in the treatment of breast cancer. We review the technical aspects and literature, including ongoing clinical trials for the following percutaneous treatment techniques: cryoablation, radiofrequency ablation, microwave ablation, laser ablation, and ultrasound ablation.

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INTRODUCTION

The treatment of breast cancer has evolved over time to include minimally invasive approaches. Earlier detection of breast cancer results in smaller lesions being detected, and thus have made them amenable to minimally invasive approaches. Several ablative modalities have emerged in recent years, which include cryoablation, radiofrequency ablation, microwave ablation, laser ablation, and ultrasound ablation. The purpose of this article is to review current clinical trials,

and past literature on various ablation techniques. Current reviews are not updated with recently completed or ongoing clinical trials[1,2].

CRYOABLATION

Cryoablation is a percutaneous technique in which a probe is inserted into the breast, and the tumor is treated through a freezing process. The benefits of cryoablation include the ability to perform the procedure in the office and with the use of local anesthesia, making it an attractive option for those patients with multiple co-morbidities. The probe is inserted through a small incision in the breast resulting in minimal scarring. Due to the fact that this is an ablative technique and does not involve removal of tissue, the cosmetic outcome is excellent.

Interestingly, there is also thought to be an immunological response to cryotherapy[3]. Cytokines are postulated to be released, and to modulate the immune response to the breast cancer. T cells are thought to stimulate cytotoxic lymphocytes and kill circulating metastatic cells. In a recent study presented at the 2014 American Society of Clinical Oncology Breast Cancer Symposium, 18 patients were divided into three study cohorts. One group was treated with cryotherapy, one with ipilimumab, a monoclonal antibody, and the final group with both cryotherapy and ipilimumab. T-cell tumor lymphocyte infiltrating density was assessed in each of these patients, and ranged from 2%-30%. Systemic immune response was measured by elevations in plasma interferon gamma, and a marker of CD 4 T cells. A greater than two times increased response in these two markers was considered positive. There were elevations in the group that received both the cryoablation and the ipilimumab, although two patients who received the ipilimumab alone also had elevated immune responses[4]. The author concluded that further studies with larger numbers are necessary to evaluate this finding, but it reinforces the idea that there is a clear systemic immune response to cryoablation.

Established criteria for treatment of breast cancers with ablation techniques are still evolving. A national phase Ⅱ clinical trial is still underway, evaluating cryoablation in the treatment of early stage breast cancers. Criteria for cryoablation of breast cancers include tumors less than 2 cm, unifocal cancers, and the absence of a significant intraductal component[5,6].

Initial research of cryoablation in the treatment of breast cancer involved cryoablation followed by excision of the cancer in a multi-institutional phase Ⅰ pilot study[5]. This study examined twenty-nine patients with invasive breast cancer. All the patients had tumors less than or equal to 2 cm. Twenty seven patients underwent cryoablation of their tumors, followed by surgical resection 4-6 wk later, consisting of either partial mastectomy (breast conservation) or mastectomy. The median age in this study was 52.5 years, with a range of 34-77 years old.

When the specimens were evaluated by the pathologists, 23 patients out of 27 patients had no evidence of invasive cancer. Four patients had residual DCIS surrounding the ablative zone. The study concluded that the size of the cancer was an important factor in terms of residual disease. There was no residual disease found in the eleven patients in the study who had tumors less than 1 cm. Sixteen patients had tumor less than 1 cm, and of these, 10 patients had no residual cancer. In three out of the five patients with either invasive lobular cancer or colloid cancer, there was residual invasive cancer. The size of the cancer was found to be larger on final pathologic evaluation than the original size estimated by preoperative imaging in these cases. With these findings, a phase Ⅱ study was recommended eliminating surgical excision. The criteria for inclusion were size of tumor less than or equal to 1.5 cm and those patients with less than 25% DCIS on the biopsy specimen. Additionally, the study concluded that those patients with a significant non-calcified DCIS component should be excluded from treatment with cryoablation.

Subsequently, a multicenter phase Ⅱ trial, ACOSOG Z-1072, has been completed. This study evaluated the use of cryotherapy in early stage breast cancer. Inclusion criteria included invasive breast cancers less than or equal to 2 cm. The study sought to evaluate the overall efficacy of cryoablation in invasive breast cancer, as well as to assess how well magnetic resonance imaging (MRI) can identify residual cancer after ablation[7]. Patients underwent cryoablation, followed by a contrast enhanced MRI within 2 wk, followed by surgery. Radiation and appropriate adjuvant systemic therapy were given according to standard clinical practice. Eighty-seven cancers were treated in this trial. Sixty (70.9%) showed no residual cancer, while 27 (31%) had residual DCIS or early stage breast cancer. 100% of patients with tumors less than 1 cm in size treated with cryoablation had no residual invasive cancer on pathologic examination of the specimen[7]. MRI showed no enhancement in 66 breasts, (75.9%). Interestingly, there were 21 (24.1%) failures, defined as residual invasive cancer and or DCIS, with no MRI enhancement after ablation.

In a study examining the efficacy of cryoablation without excision, Littrup *et al*[8] examined 11 patients, who had previously refused surgery. The patients had stage 1 to stage 4 breast cancers, and had 22 different foci of breast cancer. Tumor size ranged from 0.5 cm to 5.8 cm. The average age was 62.5 years old. The authors did not find any local complications to the skin or chest wall. Five of the patients who were included in the study had recurrent breast cancer. At a mean follow-up time of 18 mo, there were no local recurrences. Pain after the procedure was also evaluated. The mean pain scale rating was 0.3 on a scale of 0-10 at 24 h. Successful tumor treatment was measured by 1 cm of ice beyond the tumor. This was assessed using a combination of ultrasound, computed tomography, and

MRI imaging modalities, which was observed in all of the patients.

A national multicenter, clinical trial evaluating cryoablation without subsequent excision, is beginning to enroll patients. This trial is evaluating cryoablation in luminal a breast cancers, without excision, in women 65 years old or greater. This trial is predicated on the ACOSOG Z1072 trial, with the exception that the cancers are not subsequently excised. Adjuvant treatment is at the discretion of the treating physician. Local recurrence rates and disease free survival are being evaluated, as well as quality of life. This should provide important information as to the use of cryoablation alone in the treatment of breast cancer.

In summary, the current clinical trial evaluating luminal A breast cancers treated with cryoablation only, should provide important information about recurrence rates with this modality.

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) is another percutaneous tumor ablation modality, which utilizes heat to produce an area of cell death[9]. Advantages of the technique are the same as the other ablation techniques, including an office based procedure. Disadvantages of the technique are the pain associated with it. In a pilot study of seventeen patients, RFA and then excision was performed on invasive breast cancers that measured less than or equal to 1.5 cm[10]. Of the fifteen patients who ultimately completed the trial, three patients had positive margins. One patient had a tumor that was completely missed by the RFA. Similarly, Fornage *et al*[11] found that out of 21 patients who underwent RFA and then surgical excision, one patient had residual tumor beyond the zone of ablation. However, this patient initially had a 4 cm lesion, and underwent neoadjuvant chemotherapy. The authors concluded that patients who received neoadjuvant chemotherapy were not eligible for RFA.

Radiofrequency ablation has also been used to create an additional area of tumor sterilization, in a phase Ⅱ clinical trial, after local excision[12]. This study sought to examine whether radiofrequency ablation could reduce the rate of re-excisions for close margins, to possibly provide adequate local control, and obviate the need for adjuvant radiotherapy. One hundred patients were included in this study, with tumor sizes ranging from Tis to T3. Seventy-eight patients had margins that were considered negative, which was defined as a margin less than 2 mm. Twenty-two patients had margins which were less than or equal to 2 mm. Twelve of these patients had close margins, and three had focally positive margins. Seven patients underwent mastectomy for positive margins, and 2 patients subsequently chose mastectomy electively after RFA. Sixty-eight percent of all patients in the study with close or positive margins did not have re-excisions. Of the 100 patients, 24 patients underwent adjuvant radiotherapy. In the subset of patients who did not receive adjuvant radiotherapy, the mean follow-up was 62 mo ± 24 mo. During this time there were 2 recurrences near the tumor bed; two recurrences in a separate location in the same breast; and three recurrences along the biopsy track. The study also examined five year disease free survival and overall survival, which were 88% and 93%, respectively. Interestingly, the disease free and overall survival with adjuvant radiotherapy was 83%. The authors concluded that this is a safe method of treatment of small breast cancers.

In a prospective study, fourteen patients with invasive ductal carcinoma were treated with RFA and sentinel node biopsy. Breast MRI was performed 1 wk prior to RFA, and then 3 wk afterwards[13]. The goal of the study was to assess for residual lesions. The tumors were surgically excised one week after RFA. Five patients had areas of enhancement on post-RFA MRI, which was irregular. In two patients, enhancement of the initial lesion was noted, which signified failure of the RFA to ablate the cancer. Seven patients had no enhancement on post-RFA MRI. Interestingly, the patients with larger tumors had complete ablation, and no residual enhancement on post-RFA MRI. The authors concluded that breast MRI is able to detect residual abnormalities after RFA.

In summary, longer follow-up of patients treated with RFA is needed to assess for recurrence rates and for the appropriate imaging modality used for follow-up, but it holds promise as a minimally invasive treatment for breast cancer, possibly obviating the need for surgery.

MICROWAVE ABLATION

Microwave ablation is an additional percutaneous modality for treatment of breast cancer. Heat is made *via* tissue water agitation, achieved by electromagnetic frequencies of 900-2450 MHz[14]. Advantages of this technique are similar to other ablation techniques and include ability to treat lesions using local anaesthesia and good cosmetic outcomes. In a pilot study of 41 patients, Zhou *et al*[14] performed microwave ablation for breast cancers less than or equal 3 cm, followed by mastectomy. Eligibility criteria for the study included a unifocal tumor, with at least one centimeter between the skin and the tumor, and the tumor and the pectoralis muscle, as well as a limited intraductal component. The mean age of the patients was 55.5 years old. All of the patients had either invasive ductal carcinoma or DCIS. The pathologic analysis showed that 37 out of 41 cases were successfully ablated, when analyzed using alpha-NADH-diaphorase staining. There were 3 injuries to the skin and pectoralis muscle secondary to heat. The authors concluded that in small, unifocal cancers, microwave ablation may be a feasible option. However, since mastectomies were performed in all of the patients, there is no data from

this study on recurrence rates. Additionally, patients in this study underwent general anesthesia, so patient tolerance of the procedure was not assessed. Further studies are needed in larger groups of patients to determine patient tolerance and recurrence rates.

LASER ABLATION

Laser ablation is an additional percutaneous technique in which light is delivered into the tissue[15]. It has been evaluated mainly in terms of patient safety in various pilot studies. In a meta-analysis, Zhao *et al*[2] found a 13%-70% complete ablation rate of breast cancer utilizing laser ablation in the literature[1]. Dowlatshahi *et al*[16] studied 54 patients with invasive breast cancer. Median age was 60 years old, with a range of 42-80. The mean tumor size was 12 mm. Fifty patients had an invasive breast cancer, and four patients had DCIS. They were all treated with laser ablation, followed by standard surgical resection, 1 to 8 wk afterwards. The study found that the complete ablation rate was 70%. The authors concluded that it was feasible and appropriate to ablate breast cancers that were mammographically detected.

An additional study of laser ablation evaluated fourteen patients who were treated with laser ablation instead of surgery[17]. Three patients had stage 4 disease, and the treatment was for palliative therapy. Local control was demonstrated in five patients, with a disease free survival of 19-60 mo, in those patients without evidence of metastatic disease. The authors concluded that laser ablation was feasible for tumors less than 2 cm, with ductal histology, without exensive intraductal components, and vascular invasion. One patient had a skin burn, and one had a localized pneumothorax. Further large scale studies are needed to evaluate the local control rates, as well as complication rates.

HIGH INTENSITY FOCUSED ULTRASOUND ABLATION

High intensity focused ultrasound (HIFU) ablation differs from other ablation techniques in that it does not employ an incision in the skin or insertion of a probe into the breast for treatment. There is very limited data about the use of high frequency ultrasound ablation in breast cancer. In a phase Ⅱ randomized trial of HIFU ablation and breast cancer, 23 patients underwent HIFU ablation, with a mean tumor size of 3.1 cm[18]. All of the patients underwent HIFU ablation, followed by modified radical mastectomies. Complete ablation was demonstrated in 100% of patients. Small skin burns occurred in one patient. In a phase Ⅲ trial, 22 patients with breast cancer underwent HIFU ablation, followed by standard adjuvant therapy[18]. The study found that the recurrence free survival rate was 89%, and the five year disease free survival rate was 95%. The authors concluded that HIFU could be safe and feasible in the treatment of localized breast cancer, but that further clinical trials are needed.

In a study of 22 patients, with 23 breast cancers, 100% of post-procedural biopsies showed necrosis of the entire tumor[19]. Follow-up over 55 mo showed a 9% local recurrence rate, with one death. The five year disease free survival rate was 95%. Overall, larger numbers of patients need to be studied in order to determine the clinical use of this modality.

CONCLUSION

In summary, various modalities exist for the percutaneous treatment of breast cancer, which hold promise for the minimally invasive treatment approach for breast cancer. Larger clinical trials are needed for wide-spread applicability of these treatments to more advanced stage patients. Current clinical trials include the use of cryoablation without subsequent excision in the treatment of early stage breast cancers. Advantages of ablative techniques include percutaneous technique, minimal scarring, and an office procedure, thus avoiding taking the patient to the operating room. Disadvantages include inability to assess margin width and estimate of staging of breast cancer only by imaging. Additionally, hormone receptor status must be assessed on preoperative biopsy. Additional concerns include long term patient satisfaction with cosmesis, especially after adjuvant radiation, as percutaneous ablation modalities do not obviate the need for radiation, as well as other adjuvant treatment. As further research accumulates, ablation modalities may play a significant role in the future treatment of breast cancer.

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MINIREVIEWS

Cordotomy procedures for cancer pain: A discussion of surgical procedures and a review of the literature

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Abstract

Treating pain in patients with terminal cancer is challenging but essential part of their care. Most patients can be managed with pharmacological options but for some these pain control methods are inadequate. Ablative spinal procedures offer an alternative method of pain control for cancer patients with a terminal diagnosis that are failing to have their pain controlled sufficiently by other methods. This paper provides a review of ablative spinal procedures for control of cancer pain. Patient selection, surgical methods, outcomes and complications are discussed in detail for cordotomy, dorsal root entry zone (DREZ) lesioning and midline myelotomy. Cordotomy is primarily done by a percutaneous method and it is best suited for patients with unilateral somatic limb and trunk pain such as due to sarcoma. Possible complications include unilateral weakness possibly respiratory abnormalities. Approximately 90% of patients have significant immediate pain relief following percutaneous cordotomy but increasing portions of patients have pain recurrence as the follow-up period increases beyond one year. The DREZ lesion procedure is best suited to patients with plexus invasion due to malignancy and pain confined to one limb. Possible complications of DREZ procedures include hemiparesis and decreased proprioception. Midline myelotomy is best suited for bilateral abdominal, pelvic or lower extremity pain. Division of the commissure is necessary to address bilateral lower extremity pain. This procedure is relatively rare but published case series demonstrate satisfactory pain control for over half of the patients undergoing the procedure. Possible complications include bilateral lower extremity weakness and diminished proprioception below the lesion level. Unlike cordotomy and DREZ this procedure offers visceral pain control as opposed to only somatic pain control. Ablative spinal procedures offer pain control for terminal cancer patients that are not able to managed medically. This paper provides an in depth review of these procedures with the hope of improving education regarding these underutilized procedures.

Key words: Cordotomy; Cancer pain; Dorsal root entry zone; Percutaneous cordotomy; Midline myelotomy

Core tip: Pain is a significant symptom that degrades the quality of life for terminally ill cancer patients. For many terminally ill oncology patients medical management is sufficient. However, some patient's will fail medical management or have unwanted side effects from their

medical regimen. Patient's failing medical management may warrant consideration for interventional procedures such as cordotomy, dorsal root entry zone or midline myelotomy. Of these three procedures only midline myelotomy can address visceral pain, the others are best suited to somatic pain. This review discusses surgical anatomy, patient selection and surgical nuances of these techniques.

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INTRODUCTION

Pain is a common problem for cancer patients and may significantly degrade their quality of life. Most commonly management for these patients includes medical therapies such as opiates, steroids and NSAIDs. For bony metastases radiation can alleviate pain. However, some cancer patients will have pain that fails medical management. In these patients, particularly those with progressive disease and a terminal prognosis, ablative neurosurgical procedures can be considered. The spinal cord is central to the pain pathway and ablative spinal procedures are a logical choice for cancer patients with severe pain that has failed other therapies[1].

In 1912 Spiller *et al*[2] first described cordotomy, division of the anterior spinothalmic tracts in the treatment of pain. As initially described cordotomy was an open procedure. Later advancement in fluoroscopy and electrical monitoring made percutaneous cordotomy possible[3]. At some centers cordotomy is now performed in a CT guided fashion[4].

Lesioning of the dorsal root entry zone (DREZ), is another ablative spinal procedure that can be used in cancer patients. This procedure was first described by Sindou *et al*[5] in the 1970s. Nashold *et al*[6] went on to modify the procedure and recommend its use deafferentation pain associated with brachial plexus avulsion[5,6]. Now the DREZ procedure can be employed for pain control in cancer patients with inoperable upper thoracic tumors compressing the brachial plexus, such as Pancoast tumors[7].

Several authors including Mansuy *et al*[8], Gildenberg *et al*[9] and Nauta *et al*[10] have discussed midline myelotomy with or without commissurotomy[8-10]. Mansuy *et al*[8] first noted visceral pain relief despite limited division of the anterior commissure of the spinal cord. This led to anatomical studies that demonstrated visceral pain pathways in the deep dorsal columns close to the midline. Subsequent modifications of the procedure resulted in limited myelotomy sparing the anterior commissure and interrupting ascending pathways, deep in the dorsal columns close to the midline, that conduct visceral pain information[11].

This article will review the various ablative spinal procedures for control of cancer pain. Spinal anatomy and physiology as it relates to pain will be reviewed. After this foundation, a discussion of patient and procedure selection will follow. Each ablative procedure type will be discussed along with the relevant literature. At the conclusion the reader should understand ablative spinal procedures and their role in treating cancer pain.

ANATOMY OF THE PAIN PATHWAY

Appropriate diagnosis and management of pain, as with many other neurological problems, depends upon localizing the lesion. Therefore to employ ablative spinal procedures in the management of pain a thorough understanding of the pain generation and conduction is necessary. Numerous sources are available that provide a detailed discussion of spinal cord anatomy[12,13]. The following description the focus will be on the anatomy of the pain pathway and surgically relevant surrounding structures. One method of reviewing the anatomy of the pain pathway is to proceed in an anatomic order. Beginning with the first order neuron, such as the spinal ganglion, and then progress sequentially to the terminal cortical neuron in the pathway. Bearing in mind this variability a discussion of the anatomical principals of pain transmission follows.

The pain pathway generally starts with effectors, such as bare nerve endings, Paccinian corpuscles, muscle spindles, *etc.*, communicating through various nerve fiber types as sensory information flows towards the dorsal root ganglion. First order neurons for pain perception lie in the dorsal root ganglion. For the pathway conducting pain and temperature these first order neurons synapse with second order neurons in the dorsal horn in Rexed lamina Ⅰ-Ⅴ[14]. Most of the first order nociceptive fibers from the dorsal root ganglion synapse in the lamina at the entering level however a portion of the fibers travel rostrally or caudally in Lissauer's tract. First order neurons responsible for proprioception enter the dorsal root entry zone travelling along the medial aspect of the dorsal root and travel in the posterior columns to synapse in the Nucleus Gracilis or Nucleus Cuneatus for the lower and upper extremities respectively. Figure 1 demonstrates the basic architecture of the first order neurons as they relate to the dorsal root ganglion[15,16].

Second order neurons from the Rexed lamina Ⅰ-Ⅴ project through the spinal cord carrying nociceptive information. The majority of axons project through the anterior commissure of the spinal cord to the contralateral spinothalamic tract (STT). The STT is located in the anterolateral quadrant of the spinal cord just anterior to the corticospinal tract and lateral to the diaphragmatic reticulospinal tract. The STT ascends and projections are given off, in a caudal to rostral fashion, to the: nucleus raphes magnus, gigantocellular

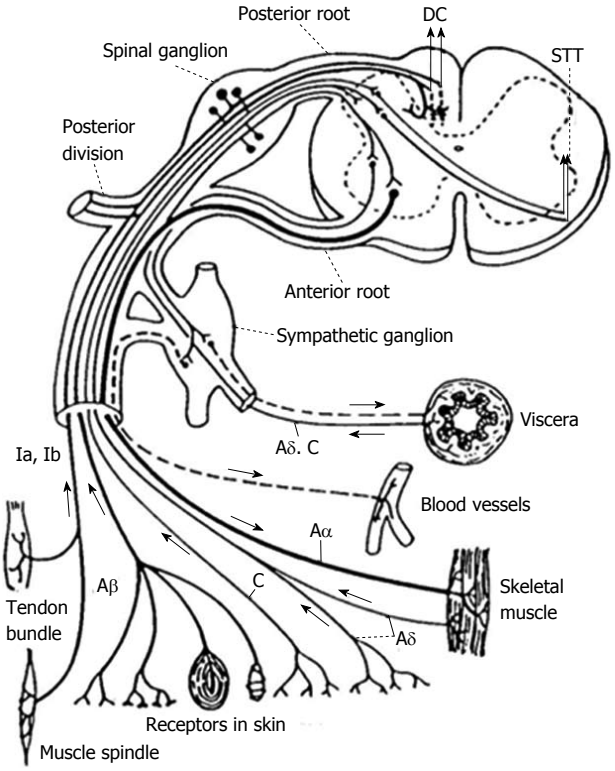
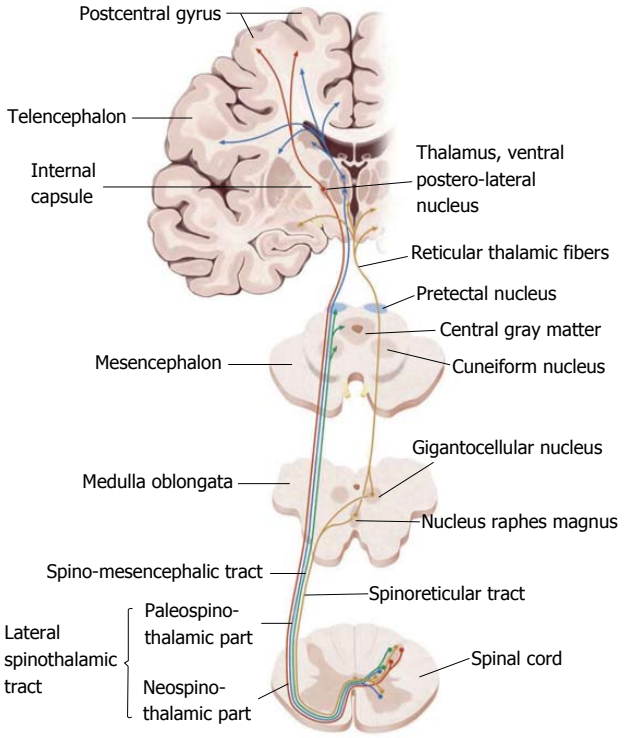


Figure 1 Peripheral and central spinal pathways. Aδ: Large myelinated afferent fiber. Type A fibers don't conduct nociception. C fibers are small unmyelinated fibers that conduct nociception. Ia and Ib fibers conduct information from muscle spindles and Golgi tendon organs, respectively. DC: Dorsal columns; STT: Spinothalamic tract.



C Ascending pain pathways from the trunk and limbs

Illustrator: Markus Voll pp. 332-333 Thieme
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Figure 2 The relationship between ascending pain afferents and their targets in the medulla, midbrain, thalamus and cortex.

magnus, cuneiform nucleus, periaqueductal gray and the pretectal nucleus. Finally the STT terminates in the ventral postero-lateral nucleus of the thalamus. From there third order neurons project to the sensory cortex where conscious pain is processed. Figure 2 summarizes the path of the second and third order neurons[17-19].

As noted in the introduction observations regarding visceral pain control following midline myelotomy with minimal commissurotomy suggested visceral pain afferent tracts in the midline at the depth of the dorsal columns. Animal studies performed by Willis demonstrated the existence of the deep dorsal column visceral pain pathways[20]. Midline myelotomy became recognized as a method for controlling intractable visceral bilateral abdominal or pelvic pain[10,11].

In addition to describing pain pathways it is useful to discuss structures with close anatomical relationship with the areas of the pain pathway. Some of the structures surrounding the pain pathways risk inadvertent injury if spinal anatomy isn't properly understood. Figure 3 demonstrates many of the important anatomical relationships of the STT in the high cervical region and the underlying somatotopy as well. Initially one should note the location of the STT in the anterolateral quadrant of the cord is just anterior to the corticospinal tract and that the STT lies anterior to the dentate ligament. Lesions deviating too posteriorly may result in hemiparesis or loss of bowel control. Lesions excessively medial can damage respiratory interneurons in the diaphragmatic reticulospinal tract leading to respiratory complications. Finally in the case of the midline myelotomy or commissurotomy it must be remembered that the anterior spinal artery, the primary blood supply for the majority of the spinal cord lies just anterior by millimeters, so care must be taken to preserve this vascular structure[3,21].

PATIENT SELECTION

With an understanding of the anatomy and physiology of the pain pathways we are now prepared to discuss patient and procedure selection. Patients selected for ablative spinal procedures must have a medically refractory malignant pain syndrome and a life expectancy of a few years or less. Additionally, the location of the malignant pain must be conduced through the pain pathway in a circuit that allows safe surgical lesioning. Malignant pain is necessitated because pain treated by ablative spinal procedures has a high rate of recurrence in patients with non-malignant pain. The pain previously treated by the lesion may recur or a new central neuropathic pain, typified by dysthesias, may result below the level of the lesion. For a satisfactory result

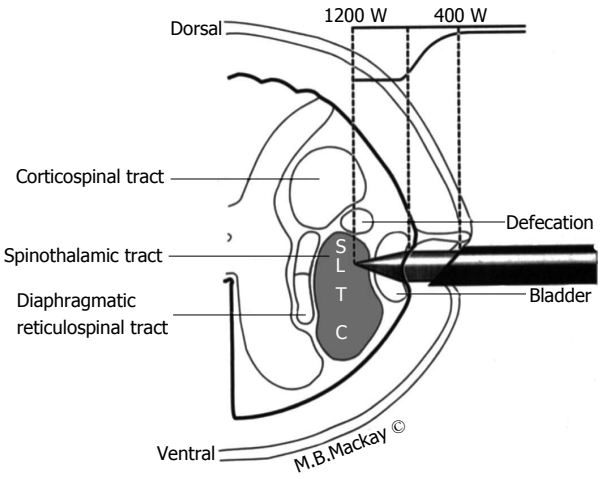

Figure 3 A schematic illustration of percutaneous cordotomy and the relative anatomical position of the spinothalamic tract and surrounding structures. S: Sacral; L: Lumbar; T: Thoracic; C: Cervical; W: Watts.

the duration of time before the pain recurrence, or the onset of neuropathic pain, must be longer than the life span of the patient. Therefore, patients with cancer and a remaining lifespan of a few years or less are best suited to ablative spinal procedures[3,22].

Appropriate patient selection also depends on pain location, namely is the pain located in a region such that the corresponding pain pathway is amenable to surgical interruption while maintaining an acceptable side effect profile. Patient and procedure selection are inextricably linked, therefore it is useful organize patient and procedure selection together.

Cordotomy

Open, or more commonly in recent years percutaneous, cordotomy is best suited for patients with malignant unilateral limb, pelvis or trunk pain. Cordotomy involves lesioning of the STT, nociception below the level of the lesion is interrupted. The side effects of this procedure include numbness and dysthesias below the level of the lesion. However, this may be an acceptable trade off in cancer patients suffering from severe medically intractable pain. Bilateral cordotomy procedures generally are not an option particularly in the high cervical region[23,24]. This is because respiratory interneurons lie just medial to the STT and if damaged bilaterally may result in respiratory depression. Unilateral limb pain due to brachial plexus avulsion is not a good option for treatment by cordotomy because patients often find the resulting dysthesias unacceptable and the pain can recur or new central neuropathic pain can occur due to the patient's lifespan. Generally satisfactory pain control begins 3 or 4 levels below the level of the cordotomy lesion due to the presence of Lissauer's tract conducting pain fibers rostrally before they cross over to join the STT[3,21].

DREZ

The dorsal root entry zone ablation alternatively known as the DREZ procedure is often considered for patients that suffer from pain due to brachial plexus avulsion. Other patients appropriate for the DREZ procedure include cancer patients suffering from medically intractable pain from tumors invading the brachial plexus, also known as Pancoast tumors, or for patients with spinal cord injury suffering from pain at the level of their injury. Unfortunately, DREZ is not generally helpful for patients with constant burning pain or limb pain associated with shoulder or pelvic pain[23,25,26].

Midline myelotomy or commisurotomy

Commissurotomy lesions the anterior commissure of the spinal cord and therefore interrupts nociceptive signals for several levels in the vicinity of the lesion. This procedure is useful in controlling malignant bilateral abdominal, pelvic or lower extremity pain. It represents a reasonable alternative to bilateral cordotomy. Generally the commissure is ablated in the conus to T10 region. Loss of proprioception can occur due to damage of the posterior columns as they are splayed apart during the course of the procedure. Care must also be taken to avoid the anterior spinal artery since it lies only millimeters away from the commissure[27].

Midline myelotomy with or without commissurotomy may also offer control of bilateral abdominal, pelvic or lower extremity pain. Lesioning of the posterior columns, particularly in the deep medial region, was noted to reduce visceral pain in addition to providing the predicted bilateral somatic pain control. These observations coupled with animal data that indicated a visceral pain pathway located deep in the posterior columns at the midline led to greater use of midline myelotomy without commissurotomy. Gildenerg and Hirshberg have even proposed limited midline myelotomy for the treatment of visceral pain[9,10].

At this point it is important to emphasize that in most cases visceral pain also travels through the sympathetic chain and through cranial nerves. This is a key concept. In general with the exception of the above mentioned midline myelotomy, ablative spinal procedures are best suited for controlling somatic cancer related pain, such as that from an extremity sarcoma, because somatic pain fibers travel exclusively through the spinal cord. Ablative spinal procedures in most cases do not effectively interrupt all pathways for visceral pain because this sensory modality is conducted through cranial nerves and the sympathetic chain in addition to the deep midline posterior column tracts. Figure 1 for an illustration of this concept[10,20,23].

SURGICAL NUANCES

Generally the patients being treated with ablative spinal cord procedures should have preoperative spinal imaging such as MRI of the spine in the area of interest or CT myelography in the area of interest. Such imaging can elucidate any relevant anatomical variations such as local metastases syringomyelia,

spinal deformity or in the case of brachial plexus avulsions, pseudomeningoceles[14]. Consultation with the patient's oncologist regarding goals of care, overall health condition and prognosis is also necessary. In the immediate preoperative and postoperative period some practitioners advocate corticosteroids, such as dexamethasone 4-6 mg every 6 h, to reduce spinal cord edema.

Open cordotomy

The patient is positioned prone. A hemi laminotomy or a full laminectomy is performed to allow access to the spinal cord contralateral to the pain symptoms at a spinal level 3-4 segments above the level of the symptoms. If possible one generally performs a laminotomy or partial laminectomy to reduce the risk of post laminectomy kyphosis. In chosing the level for the lesion it is important to note how the correspondence between spinal level and vertebral level. In the cervical cord the spinal level corresponds closely to the vertebral level. As one transitions more caudally the spinal and vertebral levels become progressively more discordant such that the sacral and coccygeal levels lie at the conus which generally terminates at L1. Once the lamina has be opened at the appropriate level the dura and arachnoid can be opened and tacked up. The dentate ligament is separated from the dura and used to rotate the spinal cord slightly to bring the anterolateral quadrant into better view. A Weck blade placed at a right angle in a Ryder needle driver is then used to divide the anterolateral quadrant of the spinal cord to a depth of 3-4 mm. An angled dissector is then swept through the same cut. The dura is closed in a water tight fashion and the fascia and skin are closed in the usual fashion[2,21,22].

In addition to the usual concerns for infection and CSF leak some complications specific to open cordotomy include: hemiparesis (usually transient occurs in 10%-30%), respiratory depression (particularly in cervical cordotomies), mirror pain (usually in thoracic cordotomies), and urinary disturbances. The complication rate for open cordotomy is on the order of 5%-10%, but for patients in debilitating medically recalcitrant pain this may be an appropriate trade off. In approximately 50% of patients undergoing this procedure the pain relief will be total and immediate. Approximately 25% will have immediate partial pain relief and the remainder will have no improvement in pain. Review of large case series indicates that some patients will have recurrence of pain if they survive to 1 year or longer[21,22,28].

Percutaneous cordotomy

With the advent of improved fluoroscopic equipment and the availability of radiofrequency ablation percutaneous cordotomy became more common than open cordotomy. Unlike open cordotomy, and the other procedures discussed here, percutaneous cordotomy can be performed without general anesthesia and this is a significant advantage in the cancer population since many of these patients have significant comorbidities. The percutaneous cordotomy also allows the practioner to perform a test lesion and this may improve the success of the procedure compared to open cordotomy[3].

The patient is placed supine in a fluoroscopy suite with the head immobilized and light sedation administered. Some local anesthetic is infiltrated to ease the orthogonal passage of the needle into the C1-2 interspace under fluoroscopic guidance (CT guidance has also been described). Injection of water-soluble, contrast such as Omnipaque, is used to verify that the needle is positioned 1-2 mm anterior to the dentate ligament. Figure 3 provides an anatomical schematic of the percutaneous cordotomy procedure. The needle is then advanced into the anterolateral quadrant of the spinal cord. At this point a change in impedence from approximately 300 Ohms to approximately 1000 Ohms will be detected and this verifies entry into the spinal parenchyma. Low frequency (approximately 3 Hz) electrical stimulation with the needle will demonstrate twitching of the ipsilateral neck if the needle position is close to the anterior rootlets. If low frequency electrical stimulation causes limb or trunk contraction this means the needle is too close to the corticospinal tract and should be repositioned. High frequency stimulation (approximately 100 Hz) should produce contralateral sensory phenomenon that corresponds to the area of desired pain control. This verifies an appropriate needle position. If the patient has ipsilateral arm or head paresthesias this means the needle is too posterior. Once appropriate needle position is determined using stimulation and patient exam it is time to create the lesion. This is done using an electrode with 2 mm of exposed tip. Heating the electrode to a temperature of 70 ℃-80 ℃ for one minute creates the lesion. The patient is examined to verify analgesia and to evaluate for reduced pinprick sensation in the area of intended pain control[3,4,23].

Respiratory depression is the most feared complication of percutaneous cordotomy but this is only a concern in bilateral procedures. The complication rate is on the order of 5% and the types of complication described are similar to those noted in open cordotomy: bladder dysfunction, temporary hemiparesis, respiratory abnormality and ataxia. Immediate pain relief following the lesion is reported to be as high as 90%. This improved success rate compared to open cordotomy may be attributable to the fact that physiological testing and patient participation is available for guidance of the lesion since the patient is awake. At 1 year only about half of the patients continue to have pain relief, once again verifying that patients must be suffering from a terminal disease to be an ideal candidate for cordotomy[3,4,23].

DREZ

The Dorsal Root Entry Zone or DREZ procedure is useful for malignant pain where the plexus is invaded by cancer

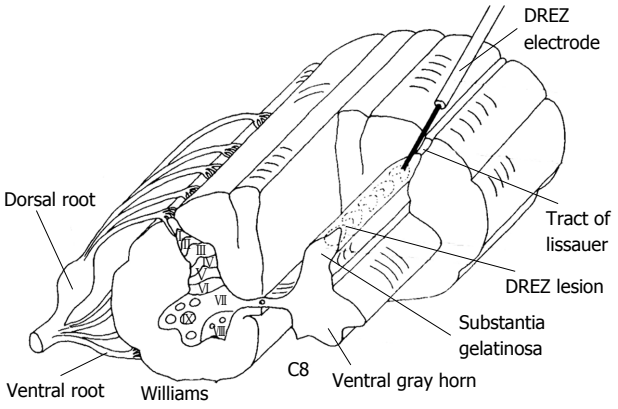

Figure 4 A schematic illustrating dorsal root entry zone lesioning at the C8 spinal level. Rexed lamina are numbered in the typical fashion Ⅰ-XIII. DREZ: Dorsal root entry zone.

and the pain is confined to a limb. This procedure is also useful for treating pain associated with brachial plexus avulsion or for segmental pain at the level of spinal cord injury. Similar to the open cordotomy discussion, the procedure begins with the patient in the prone position. Laminectomy or laminotomy is performed to expose the appropriate levels. In the case of the brachial plexus the laminectomy usually extends from C4-T1 and for conus lesioning the laminectomy is usually from T10 to L2. Some may desire to perform laminoplasty with the hope of reducing post laminectomy kyphosis and to make subsequent operative exposures easier. The dura and arachnoid are opened and tacked up. Next the dorsolateral sulcus of the spinal cord is located; this is where the dorsal roots enter. A Nashold DREZ electrode, with a 2 mm exposed tip is used to created successive lesions by heating the electrode tip to 75 ℃ for approximately 20 s. The ideal entry point of the electrode is just lateral to the point where roots enter because this also provides for lesioning of Lissauer's tract. Figure 4 provides a schematic of DREZ lesioning using a radiofrequency probe. An effort should be made to sharply puncture the pia with the electrode to prevent deformation that comes with bluntly pushing the electrode. Somatosensory evoked potential monitoring and motor evoked potential monitoring may provide warning signs if adjacent corticospinal or dorsal column tracts are being damaged. A typical DREZ lesioning case may require approximately 50 radiofrequency lesions and span approximately 4 spinal levels. Lesioning for DREZ should encompass 2 levels above the level of pain to be treated to assure that Lissauer's tract containing non-crossing ipsilateral first order fibers have been interrupted. The surgeon should also keep in mind the shifting orientation of the dorsal horn of the spinal gray matter relative to the sagittal plane. In the cervical spine the dorsal horn of gray matter is 30 degrees off sagittal while in the thoracic spine it is 20 degrees off sagittal. As an alternative to using radiofrequency lesioning for DREZ other have proposed incising the pia and using bipolar coagulation under microscope visualization[23,25,26].

Complications of DREZ include damage to the adjacent corticospinal tract leading to hemiparesis or damage to the dorsal columns causing decreased proprioception and light touch. Hemiparesis seems to be more common in patients undergoing thoracic DREZ. This is thought to be due to the narrower dorsal horn of grey matter in this region. Hemiparesis and loss of proprioception is reported in approximately 10% and 50% respectively. The best results for pain control with DREZ are reported in patients with brachial plexus avulsion pain. Relatively little data is available regarding the efficacy of DREZ procedures in patients with malignant pain due to brachial plexus or lumbar plexus invasion by cancer[23,26,29].

Midline myelotomy/commissurotomy

Commissurotomy and midline myelotomy procedures are aimed at treating patients with bilateral abdominal, pelvic or lower extremity pain. Exposure for midline myelotomy/comissurotomy is identical to that described in the open cordotomy or DREZ section. The patient is positioned prone. Midline laminectomy is preformed. The dura and arachnoid are opened and tacked up. Generally levels between T10 and L1 are targeted to provide bilateral abdominal, pelvic or lower extremity pain. The operating microscope is brought into the field after the dura is opened. Dissection is carried out between the dorsal columns in the posterior median sulcas. When the depth is reached an arachnoid knife is used along with fine micro-tipped bipolars to divide the gray matter and the anterior commissure until the pia of the anterior median sulcas is reached. Here care must be taken to avoid injury of the anterior spinal artery. Gildenberg and Hirshberg have also advocated midline myelotomy where a deep medial portion of the dorsal columns is lesioned while sparing the anterior commissure[9]. Nauta further modified this procedure to a confined transverse midline lesion. These procedures seem to serve the function of controlling bilateral visceral pain beginning 2-3 levels below the lesion level[10]. Following the myelotomy the dura and the other tissues are closed in a typical fashion. Complications of the procedure include decreased proprioception and bilateral lower extremity weakness (this occurs in approximately 25%). While the proprioceptive difficulties are well tolerated the lower extremity weakness can represent a significant morbidity. This re-enforces the concept that this procedure is best suited to patients suffering from severe, recalcitrant pelvic or abdominal pain secondary to cancer. To obtain pain relief in the bilateral lower extremities it appears to be necessary to section the commissure while for visceral pain relief midline myelotomy alone seems to be sufficient. This procedure is relatively rare and there are not extensive reports of outcomes. However, it appears that pain relief is excellent in over half of the cases in published

series[8,10,11,20,27].

CONCLUSION

Despite improved pharmacological therapies some terminal cancer patients suffer from severe recalcitrant pain that greatly degrades their quality of life in their final months. With a detailed understanding of the anatomy and physiology of the pain pathway several ablative spinal procedures have been developed that offer a much-needed option for pain relief in this terminally ill population. Cordotomy which can be performed in an open or percutaneous fashion, offers excellent pain relief for patients suffering from unilateral somatic limb or trunk pain secondary to malignancy. The side effect profile for this procedure is favorable but includes transient weakness or occasionally painful dysthesias. The DREZ procedure offers a pain relief for cancer patients suffering from unilateral limb pain, particularly that caused by brachial plexus invasion. Possible complications of DREZ include transient weakness and decreased proprioception. Midline myelotomy is the least commonly performed ablative spinal procedure for pain. This procedure may include lesioning of the deep medial dorsal columns and/or sectioning of the anterior commissure. Midline myelotomy is best suited for patients suffering from a terminal cancer producing bilateral pelvic, abdominal or lower extremity pain. Section of the anterior spinal commissure is necessary if pain control in the bilateral lower extremities is desired. This procedure differs from DREZ and cordotomy because it offers control of visceral as opposed to just somatic pain. The review presented here discusses ablative spinal procedures for cancer pain including patient selection, surgical technique, complications and outcomes. We hope that this will provide needed education on the subject of these underutilized procedures that can provide much needed pain relief to cancer patients in their final days.

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Ileo-anal pouch excision: A review of indications and outcomes

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Abstract

Restorative proctocolectomy (RP) is the surgical treatment of choice for ulcerative colitis (UC) and patients with familial adenomatous polyposis (FAP). A devastating complication for both patient and surgeon is failure of the pouch that requires excision. There is currently no single paper in the literature that consolidates the indications for ileo-anal pouch excision and the subsequent outcomes following this procedure. A literature search was carried out to identify articles on RP and ileal pouch-anal anastomosis. The main search terms used were "RP"; "ileal pouch-anal anastomosis" or "ileal reservoir" or "ileal pouch"; "failure of ileal pouch-anal anastomosis" and "excision of ileal pouch-anal anastomosis". The search was completed using electronic databases MEDLINE, PubMed and EMBASE from 1975 to June 2014. Characteristics of patients with pouch failure differ between institutions. Reported overall excision rates of the pouches vary and in this review ranged from 0.93% to 12.8%. Age and lower institutional volume (less than 3.3 cases) were independent predictors of pouch failure; however surgeon case load was not. The main reasons identified for excision are sepsis (early cause), Crohn's disease and poor functional outcomes (both late causes). Pouch cancers in UC and FAP are still rare but 135 cases exist in the literature. The most common complication following excision is persistent perineal sinus. The decision to excise a pouch should not be taken lightly and an awareness of the technical pitfalls and complications that can occur should be fully appreciated.

Key words: Indications and outcomes; Ileo-anal pouch; Pouch failure; Pouch excision

Core tip: There is currently no single paper in the literature that consolidates the indications for ileo-anal pouch excision and the subsequent outcomes.Reported overall excision rates vary and in this review ranged from 0.93% to 12.8%. Age and lower institutional volume (< 3.3 cases) were independent predictors of pouch failure; however surgeon case load was not. Main reasons identified for excision are sepsis (early), Crohn's disease and poor functional outcomes (both late causes). Pouch cancers in ulcerative colitis and familial adenomatous polyposis are rare but 135 cases exist in the literature. An awareness of the technical pitfalls and complications that can occur should be fully appreciated.

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INTRODUCTION

Restorative proctocolectomy (RP) is the surgical treatment of choice for ulcerative colitis (UC) and selected patients with familial adenomatous polyposis (FAP). The RP procedure can significantly improve a patient's quality of life[1] but it is also associated with considerable postoperative morbidity, with up to 50% of patients reporting complications[2]. However, 30 d and 1 year mortality remain low at 0.5% and 1.5% respectively[3].

A devastating complication for both patient and surgeon is failure of the pouch that requires either excision or permanent diversion with a loop ileostomy or permanent Brooke ileostomy. Characteristics of patients with pouch failure vary between institutions. Published pouch excision (PE) rates after RP range from 2% to 22%[4].

The aim of this review was to identify the reasons for RP failure that resulted in excision and to discuss the difficulties associated with removal.

RESEARCH

A literature search was carried out to identify articles on RP and ileal pouch-anal anastomosis. The search was completed using electronic databases MEDLINE, PubMed and EMBASE from 1975 to June 2014. The main search terms used were "RP"; "ileal pouch-anal anastomosis" or "ileal reservoir" or "ileal pouch"; "failure of ileal pouch-anal anastomosis" and "excision of ileal pouch-anal anastomosis". Series included patients with UC and FAP and concentrated on RP related complications and the technical aspects of excision. Additionally, references and citations from all retrieved articles were analysed for identification of similar reports. Exclusion criteria included papers published in languages other than English. Two reviewers independently screened studies for inclusion and when duplicated or updated cohorts were identified, only the most recent study was included.

DISCUSSION

Pouch failure

Failure of RP is defined as permanent diversion or PE.

The reasons for failure and subsequent excision can be broadly categorised into the following technical or disease-related causes: (1) Sepsis (including anastomotic leak, fistula, pouch-vaginal fistula); (2) Mechanical or functional problems (stricture, outlet obstruction, incontinence); and (3) Disease-related failure [Crohn's disease (CD) being the most common[5]].

Early onset pouch failure, *i.e.*, failure within 12 mo is typically caused by surgery-associated complications such as pelvic sepsis[6], anastomotic stricture and separation[7] and pouch sinus and fistula[8]. Reasons for late onset pouch failure (after 12 mo) include CD of the pouch[7,9-11], chronic pouchitis[12], refractory cuffitis, pouch strictures, prolapsed pouch, refractory pouch-vaginal fistula and carcinoma.

Further documented risk factors are mucosectomy[13,14], anal pathology, abnormal anal manometry before surgery[7], and experience of colorectal surgeons in performing pouch surgery[7,15]. Large institutional case loads are associated with reduced reoperation and failure rates[16]. A study including 5771 patients from 154 English National Health Service Trusts also found that there were significant relationships between 365-d mortality and failure rates with case volume. Age and lower institutional volume (less than 3.3 cases annually) were independent predictors of pouch failure; however individual surgeon case load was not[3]. Divergence in failure rates that occurs between high (more than 8.4 cases annually) and low volume institutions appear to occur beyond the peri-operative period. Low volume centres operated on more patients with CD; therefore, poor preoperative histological diagnosis and case selection may contribute to the higher failure rates rather than operative technique or surgical skill and technique[3].

Reasons for PE

Sepsis: Many colorectal surgeons will routinely elect to divert an RP with a loop ileostomy given the devastating complications that can occur after one-stage RP. The omission of an ileostomy still remains controversial[17] as published clinical trials comparing RP with and without a covering ileostomy lack the statistical power to provide a definitive recommendation[18]. However, a review of 17 studies comprising 1486 patients reported that the rate of pelvic sepsis was in fact significantly lower in patients with a temporary ileostomy[19]. In this review of PEs we found that most institutions opted for proximal diversion for their primary restorative RP procedures[7,20-30].

Pelvic sepsis rates are reported to be 5% to 19% of cases[6,24,25]. A meta-analysis by de Zeeuw *et al*[31] which included 14996 patients found a pooled incidence of pelvic sepsis of 7.5% (95%CI: 6.1-9.1). Anastomotic leak occurs in 7% to 15%[32,33] and both pelvic sepsis and leaks can subsequently result in a re-operation rate of 24% to 63% in this cohort of patients[20,32-34]. The management of pelvic sepsis is multi factorial which includes clinical stability of the patient, the extent of sepsis (localised or generalised, abscess, collection, and peritonitis) and services available locally. Management can involve conservative treatment with antibiotics and radiological/trans-anal drainage depending on the position of the collection; or it can also be treated surgically with salvage operations or PE as a last resort.

The St. Mark's Hospital[4] series included 996 patients who had undergone primary RP and included a further 245 patients who were referred for salvage procedures over a period of 25 years (1977-2002). Pelvic/perineal sepsis accounted for 51% (35/68)[4,35] of PEs in their series. Ninety-seven percent of patients who had their primary RP at St. Mark's had at least one or more salvage procedures before excision occurred (median 2; range 0-11). Overall 22.4% of their pouches excised were done so within 12 mo with the remaining excised at a median of 50 mo (range, 13-230 mo)[4].

The Cleveland Clinic series (1985-2009) reported a similar outcome with sepsis/fistulae contributing to 40% of their overall PEs (110/1965 patients)[26]. The Mayo Clinic (1981-1994) had a pelvic abscess rate of 4.9% (73 patients) with 19% (14/73) of these patients subsequently undergoing PE[21]. Pelvic sepsis accounted for 45% of all pouch failures within 2 years at the Mayo Clinic but for less than 2% of all subsequent failures (over 2 years)[36]. MacRae *et al*[6] (Toronto 1981-1992) overall pouch failure rate was 10.5% (58/551); 84.5% of pouches that failed required excision. Leak from the pouch or ileo-anal anastomosis were found to be significantly associated with PE $P < 0.0001$ and $P < 0.001$ respectively, as was no proximal diversion with an ileostomy ($P < 0.01$)[6]. Identification of pouch failure following pelvic sepsis is largely dependent on the duration of follow up. A meta-analysis from the Netherlands including 43 studies reported that pooled incidence rates increased from 6.8% to 8.5% if patients were followed up for at least 5 years. There was also no major difference in failure rates secondary to sepsis between series that included 200 patients and those that included 1200 patients[24].

CD/fistula: Permanent pouch failure occurs significantly more often in patients with CD when compared to those with UC (36.8% *vs* 1.4%)[37]. Reported post-operative diagnosis of CD in the current literature ranged from 0.7% to 4%[4,6,24,29,38,39] with 43% of all PEs at the Cleveland clinic found to have a final histological diagnosis of CD[26]. A diagnosis of CD can be associated with a 4-fold increase in the likelihood of pouch failure[7] and failure rate for inadvertent RP for CD can be as high as 50%[12,27,29,39]. A pre-operative diagnosis of CD is considered a contra-indication to RP as it is believed that disease recurrence and potential for fistula is high and that ultimately PE may be necessary[40]. This is certainly reflected in the literature where it has been reported that the principal reason for pouch failure in CD patients is persistent sepsis secondary to fistulating disease. In a series published from the Lahey Clinic, 40% of their pouch failures were due to fistulating CD[38] and unsurprisingly 90.9% of patients from the Mayo Clinic with CD and whom developed complex fistulating disease (median 29 mo; range, 3-60 mo) post RP required excision[29]. The Cleveland study reflected the experience of other centres and multivariate analysis found perineal (adjusted HR = 3.198, 95%CI: 1.986-5.148, $P < 0.001$) and vaginal fistulae (adjusted HR = 7.491, 95%CI: 3.031-18.514, $P < 0.001$) to be significant predictive factors of pouch failure[7]. No single risk factor for failure on multivariate analysis was statistically associated with either the early-onset (less than 12 mo) or late onset fistula (over 12 mo), and no difference in pouch failure was found between either two groups[41].

Poor functional outcome: Symptomatic anastomotic stricture is associated with an increased likelihood of pouch failure (adjusted HR = 2.692, 95%CI: 1.824-3.971, $P < 0.001$)[7] and rates of excision due to anastomotic stricture ranged from 2.03% to 27.3%[4,6,12,38,39]. Poor function is often referred to as "outlet obstruction or incontinence." At the Cleveland Clinic 30% of pouches were excised due to stricture or poor function[7] with a similar excision rate for poor function of 35% observed at St. Mark's Hospital[4]. In the series by Prudhomme *et al*[27] 50% of pouches excised was due to poor function but typically each patient who had undergone excision had more than one complication and therefore poor function is likely multi-factorial.

Pouch ischaemia: Pouch ischaemia as a result of technical failure will usually present early and is now regarded as an avoidable complication. Körsgen *et al*[12] reported a relatively high excision rate due to ischaemia (26.1%, $n = 6/23$) however only two of these cases were due to technical problems (extensive vascular mobilisation, small bowel haematoma). They reported two late cases due to rotation injury along the long axis of the small bowel mesentery and ileoanal anastomosis[12]. Karoui *et al*[4] had an excision rate due to pouch ischaemia of 1.5% and Farouk *et al*[21] a rate of 14.3%.

Chronic pouchitis: Pouchitis is rarely seen in those patients with FAP and is more common in UC patients[42]. The incidence of pouchitis increases from 40% of patients having one episode in first 10 years to 70% within 20 years[18]. The pooled incidence of at least one episode of pouchitis was 18.8% (95%CI: 15.7-22.4) from a meta-analysis of 43 studies[24]. However, current evidence suggests that pouchitis, as a single entity, is rarely the reason for pouch failure[4,6,8,30,32,34,38,43]. Approximately 5%-10% of patients develop chronic pouchitis that requires long term therapy and a small minority will have pouchitis that is refractory to medical treatment. This is the subset of patients that should be referred to a Colorectal Surgeon for a discussion surrounding permanent diversion or excision[44]. The rates of excision of a pouch for pouchitis alone were between 7.4% and 22.9%[4,6,8,20,22,26,30,35]. However, one Canadian study reported an excision rate of 54.5%

Table 1 Other reasons for excision

Ref.	Total number of excisions	Reasons for excision (% of total excision)
Farouk *et al*[21] Mayo Clinic *n* = 1508	14	Pouch ischaemia (14.3%)
Karoui *et al*[4] Cleveland Clinic *n* = 1241	68	Pouch ischaemia (1.5%) Intra-abdominal bleeding (2.9%) Redo operation and insufficient length on mesentery (1.5%)
Körsgen *et al*[12] Birmingham *n* = 180	23	Pouch ischaemia (26.1%)
Lepistö *et al*[8] Helsinki *n* = 486	24	Adrenal insufficiency and dehydration (4.2%) Patients fear of incontinence after stomal closure (4.2%) Perianal pain (4.2%)
Wexner *et al*[30] Minneapolis *n* = 180	14	Severe post-operative haemorrhage (7.1%)

(6/11) due to intractable pouchitis in their UC cohort who had undergone excision[45]. However this was in an era where the use of long term anti-biotics and biologicals were still under evaluation.

Dysplasia/cancer

Both UC and FAP predispose to neoplasia within the pouch. It is useful to consider these diseases separately.

UC and cancer: A recent study by Wu *et al*[46] (3203 patients) reported the cumulative incidence for pouch neoplasia at 5, 10, 15, 20 and 25 years after pouch construction in UC patients were 0.9%, 1.3%, 1.9%, 4.2% and 5.1% respectively. They also concluded that those patients with a final diagnosis of pouch adenocarcinoma when compared to those with dysplasia tended to be older (P = 0.04) and had a longer duration of diagnosis of IBD or pouch construction prior to the detection of neoplasia (P = 0.007 and P = 0.0013). Eleven out of fourteen patients with adenocarcinoma had resection and PE with curative intent [abdominoperineal resection (APR) with end ileostomy n = 8, APR with Kock pouch n = 2, palliative resection with end ileostomy n = 1] and 2/12 with high grade dysplasia had excision (APR with end ileostomy n = 1 and APR with Kock reservoir n = 1). The prognosis for pouch adenocarcinoma is poor and the anal transition zone was the most common site in the Cleveland Clinic Series[46]. The occurrence of neoplasia in patients with RP is not eliminated by mucosectomy[19,47].

However it is not clear whether retaining the anal mucosa using the double stapling technique and allowing the mucosa to be sampled is superior or inferior to mucosectomy. This was reviewed by M'Koma *et al*[48] in 2011, who found 43 cases of pouch cancer related to UC. Thirty two had transition zone carcinoma, 28 of whom had had a mucosectomy. There were also 11 cancers within the body of the pouch body[48]. Patients with primary sclerosing cholangitis and inflammatory bowel disease are at an increased risk of colorectal neoplasia. Rahman *et al*[49] found a cumulative 5-year incidence of pouch neoplasia of 5.6% (95%CI: 1.8%-16.1%)[49]. However, there is still insufficient evidence to implicate primary sclerosing cholangitis as a risk factor for the development of dysplasia and carcinoma of the pouch[49].

FAP and cancer: Incidence of adenomas (within pouch) in patients with FAP varied from 6.7% to 73.9%, age of the pouch is an important risk factor: 7%-16% at 5 years, 35%-42% after 10 years and 75% after 15 years. However, only 23 cases of ileal pouch carcinoma have been recorded in the literature to date[50]. Thus data suggests that the body of the pouch needs to be reviewed after 5 years in patients with FAP. In the review by Smith *et al*[50] in 2013 there were 92 cancers in total of which 23 occurred within the body of the pouch and or in the anal canal mucosa or cuff again, suggesting lifetime surveillance for FAP pouches. In the St. Marks series two pouches were excised as a result of unrecognised cancer in the rectum at the time of original RP construction (2.9%)[4], and 6.1% of pouches at the Cleveland Clinic were excised due to neoplasia of the pouch or rectal cuff[26]. Prudhomme *et al*[27] reported PE as a result of desmoid tumours in a total of three cases[27]. Other reasons for PE are outlined in Table 1.

PE

Excision of a failing pouch sacrifices a significant length of terminal ileum and there are a small number of papers that suggested transformation of a pouch to continent ileostomy (Kock reservior) may be a suitable alternative[51,52]. This would not be the authors operation of choice. However, current indications include patients who require a panproctocolectomy but cannot have a pouch constructed, those patients with failed RP who are not candidates for redo surgery and those with a Brooke ileostomy that is adversely affecting the patients quality of life[53]. Ecker *et al*[52] successfully converted 4 ileo-anal pouches to a kock reservoir and the indication was functional disturbance that could not be corrected surgically. Hultén *et al*[51] had a series of 5 patients who had transformation of their pouch for pouch-vaginal fistula considered unsuitable for local revision, unsatisfactory function and unacceptably high defecation frequency. Performing a permanent ileostomy above a pouch left *in-situ* is another reasonable alternative when PE is not feasible or recommended particularly as this is not associated with neoplasia[54]. Once the difficult decision has been taken to excise a pouch, a comprehensive and carefully constructed management plan/surgical strategy must be implemented. The urgency with which the

operation is performed will depend on the indication for excision and the clinical stability of the patient. If time permits, the authors feel that these patients should be discussed in a multi-disciplinary environment with further discussions with the patient in an appropriate setting, ideally with their own network of support available. Patients often give weight to other values besides physical health and the disappointment after unsuccessful restoration of intestinal continuity and the prospect of excision can be devastating. Lepistö *et al*[8] reported that quality of life scores are lower in PE groups when compared to the general population and this is often due to physical impairment and social restrictions. Transparency is of paramount importance in order to meet patients' expectations and the appropriate support network should be in place before excision takes place. The network should include aspects of metabolic, nutritional and psychological support as short gut may be a problem in patients some of whom will be stoma averse.

THE OPERATION

There is a paucity of information in the literature about the operative strategies for PE but the approach taken for re-operative/salvage surgery should be adopted for excision surgery (preservation of bowel length is a principle as is nerve/ureteric preservation). An exhaustive evaluation with imaging such as computed tomography, magnetic resonance imaging and endoscopy are required. When salvage surgery is undertaken at the Cleveland Clinic patients are placed in the Lloyd-Davies position and both the abdomen and perineum are prepared and draped. The abdomen is entered *via* the previous incision; the pouch mobilised to the levator ani muscles using sharp dissection and the pouch is subsequently excised. In addition, intra-operative urethral stents[55] are often necessary and would certainly be advocated by many colorectal surgeons with experience of the difficulties encountered in the re-operative pelvis. PE may be required with a temporary proximal diversion in place. This may have been for a salvage procedure or to manage sepsis, and once all sepsis has resolved (3-6 mo), further surgery can be considered[5]. Fifty-one percent of patients in the St. Mark's series had a diverting stoma for sepsis, pouchitis and poor function prior to excision[35]. PE and perineal closure can be performed using an extrasphincteric (ES), intersphincteric (IS), or sphincter preserving (SP) approach[26]. Nisar *et al*[26] from the Cleveland Clinic prefer IS dissection and reserve ES closure for cancer or extensive perineal sepsis and authors from this institution adopt this same principle. SP closure is employed when restoration of intestinal continuity may be a future option[26]. Prudhomme *et al*[27] performed 24 PEs with sphincteric dissection as follows: total sphincteric 10/24 (levator ani muscles were closed and the subcutaneous and skin layers were closed), intersphincteric 10/24, no sphincteric dissection 4/24. The St. Mark's operative strategy for PE is a combined abdominoanal approach with dissection maintained close to the pouch in order to minimise risk of damaging pelvic nerves. Dissection is commenced posteriorly after entering the presacral space behind the small bowel mesentery and continued caudally, laterally and then anteriorly to the level of the pelvic floor. The ileoanal anastomosis is disconnected and along with the anal canal is removed *via* an intersphincteric dissection. If there is evidence of pelvic sepsis the practice was to curette any granulation tissue and the perineal wound was left open in all cases. Ninety percent of these patients had a Brooke ileostomy with the remaining 10% (7/68) having a continent Kock reservoir[4]. Prudhomme *et al*[27] opted also for Brooke ileostomy in just over 90% of their patients and performed a Kock reservoir in only two patients.

There is a lack of studies that report the outcomes after excision of a pouch and this area needs more study[26]. Complications can be classified as early (within 30 d of surgery) or late. In the St. Mark's series[4] 25% of patients (n = 17) had immediate post-operative complications; one death. Seventeen patients had one or a combination of the following: sepsis (peritonitis, abdominal wound, pelvic abscess, peristomal abscess), bleeding, intestinal obstruction deep vein thrombosis. Nineteen percent overall required further surgery. Median duration of follow-up after excision was 79 (range, 3-312) mo and during this period 53.7% (95%CI: 41%-66%) were readmitted for late complications. The risk of readmission from the time of the PE was 38% (95%CI: 27%-51%) and 58% (95%CI: 45%-72%) at 1 and 5 years respectively. Perineal complications such as persistent perineal sinus (PPS) are the most common late complications. Complete healing can eventually be achieved in the majority of cases. However up to 10% of patients can still have PPS at 12 mo[27,35]. The Mayo Series had a 40% rate of PPS six months post-operatively and all of these patients required at least one further procedure with two requiring a laparotomy. Interestingly no correlation was found between indication for excision and PPS[4]. Despite an identical rate of PPS in the St. Mark's series, they stated that "PE for fistula or abscess in the pelvis or perineum was an independent predictor for PPS"[35]. The Cleveland Clinic had the largest series of PEs (110 patients, 48% CD) and had a PPS rate of 39.8% with an overall healing rate in this cohort of 80.7% with further procedures. They also found no association with PPS and closure technique or eventual healing (P = 0.37 and P = 0.94 respectively) and no significant difference in PPS was found between CD and non-CD patients. In the CD cohort where sphincter preservation was attempted four patients developed PPS. These patients achieved complete healing when sphincters were excised[26]. This outcome was also reflected in the series by Prudhomme *et al*[27] who reported that the highest rate of PPS was

in CD patients and complete healing was achieved when total sphincteric excision was subsequently performed[27]. A small but significant difference was observed in quality of life scores (SF-12 Questionnaire) for both mental (PPS 43.5 ± 10.9 *vs* No PPS 50.9 ± 9.1, $P = 0.038$) and physical (PPS 40.8 ± 10.5 *vs* No PPS 48.0 ± 8.9, $P = 0.037$) components at latest follow up when patients with PPS were compared to those without[26].

Further uncommon, late complications included small bowel obstruction, ileostomy retraction, incisonal hernia, enterocutaneous fistula from Kock reservoir and short bowel syndrome. Incidence rate of persistent impotence was 7.14% (2/28 males) which is higher than rates described following an initial RP[4].

Overview

Pouch surgery has been ongoing for over 35 years since the first RP in the 1970's[56] and the authors predict an epidemic of problematic pouches which may be attributable to the duration that pouches have remained *in situ*. Failure of an RP that then requires PE is a devastating complication and subsequent management of a failed pouch should be entirely patient focused. Pooled rate of pouch failure is 4.3% (95%CI: 3.5-6.3) and when compared to studies before the year 2000, a reduction of 2.5% is observed in the pouch failure rate ($P = 0.0038$)[31]. Reported overall excision rates of the pouches vary and in this review ranged from 0.93% to 12.8%[3,4,6-9,12,20,21,38,57]. The main reasons identified for excision are CD and poor functional outcomes (both late causes). Pouch cancers in UC and FAP are still rare but now number 135 in the literature[48,50].

The complexity of PE and the meticulous strategy and resources that are required strengthens the current discussion for centralisation of such services in order to deliver the best service possible to patients. We believe that pouch surgery should be performed by Colorectal Surgeons with a specialised interest in IBD Pouch Surgery with adequate local resources to appropriately manage and support these patients. The decision to excise a pouch should not be taken lightly and an awareness of the technical pitfalls and complications that can occur should be fully appreciated.

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MINIREVIEWS

Surgical treatment of retrorectal (presacral) tumors

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Abstract

Retrorectal (also known as presacral) tumor (RT) is a rare disease of retrorectal space. They can be classified as congenital, inflammatory, neurogenic, osseous, or miscellaneous. The most common presentation is an asymptomatic mass discovered on routine rectal examination, but certain nonspecific symptoms can be elicited by careful history and physical examination. The primary and only satisfactory treatment is surgery for RTs. Three approaches commonly used for resection are abdominal, transsacral, or a combined abdominosacral approach. Prognosis is directly related primary local control, which is often difficult to achieve for malignant lesions.

Key words: Retrorectal; Presacral; Tumor

Core tip: Since retrorectal tumors are rare in surgical practice an ordinary surgeon will have been faced a number not more than a fingers of one hand in his lifelong carrier. Diagnostic and surgical practice should be fulfilled by the small but well documented case series, reviews and meta-analyses based on them.

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INTRODUCTION

Retrorectal tumor (RT) is a rare disease. Average of two patients can be diagnosed annually in an urban area[1]. An ordinary surgeon will have been faced with a few cases in his lifelong carrier. Even many malignant cases can be encountered and necessitate aggressive surgical interventions, fortunately majority are benign. Since misdiagnosis or incorrect operative approach in case of RTs can cause serious complications, always keeping in mind as a differential diagnosis, thorough working knowledge of the etiology, presentation and treatment are essential. In a small number of patients with RT, Singer *et al*[2] reported that approximately 4.7 unnecessary diagnostic but unrelated interventions have done before definitive diagnosis.

The first reported case of RT in 1847 by Emmerich was an adult teratoma[3]. In 1885, a second case of RT (dermoid cyst) was reported in a young woman's autopsy[4]. Page reported the first successful excision of a RT in 1891[5]. The first case harboring malignancy

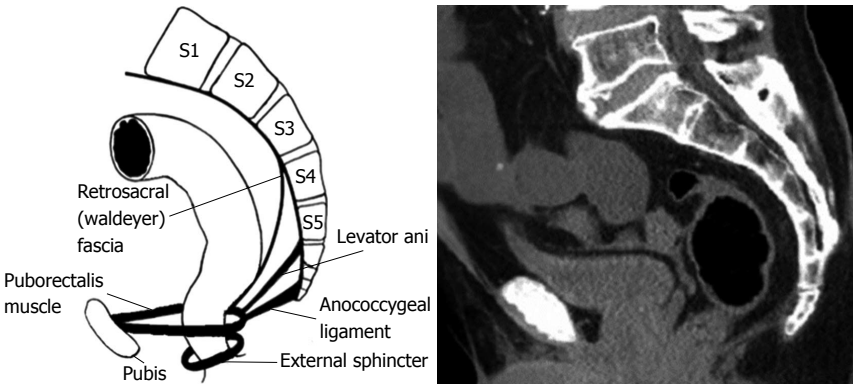

Figure 1 Schematic illustration of sacrococcyx, rectum and important ingredients of retrorectal space. (Simplified and reproduced from Nicholls *et al*[42]) and counterpart tomoscan.

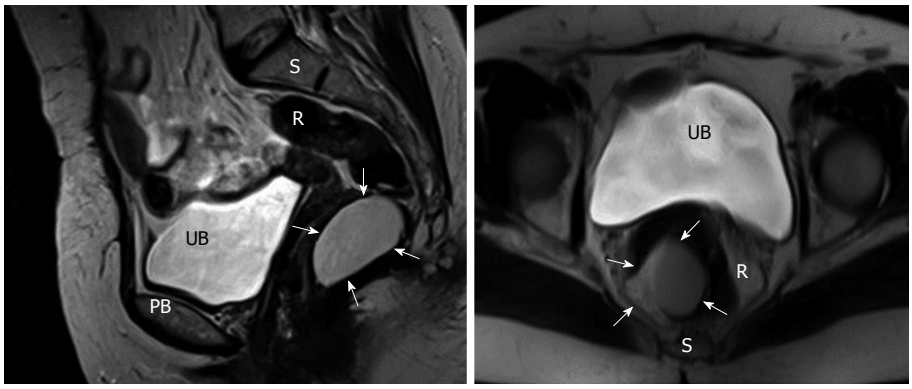

Figure 2 Coronal and axial T2A magnetic resonance imaging planes of a cystic lesion (arrows) in the retrorectal space. UB: Urinary bladder; PB: Pubic bone; R: Rectum; S: Sacrococcyx.

was a tail gut cyst described by Ballantine[6] in 1931.

The area of retrorectal space (RS) is delineated posteriorly by presacral fascia overlying the sacrum and anteriorly by fascia propria of the rectum. Lateral borders include different structures like ureters, iliac vessels and lateral borders of the rectum. It's superior and inferior ends are peritoneal layer of the rectum and Waldeyer's fascia respectively (Figures 1 and 2).

Since multiple embryologic structures rise up in RS, this area can contain variety of tumors harboring diverse histopathology. For this reason this space may be the most crowded point in which different subspecialties such as surgeons, obstetricians and gynecologists, urology, neurosurgeons, orthopedics encounter each other while managing a lesion herein.

INCIDENCE

Even though RTs are very common malignancy in the childhood, they are rare in the adults, occurring 1 of 40000 to 63000 admissions at a reference hospital admissions. Different from adults, infants frequently present with an externally visible sacrococcygeal masses showing malignant transformation in untreated cases[7]. Benign lesions in RS are more common in females whereas malignant tumors have an equivalent distribution[1]. While cystic malignancies have been described, malignancy is more common in solid lesions with a rate of 9% to 45%[8]. Estimated incidence of RT in adult population is 0.0025-0.014[9]. Retrospective series shows that 1 to 6 patients are diagnosed annually in major referral centers[1]. After 20851 proctoscopies performed in a single institute, only 3 precoccygeal cysts can be diagnosed per year[10].

The most of the knowledge accumulations are derived from individual case reports and small numbered case series. There are few cohort series with large numbers which span 12 to 35 years interval, reflecting that major referral centers will be accepted approximately 1.4 to 6.3 patients per year[1]. In fact there should be some patients who were overlooked and this may reduce the calculated incidence rate. There is only one large series of 63 patients during 30 years period from a non-referral center[1]. According to this study from an entire metropolitan area, annually diagnosed 2 patients are more representative number to make a decision of incidence in a definite area.

CLASSIFICATION

The most frequently used classification system separates RTs into five categories: congenital or developmental,

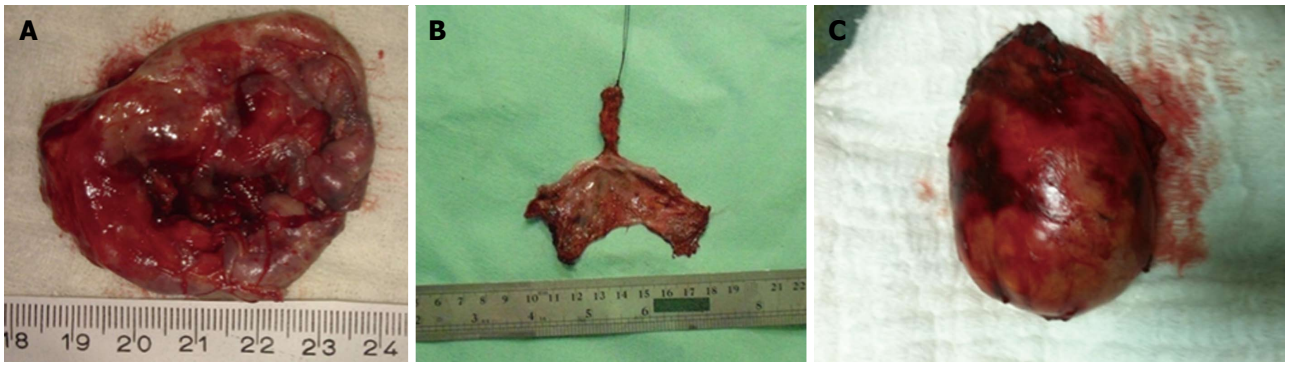

Figure 3 Macroscopic appearance of dermoid cyst (A), epithelial inclusion cyst (B) and schwannoma (C).

Table 1 Classification of retrorectal tumors

Source of origin		Histopathology
Congenital or developmental	Benign	Developmental cysts
		Dermoid cysts
		Epidermoid cysts
		Tail gut cysts
		Enteric (rectal) duplication
		Anterior sacral meningocele[1]
		Teratoma
		Adrenal rest tumors
	Malignant	Chordoma[1]
		Teratocarcinoma
Inflammatory		Granulomas (foreign body, chronic)
		Perineal/pelvirectal abscess or fistula
Neurogenic	Benign	Neurofibroma
		Neurolemmoma (schwannoma)
		Ganglioneuroma
	Malignant	Ependymoma
		Ganglioneuroblastoma
		Neurofibrosarcoma
Osseous	Benign	Osteoma Sacral bone cyst
		Osteoblastoma
		Osteogenic sarcoma
		Giant cell tumor
	Malignant	Ewing's tumor
		Chondromyxosarcoma
		Osteogenic sarcoma
		Myeloma
Miscellaneous	Benign	Lipoma
		Fibroma
		Leiomyoma
		Hemangioma
		Endothelioma
		Desmoid tumor
		Lymphangioma
		Ectopic kidney
	Malignant	Fibrosarcoma
		Liposarcoma
		Leiomyosarcoma
		Metastatic disease

[1]Sometimes classified as neurogenic in origin.

neurogenic, osseous, inflammatory, and miscellaneous[1]. This classification was further divided into benign and malignant because therapeutic approach is mainly based on the histopathology (Table 1)[11]. Other classification system divides RTs into four distinct groups; congenital *vs* acquired and benign *vs* malignant clustering in similar characteristics, diagnosis, and management[12].

Congenital or developmental

Congenital lesions are embryologic remnant which has been present from the birth. They account 55% to 75% of all presacral lesions with subgroups of developmental cysts, chordomas, anterior sacral meningoceles, rectal duplications and adrenal rest tumors[1].

Developmental cysts: About 60% of congenital RTs are developmental cysts originating from different embryologic origin. There is 1:2 female predominance[13]. This predilection may be the result of more frequent routine rectal or pelvic examination in female population than males which makes females more likely for diagnosis[14]. Depending on the origin of embryonic cell, they can be epidermoid, dermoid, tail gut cyst or teratomas. Epidermoid and dermoid cysts are derived from ectodermal tube closure defect. Dermoid cysts made up with more matured components and comprise dermal appendages like hair follicles and sweat glands whereas epidermoid cysts have squamous epithelial lying (Figure 3). Women in between 4th or 5th decades are more prone to develop dermoid and epidermoid cysts. These cysts likely contain viscid green-yellow material unless infected[15]. The next and less frequent congenital lesion sometimes referred as cystic hamartoma is tail gut cysts. Glandular, mucous producing columnar epithelium in these cysts explains it's derivation from tail gut remnants. Although cyst wall may contain scattered bundles of smooth muscle fibers, muscular and serosal coat is not present. Malignant degeneration is rare in tail gut cysts.

Teratomas: Even sacrococcyx is the most common location for teratomas in neonates, it is rare in adults. Teratomas, which have 5% to 10% malignant potential can give rise to multiple solid or cystic lesions containing various tissue types like respiratory, nervous and gastrointestinal system epithelium[16]. Nearly 30% of resected adult teratoma specimens harbor malignancy. The one tip to predict whether it is benign or malign is relation to adjacent structure. The tendency of malignant teratomas to adhere coccyx, rectum and other visceral organs is not seen in benign lesions.

Chordomas: Chordoma is the most common malignant and the most extensively studied RT. It is the second most common RT in RS occurring in three of seven patients[17]. Even one-third occurs in RS, they can be found anywhere in vertebral column[18]. Slow growing nature of chordoma postpones the diagnosis until 40 to 60 years of ages[1]. Long standing vague pain and symptoms associated with nerve compression like incontinence or impotence are frequent presentations. These frequently lobulated, gelatinous masses that attack and break down the neighboring structures need complete resection in order to prevent recurrence. The typical radiological finding for chordoma is "Fang" sign, the finding of sacral bone destruction. Recurrence rate is as high as 44% and because these recurrences are locally aggressive, patients should be warned for probable postoperative sequelae from minor urinary incontinence to paralysis[19]. Chordomas are more common in males with an expected male/female ratio of 2:1[14].

Anterior sacral meningocele: Anterior sacral meningocele is the third group of congenital RT. It is a dural hernial sac containing cerebrospinal fluid as a continuation of subdural space from a defect in the sacrum. Dural connection causes increase in cerebrospinal fluid pressure during straining or defecation. Anterior sacral meningoceles are more common in females and can present with recurrent meningitis[10].

Miscellaneous: The last category of congenital RT is adrenal rest tumors and rectal duplications. The latter can contain mucosa with crypts and villi, smooth muscle and serosa components of intestine because they are remnants of duplicated rectum. Adrenal rests tumors are very sporadic and must be managed like an ectopic pheochromocytoma.

Inflammatory

Inflammatory RTs are less common than congenital ones. They may be residues of foreign bodies of any kind. Tuberculosis, granulomatous disorders, perianal abscess, diverticulitis resulting pelvic abscess and fistulas can cause chronic inflammatory masses in the RS.

Neurogenic/osseous

Neurogenic tumors tend to be large and account 10% of RTs. This category includes neurofibromas, neurolemmomas, ependymomas, ganglioneuromas, and neurofibrosarcomas. Even benign lesions constitutes two thirds of neurogenic RTs, severe neurological sequelae can be seen if these lesions are originated from the spinal cord. Neurogenic and osseous RT can be benign or malignant. Benign ones often require complete resection but recurrence rate is high in osseous lesions.

Miscellaneous

The last but not least group of RT constitutes masses such as metastatic disease from rectum, sarcomas, malignant fibrous histiocytomas, lymphangiomas, lymphomas, fibrosarcomas, liposarcomas, hemangiomas and others that can be found anywhere else in the retroperitoneum[8]. They constitute 10% to 25% of all RTs[1].

However these classifications do not consider the location of RT in the RS which is important determinant for operative and pathologic considerations. A suggestion of a classification system based on the tumor emplacement to facilitate surgical strategy and postoperative sequelae prospection (Figure 4)[20]. According to this classification, type 1 refers to RTs without any connection to the sacrum. Type 1 RT is at the coccyx level (below S3) and separate from the bony trunk of sacrococcyx. It can easily be separated from surrounding structures and removal is not difficult[2]. Type 2 RT is also settles with the same level as type 1 but has connection with the coccyx and/or sacrum. Their surgical resection promise no neurologic deficit[12]. Type 3 RT requires a unilateral resection of the sacral nerve(s), probably resulting fecal and/or urinary incontinence because type 3 RT involves the sacrum at or above the S3 nerve root unilaterally. Type 4 RT has large communication with the sacrum at or above S3 bilaterally in which permanent sphincter deficit is almost unavoidable.

Further division of these four types is A; resection of the adjacent sacral soft tissue and bone is mandatory without adjacent organs and B; resection of organs such as rectum, bladder is obligatory.

SYMPTOMS

Asymptomatic tumor discovered on reckless pelvic or rectal screening investigation is the most common type of presentation[8]. That's why most patients don't have a positive family history despite the majority of RTs are congenital[11]. On the other hand some authors report that nearly 97% of RTS can be and are diagnosed on physical examination[21]. Every physician should put RT in differential diagnosis list on rectal or pelvic examination in order not to miss any which may be the only case of his lifelong carrier as described above.

RTs may cause mild or imprecise symptoms. Benign lesions frequently remain silent for a long period of time. Sacrococcygeal pain is the most common presenting complain in malignant or infected cases of RT[21]. Nature of pain is mostly low back or rectal pain. Presentation of pain in benign and malignant RTs is approximately 30% and 87% respectively[21]. Male gender and older age (> 60) are other predisposing factors for malignancy. Persistent pain at low back, pelvis, and buttocks which is increased by sitting is usual in chordomas.

RT can present with infection reflected as a small, dimples posterior to the anus and below the linea dentata[1]. Misdiagnosis of a retrorectal lesion as a fistula, pilonidal sinus or perianal abscess and any delay

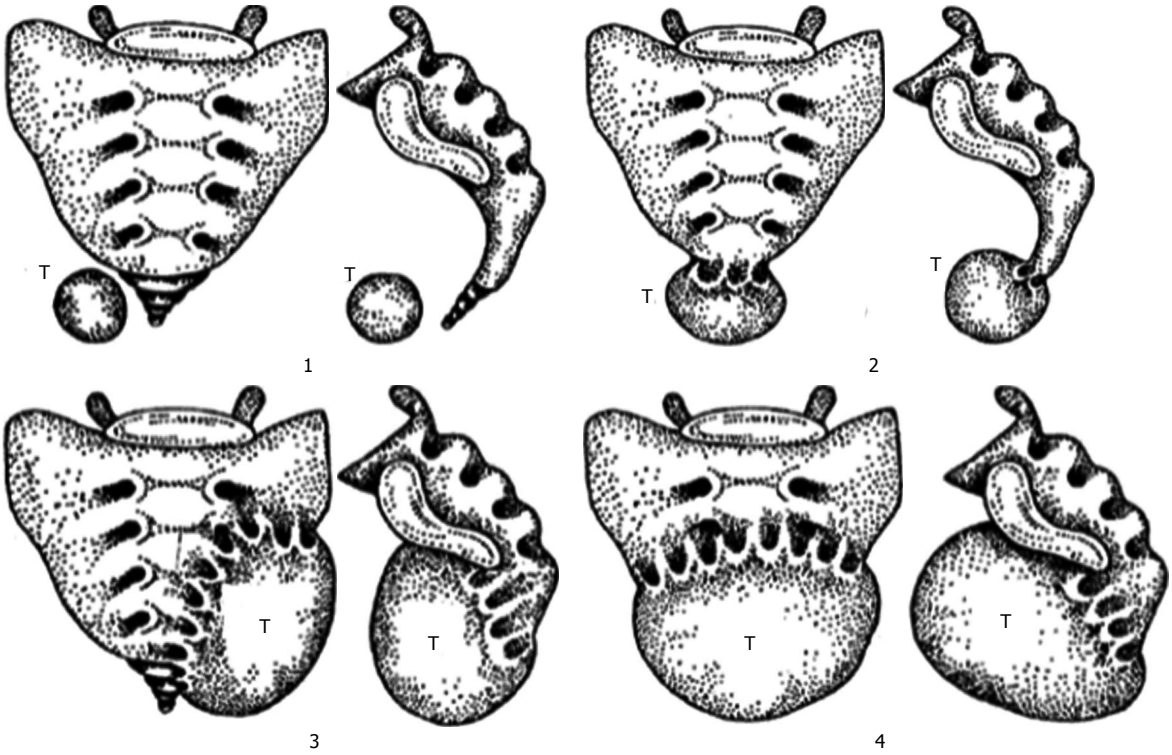

Figure 4 Classification of retrorectal space depending on its relationship with the sacrum (Losanoff *et al*[20]).

in proper management will be unavoidable if failure to understand actual pathology[1]. Incontinence of urine or stool, bowel habitus changes like constipation, sensation of inadequate emptying or tapering stools are sequelae of the change in the rectal angle at the puborectalis muscle due to mass effect. This mass effect can create vaginal canal obstruction and consequent life threatening dystocia during child birth. Anterior sacral meningocele should always be kept in mind if there is a history of headaches after straining, defecation, intercourse and existence of repeated meningitis in a case with a palpable retrorectal mass.

DIAGNOSIS

Rigorous rectal examination is crucial because the most lesions are soft, compressible, and can easily be misdiagnosed if the physician does not awake for a RT probablity[1]. By this way not only because digital rectal examination can establish the diagnosis in > 90% of the patients, but also it can help to define the proximal level of the RT, therefore the surgical approach[11,21].

Evaluation of RT begins with plain radiographs. Clinicians usually fail to value signs and symptoms of RT and consequently misdiagnoses even after extensive radiological workup. Pelvic bone demolition, proposing a malignancy or a chordoma, and numerous dense calcifications proposing a benign teratoma are helpful findings of plain radiographs. Smooth-edged, bowl-shaped border of the sacrum without clear bony demolition of the pelvis (known as "scimitar sacrum") proposes the existence of a sacral meningocele. Transrectal ultrasonography (TRUS) appears to be useful in the diagnosis of RTs. TRUS was found to have a sensitivity of 100% when combined with proctoscopy[2]. TRUS can predict rectal muscularis connection and type of operation.

Either computed tomography (CT) or magnetic resonance imaging (MRI) were became the standard for evaluation of RTs. Very small cystic or solid tumors, sacral contribution or attack to neighboring structures can easily be detected with CT[21]. MRI is more beneficial in outlining soft-tissue planes, assessing bony invasion and nerve involvement with its superior tissue contrast resolution to CT scan[11]. Histologic estimation of the RT may be best achieved with MRI[2].

Preoperative histologic diagnosis is mandatory when there is solid or heterogeneously cystic tumor[11]. Biopsy is indicated when the lesion seems to be unresectable and a definitive histopathology is required to guide adjuvant therapy. Purely cystic lesions rarely necessitate biopsy because they are usually benign and biopsy carries the risk of infection. Unnecessary biopsy can cause tumor seeding, infection of the previously sterile cystic lesions, fistula formation and fatal case of meningitis in patients with anterior sacral meningocele or exacerbates morbidity and mortality of subsequent operations[21].

The operation team should consider the way of biopsy since needle tract must be included within the specimen. Transperitoneal, transretroperitoneal, transvaginal, and transrectal biopsies are not recommended since biopsy tract may not be excised. Transrectal or transvaginal biopsies may also lead to infection, more complex and difficult excision, increased postoperative complications and recurrence. According

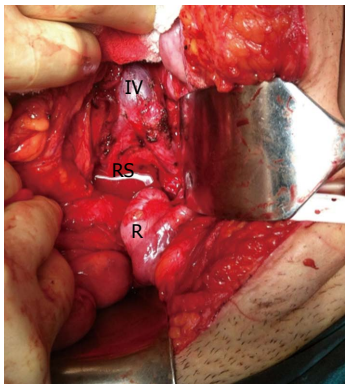

Figure 5 Laparotomy for retrorectal space. Iliac vessels and RS can easily be reached after lateralization of rectum. IV: Iliac vessels; RS: Retrorectal Space; R: Rectum.

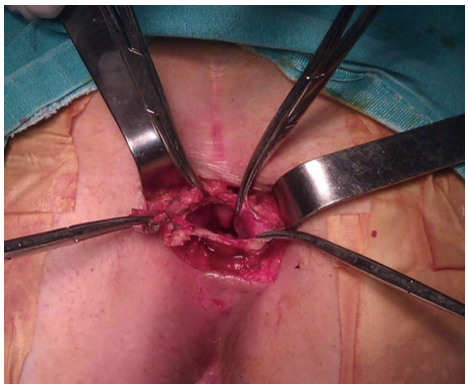

Figure 6 Excision of cystic lesion located low level in retrorectal space by using posterior approach.

to the literature, the best method is transperineal or parasacral since by this way biopsy tract can likely to be kept within the area of the upcoming surgical excision. It is logical to mark needle insertion pathway with methylene blue dye for keeping the biopsy tract within the resection specimen[22].

The consideration of the role of biopsy for the management of RT was concluded that preoperative biopsy of RT is safe and more concordant with postoperative pathology than imaging. Given the significant differences in therapeutic approach for benign *vs* malignant solid or heterogeneous solid-cystic RTs, as well as the current limitations of imaging, a percutaneous preoperative biopsy should be obtained to guide management decisions. Type of surgical resection and the role of neoadjuvant chemoradiation also necessitate actual histology. Moreover, since all malignant RTs require a wide resection including sacrectomy, preoperative tissue diagnosis is mandatory to avoid patients with benign RT from urinary and sexual dysfunction, or other unwanted outcomes[23].

TREATMENT

Surgery is a sole treatment of RTs. Probable infection and malignancy or switching into malignant cells are some convincing reasons. If currently sterile and benign looking cystic lesions once infected, they will adhere to the adjacent structures making the surgery difficult, increase the postoperative complication and recurrence rates.

Three main operative approaches for the resection of RTs are existing; anterior or abdominal, posterior or transsacral and combination of both.

Anterior or abdominal approach

Anterior approach is suitable for tumors at higher location having the lowest border above the 4th sacral bone. Absence of sacral involvement is essential for this approach. This kind of surgery has advantages of good disclosure of adjacent pelvic structures such as iliac vessels and ureters (Figure 5). Throughout the abdominal approach, rectum is first isolated and separated from resection area and after ligation of middle sacral and internal iliac vasculatures, presacral fascia is dissected. Surgeon should be in great care during tumor excision for presacral hemorrhage because the middle sacral blood vessels and the presacral venous plexus are in this region. Possible perineal necrosis can be prevented by preservation inferior gluteal artery which is terminal branch of anterior division of the internal iliac artery. The main cause of intraoperative death is hemorrhage of the presacral venous plexus. Traditional hemostasis methods may not be enough and troublesome bleedings can be overwhelmed by some challenging preventive measurements such as temporary gauze tamponade, bone wax or breast size implanter[24].

Posterior or transsacral approach

This procedure is suitable for low lying tumors which are not extending beyond 4th sacral element. Usual length of a finger can extend up to 4th sacrum. If the proximal end of the tumor is felt by digital sensation, this means that there is no extension beyond that point. The patient is positioned in a prone jack-knife position, preferably buttocks are separated apart (Figure 6). A transverse incision overlying the coccyx offers good disclosure of the retrorectal space especially in case of nerve involvement. A longitudinal incision may be used alternatively on the lower sacrum to the level of anoderm while taking care for not to cause any injury to external sphincter. After dividing the subcutaneous fat, the levator muscles and the anococcygeal ligament lying deep to the lumbosacral fascia are exposed. Transection of anococcygeal ligament allows mobilization of the coccyx. Coccyx can be transected to provide sufficient exposure for dissection, the gluteal muscle may be separated, and sacrectomy of S4-S5 can be achieved afterwards. Separation of the plane between the tumor and the mesorectum will be easy. The major disadvantages of posterior approach are injury to the lateral pelvic nerves and absence of control over pelvic

vessels. While comparing with anterior or combined procedures, probable hemorrhage can be lowered by posterior method[25]. If the lesion is benign, there should be an identifiable fat plane between the mesorectum and RT provided that there was no infection before. In case of cystic and/or small lesion, the surgeon can place the nondominant hand index finger with double-glove in the anal canal and lower rectum and then depress the tumor through the incision. Undesired injury to the rectal wall during the dissection can also be prevented with this manner. The posterior approach is embraced of different techniques such as transsphincteric, transsacral, transrectal, transanorectal, and transsacrococcygeal approaches. Every one of these techniques has its own losses and benefits and can be chosen based on the characteristics and site of the tumor and the surgeon's preferences.

Ruptured transrectal cysts and solid but well delineated lesions extending rectal muscular layer with suitable level should be subjected to this kind of surgical approach. A modification of this approach is intersphincteric resection of RT which starts with retrorectal space access *via* intersphincteric plane or a transvaginal incision, when the tumor is low enough and not in the midline, lying between vaginal wall and rectal muscularis layer. Anal sphincter damage confronts us during the above incisions but one can avoid the possibility of sacral nerve injury, postoperative urinary retention and unintentional rectal perforation with these cuttings.

Combined abdominosacral approach

This procedure is suitable for the tumor extending both vertical sides of the 4th sacral vertebra. Operation begins with the patient in modified lithotomy position and entering the retroperitoneal space through the areolar plane between the mesorectum and the presacral fascia, to gain access for dissection of the upper part of the lesion. While going down to the deep pelvis, identification of planes between the tumor and surrounding tissues will become more difficult, than patient may be repositioned in the jack-knife position for the perineal phase of the procedure. An incision is then made over the sacrum and coccyx through the anus, while being awake not to damage external sphincter. Division of anococcygeal ligament and retraction of levators can be done afterwards. The gluteus maximus muscles are then retracted away and the sacrospinous, sacrotuberous ligaments, and piriformis muscles are divided bilaterally to delineate the sciatic nerve. Any dural openings should be closed to prevent cerebrospinal fluid leakage or infection. One S3 nerve should be preserved to maintain proper fecal and urinary function. Colostomy should be matured if unilateral preservation of the S3 is not possible. In case of benign or have a low relapse probability, colonic continuation can be achieved with anastomosis but diverting ileostomy should be considered.

Major advantages of this approach appear when infection or inflammation cause disappearance of the dissection planes or exposure of the neighboring structures like rectum, ureters, iliac vessels as well as nerve roots are obligatory. This is a case in chordoma in which partial sacral excision extending above S-3 is necessary. Complete and one piece tumor excision with a hemisacrectomy can be accomplished after exposure of the sacrum through the posterior approach. Bone allograft, iliosacral screws, and Galveston type fixation are necessary for lumbopelvic stabilization as bony reconstruction after the end of tumor resection[26]. Transpelvic vertical rectus abdominis myocutaneous flap reduces wound complications[27]. In case of anterior sacral meningocele, reverse abdominoperineal approach is the operation of choice because the communications can easily be recognized by posterior approach, and then conveniently sutured at the anterior phase.

Nearby location of the RT to the rectum and the anal canal necessitate good bowel preparation before surgery. Ureteral catheter should be placed to feel and protect the ureters if indicated. Successful resection for highly vascular lesions or for reduction of blood loss during surgery can be facilitated with transcatheter arterial embolization of tumors. Beside of decreased blood loss and more clear surgical vision, possible elimination for the need of anterior approach, and R_0 resection of the sacral chordoma will be pleasing[28].

While planning the surgery, coccyx resection consideration is important. Routine resection of the coccyx this is mandatory if the coccyx is free of malignancy the histopathology is not clear. Local recurrence rate rise up to 25% to 56% if RT resection is not achieved with coccyx resection by transsacral approach[29].

Radical surgeries such as total sacrectomy in case of first sacral bone involvement has been tried out but structural and neurologic sequels are very high[20]. Postoperative neurogenic bladder rate up to 15% and fecal incontinence at a rate of 7% cause severe social life problems[21]. Immolation of sacral nerves bilaterally creates this problem in almost always every cases but unilateral sacrification can give a chance to preserve these functions well[30]. Normal continence and defecation can be protected not only with conservation of S-1 and S-2 bilaterally but also at least one S-3 nerve root is required to protect normal bowel and anorectal function[8]. Urinary and fecal incontinence and impotence in males are almost inevitable after sacrification of S2-S4 nerve roots at both side. Bilateral S2 root preservation leads to mild and reversible bladder sphincter dysfunction which responds to rehabilitative treatment in certain extend.

Laparoscopic approach is reported to be feasible and safe. Surgical trauma reduction, better visualization of the deep structures in the presacral space and less vascular and neurological injuries are benefits of laparoscopy[31]. There is a case of RT operated with the help of robotic device. Beside of the known benefits of

laparoscopy, such as pain, scar, hospital stay reduction, the greatest advantage of a robotic approach to the PS is improving surgical technique to allow retraction and handiness provided by the instruments in this confined area. Longer operative time and high cost are two potential disadvantages of the robotic technology expected to be overcome[32].

Demonstration of the efficacy of adjuvant treatment in rare and heterogeneous disease of RTs is difficult. Even though it has a minimal role in management of RTs, adjuvant chemoradiotherapies have been tried in some surgically unresectable lesions. Chordomas are the most aggressive and radiation resistant tumor at this location but high dose radiation therapy has been tried[33]. Radiation of the affected area with neutrons by high linear energy transfer therapy or charged particle carbon ion radiotherapy (CIRT) in inoperable and recurrent chordomas was able to show 54% local control rate[34]. After 3 years follow up, conventional radiotherapy and CIRT demonstrated 35% and 73% control rates respectively. Big radiosensitive tumors can be decreased in size and this can help to preserve vital elements of the pelvic region. Direct radiation to smaller field also decreases the patient morbidity[35]. However long-term response to this therapy is doubtful.

Inhibitor of epidermal growth factor receptor's tyrosine kinase domain, such as Imatinib, Cetuximab, gefitinib has been shown to be effective in the management of recurrent and metastatic chordoma[36,37]. Proceedings with Imatinib chemotherapy have helped to increase progression-free survival in advanced chordomas cases[22]. Some RTs such as Ewing sarcoma, osteogenic sarcoma, neurofibrosarcomas, and desmoid tumors necessitate neoadjuvant therapy.

PROGNOSIS

Patients with malignant RT have significantly worse perioperative and long-term complications when compared with the benign counterparts. Even the type of operation has no impact on the long-term complications, long term survival can be reduced 70% with proper oncologic resections[38]. Local recurrence rate increases from 28% to 64% if the tumor was violated during the surgery which brings to mind a well-known "no touch" subject in colorectal cancer surgery[39].

Overall survival for benign RTs was reported to be nearly 100% in most studies[8]. The recurrence rate was reported to be 0%-11.1% for benign and 47.6%-75% for malignant RTs[12,21]. In case series, the local recurrence rate was reported to be 6.7% to 11.11% for presacral lesions, 15% for developmental presacral cysts, 47.6% for malignant RTs, and 75% for chordoma[11,12].

One study demonstrating 15% recurrence rate for developmental cysts but it was soon understood that most of these relapses happened in patients with teratomas, than the frequency reduced once en bloc removal of the coccyx which frequently harbors neoplastic cells[21]. Memorial Sloan-Kettering Cancer Center demonstrated difficult local control with 48% local recurrence and 17% overall survival rates for malignant lesions[40]. More than 20% ten-year survival and 96% recurrence rates were talked about chordomas in early studies but outcomes have improved with improvements in surgical procedures and management strategies[41]. As reported more recently, 84% ten year survival rate with 44% recurrence rate were achieved[19]. A study including 400 cases of chordomas within the National Cancer Institute's Surveillance, Epidemiology and End Result program demonstrated that five and ten year survival rate for sacral chordomas were 74% and 32% respectively[18]. The most important point in determination of prognosis of chordoma is negative surgical margin. Unfortunately some authors have concluded that total excision of chordoma is nearly impossible and recurrence is inevitable[41].

It should be stressed once more that R_0 excision at the first operation is crucial because reexcision of recurrent RT is much more complicated and hopeless[11].

CONCLUSION

RTs can be classified as congenital, inflammatory, neurogenic, osseous, or miscellaneous and each of the above categories is subdivided as benign and malignant lesions. Common or nonspecific perianal, perineal or abdominal symptoms should be elicited with careful history. The most common presentation is an asymptomatic mass discovered on routine rectal examination. High index of suspicion in any patient coming with a posterior mass on digital rectal examination, or a post anal dimple, particularly in association with a fistula refractory to multiple operative interventions is essential. Tumors in this area can present diagnostic and therapeutic difficulty because RTs are located in surgically difficult anatomic location with different tissue types and etiologies. When tumor seeding, fecal fistula, meningitis, and abscess formation are brought to mind, biopsy of these lesions should be avoided to as much as possible. After appropriate diagnostic interventions, complete surgical resection remains the primary and only satisfactory treatment. There are three approaches commonly used for resection; abdominal, transsacral, or a combined abdominosacral approach. Coccyx should be excised en bloc only when involved with tumor or existence of doubtful malignant potential. R_0 resection at the first surgical intervention is the most important determinant of prognosis but it may be difficult to achieve for malignant and recurrent lesions.

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Laparoscopic liver resection for the treatment of hepatocellular carcinoma

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Abstract

Accumulation of experiences and technological advances after the first report of laparoscopic liver resection (LLR) are now revealing the characteristics and specific advantages of this approach, especially for hepatocellular carcinoma (HCC) patients with chronic liver diseases (CLD). In laparoscopic approach, there are minimum needs for: (1) laparotomy and dissection of the attachments and adhesion which may cause destructions in the collateral blood and lymphatic flows; and (2) compression of the liver which may cause parenchymal damage for the liver resection (LR). These are especially beneficial for the patients with CLD. LLR results in minimal postoperative ascites and the other complications, which could potentially lead to lowering the risk of fatal liver failure. These characteristics of LLR facilitate surgical treatment application to the patients of HCC with background CLD. Laparoscopic approach also results in improved vision and manipulation in a small operative field under several conditions, including the cases where it is necessary to perform repeat LR between adhesions. These characteristics make LLR safer and more accessible to the repeat treatment, such as multicentric and metachronous lesions in the cirrhotic liver. These advantages of LLR indicate it is a superior method than open LR under certain conditions in patients of HCC with background CLD.

Key words: Laparoscopic hepatectomy; Hepatocellular carcinoma; Liver cirrhosis; Chronic liver disease; Liver tumor; Liver resection; Repeat hepatectomy; Bridging therapy to transplantation; Ascites; Postoperative liver failure

Core tip: In laparoscopic approach, there are minimum needs for: (1) laparotomy and dissection of the attachments/adhesion which may cause destructions in the collateral blood/lymphatic flows; and (2) compression of the liver which may cause parenchymal damage for liver resection (LR). Therefore, laparoscopic LR (LLR) results in minimal postoperative ascites and following fatal complications in the patients with hepatocellular carcinoma and chronic liver disease. Laparoscopic

approach also results in improved vision and manipulation in a small operative field in the case of repeat LR between adhesions. These characteristics make LLR safer and more accessible to the repeat treatment, such as multicentric/metachronous lesions in cirrhotic liver.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related deaths[1,2]. Treatment options for HCC include liver resection (LR)[3], liver transplantation[4], transarterial chemoembolization (TACE), and local ablation therapy[5]. Most experts think LR and liver transplantation are the best hopes for cure. However, patients with HCC usually have underlying chronic liver disease (CLD), and hence are at high risk of developing significant postoperative complications and also multicentric/metachronous lesions. Although liver transplantation should be considered in patients with deteriorating liver function according to the Milan criteria[6], LR should be considered as a primary therapy in patients with well-preserved liver function[7,8]. When considering the treatment of HCC in patients with CLD, the degree of invasive surgical stress[9], especially to the background liver, should be considered in addition to the oncological effects. Patients with CLD have high rates of morbidity and mortality at surgery[10], which increase according to Child-Pugh class of the patients[11]. Even limited open LR often develops refractory ascites, which leads to fatal liver failure in severe CLD patients[12,13].

In Japan, criteria is based on three parameters for selecting patient eligibility for LR: (1) the presence or absence of ascites; (2) total serum bilirubin level; and (3) indocyanine green retention rate at 15 min (ICG R15)[14]. Although there are other treatment options for HCC, local ablation therapy and TACE, depending on the tumor condition and the liver function, a large number of patients with severe CLD are still not able to undergo those treatment modalities. This is especially true in the condition of patients that need repeat treatments for multicentric metachronous lesions occurring in chronic impaired liver. For those patients, "less invasive" laparoscopic LR (LLR) may provide a good option.

Since the first successful report of laparoscopic liver wedge resection in 1992[15], LLR is thought to be a "less invasive" procedure than open LR (OLR)[16]. In a comprehensive meta-analysis study, LLR was compared to OLR in 1678 patients across 26 studies. While it is associated with longer operating times and no differences in oncological outcomes, it is advantageous in several aspects, such as reduced amount of bleeding, decreased time of application of Pringle's maneuver, decreases in morbidity rate, and shorter hospital stay[17]. Recent technological development of devices and accumulation of experiences have facilitated the expansion of LLR indication[18,19]. In addition to common advantages of laparoscopic surgery[20], accumulation of experiences is now revealing specific advantages of LLR, especially for HCC and CLD patients.

The characteristics and advantages of LLR for HCC patients are discussed in this review.

LLR FOR HCC PATIENTS: AN OVERVIEW

LLR may be particularly advantageous for cirrhotic patients, given the potential for lower levels of parietal and hepatic injury, which leads to the preservation of venous/lymphatic collateral circulation. Several studies have shown the safety and feasibility and its short-term benefits of LLR for HCC patients[21-28]. To date, several studies[29-33], in which the groups of laparoscopic and open LR in comparison had comparable background liver condition, have investigated the major differences between the groups (Table 1)[29,34-41]. Favorable short-term results, including fewer incidences of ascites and liver failure, and shorter hospital stays, correlate with the laparoscopic procedure without the compromise of overall survival (Table 1). In addition to usual advantages of laparoscopic surgery, LLR has the advantage of minimal ascites, due to lower damage on venous/lymphatic collateral circulation, which leads to lower risk of fatal liver failure. This feature of LLR could be one of the most remarkable specific advantage.

When patients undergo LR, they are exposed three types of stresses: (1) general, whole-body surgical stress; (2) reduced liver function due to resected liver volume; and (3) surgery-induced injury to the environment around the liver caused by laparotomy and mobilization of the liver and to the liver parenchyma caused by compression of the liver. Reduction of the third injury with LLR lowers the risk of fatal complications for patients with severe CLD.

We also experienced that HCC patients with severe CLD (Child-Pugh class B/C and ICG R15 of $\geqslant$ 40%) who underwent LLR had favorable and comparable perioperative outcomes to patients with mild/moderate CLD[42]. As of June 2014, 53 patients with HCC and CLD underwent LLR in our hospital. Nine out of 53 patients had severe CLD (Child-Pugh class B/C and ICG R15 of $\geqslant$ 40%). These nine and 41 patients (Child-Pugh class A and ICG R15 of 10.1%-27.4%; three patients were excluded from analysis because of concomitant combined surgery) were compared in short-tem outcomes. The results, such as operative bleeding, day of oral intake restored, postoperative drain discharge, morbidity and mortality, were comparable in the groups. Among these nine patients, one underwent living-related liver transplantation 20 mo after hepatectomy.

This extensive review of the literature in combination

Table 1 Recent reports of laparoscopic and open liver resction comparative studies for hepatocellular carcinoma

Ref.	% of LC patients		Ascites		Liver failure		Hospital stay (d, mean ± SD)		Mortality		Overall survival (5-yr, %)	
	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR	OLR
Lai *et al*[34]	92	93.94	NA	NA	NA	NA	NA	NA	0/25	1/33	60 (3-yr)	NA
Aldrighetti *et al*[35]	56.25	56.25	0/16	1/6	NA	NA	6.3 ± 1.7	9 ± 3.8	0/16	0/16	(No significant difference)	
Tranchart *et al*[36]	73.81	80.95	3/42	11/42	0/36	4/53	6.7 ± 5.9	9.6 ± 3.4	1/42	1/42	59.5	47.4
Kim *et al*[37]	92.31	86.21	0/26	1/29	NA	NA	11.08 ± 4.96	16.1 ± 10.7	0/26	0/29	84.6 (2-yr RFS)	82.8 (2-yr RFS)
Lee *et al*[38]	84.85	64	0/33	2/50	NA	NA	NA	NA	0/33	0/50	76	76.1
Truant *et al*[39]	100	100	5/36	12/53	NA	NA	6.5 ± 2.7	9.5 ± 4.8	0/36	4/53	70	46
Ker *et al*[29]	NA	NA	2/116	26/208	NA	NA	6.2 ± 3	12.4 ± 6.8	0/116	6/208	62.2	71.8
Kanazawa *et al*[40]	100	100	3/28	18/28	0/28	0/28	10 (6-25)[1]	19 (8-49)[1]	0/28	0/28	NA	NA
Cheung *et al*[41]	87.5	71.9	0/32	1/64	NA	NA	4 (2-16)[1]	7 (4-42)[1]	2/32	12/64	76.6	57

[1]Median (range). LC: Liver cirrhosis; NA: Not available; RFS: Recurrence free survival; LLR: Laparoscopic liver resection; OLR: Open liver resection.

Table 2 Advantages and disadvantages of laparoscopic liver resection in technical aspects

Advantages
Good view and manipulation in a small operative field-minimum damages on the environment around the liver
Meticulous manipulation under magnified view
Less adhesion after surgery
Good view in the dorsal area of the liver around inferior vena cava
Dissection and handling organs/tumors using postural change and the gravity with the maintenance of similar view by the laparoscopic adjustments[43,44]
Less venous bleeding under the pneumo-peritoneal pressure
Disadvantages
Restrictions on the movements of forceps
Difficulties of handling large-sized/volume organs and tumors
These should be conquered with port arrangements and dissection and handling organs/tumors using postural change and the gravity
Lack of tactile sensation
Lack of overview of whole operative field
These easily lead to disorientation during surgery and should be conquered with preoperative (MDCT) simulation plus intraoperative US navigation

MDCT: Multidetector computed tomography; US: Ultrasonography.

with our experiences indicates that LLR is the better therapeutic option for severe CLD patients with tumors on the surface of the liver, especially after repeat treatments. LLR for severe CLD patients may also prove to be an advantageous option in bridging therapy to liver transplantation.

LLR FOR HCC PATIENTS: ADVANTAGES AND DISADVANTAGES IN TECHNICAL ASPECTS

At the introduction of LLR in 1997, we selected the patients who could undergo adequate oncological LLR for cancers. The indication of LLR had been gradually extended from liver surface partial resection to large anatomical resection (right/left hepatectomy and posterior/anterior/median sectionectomy). The inclusion criteria are now a tumor size less than 15 cm without severe adhesion, invasion to major vessels, or a need for reconstruction of vessels or biliary tract.

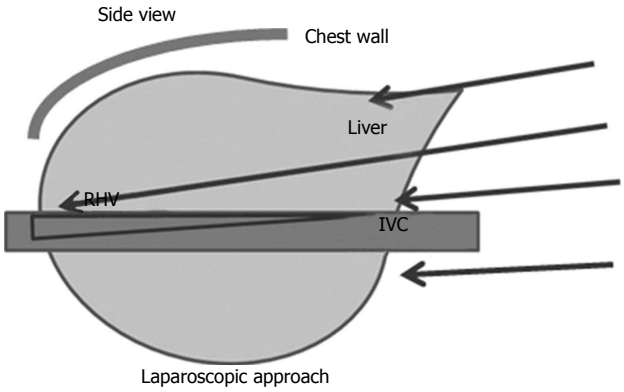

Figure 1 The subphrenic space is the cage with the liver inside. In the laparoscopic approach of hepatectomy, a laparoscope and forceps are entering into the cage directly from caudal direction and obtain a good vision and manipulation in the small operative field for resection. IVC: Peri-inferior vena cava; RHV: Right hepatic vein.

As of June 2014, we have performed 53 of LLR for HCC and CLD patients, including 17 cases of anatomical resections and 9 cases of repeat hepatectomy (including 1 patient of 4th laparoscopic hepatectomy). There was no operative-mortality and the rate of morbidity (Clavien-Dindo Grade Ⅱ or above) was 17.0%. Tumor numbers are 1-4 and sizes are 0.8-14.5 cm. The median of their operating time and blood loss was 315 min and 100 mL. From these and the other experiences, we propose advantages and disadvantages of LLR in technical aspects, listed in Table 2.

The subphrenic space is the cage with the liver inside. In the laparoscopic approach of LR, a laparoscope and forceps are entering into the cage directly from caudal direction and obtain a good vision/manipulation for resection in the small field (Figure 1). On the other hand in open approach, the cage is opened with the big subcostal incision and the liver is picked up with the dissection of retroperitoneal attachments before resection. Therefore, in the laparoscopic approach, there are minimum needs for: (1) dissection of the attachments/adhesions which may cause destructions of the collateral blood and lymphatic flows; and (2) compression of the liver which may cause parenchymal damage, in addition to the minimum abdominal wall

incision. These characteristics lead to two advantages especially beneficial for HCC patients with CLD: (1) Advantageous for repeat procedures: Repeat LLR for patients with CLD and repeat lesions was feasible and safe. The procedure resulted in less adhesion and good vision/manipulation in the small area between adhesions; and (2) Minimal invasion due to good vision and manipulation in small operative fields (a minimum need for extended dissection of attachments and adhesions): With adequate port arrangement and positioning of patients[41,42], the manipulation in the small operative field is facilitated by good vision of the peri-inferior vena cava area, subphrenic space, the area next to the attachment of retro-peritoneum, and the area between the adhesions. Therefore, there is a minimum need for dissection/adhesiolysis that could cause destructions of the collateral blood and lymphatic flows.

CONCLUSION

There are minimum needs in laparoscopic approach for: (1) laparotomy and dissection of the attachments/adhesion which may cause destructions in the collateral blood/lymphatic flows; and (2) compression of the liver which may cause parenchymal damage in laparoscopic approach. These are especially beneficial for CLD patients. LLR results in minimal postoperative ascites, which could potentially lead to lower risk of fatal complications. These characteristics of LLR facilitate the surgical treatments for HCC/CLD patients.

LLR also results in improved vision and manipulation in a small operative field under several conditions, including the cases where it is necessary to perform repeat hepatectomy between adhesions, such as multicentric/metachronous lesions in the cirrhotic liver. These characteristics could make LLR a safer and more accessible approach for patients with repeat treatments.

These advantages of LLR indicate it is a superior method when compared to OLR under certain conditions in patients with HCC and CLD.

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MINIREVIEWS

Robotic surgery *vs* conventional laparoscopy for the treatment of rectal cancer: Review of the literature

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Abstract

Laparoscopic surgery has established itself as a safe and effective alternative to open surgery for the treatment of colorectal cancer. However, laparoscopic resection of rectal cancer, and in particular of the lower rectum, remains challenging in view of the limitations of operating in the confined pelvic space, limited movement of instruments with fixed tips, assistant-dependant two-dimensional view, easy camera fogging, and poor ergonomics. The introduction of robotic surgery and its application in particular to pelvic surgery, has potentially resolved many of these issues. To define the role of robotic surgery in total mesorectal excision for rectal cancer, a review of the current literature was performed using PubMed, Embase, Cochrane Library, and Google databases, identifying clinical trials comparing short-term outcomes of conventional laparoscopic total mesorectal excision with the robotic approach. Robotic surgery for rectal cancer is a safe alternative to conventional laparoscopy. However, randomised trials are needed to clearly establish its role.

Key words: Rectal cancer; Total mesorectal excision; Laparoscopic surgery; Robotic surgery

Core tip: Robotic surgery for rectal cancer is a promising approach since it allows a better view of the pelvic cavity and enhanced freedom of instrument movements when compared to conventional laparoscopy. This would potentially translate into a better oncological dissection, and reduced risk of injury to neurovascular structures. This review of the literature shows that no definite conclusion of the potential benefits of robotic surgery can be drawn, and that larger prospective studies with long-term follow up are needed to establish the role of the procedure.

Privitera A, Salem A, Elgendy K, Sabr K. Robotic surgery *vs* conventional laparoscopy for the treatment of rectal cancer: Review of the literature. *World J Surg Proced* 2015; 5(1): 142-146 Available from: URL: http://www.wjgnet.com/2219-2832/full/v5/i1/142.htm DOI: http://dx.doi.org/10.5412/wjsp.v5.i1.142

INTRODUCTION

Laparoscopic colorectal surgery has been shown to be a safe and effective approach offering similar outcomes to open surgery. Advantages of laparoscopy in terms of pain reduction, lower incidence of postoperative ileus, shorter hospital stay and early return to unrestricted activities, have promoted the widespread use of this technique[1-3]. Fast track and enhanced recovery programs have greatly been facilitated by the introduction of laparoscopy that has been shown to reduce peri-operative stress response[4]. Laparoscopic surgery for colonic cancer has been well accepted and is currently widely practised, however, the application of the technique to rectal cancer, in particular of the lower rectum necessitating a total mesorectal excision (TME), has been limited[5]. In fact, laparoscopic surgery in the narrow pelvic space is challenging and requires a steep learning curve. Limitations include poor ergonomics, easy crowding and clashing of instruments, tremor, fogging of camera, assistant-dependent 2-dimensional view, and difficulty in performing high precision suturing[5-7]. The recent introduction of robotic surgery could overcome the limitations of conventional laparoscopy in technically demanding rectal procedures. In fact, it offers a 3-dimensional 10-fold magnification, articulating instruments, comfortable and ergonomic operating position, and other features including motion scaling and possibility of remote tele-surgical applications[8-10]. The similarity of robotic surgery to the open approach could significantly shorten the learning curve for minimally invasive TME, leading to a widespread use of this technique[11]. However, limiting factors of the robotic system include: lack of tactile and tensile sensation, cumbersome and time-consuming docking of the robotic cart, and possible delay to open conversion should serious intra-operative complications occur. Also, the high cost of the device and its maintenance have prevented many units to adopt the procedure[12,13].

The aim of this study was to analyse the current literature to evaluate whether robotic total mesorectal excision offers better short-term outcomes when compared with conventional laparoscopic surgery.

LITERATURE RESEARCH

An extensive search was conducted through electronic databases (PubMed, Embase, Cochrane Library, Science Direct, Google Scholar) by using the key words "rectal surgery," "rectal cancer", "laparoscopic", "robotic". The reference lists provided by the identified articles were additionally hand-searched for studies missed by the search strategy, and this method of cross-referencing was continued until no further relevant publications were identified. Only articles in the English language were selected. All studies comparing outcomes of robotic and laparoscopic resection for extra-peritoneal and intra-peritoneal rectal cancer were selected and included in the review process. One three-arm study (open, laparoscopic and robotic) was also selected, but studies including hand-assisted with no data separation from the purely laparoscopic cases were excluded. Studies on colonic cancer including recto-sigmoid and benign disease were excluded. Of similar studies pertaining to the same institution only the largest series was considered, unless a different design methodology was used.

The primary outcome measured was whether robotic rectal cancer surgery provides improved postoperative outcomes in comparison with the standard laparoscopic approach. Selected peri-operative variables included mean operating time, conversion to open procedure, complication rate, anastomotic leakage, and length of stay. Pathological variables included distal resection margin (DRM), number of lymph nodes harvested, and circumferential resection margin (CRM). Urinary dysfunction and erectile dysfunction (ED) data were also included.

RESULTS

Ten studies met predefined inclusion criteria[14-23]. These were all retrospective comparative studies including a case-control study[19]. Operative data showed conversion rate was significantly higher in the laparoscopic group (LG) than the robotic group (RG) in three of the studies. Robotic surgery had longer operative time in five studies (Table 1). There was no difference in complication rate including anastomotic leakage in the two groups. As regards length of stay, this was longer in the LG in three studies. In one study length of stay was longer in the RG (Table 2). No significant differences were noted between the RG and LG as regards distal resection margins and only one study showed a higher number of lymph nodes harvested in the RG. One study showed CRM positivity to be significantly higher in the laparoscopic group (Table 3). No significant difference in urinary dysfunction was reported. In one study erectile dysfunction in sexually active patients was significantly higher in the LG (Table 4).

DISCUSSION

Robotic TME has mainly been introduced in centers with a high volume of rectal cancer surgery and expertise in minimally invasive procedures[5]. The reports in the literature relate to small, non randomised, single centre experiences with consequent inability to draw definitive conclusions. An important feature of robotic surgery is the improved exposure and visualization of the surgical field, allowing for a precise dissection in the narrow pelvic cavity. Also, the free range of instrument movements, the aid offered by the fourth arm, may contribute to a less challenging dissection than laparoscopy with consequent reduction in intra-operative complications and conversion rate[21]. In our

Table 1 Intraoperative data

Ref.	Technique (*n*)		Conversion (%)			Operative time (min, mean)		
	RG	LG	RG	LG	*P* value	RG	LG	*P* value
Baek *et al*[14]	41	41	7.3	22	NS	296	315	NS
Baik *et al*[15]	56	57	0	10.5	0.013	178	179	NS
Patriti *et al*[16]	29	37	0	19	< 0.05	202	208	NS
Bianchi *et al*[17]	25	25	0	4	NS	240	237	NS
Park *et al*[18]	41	82	0	0	NS	231.9	168.6	< 0.001
Kwak *et al*[19]	59	59	0	3.4	NS	270	228	< 0.0001
Baek *et al*[20]	154	150	NA	NA	NA	285.2	219.7	0.018
D'Annibale *et al*[21]	50	50	0	6	0.011	270	275	NS
Kang *et al*[22]	165	165	0.6	1.8	NS	309	277	< 0.001
Tam *et al*[23]	21	21	5	0	NS	260	240	0.04

NS: Non significant; NA: Not available; RG: Robotic group; LG: Laparoscopic group.

Table 2 Postoperative outcomes

Ref.	Complications (%)			AL (%)			LOS (d, mean)		
	RG	LG	*P* value	RG	LG	*P* value	RG	LG	*P* value
Baek *et al*[14]	21.9	26.8	NS	8.6	2.9	NS	6.5	6.6	NS
Baik *et al*[15]	10.7	19.3	NS	1.7	7.6	NA	5.7	7.6	0.001
Patriti *et al*[16]	30.6	18.9	NS	6.8	2.7	NS	11.9	9.6	NS
Bianchi *et al*[17]	16	24	NS	1.8	8	NS	6.5	6.4	NS
Park *et al*[18]	29.3	23.2	NS	9.7	7.3	NS	9.9	9.4	NS
Kwak *et al*[19]	321	27.1	NS	13.6	10.2	NS	NA	NA	NA
Baek *et al*[20]	32.4	27.3	NS	11	12	NS	11.1	10.8	NS
D'Annibale *et al*[21]	5	11	NS	10	14	NS	8	10	0.03
Kang *et al*[22]	20.6	27.9	NS	7.3	10.8	NS	10.8	13.5	0.003
Tam *et al*[23]	43	33	NS	0	14	NS	6	5	0.05

AL: Anastomotic leakage; LOS: Length of stay; NS: Non significant; NA: Not available; RG: Robotic group; LG: Laparoscopic group.

Table 3 Postoperative outcomes

Ref.	DRM (cm)			LN (*n*)			CRM (%)		
	RG	LG	*P* value	RG	LG	*P* value	RG	LG	*P* value
Baek *et al*[14]	3.6	3.8	NS	13.1	16.2	NS	2.4	4.9	NS
Baik *et al*[15]	4	3.6	NS	17.5	17	NS	4	5	NS
Patriti *et al*[16]	2.1	4.5	NS	10.3	11.2	NS	0	0	NS
Bianchi *et al*[17]	2	2	NS	18	17	NS	0	4	NS
Park *et al*[18]	2.1	2.3	NS	14.2	17.3	NS	3.9	5.6	NS
Kwak *et al*[19]	2.2	2	NS	20	21	NS	1.7	0	NS
Baek *et al*[20]	NA	NA	NA	NA	NA	NA	NA	NA	NA
D'Annibale *et al*[21]	3	3	NS	13.1	16.2	NS	0	12	0.011
Kang *et al*[22]	1.9	2	NS	16.5	13.8	NS	4.2	6.7	NS
Tam *et al*[23]	3.9	5.5	NS	17	15	0.03	0	5	NS

DRM: Distal resection margin; LN: Lymph nodes harvested; CRM: Circumferential resection margin; NS: Non significant; NA: Not available; RG: Robotic group; LG: Laparoscopic group.

review, conversion rates were significantly lower in the RG in 3 studies. The common reasons for conversion included pelvic wall bleeding, restricted movement in very narrow pelvic cavity, and perforation of the rectal wall[15,16,21].

Significant longer operative times in the RG were reported in 5 studies[18-20,22,23]. This was mainly attributed to the time required to set up the robotic system and need for re-docking when starting the pelvic part of the procedure. However, adoption of particular trocar positions and technique modification may reduce total operating time[21,24]. An appealing feature of robotic surgery is the relatively short learning curve. Reports have shown that only 12 robotic operations are needed to become proficient in the technique, and achieve similar outcomes to those of a laparoscopic surgeon after one hundred procedures[25]. Also, proficiency in robotic rectal cancer surgery can be achieved after 25 cases[26].

Postoperative complication rates including anastomotic leakage were not statistically significant in the two groups. In one study there were fewer serious

Table 4 Postoperative outcomes

Ref.	ED (%)			UD (%)		
	RG	LG	*P* value	RG	LG	*P* value
Baek *et al*[14]	NA	NA	NA	NA	NA	NA
Baik *et al*[15]	NA	NA	NA	NA	NA	NA
Patriti *et al*[16]	5.5	16.6	NS	3.4	2.7	NS
Bianchi *et al*[17]	NA	NA	NA	NA	NA	NA
Park *et al*[18]	NA	NA	NA	0	2.4	NS
Kwak *et al*[19]	NA	NA	NA	NA	NA	NA
Baek *et al*[20]	NA	NA	NA	NA	NA	NA
D'Annibale *et al*[21]	5.5	56.5	0.045	3.5	4.2	NS
Kang *et al*[22]	NA	NA	NA	2.4	4.2	NS
Tam *et al*[23]	NA	NA	NA	NA	NA	NA

ED: Erectile dysfunction; UD: Urinary dysfunction; NS: Non significant; NA: Not available; RG: Robotic group; LG: Laparoscopic group.

complications in the RG, however, the overall complication rate that included back pain and scrotal swelling, was not statistically different[15]. Another study revealed no significant differences, though the RG had numerically fewer complications[17]. As regards length of stay, this was longer in the LG in three studies[15,21,22]. The shorter hospital stay may have been the result of a lower complication rate in robotic TME and quicker time to oral diet compared to laparoscopic TME[21]. In one study the length of stay in the RG was longer. However, this was explained by the higher number of abdomino-perineal resection and procto-colectomy in the robotic group.

There are two key points in rectal surgery: oncological adequacy of the specimen and nerve-sparing technique. Total mesorectal excision was developed to allow a complete excision of the lymph node containing mesorectum, thus reducing local recurrence, improve overall survival, and providing good quality of life[27]. The quality of the specimen is considered a parameter for the evaluation of prognosis[28]. In our review, one study showed that the CRM involvement was significantly higher in the LG[21]. Another study showed no significant differences in the CRM and DRM between the RG and LG, but the rectal cancer was closer to the anal verge in the RG. This finding together with a better macroscopic grading of quality of dissection in RG group, may support the potential benefit of robotic surgery to allow for optimal oncological resection of the lower rectum[15].

Another important potential advantage of robotic surgery is the better visualisation, identification and protection of the autonomic innervation, thus minimising the risk of sexual and bladder dysfunction. The 3-dimensional image of the robotic system, the optimal counter traction of the robotic arm, and possibility of precise dissection in the virtually created wider operating space, are pivotal features of particular benefit in obese and male patients with narrow pelvis. Unfortunately, only few studies report data pertaining urinary and erectile dysfunction. In our review, there were no significant differences in urinary dysfunction in the two groups. One study showed worsening of the International Prostate Symptom Score (IPSS) 1 mo after surgery in both groups, and a normalisation 1 year after surgery[21]. A recent report in the literature showed that bladder function improved significantly over the first 6 mo after laparoscopic TME and 3 mo after robotic TME, with better outcomes in the RG in the IPSS score[29].

As regards ED, only 2 studies reported comparative outcomes[16,21]. In one study erectile function was impaired in 5% of sexually active patients in the RG compared to 57% in the LG 1 year after surgery. This was mainly attributed to the easier preservation of autonomic nerves in the RG with the added advantage of better control of energy delivery and consequent avoidance of inadvertent nerve cauterization[21].

CONCLUSION

Robotic surgery for rectal cancer is a safe and effective alternative to conventional laparoscopic surgery. Potential benefits including shorter learning curve, better vision in the narrow surgical space facilitating better dissection with preservation of neuro-vascular structure, may well outweigh the high capital and running costs. However, only prospective clinical trials with larger number of patients and long-term follow-up can definitely answer the question of whether the advanced technology of the robotic system clearly offers advantages in terms of surgical and oncological outcomes.

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Feasibility and oncological outcomes of laparoscopic rectal resection following neo-adjuvant chemo-radiotherapy: A systematic review

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Abstract

AIM: To study the feasibility and oncological outcomes following laparoscopic total mesorectal excision (LTME) in patients who have received Neo-adjuvant long course chemo-radiotherapy (LCRT).

METHODS: A protocol driven systematic review of published literature was undertaken to assess the feasibility and oncological outcomes following LTME in patients receiving LCRT. The feasibility was assessed using peri-operative outcomes and short term results. The oncological outcomes were assessed using local recurrence, disease free survival and overall survival.

RESULTS: Only 8 studies-1 randomized controlled trial, 4 Case Matched/Controlled Studies and 3 Case Series were identified matching the search criteria. The conversion rate was low (1.2% to 28.1%), anastomotic leak rates were similar to open total mesorectal excision (0%-4.1% *vs* 0%-8.3%). Only 3 studies reported on local recurrence rates (5.2%-7.6%) at median 34 mo follow-up. A single study described disease free survival and overall survival at 3 years as 78.8% and 92.1% respectively.

CONCLUSION: LTME following LCRT is feasible in experienced hands, with acceptable short term surgical outcomes and with the usual benefits associated with minimally invasive procedures. The long term oncological outcomes of LTME after LCRT appear to be comparable to open procedures but need further investigation.

Key words: Laparoscopic total mesorectal excision; Rectal adenocarcinoma; Feasibility; Outcomes; Neo-adjuvant chemo-radiotherapy

Core tip: Laparoscopic total mesorectal excision (LTME) following long course chemo-radiotherapy (LCRT) is

feasible in experienced hands, with acceptable short term surgical outcomes and with the usual benefits associated with minimally invasive procedures. The long term oncological outcomes of LTME after LCRT appear to be comparable to open procedures but need further investigation.

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INTRODUCTION

Total Mesorectal Excision using an open approach (OTME) is now accepted as the gold standard for treatment rectal cancer[1]. In recent years, since the medical research council United Kingdom trial, neo-adjuvant long course chemo-radiotherapy is being routinely used as a part of treatment of locally advanced mid and low rectal cancers[2]. Laparoscopic rectal resection has been shown to have superior short term outcomes compared to open resections. However, long term oncological results are still debated[3]. In addition, it is generally accepted that laparoscopic low rectal resection and Abdomino-perineal resections (APR) are technically challenging[4].

Most trials comparing laparoscopic and open resections for rectal cancer suggest that laparoscopic rectal resections are technically feasible however, short and long term outcomes in this group are difficult to determine[5,6]. Also, laparoscopic total mesorectal excision (LTME) following neo-adjuvant chemo-radiotherapy (LCRT) is oncologically and technically challenging due to tissue fibrosis and scarring[7].

This systematic review addresses the feasibility and outcome of laparoscopic rectal resection following neo-adjuvant chemo-radiotherapy. There is no level 1 evidence addressing this and to the best of our knowledge there is no structured review of the published literature on this topic.

MATERIALS AND METHODS

A systematic review of literature was performed as per the protocol described below to address the issue of feasibility of laparoscopic TME following neo-adjuvant chemo-radiotherapy. PubMed, Cochrane, Embase, OVID, and CINAHL were searched for articles published between Jan 2004 to June 2014 using the search criteria as described in Table 1.

The keywords for search were laparoscopy, minimally invasive surgery, open, rectum, cancer, abdomino-perineal resection, anterior resection, colorectal neoplasms, rectal neoplasms, rectal adenocarcinoma, rectal cancer, neo-adjuvant chemo-radiotherapy, proctectomy, and total mesorectal excision. Search was done as free text words and in their variable combinations.

Table 1 Search strategy

Search strategy
1 Rectal adenocarcinoma - tracked to MeSH to include all subheadings and combining with OR and clicking the Explode box; limit to English language and Humans - no time limits selected
2 Surgery - tracked to MeSH to include all subheadings and combining with OR and clicking the Explode box; limit to English language and Humans - no time limits selected
3 Laparoscopy - tracked to MeSH to include all subheadings and combining with OR and clicking Explode box; limit to English language and Humans - no time limits selected
4 Minimally invasive surgery - tracked to MeSH to include all subheadings and combining with OR and clicking Explode box; limit to English language and Humans - no time limits selected
5 Anterior Resection - Keyword search only (not linked to MeSH headings)
6 Neo-adjuvant chemo-radiotherapy
7 Proctectomy - Keyword search only (not linked to MeSH headings)
8 Total Mesorectal Excision - Keyword search only (not linked to MESH headings)
9 Combine 1 and 2 and 5 and 6 and 7 and 8
10 Combine 1 and 3 and 4 and 5 and 6 and 7 and 8

Study selection

The retrieved results were screened by two authors (Dhruva Rao PK and Nair MS) using the title and abstracts against the inclusion and exclusion criteria as described below. Any studies that did not have published abstracts were excluded. Full text articles of potentially relevant studies were obtained and assessed independently by two authors (Dhruva Rao PK and Nair MS) considering the inclusion and exclusion criteria for review. All references of all guideline articles and review articles were searched to identify any potential articles not already identified. Disagreements were resolved through discussion and by involving the third author (Haray PN).

Inclusion criteria

Randomized studies comparing open and laparoscopic rectal resection following neo-adjuvant chemo-radiotherapy for rectal adenocarcinoma; Case matched series comparing LTME with OTME following neo-adjuvant chemo-radiotherapy for rectal adenocarcinoma; Case control studies comparing LTME with OTME following neo-adjuvant chemo-radiotherapy for rectal adenocarcinoma; Case series with > 20 patients from tertiary centres; Published in English language; Feasibility studies of laparoscopic rectal resections for cancer including historical control cohorts.

Exclusion criteria

Study groups were not clearly defined; Studies in whom the "cancer" group cannot be separated; Studies comparing resections performed for benign indications only; Studies including local resections

Table 2 Overview of studies with extractable data

Ref.	Year	Country	Type of study	Total No. of patients	Patients Lap	Patients open
Kang *et al*[9]	2010	South Korea	RCT	340	170	170
Kusano *et al*[11]	2014	Japan	Case control Study	33	19	14
Hu *et al*[14]	2013	China	Case control Study	137	51	86
Seshadri *et al*[12]	2011	India	Case control Study	144	72	72
Denoya *et al*[15]	2009	United States	Case matched series	64	32	32
[1]Saklani *et al*[13]	2013	South Korea	Case series	64	64	NA
[1]Denost *et al*[10]	2011	France	Case series	292	292	NA
Motson *et al*[7]	2011	United Kingdom	Case series	26	26	NA

[1]Data pertaining to LCRT + laparoscopic resection group of the study only extracted therefore treated as case series. NA: Not applicable; LCRT: Long course chemo-radiotherapy; RCT: Randomized controlled trial.

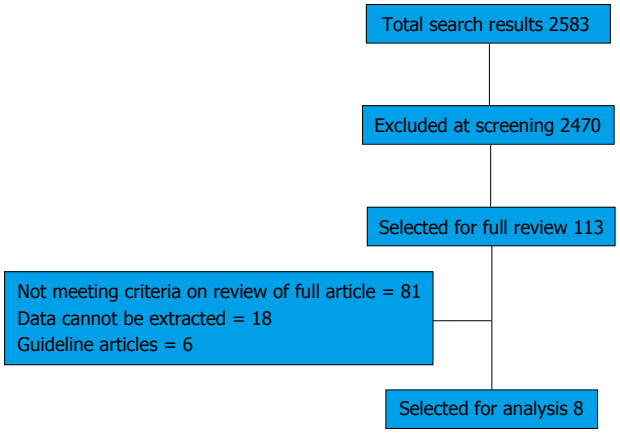

Figure 1 PRISMA flow diagram.

(trans-anal endoscopic microsurgery, trans-anal excision) but the major resection group cannot be separated; the outcomes of interest defined below were not reported or it was impossible to determine them from the published results; the surgical procedures were performed by surgical trainees or by surgeons during the learning curve for laparoscopic or conventional rectal surgery.

Data extraction

A structured proforma was used for data extraction for the patients undergoing laparoscopic resection after neo-adjuvant long course chemo-radiotherapy only. No attempt was made to contact the authors of studies if inadequate amount of information was available and such studies were excluded.

Outcome measures/end-points

We have assessed 2 sets of outcomes.

For feasibility assessment, we have considered estimated blood loss, ureteral injuries, other collateral injuries, overall peri-operative morbidity, length of hospital stay, anastomotic leakage, intra-abdominal abscess, urinary retention, postoperative ileus, 30 d mortality. We have also assessed circumferential/radial resection margin (CRM) and lymph node harvest.

For oncological outcome assessment, we have considered loco-regional recurrence, metachronous distant metastasis, disease free survival (DFS) and overall survival.

Statistical analysis

Prior to pooled analysis, the studies must pass 2 assessments of heterogeneity - qualitative and quantitative[8]. Qualitative assessment is based on 4 key concepts of study design (Patients, Interventions, Outcomes and Study Types). If studies are deemed heterogeneous on this assessment, it is inappropriate to proceed to quantitative assessment using statistical tests such as χ^2 test or Cochrane Q, *etc.*[8]. In this review the studies were deemed heterogeneous based on the above mentioned qualitative criteria and so we did not proceed to statistical analysis.

RESULTS

The initial search identified 2583 studies (Figure 1). Two thousand four hundred and seventy were excluded after initial screening of titles and abstracts. The remaining 113 studies were critically reviewed using the full article. Of these, 26 articles met the inclusion criteria and reviewed in detail. However, data relevant to this review could be extracted from only 8 studies (Table 2). Table 3 summarizes the 18 studies from which adequate extraction of appropriate data was not possible.

The selected publications included a combination of randomized controlled trial (RCT) and non RCT. Qualitative assessment of the studies revealed: (1) Type of studies identified were clearly heterogeneous (Table 2); (2) Patient selection criteria for LCRT were different in the different studies (Table 4); and (3) The LCRT regimen patients received was also different (Table 4).

Thus the studies were heterogeneous in terms of Study Design, Patient Groups and Interventions. Due to this heterogeneity, a pooled analysis or meta-analysis was considered inappropriate and hence was not carried out.

Of the 8 studies included, one was a RCT and 4 were case controlled studies or case matched series. The number of patients in the Laparoscopic group in the selected studies range from 19 to 292. The

Table 3 Studies from which data could not be extracted (sub group analysis not described/reported)

Ref.	Year	Country	Type of study	Percent having LCRT in Lap group
van der Pas *et al*[5]	2013	The Netherlands	RCT[1]	59
Lujan *et al*[6]	2009	Spain	RCT	72.3
Lujan *et al*[16]	2013	Spain	Case Control	58.1
McKay *et al*[17]	2012	Australia	Case Control	48.8
Laurent *et al*[18]	2011	France	Case Control	93.6
Patel *et al*[19]	2011	United States	Case Matched	50
Li *et al*[20]	2011	China	Case Control	34.5
Kellokumpu *et al*[21]	2011	Finland	Case Control	34
Greenblatt *et al*[22]	2011	United States	Case Control	31.6
da Luz Moreira *et al*[23]	2011	United States	Case Matched	33
Baik *et al*[24]	2010	United States	Case Matched	79.6
Westerholm *et al*[25]	2012	Canada	Case Series	7.4
Jefferies *et al*[26]	2011	United Kingdom	Case Series	43.8
Glancy *et al*[27]	2011	United Kingdom	Case Series	8
Lam *et al*[28]	2010	Belgium	Case Series	56.7
Sartori *et al*[29]	2010	Italy	Case Series	39.1
Cheung *et al*[30]	2010	Hong Kong	Case Series	21.5
Park *et al*[31]	2010	South Korea	Case Series	8.1

[1]Patients in this trial had short course radio therapy. LCRT: Long course chemo-radiotherapy; RCT: Randomized controlled trial.

Table 4 Comparison of criteria for long course chemo-radiotherapy and regimes

Ref.	Staging imaging	Criteria for LCRT	Chemo agent	Rad dose/duration
Kang *et al*[9]	CT, MRI, ERUS	cT3N0-2 M0 Mid/low rectal cancer	I/V 5FU + leucovorin or oral capecitabine	50.4 Gy over 5.5 wk (tumour boost used)
Kusano *et al*[11]	CT, MRI	T3N0-3M0[2]	Different protocols	Total dose = 45 Gy/duration not reported
Hu *et al*[14]	CT, MRI, ERUS	Stage 2/3 tumours	Capecitabine and oxaliplatin	50 Gy over 5 wk
[1]Seshadri *et al*[12]	CT	T2/T3 N+, T4 excluded	Mitomycin and 5FU	Total dose = 50 Gy/duration not reported
Denoya *et al*[15]	CT, MRI, ERUS	T3/4 or N+ disease	5FU or Xeloda	Total dose = 50.4 Gy/duration not reported
Saklani *et al*[13]	NR	T3/4 or N+ disease	5FU	Total dose = 50.4 Gy/duration not reported
Denost *et al*[10]	CT, MRI, ERUS	T3/4 = 265 (90.8%), T1/2 = 27 (9.2%)	I/V 5FU and leucovorin	45 Gy over 5 wk
Motson *et al*[7]	CT, MRI	T3/4 N+ + involved/ threatened CRM	5FU or Uftoral	45/50 Gy over 5 wk (3/4 fields)

[1]7/72 (Lap) and 6/72 (open) received only RT; cannot separate data; [2]Using TNM classification of malignant tumours 7th edition 2009. NR: Not reported; LCRT: Long course chemo-radiotherapy; CT: Computed tomography; MRI: Magnetic resonance imaging; CRM: Circumferential/radial resection margin; ERUS: Endoluminal rectal ultra-sound.

only RCT (COREAN trial[9]) that we have been able to identify had 170 patients in the study arm. The study with largest number of patients with LTME following LCRT is from France with 292 patients[10].

The patient characteristics of all the studies are shown in Table 5. As can be seen from the table, they were mid or low rectal tumours. The APR rates varied from 11.2% to 89%. All studies had reported the imaging modalities and selection criteria for LCRT with the type and dose of chemo and radiotherapy (Table 4). There was wide heterogeneity in the type, dose and duration of LCRT among the studies.

Table 6 reports the peri-operative course. The interval between LCRT and surgery was reported by all except by one study[11] with the median minimum and maximum intervals being 6 and 8 wk respectively. The reported conversion rates from laparoscopic to open operations ranged from 1.2% to 28.1%. In the Laparoscopic arm, three of the eight identified studies reported a median estimated blood loss of 200 mL.

While only two studies reported intra operative complications (Table 6), all studies have reported post-operative complications (Table 7). In the studies where comparative data was available, the laparoscopic group had a low anastomotic leak rate compared to the open group (0%-4% *vs* 0%-8.3% respectively). The COREAN trial reported a higher leak rate for LTME *vs* OTME (1.2% *vs* 0% respectively). However, 2 case series reported anastomotic leak rates of 12.7%[10] and 18.7%[7]. Interestingly these had higher conversion rates as well (18.8%[10] and 11.5%[7] respectively). Pelvic abscess was also less in laparoscopic group compared to the open group (0%-10.5% *vs* 0.6%-14.2%). Post-operative ileus was less in Laparoscopic group (0%-10% *vs* 1.2%-12.9%). Post-operative voiding difficulty varied from 2%-10% in laparoscopic group compared to 2.3%-7.1% in open group.

The short term outcomes are summarized in Table 8. All except 2 studies have reported post-operative length of stay with the median stay ranging between

Table 5 Patient characteristics

Ref.	Age (yr)		Laparoscopic Group		Open Group		BMI		Distance from Anal Verge (cm)		Laparoscopic Group		Open Group	
	Lap	Open	Men	Women	Men	Women	Lap	Open	Lap	Open	AR	APR	AR	APR
[1]Kang *et al*[9]	57.8 (11.1)	59.1 (9.9)	64.7%	35.3%	64.7%	35.3%	24.1 (3.2)	24.1 (3.2)	5.6 (2.3)	5.3 (2.5)	151 (88.8%)	19 (11.2%)	146 (85.9%)	24 (14.1%)
Kusano *et al*[11]	58 (32-82)	55 (39-73)	15 (78.9%)	4 (21.1%)	8 (57.1%)	6 (42.9%)	⩽ 25 = 14 (73.7%) > 25 = 5 (26.3%)	⩽ 25 = 9 (64.3%) >25 = 5 (35.7%)	2 (0-50)	3.7 (0-10)	11 (57.9%)	8 (42.1%)	4 (28.6%)	10 (71.4%)
Hu *et al*[14]	55 (35-78)	55 (29-82)	34 (66.7%)	17 (33.3%)	56 (65.1%)	30 (34.9%)	23.4 (16-31.2)	24.2 (16.3-36.2)	⩽ 5 = 33 (64.7%) > 5 = 18 (35.3%)	⩽ 5 = 54 (62.8%) > 5 = 32 (37.2%)	32 (62.7%)	18 (35.3%)	36 (41.9%)	44 (51.2%)
Seshadri *et al*[12]	48 (22-73)	48 (19-71)	47 (65%)	25 (35%)	45 (62%)	27 (38%)	21 (15-33)	22 (14-38)	3 (0-8)	3 (0-10)	8 (11%)	64 (89%)	8 (11%)	64 (89%)
[1]Denoya *et al*[15]	56.3	57.1	19 (59.4%)	13 (40.6%)	18 (56.3%)	14 (43.7%)	25	26.4	4.1	4.6	24 (75%)	8 (25%)	24 (75%)	8 (25%)
Denost *et al*[10]	65 (20-85)	NA	179 (61.3%)	113 (38.7%)	NA	NA	25 (16-39)	NA	< 5 = 175 (59.9%) > 5 = 117 (40.1%)	NA	NR	NR	NA	NA
Motson *et al*[7]	63 (39-81)	NA	21 (80.8%)	5 (19.2%)	NA	NA	NR	NA	< 5 = 11 (42.3%) > 5 = 15 (57.7%)	NA	16 (61.5%)	10 (38.5%)	NA	NA

Values reported as median (range) except [1]where it is Mean. NA: Not applicable; AR: Anterior resection; APR: Abdomino-perineal resection; BMI: Body mass index; NR: Not reported.

Table 6 Peri-operative outcomes

Ref.	Interval to surgery	Conversion	Estimated blood loss		Intra-op injury		Diversion stoma	
			Lap	Open	Lap	Open	Lap	Open
[1]Kang *et al*[9]	[2]6-8 wk	1.2%	Median - 200 mL	Median - 217.5 mL	Yes[1]	Yes[1]	91.4%	88.4%
Kusano *et al*[11]	NR	NR	< 200 mL = 47.4% > 200 = 52.6%	< 200 = 92.9% > 200 = 7.1%	NR	NR	NR	NR
Hu *et al*[14]	Mean 53 d (28-105 d)	5.9%	Mean 204.7 (80-1000 mL)	Mean 352.5 (100-1200) mL	No	Ureteric injury = 1.2%	NR	NR
Seshadri *et al*[12]	Median 8 (4-36) wk	4.1%	Median 200 (100-600) mL	Med 400 (150-1500) mL	NR	NR	NR	NR
Denoya *et al*[15]	Mean 6.5 wk	28.1%	Mean 313 ± 443	Mean 279 ± 229	NR	NR	75%	75%
Denost *et al*[10]	[2]6 wk	18.8%	NR	NA	NR	NA	81.2%	NA
Motson *et al*[7]	Median 11 wk	11.5%	NR	NA	NR	NA	75%	NA

[1]There were 3 patients in each group needing re-operation - indication for these were not described. Also, one patient in each group had a brachial plexus injury; [2]Study protocol - actual durations not mentioned. NR: Not reported; NA: Not applicable.

8-24 d for the laparoscopic group and 9-35 for the open group. Only 2 case series[7,10] reported procedure related mortality (0.3%-3.8%).

The markers of surgical quality are reported in Table 9. Only the COREAN trial[9] reported the TME quality with 72.4% of the resection as complete. One study[12] defined the CRM positivity as 2 mm while the others used the standard 1 mm measurement. The CRM positivity in the laparoscopic group was 1.3% to 2.9% and that for the open group was 3.5%-9.7%. The numbers of lymph nodes harvested did not differ between laparoscopic and open groups.

Only 3 studies reported a follow up period of 34 mo or above (Table 8). The rest had data on short term follow up with one study not reporting any follow up data. Local recurrence was reported as 5.2%-7.6% in the laparoscopic groups after 34 mo of follow up. Only one study reported comparative local recurrence between the laparoscopic and open groups (5.2% for laparoscopic *vs* 21.4% for open)[11]. Only one study[13] reported disease free survival and overall survival at 3 years (78.8% and 92.1 % respectively).

Table 7 Post-operative complications

Ref.	Anastomotic leak (%)		Pelvic abscess (%)		Post-op Ileus (%)		Acute voiding difficulty (%)		Stoma complications (%)	
	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open
Kang *et al*[9]	1.2	0	0	0.6	10	12.9	10	4.1	0.6	0
Kusano *et al*[11]	0	7.1	10.5	14.2	5.2	7.1	0	7.1	NR	NR
[2]Hu *et al*[14]	3.1	8.3	0	1.2	0	1.2	1.2	2.3	0	2
Seshadri *et al*[12]	4.1	8.3	NR	NR	NR	NR	11	7	NR	NR
Denoya *et al*[15]	NR	NR	NR	NR	5	5	NR	NR	NR	NR
Denost *et al*[10]	12.7	NA	NR	NA	NR	NA	NR	NA	NR	NA
[1]Motson *et al*[7]	18.7	NA	NR	NA	NR	NA	15.4	NA	NR	NA

[1]2 patients had adhesiolysis; [2]Other complications, Urinary fistula = 1 and Rectovaginal fistula = 1 both in open group. NR: Not reported; NA: Not applicable.

Table 8 Short term and long term outcomes

Ref.	Post-op length of stay		30 d mortality (%)	Length of follow-up	Local recurrence	
	Lap	Open			Lap	Open
Kang *et al*[9]	8 (7-12)	9 (8-12)	NR	3 mo	NA	NA
Kusano *et al*[11]	24 (14-92)	35 (14-70)	NR	Median 39 mo	1 (5.2%)	3 (21.4%)
Hu *et al*[14]	10 (6-34)	16 (6-44)	NR	Short term outcomes only	NA	NA
Seshadri *et al*[12]	12 (6-45)	15 (10-50)	None	Short term outcomes only	NA	NA
[1]Denoya *et al*[15]	6.1 ± 2.4	7.6 ± 2.3	NR	Short term outcomes only	NA	NA
Denost *et al*[10]	NR	NA	0.3	NR	NR	NA
Motson *et al*[7]	8 (5-17)	NA	3.8	Median 34 mo	2 (7.6%)	NA
Saklani *et al*[13]	NR	NA	NR	Median 36 mo	4 (6.3%)	NA

Reported as median (range) except [1]where it is mean. NR: Not reported; NA: Not applicable.

Table 9 Quality markers

Ref.	CRM positivity		Lymph node harvest[1]	
	Lap	Open	Lap	Open
Kang *et al*[9]	2.9%	4.1%	17 (12-22)	18 (13-24)
[3]Kusano *et al*[11]	NR	NR	< 12 = 73.7% > 12 = 26.3%	< 12 = 64.3% > 12 = 35.7%
Hu *et al*[14]	1.9%	3.5%	12 (2-20)	11 (1-25)
[4]Seshadri *et al*[12]	1.3%	9.7%	7 (1-24)	7 (1-25)
Denoya *et al*[15]	Yes[5]	Yes[5]	19 ± 9[2]	19 ± 9[2]
Denost *et al*[10]	NR	NA	NR	NA
[6]Motson *et al*[7]	Yes[6]	NA	5 (0-14)	NA

[1]Lymph node harvest reported as median (range) except [2]where it is mean and [3]where it is percent of patients with node count < or > 12; [4]Authors define CRM as 2 mm; [3]Authors report negative "radical" resection margins in all patients in discussion; [5]CRM reported as Lap 1.17 ± 0.7; Open 0.96 ± 0.5; [6]CRM reported as 5.5 mm (< 1-15 mm). NR: Not reported; NA: Not applicable; CRM: Circumferential resection margins.

DISCUSSION

The studies were heterogeneous. In spite of this, the reported short term outcomes for LTME were not inferior to OTME. Available data shows LTME offers the same short term advantages in outcomes like estimated blood loss, other collateral injuries, overall intra-operative morbidity, post-operative length of stay, intra-abdominal abscess and post-operative ileus even after LCRT. Short term surrogate measures of oncologic parameters are at least equal to the open procedure.

LCRT makes the normal anatomical planes within the pelvis challenging due to tissue fibrosis and scarring. The tissue planes can be more difficult to follow compared with non-irradiated cases[7].

The magnified view of operative field and the improving technology with efficient energy devices in addition to meticulous attention to haemostasis to maintain good views during LMTE are factors that help reduce the blood loss as reflected in the reported estimated blood loss of these studies. Pelvic abscess was also less in laparoscopic group compared to open. This may be due to the fact that the blood loss is less with consequent less postoperative haematoma, *etc*.

Irradiation causes fibrosis and ischaemia[10] and increases the thickness of the rectal wall making a safe rectal division by stapling devices technically more difficult[10]. It is also thought to increase the risk of anastomotic leak. However, the reported anastomotic leak rate in LTME was generally low. One study[7] reported a higher leak rate (18.7%) but this is probably due to low number of patients in this study.

The surrogate markers of oncological outcome like lymph node harvest, positivity of CRM margins with LTME were comparable and not inferior to both contemporaneous open procedures as well as historically reported data.

The only RCT identified, the COREAN trial[9], randomised 340 patients after LCRT to LTME or OTME. It observed no difference between CRM positivity, macroscopic quality of the total mesorectal excision, number of harvested lymph nodes or perioperative morbidity between the two groups[9]. The short term benefits were better in LTME. This trial demonstrated LTME after LCRT was safe in the hands of experienced

surgeons (participating surgeons had a median experience of 75 LTMEs). Although this trial was not sufficiently powered to address survival outcomes (one of the limitations of this trial), the long term outcome from COREAN trial is expected to shed more light on the oncological effectiveness of LTME in this group of rectal cancer patients.

The other end-points of this review were the local recurrence rates, and DFS. These results are based on case controlled study or data from experienced tertiary centres. The rate of local recurrence varied from 5.2% to 7.6% in the LTME group. Only one study[11] reported comparative data for OTME (21.4%). Only one study reported DFS of 78.8% in LTME after 3 years of follow up. Unfortunately this did not report on a similar figure for OTME[13].

We identified 18 other studies which had a subgroup of patients who underwent LCRT followed by laparoscopic rectal resection. However, insufficient data were included for relevant data extraction and analysis. An analysis of the raw data from these published studies may provide interim results quicker. However, such an exercise would require the co-operation of various authors from around the world to contribute their data to help create an international registry for analysis: this is unlikely to be feasible retrospectively. Hence, a prospective, multicentre randomised trial recruiting patients from appropriate centres and adequately powered to address survival outcomes is needed to answer the question of oncological effectiveness.

Although there is paucity of published data on the rates of local and distant disease recurrence (Disease Free Survival) following LTME after LCRT, available data shows LTME following LCRT is not inferior to open TME with the inherent advantages of Laparoscopic surgery.

LTME is feasible in experienced hands, with acceptable short term surgical outcomes and with the usual benefits associated with minimally invasive procedures. The long term oncological outcomes of LTME after LCRT appear to be comparable to open procedures but need further investigation probably with a well-designed adequately powered multicentre trial.

COMMENTS

Background

Laparoscopic total mesorectal excision (LTME) has been shown to be feasible with acceptable short and intermediate term results in management of rectal cancers. However, the increasing use of neo-adjuvant long course chemo-radiotherapy (LCRT), and the resultant increased fibrosis and alterations to the tissue planes has increased the challenges of the LTME. To the authors' knowledge, there is no level 1 evidence to support its use.

Research frontiers

Over the recent years, numerous publications addressing this area of rectal cancer management have been published. The authors aimed to conduct a systematic review of the published literature to inform future practice.

Innovations and breakthroughs

This systematic review has shown that LTME in patients undergoing LCRT is feasible with acceptable short and intermediate term surgical and oncological outcomes in experienced hands. It has also identified the need for a sufficiently powered RCT to address this issue. In the interim, this study which has assimilated and analysed the raw data from various publications could provide useful information on the subject.

Applications

This review lends support to the practice of LTME in experienced centres within the multimodal approach to rectal cancer. However, long term outcomes (as in all oncological treatments) need to be continuously monitored.

Terminology

Total mesorectal excision (TME): this is the gold standard surgical technique for the management of mid to low rectal cancers and involves the complete removal of the rectum and mesorectal tissue. As it is traditionally performed by an open approach, it can also be called open TME. Laparoscopic TME: Using the laparoscopic approach to perform TME. LCRT: Use of pre-operative course of radiotherapy with potentiating chemotherapy (neo-adjuvant treatment) over a few weeks, usually a 5 wk cycle. Following the chemo-radiation, surgery in the form of TME is performed after a delay of several weeks. The aim is to shrink the tumour or "sterilize" the circumferential resection margin.

Peer-review

This review addresses a very interesting and timely clinical issue.

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Operative management of acute diverticulitis in immunosuppressed compared to immunocompetent patients: A systematic review

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Abstract

AIM: To determine short and long-term outcomes following operative management of acute diverticulitis in immunosuppressed (IMS) compared to immunocompetent (IMC) patients.

METHODS: PRISMA guidelines were followed in conducting this systematic review. We searched PubMed (1946 to present), OVID MEDLINE(R) In-Process and Other Non-Indexed Citations, OVID MEDLINE(R) Daily and OVID MEDLINE(R) (1946 to present), EMBASE on OVID platform (1947 to present), CINAHL on EBSCO platform (1981 to present), and Cochrane Library using a systematic search strategy. There were no restrictions on publication date and language. We systematically reviewed all published cohort comparative studies, case-control studies, and randomized controlled trials that reported outcomes on operative management of acute episode of colonic diverticulitis in IMS in comparison to IMC patients.

RESULTS: Seven hundred and fifty-five thousand five hundred and eighty-three patients were included in this systematic review; of which 1478 were IMS and 754105 were IMC patients. Of the nine studies included there was one prospective cohort, seven retrospective cohorts, one retrospective case-control study, and no randomized controlled trials. With the exception of solid organ transplant patients, IMS patients appeared to be older than IMC when they presented with an acute

episode of diverticulitis. IMS patients presented with more severe acute diverticulitis and more insidious onset of symptoms than IMC patients. In the emergency setting, peritonitis was the main indication for operative intervention in both IMS and IMC patients. IMS patients were more likely to undergo Hartmann's procedure and less likely to undergo reconstructive procedures compared to IMC patients. Furthermore, IMS patients had higher morbidity and mortality rates in the emergency setting compared to IMC patients. In the elective settings, it appeared that reconstruction with primary anastomosis with or without a diverting loop stoma is the procedure of choice in the IMS patients and carried minimal morbidity and mortality equivalent to IMC patients.

CONCLUSION: Emergency operations for diverticulitis in IMS compared to IMC patients have higher morbidity and mortality, whereas, in the elective setting both groups have comparable outcomes.

Key words: Diverticular disease; Immunosuppression; Diverticulitis; Chemotherapy; Transplant; Steroids

Core tip: Immunosuppressed (IMS) patients present with more severe episodes of diverticulitis compared to immunocompetent patients and are at increased risk of an emergency operation. However, IMS patients have a vague disease presentation with insidious onset. The postoperative morbidity and mortality following emergency operations for diverticulitis is worse in the IMS patient population, whereas, in the elective setting, the morbidity and mortality is comparable to the general population.

Al-Khamis A, Abou Khalil J, Torabi N, Demian M, Kezouh A, Gordon PH, Boutros M. Operative management of acute diverticulitis in immunosuppressed compared to immunocompetent patients: A systematic review. *World J Surg Proced* 2015; 5(1): 155-166 Available from: URL: http://www.wjgnet.com/2219-2832/full/v5/i1/155.htm DOI: http://dx.doi.org/10.5412/wjsp.v5.i1.155

INTRODUCTION

Acute diverticulitis is an increasingly common problem in Western countries and is managed non-operatively in most cases[1]. However, some cases do require operative intervention. As the indications for immunosuppressant medications continue to expand, and an increasing number of patients are immunosuppressed (IMS), the management of colonic diverticulitis in this patient population has become increasingly relevant. The appropriate time and type of management for colonic diverticulitis in the IMS remains a topic of controversy. IMS patients are thought to have a higher incidence of diverticulitis, more virulent disease, and more complicated recurrences than the immunocompetent (IMC) population. In turn, authors have suggested that IMS patients may require more aggressive operative management[2-5], including an elective sigmoid resection after a single episode of uncomplicated diverticulitis[6,7]. However, these recommendations are based on anecdotal experience or on single center retrospective studies. One qualitative systematic review[8] reported high morbidity and mortality in kidney transplant recipients and patients on chronic corticosteroid therapy with acute diverticulitis. The objective of our study was to determine the post-operative morbidity, mortality and long-term outcomes following an acute episode of colonic diverticulitis in IMS compared to IMC patients in the emergency and elective operative settings.

MATERIALS AND METHODS

Inclusion criteria

Type of studies: All studies reporting on peri-operative outcomes following acute colonic diverticulitis with a comparative study design that included IMS and IMC populations were assessed for inclusion. Study designs such as randomized controlled trials, cohort comparative studies, or case control studies were included, whereas case series, case reports, and clinical guidelines were excluded (Figure 1).

Definition of acute diverticulitis

In the literature, various clinical, radiological and/or pathological findings were used to determine the diagnosis of acute diverticulitis. For this review, we relied on the individual studies' inclusion criteria to determine the diagnosis of acute diverticulitis. We included all studies that investigated colonic diverticulitis without excluding studies that had participants with ascending, transverse or descending colon diverticulitis.

Type of participants: Participants were considered IMS if one of the following conditions were met: (1) the patient was a solid organ transplant (SOT) (heart, liver, kidney, lung, and/or pancreas) recipient; (2) the patient was taking immunosuppressive medications; or (3) the patient was receiving chemotherapy for a concurrent extracolonic malignant neoplasm.

Type of intervention: Patients who underwent a procedure requiring general anesthesia in the operating room were considered as receiving operative intervention. All participants who were managed operatively for acute diverticulitis were considered eligible for inclusion. Studies, which did not include outcomes on operative management, were excluded.

Type of outcomes measured: In order to be included in the review, studies had to provide data on at least

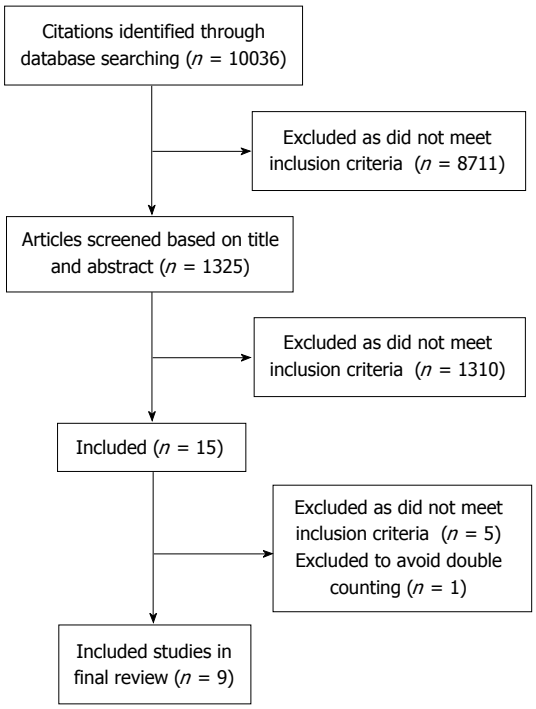

Figure 1 Flow chart.

one of the following postoperative outcomes: mortality, postoperative complications, length of hospital stay (LOS), stoma closure rate, quality of life (QoL), or cost.

Search strategy

PRISMA guidelines were followed in conducting this systematic review. We searched PubMed (1946 to present), OVID MEDLINE(R) In-Process and Other Non-Indexed Citations, OVID MEDLINE(R) Daily and OVID MEDLINE(R) (1946 to present), EMBASE on OVID platform (1947 to present), CINAHL on EBSCO platform (1981 to present), and Cochrane Library on August 12, 2013 using a systematic search strategy. The search was designed and carried out by (Torabi N), a librarian at McGill University. Individual strategies were developed for each database to accommodate for difference between subject headings and syntax among different databases. There were no restrictions on publication date and language. The final MEDLINE search strategy is provided in Table 1. In addition, we searched Clinicaltrials.gov to find possible clinical trials related to the research topic. Citation tracking (backward and forward) of selected studies using SCOPUS were conducted to locate any potentially relevant articles that had not been obtained in the original search. Abstracts were reviewed and relevant studies were identified. The identified studies were downloaded into EndNote 7.1X (Thomson Reuters, Philadelphia, PA), and duplicates were deleted. We also searched all registered clinical trials on clinicaltrials.gov and conference proceedings retrieved *via* EMBASE. We sent emails or letters to authors of abstracts published as podium presentations or posters that we deemed potential for inclusion, requesting information on unpublished data and ongoing studies. We also searched the bibliographies of all included studies and review papers to identify other potentially suitable studies.

Data collection and analysis

Selection of the studies: Two authors (Al-Khamis A/Abou Khalil J) independently examined the titles and abstracts of the articles identified in the searches as reporting potential relevant studies. From this initial assessment, we obtained full versions of all potential relevant articles. Any disagreements were resolved by a third author (Boutros M).

Data extraction and management: Data were extracted into data extraction forms by two authors (Al-Khamis A and Abou Khalil J). Any disagreements were resolved by a third author (Boutros M). For publications reporting data in more than one paper, both papers were obtained for full review, however data was extracted only from the most complete publication.

RESULTS

Characteristics of included studies

Using the search strategy specified in Table 1, 10036 citations were identified. The citations were reviewed by two reviewers (Al-Khamis A and Abou Khalil J), and 8711 citations were excluded because they did not include patients with acute colonic diverticulitis or did not include IMS patients. One thousand three hundred and twenty-five titles and abstracts were reviewed by the two reviewers, and 1310 were excluded because they were case reports, case series, review articles, clinical guidelines, or because the studies reported on medical management of acute diverticulitis or did not include peri-operative outcomes following operative management of acute diverticulitis. Fifteen full papers were reviewed by both reviewers, and 6 papers were excluded because of data duplication (1 paper) or non-comparative methodology. Thus, nine articles met inclusion criteria and were included in this review (Figure 1). Of the nine included studies, one study had a prospective cohort comparative design, seven studies used a retrospective comparative cohort design, and one study was a retrospective case-control study (Table 2). There were no randomized controlled trials.

The included studies were published between 1970 and 2014. Five studies were from centers in the United States[1,9-12], two from Spain[13,14], one from Germany[15], and one from Australia[16]. All studies were published in English except Hesterberg *et al*[15], which was published in German.

The total number of patients who were managed operatively in the included studies was 755583 patients, of those, 1478 were IMS and 754105 were IMC (Table 2). The follow-up period was not reported in

Table 1 MEDLINE-OVID search strategy

1 Colonic diverticulitis.mp. or diverticulitis, colonic/
2 Colonic diverticulosis.mp. or diverticulosis, colonic/
3 Colonic diverticulum.mp. or diverticulum, colon/
4 Colonic diverticula.mp.
5 (Colon diverticulosis or colon diverticulitis or colon diverticula or colon diverticulum).mp.
6 Diverticulitis/su [Surgery]
7 (Diverticulosis or diverticulitis).mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 HIV infections/or acquired immunodeficiency syndrome/or sexually transmitted diseases, viral/
10 Immunologic deficiency syndromes/
11 HIV infections.ab,ti.
12 "HIV/aids".ab,ti.
13 Aids positive.ab,ti.
14 HIV positive.ab,ti.
15 Chemoprevention/or chemoradiotherapy/or chemotherapy, adjuvant/
16 Chemotherapy.mp.
17 Neutropenia/or Neutropenia.mp. or febrile neutropenia/or chemotherapy-induced febrile neutropenia/
18 Corticosteroid.ab,ti.
19 Steroid.ab,ti.
20 Radiation oncology/mt (methods)
21 Radiation/ae, th (Adverse Effects, Therapy)
22 Exp organ transplantation
23 Organ transplant[a].ab,ti.
24 [(Heart or Kidney or Liver or Pancreas or Lung) adj transplant[a]].ab,ti.
25 Immunodeficient[a].ab,ti.
26 (Solid adj3 transplant).ab,ti.
27 Lymphocyte depletion.mp. or lymphocyte depletion/
28 Graft enhancement, immunologic/
29 Graft enhancement.mp.
30. Desensitization, immunologic/
31 Hyposensitization therapy.mp.
32 (Anti-Rejection Therap[a] or Antirejection Therap[a]).mp.
33 Immunosuppress[a].mp. or immunosuppressive agents/
34 Immunocompromised host.mp. or immunocompromised host
35 Immunocompromised.mp.
36 Exp immune tolerance/
37 Immunosuppression.mp. or Immunosuppression/
38 6-mercaptopurine.mp. or 6-Mercaptopurine/
39 Methotrexate.mp. or methotrexate
40 Methylprednisolone/or methyl-prednisolone.mp./
41 Basiliximab.mp.
42 Mycophenolate.mp.
43 Mycophenolic acid.mp. or mycophenolic acid
44 Copaxone.mp.
45 Exp prednisolone/
46 Cyclophosphamide/or ifosfamide/
47 Cyclophosphamide.mp.
48 Prednisone.mp. or prednisone/
49 Cyclosporine.mp. or cyclosporine/
50 Remicade.mp.
51 Daclizumab.mp.
52 Sirolimus.mp. or Sirolimus/
53 Dexamethasone.mp. or exp Dexamethasone/
54 Tacrolimus.mp. or tacrolimus/
55 Interferons.ab,ti.
56 humira.mp.
57 Imuran.mp. or azathioprine/
58 CellCept.mp.
59 Infliximab.mp.
60. Etanercept.mp.
61 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62 Postoperative complications/or surgical wound dehiscence/or surgical wound infection/
63 Perioperativeoutcome[a].mp.
64 Prognosis[a]/or treatment outcome/or treatment failure/
65 Peri-operative outcomes.mp.
66 Perioperative period.mp. or exp perioperative period/
67 Postoperative outcomes.mp.
68 Sepsis.mp. or exp sepsis/
69 Septicemia[a].mp.
70 Pyemia[a].mp.
71 Exp patient acuity/
72 Failure to rescue.mp.
73 (Surgical adj2 infection[a]).mp.
74 (Surgery adj5 infection[a]).mp.
75 Anastomosis, surgical/or anastomosis leak.mp
76 Length of stay.mp. or "length of stay"/
77 Mortality/or "cause of death"/or survival rate/
78 (Mortality or surgery).ab,ti.
79 Colectomy.mp. or colectomy/
80 (Hartmann's or Hartmanns or Hartmann).ab,ti.
81 Laparotomy.mp. or laparotomy/
82 Bowel resection.mp.
83 Colostomy.mp. or colostomy/
84 Ileostomy.mp. or ileostomy/
85 Anterior resection.mp.
86 Colon resection.mp.
87 Recurrence[a]/
88 Recurrence.ab,ti.
89 Acute kidney injury.mp. or acute kidney injury/
90 Acute renal failure.mp.
91 Complications.ab,ti.
92 Implications.ab,ti.
93 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92
94 Immunocompetent.mp.
95 Immunocompetence.mp. or immunocompetence/
96 (Immune adj competenc[a]).mp.
97 (Immuno adj competenc[a]).mp.
98 Immunocompetency.ab,ti.
99 (Nonimmunocompromised or nonimmunocompromized).ab,ti.
100 (Non adj immunocompromi?ed).ab,ti.
101 (Immunologic[a] adj Competence).ab,ti.
102 (Immune adj system).ab,ti.
103 (Control or comparison or compare or groups or normal or different or difference).ab,ti.
104 Comparative studies.ab,pt,ti.
105 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104
106 8 and 61 and 93 and 105
107 (Case Reports or Practice Guideline or Guideline or case study).pt.
108 Case series.ab,ti.
109 Case report.ab,ti.
110 107 or 108 or 109
111 106 not 110

[a]Organ transplant in the search strategy refers to solid organ transplantation which include; the pancreas, lung, heart, liver and kidney; pt: Publication type; ab: Abstract; ti: Title.

most studies; however in the two studies reporting the length of follow-up, the mean was 81[13] and 57[16] mo.

Three studies limited the IMS group to SOT patients[1,12,17], while four other studies[10,13-15] included SOT among other causes of immunosuppression in the IMS group. Canter *et al*[9] only included patients on long-term steroids in their IMS group (Table 3). Definition of immunosuppressants listed in each article is included in Table 3.

Demographic data

The age range of patients who presented with acute

Table 2 Characteristics of the included studies

Ref.	Year	Country	Study design	No. of patients[1]		Total *n*	Follow-up period (mo)
				IMS	IMC		
Canter *et al*[9]	1970	United States	Retrospective	11	38	49	NR
Perkins *et al*[10]	1984	United States	Retrospective	10	31	41	NR
Tyau *et al*[11]	1991	United States	Retrospective	23	55	78	NR
Hesterberg *et al*[15]	1994	Germany	Retrospective	12	80	92	NR
Qasabian *et al*[16]	2004	Australia	Retrospective	8	16	24	Mean 57 (SD NR)
Reshef *et al*[1]	2012	United States	Case control	51	51	102	NR
Biondo *et al*[13]	2012	Spain	Prospective	61	254	315	Mean 81.62 ± 67.62 SD
Halabi *et al*[12]	2013	United States	Retrospective	1249	753517	754766	NR
Golda *et al*[14]	2014	Spain	Retrospective	53	63	116	NR
Total				1478	754105	755583	

[1]Number of patients managed operatively. NR: Not reported; SD: Standard deviation; IMS: Immunosuppressed; IMC: Immunocompetent.

Table 3 Definition of immunosuppression

Ref.	Definition
Canter *et al*[9]	Long-term steroid use
Perkins *et al*[10]	Renal transplant
	Glomerulonephritis on steroids
	Lymphoma
	Long-term steroid use
Tyau *et al*[11]	Long-term steroid use
	Concurrent extracolonic malignant neoplasm/ chemotherapy
	Malnutrition
	Uremia
Hesterberg *et al*[15]	Long-term steroid use
	Concurrent extracolonic malignant neoplasm/ chemotherapy
	Azathioprine
	Iatrogenic leucopenia
Qasabian *et al*[16]	Heart and lung transplant
Biondo *et al*[13]	Concurrent history of immunosuppressant
	Solid organ transplant
	Concurrent extracolonic malignant neoplasm
	Emphysema
	Concurrent extracolonic malignant neoplasm/ chemotherapy
	Collagen vascular disease, arthritis
	Chronic pulmonary fibrosis
	Congenital or acquired immunodeficiency syndromes
	End stage renal failure (hemodialysis)
Reshef *et al*[1]	Liver transplant
	Heart transplant
	Lung transplant
	Renal transplant
Halabi *et al*[12]	Renal transplant
Golda *et al*[14]	Concurrent history of immunosuppressant
	Long-term steroid use
	Concurrent extracolonic malignant neoplasm
	End stage renal failure (hemodialysis, peridialysis)

Table 4 Age at episode of acute diverticulitis

Ref.	IMS (yr)	IMC (yr)
Canter *et al*[9]	60	58
Perkins *et al*[10]	NR (37-83)	64 (37-93)
Tyau *et al*[11]	64 ± 12.9 SD	59.1 ± 14.7
Hesterberg *et al*[15]	63 (38-90)	NR
Qasabian *et al*[16]	54 (41-69)	66 (45-91)
Reshef *et al*[1]	55.9 ± 9.3 SD	62.3 ± 11.3 SD
Biondo *et al*[13]	68.4 ± 11.7 SD	61 ± 15.1 SD
Halabi *et al*[12]	59 (51-67)	65 (55-77)
Golda *et al*[14]	68.5 ± 10.6 SD	59.7 ± 16.4 SD

NR: Not reported; SD: Standard deviation; IMS: Immunosuppressed; IMC: Immunocompetent.

diverticulitis was between 37 to 80 years old in the IMS and between 37 to 77 years old in the IMC groups (Table 4). Biondo *et al*[13] compared IMS to IMC at presentation and reported that the IMS group had significantly worse American Society of Anesthesiologists (ASA) scores and were significantly older (mean age of 68.4 *vs* 61 years in IMC patients, $P < 0.00$). Golda *et al*[14] also reported their IMS to be older and have worse ASA scores. Qasabian *et al*[16] also observed that the IMS population was significantly older than their IMC group. On the other hand, in the studies including mainly SOT patients in the IMS group[1,12,15], IMS patients were younger than the IMC patients.

Reshef *et al*[1] matched cases to controls with regard to timing of operation, ASA status, gender, cardiac and pulmonary comorbidities, diabetes status, and type of operative procedure, so these preoperative comorbidities could not be assessed. As with the other publications on SOT patients, the IMS group in this case matched study was significantly younger.

Halabi *et al*[12] reported IMS patients were more anemic, more likely to have chronic obstructive pulmonary disease, chronic liver disease, peripheral vascular disease, congestive heart failure, and hypertension, more likely to be smokers, diabetic, obese, and female, and had worse comorbidity scores.

Overall, in the included studies, it appears that IMS patients tend to be older than the general population when they present with an episode of acute diverticulitis, except in the SOT population, who are younger than the general population at the time of presentation. Previous studies have reported SOT patients to be relatively young compared to general population when they present with acute diverticulitis[18,19].

Clinical presentation

Clinical presentation at the time of presentation with an acute episode of diverticulitis was only described

in 4 of the 9 included studies[9,10,13,14]. Biondo *et al*[13] found that IMS patients had significantly more severe acute first (*de novo*) episodes of diverticulitis (defined as diverticulitis with abscess or perforation and/or high Hinchey peritonitis grade) compared to IMC patients. They attributed a significantly higher emergency operation rate in the IMS group compared to the IMC group (31.3% *vs* 21%, $P = 0.004$) to this significant difference in clinical presentation.

Golda *et al*[14] also reported a more severe disease presentation in the IMS compare to the IMC group, though it was not clear if IMS had previous episodes of diverticulitis. They also reported no difference in Hinchey peritonitis grade between the two groups. However, they found that the mean peritonitis severity score, a scoring system that allows stratification of patients according to mortality risk, was significantly higher in the IMS compared to the IMC group; 11.1 ± 1.3 SD *vs* 8.1 ± 1.7 SD, ($P < 0.001$) respectively.

Perkins *et al*[10] described a difference in clinical presentation between the IMS and IMC patients. IMS patients were less likely to present with abdominal pain and tenderness on clinical examination, while they were more likely to present with fever and hypotension compared to IMC patients. Canter *et al*[9] were the only study to look at the relationship between location of the perforation and immune status, and found no significant difference.

Overall, two studies found that in the emergency setting, IMS patients presented with more severe episodes of acute diverticulitis. Furthermore, one study highlighted that the insidious presentation with atypical symptoms and signs in IMS patients along with a more severe disease makes the IMS population much more challenging than IMC patients[10]. Thus, when IMS patients present with vague abdominal symptoms, fever or hypotension, the evaluating surgeon should have high level of suspicion for an acute abdominal process such as diverticulitis.

Indication for operative management

The indication for operative management in patients with complications of diverticulitis was specified in six studies[1,9-11,14,15], while the indications for operative management in the remainder of patients was not clearly specified in any study.

The most frequently reported indication for operative approach in the emergency setting in the IMS group was peritonitis and it was reported in 5 studies[1,9-11,15]. The other frequently reported indication for operative approach was abscess and it was reported in four studies[9-11,15]. Further indications for operative intervention included fistula[10,11] and bowel obstruction[1,10].

Three studies[9-11] reported the indication for operative management in the IMC patients. The most common reported indications for operative management in this group were peritonitis and fistula formation, both reported by three studies[9-11]. Other indications for operative management in the IMC patients included abscess[10,11] and recurrence[10].

Summing all included studies, it appears that peritonitis and perforation followed by intra-abdominal abscess are the main indications for operative management in both IMS and IMC patients. Tyau *et al*[11] specifically examined the difference in diverticular perforation rate as the indication for surgery in IMS and IMC patients, and found that IMS patients have a significantly higher rate of diverticular perforations requiring surgery (42.5% *vs* 14.2%, $P < 0.05$). In addition, we observed that fistula formation was reported more frequently as an indication for operative management in the IMC compared to the IMS group. This late complication of diverticulitis, which was more frequently reported in IMC patients, may be attributed to the ability of IMC patients to have more walled off and localized perforation rather than a free perforation.

Choice of operative management

Four studies included data on the operative approach[1,9,10,13]. Three studies[9,10,13] only included laparotomies, while Reshef *et al*[1] reported that 10% of operations were performed laparoscopically.

The choice of operative procedure in the emergency setting was reported in eight studies (Table 5). In each of these studies, the choice of operative intervention was based on the surgeon's preference and experience rather than institutional protocols. The most common emergency operation performed in the IMS group was Hartmann's procedure (HP), followed by resection and primary anastomosis (RPA) with a diverting loop stoma (DLS). The most common emergency operation in the IMC patients was also HP, however HP was far less frequent in IMC compared to IMS patients. The second most common operative intervention in the IMC population was RPA with DLS, similar to IMS patients but far more frequently. We also noted that RPA without diversion was rarely performed, however it was more frequently reported in IMC patients. Biondo *et al*[13] and Golda *et al*[14] both individually reported that IMS patients underwent significantly more HP and less RPA with or without DLS than IMC patients. On the other hand, Tyau *et al*[11] and Reshef *et al*[1] found no significant difference. Overall, from the data in the included studies, we found that in the emergency settings, IMS patients are more likely to undergo HP than a reconstructive procedure.

HP has been historically and still considered to be a life-saving procedure at the time of an acute severe attack of diverticulitis. However, in the general population, this operation is notably associated with a high permanent stoma rate[20] and complication rate for reversal[20]. Given the more difficult post-operative recovery in IMS compared to IMC, the observed high morbidity rate following emergency surgery in this review is expected.

Table 5 Choice of operations

Ref.		Emergency									Elective			
	Immune status (IMS/IMC)	Total *n*	Stoma and drainage	HP	RPA	RPA with DLS	Subtotal colectomy with anastomosis	Subtotal colectomy with ileostomy	Drainage only	Unknown	Total *n*	RPA	RPA with DLS	Unknown
Canter *et al*[9]	IMS	9	8						1[2]	0	2	2		0
	IMC	22	NR						NR	22	16	NR		16
Perkins *et al*[10]	IMS	10[1]	5	3	0				1	0				
	IMC	31	11	7	12				1	0				
Tyau *et al*[11]	IMS	23	4	17	1	1			0	0				
	IMC	55	8	27	14	3			3	0				
Hesterberg *et al*[15]	IMS	8	1	5	1	1				0	4	4		0
	IMC	36	NR	NR	NR	NR				36	44	NR		44
Qasabian *et al*[16]	IMS	8	6			2				0				
	IMC	16	13			3								
Reshef *et al*[1]	IMS	37	1	28	0	8				0	14	5	9	0
	IMC	37	0	28	1	8				0	14	NR	NR	14
Biondo *et al*[13]	IMS	57		37		11	3	1		5	4			
	IMC	182[2]		56		97	5	3		21	72			
Halabi *et al*[12]	IMS													
	IMC													
Golda *et al*[14]	IMS	53		42	2	9				0				
	IMC	63		15	39	9				0				
Total *n*	IMS	205	25	132	4	32	3	1	2	5	20	11	9	0
	IMC	442	32	133	66	120	5	3	4	79	132	NR	NR	67

[1]One intra-operative death; [2]With subsequent right hemicolectomy. HP: Hartmann procedure; RPA: Resection and primary anastomosis; RPA with DLS: Resection and primary anastomosis with diverting loop stoma; NR: Not reported; IMS: Immunosuppressed; IMC: Immunocompetent.

Only three studies included elective operations for diverticulitis (Table 6). Resection and primary anastomosis with or without a protective ileostomy was the only procedure performed in IMS patients. Elective operative procedures were not described for any IMC patients in the included studies.

Post-operative morbidity

Overall morbidity following emergency operations for diverticulitis in the IMS patients was 65% compared to 40% in IMC patients. Individual complications following emergency operations for acute diverticulitis were reported in four studies (Table 7). The most common reported complication in the IMS patients was wound infection followed by sepsis and intra-abdominal collections. Other complications in this group included postoperative ileus and cardiopulmonary complications. Of the seven studies including SOT patients, Hesterberg *et al*[15] were the only authors that reported on graft rejection following emergency operations for diverticulitis. They reported this complication in one of the five SOT recipients included in their study. In the IMC population, wound infection was the most commonly reported complication. Other postoperative complications in the IMC group are listed in Table 7.

Perkins *et al*[10] examined the relationship between the choice of operative intervention and the occurrence of postoperative complications and identified more complications in the IMS patients compared to the IMC patients when drainage and colostomy was performed, but not when resection and colostomy was performed.

In summary, all studies reported a higher complication rate in IMS patients following operations in the emergency setting compared to IMC patients in the same setting. This increased morbidity rate is likely due to several factors. Firstly, IMS patients tend to present with more insidious disease onset that may result in significant delays in diagnosis. Secondly, this group of patients tends to have more significant comorbidities reflected by worse ASA classification. Thirdly, the IMS state itself is associated with

Table 6 Morbidity and mortality in elective setting

Ref.	Immune status (IMS/IMC)	Total *n*	Mortality *n* (%)	Morbidity *n* (%)	Anastomotic leak *n* (%)	Abdominal collection/ Abscess *n* (%)	Wound infection *n* (%)	Sepsis *n* (%)	Reoperation *n* (%)	Post op bleed *n* (%)	Post op ileus *n* (%)	Readmission *n* (%)
Canter *et al*[9]	IMS	2	0									
	IMC	16	NR									
Hesterberg *et al*[15]	IMS	4	0									
	IMC	44	0									
Qasabian *et al*[16]												
[1]Reshef *et al*[1]	IMS	14	0	4 (29)	1 (7)	0	3 (20)		1 (7)	0	1 (7)	4 (24)
	IMC	14	0	4 (29)	1 (7)	1 (7)	2 (13)		2 (14)	1 (7)	1 (7)	2 (14)
[2]Biondo *et al*[13]	IMS	4	0	4 (100)	1 (25)		1 (25)		2 (50)			
	IMC	72	0	4 (5)	0		3 (4)		1 (1)			
Halabi *et al*[12]	IMS	471	3 (0.6)									
	IMC	404623	4856 (1)									

[1]Some patients had two or more complications; [2]3 morbidities of which 5 are not reported. NR: Not reported; IMS: Immunosuppressed; IMC: Immunocompetent.

a significant deficiency to mount a response against infection, and an inherent detrimental effect on the ability for tissue to heal following an operation[21,22].

In addition, it appeared that potentially life-threatening complications including sepsis, intra-abdominal collections and cardiopulmonary complications were more common in IMS compared to IMC patients. We did not observe differences in the distribution of other major complications between the IMS and IMC populations. Wound infections, postoperative ileus, postoperative bleed and renal complications appeared to be comparable in both populations.

Two studies examined postoperative morbidity after elective operations in patients with previous history of acute diverticulitis (Table 6). The sample size for the IMS and IMC subgroups that underwent elective operations in both these studies was small. The rate of anastomotic leak, wound infection and reoperation were the most common reported complications and appeared equivalent in IMS and IMC patients. Other postoperative complications are listed in Table 6. Data regarding complications following elective surgery in the IMS compared to the IMC population are lacking. However, from the available literature, it does not appear that there is any significant difference in complication rate between IMS and IMC groups following elective operations for diverticulitis, as both appear low.

Post-operative mortality

Following emergency surgery for diverticulitis, the mortality rate ranged from 1% to 39% in the IMS groups and 0 to 16% in the IMC groups. The mean mortality of all included studies was 11% for IMS patients and 5% for IMC patients, respectively.

All studies, but three[10,15,16] reported significantly higher mortality in the IMS compared to IMC patients. Two studies reported zero mortality in the IMC cohorts[1,10]. The majority of studies did not report the cause of mortality. Only two studies[10,11] included a description regarding the cause of death. Perkins *et al*[10] hypothesized that one case of death in an IMS patient in their study was due to a delay in diagnosis with resultant sepsis and intraoperative death. Tyau *et al*[11] reported that nearly all deaths in their study were secondary to sepsis.

Subgroup analysis of the data in Golda *et al*[14] showed significantly higher mortality associated with HP compared to reconstructive procedures. As this is a retrospective study, this finding is likely confounded by significantly worse disease in the patients who underwent HP compared to RPA.

Mortality following elective operations for diverticular disease patients was reported in five studies (Table 6). Three of the four studies reported no mortality in both IMS and IMC patients following elective resections, while one study reported no statistically significant difference in mortality between IMS and IMC patients[12] (0.6% *vs* 1% respectively, $P = 0.14$).

Data regarding mortality in IMS patients following elective operations was scarce. However, it appears that mortality in elective operations for diverticular disease in

Table 7 Morbidity and mortality in the emergency setting

Ref.	Immune status (IMS/IMC)	Total *n*	Mortality *n* (%)	Morbidity *n* (%)[2]	Anastomotic leak *n* (%)	Abdominal collection/ Abscess *n* (%)	Wound infection *n* (%)	Sepsis *n* (%)	Post-op ileus *n* (%)	Post-op bleed *n* (%)	Renal failure *n* (%)	Reoperation *n* (%)	Arrythmias/cardiac decompensation *n* (%)	Pulmonary infection/ Insufficient *n* (%)	Others *n* (%)
Canter *et al*[9]	IMS	9	3 (33)	3 (33)	3 (33)										
	IMC	22	NR	NR	0										
[1]Perkins *et al*[10]	IMS	10	1 (10)	7 (70)		3 (30)	4 (40)	5 (50)							
	IMC	31	0	NR		2 (7)	5 (16)	1 (3)							
Tyau *et al*[11]	IMS	23	9 (39)	15 (65)											
	IMC	55	1 (2)	13 (24)											
Hesterberg *et al*[15]	IMS	8	1 (13)												
	IMC	36	NR												
Qasabian *et al*[16]															
Reshef *et al*[1]	IMS	37	7 (19)	19 (51)	1 (3)	2 (5)	3 (8)		3 (8)	4 (11)			1 (3)	2 (5)	DVT; IMS, 3 IMC, 2 UTI; IMS, 2 Readmission; IMS, 5 IMC, 4
	IMC	37	0	9 (24)	1 (3)	3 (8)	5 (14)		2 (5)	1 (3)			0	2 (5)	
Biondo *et al*[13]	IMS	57	19 (33)												
	IMC	182	29 (16)												
Halabi *et al*[12]	IMS	778	57 (0.7)												
	IMC	348894	17130 (5)												
Golda *et al*[14]	IMS	53	14 (26)	42 (79)	1 (2)	11 (21)	22 (42)	13 (25)	10 (19)	0	7 (13)	16 (30)	9 (17)	11 (21)	
	IMC	63	4 (6)	40 (64)	3 (5)	4 (6)	30 (48)	7 (11)	8 (13)	1 (2)[3]	5 (8)	5 (8)	2 (3)	7 (11)	
Total	IMS	975	111/ 975 (11)	86/132 (65)	5	16	29	18	13	4	7	16	10	13	
	IMC	349320	17164/ 349320 (5)	62/155 (40)	4	9	40	8	10	2	5	5	2	9	

[1]Some patients had 2 or more complications; [2]5 studies reported overall morbidity; [3]Gastrointestinal bleed. DVT: Deep vein thrombosis; UTI: Urinary tract infection; NR: Not reported; IMS: Immunosuppressed; IMC: Immunocompetent.

the IMS population is comparably low to IMC patients.

Length of hospital stay

Length of hospital stay was poorly reported in the included studies (Table 8). Only two studies included LOS following operations in the emergency setting[1,14]. Golda *et al*[14] found that IMS patients had significantly longer hospital stay compared to IMC patients following emergency operations (mean days 24.8 ± 25.2 SD *vs* 15.5 ± 10.5 SD, $P = 0.002$). Reshef *et al*[1] also found similar trends though it was not statistically significant (mean 19 d IMS *vs* 13 d IMC, $P = 0.1$).

Similarly, only two studies reported LOS following elective resections for diverticulitis[1,13]. Both studies observed a trend towards longer hospital stay in the IMS compared to IMC patients.

From the limited existing data, it appears that IMS patients tend to stay longer, especially following emergency operations for diverticular disease.

Table 8 Length of hospital stay in the emergency and elective settings

Ref.	Immune Status (IMS/IMC)	LOS in ER setting (d)	LOS in elective setting (d)
Reshef *et al*[1]	IMS	19.3	9.6
	IMC	9.4	6.5
Biondo *et al*[13]	IMS	NR	19.3 ± 13.6 SD
	IMC	NR	9.4 ± 6.8 SD
Golda *et al*[14]	IMS	24.8 ± 25.2 SD	
	IMC	15.5 ± 10.5	

SD: Standard deviation; NR: Not reported; LOS: Length of hospital stay; IMS: Immunosuppressed; IMC: Immunocompetent; ER: Emergency.

Long-term outcomes

Stoma closure: Only one study compared stoma closure and complication rates in IMS and IMC patients[1]. They found that there was no significant difference in the interval between stoma creation and stoma closure in IMS and IMC patients (5.4 mo ± 2.9 SD *vs* 6.1 mo ± 3.4 SD respectively, $P = 0.23$). Furthermore, permanent stoma rates were similar between IMS and IMC patients (7 *vs* 8 patients, $P = 0.7$). Moreover, postoperative morbidity after all types of stoma closure was similar (16% IMS *vs* 17% IMC patients, $P = 1$). Another study reported that three of the 12 IMS patients eventually underwent stoma closure[15]. As this data represents a small sample size, it is difficult to draw any conclusions. Furthermore, it is known that Hartmann's reversal is associated with a far greater complication rate compared to ileostomy closure. Larger studies, which make this distinction, will shed more light on the complications following stoma closure in IMS and IMC patients, particularly following Hartmann's reversal.

QoL: No studies reported data about QoL following emergency or elective operations in the IMS compared to IMC patient populations.

Cost

Though an increasingly important outcome, cost was not a reported outcome in any of the included studies.

Non-operative management

Though the inclusion criteria for this systematic review were patients who underwent an operation for acute diverticulitis, few of the included studies also commented on non-operative management. As there is increasing interest in this treatment option, we have summarized the available literature.

Three studies reported data on some aspect of their non-operative management of acute diverticulitis in IMS patients[10,11,13]. Tyau *et al*[11] reported that they used non-operative management more frequently in IMC (67%) compared to IMS patients (42.5%). The severity of diverticulitis and the presence of complications secondary to diverticulitis were not reported for this subset of patients. In 1984, Perkins *et al*[10] reported that none of their IMS patients had successful medical therapy compared to 76% of the IMC group. Again, the severity of diverticulitis and the presence of complications secondary to diverticulitis were not reported for this subset of patients.

Biondo *et al*[13] was the first study to examine the risk of recurrence necessitating emergency operations in IMS patients following successful non-operative management of diverticulitis. After excluding patients who had an operation during or after the first episode, 107 IMS patients and 657 IMC patients were prospectively followed for recurrence. There was no significant difference in overall recurrence rate between the IMS and IMC patients (21.5% IMS *vs* 20.5%, respectively, $P = 0.82$). They also observed that a severe first episode (defined as abscess or perforation) in the IMS group was associated with a higher recurrence rate, and shorter interval to the first episode of recurrence of acute diverticulitis (median 3.3 mo in IMS *vs* 9 mo in IMC, $P = 0.01$). However, there was no significant difference in the rate of emergency operation for recurrence (only 17.4% IMS patients *vs* 15% IMC patients, $P = 0.77$). The mean follow up for IMS and IMC patients was 82 and 65 mo respectively. As in the previously mentioned studies, Biondo *et al*[13] also reported that IMC patients were more often treated with non-operative management compared to IMS patients.

Overall, it appears that IMS patients are less likely to be managed non-operatively compared to IMC patients. Though based on a small subgroup, Biondo *et al*[13] observed that IMS patients who are successfully managed non-operatively following a severe episode of diverticulitis are not at increased risk of emergency operations for future recurrences.

DISCUSSION

To date, this is the only systematic review comparing outcomes of operative management in IMS and IMC patients in both elective and emergency settings. Overall, we observed a worse disease severity for IMS compared to IMC patients with acute diverticulitis. Furthermore, IMS patients were more likely to fail non-operative management, undergo a HP, require a longer hospitalization, suffer complications or die following emergency operative management.

In this systematic review, we observed a higher morbidity and mortality rate following emergency surgery in the IMS compared to the IMC population. On the other hand, it appears that the morbidity and mortality associated with elective operations for both groups are low and comparable. This beckons the question whether IMS patients should be routinely offered an elective resection following a first episode of diverticulitis in order to avoid an emergency surgery. Interestingly, Biondo *et al*[13] report a similar rate of emergency operations for recurrence in IMS and IMC patients. Therefore, it seems that IMS patients are

not at higher risk of recurrence requiring emergency surgery, but the morbidity and mortality for recurrence managed operatively is not known and may be significantly higher than in IMC patients.

Limitations of the study

Despite a rigorous and inclusive search methodology, the collected available literature regarding diverticulitis in the IMS population mainly included retrospective studies with a small number of patients, from a single institution, and lacked any randomized controlled trials. In an attempt to reduce the risk of bias and heterogeneity, we only included comparative cohorts and case control studies and excluded all case series, case reports, and clinical guidelines. Nonetheless, the studies available for inclusion were mostly retrospective, without clearly specified a priori sample size/power calculations and had missing data. Thus, our results are fraught with the limitations of the original data, including information and recall bias. Furthermore, this systematic review is based on populations from the developed world where advanced peri-operative support is readily available; thus these results may not be generalizable to less developed hospital systems. Larger, multi-institutional prospective studies are required to address the optimal timing and indication for operative intervention following an episode of acute diverticulitis in this challenging population.

COMMENTS

Background

Acute diverticulitis is a common problem in western societies and is managed non-operatively in most cases. The appropriate type and timing of management in immunosuppressed (IMS) patients remains a topic of controversy. Some authors have suggested that IMS patients may require more aggressive operative management, including an elective colonic surgical resection after a single episode of acute diverticulitis. However, these recommendations are based on anecdotal experience or on single center retrospective studies.

Research frontiers

The current research goal is to investigate outcomes following operative management of colonic diverticulitis in IMS compared to immunocompetent (IMC) patients who present with a history of acute diverticulitis in both emergency and elective settings.

Innovations and breakthroughs

As the indications for immunosuppressant medications continue to expand, and an increasing number of patients are IMS, the appropriate type and time of management of acute diverticulitis in this patient population has become increasingly relevant. IMS patients are thought to have a higher incidence of diverticulitis, more virulent disease, and more complicated recurrences than the IMC patients. To date there is scarcity of data on the outcomes following operative management of colonic diverticulitis in IMS patients. In an attempt to produce a robust review article, the authors conducted an exhaustive systematic search of the literature and included the best available conducted comparative studies to form the basis of our findings. They observed that IMS patients who underwent a colectomy for acute diverticulitis in the emergency setting were more likely to present with severe disease, fail non-operative management, undergo salvage surgical procedures, stay longer in hospital, have more complications and to die compared to IMC patients. However, in following a colectomy for acute diverticulitis in the elective setting, the authors observed that IMS patients have less complications and a lower risk of death, that is comparable to IMC patients. This beckons the question whether IMS patients should be routinely offered an elective resection following a first episode of diverticulitis in the emergency setting in order to avoid an emergency surgery in subsequent attacks. Larger, multi-institutional prospective studies are required to address the actual incidence of recurrence in the IMS population, and optimal timing and indication for operative intervention following an episode of acute diverticulitis in this challenging population, as most current studies are limited by a retrospective design and limited sample size.

Applications

Emergency operations for diverticulitis in IMS compared to IMC patients are associated with increased morbidity and mortality, whereas; in the elective setting both groups have similar outcomes. These findings shed a light on whether elective surgical colon resection should be offered to IMS patients following successful non-operative management of an acute episode of diverticulitis. Elective resection of the diseased colon segment will spare these patients the increased risk of complications and death associated with emergency operation.

Terminology

Acute diverticulitis, refers to acute inflammation of colonic diverticulosis. Diverticulosis, which commonly occurs in the sigmoid segment of colon, is outpocketing of colonic mucosa and submucosa through weaknesses in the colon wall. IMS patients are those who have undergone a solid organ transplant such as lung/heart/liver/kidney and pancreatic transplants, or patients on immunosuppressive medications such as steroids or chemotherapy. IMC patients are patients from the general population who are not on immunosuppressive medications.

Peer-review

This manuscript seems to include the largest series on this topic. The authors reviewed several large studies and conducted a meta-analysis of the topic. They addressed several aspects, including demographic data, clinical presentation, indication and choice of operation, post-operative morbidity and mortality, length of hospital stay, long-term outcome and non-operative management. The analysis is detailed. Despite the limitations of the available literature, the results are reliable. The limitations of the study are inevitable and acceptable.

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META-ANALYSIS

Prophylactic oophorectomy during primary colorectal cancer resection: A systematic review and meta-analysis

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Abstract

AIM: To appraise the current evidence for prophylactic oophorectomy in patients undergoing primary curative colorectal cancer resection.

METHODS: Occult ovarian metastases may lead to increased mortality, therefore prophylactic oophorectomy may be considered for women undergoing colorectal resection. A systematic review and meta-analysis was performed for English language studies from 1994 to 2014 (PROSPERO Registry number: CRD42014009340), comparing outcomes following prophylactic oophorectomy (no known ovarian or other metastatic disease at time of surgery) *vs* no ovarian surgery, synchronous with colorectal resection for malignancy. Outcomes assessed: local recurrence, 5-year mortality, immediate post-operative morbidity and mortality, and rate of distant metastases.

RESULTS: Final analysis included 4 studies from the United States, Europe and China, which included 627 patients (210 prophylactic oophorectomy and 417 non-oophorectomy). There was one randomized controlled trials, the remainder being non-randomised cohort studies. The studies were all at high risk of bias according to the Cochrane Collaboration's assessment tool for randomised studies and the Newcastle-Ottawa Score for the cohort studies. The mean age of patients amongst the studies ranged from 56.5 to 67 years. There were no significant differences between the patients having prophylactic oophorectomy at time of primary colorectal resection compared with patients who did not with respect to local recurrence, 5-year survival and distant metastases. There was no difference in post-operative complications or immediate post-operative mortality between the groups.

CONCLUSION: Current evidence does not favour prophylactic oophorectomy for patients without known genetic predisposition. Prophylactic surgery is not associated with additional risk of post-operative complications or death.

Key words: Prophylactic surgery; Colorectal cancer; Oophorectomy

Core tip: Prophylactic oophorectomy is a potentially attractive additional procedure that can be performed

at the time of primary colorectal resection, to reduce the risk of ovarian metastasis and de novo ovarian malignancy later in a female patient's clinical course. A systematic review and meta-analysis of the available literature reveals that, though this procedure can be performed with little additional morbidity or mortality risk at the time of surgery, it confers no long term survival benefit, and carries a significant side effect profile.

Thompson CV, Naumann DN, Kelly M, Karandikar S, McArthur DR. Prophylactic oophorectomy during primary colorectal cancer resection: A systematic review and meta-analysis. *World J Surg Proced* 2015; 5(1): 167-172 Available from: URL: http://www.wjgnet.com/2219-2832/full/v5/i1/167.htm DOI: http://dx.doi.org/10.5412/wjsp.v5.i1.167

INTRODUCTION

Women who have colorectal cancer are at a higher risk of developing primary gynaecological tumours, particularly when aged less than 50[1,2], and there is a relatively high rate of ovarian metastases amongst pre-menopausal women with colorectal cancer[3,4]. Furthermore, patients who have colorectal metastases to the ovary have a poor prognosis and respond poorly to chemotherapy[5]. Although the route of spread is mostly unknown, haematogenous, lymphatic and transcoelomic routes of dissemination have all been proposed[6,7]. Prophylactic ovarian surgery has been advocated for women with hereditary syndromes such as Lynch syndrome and hereditary nonpolyposis colorectal cancer (HNPCC)[8,9]. However, prophylactic surgery for women with no known genetic risk factors is more controversial[10]. Prophylactic oophorectomy in these patients would be aimed at preventing the subsequent development of primary ovarian malignancy, or improving the local recurrence rate following colorectal cancer resection by removing occult synchronous or future metachronous metastases. The authors hypothesized that prophylactic oophorectomy would result in a reduction of local recurrence rate and mortality.

Surgeons undertaking primary curative colorectal cancer have ready access to the pelvis and therefore are ideally placed to perform the relatively straightforward procedure of oophorectomy if such surgery was considered appropriate. Concurrent oophorectomy therefore has the theoretical potential to utilize the same surgical approach (laparoscopic or open), and have similar wound-associated morbidity. Justification for prophylactic oophorectomy in these circumstances must be made on the basis of evidence of safety, improved outcomes in terms of local recurrence rate and survival of patients with colorectal cancer, and patient preference. The authors aimed to examine the current peer-reviewed literature in order to determine whether evidence in the last 20 years justifies prophylactic surgery.

MATERIALS AND METHODS

Data sources and search strategy

A systematic review was performed according to a pre-specified protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO; registry number CRD42014009340). Cochrane Database of Systematic Reviews, OVID SP, and PubMed versions of MEDLINE were searched for published articles comparing outcomes following prophylactic oophorectomy at the time of primary colorectal cancer resection with patients without prophylactic surgery. Only studies published after 1994 were included in order to capture a 20-year period to date of investigation. This systematic search was performed independently by two investigators. Search terms were use to search MEDLINE, including "prophylactic", "oophorectomy", "ovariectomy", and "colorectal cancer". Manual search of reference lists in relevant review articles was also undertaken in order to identify other studies of interest. Citations were collated (and all duplicates removed) by using EndNote Reference Manager (V.X4, Thomson Reuters). The final search was performed on 1st February 2014.

Inclusion and exclusion criteria

In order to be included in the meta-analysis, studies had to be (1) randomized controlled trials (RCTs), prospective or retrospective cohort studies; (2) reported data on at least one outcome following prophylactic oophorectomy *vs* no oophorectomy; (3) on the same occasion as primary curative colorectal cancer resection, with or without chemotherapy; and (4) no established diagnosis of ovarian neoplasia. Any primary cancer resection of the colon or rectum, regardless of laparoscopic or open technique was able to be included. Exclusion criteria were: histologically or radiologically established ovarian disease at time of colorectal resection, clearly visible or well established ovarian metastases at time of surgery, high clinical suspicion of ovarian metastases, known genetic diseases with higher risk of ovarian cancer such as lynch syndrome or HNPCC.

Data extraction

Two authors extracted data independently. Discrepancies in outcome extraction were resolved by discussion of the relevant data until consensus was achieved. Data extracted on study design included: randomisation technique, intervention arms, type of surgery. Details relating to the included patients were: number, age, indication for surgery, and site of cancer.

Definitions

Prophylactic oophorectomy was defined as the removal of both ovaries where otherwise no surgical indication exists, in the absence of any evidence of histological or

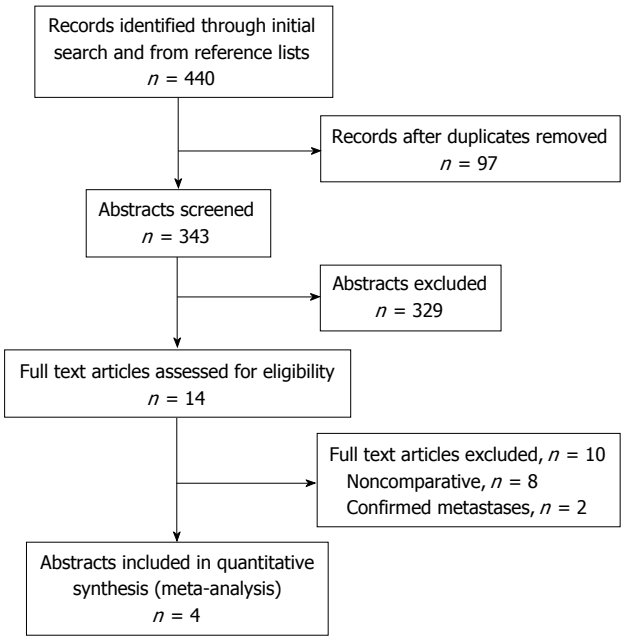

Figure 1 PRISMA diagram for study selection.

radiologically established metastases. Colorectal cancer was defined as any neoplastic process of the colon or rectum. Primary colorectal resection was defined as a curative resection (with or without adjuvant chemotherapy) of a primary colorectal cancer with no evidence of distant metastases at time of surgery.

Outcomes

The primary outcomes measured were local recurrence rate and overall 5-year survival. Secondary outcomes included immediate post-operative death, post-operative complications, and rate of distant metastases.

Assessment of bias

Assessment of bias was pre-planned, using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials[11], and the Newcastle-Ottawa score[12] for non-randomised studies. Scores were determined based on randomisation, patient selection techniques, comparability of the two intervention groups and the methods of measuring end points. Studies were deemed to be at low or high risk of bias based on these scores.

Data synthesis and analysis

Meta-analysis of survival was carried out by calculation of a pooled hazard ratio (HR) from Kaplan-Meier curves using methods described by Parmar *et al*[13]. A HR of more than 1.00 represented worse survival for the experimental group (for example oophorectomy) *vs* the control group (no oophorectomy). The HR was considered significant if the 95%CI did not include 1.0 and $P < 0.05$. Data were analysed using Review Manager 5.1 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Due to the relatively high risk of bias from heterogeneity between studies, random effects modelling were used in order to estimate the mean of a distribution of effects of all included studies.

RESULTS

Study selection

Initial literature search yielded 440 potential studies of interest, and after duplicates were removed a total of 343 study abstracts were reviewed, of which 14 of these abstracts were of interest. The majority of studies were excluded due to their study participants having known genetic disorders such as Lynch syndrome and HNPCC. Of the 14 full texts reviewed, 2 were excluded because the oophorectomy was undertaken with known diagnosis or strong suspicion of ovarian metastases. Eight studies were excluded because they did not adequately compare the outcomes of interest between the two groups. There were 4 studies[6,14-16] that could be included in the quantitative synthesis that met all inclusion criteria and directly compared the outcomes of interest (Figure 1 for preferred reporting item for systematic reviews and meta-analyses diagram).

Study characteristics

The final analysis included four studies published between 1998 and 2004, with study periods ranging from 9 to 15 years[6,14-16]. There were a total of 627 patients, with 210 patients having undergone prophylactic oophorectomy, and 417 patients with colorectal resection only, from China, France, Greece, and the United States (summarised in Table 1). All four studies reported the mean age of the patients, and these ranged from 56.5 to 69 years.

Study quality assessment

Although it had a very low attrition bias, the overall risk assessment scoring for the RCT put it at high risk of bias, due to lack of blinding, unclear randomisation and allocation. The remaining three cohort studies were all at high risk of bias, with the main concern being that selection of surgical group depended on patient choice in two studies[14,15] and was unclear in the remaining study[16]. None of the three cohorts studies scored more than 6 stars (out of a possible 9) according to NOS scoring.

Outcomes

The primary endpoints of local recurrence and five-year survival are summarised in Table 2. There was no difference in the rate of local recurrence between patients who underwent prophylactic oophorectomy at the time of primary colorectal resection and those who did not (629 patients, four studies, OR = 1.03, 95%CI: 0.62-1.70, $P = 0.920$) (Figure 2A). Furthermore, no significant difference in five-year overall survival between these patients was found (636 patients, four

Table 1 Study characteristics

Ref.	Year	Study period	Setting	Design	Total patients	Patients oophorectomy	Patients no oophorectomy	Mean age/ yr (all)
Cai *et al*[14]	2004	1991-2000	Shanghai, China	Retrospective cohort	267	43	224	56.5
Sielezneff *et al*[15]	1997	1980-1990	Marseille, France	Prospective, non randomised	90	39	51	65
Tentes *et al*[16]	2004	1987-2002	Didimotichon Greece	Retrospective cohort	124	54	70	69
Young-Fadok *et al*[6]	1998	1986-1996	Mayo clinic, United States	RCT	146	74	72	67

RCT: Randomized controlled trial.

Table 2 Local recurrence and survival for included studies

	No. of studies	No. of patients	No. of events	Random-effects model		Heterogeneity		
				OR/HR	*P*	I^2 (%)	χ^2	*P*
Oncological outcome								
Local recurrence	4	627	105	1.04 (0.62, 1.73)	0.88	19	3.69	0.300
Five-year overall survival	4	636	-	0.97 (0.18, 5.38)	0.98	0	0.07	1.00

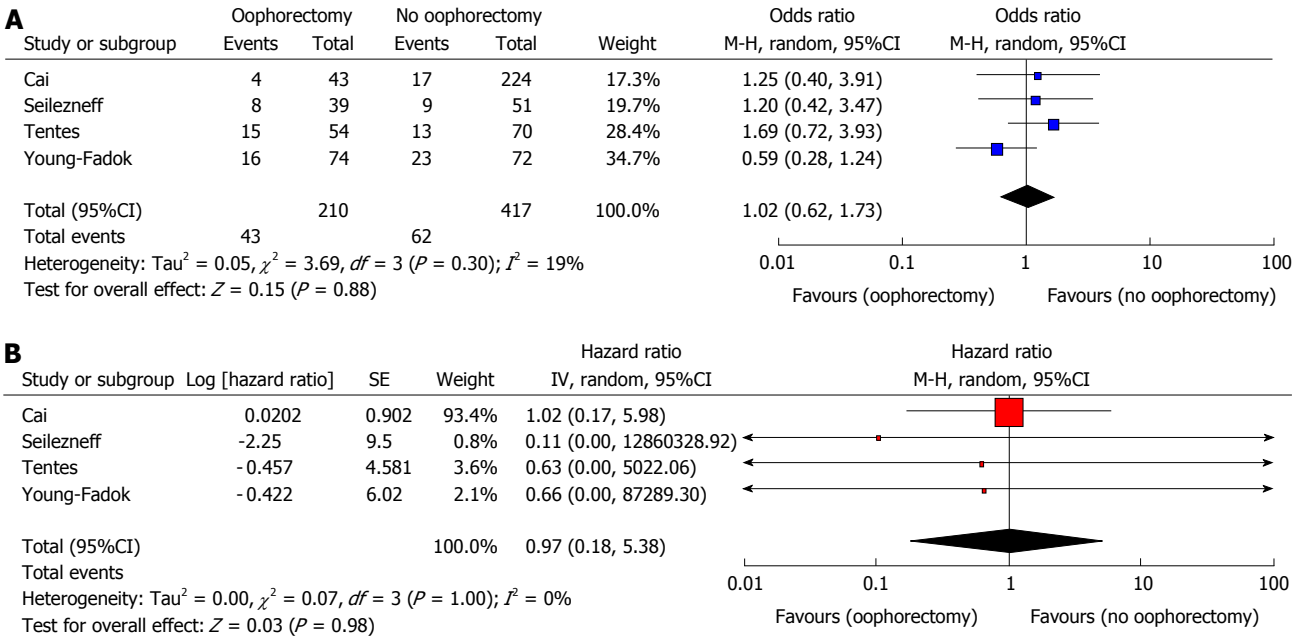

Figure 2 Meta-analysis of (A) local recurrence and (B) 5-year survival.

studies, HR = 0.97, 95%CI: 0.18-5.38, *P* = 0.980) (Figure 2B).

Only one study reported both mortality and complications in the immediate post-operative period[16]; there was no significant difference between mortality (oophorectomy group = 3/54 patients; non-oophorectomy group = 8/70 patients), or post-operative complications (oophorectomy group = 12/54 patients; non-oophorectomy group = 17/70 patients). Two studies reported distant metastases on follow up[14,15]; the first showed no significant difference between the groups (oophorectomy group = 13/43 patients; non-oophorectomy group = 16/224 patients), and similarly the second study showed no difference (oophorectomy group = 3/39 patients; non-oophorectomy group = 8/51 patients).

DISCUSSION

Main findings

The current systematic review and meta-analysis specifically analysed the differences in outcomes between patients undergoing prophylactic oophorectomy at time of curative colorectal resection and those without oophorectomy amongst women with no known established genetic predisposition to ovarian cancer. We find that published evidence on this research question in the last 20 years is sparse, and no study has been published in the peer-reviewed literature in the last 10 years regarding this question. In the 4 studies that were meta-analysed, there are no trends towards favourable outcomes amongst the prophylactic oophorectomy patients. Using the random effects models, there are

no differences in local recurrence, 5-year survival, or distant metastases between prophylactic oophorectomy and non-oophorectomy groups. However, where prophylactic surgery did take place, there were no extra risks of undertaking such surgery in terms of post-operative complications and mortality. All studies were at high risk of bias.

Comparison with other studies

Studies examining prophylactic oophorectomy for women with genetic predisposition to ovarian cancer have shown favourable outcomes[9,17]. There is some evidence that women with newly diagnosed colorectal cancer should be screened for genetic predisposition to ovarian cancer so that risk-reducing surgery might be considered[18], and that such screening may yield long-term gains in life expectancy, which outweigh the short-term detrimental effects on quality of life from testing[19]. However, opinion has been divided for decades in the surgical community regarding prophylactic oophorectomy in the absence of genetic predisposition[7]. Prophylactic oophorectomy to improve survival in women with colorectal cancer was first suggested in the 1980s by the retrospective analysis of survival in a group of 571 women in the 1970s who had undergone curative resection for colon cancer, with a suggestion that 3%-8% of women might benefit[20]. Studies published before the data collection period of the current review had recommended prophylactic oophorectomy, but these were small, retrospective reviews[21-23]. Disagreement is compounded by varying and flawed methodology in these studies; for example one earlier study demonstrated no difference in recurrence rate or survival with prophylactic oophorectomy, but patient selection was based on surgeon preference, leading to bias in stage of colorectal cancer in each arm of the study[24].

There is some evidence that prophylactic oophorectomy results in an increased rate of premature death, cardiovascular disease, dementia, osteoporosis and Parkinsonism[25]. Oophorectomy before the age of 45 has been associated with an increased risk of death in a retrospective cohort study, especially for women not receiving hormone replacement therapy[26]. Therefore oophorectomy where not otherwise indicated has its own implications separate to the colorectal cancer resection; risk of these adverse outcomes must be balanced against oncological risks. Such risk *vs* benefits analysis may however be limited by fear of physiological and psychological adverse effects, as well as gaps in knowledge regarding risk[27], and these deficiencies must be addressed if informed decisions are to be made. If prophylactic ovarian surgery is not to be undertaken, close post-operative observation as well as ovarian metastatectomy when required appears to have a survival benefit, whilst avoiding the deleterious effects of oophorectomy in those who do not require it[28].

Strengths and limitations

There is a striking paucity of data in the last 20 years regarding outcomes following prophylactic oophorectomy during resection of primary colorectal cancer, which limits this review. However such a finding is in itself important, since it implies that that there are limiting factors involved in studies which aim to test this research question. Indeed the only RCT in the last 20 years to have attempted to randomise patients was unable to accrue the anticipated number of patients after 10 years, and was forced to publish their preliminary results[6]. Although the authors of this RCT recommend further data collection, the final results have not been published, implying that the study may have been abandoned. The available evidence therefore must be based on only a handful of non-randomised cohort studies.

Conclusions and implications

Currently, the published evidence cannot make an overwhelming case for prophylactic oophorectomy or ovarian conservation at the time of colorectal resection. The 4 studies analysed all individually reported no long-term survival benefit of prophylactic oophorectomy, and meta-analysis of all data confirmed this for the whole population. In practice, young women are not routinely screened for HNPCC and other genetic risks prior to colorectal cancer resection. Although there appears to be no benefit in offering oophorectomy to women with no known genetic disorder, such an informed choice might be more practical if high-risk women were screened prior to their planned colorectal surgery.

It is likely that future RCTs may not be feasible, and therefore the current review represents the best current evidence with which to base surgical decisions on this question. This review concludes that prophylactic oophorectomy cannot be recommended based on current evidence, but if it is performed has no extra risk of post-operative morbidity or mortality. If a patient would like to opt for prophylactic oophorectomy, surgery can only be undertaken with a full, frank discussion of the risks and lack of measurable benefits, and for those at high risk, results from genetic screening.

COMMENTS

Background

The development of ovarian metastases may lead to increased death in female colorectal cancer patients, and therefore preventative oophorectomy may be considered when undergoing colorectal cancer resection. Undertaking such surgery remains controversial, and therefore robust evidence is crucial. The authors aim to appraise the current evidence for prophylactic oophorectomy in patients undergoing primary curative colorectal cancer resection.

Research frontiers

The topic of preventative surgery at the time of primary resection in of increasing importance as the cure rate for colorectal cancer improves. Cyto-reductive surgery and heated intra-peritoneal chemotherapy is being used with increasing frequency to salvage patients with recurrent or metastatic disease but carries a high morbidity and a risk of mortality. Preventative surgery may be able to avoid these risks.

Innovations and breakthroughs

The scientific literature regarding prophylactic oophorectomy at the time of primary colorectal surgery has not been reviewed since 2005 by Moran *et al*. Up to date review of evidence is required to inform colorectal surgeons about

what is known about the risks and benefits of this procedure.

Applications

This systematic review and meta-analysis is relevant to all female patients undergoing colorectal cancer. It allows patients and their doctors have an informed discussion about whether prophylactic oophorectomy is in their best interests

Terminology

Prophylactic oophorectomy-the removal of normal ovaries in an effort to prevent future disease.

Peer-review

In this study, the authors performed a systematic review and meta-analysis on the association between prophylactic oophorectomy during primary colorectal cancer resection and risk of local recurrence and overall 5-year mortality. Rationale and aim for conducting this meta-analysis on this topic are clear.

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CASE REPORT

Sentinel lymph node mapping for malignant melanoma of the external auditory canal

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Author contributions: Franco J and Moore MG contributed to case write-up, review of literature and manuscript revision; Moore MG also assisted with the surgical procedure and designed the technique for lymph node mapping for the patient described; Hansen LA, Miyamoto RT and Tann M assisted in manuscript revision; Miyamoto RT also helped with the otologic portion of the surgery; Tann M assisted with the administration of the radio-isotope at the time of the procedure.
Ethics approval: The study was reviewed and Institutional Review Board approval was not required.
Informed consent: The subject of the case report, SL, provided consent for the use of her protected health information.
Conflict-of-interest: Joel Franco (primary author) and Michael G Moore (corresponding author) have no financial or other conflicts of interest.

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Abstract

We describe a novel technique for sentinel lymph node mapping and biopsy of a primary cutaneous malignant melanoma in the medial portion of the external auditory canal. The approach is illustrated through a case report and technical description of a procedure performed under general anesthesia on a 19-year-old female patient. Due to the hidden and sensitive location of the primary tumor in the medial external auditory canal, the lymphoscintigraphy injection had to be performed by the surgeon immediately prior to the resection of her cT2aN0M0 lesion. Final pathology revealed clear margins at the primary site resection and 2 intraparotid sentinel lymph nodes with microscopic foci of metastatic malignant melanoma, which led to further surgical management. A completion left parotidectomy and neck dissection yielded no additional metastatic disease in the fifty-five nodes that were evaluated. Using this technique, sentinel lymph node mapping and biopsy accurately predicted the highest risk lymph nodes for the primary lesion of the medial portion of the external auditory canal.

Key words: Malignant melanoma; External auditory canal; Head and neck; Sentinel lymph node biopsy; Sentinel lymph node mapping

Core tip: We describe sentinel lymph node mapping and biopsy (SLNB) of a primary malignant melanoma in the external auditory canal. The usefulness of SLNB in this procedure allowed a focused surgical dissection to best assess regional lymph nodes and determine the extent of dissection needed to clear the disease. This novel technique is useful because it aids in establishing the

single most important prognostic factor of a melanoma in the external auditory canal, regional lymph node status.

Franco J, Hansen LA, Miyamoto RT, Tann M, Moore MG. Sentinel lymph node mapping for malignant melanoma of the external auditory canal. *World J Surg Proced* 2015; 5(1): 173-176 Available from: URL: http://www.wjgnet.com/2219-2832/full/v5/i1/173.htm DOI: http://dx.doi.org/10.5412/wjsp.v5.i1.173

INTRODUCTION

The incidence of malignant melanoma has surpassed that of other malignancies in recent years, at a rate of 3% per year[1]. In 2014, the American Cancer Society estimates that 76100 new cases of malignant melanoma would be diagnosed, resulting in 9710 deaths[2]. Of the malignant melanomas diagnosed, 18% are located in the head and neck and these are associated with a higher mortality rate when compared to melanomas of the trunk and extremities[1].

As treatment has evolved for melanoma, sentinel lymph node biopsy (SLNB) has been established as an integral aspect of both the surgical planning and treatment of this malignancy[3]. SLNB allows detection of minimal tumor burden and metastasis to the regional lymph nodes, an important prognostic factor in the American Joint Committee on Cancer staging system[4,5]. Other institutions including the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the Society of Surgical Oncology also recommend the routine use of SLNB. The status of regional lymph nodes portends the stratification of prognosis and assists with clinical trial determination and eligibility[6].

Melanoma of the external auditory canal is extremely rare, with fewer than 20 cases reported in the literature. The location of these lesions adds a level of difficulty to the standard surgical treatment, which is a wide local excision with margins of at least 1 cm[7]. In addition, technical aspects of radioisotope injection into the external auditory canal are more challenging because the ear canal skin is thin and requires additional instrumentation such as an otomicroscope for accessibility.

We present a case report of a patient with an intermediate stage (cT2aN0M0) cutaneous melanoma of the external auditory canal. As part of her management, a SLNB was performed. To our knowledge, this is the first description of this technique for a melanoma located in the bony portion of the external auditory canal.

Methods

Because this is a retrospective case report, per institutional protocol, no IRB approval was required. The patient has given consent to use her medical information for the case report. The medical records of the patient were accessed to obtain the clinical, radiographic and pathologic information.

CASE REPORT

The patient is a 19 years old, otherwise healthy female who presented with a complaint of a sore inside her left ear for approximately one year. The pigmented skin lesion was confined to the posteromedial aspect of the bony portion of the left external auditory canal. It did not involve the tympanic membrane nor did it involve the more lateral cartilaginous portion of the external auditory canal. There were no other skin lesions noted or any associated pathologically enlarged parotid or neck lymphadenopathy.

The patient was taken to the operating room where a biopsy was performed on the lesion, demonstrating a superficial malignant melanoma with a depth of invasion of 1.47 mm and no ulceration was observed. Appropriate staging revealed this to be a T2aN0M0 lesion. A combined positron emission tomography/computed tomography scan showed no evidence of regional lymphadenopathy or distant metastases; in addition, the bone underlying the lesion in the external auditory canal showed no erosion on preoperative imaging. After discussion with the patient, it was deemed appropriate for her to undergo resection of the lesion with a lateral temporal bone resection along with a SLNB. Due to the location of the lesion in the posteromedial aspect of the bony portion of the external auditory canal, it was most appropriate for the radioisotope injection to be performed using an otomicroscope under general anesthesia (we believe that an injection of local anesthetic to the ear canal skin would have distorted the lymphatic drainage of the area).

Injection and sentinel lymph node mapping technique

Using institutional protocol for handling of radioactive material, an aliquot of 1 mL of 1.5 mCi of Technetium labeled filtered sulfur colloid was obtained from the nuclear medicine department. A total of 0.15 mL was injected around the lesion (superior, inferior and lateral injections were used. No medial injection was performed due to the proximity to the tympanic membrane).

The patient was then prepped and draped in the normal sterile fashion and 30 min was allowed from the time of isotope injection to when the post-auricular incision was made to allow for diffusion through the lymphatics. Once the lateral temporal bone resection was completed, the hand held gamma probe was utilized to identify the most prominent sentinel lymph node which was located in the left parotid gland and had a 10 s count of 10381. The post-auricular incision was extended into the upper neck for access and this node

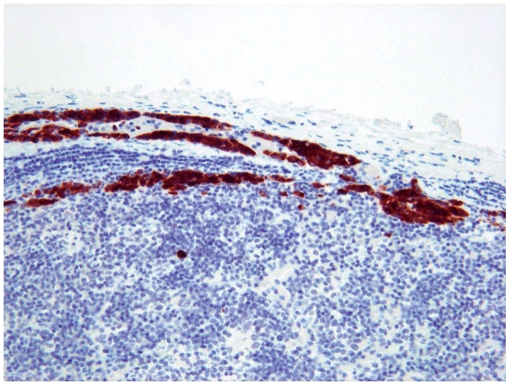

Figure 1 Lymph node stained with Melan-A demonstrating microscopic metastases of malignant melanoma.

was removed. A second lesion having a 10 s count of 4779 was also removed. The remaining parotid tail was noted to have a background higher than 10% of the original lymph node. As a result, the remaining parotid tail was removed and the associated wound background dropped to 389 on a 10 s count.

Surgical pathology of the primary lesion confirmed the 1.47 mm thick tumor and demonstrated that negative margins were obtained. Two of the seven lymph nodes removed as part of the sentinel lymph node mapping demonstrated microscopic foci of metastatic melanoma as demonstrated in Figure 1. As a result, it was recommended that the patient undergo a completion left parotidectomy and left modified radical neck dissection (MRND) with an abdominal fat graft for reconstruction. Final pathology from the completion parotidectomy and MRND showed no additional positive lymph nodes within the 55 that were removed in the completion procedure. The patient tolerated the procedure well and had no significant wound related complications or cranial nerve deficits. Due to the involvement of two intraparotid lymph nodes, the patient was referred to medical oncology. The patient subsequently underwent one year of interferon therapy and is now 20 mo post-op with no evidence of recurrent disease.

DISCUSSION

Malignant melanoma continues to claim lives and its incidence continues to increase at an alarming rate[1,2]. New techniques, such as SLNB, have developed to better serve these patients and reduce morbidity. The usefulness of SLNB in this procedure allowed a focused surgical dissection to best assess regional lymph nodes and determine the extent of dissection needed to clear the disease. This novel technique is useful because it aids in establishing the single most important prognostic factor of a melanoma in the external auditory canal, regional lymph node status[5,8-10]. Opinions on the use of SLNB for T1 lesions vary, while most authors agree on its use for T2 and T3 lesions. We demonstrate its utility in a smaller cancer located in the bony portion of the external auditory canal to accurately identify possible regional metastasis[5,6,11-13].

Studies have demonstrated that 15%-20% of patients with a primary head and neck melanoma will have lymph nodes in a regional nodal basin harboring occult metastases and that the sentinel lymph node accurately predicts the nodal basin status[14]. As such, SLNB plays an invaluable role in saving 80%-85% of patients with a primary head and neck malignant melanoma an unneeded lymph node dissection avoiding complications such as lymphedema, infection, hematoma, seroma, and nerve injury[12-15].

To date, a description of a SLNB of a malignant melanoma located in the bony portion of the external auditory canal does not exist in the literature. This paucity in literature creates uncertainty when dealing with this site-specific lesion. SLNB of the head and neck provides unique challenges related to the anatomy, technique, and interpretation of results[12]. The external auditory canal, due to its delicate and thin skin, as well as its poorly accessible location, is not easily amenable to standard sentinel lymph node mapping techniques. In our patient, the fact that both of the positive sentinel lymph nodes were the first two picked up at the time of the mapping indicates accuracy of the technique used. This is further supported by the fact that no additional positive nodes were obtained in the rest of the definitive lymphadenectomy.

We suggest that sentinel lymph node mapping for melanomas of the external auditory canal can be performed safely and successfully using our described technique.

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COMMENTS

Case characteristics

The 19-year-old female presented with a sore in the left ear for one year.

Clinical diagnosis

Pigmented skin lesion viewed with otoscopy, lesion confined to the posteromedial aspect of the bony portion of the left external auditory canal.

Differential diagnosis

Malignant *vs* benign pigmented lesion.

Laboratory diagnosis

All labs reviewed and within normal limits.

Imaging diagnosis

Positron emission tomography/computed tomography demonstrated no regional lymphadenopathy, no distant metastases, and no erosion of the bone underlying the lesion in the external auditory canal.

Pathological diagnosis

Initial biopsy demonstrated a superficial malignant melanoma with a depth of invasion of 1.47 mm and no ulceration. Two of the seven lymph nodes removed as part of the sentinel lymph node mapping demonstrated microscopic foci of metastatic melanoma.

Treatment

Isotope injection with sentinel lymph node biopsy, lateral temporal bone resection, completion parotidectomy, and one year of interferon therapy.

Related reports

To the best of the author's knowledge, a description of a sentinel lymph node mapping and biopsy (SLNB) of a malignant melanoma located in the bony portion of the external auditory canal does not exist in the literature.

Term explanation

SLNB is a biopsy of the first lymph node or group of nodes draining an anatomic region. The sentinel lymph node is the first lymph node reached by metastasizing malignant cells.

Experiences and lessons

This case presented unique challenges related to the anatomy, technique, and interpretation of results. The authors suggest that sentinel lymph node mapping for melanomas of the external auditory canal can be performed safely and successfully using our described technique.

Peer-review

The manuscript describes the application of lymph node mapping and biopsy in a case of primary malignant melanoma. It is well presented and easy to read.

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REVIEW

Central neck compartment dissection in papillary thyroid carcinoma: An update

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Abstract

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for approximatley 90% of thyroid malignancies in areas of the world without deficit of Iodine. It's universally accepted that total thyroidectomy is the minimal surgical treatment for patients with PTC higher than 1 cm. When a quality surgery is performed, the prognosis for PTC is excellent with 10 and 20-year overall survival rates around 90% and 85%, respectively. Lymph node metastases are very frequent in PTC, occurring in 50%-80% of PTC patients, the most of them being located in the central compartment of the neck (CCN) and with a high rate of occult or clinically undetectable disease. A lot of controversy exists regarding how to treat the central nodal compartment disease of PTC. The first problem is the lack of standardization of the terminology and concepts related to the CCN, which are clearly established and defined in this paper according to the most recent consensus documents of endocrine societies. This uniformity will provide a more consistent and clear communicaction between all the specialist involved in the treatment of PTC. CCN can be performed to treat patients with clinically detectable, radiologically suspected of intraoperative visualized nodal disease (this is defined as therapeutic) or when these findings are absent (also called prophylactic). Indicactions, advantages and disadvantages of both therapeutic and prophylactic CCN dissection are widely discussed and clear recommendations provided.

Key words: Thyroid; Cancer; Papillary; Central; Node; Compartment; Dissection; Prophylactic; Therapeutic

Core tip: When papillary thyroid cancer is discussed anywhere, there are two main matters of controversial which centralize the debates. The first one is the need of having an uniform standardization of the concepts related to the dissection of the central compartment: limits and terminology. The second point is about the concept of prophylactic dissection of the central compartment if patients with neither clinical nor radiological nodal disease related to papillary thryroid carcinoma. Both of the points are clearly defined in this paper and the readers will have clear ideas about what to when facing a papillary thyroid carcinoma.

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INTRODUCTION

During the period from 1973 to 2002, the incidence of thyroid cancer (TC) increased from 3.6 to 8.7 per 10^5[1]. This is almost entirely related to an increase in papillary thyroid cancer (PTC) likely influenced by detection of smaller cancers, accounting for 80% of TC and ranking as the sixth most common cancer in females[2,3]. Nowadays the most part of PTC are nonpalpable lesions incidentally diagnosed because of the proliferation and widespread of multiple different radiographic evaluations, specially neck ultrasound (US) and its increasing sensitivity in screening of small thyroid nodules. Papillary thyroid microcarcinoma, which is defined as a PTC measuring equal or less than 10 mm in diameter according to the World Health Organization classification, accounts for 38.5% of PTC in the United States, 35.7% in Shangai and 48.8% in France[4,5]. The therapeutic mainstay for PTC is resection consisting of total thyroidectomy (TT) with or without lymphadenectomy.

PTC tends to exhibit intra- and extraglandular lymphatic spread, being lymph nodes (LN) involvement and dissemination common; unlike other malignancies, and this is a very important detail, presence of LN metastases generally does not adversely influence prognosis, especially in patients under the age of 45 years. Up to 40% of patients with PTC have clinically detectable macroscopic LN metastases at initial diagnosis and up to 85% have occult or microscopic LN metastases, being clinically apparent LN more common at the extremes of age[6]. The yield of metastatic LN in every compartment of the neck is significantly related to the number of LN retrieved in the neck dissection and to the extent of pathologic examination[7,8]. At this point, it is important to know that all LN metastases are not the same in terms of their implications for locoregional recurrence and mortality, which are the main endopoints to be evaluated in the surgery of PTC. Clinical LN metastases, specially if macroscopic at the time of surgery, are associated with higher recurrence rates and poorer prognosis than are similar cases in which LN metastases are preoperatively undetectable[9-13]. In addition, an increased mortality rate has also been observed in patients with LN metastases who are 45 years or older[13,14]. By contrast, microscopic LN metastases are associated with much lower rates of recurrence and do not affect patient survival, suggesting that they remain dormant and rarely become clinically significant[15,16].

The purpose of this paper is to review and update the concepts and surgical options related to the central neck compartment (CNC) dissection in PTC, the most common well-differentiated thyroid carcinoma, according to the best evidence recently published. At this point, it is important to emphasize that no level of evidence 1 information is available in the literature with the highest reported being level 4 (http://www.cebm.net/?O=125). Papillary thyroid cancers are poorly suited for prospective studies as they tend to be clinically indolent and highly responsive to radioactive iodine (RAI) therapy, with extremely high percentage of long-term survival.

CNC: THE ANATOMICAL CONCEPT

The CNC includes LN levels Ⅵ and Ⅶ. It is bounded superiorly by the hyoid bone, laterally by the sheath of the carotid arteries, anteriorly by the superficial layer of the deep cervical fascia (undersurface of the sternothyroid muscles) and posteriorly by the deep layer of the deep cervical fascia (prevertebral fascia). Initially, the CNC was considered only as LN level Ⅵ and inferiorly bounded by the sternal notch. As the thyroid gland is located low in the neck, its lymphatic drainage is contiguous with the anterior superior mediastinum that can be accessed by a cervical approach. Then, LN level Ⅶ was added to the concept of CNC and its inferior border is actually defined approximately at the level of the innominate artery crossing the trachea on the right and the corresponding axial plane on the left (Figure 1). Anyway, this inferior boundary is more theoretical than practical and somehow arbitrary because the innominate arterial trunk does not exist in the left side and its relation with the sternal notch is variable with the artery rising above the notch in 25% of cadaveric dissections[17].

The CNC contains critical anatomical structures as the trachea, esophagus, parathyroid glands and recurrent laryngeal nerves (RLNs) (Figure 2). Other structures are the larynx, the hipopharynx, cervical thymus, superior laryngeal nerves and vessels (superior and inferior thyroid arteries and superior, middle and inferior thyroid veins).

LN IN CNC: SURGICAL ANATOMY AND TERMINOLOGY

The most commonly involved LN in the CNC in thyroid carcinoma are the prelaryngeal (also known as Delphian), pretracheal and both right and left paratracheal. Paratracheal LN have been also described as *"the nodes of the recurrent laryngeal nodes"* and typically start cranially at the lower margin of the cricoid cartilage and extend caudally to the level of the innominate artery crossing the trachea. The right sided paratracheal LN may be found posterior to the common carotid artery because of its more ventral and medial location compared with the left (Figure 3). LN related to superior pole PTC may sometimes be located in the paralaryngopharyngeal space along the course of the superior thyroid vasculature. Other nodal basins included in the CNC are retroesophageal, retropharyngeal and superior mediastinal

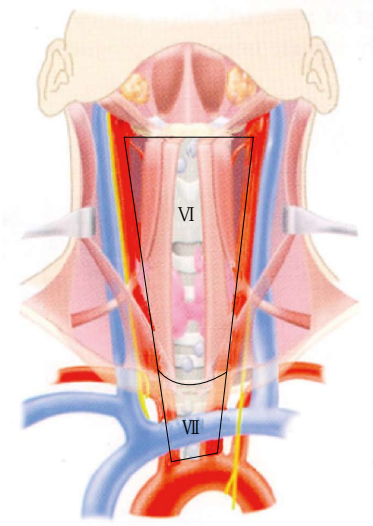

Figure 1 Lymph nodes groups of central neck compartment and their anatomic boundaries.

(inferior to the innominate artery). The mean number of LN in the paratracheal region has found to be an average of 2 to 15 in each side. Weber *et al*[18] reported a mean number of 3.9 paratracheal LN removed (range, 1 to 30) in the analysis the medical records of 645 patients who underwent total laryngectomy for squamous cell carcinoma of the larynx, hypoparynx and cervical esophagus. Pereira *et al*[19] published a mean of 8.4 ± 6.6 nodes resected in the series of 43 patients who had a TT and CNC dissection (CNCD) for PTC.

Generally, cervical LN metastases tend to spread in a stepwise fashion from the thyroid to the ipsi-lateral central LN, then to lateral compartment and/or contra-lateral central compartment. Therefore, the CNC is considered to be the first echelon of LN metastasis in PTC and its removal may theoretically alter the prognosis of this neoplasm. The surgical literature has classically lacked of standardization to define a consistent terminology relevant to the CNCD and this lacking is the main responsible of the great variability and bias in the published series. In 2009, the American Thyroid Association (ATA) published a consensus manuscript with the purpose of establishing the standard definitions to be used in future publications in order to obtain a more effective and safe CNC surgery for TC. This document was supported by the American Association of Endocrine Surgeons, American Academy of Otolaryngology - Head and Neck Surgery and the American Head and Neck Society[20]. The following definitons were suggested (and are still actually accepted) regarding a CNC.

A therapeutic CNCD (*tCNCD*) implies resection of LN metastases that are clinically apparent (cN1) in an attempt to decrease recurrence and theoretically improve survival. Clinical appearance means that there is macroscopic nodal disease grossly apparent preoperatively by physical exam (5%-10%), imaging studies (up to 30% of patients with PTC, biopsy-proven or not) or intraoperatively by visual inspection (LN larger than 1 cm and dark blue or dark appearance).

The most frequently imaging study performed is US of the neck. Preoperative US is recommended for all patients undergoing thyroidectomy for malignancy and may reduce rates of recurrent/persistent disease by allowing an adequate initial surgical treatment[21]. Some sonographic features raising suspicion for LN metastasis have been described: a diameter > 1 cm; loss of the normal fatty hilum; an irregular rounded contour with a long-access to short-access ratio < 1.5; heterogeneous echogenicity; microcalcifications; hypervascularity; and cystic changes. Anyway, US is much more sensitive for detection of metastatic LN in the lateral neck (82%-94%) than in the CNC (30%-60%)[6,22,23]. Detection of LN metastasis in the CNC using US remains difficult even in expert hands beacuse of the abnormal LN are often small in size or microscopic and frequently located deep inside the neck or just posterior to the sternum, where the overlying thyroid gland often hinders adequate visualization[21,23,24]. Kouvaraki *et al*[25] demonstrated that physical examination will miss macroscopic LN metastases in 39% of patients with PTC when a complementary neck US was performed. Although it is well accepted that intraoperative inspection underestimates the presence of pathologically detected nodal metastases, specially microscopic, a recent study documented the reliability of the surgeon to accurately determine the need for tCNCD based on a combination of preoperative US and intraoperative node inspection[26]. Neck computed tomography or magnetic resonance imaging may be appropriate for the assessment of cervical nodal status in centers where experience with neck US is lacking.

A prophylactic, elective or routine CNCD (*pCNCD*) implies resection of LN that are neither apparent clinically nor by imaging methods (cN0) with the theoretical goal of removing undetected metastatic disease and then decreasing persistent local disease. The actual role of pCNCD in PTC remains a major topic of debate and will be widely discussed in this paper.

At a minimum, CNCD should include the prealryngeal, pretracheal and at least one paratracheal LN basin (usually the ipsilateral). LN "plucking" or "berry picking" implies removal only of the clinically involved LN rather than a complete nodal group within the compartment. This LN "plucking" is not recommended because violates the nodal compartment entered without adequately addressing its disease and may be associated with higher recurrence rates.

Finally, every operative record of CNCD should indicate if it has been uni- or bilateral. When bilateral, prelaryngeal, pretracheal and paratracheal right and left nodal groups are removed; for the unilateral CNCD, the difference is that only one paratracheal (right or left) nodal basin is resected.

Thymectomy (uni or bilateral) is usually performed during the CNCD to provide a good clearance of LN level Ⅶ and has been a matter of debate. Huang *et al*[27] recently published a comparative analysis of the incidence of

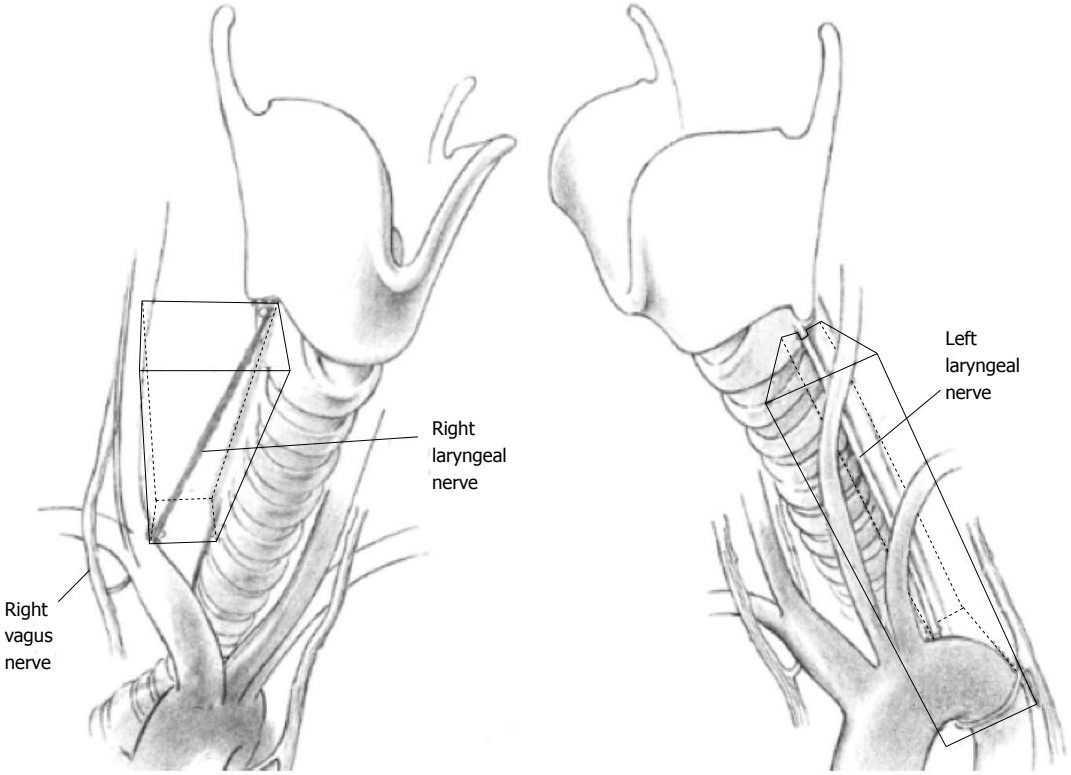

Figure 2 The way of recurrent laryngeal nerves in the central neck compartment.

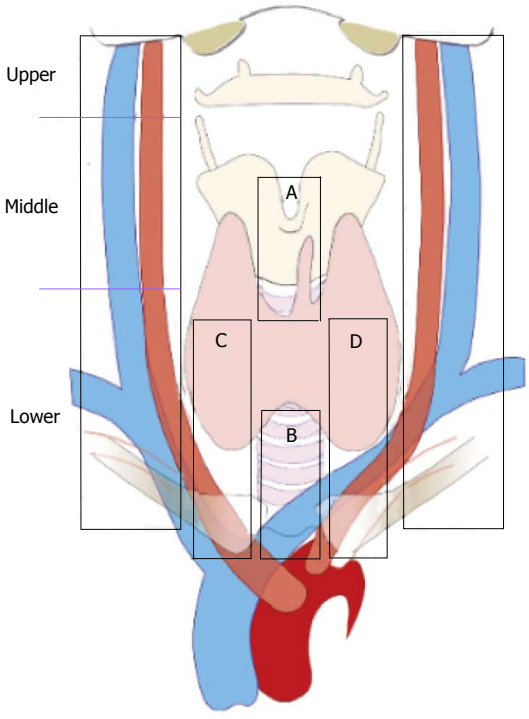

Figure 3 Boxes A, B, C and D representing lymph nodes in the central neck compartment (prelaryngeal, pretracheal and left/right paratracheal).

LN metastases in the thymus in two groups of patients undergoing CNCD with unilateral (n = 73) and bilateral (n = 82) thymectomy for PTC. A very low rate of LN micrometastasis was found in both groups (2.7% *vs* 3.6%, and always ipsilateral to the tumor) and the bilateral group presented a higher rate of transient (but not permanent) hypoparathyroidism (HP) (13.7% *vs* 52.4%). With this results, it seems clear that bilateral thymectomy during the CNCD does not provide a better carcinologic resection as no contralateral thymic metastases were found. The unilateral thymectomy with TT during the CNCD may represent an effective strategy for reducing the rate of postoperative hipocalcemia[27].

THERAPEUTIC CENTRAL NODAL COMPARTMENT DISSECTION

A general consensus exists among the different endocrine/thyroid scientific societies about TT + Therapeutic central neck compartment dissection (tCNCD) being the "gold standard" for the treatment of patients with cN1 PTC. Multiple historical and retrospective series have demonstrated that positive nodal metastases of PTC correlates with increased rates of persistent/recurrent disease and lower overall survival. Then, the rationale of removing grossly evident nodal disease along with any adjacent subclinical disease includes reducing the risk of recurrence and potentially increasing survival.

The first important reference in the medical literature defining the negative impact of age and LN involvement in local recurrence of differentiated thyroid cancer was reported in the classical paper of Harwood *et al*[9]. Globally, tumor recurrence and mortality rates were in 32%/24% and 14%/8% for LN(+) and LN(-) patients, respectively. In patients with more than 40 years old, mortality related

to the tumor was 41% and 15%, respectively, for LN(+) and LN(-) cases[9]. These results were confirmed by Tubiana *et al*[10] (*n* = 546) and Sellers *et al*[11] (*n* = 76), who published both of them series with more than 34 years of follow-up in which age older than 45-50 years old and the presence of cervical LN metastases (specially if palpable) were negative prognostic factors for poorer survival and higher locoregional recurrence[10,11]. Wada *et al*[28], in a retrospective study of 259 patients with PT microcarcinoma and routine CNCD found that recurrence was 16.7% for cN1 (*n* = 24) and only 0.43% (*n* = 235) for cN0 (this latter did not differ with a control group of non-performed CNCD, 0.65%).

Lundgren *et al*[12], in a large popullation-based control-case study, reported a 2.5-fold higher disease-related mortality in patients with differentiated thyroid cancer and LN metastases. Zaydfudim *et al*[13], in a review of the Surveillance, Epidemiology and End Results (SEER) registry found an increased risk of death in patients with PTC aging 45 years or older and having nodal metastasis, with no difference in survival in patients younger than 45 years with or without nodal metastasis. The review of the SEER by Podnos *et al*[29] described a survival at 14 years of 82% for node-negative patients and 79% for node-positive ($P < 0.0001$) being this difference also remarkable in the group with age 45 years or younger (96% N0 *vs* 90% N1). Ito *et al*[30] reviewed retrospectively 759 patients with PTC and found a 63% of central LN metastases which independently predicted worse disease free survival.

National Cancer Comprehensive Network, version 2.2014, establishes that "clinically positive and/or biopsy-proven nodal metastases should be treated with a formal compartmental resection. In the central neck, this is achieved through a unilateral or bilateral level Ⅵ dissection"[31]. The British Thyroid Association and the Royal College of Physicians, in the third edition of their guidelines in the management of thyroid cancer (2014), recommended that "overt disease in the central compartment discovered prior to/at surgery should be treated by a therapeutic level Ⅵ/Ⅶ node dissection"[32]. The ATA, in the 2009 revised Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer says in recommendation number 27 that "therapeutic central-compartment neck dissection for patients with clinically involved central or lateral neck LN should accompany TT to provide clearance of disease from the central neck"[33]. The Société Française d'Oto Rhino Laryngologie clearly defines the role of tCNCD, with recommendation number 7 being as follows: "when facing cN1 LN disease in the central compartment, it is recommended to avoid performing a berry picking and it is always preferred a compartment oriented central dissection when technically feasible"[34]. Finally, recommendation number 18 of the German Association of Endocrine Surgeons Guidelines is very convincing treating the role of tCNCD: "for clinically node-positive PTC, whatever the size of the thyroid primary, central compartment dissection should be combined with TT *to* diminish the risk of locoregional recurrence and improve survival"[35].

As it can be observed, there is a lot of surgical literature of low evidence level confirming the negative association between LN metastases and recurrence or survival in PTC. Nonetheless, it is also important to remark that data demonstrating improved survival and/or long-term recurrence risk among differentiated thyroid cancer patients treated with tCNCD are also lacking.

PROPHYLACTIC CENTRAL NODAL COMPARTMENT DISSECTION

Although it was longly abandoned at the end of the last century, the debate over the usefulness of prophylactic central neck compartment dissection (pCNCD) has been renewed over the past 10-15 years. During this period, the most important endocrine/thyroid medical and surgical societies have treated this topic in their published guidelines and, curiously, have been changing and swinging their recommendations about the indication of performing pCNCD in PTC. It must be considered that no level of evidence 1 information from prospective randomized trials is available in the literature and that the highest evidence reported is level 4 from retrospective studies comparing contemporaneous cohorts of patients treated with TT with or without pCNCD associated.

The main points for discussion about performing pCNCD are: rates of recurrence free survival and mortality; postoperative thyroglobulin (Tg) levels; importance of accurate staging; and, safety.

It is unknown what the natural history is in patients with PTC with microscopic LN involvement or subclinical nodal metastases (cN0). It is doubtful that they would eventually develop into clinically significant recurrences in the future as the studies of Wada *et al*[28] and Gemsenjäger *et al*[36] reported, the latter with only 17% of LN involved in pCNCD dissection and only 3.44% of nodal recurrence with no deaths related.

An example of how this issue is controversial can be appreciated in the different conclusions of recently reported meta-analysis. The good prognosis of PTC and its natural evolution has resulted in the inability of several studies to demonstrate a difference between TT+pCNCD compared with TT alone because of the short term follow-up. The one published by Lang *et al*[37] included 3331 patients and reported a 35% reduction in the risk of locoregional recurrence for patients with pCNCD (4.7% *vs* 8.6%) but it is not posible to know how much of this reduction is related to an increased rate of patients who underwent postoperative RAI-131 ablation (71.7% *vs* 53.1%). A previous meta-analysis published by Zetoune *et al*[38]. found no difference in recurrence rates favouring pCNCD, and Wang *et al*[16] also failed to evidence a significant difference between TT+pCNCD and TT, but they observed a trend toward a lower local recurrence (4.7% *vs* 7.9%). In Table 1 it can be seen that recent guidelines of the most important endocrine scientific societies about

Table 1 Recommendations of the different international endocrine and thyroid societies about prophylactic central nodal compartment dissection

Scientific Thyroid Society	Year	Recommendations about prophylactic central neck compartment dissection
European Society of Endocrine Surgeons[36]	2014	Recommended in T3 or T4 tumors; age > 45-yr or < 15-yr; male sex; bilateral or multifocal tumors; and, evidence of involved lateral LN
British Thyroid Association[32]	2014	Central compartment neck dissection is not recommended for patients without clinical or radiological evidence of lymph node involvement. May be considered for patients: PTC non-classical type; > 45-yr; multifocal tumors; > 4 cm; and extra-thyroidal extension on US, but benefit is unclear
National Comprehensive Cancer Network (NCCN version 2.2014)[31]	2014	Consider prophylactic CNC dissection in patients with known distant metastases; bilateral nodularity; extrathyroidal extension; tumor > 4 cm; poorly differentiated histology (although the level of evidence is low, NCCN considers the intervention as appropriate)
Japanese Society of Thyroid Surgeons and Japan Association of Endocrine Surgeons[40]	2014	Previous 2010 JSTS/JAES guidelines recommended routine bilateral central node dissection in patients who underwent total thyroidectomy. At present guidelines, it is not routinely considered and the indication may depend on institutional policy and surgeons' skill levels, joining ATA phylosophy
Société Française d'Oto Rhino Laryngologie et de Chirurgie de la Face et du Cou[34]	2012	In patients cN0, the diagnostic value of surgical exploration of the CNC is weak. Two different strategies are recommended: a compartment oriented CNC or not performing any surgical tecnique. Nonetheless, in patients with T3/T4 tumors prophylactic CNC dissection is strongly recommended
European Society of Medical Oncology Clinical Practice Guidelines[38]	2012	The benefit of prophylactic central node dissection in the absence of evidence of nodal disease is controversial. There is no evidence that it improves recurrence or mortality rate, but it permits an accurate staging of the disease that may guide subsequent treatment and follow-up
American Thyroid Association[33]	2009	Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4)
German Association of Endocrine Surgeons[35]	2013	The clinical benefit regarding locoregional recurrence and survival after prophylactic compartment dissection for clinically node-negative PTC > 10 mm is unproven although occult lymph node metastases are common in this setting. To prevent the risk of surgical complications from outweighing a conceivable oncological benefit, prophylactic lymph node dissection is not advised unless the requisite surgical expertise is available

PTC: Papillary thyroid carcinoma; CNC: Central neck compartment; NCCN: National Comprehensive Cancer Network; ATA: American Thyroid Association; JSTS: Japanese Society of Thyroid Surgeons; JAES: Japanese Association of Endocrine Surgeons; LN: Lymph nodes.

pCNCD are dim and use very vague expressions[31-35,39-41]. A global analysis of this table led us to consider pCNCD only in selected group of patients with recognized factors of higher locoregional recurrence (specially T3/T4 tumors, bilateral or multifocal tumors and age older than 45 years). Some reports agree that the mutation of BRAF V600E is associated with tumor aggressiveness, a poor prognosis, resistance to postoperative RAI therapy and the need for a more extended surgery. However, the potential role of the preoperative assessment of BRAF V600E mutation status in decisions regarding whether to perform pCNCD remains controversial. When the necessity of pCNCD in patients with PTC is preoperatively determined, we should recommend to perform pCNCD if BRAF V600E mutation and other conventional clinical risk factors are coexistent[42]. All these data suggest that the benefit provided by a pCNCD in cN0 patients may only be limited in terms of recurrence and that a prospective study with a very long follow-up, homogenous population and rigurous inclusion criteria is needeed. Nonetheless, a randomized controlled trial will hardly be performed because it has been estimated to cost $20000000 and would need 5840 patients to achieve statistical power[43].

As it would be expected, pCNCD has not shown any cancer-specific survival benefit. Costa *et al*[44], in a study on a group of 244 PTC who underwent TT+pCNCD or TT alone, did not find any difference in recurrence rates (6.3% *vs* 7.7%) or survival even when 47% of pCNCD showed LN involvement. Zuniga *et al*[45] also had a rate of 82.3% patients with LN involved after pCNCD but similar 5-year disease-free survival (88.2% *vs* 85.6%) was obtained for this cohort when compared to that having only TT. The most recent controversy has been provided by Barczyński *et al*[46], who has published the first paper in the literature showing a benefit not only for local recurrence (5.5% *vs* 12.4%) but also for specific disease survival (98% *vs* 92.5%) for patients with PTC having TT + pCNCD (n = 358) in comparison with those who had only TT (n = 282). Major bias in this study are its retrospective nature and that patients considered at risk in any group had RAI treatment.

Complete remission of PTC is defined by normal US and negative Tg levels in blood in the follow-up. Theoretically, pCNCD will result in higher rate of undetectable levels of Tg, facilitating follow-up and cancer surveillance and being a good surrogate for recurrence. Nonetheless, this difference may be overlaped by administration of postoperative RAI.

Lang *et al*[47] examined the results of surgical treatment of 185 patients PTC having TT + pCNCD (n = 82) or only TT (n = 103). The first group had lower median postoperative Tg levels (0.5 μg/L *vs* 6 μg/L) and higher rate of athyroglobulinemia (51.2% *vs* 22.3%) both of the differences with $P < 0.05$. When RAI was indicated by clinical or histological risk criteria, similar values with no significative differences were achieved six mo later. The only explanation posible is that residual microscopic disease not treated by pCNCD surgery in the TT-alone group was ablated by radioiodine administration. So *et al*[48], in a similar study comparing 113 patients having

TT alone with 119 undergoing TT+pCNCD found that the latter had significative lower levels of Tg (1.07 ng/mL *vs* 2.24 ng/mL), but this difference disappeared when low-dose RAI ablation was given and 3 years locoregional control was similar in both groups (96.5% *vs* 98.3%). Sywak *et al*[49] used Tg levels in an attempt to support pCNCD in his study of 447 PTC patients cN0 undergoing TT alone (n = 391) or TT+pCNCD (n = 56) and having RAI ablation following a similar algorithm. Mean postablation Tg levels were lower in the pCNCD (0.4 mg/L *vs* 9.3 mg/L, $P < 0.02$) and also was the rate of undetectable Tg levels (72% *vs* 43%, $P < 0.001$). However, no significant differences were found in locoregional recurrence rates (3.2% *vs* 5.6%) or cancer-specific mortality rates (0% *vs* 0%) despite a shorter median follow-up duration (25 mo *vs* 70 mo) in the pCNCD group. It can be thought that the impact of performing pCNCD to obtain an analytical control of the disease is more theoretical than really useful[49].

Performing a pCNCD provides the most real and adequate TNM staging for PTC and upstages 30%-50% of patients from cN0 to pN1. Then, patients aging 45 yr or older and having tumors staged as TNM Ⅰ (T1N0) or Ⅱ (T2N0) become TNM Ⅲ (T1 or T2 with N1a/b). The immediate consequence of stage migration is a different rate of overall cancer-specific survival (85%-90% for stage Ⅲ, 95% for stage Ⅰ). In addition, pN1 patients will be included in the ATA group of intermediate risk of recurrence and will receive RAI ablation at higher dosis, while T1 or T2 with cN0 patients are usually included in the low risk of recurrence group and receive lower dosis of RAI ablation. A recent systematic review published by Sawka *et al*[50] showed, however, that there is no benefit from RAI in reducing disease-specific mortality or recurrence in early stages (T1/T2). Bonnet *et al*[51] reviewed the records of 115 patients with PTC < 2 cm (T1) and cN0 undergoing pCNCD, considering the ATA guidelines and indicating RAI ablation for T1 PTC only if LN involvement existed. LN metastases were found in 42% and, globally, 58% of patients received RAI treatment (age < 18 years, aggressive cell types on pathology and vascular or capsular invasion were the other indications diferent than LN+ for RAI ablation). LN status modified the indication of RAI treatment in 30.5% of patients (14.65% were T1a tumors, < 1 cm, which resulted in pN0 and 15.85% were T1b tumors, between 1-2 cm, which resulted in pN1). Morbidity was limited to a 0.9% of permanent HP and the same percentage of RLN palsy. One year follow-up revealed 97.4% of patients with normal neck US and undetectable Tg levels, concluding the authors that, for T1 PTC, a pCNCD may change the need for RAI ablation without increasing the standard rate of complication or the risk of local recurrence[51].

Hughes *et al*[52] observed that patients with TT + pCNCD had higher dose of RAI than those with only TT (150 *vs* 30 mCi, P = 0.01), and Moo *et al*[53] found similar results (102.7 *vs* 66.3 mCi, P = 0.002). In both series, there was no difference in the rates of central neck recurrence or survival between both groups. Then, pCNCD allows better staging and stratification with more patients in early stage recieving higher dose of RAI ablation. Nevertheless, neither local recurrence rates nor survival are affected, some patients who will have no oncological benefit are exposed to potential side effects of RAI and, finally, health care costs are increased.

Safety can not be used nowadays to justify not performing a pCNCD in patients with PTC. CNC resection means wide dissection and sometimes gentle manipulation of the RLNs (which may result in temporary or permanent dysphonia up to 1%-3%) and clearance of all the fatty and lymphatic tissue aorund the parathyroid glands (which may be unintentionally removed o devascularised causing permanent or transient HP in, respectively, 2%-5% and 10%-50% respectively).

Lang *et al*[37] found that patients with pCNCD were 2.5 times more likely to have temporary HP than those undergoing TT alone in a systematic review reporting short-term results of patients operated for PTC. A recent meta-analysis about adverse effects of TT compared with TT + pCNCD included 1132 patients from 5 retrospective studies and found that there was one extra case of transient HP for every 8 (most exactly, 7.7) pCNCD performed. However, there was no increased risk of permanent HP and RLN injury[54]. Although some isolated series have reported higher rates of temporary RLN lesions with pCNCD (always with non-significant values of "*P*"), to date no studies have shown an increased risk of permanent RLN injury[55-57].

If pCNCD is not performed, the patient is at risk for central recurrence and may require a second operation in order to remove persistent or recurrent nodal disease. Because of the presence of fibrosis and scar tissue, re-operation may be associated with higher morbidity than pCNCD done at the first surgery. Segal *et al*[58] reviewed 503 patients retrospectively operated on for PTC, and the 48 requiring reoperation had higher complication rates of permanent RLN injury (25% *vs* 8%) and permanent HP (8.3% *vs* 5%). Simon *et al*[59] reported 77 patients undergoing a second surgery for recurrence out of a total of 252 primarily operated PTC, also being rates of permanent RLN palsy (6.8% *vs* 2.6%) and HP (3.9% *vs* 1.7%) higher for the re-operative group. On the other hand, Shen *et al*[60] found similar results in all the parameters analysed related to morbidity between first time performed pCNCD (n = 189) and re-operated patients (n = 106) with PTC (permanent HP, 0.5% *vs* 0.9%; permanent hoarseness, 2.6% *vs* 1.9%; and, transient hoarseness, 4.8% *vs* 4.7%).

As a conclusion, when an extensive review of the literature is done there seems to be no arguments favouring routine or pCNCD as an universal rule for patients with PTC. The guidelines and consensus documents of the most important medical and surgical societies are in the direction of selecting subgroups of patients with high risk of recurrence for pCNCD, specially T3 or T4 tumors, multifocal/bilateral tumors and patients with BRAF V600E mutation detected in the preoperative setting. In the rest

of PTC, which are the majority, TT must be considered an oncological proper treatment providing the best overall survival.

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REVIEW

Comprehensive treatment for the peritoneal metastasis from gastric cancer

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Abstract

Recently, a novel comprehensive treatment consisting of cytoreductive surgery (CRS) and perioperative chemotherapy (POC) was developed for the treatment of peritoneal metastasis (PM) with a curative intent. In the treatment, the macroscopic disease is completely removed by the peritonectomy techniques in combination with POC. This article reviews the results of the comprehensive treatment for PM from gastric cancer, and verifies the effects of CRS and POC, including neoadjuvant chemotherapy (NAC) and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). Completeness of cytoreduction, peritoneal carcinomatosis index (PCI) less than the threshold levels after NAC,

absence of ascites, cytologic status, pathologic response after NAC are the independent prognostic factors. Among these prognostic factors, PCI threshold level is the most valuable independent prognostic factor. After staging laparoscopy, patients with PM from gastric cancer are recommended to treat with NAC before CRS. After NAC, indication for CRS is determined by laparoscopy. The indications of the comprehensive treatment are patients with PCI less than the threshold levels, negative cytology, and responders after NAC. Patients satisfy these factors are the candidates for the CRS and HIPEC.

Key words: Gastric cancer; Hyperthermic intraoperative intraperitoneal chemotherapy; Peritoneal metastasis; Peritonectomy

Core tip: This article reviews the results of the comprehensive treatment for peritoneal metastasis from gastric cancer, and verifies the effects of cytoreductive surgery and perioperative chemotherapy, including neoadjuvant chemotherapy (NAC), and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). Multivariate analyses revealed that the completeness of cytoreduction, peritoneal cancer index less than the threshold levels after NAC, cytologic status, pathologic response after NAC are the independent prognostic factors. Patients satisfying these factors are recommended to undergo D2-gastrectomy combined with complete removal of PC and HIPEC.

Yonemura Y, Canbay E, Endou Y, Ishibashi H, Mizumoto A, Li Y, Liu Y, Takeshita K, Ichinose M, Takao N, Saitou T, Noguchi K, Hirano M, Glehen O, Brűcher B, Sugarbaker PH. Comprehensive treatment for the peritoneal metastasis from gastric cancer. *World J Surg Proced* 2015; 5(2): 187-197 Available from: URL: http://www.wjgnet.com/2219-2832/full/v5/i2/187.htm DOI: http://dx.doi.org/10.5412/wjsp.v5.i2.187

INTRODUCTION

Peritoneal metastasis (PM) was considered as a terminal stage with very poor prognosis. In the late 1990s, Peritoneal Surface Malignancy Oncology Group International proposed a novel comprehensive treatment consisting of cytoreductive surgery (CRS) and perioperative chemotherapy (POC). In the comprehensive treatment, the macroscopic disease is completely removed by the peritonectomy techniques in combination with POC. POC includes neoadjuvant intraperitoneal/systemic chemotherapy (NIPS), bidirectional intraperitoneal and systemic induction chemotherapy (BISIC), laparoscopic hyperthermic intraperitoneal chemotherapy (LHIPEC), hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC), extensive intraoperative peritoneal lavage (EIPL), early postoperative intraperitoneal chemotherapy and late postoperative systemic chemotherapy[1-3].

This article reviews the rationale of the comprehensive treatment for PM from gastric cancer.

Quantitative evaluation of PM

Preoperative and intraoperative diagnosis for PM should provide reliable information about the tumor burden and distribution of PM[4,5]. At present, the peritoneal carcinomatosis index (PCI) is used worldwide[5]. The abdominal compartments were divided into 13 sectors. The tumor involvement in each compartment is macroscopically evaluated by the lesion size scores from 0 to 3. PCI described the tumor load in the abdominal cavity from 0 to 39. PCI score is considered an important prognostic indicator after CRS. Threshold levels of PCI for favorable *vs* poor prognosis were reported from several high volume centers. Glehen *et al*[6,7] reported that all patients died within 3 years after CRS when the PCI score was higher than 12. Even if complete cytoreduction appears to be possible, patients with PCI of higher than 12 should be contraindicated for the aggressive CRS[7]. Yonemura *et al*[8] reported patients with PCI of lower than 6 survived significantly better than those with PCI of higher than 7. Yang *et al*[9] proposed the best candidates for the CRS could be patients with PCI < 20. To select patients for CRS, PCI assessed by preoperative computed tomography (CT) may have an important role. However, the accuracy of CT for the preoperative evaluation of PM from gastric cancer is limited, because the size of PM from gastric cancer is usually small[10].

In the preoperative evaluation for PM, Hong *et al*[11] proposed a new classification consisting of three grades. Grade 0 was defined as PM detected during operation with no evidence of PC in the preoperative evaluation, and grade 1 was defined as PM or ascites detected by CT scan, however, no bowel involvement or need for paracentesis was recorded. Grade 2 was defined as bowel wall involvement or a large amount of ascites requiring paracentesis[11]. When the grade 0 and grade 1 were summed as low-grade and grade 2 was defined as high-grade, survival of patients with low-grade PM was significantly longer than the patients with high-grade PM. Among the patients with low-grade PC, patients who received a gastrectomy had longer survival than those who did not receive a gastrectomy[11]. This staging system is useful to determine the indication of gastrectomy or systemic chemotherapy.

In the Japanese general rules of gastric cancer treatment, status of PM is grouped into three categories: P0/Cy0, Po/Cy1, and P1[12]. P0/Cy0 status is no macroscopic PM and a negative peritoneal wash cytology. P0/Cy1 status shows no macroscopic PM but positive peritoneal wash cytology, and P1 status means the macroscopic PM with or without a positive peritoneal cytology. The survival of patients with P0/Cy1 is similar to that of patients with P1[13,14]. The proliferative activities of peritoneal free cancer cells (PFCCs) is considered

high[14]. Accordingly P0/Cy1 status is classified into stage Ⅳ disease even in patients with no macroscopic PM. Bando *et al*[13] reported that 114 (11%) of 1039 potentially curable patients showed positive cytology (P0/Cy1).

However, there is no universal consensus on the most appropriate treatment regimen for this particular group of patients. Cabalag *et al*[15] performed a meta-analysis of treatment results in patients with P0Cy1 status. The use of S1 monotherapy was associated with a significant survival benefit[16]. A recent randomized controlled trial examining EIPL with intraperitoneal chemotherapy (IPC) showed a significant improvement on overall survival (5-year overall survival, 43.8% for EIPL plus IPC group compared with 4.6% for IPC group)[17]. In addition, the role of gastrectomy remains unclear in patients with P0/Cy1[18]. Furthermore, Kang *et al*[19] reported that peritoneal washing cytology was not able to predict peritoneal recurrence or survival in gastric cancer patients[19]. These results indicate that more clinical trials should be done to define the best treatment option for patients in P0/Cy1 status.

Score of the completeness of cytoreduction

Score of the completeness of cytoreduction score (CC score) is an assessment grade after CRS[4]. The residual disease after CRS is classified into four grades of CC-0 to CC-3. CC-0 indicates a status of no macroscopic residual tumors after CRS. CC-1 means residual tumor burden of less than 2.5 mm in diameter. CC-2 shows that the total tumors between 2.5 mm and 25 mm in diameter are left. CC-3 means the residual tumor of greater than 25 mm in diameter. The CC-1, CC-2 and CC-3 are evaluated as the incomplete cytoreduction. Histological positive margin is classified CC-1[2].

The role of CRS in the comprehensive treatment

CRS or chemotherapy alone can not confer the cure for patients with PM. In contrast, CRS combined with intraperitoneal chemotherapy applications improves a long-term survival, because invisible metastasis left after CRS can be eradicated by intraperitoneal chemotherapy[3]. Accordingly, the comprehensive treatment is now justified a state-of-the-art treatment for patients with PM.

Among the treatment options using in the comprehensive treatment, the completeness of CRS is the important prognostic factor[8,20]. Survival of patients underwent incomplete cytoreduction was not improved, as compared with that of patients treated with chemotherapy alone[2]. In contrast, patients underwent complete cytoreduction survived significantly longer than those treated with incomplete cytoreduction or chemotherapy alone. PCI score correlates with the completeness of cytoreduction. CC0 was achieved in 91% of the patients when the PCI score was lower than 6, but in only 42% of the patients with a PCI $\geqslant$ 7[8]. Even in patients with complete cytoreduction, all patients with PCI higher than the threshold value died of the recurrence[7,8]. Accordingly, surgeons should decide to perform CRS for CC-0 after counting PCI score.

Peritonectomy techniques to achieve CC-0 CRS for PC from gastric cancer

The final goal of CRS is to remove all macroscopic PM, including primary tumor, the regional lymph nodes and PM, using peritonectomy technique[1,8,14]. Peritonectomy procedures include parietal and visceral peritonectomy. In parietal peritonectomy right and left subdiaphragmatic peritonectomy, pelvic peritonectomy, peritonectomy of right and left para-colic gutter and Morrison's pouch are removed. In visceral peritonectomy, multivisceral resection of small bowel, colon, rectum, spleen, gall bladder, uterus, vagina, lesser omentum, and omental bursa, are performed when they are involved. To remove primary tumor, total gastrectomy in combination with D2 lymph node dissection is usually done. Piso *et al*[21] reported that the incidences of postoperative morbidity and mortality after gastric resection and peritonectomy were acceptable even when combined with HIPEC.

For the skin incision, a generous midline skin incision starting at the xiphi-sternal junction above to symphysis pubis below is designed. If there is a scar of previous operation, it should be included in the skin incision. Ascites is then aspirated through a small window made on the peritoneum, and the ascites is studied for cytological examination. Before starting CRS, EIPL is done[17]. The peritoneal cavity is extensively shaken and washed after injection of 1 L of saline, and then the saline is completely aspirated. This procedure is repeated 10 times[17]. The rationale of EIPL is the removal of PFCCs from the peritoneal cavity by 10 times wash with 1 L of saline according to the "limiting dilution theory".

Parietal peritoneum is dissected off from the posterior sheath of rectus muscle (Figure 1). Then the dissection between diaphragm and peritoneum is done by ball-tip electrosurgery[14]. On the left upper quadrant, spleen and right subdiaphragmatic peritoneum are dissected from the anterior renal fascia, and the dissection plane reaches to the left side of celiac axis (Figures 2 and 3). Stomach is isolated from the attachment of lesser onentum to the Arantius' duct, and hepatoduodenal ligament by ligation of right gastric artery (Figure 4). On the right upper quadrant, complete stripping of the peritoneum covering subdiaphragmatic muscle, and the retroperitoneum covering on Morrison's pouch is dissected. Second portion of duodenum is identified and the anterior leaf of transverse mesocolon is removed with greater omentum (Figures 5 and 6). Then, 1st portion of the duodenum is cut at 1cm from pyloric ring. The proper hepatic artery and common hepatic artery are skeletonized by electro-surgical techniques. The left gastric artery and left coronary vein are cut at the roots. Esophagus is transected above the esophago-gastric junction, and the proximal margin of esophagus is sent to pathologic department to confirm the negative proximal surgical margin. Next, lymph nodes along splenic artery and splenic hilum are dissected and then splenic artery and

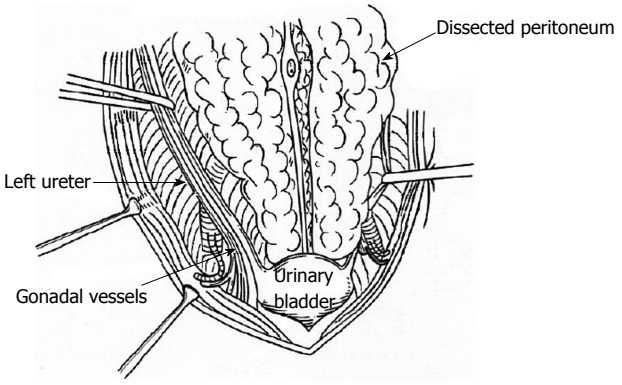

Figure 1 Dissection of the lower parietal peritoneum.

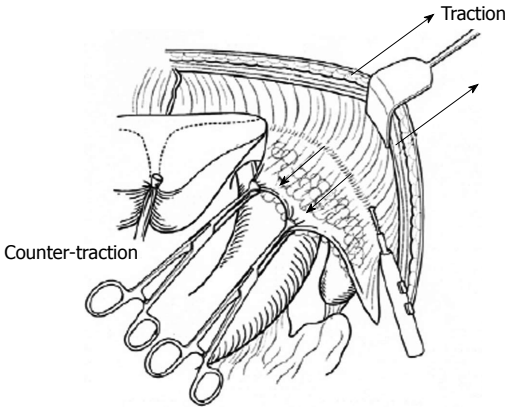

Figure 2 Dissection of the upper right parietal peritoneum.

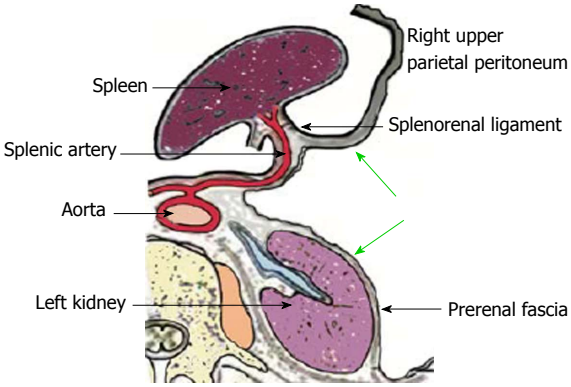

Figure 3 Mobilization of spleen and pancreas tail. The prerenal fascia is cut and the anterior surface of the left adrenal gland is visualized.

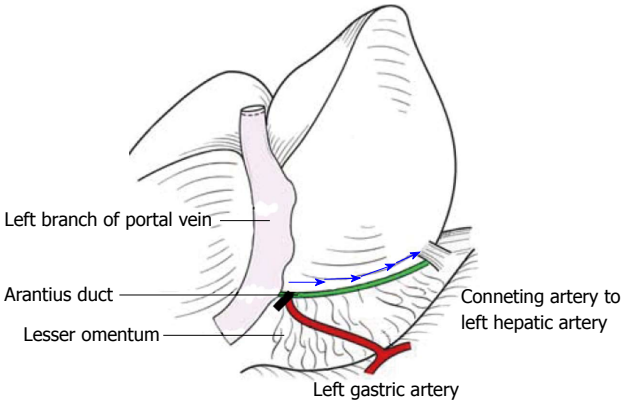

Figure 4 Detachment of lesser omentum from Arantius' duct.

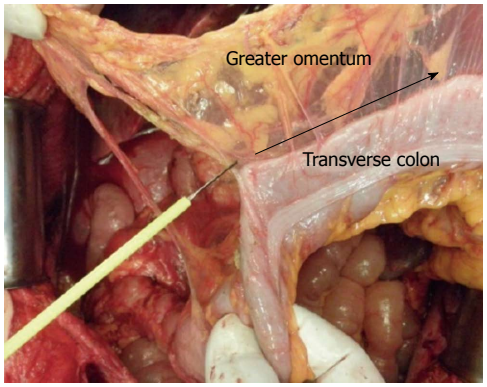

Figure 5 Detachment of greater omentum from transverse colon.

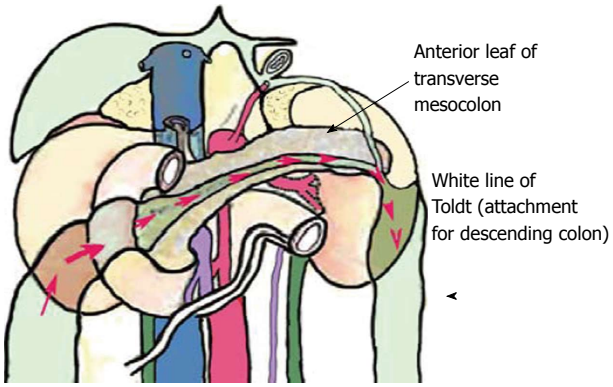

Figure 6 Dissection plane between posterior and anterior transverse mosocolon.

vein are cut at proximal part of their divergence.

Pelvic peritonectomy is started by stripping the peritoneum covering the urinary bladder. In male, anterior dissection plane reaches to the rectovesical pouch. In female, vagina is cut below the uterine cervix (Figure 7). After cutting and ligating the uterine vessels, vagina is transected with electric knife. Then, the posterior wall of vagina is dissected from the rectum. Rectum is freed from the pelvic structure. The posterior dissection reaches to the S4 presacral space by the preservation of pelvic nerve plexus and hypogastric nerve.

If the rectum is not involved, rectum-preserving pelvic peritonectomy is done (Figure 8).

When the rectum is involved, rectum is transected at 2 cm below cul-de-sac (Figure 9).

In terms of the treatment of ovarian metastasis from appendiceal mucinous neoplasm, Elias *et al*[22] proposed the preservation of ovaries in young women with appendiceal mucinous neoplasm for the childbearing, when the ovaries are macroscopically normal. Recurrence in the preserved ovary was found in 14% (3/21), and two women became pregnant after ovary-preserving peritonectomy. In patients with PM from gastric cancer,

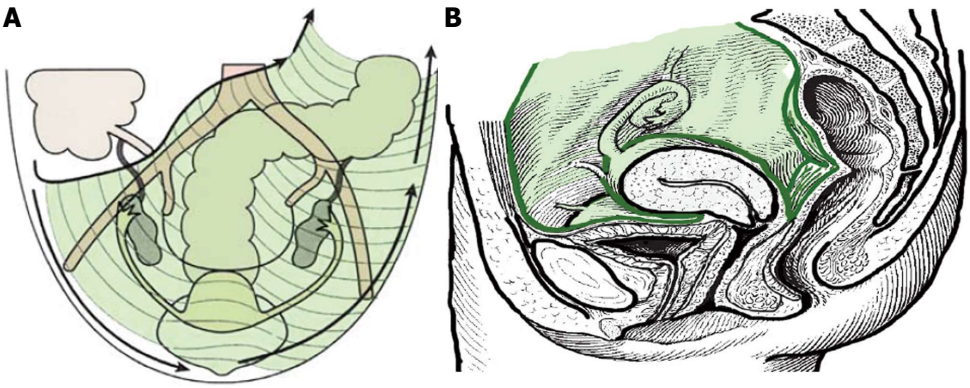

Figure 7 Stripping of the pelvic peritoneum. A: Stripping of the pelvic peritoneum from the urinary bladder and side walls of the pelvis in male; B: Stripping of the pelvic peritoneum with uterus and ovaries in female.

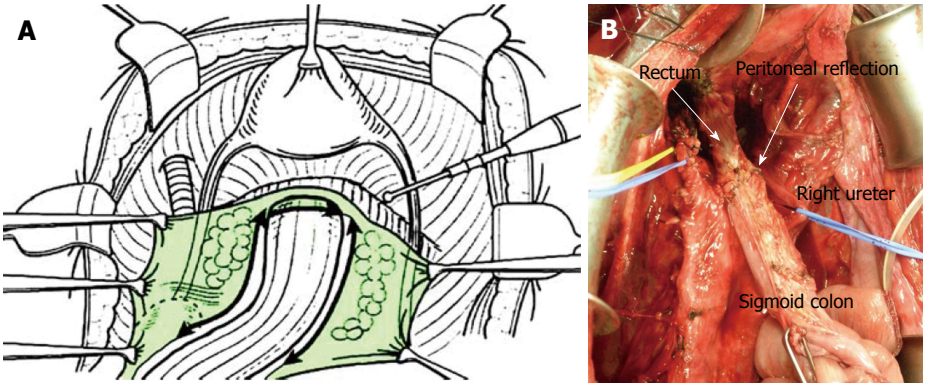

Figure 8 Rectum-preserving peritonectomy. A: The pelvic peritonectomy is started by stripping the peritoneum covering urinary bladder and recto-vesical pouch in male.and the dissection plane reaches the anterior wall of the rectum; B: Photograph after removal of pelvic peritoneum. Rectum is preserved completely.

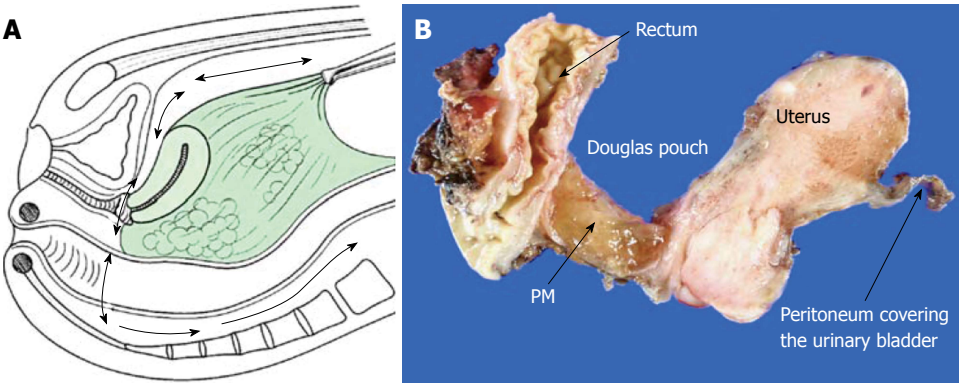

Figure 9 Pelvic peritonectomy combined with the resection of rectum, uterus and vagina (A) and cut-section in a specimen of low anterior resection of rectum/hysterectomy/bilateral salphyngo-oophorectomy shows peritoneal metastasis on Douglas pouch (B).

however, ovaries should be removed, because the incidences of ovarian and uterine involvement are higher than those from appendiceal mucinous neoplasms. In addition, the biological behavior of gastric cancer is more malignant than that of appendiceal mucinous neoplasms.

NEOADJUVANT CHEMOTHERAPY

Complete cytoreduction is the strongest independent prognosticator[2-4]. However, survival of patients with PCI higher than the threshold value is poor, even if they received complete cytoreduction.

By the preoperative laparoscopic examination, Yonemura *et al*[23] reported that 21 (60%) of 35 patients without NAC showed the PCI score higher than the threshold level. Valle also reported that CC-0 can be achieved only in fewer than 30% of the cases who had not been treated with neoadjuvant chemotherapy (NAC)[24]. These results indicate that the patients with PCI higher than the threshold value diagnosed by

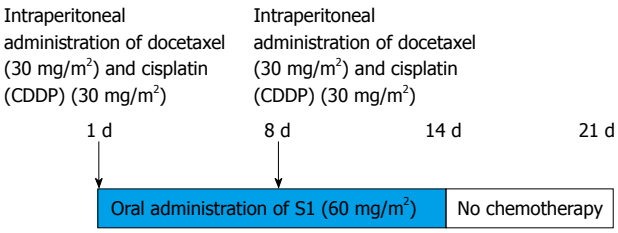

Figure 10 Neoadjuvant intraperitoneal/systemic chemotherapy. Oral S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is administered for 14 d at a dose of 60 mg/m^2, following 7 d rest. Docetaxel (30 mg/m^2) and cisplatin (CDDP) (30 mg/m^2) are administered by intraperitoneal infusion on day 1 and days 8. Therapy is repeated three times, and laparptomy is done 3 to 4 wk after the last cycle.

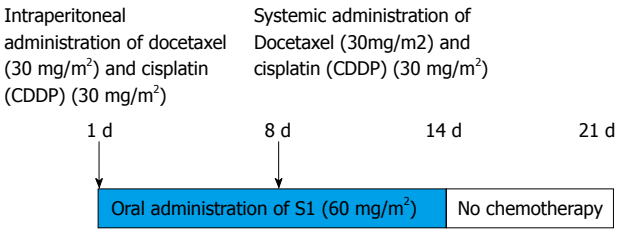

Figure 11 Bidirectional intraperitoneal and systemic induction chemotherapy. Oral S-1 is administered for 14 d at a dose of 60 mg/m^2, followed 7 d rest. Docetaxel (30 mg/m^2) and cisplatin (CDDP) (30 mg/m^2) are administered by intraperitoneal infusion on day 1, and the same dose of docetaxel and CDDP are systemically administered on days 8. Therapy is repeated three times, and laparotomy is done 3 to 4 wk after the last cycle.

Table 1 Peritoneal wash cytology before and after bidirectional intraperitoneal and systemic induction chemotherapy

Cytology	Cytology after BIPSC		
Before BIPSC	Negative	Positive	Total
Negative	15	0	15
Positive	26 (79%)	7	33
	41	7	48

Peritoneal wash cytology was done through a peritoneal port system after intraperitoneal administration of 500 mL of saline. BIPSC: Bidirectional intraperitoneal and systemic induction chemotherapy.

Table 2 Peritoneal wash cytology before and after neoadjuvant intraperitoneal/systemic chemotherapy

Cytology	Cytology after NIPS		
Before NIPS	Negative	Positive	Total
Negative	47	1	48
Positive	69 (70%)	30	99
	116	31	147

NIPS: Neoadjuvant intraperitoneal/systemic chemotherapy.

preoperative laparoscopy should be treated by NAC to reduce PCI less than the threshold level for good prognosis before CRS.

The aims of NAC are to achieve stage reduction to eradicate micrometastasis and PFCCs in the peritoneal cavity, and to improve the incidence of complete cytoreductiom.

Although systemic chemotherapy is still the standard treatment option for NAC[23,25,26], the response rates for PM after systemic chemotherapy were reported to be very low[23,26]. After systemic chemotherapy, treatment failure as a result of toxicity was also reported[26-29]. The reason why systemic chemotherapy does not work on PM is considered the existence of a blood-peritoneal barrier (BPB). BPB is a barrier consisting of stromal tissue between mesothelial cells and submesothelial blood capillaries[30]. BPB hinders the penetrating of drugs from systemic circulation into the peritoneal cavity. Accordingly, significantly larger amount of the drugs administered by systemic chemotherapy moves to the vital organs other than the peritoneum, resulting in the development of adverse effects.

In contrast, intraperitoneal (IP) chemotherapy generates a higher locoregional intensity of drugs in the peritoneal cavity than systemic chemotherapy[31,32]. During IP chemotherapy, the area under the curve (AUC) ratios of IP *vs* plasma exposure (PE) become high. Significant high AUC IP/PE ratios were found after the IP administration of paclitaxel, docetaxel, gemcitabine, 5-fluorouracil and doxorubicin[32]. The intraperitoneal concentrations of these drugs maintain long time because the molecular weights of these drugs are high.

In IP chemotherapy, penetration distance varies from drug to drug and drugs with a high penetration activity into the PM nodules should be selected. In the experimental PM, cisplatin penetrate approximate 2 mm from the surface of PM[31,32].

Recently, a combination chemotherapy of IP administration of cisplatin and docetaxel in combination with the oral administration of S-1 was developed and this method is designated NIPS (Figure 10)[28]. Yonemura *et al*[33] reported that PFCCs were eradicated by NIPS in 69% of patients with positive cytology before NIPS. Histologic examination of the resected specimens of PM after NIPS showed a complete histologic response rate of 37%. In addition, down staging was experienced in 15% of patients[33], and the survival of histological responder after CRS was significantly better than that of non responders. Accordingly, NIPS improves the complete cytoreduction rates, resulting in the long term survival after NIPS plus CRS.

More recently, a new regimen consisting of alternate administration of systemic and intraperitoneal chemotherapy was proposed. This method is called BISIC. By the alternate administration of systemic and IP chemotherapy, a wider treatment area can be treated than IP administration alone. Yonemura *et al*[34] reported a new method of BISIC. Oral S-1 is administered for 14 d at a dose of 60 mg/m^2 per day, followed by 7 d rest. Docetaxel (30 mg/m^2) and cisplatin (CDDP, 30 mg/m^2) are administered by IP infusion on day 1, and the same dose of docetaxel and CDDP are administered intravenously on day 8 (Figure 11). Therapy is repeated three times, and laparotomy is done two weeks after the last administration of S-1 (Figure 10). As shown in Table 1, 79% of patients with positive cytology before BISIC

Table 3 Histoloogic effects of primary tumor and peritoneal carcinomatosis in 41 patients after bidirectional intraperitoneal and systemic induction chemotherapy

	EF-0	EF-1	EF-2	EF-3	Total
Primary tumors	3 (12%)	15 (58%)	7 (27%)	1 (4%)	26 (100%)
Peritoneal metastasis	7 (17%)	18 (44%)	7 (17%)	9 (22%)	41 (100%)

EF-0: No histological change or histologic change is found in less than one-third of the tumor tissue; EF-1: Degeneration of cancer cells is detected in the tumor tissue ranging from one-third to less than two thirds; EF-2: The degeneration of cancer cells is found in more than two-thirds of the tumor tissue; EF-3: Complete disappearance of cancer cells.

Table 4 Histoloogic effects of primary tumor and peritoneal carcinomatosis in 147 patients with PC treated with neoadjuvant intraperitoneal/systemic chemotherapy

	EF-0	EF-1	EF-2	EF-3	Total
Primary tumors	13 (18%)	38 (54%)	20 (28%)	0	71 (100%)
Peritoneal metastasis	59 (40%)	35 (24%)	14 (10%)	39 (25%)	147 (100%)

Table 5 Side effects during bidirectional intraperitoneal and systemic induction chemotherapy

Grade 0	Grade 1-2	Grade 3	Grade 4	Grade 5	Total
44 (76%)	8 (14%)	4 (7%)	2 (3%)	0 (0%)	58

Experienced grade 3 side effects were meningitis in 1, ileus in 1 and bone marrow suppression in 2 patients. Grade 4 side effects of diarrhea and port infection were experienced in two patients.

became negative cytology after 3 cycles of BISIC (Table 1). Table 2 shows the changes of the cytologic status before and after NIPS. After NIPS, 70% of patients with positive cytology before NIPS became negative cytology. Histologic response rates in PC after BISIC and NIPS were 83% (34/41) and 60% (88/147), respectively (Tables 3 and 4). There was a statistical significance in histologic response rate between BISIC and NIPS. Complete pathologic response on primary tumor and PM were found in 4%, (1/26), and 22% (9/41) of patients treated with BISIC (Table 3).

Ishigami *et al*[35] reported a new BISIC method using systemic and IP paclitaxel (PTX) combined with S-1. The overall response rate was 56%, and one-year overall survival rate was 78%.

A systemic review and meta-analysis, IP chemotherapy combined with CRS is associated with significant improved overall survival[36].

From these results, NIPS and BISIC are effective treatments to eradicate PFCCs and to reduce PCI before CRS.

Yonemura *et al*[34] reported that the incidences of major complications (grade 3, 4, and 5) during NIPS and BISIC were 10.4% and 9.9%[35-37] (Table 5). These values are similar to the major complication rates after systemic chemotherapies[28,38], and are considered to be acceptable.

Although NIPS/BIPSC may improve the incidence of complete cytoreduction at CRS, NIPS might increase the morbidity and mortality after CRS. Yonemura *et al*[38] reported that the hospital death occurred in 3.7% of patients after NIPS plus CRS, and postoperative major complications occurred in 24.4% of patients. Reoperation was done in 7.6% (6/79) of patients. Glehen *et al*[7] reported a mortality rate of 4%, and a major complication rate of 27%. The magnitude of surgery, number of resected organs and anastomoses, and the operation time contribute to the development of complication after CRS plus HIPEC. To avoid futile CRS, the patients for the candidate of CRS should be strictly selected. For the selection of patients, preoperative PCI assessment by laparoscopy is important.

ROLES OF LAPAROSCOPY

There are limitations to estimate the precise PCI by CT, magnetic resonance imaging and positron emission tomography[10]. The sensitivity of the diagnosis for the PM smaller than 10 mm in diameter by CT is reported to be only 8%[10].

To improve the preoperative correct diagnosis of PCI and to select the patients for CRS, staging laparoscopy was introduced[39]. Laparoscopy enables to know the histological and cytological diagnosis and to evaluate the effects of NAC. In addition, LHIPEC just after the laparoscopic diagnosis of PM was developed[39]. Very high response on ascites by LHIPEC was reported[39]. Penetration distance of drugs into the PM in LHIPEC (closed HIPEC) is longer than that in open HIPEC performed under the laparotomy, because the intraperitoneal pressure in closed HIPEC is significantly higher than that in the open HIPEC[40].

So far, no evidence was reported about the direct effects on PM by HIPEC. Yonemura *et al*[23] first reported a direct effect of HIPEC on PM from gastric cancer. Two cycles of diagnostic laparoscopy and LHIPEC with an interval of one month were done for 50 gastric cancer patients with PM. Ascites completely disappeared or decreased in 64.7% (22/34) of patients and 20 patients with positive peritoneal cytology at the 1st LHIPEC became negative cytology in 14 (70%) patients at the 2nd LHIPEC. Six (12%) patients showed complete disappearance of PM and PCI was significantly reduced from 14.3 ± 10.2 at the 1st LHIPEC to 10.8 ± 10.5 at the 2nd LHIPEC ($P < 0.05$). Furthermore, total PCI scores (6.56 ± 2.92) on small bowel mesentery (BS-PCI) at 1st HIPEC were significantly decreased at 2nd LHIPEC (5.25 ± 3.78) ($P = 0.016$). LHIPEC reduces the SB-PCI before CRS, and the incidence of complete cytoreduction may improve.

Diagnostic laparoscopy is a convenient method to select patients for CRS and neoadjuvant LHIPEC is an effective therapy for the control of ascites and for the eradication of PFCCs. Furthermore, PCI levels can be reduced by LHIPEC and LHIPEC increase the number of patients who will undergo complete CRS. Accordingly,

LHIPEC is recommended to perform as a neoadjuvant induction treatment before CRS.

MECHANISMS OF HIPEC

The first report of CRS and HIPEC in a patient with PC from gastric cancer dates back to 1980s[41-43]. Since then, CRS and HIPEC have been performed to treat for this group of patients. However, there has been only one prospective randomized trial[43]. From the literatures, benefit of the HIPEC is to eradicate micrometastasis left after complete cytoreductio[35,44].

In many institutes, HIPEC is usually performed at the temperature of lower than 42 ℃ for 90 min.

Heat lower than 42 ℃ (mild hyperthermia) can not eradicate cancer cells by the thermal tolerance *via* the upregulation of heat shock protein[45]. Heat shock protein repair degenerated protein by mild hyperthermia, and cancer cells survive. Even in the mild hyperthermia, however, the fraction of hypoxic cells locate apart from vasculature are killed and thus cellular acidity increase thermal sensitivity *in vivo*. Generally, a temperature of Arrhenius "break" temperature of 43 ℃ and treatment time of at least 30 min are recommended. In United States and European institutes, mild hyperthermia of 41 ℃-42 ℃ for 60 to 90 min. is carried out[7,21,24]. In Japan, 43 ℃ to 43.5 ℃ for 30 min. is a standard thermal dose of HIPEC[8]. Thermal dose is a treatment unit provided by the temperature and exposure time during hyperthermia.

Cells are killed according to the exponential manner if the temperature is higher than 43 ℃ *in vivo*. The cytocidal effects by the 43 ℃ hyperthermia are equivalent to those by 42 ℃ hyperthermia for three- to four-fold longer treatment time than by 43 ℃ hyperthermia. Namely, to obtain the same cytocidal effect by 43 ℃ for 30 min requires 90 to 120 min by 42 ℃ hyperthermia[46].

Hyperthermia enhances the cytotoxic effects of some anti-cancer drugs. Melphalan, mitomycin C, cisplatin, docetaxel, gencitabine, and irinotecan[47-50] enhance cytotoxicity when combined with hyperthermia. In HIPEC for gastric cancer, direct cytotoxic agents like mitomycin C, cisplatin and docetaxel are used[33,41,51].

Pharmacokinetic studies revealed that approximately 70% of mitomycin C is absorbed from the perfusate after 2 h HIPEC[52]. In cisplatin, 75% is eliminated from the perfuate after 90 min HIPEC, but only 20% of the cisplatin moves to the systemic circulation[53]. Accordingly, 50% of ciplatinum is absorbed in the PM nodules and peritoneal tissue during 90 min of HIPEC.

In the case of docetaxel, 40% is adsorbed during 40 min HIPEC at 43 ℃-43.5 ℃[51].

Temperature higher than 39 ℃ increases drug penetration distance[54]. The drug penetration into the peritoneal nodules is limited, because stromal pressure in PM is higher than that in normal tissue[54]. Carboplatin and cisplatin penetrate 1-2 mm from the peritoneal surface during intraperitoneal perfusion without hyperthermia, but penetration distance increases up to 2-3 mm when hyperthermia is combined[31]. Penetration depth from the peritoneal surface depends on the treatment time. Membrane permeation index (Paap) is the penetration distance of the drugs from peritoneal surface per minute, and is calculated by the following equation; Papp (cm/h) = CLp (drug clearance from peritoneal cavity, mL/h)/peritoneal surface area (cm^2). From this equation, Papp after 40 min. HIPEC using 40 mg of docetaxel was 1.5 mm/40 min[51]. If the tumors larger than 1.5 mm in diameter are treated by HIPEC with docetaxel, treatment time should be prolonged to increase the penetration distance of drugs.

However, HIPEC increases the operation time and may cause morbidity. A meta-analysis did not show a significant difference in the mortality rates between HIPEC and control group[44]. However, a significant increase was found in the incidence of abdominal abscess and neutropenia after HIPEC.

A randomized control study for colorectal carcinomatosis revealed significant better survival of CRS plus HIPEC group than that of traditional systemic chemotherapy plus CRS group[55].

At present, combination of CRS plus HIPEC is the standard of care recommended for PM from appendiceal mucinous neoplasm and diffuse malignant peritoneal mesothelioma[56].

Before 2011, there was no randomized control study to confirm the effect of HIPEC on survival of gastric cancer patients with PM. Yang *et al*[43] first reported the efficacy of HIPEC on survival by phase Ⅲ randomized clinical trial. They reported that CRS + HIPEC with mitomycin C 30 mg and cisplatin 120 mg improved the survival with acceptable morbidity. Further phase Ⅲ trials should be done to confirm the effects of HIPEC on PM from gastric cancer.

INDICATION OF THE COMPREHENSIVE TREATMENT

A multivariate analysis using Cox proportional hazard model revealed that CC score, PCI threshold, histologic effect after NAC, cytologic status and HIPEC were independent prognostic factors (Table 6)[7,8]. Among these prognostic factors, PCI threshold level after NAC is the strongest prognostic factor. Survival of patients who received incomplete CRS after NIPS was similar to that of patients treated with NIPS alone (Figure 12). Accordingly, patients who are diagnosed as receiving incomplete CRS by laparoscopy should be excluded from the candidates for CRS.

Survival of histological responders after NAC with negative cytology and PCI ≤ 6 after complete CRS and HIPEC is shown in Figure 13. Five-year survival rate was 32.4%.

CONCLUSION

Patients with PM from gastric cancer are recommended to treat with NIPS or BISIC before CRS. Indication

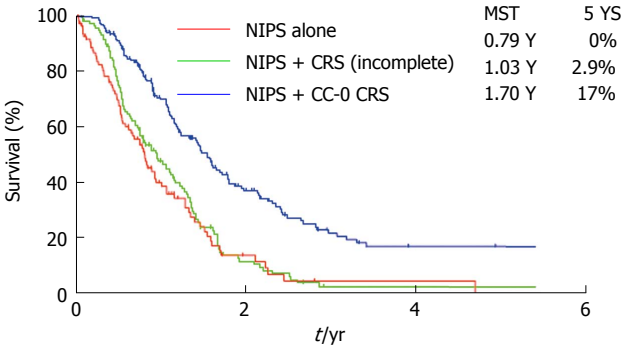

Figure 12 Survival curves of patients treated with cytoreductive surgery and neoadjuvant intraperitoneal/systemic chemotherapy alone. CRS: Cytoreductive surgery; NIPS: Neoadjuvant intraperitoneal/systemic chemotherapy.

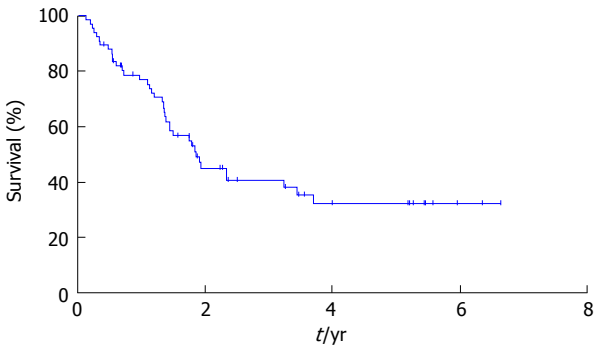

Figure 13 Survival of histological responders with negative cytology and peritoneal cancer index ⩽ 6 after complete cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy.

Table 6 Multivariate analysis of 304 patients with peritoneal metastasis treated with a comprehensive treatmnent

Prognostic factors	χ^2	*P* value	HR	95%CI	
Sex male *vs* female	0.263	0.60752	0.9218	0.676	1.257
CC score: complete *vs* incomplete	4.03	0.04468	1.504	1.01	2.24
Nodal involvement: N0-1 *vs* N2-3	0.445	0.50454	1.1338	0.784	1.639
Neoadjuvant chemo.: negative *vs* positive	2.517	0.11259	1.3445	0.933	1.938
PCI: ⩽ 6 *vs* ⩾ 7	8.809	0.00299	1.7863	1.218	2.621
HIPEC: Not done *vs* done	8.218	0.00414	0.6322	0.462	0.865
Histilogicl effects: EF 0-1 *vs* EF 2-3	12.305	0.00045	0.469	0.307	0.716
Cytology: Negative *vs* positive	8.2163	0.00415	1.8458	1.213	2.806

PCI: Peritoneal carcinomatosis index; HIPEC: Hyperthermic intraoperative intraperitoneal chemotherapy.

of CRS should be determined by laparoscopy. The best indications of the comprehensive treatment are patients with PCI levels within threshold level, and responders after NAC. Patients who satisfy these factors should undergo gastrectomy combined with D2 lymph node dissection and complete removal of PM using peritonectomy techniques. Just after complete cytoreduction, HIPEC should be done[35].

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REVIEW

In utero and *exo utero* fetal surgery on histogenesis of organs in animals

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Abstract

Until recently, fetal surgery was only used for fetuses with very poor prognosis who were likely to die without intervention. With advances in imaging, endoscopic techniques, anesthesia and novel interventions, fetal surgery is becoming a realistic option for conditions with less severe prognoses, where the aim is now to improve quality of life rather than simply allow survival. Until forty years ago, the uterus shielded the fetus from observation and therapy. Rapid changes in the diagnosis and treatment of human fetal anatomical abnormalities are due to improved fetal imaging studies, fetal sampling techniques (*e.g.*, amniocentesis and chorionic villus sampling), and a better understanding of fetal pathophysiology derived from laboratory animals. Fetal therapy is the logical culmination of progress in fetal diagnosis. In other words, the fetus is now a patient. Now-a-days, *in utero* (*IU*) and *exo utero* (*EU*) surgical methods are popular for experimental analyses of the histogenesis of organ development. Using these surgical methods, developmental anomalies can be created and then repaired. By applying microinjection and/or fetal surgery with these methods, models of developmental anomalies such as neural tube defects, temporomandibular joint defects, hip joint defects, digit amputation, limb and digit development and regeneration, and tooth germ transplantation in the jaw could be created and later observed. After observing different types of anomalies, novel *IU* and *EU* surgical techniques would be the best approach for repairing or treating those anomalies or diseases. This review will focus on the rationale for the *IU* and *EU* creation of animal models of different organ defects or anomalies and their repair, based on analyses of organ histogenesis and pathologic observations. It will also focus in detail on the surgical techniques of both *IU* and *EU* methods.

Key words: Myelomeningocele; Microinjection; Rodent; Sheep; Neural tube defect; Temporomandibular joint; Fetal surgery; *In utero*; *Exo utero*

Core tip: Fetal surgery in animal models has become a promising technique for analyses of organ histogenesis

and organogenesis. Using unique *in utero* (*IU*) and *exo utero* (*EU*) methods, developmental anomalies could be created and repaired during the prenatal period. Here, we review the *IU* and *EU* surgical techniques, focusing on methods and outcomes in various experimental animals.

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INTRODUCTION

Fetal surgery has a potential role in managing structural anomalies, where antenatal intervention might theoretically result in an improved outcome for the baby. Many anomalies do not meet these criteria and are likely to remain best managed after birth.

The first attempted intrauterine surgical intervention was a transfusion for Rh incompatibility in 1961. In the 1980s, the developmental pathophysiology of potentially correctable anatomical malformations was studied in animal models. Serial observations, using advances in imaging techniques, helped elucidate the natural history of certain anomalies in human fetuses. Novel obstetric therapies, endoscopic techniques and instruments now make it possible to correct some structural anomalies *in utero (IU)*.

The fundamentals of fetal surgery[1,2] are to (1) understand the natural history of the untreated anomaly *IU*; (2) have a sound pathophysiological rationale for prenatal treatment; (3) demonstrate the safety and efficacy of the fetal procedure in an animal model; and (4) define inclusion and exclusion selection criteria for treatment.

Until recently, only fetuses with a poor prognosis and a life-threatening anomaly were considered for prenatal intervention. Advances in techniques and a better understanding of the natural history of the anomalies have allowed intervention for non-life-threatening conditions, where outcome might be substantially improved. Life-threatening defects include myelomeningocele (MMC), congenital diaphragmatic hernia (CDH), airway obstruction, aqueductal stenosis, twin-to-twin transfusion syndrome, cleft lip and palate, and metabolic and cellular defects. Upadhyaya reviewed how to correct these types of defects[3]. Over the past two decades, the concept of developmental origins of health and disease has gained importance in the medical sciences. Based on the results of several human and animal studies, it is hypothesized that chronic diseases, such as cardiovascular disease and type 2 diabetes, originate from adaptive changes in the epigenetic control of metabolism and organ histogenesis during fetal development[4-6].

The *exo utero* (*EU*) developmental system was introduced by Muneoka *et al*[7]. This experimental system allows researchers to manipulate or operate on mid-to-late-gestation live mouse or rat embryos and to keep them alive *in situ* until the analysis of their effects at a desired pre- or postnatal time point. The *EU* system enables time- and region-specific intervention into developmental phenomena, simply by allowing us to choose the desired time and region for manipulation. This system is far simpler and more time- and cost-effective for *in vivo* functional analyses than establishing genetically altered mouse and rat lines. Compared to the *IU* method, one merit of the *EU* method for embryo manipulation is its clear visualization of the fine details of embryos, making it easier to locate the organs for manipulation. In contrast, because *EU* embryos are not clearly visible before embryonic day (E) 11.5 in mice due to their thick embryonic membranes, use of the *EU* system is mainly limited to the mid-to-late gestational period[8]. However, the *EU* system is a useful method not only for analyses of the developing nervous system but also for investigations of almost all organ systems during the histogenetic period[6,8].

For many genetic disorders, early onset and irreparable tissue and organ damage necessitate innovative methods that allow therapeutic intervention early in development, if a full cure is to be realized. The studies outlined in this review focused on *IU* and *EU* surgery for intervention during organ histogenesis using a variety of animals, including large mammals such as sheep, pigs and primates, and small mammals such as mice and rats. Larger mammals, such as sheep and monkeys, carry on average one embryo per pregnancy and typically tolerate surgical manipulations well, but are more expensive and have longer gestations (145 and 160-180 d, respectively) as well as higher ethical limitations. These factors reduce the number of experiments that can be performed in a given time frame. Most small experimental animals are multiparous, allowing for experimentation on large numbers of embryos, ranging from 3 to 10 embryos per pregnancy and shorter gestational periods of 3-4 wk. Drawbacks include difficulties with the manipulation of the uterus and the subsequent survival of the embryo. To this end, we can use the *IU* and *EU* development systems to screen the functions of various proteins/cells by injecting them into embryos, or to perform fetal surgery and follow up on consequences later in life. Here, we review procedures for mammalian embryo surgery both *IU* and *EU* and highlight technical innovations that have been published using this approach.

GENERAL PREPARATION FOR *IU* AND *EU* SURGERY

Here, we describe in detail *IU* surgical procedures in rodents and briefly describe these in other animals such as sheep, pigs and primates. We will only describe the *EU* surgical procedure in rodents, as thus far no experimental works or reports have been published applying this

method in other mammals. Preparation of pregnant mice or rats and abdominal surgery for *IU* and *EU* surgery are identical, to some extent. Similar procedures in rodents are described below, and later, we separately describe the procedural differences between *IU* and *EU* surgery.

Preparation for IU and EU surgery in rodents

The two generally used approaches are *IU* or *EU* surgery. Both are demanding procedures that require some level of expertise. The post-implantation embryo is encased in its extraembryonic membranes (amnion and yolk sac) within the tubular uterus. The embryo can be accessed by injection, passing through the layers of the uterine wall (perimetrium, myometrium, and endometrium) and the extraembryonic membranes. Intrauterine embryo injections can be successfully carried out on mouse embryonic stages as early as E8[9,10]. For direct surgery on the embryo, *IU* studies require opening and closing the uterus and extraembryonic membranes. This approach is restricted to late embryonic/fetal stages (E14.5 and later) because early embryos are too fragile to survive the postsurgical forces resulting from the contracting uterus. *EU* surgery is based on the finding that embryonic development is not perturbed when the uterine tube is opened but not sutured closed[7]. The embryos remain attached to the open uterus *via* the placentae and develop suspended within the abdominal cavity of the female. When embryos are exposed in this manner, it is possible to perform various embryo surgeries at early embryonic stages. Injection experiments using *EU* surgery have been carried out on stages as early as E8.5[11], and direct surgery on the embryo can be carried out on E11.5 embryos and older[12]. While technically demanding, direct manipulation of the rodent embryo is possible and, in combination with other experimental approaches, provides another avenue for experimental studies of mammalian development.

Preparation of animals and required instruments before surgery were described in detail by Yamada *et al*[13].

Anesthesia: Several different approaches to anesthesia have been used for studies on embryonic and fetal rodents, as reviewed in Ngo-Muller and Muneoka[14]. In all cases, the anesthetic target is the pregnant female and not the embryo/fetus, although the embryo/fetus is exposed to maternal levels of the drug. Anesthesia with ketamine/xylazine (K/X) or pentobarbital induces prolonged anesthesia (30-45 min with K/X; > 45 min with pentobarbital) and is administered by intraperitoneal (*i.p.*) injection. For mice, K/X is administered at a dose of 100 mg/kg of ketamine and 10 mg/kg xylazine (80 mg/kg ketamine and 8 mg/kg xylazine for rats). Reversal of K/X anesthesia can be obtained by injecting the antagonist yohimbine (1.0 mg/kg, *s.c.*) when surgery has been completed[14]. Alternatively, the pregnant female mouse/rat is also anesthetized with sodium pentobarbital (Nembutol) (50 mg/kg body weight *i.p.*)[8,13]. Recently, a combination of anesthetics (Medetomidine/Midazolam/Butorphanol) in solution is widely used. This combination is prepared with 0.3 mg/kg of medetomidine, 4.0 mg/kg of midazolam, and 5.0 mg/kg of butorphanol (M/M/B: 0.3/4/5)[15]. The induction time of M/M/B was identical to the induction time of K/X. The emergence time of M/M/B was the similar to that of K/X. The anesthetic time of M/M/B, however, was longer than the anesthetic time of K/X[15].

Abdominal incision: A sterilized operating aluminum or stainless steel plate is used during operation. Operating field (abdominal skin) of the pregnant dam should be wiped by 70% ethanol after removal of the hair, and the mouse/rat is placed in a supine position on the operating plate. To open the abdomen, an initial large midline incision of the belly skin is made with microdissection scissors. Blunt forceps should be used to handle the skin. A second incision is made along the linea alba to open the abdomen. With the abdomen open, the uterine horns can be found in the lateral regions of the abdominal cavity and simply pulled out onto sterile damp gauze placed on the ventral surface.

IU SURGERY

Mammalian development has been best characterized using rodent (mouse, rat) models. Direct intervention of the post-implantation mouse/rat embryo *IU* represents one of several experimental methods that can be used to probe mammalian embryogenesis. Here, we will elaborately describe the surgical technique in the mouse/rat and also briefly describe it in other animal models.

Rodents

Most studies using *IU* manipulation were performed on mouse embryos, though a few studies have been applied to rat embryos[2,16-18]. *IU* surgery requires that the abdomen be opened to access the uterus. After the surgical procedure, the abdomen is closed and the animal is allowed to recover.

Microinjection

IU manipulations generally involve injections into the embryo that must pass through the uterine wall and the extraembryonic membranes (yolk sac and amnion). The injection should avoid any blood vessels. Embryo manipulation is best performed using a stereo zoom surgical microscope. Injections generally utilize glass needles made from micropipettes of varying size. The making procedure was described in detail by Yamada *et al*[13]. Injection studies include the use of markers, such as carbon particles for establishing fate maps[19] or lipophilic tracers such as DiI (CellTracker; Molecular Probes) to characterize cell migration patterns[10,20-22]. Injection of virus has been used to study cell lineage[23] and the targeted effect of a specific virus on develop-

ment[24,25]. Targeted injection of purified growth factors or signal transduction antagonists directly into the embryo has been used to study signaling during normal and abnormal development[26-28]. Electroporation has been applied to inject plasmids encoding genes for functional studies and/or marker genes for cell labeling studies[29-36], plasmids encoding short hairpin RNA for RNA interference[2,16-18,37], and dual-fluorescence reporter/sensor plasmids for single-cell detection of microRNAs[38].

Recent studies demonstrate that cell transplantation (CT) at progressively earlier embryonic stages resulted in higher levels of chimerism[39]. Clinically relevant studies include the rescue of a genetic mouse model of autosomal recessive osteopetrosis, a human disorder associated with defective osteoclasts, with allogenic fetal liver CT[40], and the rescue of a mouse model of osteogenesis imperfecta with transplantation of adult bone marrow cells[41].

Fetal surgery

Open spina bifida, or MMC, the most common type of neural tube defect (NTD), is defined as a protrusion of the spinal cord and/or meninges through a defect in the vertebral arches. Creating the ideal animal model to study the effects of intrauterine surgery requires that the mechanisms of aberrant primary neurulation, resulting in an open NTD and associated nervous system anomalies, be reproduced. To create the NTD lesion fetus and repair experiments by Heffez, two studies utilized this animal model[42,43]. In the first study[42], pregnant rats at day 18 of a 22-d gestation were anesthetized, and the surgery was performed using an operating microscope. A single horn of the bifid uterus was exteriorized through a midline abdominal incision. Only the fetus being treated was mobilized. Following the opening of the uterus and amniotic membrane, a 2- to 3-level laminectomy was done, and the dura was opened. This group of fetal rats was returned to the uterus with the lesion. In a second study, identical surgical techniques were used by the same authors to lesion fetal rats, and a second group received a repair treatment prior to return to the uterus[42,43]. The rat model utilized two strategies to repair the spinal defect at embryonic day 18[42]. The open spinal cord was either repaired immediately with a nonocclusive peritoneal cover from the mother, or was re-exposed the following day and underwent a primary skin closure. Control embryos did not recover any function and had significant degradation of the spinal cord. The embryos that were repaired by primary skin closure, even after a 24-h delay, demonstrated better outcome than the embryos with closure using peritoneum. The results of this study point to the harmful effects of amniotic fluid, due to the worse outcome after a nonocclusive barrier (peritoneum) was used instead of skin. Stiefel studied the curly tail mouse model of exposed lumbosacral spina bifida and revealed the progressive deterioration of neuroanatomic appearance and neurologic function with increasing gestational age[44]. Danzer developed a retinoic acid-induced MMC model in fetal rats, and histopathology confirmed the entire spectrum of severity observed in human MMC, as well as features of the Arnold-Chiari malformation[45,46]. While these studies support the principle of improved neurologic function with *IU* coverage of the spinal cord, a large animal model with lengthy periods of time *IU* after surgical manipulation is needed before the extrapolation of these findings to humans.

Sheep

Sheep are much easier to breed and maintain and are a well-established animal model of human fetal physiology. Sheep have a consistent gestation period of 145 d, and the development of the fetus and its immune system is very similar to that of humans. Fetal sheep have been used widely to study mammalian fetal physiology, and the results obtained with this model have been directly applicable to the understanding of human fetal growth and development[47]. The first attempt at *IU* gene therapy in the sheep[48] utilized a stem CT based method, in which peripheral blood was collected from 110-d-old fetal sheep by exchange transfusion. Once its full clinical potential has been realized, hematopoietic stem cell-based gene therapy promises to cure a wide array of both inborn and acquired diseases. Both hematopoietic cells and non-hematopoietic cells within the liver and lung are transduced following the direct injection of murine retroviral vector supernatants into the peritoneal cavity of pre-immune fetal sheep, suggesting that the developmental stage of each organ at the time of injection may determine its susceptibility to *IU* gene transfer[49]. Using pregnant sheep, David *et al*[50] have adapted ultrasound-guided injection techniques from fetal medicine practice and established new methods to deliver gene therapy to fetal sheep, including intratracheal injection to target the distal respiratory epithelium[51], intragastric injection to target the intestinal mucosa[52], and fetoscopic techniques including the placement of an intratracheal balloon at the time of vector installation to enhance pulmonary epithelial transduction[53]. The combination of ultrasound guidance and fetoscopic techniques was described in detail[1].

Sheep models have also been used to study the embryopathy and pathophysiology of neurological deterioration in NTD. For NTD treatment, spina bifida lesions were created in fetal sheep by *IU* surgery techniques (reviewed in[54]). The model that most closely simulated the human disease and most clearly demonstrated the feasibility of fetal MMC surgery was the fetal lamb model of MMC introduced by Meuli *et al*[55]. Pregnant sheep were placed under general halothane oxygen anesthesia. The fetuses were then exteriorized through an infra-umbilical midline laparotomy, followed by hysterotomy to expose the backs of the fetuses. A MMC lesion was made using low-power loupe magnification with microsurgical instruments at 75 d. The fetuses with the open spinal defect were then returned to the uterus,

and the amniotic fluid volume was restored with warm sterile saline. The sheep fetuses that underwent repair of the spina bifida defect were lesioned, and the defect was then closed using a latissimus dorsi muscle flap at 100 d of gestation[55,56]. The fetal sheep MMC model was the first large animal model to demonstrate that a spinal cord lesion could be created *IU* and covered at a later time point, with preservation of neurologic function. Unlike previous animal models, this sheep model more closely resembled that of human MMC in the duration of the exposure of the cord to the environment, clinical examination, and histology.

Pigs

IU cell transplantation (IUCT) and potential tolerization are based on the immunologic immaturity of the early developing fetus, leading to the possibility of donor or species specific tolerance to xenogeneic cells. Fisher's group established an IUCT procedure by which piglets are stably engrafted with human hepatocytes during early gestation and explored the possibility of producing a state of hyporesponsiveness in pigs to human hepatocytes by transplanting human hepatocytes into fetal pig livers[57]. Briefly, at gestational day 40, all gilts underwent general anesthesia and lower midline laparotomy. Both uterine horns were exposed. All fetuses in the right uterine horn received direct intrahepatic injection under ultrasound guidance using a 1.5 inch 25 gauge needle.

Furthermore, to determine whether cells could transfer between porcine littermates, McConico[58] performed IUCT. Briefly, at 40-43 d gestation, pregnant pigs/swine were anaesthetised with intra-muscular (*i.m.*) injections of telazol (5 mg/kg), xylazine (2 mg/kg) and glycopyrolate (0.06 mg/kg). Anaesthesia was maintained with inhaled isoflurane (3%-5%). A paramedian incision was made along the dorsolateral margin of the mammary glands, with the pig in lateral recumbency. One horn of the uterus, containing four to eight fetal swine, was then exposed. Guided by ultrasound, 50 million T cell-depleted umbilical cord blood cells were injected into the peritoneum of three to four fetal swine per litter[58].

If an intrauterine event has occurred, then intrauterine interventions, such as surgical repair, might prevent progressive neurological deterioration. Animal models of spina bifida or NTD repair *IU* have been designed by Heffez[42] and reviewed by George[54]. Surgical manipulation of pregnant Hanford mini-pig sows began with sedation *via* intramuscular administration of ketamine and acepromazine. The sows were intubated, ventilated and anesthetized with isoflurane. The fetal pigs were operated on at day 80-85 of the 114-d gestation period. Surgery was performed with an operating microscope. One horn of the uterus was exteriorized. The fetus underwent a two-level laminectomy with opening of the dura. In one group, fetal pigs received repair treatment following lesioning before being returned to the uterus. In the second group, fetal pigs were returned to the uterus with an open wound. The abdominal wall of the sow was closed in two layers[42,54].

Rhesus monkeys

Several animal models of MMC have been developed to test the hypothesis that *IU* intervention can prevent further spinal cord damage and the consequent neurological deficits. Primate (Macaca mulatta) was the first model, developed by Michejda, in which a fetal L3–L5 laminectomy was done late in gestation[59]. Surgical methodologies employed on pregnant rhesus monkeys began with induction of general halothane-oxygen anesthesia. The lumbosacral region of the fetuses was exteriorized *via* hysterotomy. A vertebral opening *via* a lumbar laminectomy in the L3-L5 region was created, and the spinal cord was exposed following the opening of the dura over the spinal cord. The exact techniques, magnification and precise instrumentation were not described in the methodology[59]. A total of 8 fetuses at gestational day 110-125 were manipulated, with full gestational term at approximately day 160-180[60]. The unrepaired embryos showed cystic MMC-like lesions at birth and had neurological deficits. A similar group of monkeys underwent immediate repair of the laminectomy *IU* using allogeneic bone paste to reconstruct the resected dorsal arches. These fetuses, repaired *IU,* were neurologically normal at birth. Unfortunately, the experiment did not include an initial procedure for creation of the defect with a period of exposure to the uterine environment prior to closure.

EU SURGERY

The rodents' *EU* development system is useful for analyzing the roles of molecules or interactions between tissues in the histogenesis of organs from mid to late gestational period. Previously published technical reviews on *EU* surgery are of value to the new investigator, and this surgical treatment has been only performed in rodents (mouse/rat)[8,13,14,61]. The general operation involves making a longitudinal incision along the entire length of the uterus, so that the embryos remain attached to the uterus but are not contained within the uterine cavity. The exposed uterus is returned into the abdominal cavity, where development continues *EU*. In the original study, embryos from E9.5 to E13.5 were found to develop normally to term[7]. In a subsequent study by Serbedzija *et al*[11], *EU* survival of embryos that received injections into the amnionic cavity as early as E8.5 was reported. Early stage embryos are surrounded by a layer of decidual tissue that obscures the visualization of the embryo. Removal of this layer compromises embryo survival. In general, our experience is that the survival rate of mothers is 100%. That of manipulated embryos increases with later stages and with less invasive manipulations, and can reach 100% in cases without invasive manipulation.

Both the *IU* and *EU* surgical procedures were

identical, up to the abdominal incision before the uterine wall was cut. Yamada *et al*[13] described in detail how to relax and cut the myometrial wall, clearly observing the targeting live embryos and how to replace the manipulated embryos into the abdomen. Here, we briefly describe the procedure about how to manipulate the live embryos.

Embryo manipulations

The embryos were enveloped by very thin and transparent amniotic membrane. The amniotic membrane must be kept wet and covered by sterile gauze soaked with sterile saline, otherwise it will become dry and lose its translucency which causes difficulties. *EU* surgery is a lengthier procedure than *IU* manipulation, and not all embryos are manipulated in a single female. In cases where embryo surgery is compromising embryo survival, removing all unoperated embryos can dramatically improve the survival of operated embryos[62]. Two different techniques have been reported for removing embryos from the uterine horn during *EU* surgery.

To increase the viability rate, we have routinely left three embryos on both side of the uterus taking special care for bleeding and adhesion as Yamada *et al*[13] described in detail. Ngo-Muller and Muneoka[14] reported that they removed all but four embryos, leaving two embryos in each horn in positions toward the ovarian end of the uterus. Embryos and placentae are removed by placing a dry cotton-tipped applicator at the placental-uterine junction and gently rolling it across the placenta. This procedure separates the placenta from the uterus and causes a small amount of bleeding from the uterus. Bleeding is controlled by applying direct pressure with the cotton-tipped applicator at the former placental attachment site.

Once embryos are removed and any bleeding is controlled, the abdominal cavity is flushed with saline to remove any tissue debris that might induce a postsurgical fibrotic response. After the abdominal cavity is flushed, it is filled with sterile saline. The embryos are maintained submerged in saline during and after the operation. For older stage embryos, it may not be necessary to keep the embryos submerged. The various types of manipulations that have been accomplished using the *EU* approach are summarized below.

Microinjection

The use of sharp-tipped micropipettes is the most critical for a successful microinjection, since tear of the fetal membrane causes leakage of amniotic fluid. Fetal deaths are often attributable to damages of the embryonic membrane or placenta. Injections generally utilize glass needles made from micropipettes of varying size. Yamada *et al*[13] described how to make glass micropipettes with a beveled point using a microforge. The micropipette is connected to an automated hydrolic (mineral oil) microinjection system (*e.g.*, UltraMicro Pump, WPI Inc.) fitted with a Hamilton-type syringe that allows precise control over injection volume. It is often useful to co-inject a vital dye (*e.g.*, 0.05% Nile blue sulfate or 1% Fast Green) to monitor the injection procedure. Targeted injection of purified growth factors or signal transduction antagonists directly into the embryo has been used to study signaling during normal and abnormal development[26-28].

Cells have been introduced into the embryo by targeted injection for use as *in vivo* reporters, or to characterize the behavior of stem cells in the embryonic and adult environment. Fibroblasts introduced into the embryonic mouse limb proliferate and differentiate in a position-dependent manner[63,64]. The injection of cells that secrete high levels of specific hormones has been used to experimentally perturb embryogenesis[65-67]. Targeted injection of genetically labeled liver stem cells into the embryonic liver results in chimeric livers that persist to adult stages and can be used for both the investigation of liver development and regeneration[62].

Embryonic surgery

In many instances, experimental design calls for direct surgery on the embryo. For early stage embryos, such studies are best performed using the *EU* approach, because it eliminates the need to incise and suture the uterus and avoids postsurgical complications arising from uterine contractions. Clean visualization is the most critical and important factor for embryo manipulation/surgery, thus *EU* is the better option compared to the *IU* surgical procedure. Mechanical strain plays an important role during tissue morphogenesis, and many developmental processes depend on external and internal mechanical forces[68]. In our laboratory, we performed fetal joint movement restriction by surgical techniques using this *EU* method and observed how developmental processes were related to prenatal mechanical forces.

Hip joint movement restriction: Congenital dislocation of the hip (CDH) is one of the most common congenital skeletal deformities. The prevalent type, which constitutes up to 98% of CDH cases, is exhibited at birth by a dysplasia of the hip consisting of a flat acetabular roof and an underdeveloped proximal end of the femur, relatively minor anomalies that predispose to dislocation[69]. In our laboratory, Hashimoto and Kihara created a CDH model[70,71] to clarify its etiology and to develop prevention and treatment therapies. For these purpose, at E16.5 the hind limb of the rat embryos' one side was sutured with 9-0 thread for ophthalmic surgery at the knee joint or more distally to the amniotic membrane, whereas the other side was left unoperated. The hind limbs were tied *in situ* and were not forced into any specific abnormal positions[70,71].

TMJ movement restriction: To observe the proper development of the mandibular condylar cartilage, articular disc and temporalis muscle as related to mec-

hanical forces, we restrained jaw movement by this *EU* surgery technique. In mouse embryos at E15.5, both the upper and lower jaws (mandible and maxilla) were sutured or fixed through the embryonic membrane with 8-0 nylon. The embryos underwent *EU* development[72-75].

Other surgical techniques: Another surgical technique is the resection of parts of the fetal organs. Naruse and Kameyama[76] combined the *EU* system with argon laser irradiation to the extra digits of genetic polydactyly mice. To explore the relationship between agenesis of the olfactory bulb and that of the corpus callosum, Naruse and Keino[77] performed fetal *EU* laser surgery to induce arhinencephaly in mice and clarified that agenesis of the olfactory bulbs induced agenesis of the corpus callosum[78]. In this *EU* system, they induced fetal tissue destruction without damage to the yolk sac membrane and amnion or leakage of amniotic and extra-embryonic fluid to yield embryos with high viability. Sequential observation of NTD by the *EU* method was successfully utilized to analyze the mechanism of generation of anencephaly[46]. In our laboratory, Matsumoto *et al*[46] created anencephaly mouse embryos. Pregnant mice were administered 1 mg/kg body weight 5-azacytidine (Sigma Chemical, St. Louis, Mo.) dissolved in physiologic saline by intraperitoneal injection at E7.5. After that, they observed the sequences of exencephaly, and their subsequent morphological changes, and mechanism of transformation from exencephaly to anencephaly by the *EU* development system at different embryonic days[46]. The most invasive studies to date include amputations of the limb or digit to study regenerative responses. It is possible to transplant tissues between mouse embryos to study cell–cell interactions during development. Examples include studies of the interaction between anterior and posterior tissues during mouse limb development[12] and grafts of digits in association with amputation studies[79]. Amputation studies have also been carried out on mice with targeted mutations to identify genes that are functionally required for a regenerative response[80] and to explore the diastema region of the jaw as a permissive site for the development of a transplanted tooth germ[81]. Other surgical manipulations that have been carried out on mouse embryos using a surgical approach to experimentally induce spina bifida aperta[82].

Restraining movement, amputation, wound healing and tissue grafting surgeries cause significant trauma to the embryo and can compromise embryo survival. In our and other researchers experiences, these types of embryo surgeries can have a high level of success from E13.5 and later, whereas similar manipulations at earlier stages are more challenging yet feasible[12]. This study demonstrates how multiple targeted manipulations can be successfully combined using an *EU* approach.

For both *IU* and *EU* surgery in rodents, Yamada *et al*[13] reviewed in detail about abdominal closure, recovery and post-operative care.

CONCLUSION

Advances in fetal interventions can be predicted over the next decade, driven by novel biological and endoscopic techniques. Developmental biologists have repeatedly used animal models (*e.g.*, mammals such as rodents, sheep, pigs, and monkeys; amphibians; birds) for experimental analyses of histogenesis or organogesis, or to develop powerful tools for studying the function of specific genes during development. We have explained on the methodological procedures of the *IU* (mouse/rat, sheep, pig and monkey) and *EU* (rodents) development system. These systems are useful methods for *in vivo* functional analyses from early/late organogenetic to histogenetic phases. The number of studies using *IU* or *EU* approaches has increased over the past 30 years. Now it is clear that we can successfully probe the *IU* environment of the mammalian embryo both classically (amputation, tissue transplantation, NTD creation and repair) and genetically (electroporation, gene therapy). The *EU* technique is far simpler and more time- and cost-effective than establishing genetically modified mouse/rat lines and provides a convenient experimental design for developmental research. To explore development, especially as it pertains to human health issues, there is clearly a need to develop and expand new strategies that enhance our ability to directly access the post-implantation mammalian embryo.

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MINIREVIEWS

Current management of acute type B aortic dissection

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Abstract

Acute type B aortic dissection (TBAD) occurs as a result of an intimal tear within the proximal thoracic aorta. Patients are typically managed acutely with aggressive antihypertensive therapy. Surgical repair is reserved for those who develop complications such as rupture or malperfusion. The surgical management of acute TBAD has changed considerably in the last decade secondary to the advent of thoracic stent grafting. Thoracic endovascular aortic repair (TEVAR) has improved early mortality and morbidity rates for patients presenting with complicated TBAD. The role of TEVAR in patients presenting with acute and subacute uncomplicated TBAD is less clear. TEVAR has been associated with increased late survival and better aortic remodeling, with low perioperative morbidity in selected patients. Recent literature suggests certain radiographic criteria may be used to predict patients developing late aortic events who would benefit from early TEVAR. The purpose of this article is to review the contemporary management of acute TBAD, discuss controversies in management and evaluate the latest research findings.

Key words: Aorta thoracic; Vascular grafting; Aneurysm dissecting; Aortic rupture; Endovascular procedure; Stent

Core tip: Current recommendations and controversies within the surgical management of acute type B aortic dissection are discussed. The increased use of thoracic endovascular aortic repair has been associated with improved patient outcomes, though data on patients presenting with acute and subacute dissection is less clear. Certain radiographic findings may predict those at higher risk of developing late aortic-related complication.

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INTRODUCTION

Acute type B aortic dissection (TBAD) remains a complex clinical entity associated with a high rate of morbidity and mortality[1]. The majority of patients are able to be managed medically in the acute setting, though a subset of patients require acute surgical intervention. Open surgical therapy has traditionally been associated with high rates of in hospital death and morbidity. Surgical complications have been reduced by endovascular technology, specifically thoracic endovascular aortic repair (TEVAR). Unfortunately strong evidence is lacking regarding the optimal management of patients with acute TBAD. One of the difficulties in interpreting the literature on this topic involves the retrospective, single-institution nature of most studies. Few prospective, randomized trials exist to help guide vascular surgeons in selecting optimal management strategies. This paper will focus on reviewing the contemporary management of acute TBAD, controversies and future directions.

PATHOPHYSIOLOGY

The primary etiology of TBAD is the separation of the layers of the aortic wall from each other, originating at a site known as the entry tear. This injury occurs within the intima at the proximal descending aorta, most often just distal to the origin of the left subclavian artery. A study of hemodynamic forces within the aortic arch by Nathan *et al*[2] demonstrates this area to be particularly susceptible to shear forces. This, in part, explains the frequency with which this location is involved. Microscopic analysis reveals that the dissection occurs into the media, functionally separating the intima from the adventitia. The "false lumen" (between the intima and adventitia) becomes pressurized, and, since the adventitia is stronger than the intima, the true lumen may become compressed. Compression of the true lumen may result in propagation of the dissection in a caudal (or occasionally cranial) direction and compromise of the distal branch arteries to the viscera, spinal cord or extremities. A novel *ex vivo* model for aortic dissection by Faure *et al*[3] highlights the spiral dissection plane that descends caudally. Often the celiac, superior mesenteric and right renal arteries originate from the true lumen while the left renal originates from the false lumen.

Symptoms from malperfusion may result from either static or dynamic obstruction. Static obstruction occurs when a highly pressurized false lumen dissects around, and circumferentially occludes, the orifice of a branch vessel. In contrast, dynamic obstruction occurs when a branch vessel orifice is occluded intermittently by extrinsic compression of the true lumen by pulsatile flow within the false lumen. This phenomenon is best observed using intravascular ultrasound (IVUS) to evaluate a patient with severe true lumen compression (Figure 1).

The initial presentation of dissection is that of tearing chest pain radiating to the back. This may be accompanied by symptoms of end-organ ischemia such as abdominal pain, oligo-anuria, lower extremity ischemia, paresis or paraplegia depending on the end organs involved. When malperfusion occurs, often several vascular territories are involved[4]. In the setting of rupture, patients may develop hypotension, abdominal distention or a left pleural effusion. Diagnosis is most commonly made by computed tomography angiography (CTA) or transesophageal echocardiography (TEE). TEE, when readily available, can identify the proximal entry tear and its origin. It is also effective in differentiating type A and type B dissections, and can assess cardiac function without the use of contrast or ionizing radiation. CTA, however, has the advantage of being readily available in most emergency rooms and is less operator dependent. It can also identify rupture, end organ ischemia, the extent of distal dissection and the relative size of the true and false lumens. For this reason CTA has emerged as the study of choice in acute TBAD[5] (Figures 2 and 3).

MEDICAL MANAGEMENT

Medical management is critical for all patients with acute TBAD, whether or not surgery is performed. Initial management is focused on strict blood pressure and heart rate control. At our institution we favor initiation of anti-impulse therapy with a beta blocker followed by a vasodilator to prevent further propagation of the dissection and to manage the patient's symptoms. These medications are best administered in a closely monitored unit aided by an arterial line and urinary catheter. Target systolic blood pressure goals include 110-120 mmHg, with heart rate goals between 60-80 BPM[5]. These targets may be lowered if the patient's symptoms persist, as long as adequate perfusion as judged by urine output and mentation persists. Patients who respond to this regimen are transitioned to oral antihypertensive medications once their hypertension is controlled. Repeat imaging is typically performed prior to discharge and at regular outpatient intervals, evaluating for patency of the false lumen and aneurysmal degeneration. Established indications to proceed with operative intervention in the acute setting include: rupture, malperfusion, and persistent/refractory pain in the face of maximal medical therapy. The existence of one of these criteria is defined as complicated aortic dissection.

Estrera *et al*[6] evaluated 159 patients presenting with acute TBAD in a single center. In-hospital mortality for patients requiring only medical therapy (*i.e.,* uncomplicated) was 7.3%. Complication rates in medically managed patients included rupture in 5%, stroke in

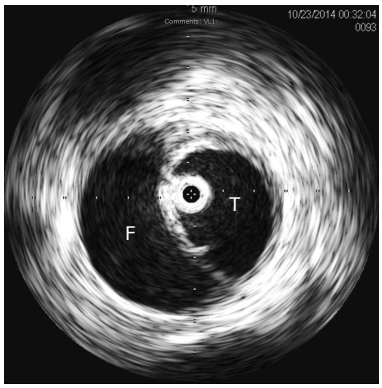

Figure 1 Intravascular ultrasound evaluation during thoracic stent grafting. The IVUS probe (image center) is seen confirming correct orientation within the true lumen. T: True lumen; F: False lumen; IVUS: Intravascular ultrasound.

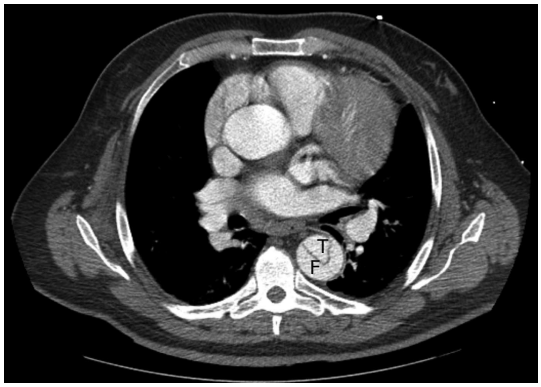

Figure 2 Computed tomography angiogram of a patient presenting with acute type B aortic dissection. T: True lumen; F: False lumen.

5%, spinal cord ischemia in 8.2%, mesenteric ischemia in 5.7%, dialysis dependence in 13.8%, and lower extremity ischemia in 3.8%. Survival at 1 year and 5 years was 83% and 75%, respectively. Approximately 14.5% of patients progressed to complicated aortic dissection requiring intervention; the in-hospital mortality for this cohort rose to 17%. Tsai *et al*[7] reviewed data from the multi-institution International Registry of Acute Aortic Dissection(IRAD). They identified a 10% in hospital mortality rate for patients receiving medical therapy alone. They reported a similar incidence of overall morbidities as Estrera *et al*[6] Approximately 11% of patients in that cohort required surgical intervention. In addition, they reported 1 year and 3 years survival rates for patients treated initially with medical therapy at 90.3% and 77.6%. These data show that the overwhelming majority of patients present with uncomplicated aortic dissection, and they can safely be managed medically. There is, however, a notable incidence of late aortic events and decline in survival in the medically managed patients after several years.

SURGICAL MANAGEMENT

The goals of surgical management are to prevent or treat

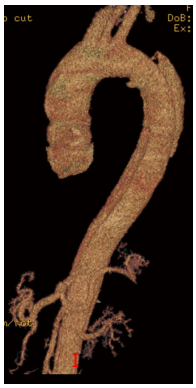

Figure 3 3D reconstruction from a computed tomography angiography of a patient presenting with acute type B aortic dissection, highlighting the entry tear originating distal to the origin of the left subclavian artery. The dissection plan is seen to extend well into the abdominal aorta.

rupture and/or ischemia from vessel malperfusion. This can be accomplished in one of two ways: (1) sealing the entry tear to promote false lumen thrombosis; or (2) equalizing the pressure between the true and false lumen by fenestration of the dissection septum to prevent progression of the dissection and reestablish perfusion to compromised end organs. The choice of therapy depends on the clinical and anatomic presentation of the patient. Efforts at sealing the entry tear are most likely to cause false lumen thrombosis and restore distal perfusion through the true lumen when there is a relatively discrete entry tear with a highly pressurized false lumen. However, when a major branch vessel is perfused exclusively through the false lumen, successfully sealing the entry tear may induce ischemia in the territory that vessel supplies. This can result in renal, intestinal, extremity or spinal cord compromise. Furthermore, when multiple entry and re-entry tears are present, sealing the proximal entry tear alone often will not be sufficient to depressurize the false lumen. Our current diagnostic capabilities make it difficult to definitively predict when such conditions may occur and this uncertainty has tempered enthusiasm for surgery as a first approach.

The principle of fenestration is the opposite of that underlying entry tear coverage. The aim of this technique is to increase communication between the true and false lumen, equalizing pressures within them and stabilizing the dissection process. The technique seeks to create the situation that occurs in many TBADs that respond to medical management alone, *i.e.,* equilibrium between true and false lumens. This technique is most often performed percutaneously and will be described under "endovascular approaches." It is important to recognize that this technique does not "treat" dissection, only malperfusion, and cannot prevent rupture or late aneurysmal dilation of the dissected arterial segment.

Correction of malperfusion may require more than one approach. When the entry tear is sealed and the false lumen depressurized, dynamic malperfusion will be reversed. Equilibration of the pressure in the true and false lumens may also reverse dynamic obstruction.

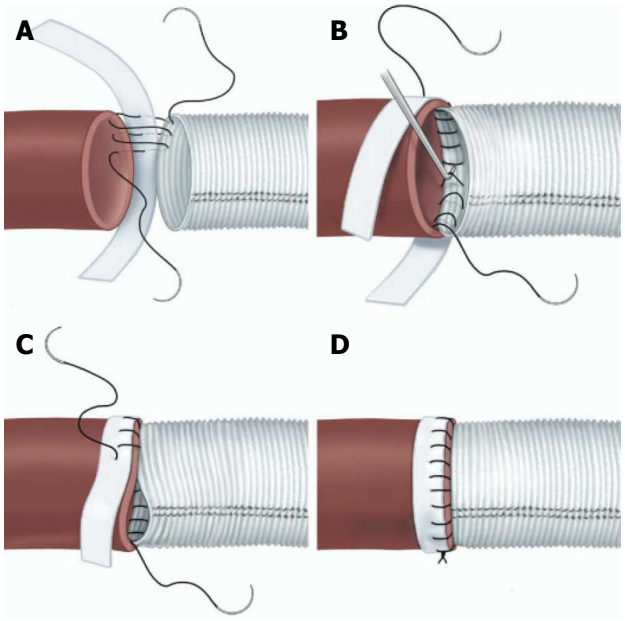

Figure 4 Suture line reinforcement with felt pledgets. A: Performing the posterior wall of the anastomosis first, in a "parachute" fashion. The suture travels from the prosthetic graft, to native aorta, then finally through the pledget; B: The suture line is tightened with the use of a nerve hook, and care taken to place the pledge on the outer surface of the aorta; C: Once the posterior wall of the anastomosis is completed, the anterior wall of the anastomosis is completed. The graft is somewhat invaginated within the aorta; D: The completed anastomosis, whereby the native aorta is buttressed on either end with pledget and graft. Source: "Long-term integrity of teflon felt-supported suture lines in aortic surgery," by Strauch *et al*[9]. Copyright 2005 by Elsevier, reprinted with permission.

Therefore sealing the entry tear, or fenestration of the aorta may be all that is necessary in some cases. However when a static obstruction exists, flow must be restored by another means. When ischemia is restricted to the lower extremities this may be accomplished by extra-anatomic bypass without addressing the aortic dissection itself. However when ischemia persists after initial treatment of malperfusion, vascular reconstruction directed at the ischemic territory is required. When the viscera are involved this is most often done from and endovascular approach using self-expanding stents or covered stents, since aortovisceral bypass in these circumstances is hazardous. These will be discussed in more detail in the "endovascular management" section. When lower extremity ischemia is present either endovascular stents or extra-anatomic bypass may be performed.

OPEN SURGICAL MANAGEMENT

Open surgical management is generally directed at sealing the entry tear and treating any acute complication (rupture or malperfusion) rather than definitive treatment of the aortic pathology. The urgent nature of the operation and unstable character of the aorta dictates a focal approach directed at saving life and limb. Classically, open surgical management of ruptured TBAD involves direct aortic replacement of the ruptured area. When malperfusion is present rather than rupture, management options include a short interposition graft to covering the proximal entry tear, aortic fenestration, or extra-anatomic bypass. Coverage of the entry tear requires a proximal suture line in an area of aorta free of dissection. The graft itself may be relatively short since the goals are simply to seal the entry tear and direct blood into the true lumen. This technique relieves malperfusion secondary to dynamic obstruction. Fenestration involves a transverse aortotomy at or below the location of the branch vessels at risk, with partial resection of the septum to equalize pressure in the true and false lumens[8]. Distal flow is directed exclusively into the true lumen. In both approaches, accurate identification of the distal true lumen and obliteration of the false lumen is critical and this may sometimes be difficult. The suture lines require reinforcement with pledget strips, placed circumferentially (Figure 4), both between the intima and adventitia in the false lumen of the dissected aorta and outside the adventitia at both proximal and distal suture lines, to maintain anastomotic integrity[9]. Aorto-visceral bypass, if required, should originate from the graft itself since the aorta is diseased. Definitive aortic repair is not the goal of open treatment in the acute setting. Spinal cord ischemia, when it occurs, is not reversible.

In patients who manifest only lower extremity ischemia, extra-anatomic bypass grafting, directed at restoring perfusion to the ischemic extremity, may be undertaken without addressing the aortic dissection itself, which is managed medically. In patients with unilateral ischemia a femoral-femoral bypass may be sufficient while in patients with bilateral ischemia axillo-bifemoral grafting is appropriate. As in the thoracic aorta, accurate identification of the distal true lumen is critical to avoid perpetuating the dissection distally. External reinforcement with pledgets may be required.

In a high volume single institution, Bozinovski *et al*[10] retrospectively reviewed 76 patients who underwent aortic replacement. Operative mortality was reported to be 22.4%. The relevant morbidity rates included: stroke (6.6%), paraplegia (6.6%), dialysis dependence (10.5%), left vocal cord paralysis (39.5%) and cardiac complications (43.4%). In their examination of the multi-institution IRAD dataset, Trimarchi *et al*[11] found a 29.3% mortality rate for 82 patients undergoing any open intervention for complicated TBAD. The majority (69.3%) of these patients underwent aortic replacement. Stroke and paralysis occurred in 9.0% and 4.5%, respectively. Sachs *et al*[12] analyzed data from the Nationwide Inpatient Sample (NIS), identifying a 20% in-hospital mortality rate for patients undergoing emergent open aortic replacement, despite being utilized in a younger, less comorbid patient population. Taken as a whole, open surgical intervention is associated with significant mortality and morbidity rates. For this reason it is not recommended in patients without life threatening complications.

ENDOVASCULAR MANAGEMENT

The principles of therapy using endovascular techniques remain the same as those with open surgery: either covering the entry tear to induce false lumen thrombosis or equalizing the pressure in the true and false lumen by fenestration. As with open fenestration, percutaneous fenestration treats malperfusion secondary to dynamic obstruction. Its advantages over open fenestration include avoidance of aortic cross clamping and general anesthesia. It can be performed rapidly in an interventional suite and document the perfusion of branch vessels. Furthermore in patients where visceral vessels are perfused through both the true and false lumens the risk of inducing ischemia by false lumen thrombosis is eliminated. Though the technique is not standardized, common methods include the use of IVUS to determine the locations of the true and false lumens. With a wire passed from one lumen into the other, a fenestration is created then enlarged *via* large balloon angioplasty or balloon-expandable stent placement. When visceral/extremity malperfusion occurs secondary to static obstruction, percutaneous branch vessel stent placement (*via* bare-metal or covered stents) may be utilized alone or in conjunction with other endovascular techniques described in this article.

There has been a robust experience with this technique to treat malperfusion in selected centers of excellence. Patel *et al*[4] published their results in treating 69 patients presenting with acute TBAD with visceral malperfusion. Treatment options included true lumen stenting, branch vessel stenting, fenestration, and a combination of all three modalities. When all ischemic territories were examined, angiographic reperfusion was obtained in 95.7% of cases. Early mortality was reported at 17.4%, with a 4.3% incidence of stroke, 2.9% incidence of spinal cord ischemia, and 14.5% of dialysis dependent renal failure. During the follow-up period, the authors noted 1 year and 3 years survival rates of 76.2% and 63.5%, respectively. Despite the immediate success with endovascular fenestration, the authors documented the technique's shortcomings – the inability to reduce long term aortic-related events. After successful fenestration the dissection will persist, the false lumen will not thrombose and the risk of late aneurysmal dilation persists. At 5 years, the rate of freedom from aortic rupture or repair was 67.7%. With the advent of stent graft coverage of the entry tear, the use of fenestration has diminished.

The biggest change in surgical management of TBAD is the evolution of TEVAR to substitute for open surgical sealing of the entry tear. Like percutaneous fenestration, TEVAR has the potential benefit of an "indirect" intraluminal approach to the dissected aorta as well as the ability to avoid aortic cross clamping and minimize additional end organ ischemia. Through this minimally invasive approach, TEVAR has significantly altered treatment algorithms in patients presenting acutely. The goals of TEVAR use in the acute setting are to seal the entry tear, decompress the false lumen, expand the true lumen, and prevent rupture. Until recently, thoracic endografts were being utilized in an off-label fashion in the United States. In 2014, two endografts, the TAG device (WL GORE) and the Valiant device (Medtronic), received United States Food and Drug Administration approval for use specifically in aortic dissection[13,14]. Several other devices remain under investigation.

Qin *et al*[15] recently reviewed their single center experience performing TEVAR in 152 patients presenting with complicated TBAD. They achieved technical success in 94.7% of cases, with an in-hospital mortality rate of 2%, stroke rate of 1.3%, and paralysis rate of 1.3%. They also reported a 2.6% incidence of type Ⅰ endoleak formation and a 1.3% rate of retrograde dissection. Fattori *et al*[16] reported a slightly higher mortality rate of 10.9% in their review of 290 patients from the IRAD dataset. Rates of stroke (2.3%) and paralysis (1.3%) remained low. In the long term follow up, the group did note that 30.6% of patients required a repeat intervention, and 13.4% developed any endoleak. The 5 year mortality rate was reported at 15.5%. Data from the NIS dataset revealed similar rates of in-hospital mortality (13.1%) and related morbidities[12]. Sachs *et al*[12] also documented a continual increase in the utilization of TEVAR throughout the study period. Hanna *et al*[17] reviewed their experience performing endovascular repair in 50 patients presenting with complicated TBAD. They reported no in-hospital deaths, with low (2%) rates of stroke and spinal cord ischemia. They noted a 20% utilization of adjunct procedures (branch vessel stenting and extra anatomic bypass). Though studied only retrospectively, TEVAR utilized in the acute complicated setting is associated with overall lower rates of mortality and morbidity compared with open repair.

TEVAR and percutaneous fenestration may not completely resolve end organ ischemia and supplemental endovascular techniques may be required[18]. Persistence of visceral malperfusion after true lumen expansion with TEVAR, or in the setting of static obstruction, typically warrants treatment with visceral branch vessel stenting. The choice of using bare-metal, covered, self-expanding or balloon expandable stents is left to the discretion of the surgeon, as all devices have been used to manage branch vessel malperfusion[19,20].

ROLE OF TEVAR IN ASYMPTOMATIC TBAD

The reduced morbidity and mortality of TEVAR compared to open repair raises the question of prophylactic TEVAR in asymptomatic patients. The rationale of such an approach would be to seal the entry tear at an early point in the process, depressurizing the false lumen and thereby reducing risk of rupture and progression to malperfusion in the acute setting or aneurysmal dilation in the long term. It is well known that in chronic dissection the septum between the true and false lumen

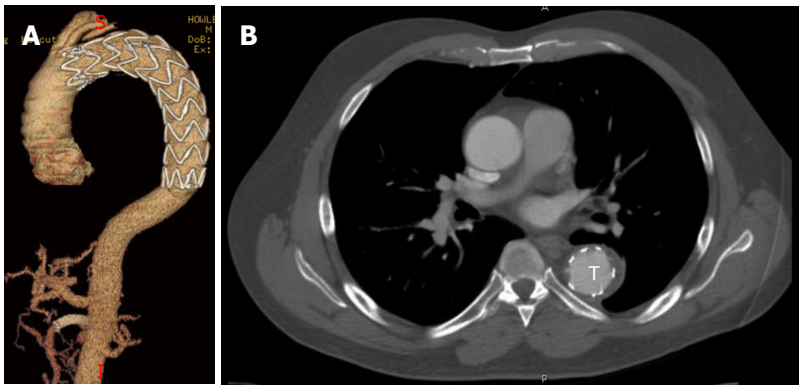

Figure 5 Remodeling after thoracic endovascular aortic repair. A: Follow-up 3D reconstruction from a computed tomography angiography of a patient who underwent TEVAR with adjunct superior mesenteric artery stenting for acute type B aortic dissection with malperfusion. There no evidence of endoleak or aneurysmal degeneration; B: Axial sections from same patient highlighting T expansion with evidence of false lumen thrombosis. TEVAR: Thoracic endovascular aortic repair; T: True lumen.

becomes stiff and repair by endovascular means is more complex and often impossible. The goal of early prophylactic intervention would be to promote false lumen thrombosis, thereby increasing aortic remodeling and reducing the incidence of late aneurysmal degeneration and the frequency of late open repair.

In an attempt to evaluate the role of TEVAR in uncomplicated TBAD, the Investigation of Stent Grafts in Aortic Dissection (INSTEAD) trial randomized approximately 140 patients presenting with subacute (> 14 d) uncomplicated TBAD to best medical therapy with TEVAR or best medical therapy alone[21]. Perioperative mortality rates in the TEVAR group were reported at 2.8%, with a 2.9% incidence of spinal cord ischemia and a 1.5% incidence in major stroke. At 2 years of follow up, the investigators were unable to demonstrate any mortality benefit from TEVAR compared with medical management, with an 88.9% survival in the TEVAR arm and a 95.6% survival in the medical therapy arm. There was no statistical difference seen in the rates of aortic-related deaths (2.9% medical *vs* 5.6% TEVAR), secondary interventions (22.1% medical *vs* 18.1% TEVAR) or spinal cord ischemia (1.4% medical *vs* 2.8% TEVAR) at the end of the 2 years study period. The authors concluded that there was no short or midterm benefit for TEVAR in patients with uncomplicated TBAD and the technique should be reserved for use in those presenting with complications.

There are several shortcomings of the INSTEAD Trial. The major criticisms were that the endpoints of death and complications at two years may not reflect the potential late benefits of TEVAR on false lumen thrombosis, aortic remodeling and late aortic related events and that the trial did not address the role of TEVAR in acute (< 14 d) aortic dissection.

The INSTEAD investigators acknowledged that two years may have been inadequate to capture enough aortic-related deaths within the medical therapy group. To that end, they published outcomes on the same cohort patients followed from 2-5 years from the initial randomization. At 5 years, all-cause mortality statistically differed between the medical (19.3%) and the TEVAR (11.1%) arms[22]. When examining aortic specific mortality, the difference between the medical (19.3%) and TEVAR (6.9%) groups is even more pronounced, with the majority of aortic-related deaths in the medical arm occurring between 2 and 5 years. The authors demonstrated a late survival benefit occurring between 2 and 5 years in patients undergoing TEVAR. It was concluded the survival benefit with TEVAR occurs at a cost of initially increased perioperative morbidity and mortality.

The INSTEAD investigators were also able to demonstrate an improvement in false lumen thrombosis and aortic remodeling in the TEVAR patients. Aortic remodeling is defined as an increase in the true lumen diameter with a subsequent reduction in the false lumen diameter over time, reflecting resolution of the dissection process (Figure 5). No specific criteria exist for objectively quantifying this phenomenon, though several techniques include measuring the true and false lumen diameters at different sites along the thoracic aorta, measuring luminal cross-sectional area, and by volumetric analysis[23]. At 2 years in the INSTEAD trial, only 19.4% of patients undergoing medical therapy were noted to have complete false lumen thrombosis, in contrast to 91.3% of patients undergoing TEVAR[21]. When carried out to 5 years, 22% of patients treated medically showed complete false lumen thrombosis compared with 90.6% of patients undergoing TEVAR[22]. Patterson *et al*[24] attempted to review the available literature on aortic remodeling. Despite being limited by multiple small-sized retrospective series, series with both acute and chronic dissection, and the heterogeneity in which aortic remodeling was quantified, the authors were able to confirm a high (80% to 90%) rate of complete false lumen thrombosis within the proximal thoracic aorta in patients with TBAD undergoing TEVAR. There is evidence to support the connection between aortic remodeling and improvement in long term survival, albeit limited. In a series of patients treated with TEVAR for chronic TBAD, Mani *et al*[25] demonstrated an 89% 3-year survival in

patients with evidence of aortic remodeling, in contrast to a 54% 3-year survival in patients who did not show this feature.

It is important to note that the INSTEAD trial did not address the optimal management of acute TBAD*; i.e.,* all patients survived at least two weeks without developing complications related to their dissection. In patients randomized to TEVAR, the time from diagnosis to treatment averaged 51 d. This may reflect a group of patients in whom the dissection process has already stabilized and who are less likely to develop early or mid-term complications with persistent medical management. Indeed the medical arm had a 95.6% survival and 2.9% aorta related mortality, lower than the 10% mortality reported form the medically managed patients in the IRAD registry[7]. Thus the proper endpoints might have been late rather than early mortality. In fact the 5 years results suggest that the impact of TEVAR is significant in patients who have a longer life expectancy.

INSTEAD did not address the question of how best to deal with patients with acute TBAD who remain asymptomatic but may be at risk for developing complications. While it is clear that this will not occur in the majority of patients, it is equally intuitive that intervention before rupture or malperfusion occurs would be the optimal way to reduce overall morbidity and mortality. The Acute Dissection: Stent Graft or Best Medical Therapy (ADSORB) trial is underway to clarify this issue. A prospectively randomized control study, the ADSORB trial randomized approximately 60 patients presenting with TBAD of less than 14 d duration to either best medical therapy or TEVAR utilizing a Gore TAG device. In contrast to the INSTEAD trial, the ADSORB trial's primary composite endpoint was freedom from either false lumen patency, aortic dilation, or aortic rupture. Mean time to randomization was 4.77 d, with 0.88 d to treatment. Although the study is ongoing, preliminary one year data has been presented. There were no in hospital occurrences of death, stroke or spinal cord ischemia. False lumen thrombosis and freedom from the composite endpoint was reported to be markedly higher in the TEVAR group (57%) compared to the medical only group (3%)[26].

It would be ideal to identify patients at high risk for developing complicated TBAD so that selective use of TEVAR in an asymptomatic setting could occur in at-risk patients, while patients likely to develop false lumen thrombosis with medical management alone could be spared surgical intervention. Several reports have been published that highlight specific cohorts of patients (identified *via* specific radiographic findings) that would potentially benefit the most from early TEVAR. In a recent retrospective review of 228 patients presenting with acute TBAD, Ueki *et al*[27] identified the descending aortic diameter and location of the entry tear as predictors of aortic-related events (dissection-related death, surgical intervention, aneurysmal degeneration or retrograde dissection). In patients treated medically, those with an aortic diameter less than 40 mm and an entry tear located greater than 50 mm from the left subclavian artery experienced an 82.5% rate of freedom from aortic events by 5 years. In contrast, those with aortic diameters greater than 40 mm and a proximal (less than 50 mm from the left subclavian) entry tear experienced a 53.5% freedom from aortic event rate over a similar time period. Marui *et al*[28] also retrospectively examined a group of patients with TBAD treated medically. They identified an aortic diameter greater than 40 mm, persistent false lumen patency and a fusiform dilation index as significantly associated with late aortic events. In a retrospective review of 110 patients presenting with TBAD, Akutsu *et al*[29] identified an aortic diameter of 45 mm on presentation and false lumen patency as independent risk factors for future dissection-related mortality. When examining a series of patients presenting with acute type A and TBADs, Song *et al*[30] identified a false lumen diameter of 22 mm or greater as an independent predictor of late aneurysmal degeneration and aneurysm related death.

FUTURE DIRECTIONS AND CONCLUSION

Management of TBAD has undergone dramatic alterations within the past decade and the management of this problem continues to evolve. The high mortality associated with open repair of patients with complicated TBAD has been reduced by the increasing use of thoracic stent grafts to seal the entry tear and restore perfusion. Initial enthusiasm for percutaneous fenestration is being replaced for the most part by TEVAR, which affords entry tear sealing (and subsequent aortic remodeling) in a minimally invasive fashion. Moreover, the success of TEVAR in managing malperfusion has led investigators to study its use in uncomplicated TBAD. Data supporting this indication is not definitive, but what exists suggests that elective TEVAR in the subacute phase is associated with an improvement in 5 years aortic-related survival, at the cost of some increase in perioperative morbidity. The use of TEVAR also appears to improve aortic morphology over time, potentially explaining its long term survival benefit. This causal relationship, however, has not been definitely proven. Current trials are underway to determine feasibility in applying TEVAR in cases of early (< 14 d) uncomplicated TBAD, although the optimal timing of intervention and criterion for patient selection remain unclear. Observational data has aided in identifying specific radiographic criteria that may select out potential subgroups that may be more likely to benefit from TEVAR than medical therapy alone. Fruitful areas for further investigation include: the development of new devices with lower profile and better conformability to reduce perioperative complications; new techniques to increase incidence of false lumen thrombosis and identifying clinical and radiographic characteristics which can predict patients at high and low risk of developing complications with medical management.

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Versatility of therapeutic reduction mammoplasty in oncoplastic breast conserving surgery

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Abstract

Oncoplastic breast conserving surgery is the gold standard approach for the surgical treatment of early breast cancer. There is a well defined technique named "therapeutic mammoplasty" which is characterized for using a reduction mammaplasty technique to treat breast cancer conservatively. In our current practice, "therapeutic mammoplasty" or therapeutic reduction mammaplasty is our favorite oncoplastic breast conserving approach which it used in almost half of our patients. This technique is very versatile allows us the resection of tumors located in all breast quadrants of patients with moderate-to large-sized breasts. We describe a series of 57 patients who were treated using a therapeutic reduction mammaplasty. All surgical procedures were carried out by one comprehensive breast surgeon who planned and designed the surgery performing both oncologic and reconstructive procedures. Surgical margins were insufficient in eight patients (14%). Nine patients (15.8%) had a complication in early postoperative period and in one of them adjuvant radiotherapy was delayed four months due to a wound dehiscence. The rate of synchronous contralateral symmetrization was 31.6%. Our conclusion is that reduction mammaplasty is a useful and safe skill to treat breast cancer conservatively playing a very important role therefore it must be situated in the priority of learning objectives.

Key words: Breast conserving surgery; Oncoplastic; Oncoplastic breast surgery; Reduction mammoplasty; Therapeutic mammaplasty

Core tip: Reduction mammaplasty techniques are a really useful and safe skills to treat breast cancer conservatively allowing breast surgeons manage tumors located in all breast quadrants with low morbidity in moderate to large breasted patients, thanks their versatility they play a very important role in oncoplastic conservative surgery therefore they must be situated in the priority of learning objectives.

Hernanz F, González-Noriega M, Pérez RV, Gómez-Fleitas M. Versatility of therapeutic reduction mammoplasty in oncoplastic breast conserving surgery. *World J Surg Proced* 2015; 5(3): 217-222 Available from: URL: http://www.wjgnet.com/2219-2832/full/v5/i3/217.htm DOI: http://dx.doi.org/10.5412/wjsp.v5.i3.217

INTRODUCTION

Currently, oncoplastic breast conserving surgery (OBCS) should be the gold standard approach for the surgical treatment of early breast cancer[1-3]. Oncoplastic techniques (OT) offer clear advantages on nearly forty percent of patients in who common breast conserving treatment (BCT) (surgery plus radiotherapy) are followed by cosmetic sequelaes[4] besides the rest of the patients who also could be benefited from many surgical tricks which can improve aesthetic outcomes[5]. Since 1998, when Audretsch *et al*[6] described the use of plastic surgery techniques to reshape the breast at the time of lumpectomy or quadrantectomy introducing the term "oncoplastic", it has passed enough time to be able to evaluate long-term oncologic outcomes, therefore a meta-analysis gathering 3165 patients treated by OBCS *vs* 5494 treated BCT have demonstrated that OBCS obtain similar results to standard breast conserving surgery improving cosmetic outcome and patients' satisfaction[7].

There is a large amount of OT but these can be classified in two main groups: Volume replacement or displacement techniques. Nowadays, the last ones, which are more frequently used[8], have a broad technical variety with different patters incisions, pedicles used for nipple areola complex (NAC) movement, ways to fill tumor removal defect and their multiple combinations. Several authors[9-13] have created different algorithms attempting to optimize OT and offering us a method to select the most appropriate OT in each patient. These algorithms for immediate conservative surgery reconstruction are based on some aspects such as type and size of the breast, extent of tumor removal defect, ptosis degree, breast tissue density and location of the tumor in the breast. Other aspects very important in the process of decision are patient preferences and surgeon expertise.

In OT displacement volume group there is well defined technique a "therapeutic mammoplasty" term coined by McCulley *et al*[14,15] which is characterized for using a reduction mammaplasty technique and radiotherapy to treat breast cancer. These authors described two different scenarios depending if the tumor lies or not within the routine pattern incision and excision dividing the breast in nine areas with theirs corresponding approaches. Therapeutic mammaplasty is especially useful in large breasted patients in who a bilateral reduction mammaplasty offers clear advantages which are both oncological and functional which cause better radiation therapy and beside relieving the symptoms related to breast hypertrophy thus improves quality of life[16], even more, this approach is a better option than skin-sparing total mastectomy and immediate reconstruction having lower morbidity and more favorable cosmesis[17].

Munhoz *et al*[18], wrote that the main advantages of the therapeutic reduction mammaplasty (TRM) should include reproducibility, low interference with oncological treatment and long-term results. We agree completely with him and it is more, based on our experience, we would like to add that this technique is versatile because it could be used to treat tumors located in all breast quadrants with the condition that the patient having a moderate to large-sized breast.

The aim of this work was to communicate our experience with TRM showing the distribution of tumors into the breast, rate of affected margins, early surgical complications, and synchronous contralateral breast symmetrization.

PATIENTS AND METHODS

Between 2005 and 2013, 57 patients suffering from breast cancer suitable for BCT underwent TRM at our Oncoplastic Breast Unit, Hospital Valdecilla (Santander, Spain). All surgical procedures were carried out by one comprehensive breast surgeon (FH) who planned and designed the surgery performing both oncologic and reconstructive procedures. Data from patient and tumor characteristics, surgical procedures, early complications and pathological study were prospectively collected and stored in IBM SPSS statistics program.

RESEARCH RESULT

Characteristic of patients and tumours are described in Tables 1 and 2. Seven patients were treated before surgery with neoadjuvant chemotherapy. Most of tumor excisions were guided by needle-wires (84.2%) according to our method previously published[19]; wires were inserted 1 cm distant to radiologic tumors limits as markers of optimal limit resection, sufficiently of resection margins was per-operatively tested by X-ray analysis of surgical specimen. Biopsy of sentinel lymph node (49) and axillary linfadenectomy (10) was performed in mostly patients by the T inverted pattern incision. Opposite breast surgery by reduction mammaplasty was carried out in eighteen patients (31.6%).

Surgical margins status

Margins were insufficient in eight patients (14%), five affected and three with focal involvement. Two of them having affected margins underwent total mastectomy. Pathologic study of mastectomy showed residual invasive carcinoma and carcinoma *in situ* in one patient and residual ductal carcinoma *in situ* in the other.

Early surgical complications

Nine patients (15.8%) had a complication in early

Table 1 Characteristics of the series of 57 patients *n* (%)

Age (yr)	57, 8.9 SD
Status menstrual	
Premenopausal	13 (22.8)
Postmenopausal	44 (77.2)
Affected breast	
Right	19 (33.3)
Left	38 (66.7)
Tumour location through the breast (quadrant)	
Upper outer	16 (28.1)
Upper inner	3 (5.3)
Lower Inner	3 (5.3)
Central	12 (21.1)
Intersection upper quadrants	7 (12.3)
Intersection lower quadrants	5 (8.8)
Intersection inner quadrants	3 (5.3)
Intersection outer quadrants	7 (12.3)
Inframmary fold	1 (1.8)
Multifocal	14 (24.6)
Radiological tumour size (mm)	21.7, 12.58 SD

Table 2 Characteristic of 57 breast carcinomas *n* (%)

In situ	7 (12.3)
Invasive	50 (87.7)
Type of histology	
Ductal	39
Lobular	6
Mixed	1
Papilar	1
Others	3
Positive estrogenic receptors	38
Positive progesterone receptors	37
Positive Herb2 receptors	7
Ki67 (n = 42)	
> 10%	15
10%-50%	19
51%-75%	3
> 75%	4
Pathologic tumour size (mm)	17.1, 9.77 SD
Patients with lymph nodes positives	12 (14)

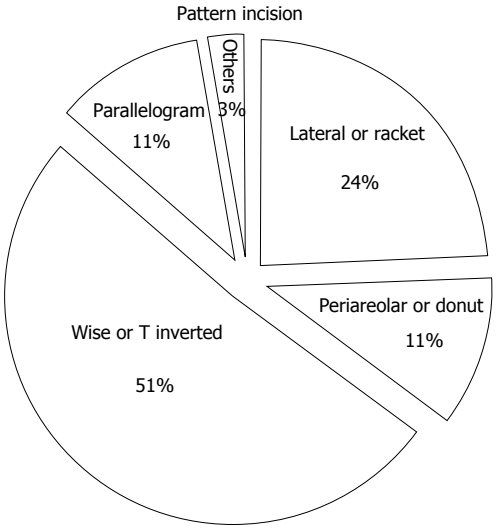

Figure 1 Distribution of the pattern incisions used in breast cancer patients treated using oncoplastic conservative approach at our unit.

postoperative period (five a hematoma, four a minor wound dehiscence) and three of them had to be re-operated for evacuating a hematoma. There were no major complications such necrosis of NAC or severe breast infections and only one adjuvant radiotherapy was delayed four months in one patient due to a wound dehiscence.

DISCUSSION

Although some OT are specifically useful to manage some determined tumor locations such as a lateral or tennis racket mammaplasty[20] for tumors located at upper outer quadrant or LIQ-V mammaplasties[21] for these located at lower inner quadrants, reduction mammaplasty with T inverted pattern incision appropriately adapted is be able to treat tumors situated at all breast quadrants. In a very large series of 540 consecutive cases published by Fitoussi *et al*[22] in which a variety of OT were used, T inverted pattern incision was the most frequently utilized in 40% of patients. Our current BCT entails 77.2% of breast cancer surgery and in oncoplatic breast conserving experience using volume displacement technique this pattern incision is the most common (Figure 1) used in 52% of cases, and our favorite approach (unpublished data).

As inner quadrants were the less frequent tumor localizations with 10.6% and the outer ones were the most frequent our first choice to move NAC was a superomedial pedicle but in this series we also used inferior and bipedicled ones. In those patients with central tumors in who NAC had to be removed we reconstructed NAC using different techniques, for example, contralateral areola (Figure 2) or skin graft plus arrow flap for nipple reconstruction. The variation of localizations shows the versatility of TRM in breast with moderate or large size.

Early complications rate was 15.8%, these were minor; our experience is similar to others authors such as Gulcelik *et al*[23] who reported a rate of minor early complications of 16.3% and major ones of 1.9% without differences between reduction mammaplasy used for macromastia treatment and breast cancer. A wide range of complications rate of therapeutic reduction mammaplasty has been reported[24] likely due to differences in criteria and collecting data but, one conclusion is uniform that they usually are minor not impacting seriously on delivery of adjuvant therapies unless they were severe, McIntosh *et al*[25] in a systematic review found that delayed adjuvant treatment in only 6% of cases.

The rate of synchronous contralateral symmetrization was 31.6% but most of these patients were operated in the first half of the series before 2011; like as Fitoussi *et al*[22] our current preference is delayed contralateral symmetrization. The reasons for that have been clearly exposed by Kaviani *et al*[26] who categorized the patients in three groups: Patients unwilling any contralateral

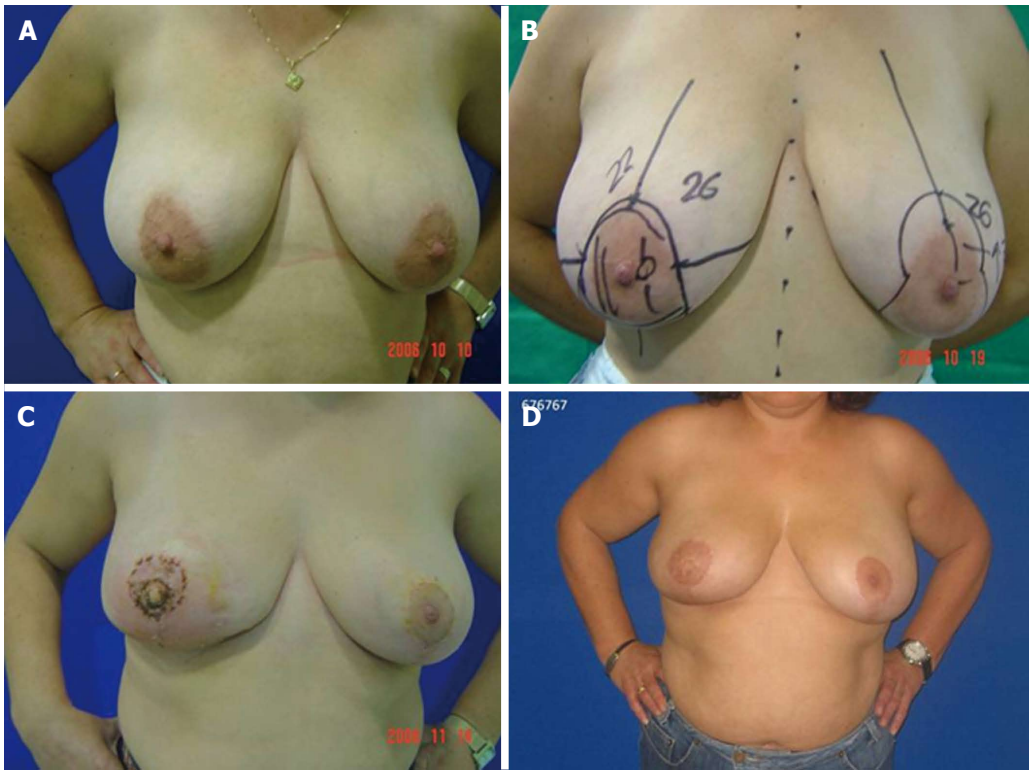

Figure 2 A 40-year-old postmenopausal woman with an invasive ductal carcinoma with positive estrogenic, progesterone and Herb2 receptors situated at central quadrant of right breast which sized 15 mm on mammograms. A and B: Appearance of patient. Design of pattern of therapeutic reduction mammaplasty; C and D: Nipple areola complex right reconstructed by contralateral areola graft. Long-term aesthetic outcome.

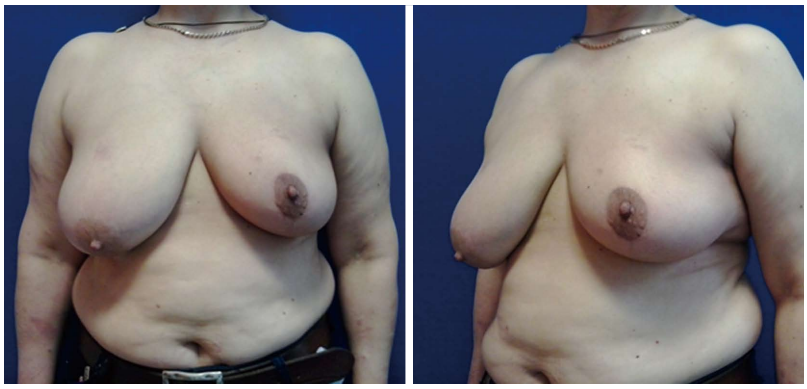

Figure 3 Appearance of a 49-year-old woman after underwent oncoplastic breast conserving surgery and posterior adjuvant chemotherapy and radiotherapy. She had a bifocal invasive lobulillar carcinoma situated at intersection of upper quadrants with positive estrogenic and progesterone receptors and $T_2N_0M_0$ pathological staging. She presents breast asymmetry which she wants it to be corrected.

procedures, patients preferring an all-in-one operation willing immediate symmetrization and patients desiring optimal aesthetic results; only patients belonging to the second group are candidates to immediate contralateral symmetization. In our experience, our average patient is in the first group. Figure 3 shows the appearance of a patient belonging to third group with breast asymmetry which she wants it to be corrected; we will carry out symmetrization of the right breast when she stabilized her weight because she put on weight during chemotherapy treatment.

Patient satisfaction and aesthetic outcomes reported are very high with a low rate of failure as which summarized by the fact that almost none patients regretted to chose this type of surgery[18]. Changes of aesthetic outcomes over the time after completing radiotherapy have been commented not affecting negatively patient satisfaction. In our experience, TRM as reduction mammaplasty technique has the same limitations and aesthetic outcomes can be deteriorated over the time by pseudoptosis (Figure 4) or excessive weight gain.

Finally, all OT and more specifically those of level Ⅱ are based on the knowledge of reduction mammaplasty techniques; independently, which model for oncoplastic approach can be chosen "comprehensive breast surgeon" or "oncologic and plastic team", skill sharing

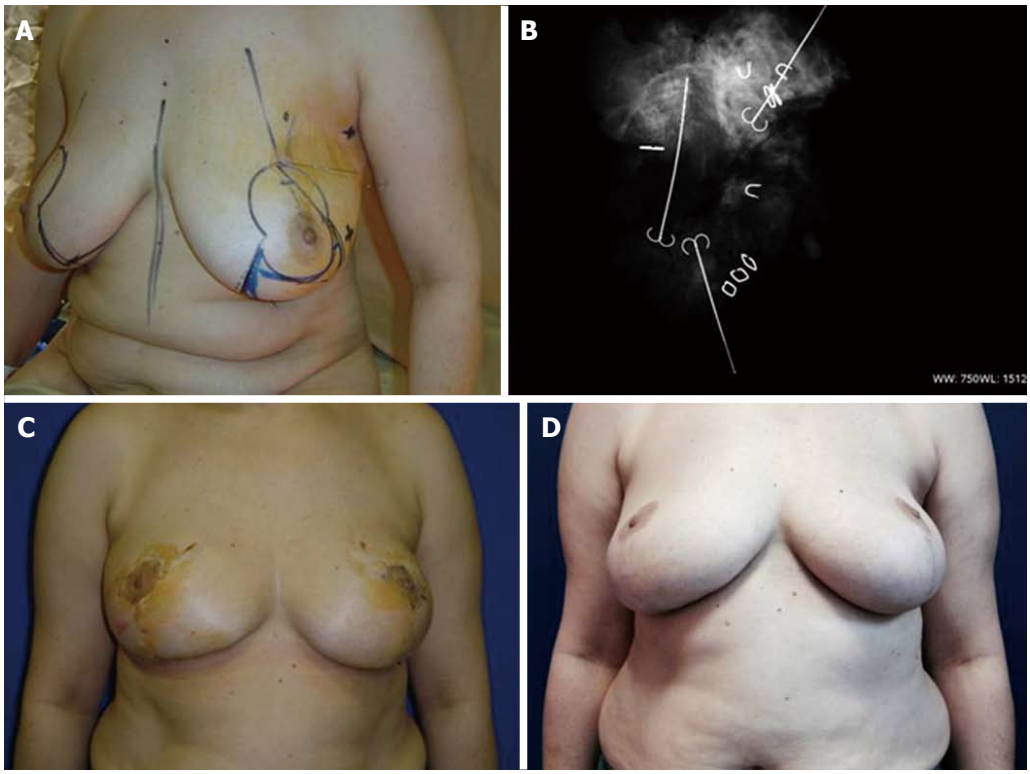

Figure 4 A 44-year-old premenopausal female with an invasive ductal carcinoma at upper outer quadrant of the left breast which sized 35 mm on mammograms who was treated with neoadjuvant chemotherapy before surgery. A therapeutic bilateral reduction mammaplasty with T inverted pattern incision and superomedial pedicle used for shifting nipple areola complex and an infero-lateral one to fill the breast defect caused by extirpation of a surgical specimen weighted 223 g was carried out. Pathological study showed a tumor size 12 mm, one negative sentinel lymph node and free surgical margins. A: Design of pattern incision with three wires inserted to guide tumor excision; B: X-ray of surgical specimen showed complete radiological removal of tumor; C: Appearance on early postoperative period; D: Long-term aesthetic outcome three years after breast conserving treatment shows both breasts with pseudotosis.

between breast unit members is eagerly desirable and, in our opinion, about reduction mammaplasty techniques the former statement is essential. Accepting the lack of oncoplastic training[27] and the fact that expertise requires long time[28], we proposed a management policy[29] to mitigate this situation incorporating the surgical treatment of symptomatic macromastia into Breast Cancer Unit[30]. One step in this direction is the inclusion of gynaecomastia and congenital asymmetry surgical treatment into several Oncoplastic Breast Surgery Units in United Kingdom.

CONCLUSION

Reduction mammaplasty technique is a useful and safe skill to treat breast cancer located in all breast quadrants with low morbidity playing a very important role in oncoplastic conservative surgery in moderate to large breasted patients therefore it must be situated in the priority of learning objectives.

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ORIGINAL ARTICLE

Retrospective Study

Are stapler line reinforcement materials necessary in sleeve gastrectomy?

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Author contributions: Sakcak I solely wrote this paper.

Institutional review board statement: Ethics committee approval is not obligatory in Turkey for retrospective studies (Clinical Study Regulation, Turkish Official Gazette, Date: April 13, 2013, No: 28617), therefore ethics committee approval was not obtained.

Informed consent statement: All patients provided their informed consent for surgery (informed consent could not be obtained for study due to its retrospective nature).

Conflict-of-interest statement: None.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at ibrahimsakcak66@gmail.com. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To investigate the effect of staple line reinforcement materials on decreasing complications related to sleeve gastrectomy.

METHODS: In this retrospective study, we analyzed 84 patients who had sleeve gastrectomy due to obesity between April 2012 and April 2015. Sleeve gastrectomy procedure was performed in patients with a body mass index (BMI) more than 40 kg/m^2, and the ones with a BMI between 32 and 40 kg/m^2 in the presence of comorbid diseases. Reinforcement materials were used in 45 patients while they were not used in 39 patients. Materials such as Peristrip, 3/0 prolene, and V-lock were used for reinforcement in the reinforcement group (RG), and the materials used showed variations during the study period. The baseline characteristics, duration of surgery, hospital stay, comorbidities including hypertension, type 2 diabetes mellitus, hypertension, hepatosteatosis, gallstones, osteoarthritis, gastroesophageal reflux, sleep disorders, as well as the complications including leaks and bleeding after surgery were recorded and compared between the reinforcement and non-RGs (NRGs).

RESULTS: There were no differences between the reinforcement and NRGs for baseline characteristics including age (P = 0.689), gender (P = 0.057), height (P = 0.483), weight (P = 0.889), BMI (P = 0.971), hospital stay (P = 0.888), or duration of surgery (P = 0.229). The most common comorbidities in the RG were hypertension (24.4%) and hepatosteatosis (24.4%), while type 2 diabetes mellitus (28.2%) and

hepatosteatosis (28.2%) were the most frequent comorbidities in the NRG. There were no differences between the reinforcement and NRGs for the rates of comorbidities (P > 0.05). Leak was observed in one (2.2%) patient in the RG, and there was leak in 2 (5.1%), and bleeding in 2 (5.1%) patients in the NRG. There were no differences between the reinforcement and NRGs for the rate of staple line leaks (P = 0.446) or bleeding (P = 0.213). One of the patients with leak died in the NRG while there were no deaths in the RG.

CONCLUSION: Although staple line reinforcement materials decreased morbidity and mortality, the differences between the two groups were not statistically significant.

Key words: Obesity; Sleeve gastrectomy; Staple line; Reinforcement

Core tip: Sleeve gastrectomy is one of the most frequently performed surgical procedures in the treatment of obesity. In this study, we investigated the efficiency of use of staple line reinforcement materials in decreasing these complications. We included 84 patients in our study. Reinforcement materials were used in 45 patients while they were not used in 39 patients. Although we found that staple line reinforcement materials decreased morbidity and mortality, the differences between the two groups were not statistically significant for complications or mortality. There is a need for prospective randomized studies on larger patient populations to further clarify the subject.

Sakcak I. Are stapler line reinforcement materials necessary in sleeve gastrectomy? *World J Surg Proced* 2015; 5(3): 223-228 Available from: URL: http://www.wjgnet.com/2219-2832/full/v5/i3/223.htm DOI: http://dx.doi.org/10.5412/wjsp.v5.i3.223

INTRODUCTION

The data published by the World Health Organization in 2014 indicate that 39% of the world population over 18 years of age are overweight and 14% of them are obese, and some problems including hypertension, cardiovascular diseases and gastroesophageal reflux appear due to obesity[1]. Obesity is a significant health problem in the developed countries, and its prevalence has been increasing in the developing countries. In Turkey, which is a developing country, the prevalence of obesity in adults increased two-fold in the last 15 years, and reached 29.5%.

Laparoscopic sleeve gastrectomy is one of the most frequently performed bariatric procedures with an increasing popularity owing to its efficiency in weight loss, and its ability to improve comorbidities. Sleeve gastrectomy shows its effect on weight loss by three different mechanisms: (1) Stomach volume is decreased by 80%-85%; (2) The concentration of ghrelin, an ergogenic hormone, decreases; and (3) Gastric emptying rate increases[2].

The main disadvantages of sleeve gastrectomy are staple line leaks (SLLs) and bleeding. SLLs are seen in 1%-3% of patients after primary procedures[2]. Leaks subsequently result in abdominal sepsis, chronic gastric fistula, necrotizing fasciitis, multi-organ failure and eventually sepsis, and they are the most important causes of mortality[3,4]. A number of surgeons use staple line reinforcement materials (SLRMs) to decrease this complication while some others claim that those materials are not necessary, and use of them does not decrease SLLs[5,6].

In this study, we aimed to investigate whether use of SLRM in patients who had sleeve gastrectomy due to obesity decreased complications such as SLLs and bleeding.

MATERIALS AND METHODS

This retrospective study included 84 patients who had sleeve gastrectomy due to obesity at Ankara Numune Education and Research and Medicalpark Ankara Hospitals between April 2012 and April 2015. The patients were divided into two groups as the reinforcement group (RG) in which a reinforcement material was used to reinforce the staple line, and non-RG (NRG) in which a staple line reinforcement material was not used. Selection of the patients into the RG or NRG group was the surgeon's preference. Demographic characteristics, comorbidities, and morbidities of the patients were recorded.

Sleeve gastrectomy procedure was performed in patients with a body mass index (BMI) more than 40 kg/m^2, and in the ones with a BMI between 32 and 40 kg/m^2 in the presence of comorbid diseases.

Enoxaparin sodium (Sanofi Winthrop Industrie, Maisons-Alfort/France) 60 mg was injected subcutaneously 12 h before surgery for prophylaxis of venous thromboembolism, and the patients wore anti-embolism socks on the day of surgery. Surgery was performed in the supine position, and the surgeon performed the surgery standing between the legs of the patient. Procedure was performed through 5 trocars: One 15 mm trocar for stapler handle, one 10 mm trocar for the camera, and three 5 mm trocars for instruments and liver retractor. The greater omentum was separated from the greater curvature, starting 2 cm proximal to the pylorus with Harmonic (Ethicon, United States) or Ligasure (Covidien, United States). The stomach was divided approximately 3 cm proximal to pylorus, targeting 1 cm lateral to the esophagogastric junction. Echelon 60 (Ethicon-Mexico) and Covidien 60 (Covidien, United States) staplers were used to divide the stomach.

A thick tissue stapler was used in the antrum, a thin tissue stapler used in the fundus, and a medium-

Table 1 Baseline characteristics of 84 patients that had laparoscopic sleeve gastrectomy

	RG (n = 45)	NRG (n = 39)	P
Age (yr)			
Male, n (%)	9 (20.0)	7 (17.9)	0.811
Female, n (%)	36 (80.0)	32 (82.1)	
Height (cm)	167.1 ± 8.5	166.1 ± 8.1	0.483
Weight (kg)	122.3 ± 23.2	120.9 ± 20.6	0.889
BMI (kg/m^2)	43.1 ± 7.4	43.3 ± 8.2	0.971
Hospital stay (d)	5.0 ± 2.3	4.3 ± 2.3	0.888
Duration of surgery (min)	82.9 ± 33.2	78.2 ± 30.3	0.229

RG: Reinforcement group; NRG: Non-reinforcement group; BMI: Body mass index.

Table 2 Comorbidities of the patients n (%)

	RG (n = 45)	NRG (n = 39)	P
Hypertension	11 (24.4)	10 (25.6)	0.899
Hyperlipidemia	9 (20.0)	10 (25.6)	0.926
Type 2 diabetes mellitus	9 (20.0)	11 (28.2)	0.883
Sleep disorders	7 (15.6)	6 (15.4)	0.560
GERD	10 (22.2)	10 (25.6)	0.714
Depression	7 (15.6)	6 (15.4)	0.560
Hepatosteatosis	11 (24.4)	11 (28.2)	0.696
Gallstone	8 (17.8)	8 (20.5)	0.750
Osteoarthritis	4 (8.9)	4 (10.3)	0.560

RG: Reinforcement group; NRG: Non-reinforcement group; GERD: Gastroesophageal reflux disease.

Table 3 Staple-line bleeding and leaks after sleeve gastrectomy n (%)

	RG (n = 45)	NRG (n = 45)	P
Staple-line leaks	1 (2.2)	2 (5.1)	0.446
Staple-line bleeding	0	2 (5.1)	0.213

RG: Reinforcement group; NRG: Non-reinforcement group.

Table 4 Comparison of the groups for the complications other than staple line leaks and bleeding n (%)

	RG (n = 45)	NRG (n = 45)	P
Venous thromboembolism	0	1 (2.6)	0.464
Surgical field infection	3 (6.7)	2 (5.1)	0.568
Pulmonary complications	0	1 (2.6)	0.464

RG: Reinforcement group; NRG: Non-reinforcement group.

thick tissue stapler in the tissues between. An orogastric tube was inserted during surgery, the stomach contents were aspirated. The tube was then removed, and a 36 F calibration tube was inserted. Diluted methylene blue was given through the calibration tube to test the presence of any leak, and then the tube was removed. Materials such as Peristrip, 3/0 prolene, and V-lock were used for reinforcement in RG. The type of the material showed variations during the study period. Peristrip was used in 27 of 45 patients, 3/0 prolene was used in 12, and V-lock suture was used in 6 patients that had surgery after October 2014. The stomach tissue was removed through the 15-mm trocar incision. A Jackson-Pratt drain was placed, and it was removed when the drainage was less than 30 mL. The patient drank 100 mL methylene blue on postoperative day 1, and the drain was checked for the presence of methylene blue. The patient was given oral liquids after making sure that there was no leak.

Statistical analysis

SPSS version 22.0 (SPSS Inc, Chicago, IL) was used for statistical analyses. The categorical variables were compared by Fisher exact χ^2 test. Numerical data are presented as mean ± SD, and one sample t-test was used to determine whether they were parametric or not. Since the numerical data were determined to be non-parametric, Mann Whitney-U test was used to compare the two groups.

RESULTS

The baseline characteristics of 84 patients are presented in Table 1. There were no significant differences between the two groups.

There were 9 different comorbidities in the two groups. The most common comorbidities in RG were hypertension and hepatosteatosis (24.4%), while type 2 diabetes mellitus and hepatosteatosis were the most frequent comorbidities (28.2%) in NRG (Table 2).

Leak, which is the most distressing complication in sleeve gastrectomy, was seen in one patient in RG (2.2%), and in 2 (5.1%) patients in NRG (P = 0.446). Leaks were recognized within three days after surgery, and the patients were followed conservatively first. However, none of the patients responded to conservative treatment. The leak orifice was closed endoscopically with over-the-scope clips at postoperative 2nd-4th wk. All patients recovered with this intervention. There were no bleeding in RG, however, it developed in 2 (5.1%) patients in NRG. The difference between the groups was not statistically significant (P = 0.213) (Table 3).

Comparison of the groups for the complications other than SLLs and staple line bleeding is presented in Table 4. Infection of the surgical field was seen in 3 patients in RG. Venous thromboembolism was seen in 1, surgical field infection was seen in 2, and pulmonary complications were seen in 1 patient in NRG. One patient in RG and 2 patients in NRG also had SLLs. Antibiotics and conservative treatment were administered to those patients. One patient in NRG died despite all those treatments, and other patients recovered.

DISCUSSION

SLL is the most important cause of mortality and morbidity after sleeve gastrectomy. Stapler line is reinforced

in order to minimize this distressing complication[7]. Various SLRMs are used for this purpose, and the staple line is sutured. The primary SLRM used is a synthetic bioabsorbable material composed of the copolymer polyglycolic acid/trimethylene carbonate (GORE SEAMGUARD Bioabsorbable Staple Line R, W.L. Gore and Associates, Elkton, MD, United States) put into the stapler cartridge, and Peri-Strips Dry with veritas. A recent meta-analysis including 56 studies and 6578 patients reported that SLRMs were used in 56% of the patients that had laparoscopic sleeve gastrectomy[8]. The results of this meta-analysis indicated that use of SLRMs decreased the leak rate from 3.2% to 2%, without any statistically significant difference in between. Knapps *et al*[4] reviewed 30 papers including 4881 patients, and did not find any statistically significant difference for leaks or bleeding with use of SLRM. Albanopoulos *et al*[9] performed a randomized study on 40 patients, and reported that use of SLRMs did not decrease the leak rate. On the other hand, some surgeons claimed that use of those materials decreased SLLs. Ser *et al*[10] performed a study on 118 patients, and reported the SLL rate as 10% without use of SLRMs, and as 0% with use of SLRMs. The results of that study reported a great difference between the two groups. However, it must be noted that the study of Ser *et al*[10] included smaller number of patients when compared to other meta-analyses and reviews. In our study, SLL was seen in 1 (2.2%) patient in RG, and in 2 (5.1%) patients in NRG, and bleeding was seen in 2 (5.1%) patients in NRG.

The pathophysiological basis of stapler line reinforcement is not clear. Poor blood flow at staple line, insufficient closure of stapler cartridge, postoperative gastroparesis and pyloric dysfunction have been accused for SLLs[11]. In addition, a staple line closure which is not straight is one of the most important causes for leaks.

Some stapler-related and tissue-related factors affect the morbidity of surgery. The stomach has the most variable wall thickness among the gastrointestinal system organs. Its wall is the thickest in prepyloric antrum, and the thinnest in the fundus. The thickness of the stomach wall decreases as one gets closer to the greater curvature, along the axis of the stomach[7]. The tissue thickness must be taken into consideration when performing sleeve gastrectomy. The most important features of staplers are their leg lengths, closing characteristics, and the type of metal. Tissue-related characteristics are viscosity and thickness. The risk for leaks and bleeding increases with a long leg length, on the other hand, the leak risk also increases with a short leg length due to tissue ischemia and necrosis[12]. Staplers with a long leg length must be used in the antrum, and those with a short leg length must be used in fundus. If a stapler with a short leg length is used in the antrum, this may cause dehiscence at the staple line[13]. We preferred staplers with a long leg length in the antrum, staplers with a medium leg length in the corpus, and staplers with a short leg length in the fundus.

The likelihood of leak through the cut edge of the stomach differs after sleeve gastrectomy. Of all leaks, 6.8%-14.3% were seen in distal 1/3 of the stomach while 75%-100% of them occurred in the proximal 1/3 of the stomach, particularly at the level of the esophagogastric junction[14]. The leaks occurring in 3 patients in our series were at the level of the esophagogastric junction, in other words, in the proximal 1/3 of the stomach. Thin walls and poor vascularity in this part of stomach may be responsible for the leaks.

Leaks usually occur due to mechanical and ischemic factors. Wrong firing of stapler, and cutting in irregular zig-zags are among the mechanical factors, and they usually cause leak in the first postoperative 2 d. Ischemic factors are dissection of the tissues excessively with energy devices (Harmonic, Ligasure) and disturbance of the vasculature[3]. Therefore, the tissues must be held carefully while using energy devices, and their use must be avoided in distal narrowings. Some surgeons wait for a while after squeezing the tissue with stapler in order to prevent leaks and bleeding, and they think that the fluid content of the tissue decreases and the vessels collapse in this way[15]. Our team also practices this method, and we think that it is effective.

The thickness of the bougies used in sleeve gastrectomy for calibration and standardization is still debated. Bariatric surgeons usually use bougies with a diameter of 32-40 F[16]. Some studies suggest that use of small-diameter bougies accelerates weight loss, however, increases the frequency of SLLs. The reference point here is higher intraluminal pressure in the stomach in case of a smaller diameter. Usually 34 and 36 F bougies have been recommended. Larger bougies may make reaching the ideal weight difficult[17]. We used 36 F bougies in our series.

The mechanism of leak and bleed prevention by SLRMs is not known. However, it is sure that the materials used show a compressive effect. It is not known how effective this compression is. Some argue that compressive materials shorten operation time more than oversewing sutures[18]. Durmush *et al*[19] studied 518 patients retrospectively, and reported that materials that were implanted to stapler cartridge shortened operation time by 13 min when compared to oversewing. Kasalicky *et al*[20] reported their experience on 207 patients, and stated that they did not use any reinforcement materials at the staple line or sutured it, the duration of operation shortened by 10 min, and the risk of bleeding did not increase. On the other hand, in their series with 100 patients, Shah *et al*[21] reported that SLRM shortened operation time by 14 min on average (58.8 ± 19.7 min *vs* 72.8 ± 25.8 min, $P = 0.0153$). In our series, the operation time was approximately 5 min longer in RG, however, the difference between the two groups was not statistically significant.

One of the reasons for increased SLLs is revision surgery. Revision surgery is usually performed in patients who had laparoscopic adjustable gastric band surgery, and later had band removal due to band-related problems. The risk of leak is higher than 10% in those

patients[22]. This high risk is due to insufficient stapler closure resulting from increased fibrosis and edema. Staged surgery was recommended to reduce this risk. Gastric band is removed in the first operation, and one week later, sleeve gastrectomy is performed[23]. Four of our patients had had laparoscopic gastric band before, and our team had removed the band. We performed staged surgery in all those patients, and no leaks were observed.

Early diagnosis and treatment of SLLs are important to decrease morbidity and mortality. Therefore, an appropriate method must be used to identify leaks. Methylene blue, air-liquid test, and observation of the staple line with endoscopes are used for this purpose[24,25]. In our study, leak test was performed by administration of diluted methylene blue both during surgery, and on postoperative day 1. A positive methylene blue test was confirmed in all of our patients by whole abdomen computerized tomography obtained after the patient was given an oral contrast material.

We could not have a final judgment on the use of SLRMs. The reasons for this is a small number of patients included in our study, retrospective and non-standardized study design, and no standardization of the materials used for reinforcement, which are limitations of our study. There is a need for further studies on a larger patient population with use of standard reinforcement materials.

In conclusion, sleeve gastrectomy is one of the most frequently performed bariatric procedures. Leak and bleeding are the most worrisome complications of this surgical technique. Various materials are used to reinforce the staple line to prevent those complications. However, there is no consensus in the literature on whether use of reinforcement materials decreased the complications or not. Although we could not have a final judgment in our study on use of SLRMs, we will go on using those materials in some patients depending on patient factors and course of surgery.

COMMENTS

Background

Sleeve gastrectomy is one of the most frequently performed surgical procedures in the treatment of obesity. However, it may result in some complications such as staple line leaks and bleeding, and even death.

Research frontiers

Reducing morbidities, particularly staple line leaks and bleeding, will increase the safety of the procedure. A number of surgeons use staple line reinforcement materials to decrease this complication while some others claim that those materials are not necessary, and use of then does not decrease staple line leak. There is still a need for research in this area.

Innovations and breakthroughs

In the authors' study, staple line leak was seen in 1 (2.2%) patient in the reinforcement group (RG), and in 2 (5.1%) patients in the non-RG (NRG), and bleeding was seen in 2 (5.1%) patients in the NRG, without any significant differences between the groups. The leaks occurred in 3 patients in their series were at the level of the esophagogastric junction, in other words, in the proximal 1/3 of the stomach. They preferred staplers with a long leg length in the antrum, staplers with a medium leg length in the corpus, and staplers with a short leg length in the fundus since the stomach wall is the thickest in the prepyloric antrum, and the thinnest in the fundus. They waited for a while after squeezing the tissue with stapler in order to prevent leaks and bleeding, and they think that the fluid content of the tissue decreases and the vessels collapse in this way. They performed staged surgery in gastric band patients, and no leaks were observed.

Applications

The authors could not have a final judgment on the use of staple line reinforcement materials. The reasons for this is a small number of patients included in their study, retrospective and non-standardized study design, and no standardization of the materials used for reinforcement. There is a need for further studies on a larger patient population with use of standard reinforcement materials.

Terminology

Laparoscopic sleeve gastrectomy was performed through 5 trocars: One 15 mm trocar for stapler handle, one 10 mm trocar for the camera, and three 5 mm trocars for instruments and liver retractor. The greater omentum was separated from the greater curvature, starting 2 cm proximal to the pylorus with Harmonic (Ethicon, United States) or Ligasure (Covidien, United States). The stomach was divided approximately 3 cm proximal to the pylorus, targeting 1 cm lateral to the esophagogastric junction. Echelon 60 stapler (Ethicon-Mexico) and Covidien 60 (Covidien, United States) stapler were used to divide the stomach, and a thick tissue stapler was used in the antrum, a thin tissue stapler was used in the fundus, and a medium-thick tissue stapler was used in the tissues between. A 36 F calibration tube was used to determine the width of the remaining stomach.

Peer-review

The manuscript on staple line reinforcement is well-written and thus, of interest for the readers of the journal.

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CASE REPORT

Malignant melanoma in the pediatric population

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Abstract

Controversial pigmented lesions in children are a problem for pathologist, clinicians and families that are confronted with this dilemma. Some skin lesions in this population defy diagnosis with pathologists split between a benign diagnosis and a cancer diagnosis. Three cases of controversial pigmented lesions in the pediatric population are presented. Three patients underwent radical resection of the controversial pigmented lesion, intra-operative lymphatic mapping and sentinel lymph node (SLN) biopsy. Due to the low morbidity of the SLN procedure a case is made to perform lymphatic mapping in this clinical scenario. If the SLNs are negative, not much is lost except for the scar and this becomes another line of evidence that perhaps the original lesion was benign. If the SLN shows metastatic cells, then the original skin lesion must be malignant and the patient is offered stage Ⅲ recommendations that would include complete node dissections and adjuvant Interferon therapy. This strategy provides for adequate treatment of the worse-case scenario, that the skin lesion is malignant. The cost to the patient is a low morbidity procedure, the SLN biopsy.

Key words: Pediatric pigmented skin lesions; Sentinel lymph node biopsy; Melanoma

Core tip: The sentinel lymph node staging procedure can be used to treat effectively pediatric patients with ambiguous pigmented skin lesions.

Psaltis J, Reintgen E, Antar A, Giori M, Alvin L, Benjamin A, Budny B, Gianangelo T, Gruman A, Stamas A, Reintgen M, Giuliano R, Smith J, Reintgen D. Malignant melanoma in the pediatric population. *World J Surg Proced* 2015; 5(3): 229-234 Available from: URL: http://www.wjgnet.com/2219-2832/full/v5/i3/229.htm DOI: http://dx.doi.org/10.5412/wjsp.v5.i3.229

INTRODUCTION

Malignant melanomas are remarkably rare in children. Roughly 2% of melanomas occur in children under the age of 20 and approximately 0.4% of cases occur in prepubescent children[1]. In the United States, childhood and adolescent melanoma accounts for only 1.3% of all cases of melanoma[2]. Nevertheless, malignant melanoma (MM) is a potentially fatal disease, and it is critical to consider MM as a differential diagnosis of any pigmented lesion in a child. Clinically, childhood melanoma presents similarly to adult melanoma, and the use of the asymmetry, borders, color, diameter, and evolution of early diagnosis criteria can be used to screen children as well[3]. It has been shown that children diagnosed with melanoma have the same prognostic outcomes as their adult counterparts, while those diagnosed with melanoma before the age of 10 have a better outcome than those diagnosed between the ages of 10 and 20[3].

Nevi can be a common finding amongst children. Depending on the size of the lesion, a congenital melanocytic nevus is one of the risk factors for developing childhood melanoma due to the potential malignant transformation[4]. In dealing with pigmented lesions in this population of particular concern is the Spitz nevus, a benign lesion with morphological features similar to malignant melanoma, first described by Sophie Spitz in 1948[5-9]. Spitz stated that although this type of nevus was histologically malignant, it behaved in a benign manner[10]. As such, one of the biggest difficulties in diagnosing melanoma in children is differentiating a malignant melanoma from a benign Spitz Nevus[7,8]. Such lesions of uncertain biological potential are termed atypical spitzoid melanocytic neoplasms[7]. One study demonstrated that even amongst an experienced panel of pathologists, the variability in diagnosis was still substantial[9]. The differential diagnosis between a melanoma and a dysplastic Spitz nevus was still confusing, with the most common error being an interpretation of a benign lesion when it was actually malignant[11]. In addition pathologists are wary of saddling a child with a malignant diagnosis if indeed the skin lesion behaves in a benign fashion. Under-diagnosing or over-diagnosing controversial pigmented lesions in the pediatric population have repercussions either way. If under-diagnosed, the patient may not receive the standard definitive cancer treatment, such as a radical resection and a sentinel lymph node (SLN) biopsy. Although somewhat controversial, this primary treatment has been associated with a survival benefit in adults if indeed the SLN is found to contain metastatic disease. By under-treating children with MM, life-saving treatment may be denied[4,12-15]. If over-diagnosed, the patient may have procedures that are not necessary, resulting in increased morbidity. In addition the children are then labeled with a cancer diagnosis for the remainder of their lives. Patients mistakenly diagnosed with melanoma may exhibit fear of relapse and may not be able to obtain life or health insurance[14].

The misdiagnosis of melanoma is the second most common reason for cancer malpractice claims in the United States, second only to mistakes in breast cancer diagnosis[16]. All these claims are involved in the under-diagnosis of melanoma and physicians have always been willing to practice defensive medicine, despite increasing the costs of care, to guard against under-diagnosis and less than standard treatment.

In this report we describe three patients with controversial pigmented lesions in the pediatric population. The reports have complete pathology that helps to define the difficulty of the diagnosis, and the full spectrum of issues that arise in dealing with atypical pigmented skin lesions in this population is illustrated. A case is made for lymphatic mapping and SLN biopsy in this setting since the procedure exhibits low morbidity and finding metastatic cells in the SLN can help with the primary diagnosis. Finally a "standard of care" treatment is given for the metastatic disease.

CASE REPORT

Case 1

A previously healthy 2-year-old girl presented to outside physicians with an irregular mole on her right calf. A biopsy was performed and pathology showed an atypical nevus (Spitz nevus) *vs* melanoma. The patient underwent a radical resection of the primary melanoma and SLN biopsy. Pathology showed a 4.1 mm melanoma with clear margins at the primary site. However 2/3 right groin SLNs were positive for metastatic melanoma. The patient underwent a complete lymph node dissection (CLND) of her right groin and all further nodes were negative. The patient was referred to St. Jude's Children Hospital where she received 1 year of adjuvant Interferon therapy.

Case 2

This case involves an otherwise healthy 4-year-old white male who presented with a solid mass in his pinna of the right ear that appeared mostly subcutaneous. It had increased in size and became painful and irritating to the patient.

The patient underwent an excisional biopsy of the mass and pathology revealed features of an intradermal Spitz nevus, with low mitotic rate, nuclear atypia and incomplete maturation of melanocytes at the base of the lesion. Local pathology showed an atypical nevus with the proliferation of large melanocytes. The lesion was positive for Melan-A and S-100 and negative for cytokeratin AE1/AE3, desmin, ESA, GFAP, muscle specific actin and Ki-67. Ki-67 stain was positive and showed increased proliferative activity in the tumor cells. The case was then sent for consultation with the Mayo Clinic, which reported a non-ulcerated malignant spitzoid melanoma with a Breslow thickness of 3.6 mm. The lesion was analyzed at UCSF and pathology was interpreted as an atypical compound proliferation

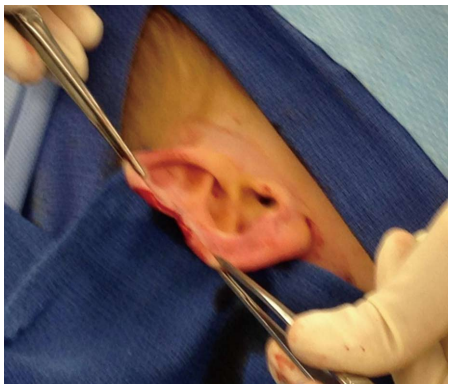

Figure 1 Intra-operative photograph of wedge resection of the right ear as a primary treatment of the melanoma from case 2.

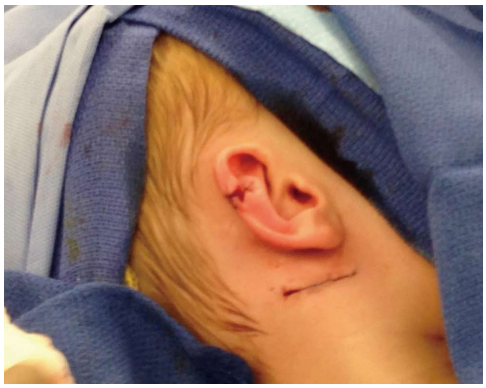

Figure 2 Intra-operative photograph of repair of wedge resection of right ear and sentinel lymph node biopsy of the right posterior triangle.

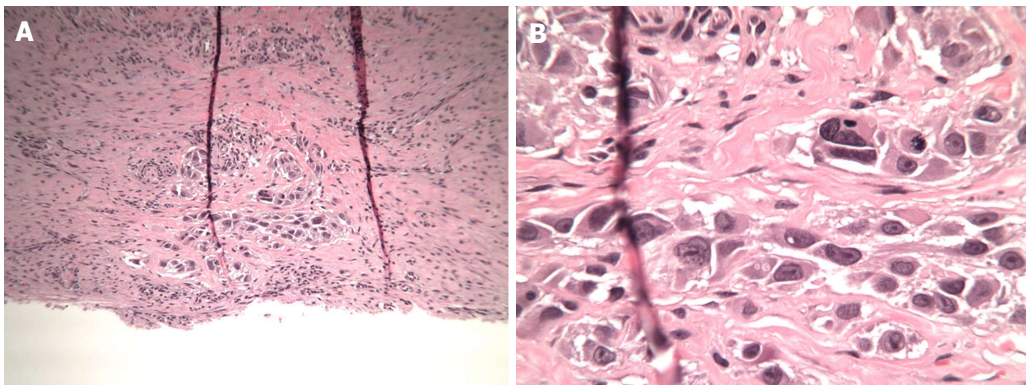

Figure 3 Photomicrography of the wedge resection of the right ear (H and E stain) (A) and higher magnification of malignant melanoma cells (B). In the deep dermis there were nests of large malignant appearing melanocytes with some mitotic figures.

of spitzoid melanocytes consistent with a spitzoid melanoma. Fluorescence *in situ* hybridization analysis of the tumor demonstrated gain in chromosomes 6p, 11q and 8q. These molecular findings favor interpretation as a spitzoid melanoma. Immunostaining for p16 demonstrated relative prominent positivity to verify no loss in chromosome 9p.

The patient was taken to the OR where, under general anesthesia, he underwent a radical resection of the melanoma of the right ear (wedge resection), intra-operative lymphatic mapping and SLN biopsy (Figures 1 and 2). Histologic examination revealed the SLNs to be negative for any evidence of metastatic disease. The wedge resection of the ear showed a nest of malignant appearing melanocytes deep within the dermis (Figure 3) and margins were free. The final diagnosis was residual malignant spitzoid melanoma with clear margins and negative SLNs.

Case 3

A previously healthy 12-year-old girl presented to her local dermatologist with an atypical nevus on her left forearm. A biopsy was performed that had the differential diagnosis of a dysplastic nevus *vs* melanoma (Figure 4A). The patient was treated under the melanoma protocol at USF with a radical resection of the primary site, intra-operative lymphatic mapping and SLN biopsy. Pathology showed clear margins from the primary site but the SLN was initially diagnosed as positive for micrometastatic disease (Figure 4B). A second opinion on the pathology showed a dysplastic nevus and benign nevus cells in the SLN (Figure 5). The patient is being observed.

The melanoma database at the University of South Florida (USF) and Florida Hospital - North Pinellas is a prospective database that is used for day-to-day clinical care and for clinical research. Under a USF IRB approval, all patients registered in the database are consented to have their data de-identified and used in future research projects. Case reports at USF do not require IRB approval.

DISCUSSION

Despite such difficulties in diagnosing malignant melanoma, it is important to avoid a delay in the diagnosis because early detection and aggressive treatment improves the patient' chances of survival[6,10,12]. The recommended course of action after detection and diagnosis of malignant melanoma is a radical resection of the primary site and if the melanoma is greater than 0.76 mm in thickness, a SLN biopsy. Complete lymph node dissections are reserved for those patients with a positive SLN[6-10]. The nosologic category of childhood

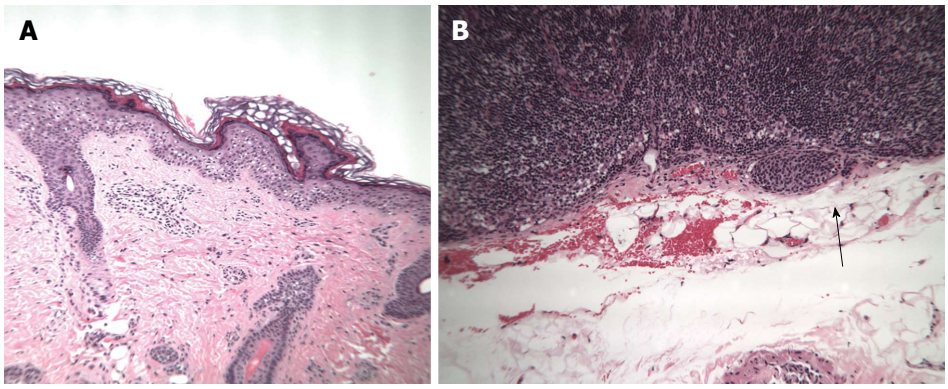

Figure 4 H and E stain. A: Photomicrograph of primary lesion removed from the left forearm from case 3; B: Photomicrograph of the sentinel lymph node from case 3 - H and E stain - showing subcapsular deposits of pigmented cells (arrow).

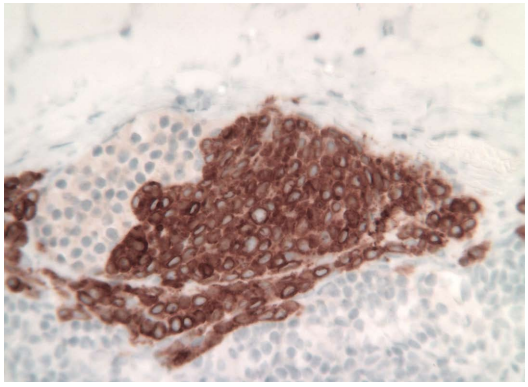

Figure 5 Immunostaining (MART-1) of the sentinel lymph node from case 3.

spitzoid melanoma refers to an emerging entity that seems distinct from conventional adult melanoma. Such tumors often lack BRAF mutations and are reported in the past literature under such flawed designations as malignant Spitz nevus. Findings to date suggest a small risk for metastases to regional lymph nodes with a low risk for widespread dissemination. It is thought that such lesions represent a low-grade form of melanoma[14]. Immunohistochemical differentiation with S-100 protein and HMB-45, although useful in identifying melanocytic cells, is not useful in distinguishing between malignant melanoma and Spitz Nevi, as both lesions stain positive with both markers[6,17]. A newer diagnostic assay using 5 markers (ARPC2, FN1, RGS1, SPP1 and WNT2) has been shown to be effective in differentiating between malignant melanoma and Spitz nevi[17]. Using an algorithm based on the pattern and intensity of these 5 markers with varying skin lesions, this multi-marker assay was able to correctly diagnose a high percentage of melanomas, Spitz nevi, dysplastic nevi, and other misdiagnosed lesions[17]. The multi-marker assay corrected three-quarters of cases in which incorrect pathological diagnosis were rendered, including melanomas initially diagnosed as nevi[17]. The test could be used to aid in the histologic diagnosis of melanoma, preventing errors in under diagnosis[17]. Regardless, it still remains difficult for clinicians and pathologists to differentiate between the two diagnoses (benign *vs* malignant), even for those who deal with such cases on a daily basis.

Performing a SLN biopsy after a wide local excision of the lesion can serve both a diagnostic and therapeutic purpose. Histopathological examination of the harvested SLNs can be used to support the diagnosis of the lesion as benign, helping to avoid incorrectly burdening a young patient with a lifelong diagnosis of malignancy as well as decrease the morbidity from subsequent and more invasive procedures such as a CLND. However, if the pathology reveals that the lesion is malignant, then the nodes can still serve a further diagnostic purpose by allowing clinicians to better stage and grade the harmful lesion, and determine if further surgery is indicated. In addition to these diagnostic benefits, the removal of the SLN can serve a therapeutic purpose by removing all disease, since in all stage Ⅲ patients (regional nodal disease), the metastatic disease is confined to the SLN 85% of the time. That is, the SLN acts as an effective trap in the regional basin to spread of the metastatic disease to higher non-SLNs[18].

Although controversy exists on whether performing the SLN procedure provides a survival benefit to the patient, we know that the best evidence of efficacy for the SLN procedure is displayed in those patients with documented stage Ⅲ disease, and a positive SLN[12-15].

Controversial pigmented lesions in children refer to the fact that some skin lesions in this population are problematic in trying to determine a benign pathology from a malignant. Many times multiple pathologists will render an opinion on the skin biopsy with some basing their benign reading on the prognosis for a Spitz nevus quoted in the literature for patients even though the cytology of the cells are malignant. Other pathologists prefer to interpret the skin histology based on what they observe with their microscopic examination. Newer genetic profiling of these skin lesions may be helpful in differentiating these lesions into appropriate benign *vs* malignant categories. However, clinicians are left with little guidance in trying to care for patients with this clinical scenario.

For the last 10 years the Cutaneous Oncology Pro-

gram at USF/FH-N Pinellas has implemented a protocol for dealing with these difficult cases. Since the lymphatic mapping and SLN procedure is a low morbidity procedure, pediatric patients with controversial pigmented lesions are treated as if they carry the melanoma diagnosis, and are considered candidates for a radical resection of the primary melanoma to obtain clear margins and SLN biopsy for nodal staging. This protocol can accomplish the following: (1) If the SLN is negative for metastases, then that data would be considered a line of evidence that the skin lesion is benign and the patient has a good prognosis; (2) If the SLN is positive for metastases, this is a good indication that the original skin lesion is malignant making the patient eligible for CLNDs and adjuvant Interferon therapy. Case 3 illustrates the fact that benign nevus cell rests in the SLN must be differentiated from metastatic melanoma cells in the SLN; and (3) Patients will not be under treated if indeed they have the malignant phenotype. Likewise any over treatment of the patients is associated with a low morbidity operation, the SLN biopsy.

Even though malignant melanoma diagnoses in children are rare, we must be cognizant of such a possibility because early diagnosis is crucial to patient outcome. Despite new methods used to distinguish nevi and melanoma from each other, a certain protocol system, such as that implemented at the Cutaneous Oncology Program at USF/FH-N Pinellas, is crucial in assuring the appropriate patient treatment.

As recurrences and melanoma-related death inevitably remain a possibility years after patient diagnosis, it is necessary for long-term patient follow-up, including full-body skin examination in this population for the remainder of their lives[3,19].

COMMENTS

Case characteristics

Pediatric patients with controversial pigmented skin lesions are problematic in treatment and for assigning prognosis.

Clinical diagnosis

Three patients are described with skin lesions where the histologic diagnosis of benign or malignant is in doubt.

Differential diagnosis

The differential diagnosis is between a benign dysplastic nevus and a malignant melanoma.

Laboratory diagnosis

Histologic examination using routine hematoxolin and eosin stain and immunohistochemistry with S-100 and HMB-45 stains was performed.

Imaging diagnosis

Pre-operative lymphoscintigraphy was performed to identify all nodal basins at risk for metastases.

Pathological diagnosis

The primary site differential was between dysplastic nevi *vs* malignant melanoma. The differential diagnosis in the sentinel lymph nodes (SLNs) was metastatic melanoma *vs* benign nevus cells.

Treatment

All 3 patients underwent radical resection of their primary sites and SLN biopsy. The patient with a positive SLN was administered adjuvant Interferon alfa-2b for 1 year.

Term explanation

The SLNs are all nodes in the regional basin that have a direct connection by way of afferent lymphatics to the primary melanoma site. SLNs are identified with either a blue dye or radiocolloid mapping technique.

Experiences and lessons

Since the lymphatic mapping and SLN procedure is a low morbidity procedure, pediatric patients with controversial pigmented lesions are treated as if they carry the melanoma diagnosis, and are considered candidates for a radical resection of the primary melanoma to obtain clear margins and SLN biopsy for nodal staging.

Peer-review

This article includes valuable information regarding the complexities of distinguishing benign nevi from malignant melanoma in the pediatric population.

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