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EDITORIAL

- 5796 Induced pluripotent stem cells as an innovative model to study drug induced pancreatitis
Genova E, Stocco G, Decorti G

OPINION REVIEW

- 5803 Screening for nonalcoholic fatty liver disease-when, who and how?
Dietrich CG, Rau M, Geier A

REVIEW

- 5822 Environmental perspectives of COVID-19 outbreaks: A review
Samanta P, Ghosh AR
- 5851 Pancreatic cancer in 2021: What you need to know to win
Tonini V, Zanni M
- 5890 Gastrinoma and Zollinger Ellison syndrome: A roadmap for the management between new and old therapies
Rossi RE, Elvevi A, Citterio D, Coppa J, Invernizzi P, Mazzaferro V, Massironi S

MINIREVIEWS

- 5908 Optical diagnosis of colorectal polyps using convolutional neural networks
Kader R, Hadjinicolaou AV, Georgiades F, Stoyanov D, Lovat LB
- 5919 Liver-spleen axis dysfunction in COVID-19
Cococcia S, Lenti MV, Santacroce G, Achilli G, Borrelli de Andreis F, Di Sabatino A
- 5932 Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment
Diamantidis MD, Papaioannou M, Hatjiharissi E

ORIGINAL ARTICLE**Basic Study**

- 5946 Proteomics identifies a novel role of fibrinogen-like protein 1 in Crohn's disease
Sun XL, Qiao LC, Gong J, Wen K, Xu ZZ, Yang BL

Retrospective Study

- 5958 Effectiveness and safety of over-the-scope clip in closing perforations after duodenal surgery
Wang ZZ, Zhou XB, Wang Y, Mao XL, Ye LP, Yan LL, Chen YH, Song YQ, Cai Y, Xu SW, Li SW

- 5967** Hepatic perivascular epithelioid cell tumor: Clinicopathological analysis of 26 cases with emphasis on disease management and prognosis

Zhang S, Yang PP, Huang YC, Chen HC, Chen DL, Yan WT, Yang NN, Li Y, Li N, Feng ZZ

- 5978** Diagnosis of focal liver lesions with deep learning-based multi-channel analysis of hepatocyte-specific contrast-enhanced magnetic resonance imaging

Stollmayer R, Budai BK, Tóth A, Kalina I, Hartmann E, Szoldán P, Bérczi V, Maurovich-Horvat P, Kaposi PN

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Pancreatic cancer in 2021: What you need to know to win

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Abstract

Pancreatic cancer is one of the solid tumors with the worst prognosis. Five-year survival rate is less than 10%. Surgical resection is the only potentially curative treatment, but the tumor is often diagnosed at an advanced stage of the disease and surgery could be performed in a very limited number of patients. Moreover, surgery is still associated with high post-operative morbidity, while other therapies still offer very disappointing results. This article reviews every aspect of pancreatic cancer, focusing on the elements that can improve prognosis. It was written with the aim of describing everything you need to know in 2021 in order to face this difficult challenge.

Key Words: Pancreatic cancer treatment; Advanced pancreatic cancer; Metastatic pancreatic cancer; Pancreatic cancer surgery; Pancreatic cancer chemotherapy; Pancreatic cancer screening

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Core Tip: Pancreatic cancer is a very dangerous enemy and the results are still very unsatisfactory. But we have not given up. Research is running fast on many paths, without losing its enthusiasm. The number of articles published on this subject in the last two years is impressive. I have tried to summarize all the most significant data from the different lines of research, ranging from screening and early diagnosis to new developments in surgery and associated therapies. I hope I have succeeded in the task of describing as comprehensively as possible the most promising fields of research available to us today, in order to achieve the improved results we desire.

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INTRODUCTION

Pancreatic cancer is currently the seventh leading cause of cancer death worldwide and the fourth following lung, colorectal and breast cancers in the United States and Europe. It will become the third by 2030. It is an age-related neoplasm and this trend is similar between males and females. In particular the number of both deaths and incident cases peaked at the ages of 65-69 years in males, whereas the peak in females was observed at the ages of 75-79 years[1-4]. The commonly used term "pancreatic cancer" usually refers to ductal adenocarcinoma (PDAC), which represents 85% of all pancreatic tumor[4]. Complete surgical resection significantly prolongs survival, but the tumor is often diagnosed at an advanced stage and only a small percentage of patients are therefore candidates for surgery. Moreover, surgery is still associated with high post-operative morbidity. Despite ongoing developments, PDAC remains one of the most difficult tumors to treat, and the five-year survival rate is less than 10%[5]. There are four fundamental challenges that underlie the high mortality. First, the retroperitoneal location of the pancreas, deep in the abdomen, protects growing tumors from detection. The symptoms are late and therefore the diagnosis is made when the tumor is already in an advanced stage. Second, PDAC has an aggressive biology characterized by early metastasis and 50% of patients has metastatic disease at presentation. In addition, a large number of patients undergoing surgery develop metastases within 4 years. This suggests the presence of micrometastasis in apparently localized cases[6]. Third, pancreatic cancer dramatically weakens patients, limiting their ability to withstand aggressive treatments. Finally, it shows resistance to many antineoplastic therapies[7,8]. Advances in prevention, screening, early detection, and therapy, particularly on new frontiers, are essential to improve outcomes. This article has been written with the aim of describing everything you need to know in 2021 in order to face this difficult challenge.

NON-FAMILIAL RISK FACTORS AND PREVENTION

Identification of risk factors, high-risk populations and early detection markers is the first and crucial step to change the pancreatic cancer horizon[9]. PDAC incidence rates are nearly four times higher in high-income countries such as the United States and Western European countries than in middle- and low-income countries[3]. The different incidence seems to be related with different lifestyles.

Obesity, smoking, alcohol consumption and type 2 diabetes are considered non-familial risk factors for pancreatic cancer. Chronic pancreatitis, cystic fibrosis and intraductal papillary mucinous neoplasm (IPMN) should also be considered. An increased risk of pancreatic cancer has been observed following gastrectomy[10-17].

One-third of all cancers could have been prevented through lifestyle correction[18]. A 2020 European prospective study (EPIC) evaluated the association between the healthy lifestyle index score and PDAC[19-22]. Healthy lifestyle habits were inversely related to the risk of PDAC. Adherence to healthy behaviors, corresponding to a three-point increase in the score, was associated with a 16%-23% lower risk. The result summarizes many previous studies[23-29] and support the adoption of healthy lifestyles in PDAC prevention.

A recent nutrigenomic study has highlighted nutrients capable of preventing cancer through epigenetic modifications. An optimal diet should include omega 3 fatty acids, polyphenols, folic acid, selenium and zinc. Particularly important for PDAC prevention could be the epigallocatechin, a polyphenol from tea and green tea[30,31].

Data linking type 2 diabetes with pancreatic cancer suggest that the new onset of diabetes in a lean older adult should prompt consideration of PDAC. This is even more valid if new-onset diabetes is associated with unintentional weight loss[32-34]. A Mayo Clinic study evaluated the use of computed tomography (CT) at the time of diabetes diagnosis in otherwise asymptomatic patients. A higher likelihood of showing potentially resectable tumors was observed compared with scans performed six months later[32]. However, CT screening of all elderly subjects with new-onset

diabetes is not feasible[33]. With the identification of these characteristics that differentiate pancreatic cancer-associated diabetes from other cases of new-onset diabetes, perhaps the guidelines will update[35].

HEREDITARY RISKS FACTORS

PDAC can be hereditary. There are two categories of inherited risk for PDAC: Genetic syndromes (20% of cases) and familial pancreatic cancer (80%). Familial pancreatic cancer is defined as a predisposition that is based on familial clustering in families in which there is at least one pair of first-degree relative (FDR) relatives with PDAC in the absence of a known genetic syndrome. Genetic syndromes that predispose to pancreatic cancer are listed in Table 1. Table 1 also shows in parentheses the frequencies of mutated genes in PDAC patients[36-42].

Knowledge of inherited risk factors is important because it allows us an effective stratification and management of patients. According to American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines, all patients diagnosed with PDAC should be evaluated to understand if there is a risk of familial predisposition to cancer. All patients should undergo risk assessment for syndromes associated with an increased risk of PDAC. Germline genetic testing is recommended for patients with PDAC and an unremarkable family history[43,44].

SCREENING

Screening aims to detect preinvasive lesions (IPMNs and pancreatic intraepithelial neoplasias) with high-grade neoplastic changes and early invasive tumors that are more amenable to potentially curative resection[45-49].

Candidates for screening

(1) Patients with Peutz-Jeghers syndrome or CDKN2A mutation, regardless of family history; (2) BRCA2 mutation with at least one affected FDR or at least two affected relatives of any degree; (3) BRCA1, partner and localizer of BRCA2 (PALB2), ataxia-telangiectasia mutated (ATM), and Lynch syndrome mutation carriers with one or more affected FDRs; (4) Hereditary pancreatitis with a PRSS1 mutation; and (5) Regardless of gene mutation status: (a) At least three affected relatives on the same side of the family, of whom at least one is an FDR of the individual being considered for surveillance; (b) At least two affected relatives who are FDRs of each other, of whom at least one is an FDR of the individual being considered for surveillance; and (c) At least two affected relatives on the same side of the family, of whom at least one is an FDR of the individual being considered for surveillance.

General population-based screening for average-risk patients is not recommended [33] because the average lifetime risk for developing PDAC is too low[49].

Screening modality

The current recommendation provides for the execution of endoscopic ultrasonography (EUS) or magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP). It has been demonstrated that they detect more lesion as compared with CT scan[50]. Screening is recommended at age 50 years or 10 years younger than the youngest relative with PDAC in familial pancreatic cancer relatives. In other cases, screening is carried out between 35 and 45 years. For patients with a normal pancreas on imaging, repeat the procedure every year alternating EUS and MRCP. The age for stopping screening should be individualized based on each patient's medical status, life expectancy, and preferences.

SURGICAL RESECTION FOR IPMNS AND OTHER CYSTIC LESIONS

Surgical resection is indicated in patients with any of the following[45]: (1) Solid pancreatic lesion ≥ 5 mm of indeterminate pathology or if additional evaluation does not yield a definitive preoperative diagnosis; (2) Any positive fine-needle aspiration (FNA) result, except for a pancreatic neuroendocrine tumor; (3) Main-duct IPMNs with any one of the following: (a) Main pancreatic duct dilation of ≥ 10 mm; (b) Main pancreatic duct stricture; or (c) Mural nodules; (4) Branch duct IPMNs (BD-IPMNs)

Table 1 Genetic syndromes predisposing to pancreatic cancer (the frequency of mutated genes among patients with pancreatic ductal adenocarcinoma is indicated in brackets)

Genetic syndrome	Mutated genes
Hereditary breast/ovarian cancer syndrome[36,37]	<i>BRCA1</i> (0.7%), <i>BRCA2</i> (1.4%), <i>PALB2</i> (1%)
Familial atypical multiple mole melanoma syndrome[38]	<i>CDKN2A</i> (0.7%)
Peutz-Jeghers syndrome[39]	<i>STK11</i>
Familial adenomatous polyposis	<i>APC</i> (0.4%)
Lynch syndrome[40]	<i>MLH1</i> , <i>MSH2</i> (0.4%), <i>PMS2</i> (0.3%)
Hereditary pancreatitis[41]	<i>PRSS1</i> , <i>SPINK1</i>
Ataxia telangiectasia[42]	<i>ATM</i> (1.4%)
Li-Fraumeni syndrome[42]	<i>P53</i> (0.4%)

with any one of the following: (a) Rapid growth (> 5 mm over six months); (b) Mural nodules or an enhancing solid component; (c) Abrupt main pancreatic duct caliber change with distal atrophy (even if no mass is visible); (d) Main pancreatic duct dilation of ≥ 10 mm; (e) Positive cytology; or (f) Associated symptoms of pancreatitis, jaundice, or pancreatic-type pain; or (5) Asymptomatic main pancreatic duct stricture with an associated suspicious mass.

For patients who do not meet these criteria for surgery, repeat imaging in three months if worrisome features are present[47,51]. Worrisome features include the following: (1) Solid lesion with main pancreatic duct size of 5 mm to 9 mm in diameter; (2) Main pancreatic duct stricture and/or dilation ≥ 6 mm of unknown etiology without an associated mass; and (3) Solid lesion < 5 mm of uncertain significance.

Repeat imaging in six months is recommended for patients who have the following imaging abnormalities: (1) Cystic lesion (presumed BD-IPMN) ≥ 3 cm in size; (2) Cystic lesion with associated main pancreatic duct 5 mm to 9 mm; (3) Cystic lesion associated with lymphadenopathy; (4) Cyst growth rate of ≥ 5 mm in two years; and (5) Increased serum carbohydrate antigen 19-9 (CA 19-9).

Individuals without worrisome features of malignancy should undergo repeat imaging in 12 mo[47,51].

Screening/surveillance should be continued until the patient is no longer a surgical candidate.

A 2020 paper analyzed the benefits of screening. Nine out of 10 screen-detected PDAC were resectable, with a three-year survival of 85%, compared with 25% in PDAC detected outside surveillance. With continued follow-up of patients with resectable PDAC, the five-year overall survival (OS) rate was 60%[49].

BIOMARKERS AND EARLY DETECTION

Different biomarkers are being evaluated to improve early diagnosis of tumor not detectable by imaging and to differentiate cancer and high-grade dysplasia from benign disease[52].

Blood tests

The most useful serum tumor marker for PDAC is CA 19-9. It is recommended adding this test when there are worrisome features on abdominal imaging. The sensitivity and the specificity of elevated CA 19-9 to detect PDAC are 79% and 82%, respectively[53-55]. It becomes more precise when used in combination with CA 125[56,57]. Other carbohydrate markers, such as CA 50, CA 72.4 and CA 242, were extensively analyzed in PDAC patients. Although they exhibited less sensitivity than CA 19-9 for the diagnosis, they improved specificity[58-61]. Satake and Takeuchi[62] also studied SPan-1 and DUPAN-2. SPan-1 has a high sensitivity for PDAC (81.4%), but the specificity (67.5%) and diagnostic accuracy (71%) are lower than those of CA19-9. SPan-1 may be considered as an additional useful serum marker, but it does not significantly improve the diagnostic accuracy obtained with CA 19-9. In contrast, DUPAN-2 has a high specificity (85.3%) and low sensitivity (47.7%). Furthermore, it seems that serum levels of DUPAN-2 are influenced by liver function. SPan-1 and DUPAN-2 unfortunately have not yet shown the sensitivity and specificity needed to

be used for early detection[62,63].

A huge step forward in the early detection of pancreatic cancer could come from studying cell-free DNA (cfDNA), which consists of circulating double-stranded DNA molecules that can be found in plasma or blood serum. From the analysis of these molecules, it is possible to understand if we are in the presence of a tumor DNA and to go back to the tissue of origin. By analyzing the methylation status of two genes in cfDNA, ADAMTS1 and BNC1, early stage cancer can be identified with a sensitivity of 94.8% and a specificity of 91.6%[64].

Innovative discoveries have also been made in the field of RNA. Abnormal microRNA expressions are potential diagnostic markers for several cancers, including PDAC. Multiple microRNA tests performed in combination with CA 19-9 can improve diagnostic accuracy, particularly miR-216[65-69]. Permutth *et al*[70] demonstrated that a combination of eight lncRNAs helps in the differential diagnosis between malignant and non-malignant IPMNs. Furthermore, three lncRNAs (HAND2-AS1, CTD-2033D15.2, and lncRNA-TGF) could be exploited as early diagnostic biomarkers of IPMN[71,72].

Pancreatic juice and pancreatic cyst fluid

Pancreatic juice collected at the time of ERCP and cyst fluid obtained by EUS-guided FNA can be analyzed for molecular markers. These procedures also have broad potential in terms of early diagnosis of PDAC. Next-generation sequencing can be performed at low cost to detect low-frequency mutations. Potential markers include mutant GNAS (specific for IPMNs) and mutant KRAS. TP53, SMAD4, PIK3CA, PTEN, and AKT1 mutants are also useful as they correlate with IPMN-associated tumors[73-75]. According to Suenaga *et al*[76], a pancreatic juice collection, to ensure optimal yield of mutations for pancreatic screening assays, should be performed 10 min after secretin administration. The authors detected 40 patients with KRAS mutations in pancreatic juice out of 45 undergoing surveillance with EUS, reconfirming the usefulness of these analysis[76].

There are many other biomarkers that are currently being validated for clinical use, such as mucins (MUC). Normal pancreatic ductal epithelium expresses low levels of MUC, while an upregulation of MUC occurs in BD-IPMNs and more pronounced changes in expression in PDAC. Normal pancreatic ductal epithelium expresses low levels of MUC, while upregulation of MUC occurs in BD-IPMN and PDAC[77-83]. The analysis of mucin changes in the fluid of pancreatic cysts allows us to differentiate mucinous from non-mucinous pancreatic cysts with high sensitivity and specificity and to diagnose PDACs associated with IPMN at an early stage[84]. MUC4 and MUC16 have been reported to be 100% specific for PDAC, while associated with sensitivities of 63% and 67%, respectively[85].

Interesting data were reported about interleukins (IL). Higher concentrations of IL-1b, IL-5, and IL-8 have been identified in cystic lesions with high grade dysplasia or malignancy[86]. IL-1b is a potentially useful factor in differentiating high-risk from low-risk pancreatic cysts.

The Das-1 monoclonal antibody is also capable of detecting pancreatic cysts at risk of malignancy with high levels of sensitivity (88%) and specificity (98%)[87,88]. Das-1, IL and MUC could be used in conjunction with clinical guidelines to identify patients at risk for malignancy.

Saliva

Saliva is a suitable substance for screening because it is obtained in a simple and noninvasive manner. In addition, salivary mRNA is relatively stable and informative for disease diagnosis, including cancer. Zhang *et al*[89] identified 7 up-regulated genes (MBD3L2, KRAS, STIM2, DMXL2, ACRV1, DMD, and CABLES1) and 5 down-regulated genes (TK2, GLTSCR2, CDKL3, TPT1, and DPM1) in subjects with PDAC compared with healthy controls or those with chronic pancreatitis. A combination of 4 mRNAs (MBD3L2, KRAS, ACRV1, and DPM1) can discriminate diseased patients from healthy ones with sensitivity and specificity over 90%[89]. Xie *et al*[90] worked on miR-3679-5p and miR-940. The former is down-regulated, while the latter is up-regulated in PDAC patients compared to controls. The combination of the two miRNAs identifies diseased subjects with sensitivity and specificity of 70%. The same group evaluated the expression of salivary long non-coding RNAs (lincRNAs). They identified HOTAIR and PV1T as significantly up-regulated lincRNAs in the PDAC group compared with controls and benign pancreatic tumors. The combination of salivary HOTAIR and PVT1 differentiated PDAC from healthy controls with a sensitivity of 78.2% and specificity of 90.9% and PDAC from benign tumors with a sensitivity of 81.8% and specificity of 95%[90,91]. Another important mRNA studied in

serum, urine, and saliva is MIR1246. Salivary expression of miR-1246 is related to serum CA19-9 levels[92]. Significantly higher expression of MIR1246 in serum and urine was observed in patients with cancer compared with healthy controls. Ishige *et al* [93] observed an AUC for MIR1246 in serum of 0.87 (sensitivity, 92.3%; specificity, 73.3%), for MIR1246 in urine of 0.90 (sensitivity, 90.2%; specificity, 83.3%). Combining the expression of MIR1246 in serum and urine resulted in a sensitivity of 85%. These results indicate that MIR246 may be a useful diagnostic biomarker for pancreatic cancer. The accuracy further increases if we consider miR-1246 and miR-4644 simultaneously[92].

Urine

Several biomarkers have also been evaluated in urine. Radon *et al*[94] used three protein biomarkers (REG1A, TFF1 and LYVE1) to form a powerful urinary panel that can detect patients with stages I-II PDAC, with over 90% accuracy. Brezgyte *et al*[95] found four miRNAs (miR-143, miR-204 and miR-223) in significantly higher amounts and one miRNA (miR-30e) in lower amounts in the urine of PDAC Stage I patients compared to the healthy population. These miRNAs (except for miR-204) also showed a decreased expression in Stage II-IV compared to Stage I[95]. However, more studies are needed to validate the clinical utility of these biomarkers.

CLINICAL FEATURES

The presenting symptoms in patients with PDAC varies according to location. Tumors in the body and tail present with pain and weight loss, while tumor of the head cause jaundice and steatorrhea[96]. Pain associated with PDAC is usually insidious, visceral, generally epigastric, radiating to the sides or straight through to the back. It is worse by eating or lying supine at night. Rarely, it develops acutely on account of acute pancreatitis due to tumoral occlusion of the main pancreatic duct[97]. Pancreatic cancer may result in an onset of diabetes mellitus[98,99]. The hypercoagulable state that accompanies PDAC can result in Trousseau syndrome, which consists of superficial, sometimes migratory thrombophlebitis[100]. Thromboembolic complications occur more commonly in patients with tumors arising in the tail or body of the pancreas[101]. Skin manifestations could occur as paraneoplastic phenomena[102]. Rarely, erythematous subcutaneous areas of nodular fat necrosis (pancreatic panniculitis), typically located on the legs, may be evident. It is more frequent in patients with the acinar cell variant of PDAC. It is not pathognomonic for an PDAC, because it has also been described in associated with pancreatic neuroendocrine tumors, IPMNs and chronic pancreatitis[103].

When assessing symptoms, it should be borne in mind that PDAC tends to infiltrate nearby organs and structures and to give distant metastases very early. Local extension typically involves adjacent structures, such as the duodenum, the portal vein (PV), or the superior mesenteric vessels. PDAC also show a striking tendency toward perineural invasion, both within and beyond the pancreas. The difficulty in achieving a wide resection margin due to the proximity to the vessels accounts for the fact that the retroperitoneal tissue behind the head of the pancreas represents the most common site of disease recurrence. Sometimes the tumor extends to the spleen, adrenal glands, vertebral column, transverse colon, and/or stomach. In these cases, tumors are not resectable. Tumor may metastasize to regional peripancreatic lymph nodes or less often to distant lymph node, peri-gastric, mesenteric, omental or porta-hepatic nodes. Distant metastasis may affect the liver, peritoneum, lungs, and less frequently, bone. Signs of advanced, incurable disease include an abdominal mass, ascites, Virchow's node, Sister Mary Joseph's node or a palpable rectal shelf. Pancreatic cancer is the origin of a cutaneous metastasis to the umbilicus in 7% to 9% of cases[104].

DIAGNOSIS

CT

CT is considered the gold standard for pancreatic cancer's diagnosis. Protocol pancreatic CT is performed for evaluation of suspected PDAC or if a routine CT scan was not sufficient for initial staging[105,106]. This protocol consists of evaluating the patient at different stages of contrast injection. The arterial phase provides excellent opacification of the celiac axis, superior mesenteric artery (SMA), and peripancreatic

arteries. An attenuation difference between tumor and normal pancreas is best achieved after peak enhancement of the aorta in the arterial phase but before the one of the liver, in the portal venous phase. This is sometimes termed the "pancreatic phase". The portal venous phase provides better enhancement of the superior mesenteric vein (SMV), splenic and PVs. In addition, peak hepatic enhancement, which optimizes the detection of hepatic metastases, also occurs in the portal venous phase[107,108].

The typical CT appearance of a PDAC is an ill-defined hypoattenuating mass within the pancreas. Smaller lesions may be iso-attenuating, making difficult their identification[109]. Secondary signs of PDAC include a dilatation of the pancreatic duct or common bile duct, parenchymal atrophy, and contour abnormalities. Dilatation of both the pancreatic duct and the common bile duct, commonly referred to as the "double duct sign" is not diagnostic for a pancreatic head malignancy[110]. Routine preoperative CT helps to identify hepatic vascular anatomy and prepares the surgeon for any potential vascular anomalies. It can detect hemodynamically significant arterial stenosis[111]. The contrast-enhanced CT scan is the best technique for PDAC staging [112] and it is essential to detect vascular invasion. CT criteria for vascular invasion include arterial embedment in the tumor mass or venous obliteration, tumor involvement exceeding one-half the circumference of the vessel, vessel wall irregularity, vessel caliber stenosis, or a "teardrop" sign of the SMV[113]. Classic CT criteria for vascular involvement are not reliable in patients who have undergone neoadjuvant therapy with a highly active chemotherapy combination such as mFOLFIRINOX (mFFX). In such cases, surgical exploration may be the only method to assess resectability[114].

MRI

Contrast-enhanced MRI of the pancreas may be useful in staging patients at initial presentation. MRI is the best technique for detection of small liver metastases[115]. The importance of MRI also lies in the ability to diagnose pancreatic cancer by identifying changes in the body that indicate systemic effects of PDAC. It has been well recognized that anorexia, sarcopenia, and weight loss are hallmarks of PDAC. Consequently, it can be used to measure adipose and muscle mass in high-risk populations to identify early disease[116-118].

EUS

EUS is considered the most sensitive method to detect early neoplasia in the pancreas. PDAC on EUS appears as a hypoechoic mass, typically with dilation of the proximal pancreatic duct and the border of the lesion may have an irregular contour. This is the best accurate technique for local T and N staging, and for predicting vascular invasion. However, EUS is inferior to CT for evaluation of distant metastases. In addition, the specificity of EUS for excluding vascular invasion in small tumors is limited, particularly when inflammatory changes are present[119].

EUS is mainly used as part of the workup to obtain fine needle aspiration or biopsy material in patients suspected of having a PDAC[120]. EUS is not readily accessible and as a result is considered a complementary modality to the pancreatic protocol CT. Emerging area for endoscopic ultrasound includes the incorporation of elastography. Elastography shows significantly lower elasticity values for PDAC than for normal pancreatic tissue[121]. Incorporation of elastography in the evaluation of solid pancreatic lesions improves diagnostic accuracy[122,123].

Endoscopic retrograde cholangiopancreatography

A meta-analysis demonstrated a 92% sensitivity and 96% specificity of endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of PDAC[124]. Findings suggestive of a malignant tumor of the pancreatic head include stenosis or obstruction of the common and pancreatic bile ducts (the "double duct" sign), a pancreatic duct stenosis greater than 1 cm in length, and pancreatic duct obstruction. In addition, ERCP provides an opportunity to collect tissue samples for cytohistologic analysis [124].

Some early-stage pancreatic tumors are not detected by CT, MRI, or EUS. Especially for carcinoma in situ, localized stenosis of the main pancreatic duct is often the only imaging finding. Pancreatic duct imaging evaluation by ERCP and subsequent pancreatic juice cytology are critical for diagnosis.

On the other hand, ERCP is an invasive procedure that can cause acute pancreatitis, bleeding, and cholangitis. Consequently, it has purely therapeutic value for patients with cholestasis due to tumor obstruction of the biliary system and require placement of a biliary stent[125].

Positron emission tomography

The role of positron emission tomography (PET) is limited for PDAC due to the high number of false positives and false negatives[126]. However, the degree of fluorodeoxyglucose (FDG) uptake correlates with histopathology, aggressiveness, and metastatic potential[127,128]. According to a meta-analysis, PET/CT is more accurate than CT in detecting distant metastases. Preoperatively, it may therefore be useful in avoiding unnecessary resection if unexpected metastases are found[129,130]. After treatment, FDG-PET is instead used to detect residual or recurrent cancer. It can also be applied to assess and monitor response to therapy in unresectable or metastatic disease[127,131].

Other molecular imaging agents including overexpressed proteins, signaling pathways, and tumor stroma may also be used[132]. Among these, promising results appear to involve ⁶⁸Ga-cicratide, an integrin $\alpha\beta 6$ -specific radiotracer, which has favorable pharmacokinetics and is capable of detecting pancreatic cancer lesions and monitoring response to therapy[133]. Another molecular imaging method that is of interest for early detection is hyperpolarized MRI. It can identify metabolic aberrations in the pancreas that indicate preneoplasia[134].

Staging laparoscopy

Sub-centimeter metastases of the liver or peritoneum that are rarely visible by CT, MRI or PET may be visualized laparoscopically. Up to one-third of patients thought to be resectable by imaging will be found to be unresectable based upon laparoscopic findings[135,136].

Some experts suggest a selective approach to staging laparoscopy, limiting the procedure to those with the highest likelihood of occult metastatic disease[137,138]. First, this includes tumors of the body or tail of the pancreas that appear potentially resectable by CT scan. Second, it includes large (> 3 cm) primary tumors and patients with a high initial CA 19-9 level (> 100 units/mL)[139].

Biopsy

Biopsy of a pancreatic mass can be performed either percutaneously or *via* EUS. EUS-guided FNA is the best modality for obtaining a tissue diagnosis. EUS-FNA is a safe method with a 0.98% morbidity and a 0.02% mortality. Although the most common adverse events of EUS-FNA include pancreatitis and postprocedural pain, there is also some concern regarding tumor cell seeding[140]. According to a study by Yane *et al* [141] the cumulative needle tract seeding rate at five years was 3.8%. However the preoperative EUS-FNA has no negative effect on recurrence-free survival and OS.

In many cases, the diagnosis will not yet be histologically confirmed. Once PDAC is suspected on imaging studies, the next step is generally a staging evaluation rather than biopsy. Patients who are fit for major surgery and who appear to have potentially resectable PDAC, they do not necessarily need a biopsy before surgery. Biopsy could be indicated if there is evidence of systemic spread or local evidence of unresectability on staging studies. It is also indicated if the patient is unfit for major surgery or if other diagnoses need to be excluded[142,143].

Pancreatic incidentaloma

A 2014 systematic review[144] evaluated 5 studies enrolling patients with incidentalomas and concluded that most solid lesions are malignant. Histologic definition of a solid lesion of the pancreas should be the first option, as opposed to radiologic monitoring alone. It is important to avoid operating on benign solid lesions such as chronic focal pancreatitis or autoimmune pancreatitis.

In case of cystic lesion, surgery is the first option for cystadenomamucinous and IPMN with high-risk stigmata. A recent review defined high-risk stigmata as the presence of obstructive jaundice, vascularized mural nodules ≥ 5 mm, main duct diameter ≥ 10 mm[145].

STAGING

The goal of the staging workup is to delineate the extent of disease spread and to identify patients who are eligible for resection with curative intent. Patients with PDAC can be staged according to the eighth edition of TNM system of American Joint Committee on Cancer (AJCC). However, most clinicians use a four-tiered staging system including resectable, borderline resectable, locally advanced (LA), and

metastatic cancer[146,147] (Table 2). In 2017, a classification was published, by the International Association of Pancreatology, which redefines the concept of resectability in relation to biological risk and patient conditions[148]. Table 3 summarizes the different resectability criteria assumed by the different scientific societies.

SURGERY

Surgical resection is the only potentially curative treatment. Unfortunately, PDAC is often diagnosed at an advanced stage and radical surgery could be performed in a very limited number of patients. The surgical interventions that can be performed are different depending on the tumour location and extension. In all cases the operation involves the removal of the tumour with free margins and at least twelve lymph nodes, which are necessary for staging. Tumors of the head require more complex operations, which still have a high operative morbidity. In high-frequency surgical centres mortality after pancreatoduodenectomy (PD) is now less than 2%, but post-operative morbidity remains high, 30%-50%. Anastomotic dehiscences, are the most serious post-operative complication. They are difficult to manage and are unfortunately associated with a still high mortality rate. Tumors of the tail and body require easier operations than head tumors, with a low operative morbidity and mortality. Unfortunately, because of their late symptomatology, they are more frequently unresectable.

Pancreaticoduodenectomy

PD is the classic operation performed for pancreatic tumors of the head or uncinate process. Conventional pancreaticoduodenectomy involves removal of the pancreatic head, duodenum, first 15 cm of the jejunum, common bile duct, gallbladder, and a partial gastrectomy. It is a complex procedure and patients may experience several complications. These complications could be intra-operative or post-operative[149, 150].

The most important intraoperative complication of PD is bleeding. Most patients undergoing PD for PDAC have an obstructive jaundice with associated coagulopathy. Bleeding can occur from multiple sites during the various phases of mobilization and resection, so hemostasis must be monitored and assured before reconstruction begins.

Postoperative complications can be further divided into short-term and long-term complications. The short-term ones are pancreatic fistula, delayed gastric emptying, and postoperative bleeding. The long-term ones are biliary stenosis and cholangitis, pancreatitis, peptic ulcer disease, small bowel obstruction, and incisional hernia[149, 150].

Modifications of the conventional PD procedure have been developed in an attempt to improve outcomes or minimize the morbidity associated with this operation. The pylorus-preserving pancreaticoduodenectomy preserves the gastric antrum, pylorus, and proximal 3 cm to 6 cm of the duodenum. It can decrease the incidence of post-operative dumping, marginal ulceration, and bile reflux gastritis, without negative effect on the morbidity, mortality and long-term survival[151]. Instead, the subtotal stomach-preserving pancreaticoduodenectomy is performed with the aims to preserve as much stomach as possible, minimizing the delayed gastric emptying that are associated with preserving the pyloric ring in the face of vagal denervation. In this procedure, the duodenum, pylorus, and 1 cm to 2 cm of stomach are resected with the pancreatic specimen. Although described, this modification has yet to be validated, and it is uncommonly performed[152].

The "Artery-first" approach is a surgical technique or set of techniques that have in common the dissection of the main arterial vasculature involved in pancreatic cancer, prior to performing any irreversible surgical step (transection of the pancreatic neck or bile duct division). The "Artery-first" approach has the potential to reduce blood loss and increase R0 resection rates and OS, as demonstrated in a recent meta-analysis[153].

Modified child reconstruction aims to reduce the incidence of cholangitis due to digestive reflux through hepatic-digiunal anastomosis. In case of pancreatic-digiunal anastomosis, the hepatic-digiunal anastomosis is made downstream of the previous one. In case of pancreatigo-gastric anastomosis, the hepatico-digiunal anastomosis is made near the previously closed loop. Whatever the type of pancreatigo-digestive anastomosis, the digestive anastomosis (gastro-digiunal or duodeno-digiunal) is made 60 cm downstream of the hepatico-digiunal anastomosis, to reduce digestive reflux into the biliary tract.

Table 2 Resectability criteria

Resectability status		Resectable	Borderline resectable	Locally advanced
Arterial involvement	Celiac artery	None	≤ 180°; > 180°, without involvement of aorta o GDA (body/tail)	>180° (head/uncinate); Solid tumor contact with CA and aorta
	SMA common hepatic artery	None	≤ 180°; Solit tumor contact without extension into CA or hepatic artery bifurcation	> 180°
Venous involvement (portal vein/smv)		None; ≤ 180° contact without contour irregularity	> 180°; ≤ 180° with contour irregularity or thrombosis, with reconstructible PV/SMV; Solid tumor contact with IVC	Unreconstructible PV/SMV due to tumor involvement or occlusion

CA: Celiac artery; GDA: Gastroduodenal artery; IVC: Inferior vena cava; PV: Portal vein; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein.

Table 3 Resectability criteria and societies

Vessel involvement	NCCN 2019	MDACC	ACTO	AHPBA/SSAT/SSO
CA abutment (≤ 180°)	Borderline	Borderline	Borderline	Unresectable
CA encasement (> 180°)	Borderline (body/tail); locally advanced (head/uncinate)	Unresectable	Unresectable	Unresectable
SMA abutment (< 180°); SMA encasement (> 180°); CHA abutment or encasement	Borderline; Locally advanced; Borderline	Borderline; Unresectable; Borderline	Borderline; Unresectable; Borderline	Borderline; Unresectable; Borderline
PV/SMV encasement (> 180°) or abutment (≤ 180°) with contour abnormality	Borderline	Borderline	Borderline	Borderline

ACTO: Alliance for Clinical Trials in Oncology; AHPBA: American Hepato-Pancreato-Biliary Association; CA: Celiac artery; CHA: Common hepatic artery; MDACC: The University of Texas MD Anderson Cancer Center; NCCN: National Comprehensive Cancer Network; PV: Portal vein; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein; SSAT: Society for Surgery of the Alimentary Tract; SSO: Society for Surgical Oncology.

Post-operative pancreatic fistula (POPF) is the main and most frequent complication after pancreatic resection surgery. It is caused by leakage of pancreatic juice into the abdominal cavity, which is collected and conveyed to the outside by the drains normally placed at the end of surgery or during postoperative care if necessary. The diagnosis is made on the basis of the quality of the drainage fluid (varying from transparent to coffee-colored to brown) and the value of amylase in the fluid itself, greater than three times the normal limit of serum amylase[149,150].

POPFs are classified into three grades based on clinical impact. Grade A fistulas do not involve any special intervention and do not significantly modify the postoperative hospital stay. Grade B fistulas require a longer postoperative stay, the retention of surgical drains, the possible placement of additional drains under radiological guidance, antibiotic therapy and the use of artificial nutrition (enteral or parenteral). In grade C fistulas, reoperation is required to resolve the complication.

Several methods have been used to reduce the risk of pancreatic fistula, including the use of octreotide, pancreatic duct occlusion, pancreatic duct stenting, pancreaticojejunostomy, anastomosis modification, and pancreaticogastrostomy. The efficacy of octreotide in preventing POPF is still a hotly debated topic. According to a 2020 meta-analysis[154], somatostatin analogs did not affect POPF after PD, but rather appeared to be associated with a lower rate of POPF after distal pancreatectomy. Therefore, reconstruction technique is the most important factor in reducing the risk of this complication. Recently, interesting results concern the blumgart anastomosis (BA), which combines the duct-mucosal principle with the transpancreatic U-suture technique. Unlike other duct-mucosal anastomoses such as Cattell-Warren anastomosis and Kakita anastomosis, U-shaped sutures and horizontal mattress suture technique are used in BA. The difference is that Blumgart's technique involves the placement of 3 to 6 transpancreatic and digestive seromuscular U-sutures to bring the pancreatic stump and jejunum closer together. A meta-analysis conducted by Ricci *et al* [155] demonstrated the ability of BA to reduce the risk of pancreatic fistula compared with non-blumgart duct-to-mucosal anastomoses (non-BA DtoM). The reduction seems clinically significant, with a number needed to treat of 9 which means that one pancreatic fistula can be avoided every ten patients treated with BA instead of non-BA

DtoM[155,156].

Indications for the preoperative treatment of jaundice in patients who are candidates for surgery are still under debate. It increases post-operative complications and should be reserved to patients with cholangitis or with bilirubin levels greater than 15 mg/dL[157].

Distal pancreatectomy

Distal pancreatectomy with splenectomy is the conventional operation for PDAC located in the body or tail of the pancreas. It can provide a margin-negative resection and ensure a sampling of at least 12 regional lymph nodes. A systematic review, that included 29 observational studies, found less blood loss and reduced length of hospital stay in patients operated with laparoscopic approach. However, the laparoscopic technique has some disadvantages that may lead to inadequate resection margins: Technical difficulties, inability to palpate the gland, difficulty in closing the pancreatic stump. Generally, surgeons advocate an open approach when the concern for malignancy is high, reserving laparoscopic resection for benign or premalignant indications[158-160].

Petrucciani *et al*[161] evaluated the prognosis of patients with positive surgical margin (R1). A better OS was observed in patients with R0 margin *vs* R1. However, an extension of the surgical resection following R1 pancreatectomy did not improve long term survival.

Total pancreatectomy

Sometimes, because of the extent or location of the tumor, a total pancreatectomy is required to achieve microscopically negative resection margins[162,163]. However, the metabolic consequences of this procedure, which include permanent exocrine insufficiency and brittle diabetes, have a detrimental impact on the quality of life and long-term survival[164]. A recent study showed a moderately reduced summary score of 76%, compared with a general population score of 86% using the EORTC QLQ-C30 questionnaire to evaluate the overall quality of life. Diarrhea is the most important symptom[165].

Lymphadenectomy

Tomlinson *et al*[166] evaluated the minimum number of lymph nodes removed during pancreatectomy that are essential for proper staging. They consider a number of 15 Lymph nodes as the optimal cut-off. Therefore, the cut-off of 12 lymph nodes reported by Schwarz, represents a more easily threshold value, but sufficient for correct staging.

Standard lymphadenectomy should strive to resect lymph node stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b[167].

In some centres, mainly in Japan, surgeons routinely perform extensive lymph node dissection, including all 8, 9, all 12, all 14, 16a2, and 16b1 lymph nodes. A systematic review comparing standard *vs* extended lymphadenectomy demonstrated that there are no differences in OS between the two groups at one, three, or five years. However, the risk of complications was significantly increased after extended lymphadenectomy [168].

Vascular resection

If the pancreatic tumor involves the PV or SMV, pancreatic resection with PV or SMV resection may be considered: (1) When the vascular resection allows for adequate vascular flow; (2) When the tumor does not involve the SMA or hepatic artery; and (3) When an R0 resection can be accomplished. Nevertheless, many surgeons prefer to treat patients with PV or SMV involvement with neoadjuvant systemic chemotherapy before surgery.

A systematic review of 12 single-center reports concluded that pancreatectomy with PV/SMV resection is a safe and feasible procedure. It increases the number of patients who can undergo curative surgery and improves long term prognosis in a selected group of patients[169]. However, post-operative morbidity and mortality increase markedly when arterial resections are performed and few data are available to support these procedures[170-172].

Open vs minimally invasive approach

A systematic review identified 27 retrospective studies, including close to 7000 patients who underwent pancreatectomy (1306 minimally invasive, 5603 open)[173]. The laparoscopic approach was associated with longer operative times [mean difference (MD) 71 min], but lower intraoperative blood loss (MD -300 mL). The rate of

lymph node retrieval was significantly higher in the minimally invasive group (MD 1.34 nodes), and the likelihood of an R0 resection was also higher (odds ratio 1.45). Hospital stay, postoperative hemorrhage and wound infection were significantly lower in the laparoscopic group, while the rate of overall mortality, reoperations, vascular resection, pancreatic fistula, delayed gastric emptying and bile leak were similar between the two groups[174-176].

In some high-volume surgical centres, robotic-assisted pancreatic resection has been adopted. Experienced surgeon reported the same morbidity and mortality of open surgery. Decreased blood loss, higher number of adequate lymphadenectomy and improved gastric emptying are reported in some studies. These results may improve OS, but, because robotic-assisted pancreasectomy is still in its infancy, available long-term oncologic outcomes are limited[177-181].

CHEMOTHERAPY FOR RESECTABLE AND BORDERLINE RESECTABLE PANCREATIC CANCER

The only treatment with curative potential for pancreatic cancer is surgery. Five-year survival ranges from 10% to 25%.

For patients with PDAC resectable or borderline resectable, surgical resection is followed by adjuvant chemotherapy. Some high-volume centers also use neoadjuvant therapy in these categories of patients[182,183].

Adjuvant chemotherapy

Several adjuvant chemotherapy regimens have been evaluated in randomized controlled trials[184-190]. Currently, mFFX is the recommended therapy for patients with a good performance status. Gemcitabine (+/- capecitabine) remains a treatment option for patients not sufficiently fit or with contraindications to mFFX[182,191]. Because mFFX has a high toxicity, Brown University Oncology Research Group suggests FOLFOX + nab-paclitaxel (FOLFOX-A) as an alternative[192].

According to a meta-analysis[193], S1 was ranked best for overall and disease-free survival followed by mFFX. Whilst there was no significant difference between S1 and mFFX for OS, S1 had significantly longer disease-free survival (MD 2.8 mo) and was ranked best for lowest overall and haematological grade 3/4 toxicities[194]. However, the results should be interpreted with care, as S-1 has shown good results in the Asian population, but its performance in Caucasians remains unclear due to the different expression of cytochrome P-450.

Adjuvant chemotherapy should be administered between 28 and 59 d after surgery. This timing appears to provide better survival than administering before 28 or after 59 d[182,194].

A 2020 study compared the efficacy between adjuvant chemotherapy and chemoradiation therapy in relation to AJCC stage. Monochemotherapy and combination chemotherapy + chemoradiotherapy (CRT) showed better OS and disease free survival than CRT alone in patients with AJCC stage III, whereas there was no significant difference in OS in patients with AJCC stage I/II[195].

Neoadjuvant chemotherapy

The main purpose of neoadjuvant chemotherapy (NACT) differs according to the stage. For patients with BR-PDAC the objective of the therapy is to decrease tumor size and to control the micro metastases. For patients with primary resectable PDAC the purpose is to increase the proportion of patients receiving chemotherapy, because half of patients undergoing surgery, do not receive adjuvant chemotherapy due to postoperative morbidity or poor general condition[196].

In 2020, important advances were made in this field. For patients with BR-PDAC several studies confirmed the benefits on R0 resection rates and survival of NACT with mFFX[197-200] or multi-agent gemcitabine[201]. Moreover, in the PREOPANC-1 trial, patients receiving neoadjuvant CRT with gemcitabine obtained the same benefits of mFFX[202]. A study of the University of Texas showed that patients who received neoadjuvant CRT had significantly improved R0 resection rates, lymph node resection rates, and locoregional recurrence rates, compared with those who received NACT [203]. Although early data suggest the importance of integrating both NACT and CRT into the treatment, large prospective trial data are lacking[204]. New evidence for a standard regimen for BR-PDAC will be established by the result of the ESPAC-5F trial (ISRCTN89500674)[205].

For primary resectable cancer, the potential benefit of NACT has been validated, particularly when initiated within 6 wk of diagnosis[206]. The SWOG S1505 study observed that patients who received gemcitabine and nab-paclitaxel had a greater pathologic response and median survival comparable to those who received mFFX [207]. Several chemotherapeutic agents for resectable pancreatic cancer are currently being studied in several RCTs[208]. The NorPACT-1 study[209] and the Panache-01 study[210] are evaluating the effect of NACT with mFFX, and the NEONAX study [211] of NACT with 2 cycles of nab-paclitaxel/ gemcitabine.

In the Asian population, treatment regimens differ. The Prep-02/JSAP-05 study demonstrated, in patients with resectable PDAC, that NACT with gemcitabine plus S-1 (GS therapy) improves median OS compared with initial surgery (37 mo vs 27 mo). The resection rate and morbidity of surgery remain the same[212].

Based on these results, the latest Japanese guidelines recommend GS therapy as standard neoadjuvant therapy for patients with resectable PDAC. In this regimen, patients receive intravenous gemcitabine at a dose of 1000 mg/m² on days 1 and 8, plus oral S-1, twice daily, at a dose based on body surface area (80, 100, 120 mg/d) on days 1-14 every 3 wk for 2 cycles. For patients with BR-PDAC, they recommend NACT, but have refrained from recommending any specific regimens[212-214]. Among several ongoing RCTs on treatments for borderline resectable pancreatic cancer, a Japanese trial is comparing neoadjuvant therapy with gemcitabine plus nab-paclitaxel and CRT therapy with S-1[215].

A subset of patients does not respond to NACT. There is therefore a need to find markers that can predict response to NACT. At the moment the best ones seem to be GRP78, CADM1, PGES2 and RUXF[216] (Table 4).

CHEMOTHERAPY FOR LA PANCREATIC CANCER

Thirty to forty percent of patients with PDAC are initially diagnosed LA PDAC[182, 215]. LA PDAC is still nonmetastatic, but due to the local growth, curative resection is not possible at the time of diagnosis. Treatment involves chemotherapy with regimens that are also used in the metastatic setting, such as mFFX or gemcitabine plus nab-paclitaxel[217-219]. A small percentage of patients, with excellent response to chemotherapy, may become eligible for surgical resection. The majority have incurable disease. A systematic review of studies investigating mFFX in LA-PDAC revealed a median OS ranging from 10.0 mo to 32.7 mo[220], while in the LAPACT study, about the Nab-Paclitaxel + Gemcitabine regimen, OS 18.8 mo[221]. Recently, Kunzmann *et al* [222] compared two different NACT regimens, mFFX and gemcitabine plus nab-paclitaxel. The mFFX was superior in both the conversion rate to surgery (45.0% vs 30.6%) and the rate of R0 resections achieved (74% vs 68%). A subsequent study confirmed that mFFX patients had greater tumor size reduction, fewer positive lymph nodes, longer OS and distant metastasis-free survival compared to the nab-P/G patients[223].

The role of CRT for LA disease is still unclear. According to the LAP07 study, CRT improves the rate of local control but does not prolong survival in patients with LA PDAC after treatment with chemotherapy (gemcitabine with or without erlotinib) [224]. It is unclear whether these conclusions still hold true in the setting of newer combination chemotherapy regimens and improved radiation therapy techniques, such as stereotactic radiation therapy and proton therapy. The PAULA-1 study compared two cohorts of LAPDAC patients treated with stereotactic body radiotherapy (SBRT) ± chemotherapy vs CRT ± chemotherapy in terms of local control, distant metastases-free survival (DMFS), progression-free survival (PFS), OS, and toxicity. Patients treated with SBRT showed higher local control rate and similar OS, DMFS, PFS and toxicity compared to CRT[225].

CHEMOTHERAPY FOR METASTATIC PDAC

Half of patients have metastatic disease at the time of diagnosis. The primary treatment is systemic chemotherapy, with the goal of increasing survival and palliating cancer-related symptoms. Both mFFX and gemcitabine plus nab-paclitaxel improve median OS compared to gemcitabine monotherapy[226,227]. In clinical practice, for patients who are fitter, mFFX is generally preferred, reserving gemcitabine plus nab-paclitaxel as a second-line option if they have adequate performance status[228,229]. For patients who have received first-line gemcitabine and

Table 4 Phase of trial and level of evidence of trial about chemotherapy for resectable and borderline resectable pancreatic ductal adenocarcinoma

Ref.	Phase of trial	Level of evidence
Neoptolemos <i>et al</i> [185]	III	II
Oettle <i>et al</i> [186]	III	I
Neoptolemos <i>et al</i> [187]	III	I
Neoptolemos <i>et al</i> [188]	III	I
Conroy <i>et al</i> [189]	III	I
You <i>et al</i> [195]	III	II
van Roessel <i>et al</i> [198]	IV	II
Versteijne <i>et al</i> [202]	III	II
Ghaneh <i>et al</i> [205]	II	II
Sohal <i>et al</i> [207]	IV	II
Labori <i>et al</i> [209]	III	II
Schwarz <i>et al</i> [210]	II	I
Ettrich <i>et al</i> [211]	II	II
Motoi <i>et al</i> [212]	III	II
UMIN-CTR Clinical Trial[215] (UMIN000026858)	III	II

have progressed, a good option might be the combination of fluorouracil plus leucovorin with nanoliposomal irinotecan[230]. Golan *et al*[231] evaluated patients with metastatic PDAC and BRCA1-2 germline mutation. In these patients, disease progression had not occurred during at least 4 mo of first-line platinum derivative-based chemotherapy. Patients were randomized to receive olaparib or placebo. Olaparib showed a benefit in terms of PFS and a relatively safe toxicity profile. Although AIFA has not yet approved the indication, this study suggests a role for olaparib as maintenance therapy[231].

Finally, we look forward to the results of the AVENGER 500 trial (NCT03504423) to evaluate the efficacy of mFFX with or without CPI-613. CPI613 (devimistat) is an inhibitor of pyruvate dehydrogenase and α -ketoglutarate, key enzymes of the Krebs cycle. It has already shown good results in a phase I study[232].

STROMA-TARGETING THERAPY

Although chemotherapy is the recommended treatment for patients with advanced PDAC, its efficacy is not satisfactory. The major hurdle is considered the dense dysplastic stroma. The stroma components occupy more than 70% of the total tumor volume. The dense desmoplastic stroma of PDAC leads to vascular compression and a hypoxic microenvironment, which in turn influences drug pharmacokinetics/pharmacodynamics. It also prevents proper action of immune system cells, which are unable to reach the target site. The result is a chemoresistant and immunoresistant tumor[233,234].

One of the major components of the PDAC stroma is hyaluronic acid (HA). HA promotes the survival, proliferation, and migration of tumor cells[235]. HA is a potential therapeutic target using pegylated hyaluronidase (PEGPH20). The HALO-109-202 study demonstrated that PEGPH20, combined with Abraxane (nab-paclitaxel) and gemcitabine, improves progression-free and OS in patients with high HA levels [236]. However, poor results were obtained from the subsequent HALO-109-301 study (NCT02715804). Another element to be acted upon is the Hedgehog signaling pathway, which is generally overactivated in pancreatic cancer. Vismodegib, in combination with gemcitabine or erlotinib, was studied for this purpose. It did not significantly affect survival compared with these two drugs administered as monotherapy[237,238].

In tumors, Angiotensin II activates transforming growth factor- β through the AT1R and stimulates proliferation, so several angiotensin system inhibitors have been used to target PDAC stroma[233]. One study evaluated the efficacy of mFFX combined with losartan in a neoadjuvant regimen in patients with LA PDAC. The therapy was associated with an increased R0 resection rate[239].

A clinical trial evaluated the efficacy of focused ultrasound combined with gemcitabine microbubble delivery in PDAC patients. Patients treated with the combination tolerated multiple chemotherapy cycles of gemcitabine. A prolongation of median survival by almost 9 mo and, in 50% of cases, a reduction in tumor size were observed[240].

Poor results were obtained from stroma depletion in clinical settings. They are due to the fact that, although stroma-targeting therapy enhances the delivery of chemotherapeutic agents, it might also promote tumor chemoresistance and metastasis (a double-edged sword)[241]. According to several experts, future research should focus on the tumor ECM biology, biomarkers correlated with treatment benefit (as ADAM12)[242] and pharmacological agents able to alter the tumor microenvironment (TME). One of the most interesting discoveries in this regard involves clodronate liposomes. They prevent metastasis formation by inhibiting the activity of PDAC-associated macrophages and altering the microenvironment of key organs that are sites of metastatic invasion. They are therefore valuable candidates to be evaluated in combination with target therapy against stroma[243].

IMMUNOTHERAPY

Immune checkpoint inhibitors

Checkpoint inhibitors activates the function “kill the tumor” of the immune system, targeting immune checkpoint molecules (PD-1, PD-L1, CTLA-4) that negatively regulate T-cell function. Although they resulted in remarkable successes in other cancers, ipilimumab, BMS-936559 and tremelimumab showed little efficacy in PDAC [244-247]. The reasons of failure of immune checkpoint inhibitors are the low baseline PD-1+ T-cell infiltration into the tumor and a paucity of neoepitopes[248,249]. Indeed, in a very small subset of PDAC patients with a high burden of microsatellite instability (MSI-high) PD-1 inhibitor is effective and was recently FDA approved[250,251].

Currently, the development of immune checkpoint inhibitors for PDAC is focused on combination therapy with chemotherapeutic agents[252-255].

Therapeutic cancer vaccines

Therapeutic cancer vaccines present of immunogenic tumor antigens to the immune system, resulting in activation of the anti-cancer response. GVAX is an allogeneic vaccine irradiated with tumor cells engineered to express GM-CSF. It was studied alone and in combination with CRS-207 and cyclophosphamide, however it didn't correlate with improved survival[256,257].

More promising results were instead obtained with KIF20A-66[258-260].

K-RAS vaccines have been tested in the past, but data remain unclear and with no prominent advantages in metastatic patients[261-264].

We are currently awaiting the results of some studies: (1) TLP0-001, a phase III study of a dendritic cell (DC) vaccine loaded with WT1 peptides in patients with advanced PDAC refractory to standard chemotherapy[265,266]; (2) A clinical trial using GV1001 with GM-CSF in patients with LA-PDAC in combination with gemcitabine chemotherapy, tadalafil and radiation therapy (NCT01342224); and (3) NCT01836432, NCT02405585 and NCT01072981 evaluating algenpantucel-L in combination with chemotherapy and CRT therapy. They involve patients with borderline resectable and LA unresectable PDAC.

CAR-T cell

CAR-T cell therapy is a type of adoptive cell therapy. CAR-T cells are T lymphocytes that are extracted from a patient's blood sample or from a donor by apheresis, genetically modified to express the receptor for chimeric antigen (CAR), and cultured in the laboratory. They are then re-infused into the patient. The resulting T cells are able to recognize tumor cells and activate the immune system response against the disease[267]. The target antigens of CAR-T cells include mesothelin, prostate stem cell antigen (PSCA), CEA, HER2, MUC-1, and CD133[268,269]. In a study of metastatic PDAC, autologous mesothelin-specific T lymphocytes improved PFS in two patients of the six examined. An additional patient had complete remission of all liver metastases

[270].

Combination of immunotherapy drugs was experienced and showed good results over time. Le *et al*[271] compared the efficacy of Ipilimumab as monotherapy (arm 1) and Ipilimumab in combination with GVAX (arm 2) in patients with already treated PDAC. Combination therapy showed an increase in median OS (5.7 mo *vs* 3.6 mo) and 1-year OS (27% *vs* 7%). Chung *et al*[272] evaluated the combination of Pembrolizumab with modified p53-expressing Ankara vaccinia virus (p53MVA). Three of eleven patients experienced disease stabilization by 30, 32, and 49 wk. Good OS and PFS results were also obtained using DC and cytokine-induced killer cell immunotherapy in combination with S-1 chemotherapy, compared with chemotherapy or supportive care alone[256].

Several trials of immunotherapy-based treatment combinations with targeted agents are ongoing for patients with pancreatic cancer[273-275].

Oncolytic viruses

Oncolytic viruses are modified therapeutic drugs that selectively infect and self-replicate in tumor cells with tumor-dissolving effect. They also activate the anti-tumor immunity and change the TME from an immunosuppressed state to an immune-activated state. Furthermore, oncolytic viruses have the advantages of specificity, low toxicity, and low drug resistance[276]. Adenovirus, Herpes Simplex Virus, Protoparvovirus, Reovirus and Vaccinia Virus have been tested. However most of the studies have shown unsatisfactory results. The only positive results derive from ParvOryx02 (NCT02653313). A single-arm study published in 2020 showed an encouraging efficacy of pembrolizumab in combination with Pelareorep and chemotherapy in patients progressed after first-line treatment[277-281] (Table 5).

GENETIC MUTATION AND TARGET THERAPY

Some genetic alterations produce cellular changes in neoplastic cells that are potentially therapeutically targetable. BRAF mutations occur in 1%-3% of PDAC. They showed to be targetable in metastatic colon cancer where the combination of Encorafenib and Cetuximab has recently been approved[282,283]. Encorafenib and Cetuximab should also be evaluated in PDAC. Furthermore, pancreatic tumors with NTRK gene fusions can be treated with tropomyosin receptor kinase inhibitors[284, 285]. Similarly, some wild-type Kras pancreatic tumors hosting somatic NRG1 gene fusions respond to treatment with a kinase inhibitor of the HER family[286,287].

However, the results of the targeted therapies have been unsatisfactory, mainly due to the low life expectancy. There is no time to sequence the tumors and develop a treatment based on mutations[288].

The exceptions were the germline alterations. Patients with mutations of BRCA1, BRCA2 or PALB1 are remarkably sensitive to treatment with DNA cross-linking agents, such as platinum-based drugs, and poly(ADP-ribose) polymerase (PARP) inhibitors[289-291]. Patients with Lynch syndrome (MSI-high) respond well to treatment with immune checkpoint inhibitors[292-294] and those with ATM mutations could respond to the drugs, targeting the ATR-checkpoint kinase 1 (Chk1) pathway [295,296].

The elephant in the targeted therapy room remains Kras[297]. It has been considered "undrinkable"[297-299] because the protein lacks an efficient small-molecule binding pocket and has a high affinity for cellular guanosine triphosphate (GTP), which is highly concentrated in the cytoplasm. Furthermore, other than the GTP/GDP binding pocket, KRAS has no other pockets for small-molecule inhibitor binding. A druggable variant of Kras appears to be G12C. Enormous progress has been made in this regard and several drugs (AMG 510, MRTX849, JNJ-74699157 and LY3499446) are currently in clinical trials[299]. The importance of these can be deduced from the fact that 95% of pancreatic cancers harbor mutations in the Kras gene (the four Kras mountains, TP53, CDKN2A and SMAD4 present in > 50% of tumors)[300,301]. Although Kras G12C mutations are only a small fraction of Kras mutations in PDAC, these drugs represent a chance to take down a previously thought invincible adversary.

PANCREATIC CANCER AND GUT MICROBIOTA

Recent studies have shown the gut microbiota (GM) may play a role in the

Table 5 Phase and level of evidence of trials about immunotherapy for pancreatic ductal adenocarcinoma

Ref.	Phase of trial	Level of evidence
Royal <i>et al</i> [245]	II	II
Brahmer <i>et al</i> [246]	I	I
O'Reilly <i>et al</i> [247]	II	II
Tumeh <i>et al</i> [248]	II	III
Le <i>et al</i> [250]	II	II
Le <i>et al</i> [251]	II	II
Wainberg <i>et al</i> [252]	I	II
Weiss <i>et al</i> [253]	Ib/II	II
National Institute of Public Health[254] (JapicCTI-184230,ONO-4538)	II	II
Wang-Gillam <i>et al</i> [255]	II	II
Le <i>et al</i> [257]	IIb	I
Asahara <i>et al</i> [258]	I/II	II
Suzuki <i>et al</i> [259]	II	III
Miyazawa <i>et al</i> [260]	II	II
Wedén <i>et al</i> [261]	IV	III
Toubaji <i>et al</i> [262]	I	III
Abou-Alfa <i>et al</i> [263]	I/II	III
Cohn <i>et al</i> [264]	I	III
Katsuda <i>et al</i> [265]	III	I
Katsuda <i>et al</i> [266]	I/II	II
Beatty <i>et al</i> [270]	I	III
Le <i>et al</i> [271]	Ib	II
Chung <i>et al</i> [272]	I	III
Wang-Gillam <i>et al</i> [273]	I	III
Reiss <i>et al</i> [274]	II	III
Desai <i>et al</i> [275]	Ib/II	Ongoing trial
Chang <i>et al</i> [278]	I	III
Noonan <i>et al</i> [279]	II	II
Mahalingam <i>et al</i> [280]	Ib	III

development of PDAC and its response to therapy. GM alterations result in reduced mucus thickness, leading to decreased antimicrobial defenses and increased exposure to bacterial components such as LPS, flagellin, single or doubled DNA and CpG DNA. These agents activate Toll-like-receptors and trigger chronic inflammation that are related to carcinogenesis. Moreover, inflammation and dysbiosis lead to mutation of *Kras*, that accelerates carcinogenesis, activating nuclear factor- κ B pathway[302-304].

Several bacterial products are considered potential carcinogens. Cyclomodulins promote tumorigenesis through active interference with host cell cycles. Colibactin and *Bacteroides fragilis* toxin act synergistically with *Escherichia coli* to create double-stranded DNA damage[305]. *E. coli* cytotoxic necrotizing factor and CagA lead to uncontrolled cell proliferation, while cytolytic distending toxin and cycle inhibitory factor participate in genetic alterations and induce hyperploidy even in the absence of cell division[306]. The presence of an *Helicobacter pylori* infection and high concentrations of *Fusobacterium* spp and *Porphyromonas gingivalis* (bacteria generally present in the oral cavity) are associated with an increased risk of pancreatic cancer [307-310].

Moreover, other studies correlated a large number of microbes with immune suppression, downregulation of tumor suppressive pathways and the upregulation of oncogenic pathways[311].

Dysbiosis is also related to obesity, chronic pancreatitis and diabetes, well-established risk factors of PDAC[312,313].

Because it participates in drug metabolism and biotransformation and immune regulation, the GM is implicated in the efficacy of chemotherapeutic agents[314]. The innate immune response activated by the GM potentiates the action of oxaliplatin [315]. Gentamicin activity may be reduced by the enzymes pyrimidine nucleoside phosphorylase and cytidine deaminase, which are produced by Gamma-proteobacteria and mycoplasmas within PDAC. Thus, these data suggest the possibility of modulating GM to counteract the chemoresistance characteristic of pancreatic cancer [316].

Intratumoral microorganisms can play a key role in anticancer therapy[317]. Indeed, they can stimulate host immune responses with positive or negative impacts on therapy. *Gammaproteobacteria*, *Escherichia Coli* and *Fusobacteria* are most commonly present in PDAC. Gamma proteobacteria contain the enzyme CDD which could be responsible for the ineffectiveness of gemcitabine[318]. *Escheria Coli* is capable of inducing chemical changes in the structure of gemcitabine, fludarabine, cladribine, and CB1954[319]. The desmoplastic response induced by tumor cells is dependent on MyD88. It is activated by *Fusobacterium* species.

The intratumoral microbiota thus emerges as a major proponent of the chemo-immunoresistant phenotype of pancreatic cancer and is related to long-term survival in PDAC patients.

PROGNOSIS

The most important prognostic factor is tumor stage. The median survival time after resection for patients with stage IA, IB, IIA, IIB, and III was 38, 24, 18, 17, and 14 mo, respectively[320]. Other factors may influence the prognosis of PDAC after surgery: Surgical margin status, tumor grading, presence of lymphatic invasion, preoperative and postoperative serum levels of CA 19-9, and cigarette smoking[321-329]. Squamous subtypes have a poor prognosis. They are enriched with TP53 and KDM6A mutations, upregulation of TP63ΔN transcriptional network, hypermethylation of pancreatic endoderm cell fate determining genes[330].

Several studies have investigated novel factors influencing prognosis: (1) Increased expression of CDK1 and CCNA2 is associated with poor prognosis, although they may be potential therapeutic targets[331]; (2) The autophagy regulatory genes MET and RIPK2 play a prognostic role in PDAC[332]; (3) High expression of GPDAC2, GPDAC3 and GPDAC5 has been significantly associated with favorable survival[333]; (4) High expression of Hic-5 is negatively correlated with postoperative survival time, as Hic-5 stimulates tumor proliferation, migration, and invasion[334]; (5) PRMT1 promotes pancreatic cancer growth by increasing cellular β-catenin levels and predicts poor prognosis[335]; (6) Patients with first recurrence in the lung have a better prognosis than patients with first recurrence in the liver[336]; (7) Increased levels of ZIP4 correlate with poorer survival. ZIP4 inhibits the expression of the gemcitabine transporter ENT1, so that cells take up smaller amounts of the drug. Activation of this pathway participates in the chemoresistance of pancreatic cancers[337]; (8) The highly upregulated in liver cancer (HULC) lncRNA distinguishes patients with pancreatic cancer, patients with benign pancreatic disease, and healthy subjects and correlates with TNM stage. Subjects with low HULC expression have significantly higher 3- and 5-year OS than those with high expression. Therefore, HULC lncRNA could be considered an effective marker for the diagnosis and prognosis of PDAC[338]; (9) Upregulation of TYMS leads to unfavorable OS and RFS[339]; and (10) The GINS complex has four subunits, encoded by the GINS1, GINS2, GINS3, and GINS4 genes, all of which are overexpressed in PDAC. The expression of each member is associated with the histological grade of PDAC and is a negative prognostic marker[340].

CONCLUSION

Pancreatic cancer is a very treacherous, dangerous enemy and the results are still very unsatisfactory. But we have not given up. Research is running fast on many paths, without losing its enthusiasm. It is proof that we are encircling it, and at the end, we

will win. The success of a fight is linked to the ability to move from one failure to another without losing one's enthusiasm.

REFERENCES

- GBD 2017 Pancreatic Cancer Collaborators.** The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2019; **4**: 934-947 [PMID: 31648972 DOI: 10.1016/S2468-1253(19)30347-4]
- GBD 2015 Mortality and Causes of Death Collaborators.** Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1459-1544 [PMID: 27733281 DOI: 10.1016/S0140-6736(16)31012-1]
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A.** Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
- Ilic M, Ilic I.** Epidemiology of pancreatic cancer. *World J Gastroenterol* 2016; **22**: 9694-9705 [PMID: 27956793 DOI: 10.3748/wjg.v22.i44.9694]
- Oldfield LE, Connor AA, Gallinger S.** Molecular Events in the Natural History of Pancreatic Cancer. *Trends Cancer* 2017; **3**: 336-346 [PMID: 28718411 DOI: 10.1016/j.trecan.2017.04.005]
- Siegel RL, Miller KD, Jemal A.** Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]
- Grasso C, Jansen G, Giovannetti E.** Drug resistance in pancreatic cancer: Impact of altered energy metabolism. *Crit Rev Oncol Hematol* 2017; **114**: 139-152 [PMID: 28477742 DOI: 10.1016/j.critrevonc.2017.03.026]
- He J, Blair AB, Groot VP, Javed AA, Burkhardt RA, Gemenetzis G, Hruban RH, Waters KM, Poling J, Zheng L, Laheru D, Herman JM, Makary MA, Weiss MJ, Cameron JL, Wolfgang CL.** Is a Pathological Complete Response Following Neoadjuvant Chemoradiation Associated With Prolonged Survival in Patients With Pancreatic Cancer? *Ann Surg* 2018; **268**: 1-8 [PMID: 29334562 DOI: 10.1097/SLA.0000000000002672]
- Singhi AD, Koay EJ, Chari ST, Maitra A.** Early Detection of Pancreatic Cancer: Opportunities and Challenges. *Gastroenterology* 2019; **156**: 2024-2040 [PMID: 30721664 DOI: 10.1053/j.gastro.2019.01.259]
- Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, Negri E, Li D, Risch HA, Olson SH, Gallinger S, Miller AB, Bueno-de-Mesquita HB, Talamini R, Polesel J, Ghadirian P, Baghurst PA, Zatonski W, Fontham E, Bamlet WR, Holly EA, Bertuccio P, Gao YT, Hassan M, Yu H, Kurtz RC, Cotterchio M, Su J, Maisonneuve P, Duell EJ, Boffetta P, La Vecchia C.** Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Ann Oncol* 2012; **23**: 1880-1888 [PMID: 22104574 DOI: 10.1093/annonc/mdr541]
- Carreras-Torres R, Johansson M, Gaborieau V, Haycock PC, Wade KH, Relton CL, Martin RM, Davey Smith G, Brennan P.** The Role of Obesity, Type 2 Diabetes, and Metabolic Factors in Pancreatic Cancer: A Mendelian Randomization Study. *J Natl Cancer Inst* 2017; **109** [PMID: 28954281 DOI: 10.1093/jnci/djx012]
- Li D, Morris JS, Liu J, Hassan MM, Day RS, Bondy ML, Abbruzzese JL.** Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA* 2009; **301**: 2553-2562 [PMID: 19549972 DOI: 10.1001/jama.2009.886]
- O'Rourke MA, Cantwell MM, Cardwell CR, Mulholland HG, Murray LJ.** Can physical activity modulate pancreatic cancer risk? *Int J Cancer* 2010; **126**: 2957-2968 [PMID: 19856317 DOI: 10.1002/ijc.24997]
- Huang J, Magnusson M, Törner A, Ye W, Duberg AS.** Risk of pancreatic cancer among individuals with hepatitis C or hepatitis B virus infection: a nationwide study in Sweden. *Br J Cancer* 2013; **109**: 2917-2923 [PMID: 24178755 DOI: 10.1038/bjc.2013.689]
- Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, Arslan AA, Bueno-de-Mesquita HB, Gross M, Helzlsouer K, Jacobs EJ, LaCroix A, Zheng W, Albanes D, Bamlet W, Berg CD, Berrino F, Bingham S, Buring JE, Bracci PM, Canzian F, Clavel-Chapelon F, Clipp S, Cotterchio M, de Andrade M, Duell EJ, Fox JW Jr, Gallinger S, Gaziano JM, Giovannucci EL, Goggins M, González CA, Hallmans G, Hankinson SE, Hassan M, Holly EA, Hunter DJ, Hutchinson A, Jackson R, Jacobs KB, Jenab M, Kaaks R, Klein AP, Kooperberg C, Kurtz RC, Li D, Lynch SM, Mandelson M, McWilliams RR, Mendelsohn JB, Michaud DS, Olson SH, Overvad K, Patel AV, Peeters PH, Rajkovic A, Riboli E, Risch HA, Shu XO, Thomas G, Tobias GS, Trichopoulos D, Van Den Eeden SK, Virtamo J, Wactawski-Wende J, Wolpin BM, Yu H, Yu K, Zeleniuch-Jacquotte A, Chanock SJ, Hartge P, Hoover RN.** Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. *Nat Genet* 2009; **41**: 986-990 [PMID: 19648918 DOI: 10.1038/ng.429]
- Yamada A, Komaki Y, Komaki F, Micic D, Zullo S, Sakuraba A.** Risk of gastrointestinal cancers in patients with cystic fibrosis: a systematic review and meta-analysis. *Lancet Oncol* 2018; **19**: 758-

- 767 [PMID: 29706374 DOI: 10.1016/S1470-2045(18)30188-8]
- 17 **Pergolini I**, Sahara K, Ferrone CR, Morales-Oyarvide V, Wolpin BM, Mucci LA, Brugge WR, Mino-Kenudson M, Patino M, Sahani DV, Warshaw AL, Lillemoe KD, Fernández-Del Castillo C. Long-term Risk of Pancreatic Malignancy in Patients With Branch Duct Intraductal Papillary Mucinous Neoplasm in a Referral Center. *Gastroenterology* 2017; **153**: 1284-1294.e1 [PMID: 28739282 DOI: 10.1053/j.gastro.2017.07.019]
 - 18 **IARC Working Group on the Evaluation of Carcinogenic Risks to Humans**. Personal habits and indoor combustions. Volume 100 E. A review of human carcinogens. *IARC Monogr Eval Carcinog Risks Hum* 2012; **100**: 1-538 [PMID: 23193840]
 - 19 **Riboli E**, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondière UR, Hémon B, Casagrande C, Vignat J, Overvad K, Tjønneland A, Clavel-Chapelon F, Thiébaud A, Wahrendorf J, Boeing H, Trichopoulos D, Trichopoulou A, Vineis P, Palli D, Bueno-De-Mesquita HB, Peeters PH, Lund E, Engeset D, González CA, Barricarte A, Berglund G, Hallmans G, Day NE, Key TJ, Kaaks R, Saracci R. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002; **5**: 1113-1124 [PMID: 12639222 DOI: 10.1079/PHN2002394]
 - 20 **McKenzie F**, Biessy C, Ferrari P, Freisling H, Rinaldi S, Chajès V, Dahm CC, Overvad K, Dossus L, Lagiou P, Trichopoulos D, Trichopoulou A, Bueno-de-Mesquita HB, May A, Peeters PH, Weiderpass E, Sanchez MJ, Navarro C, Ardanaz E, Ericson U, Wirfält E, Travis RC, Romieu I. Healthy Lifestyle and Risk of Cancer in the European Prospective Investigation Into Cancer and Nutrition Cohort Study. *Medicine (Baltimore)* 2016; **95**: e2850 [PMID: 27100409 DOI: 10.1097/MD.0000000000002850]
 - 21 **Chajès V**, Biessy C, Byrnes G, Deharveng G, Saadatian-Elahi M, Jenab M, Peeters PH, Ocké M, Bueno-de-Mesquita HB, Johansson I, Hallmans G, Manjer J, Wirfält E, Jakszyn P, González CA, Huerta JM, Martinez C, Amiano P, Suárez LR, Ardanaz E, Tjønneland A, Halkjaer J, Overvad K, Jakobsen MU, Berrino F, Pala V, Palli D, Tumino R, Vineis P, de Magistris MS, Spencer EA, Crowe FL, Bingham S, Khaw KT, Linseisen J, Rohrmann S, Boeing H, Nöthlings U, Olsen KS, Skeie G, Lund E, Trichopoulou A, Zilis D, Oustoglou E, Clavel-Chapelon F, Riboli E, Slimani N. Ecological-level associations between highly processed food intakes and plasma phospholipid elaidic acid concentrations: results from a cross-sectional study within the European prospective investigation into cancer and nutrition (EPIC). *Nutr Cancer* 2011; **63**: 1235-1250 [PMID: 22043987 DOI: 10.1080/01635581.2011.617530]
 - 22 **Saadatian-Elahi M**, Slimani N, Chajès V, Jenab M, Goudable J, Biessy C, Ferrari P, Byrnes G, Autier P, Peeters PH, Ocké M, Bueno de Mesquita B, Johansson I, Hallmans G, Manjer J, Wirfält E, González CA, Navarro C, Martinez C, Amiano P, Suárez LR, Ardanaz E, Tjønneland A, Halkjaer J, Overvad K, Jakobsen MU, Berrino F, Pala V, Palli D, Tumino R, Vineis P, Santucci de Magistris M, Spencer EA, Crowe FL, Bingham S, Khaw KT, Linseisen J, Rohrmann S, Boeing H, Nöthlings U, Olsen KS, Skeie G, Lund E, Trichopoulou A, Oustoglou E, Clavel-Chapelon F, Riboli E. Plasma phospholipid fatty acid profiles and their association with food intakes: results from a cross-sectional study within the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr* 2009; **89**: 331-346 [PMID: 19056549 DOI: 10.3945/ajcn.2008.26834]
 - 23 **Jiao L**, Mitrou PN, Reedy J, Graubard BI, Hollenbeck AR, Schatzkin A, Stolzenberg-Solomon R. A combined healthy lifestyle score and risk of pancreatic cancer in a large cohort study. *Arch Intern Med* 2009; **169**: 764-770 [PMID: 19398688 DOI: 10.1001/archinternmed.2009.46]
 - 24 **Ferrari P**, Licaj I, Muller DC, Kragh Andersen P, Johansson M, Boeing H, Weiderpass E, Dossus L, Dartois L, Fagherazzi G, Bradbury KE, Khaw KT, Wareham N, Duell EJ, Barricarte A, Molina-Montes E, Sanchez CN, Arriola L, Wallström P, Tjønneland A, Olsen A, Trichopoulou A, Benetou V, Trichopoulos D, Tumino R, Agnoli C, Sacerdote C, Palli D, Li K, Kaaks R, Peeters P, Beulens JW, Nunes L, Gunter M, Norat T, Overvad K, Brennan P, Riboli E, Romieu I. Lifetime alcohol use and overall and cause-specific mortality in the European Prospective Investigation into Cancer and nutrition (EPIC) study. *BMJ Open* 2014; **4**: e005245 [PMID: 24993766 DOI: 10.1136/bmjopen-2014-005245]
 - 25 **Naudin S**, Li K, Jaouen T, Assi N, Kyrø C, Tjønneland A, Overvad K, Boutron-Ruault MC, Rebours V, Védié AL, Boeing H, Kaaks R, Katzke V, Bamia C, Naska A, Trichopoulou A, Berrino F, Tagliabue G, Palli D, Panico S, Tumino R, Sacerdote C, Peeters PH, Bueno-de-Mesquita HBA, Weiderpass E, Gram IT, Skeie G, Chirlaque MD, Rodríguez-Barranco M, Barricarte A, Quirós JR, Dorronsoro M, Johansson I, Sund M, Sternby H, Bradbury KE, Wareham N, Riboli E, Gunter M, Brennan P, Duell EJ, Ferrari P. Lifetime and baseline alcohol intakes and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition study. *Int J Cancer* 2018; **143**: 801-812 [PMID: 29524225 DOI: 10.1002/ijc.31367]
 - 26 **Molina-Montes E**, Sánchez MJ, Buckland G, Bueno-de-Mesquita HB, Weiderpass E, Amiano P, Wark PA, Kühn T, Katzke V, Huerta JM, Ardanaz E, Quirós JR, Affret A, His M, Boutron-Ruault MC, Peeters PH, Ye W, Sund M, Boeing H, Iqbal K, Ohlsson B, Sonestedt E, Tjønneland A, Petersen KE, Travis RC, Skeie G, Agnoli C, Panico S, Palli D, Tumino R, Sacerdote C, Freisling H, Huybrechts I, Overvad K, Trichopoulou A, Bamia C, Vasilopoulou E, Wareham N, Khaw KT, Cross AJ, Ward HA, Riboli E, Duell EJ. Mediterranean diet and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition cohort. *Br J Cancer* 2017; **116**: 811-820 [PMID: 28170373 DOI: 10.1038/bjc.2017.14]
 - 27 **Rawla P**, Thandra KC, Sunkara T. Pancreatic cancer and obesity: epidemiology, mechanism, and

- preventive strategies. *Clin J Gastroenterol* 2019; **12**: 285-291 [PMID: 30788774 DOI: 10.1007/s12328-019-00953-3]
- 28 **Genkinger JM**, Kitahara CM, Bernstein L, Berrington de Gonzalez A, Brotzman M, Elena JW, Giles GG, Hartge P, Singh PN, Stolzenberg-Solomon RZ, Weiderpass E, Adami HO, Anderson KE, Beane-Freeman LE, Buring JE, Fraser GE, Fuchs CS, Gapstur SM, Gaziano JM, Helzlsouer KJ, Lacey JV Jr, Linet MS, Liu JJ, Park Y, Peters U, Purdue MP, Robien K, Schairer C, Sesso HD, Visvanathan K, White E, Wolk A, Wolpin BM, Zeleniuch-Jacquotte A, Jacobs EJ. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. *Ann Oncol* 2015; **26**: 2257-2266 [PMID: 26347100 DOI: 10.1093/annonc/mdv355]
- 29 **Song S**, Wang B, Zhang X, Hao L, Hu X, Li Z, Sun S. Long-Term Diabetes Mellitus Is Associated with an Increased Risk of Pancreatic Cancer: A Meta-Analysis. *PLoS One* 2015; **10**: e0134321 [PMID: 26222906 DOI: 10.1371/journal.pone.0134321]
- 30 **Bimonte S**, Cascella M, Leongito M, Palaia R, Caliendo D, Izzo F, Cuomo A. An overview of pre-clinical studies on the effects of (-)-epigallocatechin-3-gallate, a catechin found in green tea, in treatment of pancreatic cancer. *Recenti Prog Med* 2017; **108**: 282-287 [PMID: 28631776 DOI: 10.1701/2715.27715]
- 31 **Nasir A**, Bullo MMH, Ahmed Z, Imtiaz A, Yaqoob E, Jadoon M, Ahmed H, Afreen A, Yaqoob S. Nutrigenomics: Epigenetics and cancer prevention: A comprehensive review. *Crit Rev Food Sci Nutr* 2020; **60**: 1375-1387 [PMID: 30729798 DOI: 10.1080/10408398.2019.1571480]
- 32 **Pelaez-Luna M**, Takahashi N, Fletcher JG, Chari ST. Resectability of presymptomatic pancreatic cancer and its relationship to onset of diabetes: a retrospective review of CT scans and fasting glucose values prior to diagnosis. *Am J Gastroenterol* 2007; **102**: 2157-2163 [PMID: 17897335 DOI: 10.1111/j.1572-0241.2007.01480.x]
- 33 **US Preventive Services Task Force**, Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, Curry SJ, Doubeni CA, Epling JW Jr, Kubik M, Landefeld CS, Mangione CM, Pbert L, Silverstein M, Simon MA, Tseng CW, Wong JB. Screening for Pancreatic Cancer: US Preventive Services Task Force Reaffirmation Recommendation Statement. *JAMA* 2019; **322**: 438-444 [PMID: 31386141 DOI: 10.1001/jama.2019.10232]
- 34 **Yuan C**, Babic A, Khalaf N, Nowak JA, Brais LK, Rubinson DA, Ng K, Aguirre AJ, Pandharipande PV, Fuchs CS, Giovannucci EL, Stampfer MJ, Rosenthal MH, Sander C, Kraft P, Wolpin BM. Diabetes, Weight Change, and Pancreatic Cancer Risk. *JAMA Oncol* 2020; **6**: e202948 [PMID: 32789511 DOI: 10.1001/jamaoncol.2020.2948]
- 35 **Naudin S**, Viallon V, Hashim D, Freisling H, Jenab M, Weiderpass E, Perrier F, McKenzie F, Bueno-de-Mesquita HB, Olsen A, Tjønneland A, Dahm CC, Overvad K, Mancini FR, Rebours V, Boutron-Ruault MC, Katzke V, Kaaks R, Bergmann M, Boeing H, Peppas E, Karakatsani A, Trichopoulou A, Pala V, Masala G, Panico S, Tumino R, Sacerdote C, May AM, van Gils CH, Rylander C, Borch KB, Chirlaque López MD, Sánchez MJ, Ardanaz E, Quirós JR, Amiano Exezarreta P, Sund M, Drake I, Regnér S, Travis RC, Wareham N, Aune D, Riboli E, Gunter MJ, Duell EJ, Brennan P, Ferrari P. Healthy lifestyle and the risk of pancreatic cancer in the EPIC study. *Eur J Epidemiol* 2020; **35**: 975-986 [PMID: 31564045 DOI: 10.1007/s10654-019-00559-6]
- 36 **Lal G**, Liu G, Schmocker B, Kaurah P, Ozelik H, Narod SA, Redston M, Gallinger S. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. *Cancer Res* 2000; **60**: 409-416 [PMID: 10667595]
- 37 **Holter S**, Borgida A, Dodd A, Grant R, Semotiuk K, Hedley D, Dhani N, Narod S, Akbari M, Moore M, Gallinger S. Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma. *J Clin Oncol* 2015; **33**: 3124-3129 [PMID: 25940717 DOI: 10.1200/JCO.2014.59.7401]
- 38 **Goldstein AM**, Fraser MC, Struewing JP, Hussussian CJ, Ranade K, Zimetkin DP, Fontaine LS, Organic SM, Dracopoli NC, Clark WH Jr. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. *N Engl J Med* 1995; **333**: 970-974 [PMID: 7666916 DOI: 10.1056/NEJM199510123331504]
- 39 **van Lier MG**, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am J Gastroenterol* 2010; **105**: 1258-64; author reply 1265 [PMID: 20051941 DOI: 10.1038/ajg.2009.725]
- 40 **Park JG**, Park YJ, Wijnen JT, Vasen HF. Gene-environment interaction in hereditary nonpolyposis colorectal cancer with implications for diagnosis and genetic testing. *Int J Cancer* 1999; **82**: 516-519 [PMID: 10404064 DOI: 10.1002/(sici)1097-0215(19990812)82:4<516::aid-ijc8>3.0.co;2-u]
- 41 **Whitcomb DC**. Inflammation and Cancer V. Chronic pancreatitis and pancreatic cancer. *Am J Physiol Gastrointest Liver Physiol* 2004; **287**: G315-G319 [PMID: 15246966 DOI: 10.1152/ajpgi.00115.2004]
- 42 **Yurgelun MB**, Chittenden AB, Morales-Oyarvide V, Rubinson DA, Dunne RF, Kozak MM, Qian ZR, Welch MW, Brais LK, Da Silva A, Bui JL, Yuan C, Li T, Li W, Masuda A, Gu M, Bullock AJ, Chang DT, Clancy TE, Linehan DC, Findeis-Hosey JJ, Doyle LA, Thorne AR, Ducar MD, Wollison BM, Khalaf N, Perez K, Syngal S, Aguirre AJ, Hahn WC, Meyerson ML, Fuchs CS, Ogino S, Hornick JL, Hezel AF, Koong AC, Nowak JA, Wolpin BM. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. *Genet Med* 2019; **21**: 213-223 [PMID: 29961768 DOI: 10.1038/s41436-018-0009-5]
- 43 **Stoffel EM**, McKernin SE, Brand R, Canto M, Goggins M, Moravsek C, Nagarajan A, Petersen GM,

- Simeone DM, Yurgelun M, Khorana AA. Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion. *J Clin Oncol* 2019; **37**: 153-164 [PMID: 30457921 DOI: 10.1200/JCO.18.01489]
- 44 **Ohmoto A**, Yachida S, Morizane C. Genomic Features and Clinical Management of Patients with Hereditary Pancreatic Cancer Syndromes and Familial Pancreatic Cancer. *Int J Mol Sci* 2019; **20** [PMID: 30699894 DOI: 10.3390/ijms20030561]
- 45 **Goggins M**, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, Bassi C, Carrato A, Farrell J, Fishman EK, Fockens P, Gress TM, van Hooft JE, Hruban RH, Kastrinos F, Klein A, Lennon AM, Lucas A, Park W, Rustgi A, Simeone D, Stoffel E, Vasen HFA, Cahen DL, Canto MI, Bruno M; International Cancer of the Pancreas Screening (CAPS) consortium. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut* 2020; **69**: 7-17 [PMID: 31672839 DOI: 10.1136/gutjnl-2019-319352]
- 46 **Syngal S**, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol* 2015; **110**: 223-62; quiz 263 [PMID: 25645574 DOI: 10.1038/ajg.2014.435]
- 47 **Brand RE**, Lerch MM, Rubinstein WS, Neoptolemos JP, Whitcomb DC, Hruban RH, Brentnall TA, Lynch HT, Canto MI; Participants of the Fourth International Symposium of Inherited Diseases of the Pancreas. Advances in counselling and surveillance of patients at risk for pancreatic cancer. *Gut* 2007; **56**: 1460-1469 [PMID: 17872573 DOI: 10.1136/gut.2006.108456]
- 48 **Aslanian HR**, Lee JH, Canto MI. AGA Clinical Practice Update on Pancreas Cancer Screening in High-Risk Individuals: Expert Review. *Gastroenterology* 2020; **159**: 358-362 [PMID: 32416142 DOI: 10.1053/j.gastro.2020.03.088]
- 49 **Hirono S**, Yamaue H. Surgical strategy for intraductal papillary mucinous neoplasms of the pancreas. *Surg Today* 2020; **50**: 50-55 [PMID: 31807871 DOI: 10.1007/s00595-019-01931-5]
- 50 **Canto MI**, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, Topazian M, Takahashi N, Fletcher J, Petersen G, Klein AP, Axilbund J, Griffin C, Syngal S, Saltzman JR, Mortelet KJ, Lee J, Tamm E, Vikram R, Bhosale P, Margolis D, Farrell J, Goggins M; American Cancer of the Pancreas Screening (CAPS) Consortium. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology* 2012; **142**: 796-804; quiz e14 [PMID: 22245846 DOI: 10.1053/j.gastro.2012.01.005]
- 51 **Grover S**, Syngal S. Hereditary pancreatic cancer. *Gastroenterology* 2010; **139**: 1076-1080, 1080.e1 [PMID: 20727885 DOI: 10.1053/j.gastro.2010.08.012]
- 52 **Matthaei H**, Schulick RD, Hruban RH, Maitra A. Cystic precursors to invasive pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 141-150 [PMID: 21383670 DOI: 10.1038/nrgastro.2011.2]
- 53 **Del Chiaro M**, Verbeke CS, Kartalis N, Pozzi Mucelli R, Gustafsson P, Hansson J, Haas SL, Segersvärd R, Andren-Sandberg Å, Löhr JM. Short-term Results of a Magnetic Resonance Imaging-Based Swedish Screening Program for Individuals at Risk for Pancreatic Cancer. *JAMA Surg* 2015; **150**: 512-518 [PMID: 25853369 DOI: 10.1001/jamasurg.2014.3852]
- 54 **Tanaka M**, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K; International Association of Pancreatology. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatol* 2012; **12**: 183-197 [PMID: 22687371 DOI: 10.1016/j.pan.2012.04.004]
- 55 **Canto MI**, Kerdshirachairat T, Yeo CJ, Hruban RH, Shin EJ, Almario JA, Blackford A, Ford M, Klein AP, Javed AA, Lennon AM, Zaheer A, Kamel IR, Fishman EK, Burkhart R, He J, Makary M, Weiss MJ, Schulick RD, Goggins MG, Wolfgang CL. Surgical Outcomes After Pancreatic Resection of Screening-Detected Lesions in Individuals at High Risk for Developing Pancreatic Cancer. *J Gastrointest Surg* 2020; **24**: 1101-1110 [PMID: 31197699 DOI: 10.1007/s11605-019-04230-z]
- 56 **Lennon AM**, Wolfgang CL, Canto MI, Klein AP, Herman JM, Goggins M, Fishman EK, Kamel I, Weiss MJ, Diaz LA, Papadopoulos N, Kinzler KW, Vogelstein B, Hruban RH. The early detection of pancreatic cancer: what will it take to diagnose and treat curable pancreatic neoplasia? *Cancer Res* 2014; **74**: 3381-3389 [PMID: 24924775 DOI: 10.1158/0008-5472.CAN-14-0734]
- 57 **Goonetilleke KS**, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol* 2007; **33**: 266-270 [PMID: 17097848 DOI: 10.1016/j.ejso.2006.10.004]
- 58 **Rawla P**, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. *World J Oncol* 2019; **10**: 10-27 [PMID: 30834048 DOI: 10.14740/wjon1166]
- 59 **Meng Q**, Shi S, Liang C, Liang D, Xu W, Ji S, Zhang B, Ni Q, Xu J, Yu X. Diagnostic and prognostic value of carcinoembryonic antigen in pancreatic cancer: a systematic review and meta-analysis. *Oncol Targets Ther* 2017; **10**: 4591-4598 [PMID: 28979147 DOI: 10.2147/OTT.S145708]
- 60 **Ni XG**, Bai XF, Mao YL, Shao YF, Wu JX, Shan Y, Wang CF, Wang J, Tian YT, Liu Q, Xu DK, Zhao P. The clinical value of serum CEA, CA19-9, and CA242 in the diagnosis and prognosis of pancreatic cancer. *Eur J Surg Oncol* 2005; **31**: 164-169 [PMID: 15698733 DOI: 10.1016/j.ejso.2004.09.007]
- 61 **Khomiak A**, Brunner M, Kordes M, Lindblad S, Miksch RC, Öhlund D, Regel I. Recent Discoveries of Diagnostic, Prognostic and Predictive Biomarkers for Pancreatic Cancer. *Cancers (Basel)* 2020; **12** [PMID: 33147766 DOI: 10.3390/cancers12113234]

- 62 **Satake K**, Takeuchi T. Comparison of CA19-9 with other tumor markers in the diagnosis of cancer of the pancreas. *Pancreas* 1994; **9**: 720-724 [PMID: 7846015 DOI: 10.1097/00006676-199411000-00008]
- 63 **Bussom S**, Saif MW. Methods and rationale for the early detection of pancreatic cancer. Highlights from the "2010 ASCO Gastrointestinal Cancers Symposium". Orlando, FL, USA. January 22-24, 2010. *JOP* 2010; **11**: 128-130 [PMID: 20208319]
- 64 **Eissa MAL**, Lerner L, Abdelfatah E, Shankar N, Canner JK, Hasan NM, Yaghoobi V, Huang B, Kerner Z, Takaesu F, Wolfgang C, Kwak R, Ruiz M, Tam M, Pisanic TR 2nd, Iacobuzio-Donahue CA, Hruban RH, He J, Wang TH, Wood LD, Sharma A, Ahuja N. Promoter methylation of ADAMTS1 and BNC1 as potential biomarkers for early detection of pancreatic cancer in blood. *Clin Epigenetics* 2019; **11**: 59 [PMID: 30953539 DOI: 10.1186/s13148-019-0650-0]
- 65 **Shen SY**, Singhania R, Fehringer G, Chakravarthy A, Roehrl MHA, Chadwick D, Zuzarte PC, Borgida A, Wang TT, Li T, Kis O, Zhao Z, Spreafico A, Medina TDS, Wang Y, Roulois D, Ettayebi I, Chen Z, Chow S, Murphy T, Arruda A, O'Kane GM, Liu J, Mansour M, McPherson JD, O'Brien C, Leighl N, Bedard PL, Fleshner N, Liu G, Minden MD, Gallinger S, Goldenberg A, Pugh TJ, Hoffman MM, Bratman SV, Hung RJ, De Carvalho DD. Sensitive tumour detection and classification using plasma cell-free DNA methylomes. *Nature* 2018; **563**: 579-583 [PMID: 30429608 DOI: 10.1038/s41586-018-0703-0]
- 66 **Cirmena G**, Dameri M, Ravera F, Fregatti P, Ballestrero A, Zoppoli G. Assessment of Circulating Nucleic Acids in Cancer: From Current Status to Future Perspectives and Potential Clinical Applications. *Cancers (Basel)* 2021; **13** [PMID: 34298675 DOI: 10.3390/cancers13143460]
- 67 **Bloomston M**, Frankel WL, Petrocca F, Volinia S, Alder H, Hagan JP, Liu CG, Bhatt D, Taccioli C, Croce CM. MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis. *JAMA* 2007; **297**: 1901-1908 [PMID: 17473300 DOI: 10.1001/jama.297.17.1901]
- 68 **Duell EJ**, Lujan-Barroso L, Sala N, Deitz McElyea S, Overvad K, Tjonneland A, Olsen A, Weiderpass E, Busund LT, Moi L, Muller D, Vineis P, Aune D, Matullo G, Naccarati A, Panico S, Tagliabue G, Tumino R, Palli D, Kaaks R, Katzke VA, Boeing H, Bueno-de-Mesquita HBA, Peeters PH, Trichopoulou A, Lagiou P, Kotanidou A, Travis RC, Wareham N, Khaw KT, Ramon Quirios J, Rodríguez-Barranco M, Dorransoro M, Chirlaque MD, Ardanaz E, Severi G, Boutron-Ruault MC, Rebours V, Brennan P, Gunter M, Scelo G, Cote G, Sherman S, Korc M. Plasma microRNAs as biomarkers of pancreatic cancer risk in a prospective cohort study. *Int J Cancer* 2017; **141**: 905-915 [PMID: 28542740 DOI: 10.1002/ijc.30790]
- 69 **Liu J**, Gao J, Du Y, Li Z, Ren Y, Gu J, Wang X, Gong Y, Wang W, Kong X. Combination of plasma microRNAs with serum CA19-9 for early detection of pancreatic cancer. *Int J Cancer* 2012; **131**: 683-691 [PMID: 21913185 DOI: 10.1002/ijc.26422]
- 70 **Permeth JB**, Chen DT, Yoder SJ, Li J, Smith AT, Choi JW, Kim J, Balagurunathan Y, Jiang K, Coppola D, Centeno BA, Klapman J, Hodul P, Karreth FA, Trevino JG, Merchant N, Magliocco A, Malafa MP, Gillies R. Linc-ing Circulating Long Non-coding RNAs to the Diagnosis and Malignant Prediction of Intraductal Papillary Mucinous Neoplasms of the Pancreas. *Sci Rep* 2017; **7**: 10484 [PMID: 28874676 DOI: 10.1038/s41598-017-09754-5]
- 71 **Ding J**, Li Y, Zhang Y, Fan B, Li Q, Zhang J. Identification of key lncRNAs in the tumorigenesis of intraductal pancreatic mucinous neoplasm by coexpression network analysis. *Cancer Med* 2020; **9**: 3840-3851 [PMID: 32239802 DOI: 10.1002/cam4.2927]
- 72 **Nasca V**, Chiaravalli M, Piro G, Esposito A, Salvatore L, Tortora G, Corbo V, Carbone C. Intraductal Pancreatic Mucinous Neoplasms: A Tumor-Biology Based Approach for Risk Stratification. *Int J Mol Sci* 2020; **21** [PMID: 32887490 DOI: 10.3390/ijms21176386]
- 73 **Kanda M**, Knight S, Topazian M, Syngal S, Farrell J, Lee J, Kamel I, Lennon AM, Borges M, Young A, Fujiwara S, Seike J, Eshleman J, Hruban RH, Canto MI, Goggins M. Mutant GNAS detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. *Gut* 2013; **62**: 1024-1033 [PMID: 22859495 DOI: 10.1136/gutjnl-2012-302823]
- 74 **Kanda M**, Sadakari Y, Borges M, Topazian M, Farrell J, Syngal S, Lee J, Kamel I, Lennon AM, Knight S, Fujiwara S, Hruban RH, Canto MI, Goggins M. Mutant TP53 in duodenal samples of pancreatic juice from patients with pancreatic cancer or high-grade dysplasia. *Clin Gastroenterol Hepatol* 2013; **11**: 719-30.e5 [PMID: 23200980 DOI: 10.1016/j.cgh.2012.11.016]
- 75 **Singhi AD**, McGrath K, Brand RE, Khalid A, Zeh HJ, Chennat JS, Fasanella KE, Papachristou GI, Slivka A, Bartlett DL, Dasyam AK, Hogg M, Lee KK, Marsh JW, Monaco SE, Ohori NP, Pingpank JF, Tsung A, Zureikat AH, Wald AI, Nikiforova MN. Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. *Gut* 2018; **67**: 2131-2141 [PMID: 28970292 DOI: 10.1136/gutjnl-2016-313586]
- 76 **Suenaga M**, Dudley B, Karloski E, Borges M, Irene Canto M, Brand RE, Goggins M. The Effect of Pancreatic Juice Collection Time on the Detection of KRAS Mutations. *Pancreas* 2018; **47**: 35-39 [PMID: 29200129 DOI: 10.1097/MPA.0000000000000956]
- 77 **Garcia-Carracedo D**, Chen ZM, Qiu W, Huang AS, Tang SM, Hruban RH, Su GH. PIK3CA mutations in mucinous cystic neoplasms of the pancreas. *Pancreas* 2014; **43**: 245-249 [PMID: 24518503 DOI: 10.1097/MPA.0000000000000034]
- 78 **Garcia-Carracedo D**, Turk AT, Fine SA, Akhavan N, Tweel BC, Parsons R, Chabot JA, Allendorf JD, Genkinger JM, Remotti HE, Su GH. Loss of PTEN expression is associated with poor prognosis

- in patients with intraductal papillary mucinous neoplasms of the pancreas. *Clin Cancer Res* 2013; **19**: 6830-6841 [PMID: 24132918 DOI: 10.1158/1078-0432.CCR-13-0624]
- 79 **Kaur S**, Kumar S, Momi N, Sasson AR, Batra SK. Mucins in pancreatic cancer and its microenvironment. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 607-620 [PMID: 23856888 DOI: 10.1038/nrgastro.2013.120]
- 80 **Nagata K**, Horinouchi M, Saitou M, Higashi M, Nomoto M, Goto M, Yonezawa S. Mucin expression profile in pancreatic cancer and the precursor lesions. *J Hepatobiliary Pancreat Surg* 2007; **14**: 243-254 [PMID: 17520199 DOI: 10.1007/s00534-006-1169-2]
- 81 **Moniaux N**, Chaturvedi P, Varshney GC, Meza JL, Rodriguez-Sierra JF, Aubert JP, Batra SK. Human MUC4 mucin induces ultra-structural changes and tumorigenicity in pancreatic cancer cells. *Br J Cancer* 2007; **97**: 345-357 [PMID: 17595659 DOI: 10.1038/sj.bjc.6603868]
- 82 **Gold DV**, Modrak DE, Ying Z, Cardillo TM, Sharkey RM, Goldenberg DM. New MUC1 serum immunoassay differentiates pancreatic cancer from pancreatitis. *J Clin Oncol* 2006; **24**: 252-258 [PMID: 16344318 DOI: 10.1200/JCO.2005.02.8282]
- 83 **Haab BB**, Porter A, Yue T, Li L, Scheiman J, Anderson MA, Barnes D, Schmidt CM, Feng Z, Simeone DM. Glycosylation variants of mucins and CEACAMs as candidate biomarkers for the diagnosis of pancreatic cystic neoplasms. *Ann Surg* 2010; **251**: 937-945 [PMID: 20395854 DOI: 10.1097/SLA.0b013e3181d7738d]
- 84 **Sinha J**, Cao Z, Dai J, Tang H, Partyka K, Hostetter G, Simeone DM, Feng Z, Allen PJ, Brand RE, Haab BB. A Gastric Glycoform of MUC5AC Is a Biomarker of Mucinous Cysts of the Pancreas. *PLoS One* 2016; **11**: e0167070 [PMID: 27992432 DOI: 10.1371/journal.pone.0167070]
- 85 **Horn A**, Chakraborty S, Dey P, Haridas D, Soucek J, Batra SK, Lele SM. Immunocytochemistry for MUC4 and MUC16 is a useful adjunct in the diagnosis of pancreatic adenocarcinoma on fine-needle aspiration cytology. *Arch Pathol Lab Med* 2013; **137**: 546-551 [PMID: 23544943 DOI: 10.5858/arpa.2011-0229-OA]
- 86 **Maker AV**, Katabi N, Qin LX, Klimstra DS, Schattner M, Brennan MF, Jarnagin WR, Allen PJ. Cyst fluid interleukin-1beta (IL1beta) levels predict the risk of carcinoma in intraductal papillary mucinous neoplasms of the pancreas. *Clin Cancer Res* 2011; **17**: 1502-1508 [PMID: 21266527 DOI: 10.1158/1078-0432.CCR-10-1561]
- 87 **Hao S**, Takahashi C, Snyder RA, Parikh AA. Stratifying Intraductal Papillary Mucinous Neoplasms by Cyst Fluid Analysis: Present and Future. *Int J Mol Sci* 2020; **21** [PMID: 32050465 DOI: 10.3390/ijms21031147]
- 88 **Das KK**, Geng X, Brown JW, Morales-Oyarvide V, Huynh T, Pergolini I, Pitman MB, Ferrone C, Al Efshat M, Haviland D, Thompson E, Wolfgang C, Lennon AM, Allen P, Lillemoie KD, Fields RC, Hawkins WG, Liu J, Castillo CF, Das KM, Mino-Kenudson M. Cross Validation of the Monoclonal Antibody Das-1 in Identification of High-Risk Mucinous Pancreatic Cystic Lesions. *Gastroenterology* 2019; **157**: 720-730.e2 [PMID: 31175863 DOI: 10.1053/j.gastro.2019.05.014]
- 89 **Zhang L**, Farrell JJ, Zhou H, Elashoff D, Akin D, Park NH, Chia D, Wong DT. Salivary transcriptomic biomarkers for detection of resectable pancreatic cancer. *Gastroenterology* 2010; **138**: 949-57.e1 [PMID: 19931263 DOI: 10.1053/j.gastro.2009.11.010]
- 90 **Xie Z**, Yin X, Gong B, Nie W, Wu B, Zhang X, Huang J, Zhang P, Zhou Z, Li Z. Salivary microRNAs show potential as a noninvasive biomarker for detecting resectable pancreatic cancer. *Cancer Prev Res (Phila)* 2015; **8**: 165-173 [PMID: 25538087 DOI: 10.1158/1940-6207.CAPR-14-0192]
- 91 **Satoh K**. Molecular Approaches Using Body Fluid for the Early Detection of Pancreatic Cancer. *Diagnostics (Basel)* 2021; **11** [PMID: 33671729 DOI: 10.3390/diagnostics11020375]
- 92 **Setti G**, Pezzi ME, Viani MV, Pertinhez TA, Cassi D, Magnoni C, Bellini P, Musolino A, Vescovi P, Meleti M. Salivary MicroRNA for Diagnosis of Cancer and Systemic Diseases: A Systematic Review. *Int J Mol Sci* 2020; **21** [PMID: 32019170 DOI: 10.3390/ijms21030907]
- 93 **Ishige F**, Hoshino I, Iwatate Y, Chiba S, Arimitsu H, Yanagibashi H, Nagase H, Takayama W. MIR1246 in body fluids as a biomarker for pancreatic cancer. *Sci Rep* 2020; **10**: 8723 [PMID: 32457495 DOI: 10.1038/s41598-020-65695-6]
- 94 **Radon TP**, Massat NJ, Jones R, Alrawashdeh W, Dumartin L, Ennis D, Duffy SW, Kocher HM, Pereira SP, Guarner posthumous L, Murta-Nascimento C, Real FX, Malats N, Neoptolemos J, Costello E, Greenhalf W, Lemoine NR, Crnogorac-Jurcevic T. Identification of a Three-Biomarker Panel in Urine for Early Detection of Pancreatic Adenocarcinoma. *Clin Cancer Res* 2015; **21**: 3512-3521 [PMID: 26240291 DOI: 10.1158/1078-0432.CCR-14-2467]
- 95 **Brezgzyte G**, Shah V, Jach D, Crnogorac-Jurcevic T. Non-Invasive Biomarkers for Earlier Detection of Pancreatic Cancer-A Comprehensive Review. *Cancers (Basel)* 2021; **13** [PMID: 34072842 DOI: 10.3390/cancers13112722]
- 96 **Porta M**, Fabregat X, Malats N, Guarner L, Carrato A, de Miguel A, Ruiz L, Jariod M, Costafreda S, Coll S, Alguacil J, Corominas JM, Solà R, Salas A, Real FX. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. *Clin Transl Oncol* 2005; **7**: 189-197 [PMID: 15960930 DOI: 10.1007/BF02712816]
- 97 **Mujica VR**, Barkin JS, Go VL. Acute pancreatitis secondary to pancreatic carcinoma. Study Group Participants. *Pancreas* 2000; **21**: 329-332 [PMID: 11075985 DOI: 10.1097/00006676-200011000-00001]
- 98 **Chari ST**, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology* 2005; **129**: 504-511 [PMID:

- 16083707 DOI: [10.1016/j.gastro.2005.05.007](https://doi.org/10.1016/j.gastro.2005.05.007)]
- 99 **Aggarwal G**, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas* 2013; **42**: 198-201 [PMID: [23000893](https://pubmed.ncbi.nlm.nih.gov/23000893/) DOI: [10.1097/MPA.0b013e3182592c96](https://doi.org/10.1097/MPA.0b013e3182592c96)]
 - 100 **Khorana AA**, Fine RL. Pancreatic cancer and thromboembolic disease. *Lancet Oncol* 2004; **5**: 655-663 [PMID: [15522652](https://pubmed.ncbi.nlm.nih.gov/15522652/) DOI: [10.1016/S1470-2045\(04\)01606-7](https://doi.org/10.1016/S1470-2045(04)01606-7)]
 - 101 **Pinzon R**, Drewinko B, Trujillo JM, Guinee V, Giacco G. Pancreatic carcinoma and Trousseau's syndrome: experience at a large cancer center. *J Clin Oncol* 1986; **4**: 509-514 [PMID: [3958764](https://pubmed.ncbi.nlm.nih.gov/3958764/) DOI: [10.1200/JCO.1986.4.4.509](https://doi.org/10.1200/JCO.1986.4.4.509)]
 - 102 **Bravo-Piris J**, Villaron LG, Martinez C, Garcia-Perez A. Pipillon-Lefèvre syndrome: report of two familial cases. *Dermatologica* 1976; **152**: 168-176 [PMID: [133038](https://pubmed.ncbi.nlm.nih.gov/133038/) DOI: [10.1111/j.1365-2230.1992.tb02541.x](https://doi.org/10.1111/j.1365-2230.1992.tb02541.x)]
 - 103 **Marcos P**, Kieselova K, Cunha M. Pancreatic Panniculitis. *Am J Gastroenterol* 2017; **112**: 1218 [PMID: [28766564](https://pubmed.ncbi.nlm.nih.gov/28766564/) DOI: [10.1038/ajg.2017.161](https://doi.org/10.1038/ajg.2017.161)]
 - 104 **Galvañ VG**. Sister Mary Joseph's nodule. *Ann Intern Med* 1998; **128**: 410 [PMID: [9490607](https://pubmed.ncbi.nlm.nih.gov/9490607/) DOI: [10.7326/0003-4819-128-5-199803010-00017](https://doi.org/10.7326/0003-4819-128-5-199803010-00017)]
 - 105 **Lee ES**, Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. *World J Gastroenterol* 2014; **20**: 7864-7877 [PMID: [24976723](https://pubmed.ncbi.nlm.nih.gov/24976723/) DOI: [10.3748/wjg.v20.i24.7864](https://doi.org/10.3748/wjg.v20.i24.7864)]
 - 106 **Garces-Descovich A**, Beker K, Jaramillo-Cardoso A, James Moser A, Mortelet KJ. Applicability of current NCCN Guidelines for pancreatic adenocarcinoma resectability: analysis and pitfalls. *Abdom Radiol (NY)* 2018; **43**: 314-322 [PMID: [29392370](https://pubmed.ncbi.nlm.nih.gov/29392370/) DOI: [10.1007/s00261-018-1459-6](https://doi.org/10.1007/s00261-018-1459-6)]
 - 107 **Wong JC**, Raman S. Surgical resectability of pancreatic adenocarcinoma: CTA. *Abdom Imaging* 2010; **35**: 471-480 [PMID: [19468791](https://pubmed.ncbi.nlm.nih.gov/19468791/) DOI: [10.1007/s00261-009-9539-2](https://doi.org/10.1007/s00261-009-9539-2)]
 - 108 **Fletcher JG**, Wiersema MJ, Farrell MA, Fidler JL, Burgart LJ, Koyama T, Johnson CD, Stephens DH, Ward EM, Harmsen WS. Pancreatic malignancy: value of arterial, pancreatic, and hepatic phase imaging with multi-detector row CT. *Radiology* 2003; **229**: 81-90 [PMID: [14519871](https://pubmed.ncbi.nlm.nih.gov/14519871/) DOI: [10.1148/radiol.2291020582](https://doi.org/10.1148/radiol.2291020582)]
 - 109 **Yoon SH**, Lee JM, Cho JY, Lee KB, Kim JE, Moon SK, Kim SJ, Baek JH, Kim SH, Lee JY, Han JK, Choi BI. Small (≤ 20 mm) pancreatic adenocarcinomas: analysis of enhancement patterns and secondary signs with multiphasic multidetector CT. *Radiology* 2011; **259**: 442-452 [PMID: [21406627](https://pubmed.ncbi.nlm.nih.gov/21406627/) DOI: [10.1148/radiol.11101133](https://doi.org/10.1148/radiol.11101133)]
 - 110 **Shukla PJ**, Barreto SG, Kulkarni A, Nagarajan G, Fingerhut A. Vascular anomalies encountered during pancreatoduodenectomy: do they influence outcomes? *Ann Surg Oncol* 2010; **17**: 186-193 [PMID: [19838756](https://pubmed.ncbi.nlm.nih.gov/19838756/) DOI: [10.1245/s10434-009-0757-1](https://doi.org/10.1245/s10434-009-0757-1)]
 - 111 **Chu LC**, Goggins MG, Fishman EK. Diagnosis and Detection of Pancreatic Cancer. *Cancer J* 2017; **23**: 333-342 [PMID: [29189329](https://pubmed.ncbi.nlm.nih.gov/29189329/) DOI: [10.1097/PPO.0000000000000290](https://doi.org/10.1097/PPO.0000000000000290)]
 - 112 **Li H**, Zeng MS, Zhou KR, Jin DY, Lou WH. Pancreatic adenocarcinoma: the different CT criteria for peripancreatic major arterial and venous invasion. *J Comput Assist Tomogr* 2005; **29**: 170-175 [PMID: [15772532](https://pubmed.ncbi.nlm.nih.gov/15772532/) DOI: [10.1097/01.rct.0000155060.73107.83](https://doi.org/10.1097/01.rct.0000155060.73107.83)]
 - 113 **Xia BT**, Fu B, Wang J, Kim Y, Ahmad SA, Dhar VK, Levinsky NC, Hanseman DJ, Habib DA, Wilson GC, Smith M, Olowokure OO, Kharofa J, Al Humaidi AH, Choe KA, Abbott DE. Does radiologic response correlate to pathologic response in patients undergoing neoadjuvant therapy for borderline resectable pancreatic malignancy? *J Surg Oncol* 2017; **115**: 376-383 [PMID: [28105634](https://pubmed.ncbi.nlm.nih.gov/28105634/) DOI: [10.1002/jso.24538](https://doi.org/10.1002/jso.24538)]
 - 114 **Holzappel K**, Reiser-Erkan C, Fingerle AA, Erkan M, Eiber MJ, Rummeny EJ, Friess H, Kleeff J, Gaa J. Comparison of diffusion-weighted MR imaging and multidetector-row CT in the detection of liver metastases in patients operated for pancreatic cancer. *Abdom Imaging* 2011; **36**: 179-184 [PMID: [20563868](https://pubmed.ncbi.nlm.nih.gov/20563868/) DOI: [10.1007/s00261-010-9633-5](https://doi.org/10.1007/s00261-010-9633-5)]
 - 115 **Motosugi U**, Ichikawa T, Morisaka H, Sou H, Muhi A, Kimura K, Sano K, Araki T. Detection of pancreatic carcinoma and liver metastases with gadoteric acid-enhanced MR imaging: comparison with contrast-enhanced multi-detector row CT. *Radiology* 2011; **260**: 446-453 [PMID: [21693662](https://pubmed.ncbi.nlm.nih.gov/21693662/) DOI: [10.1148/radiol.11103548](https://doi.org/10.1148/radiol.11103548)]
 - 116 **Carrara G**, Pecorelli N, De Cobelli F, Cristel G, Damascelli A, Beretta L, Braga M. Preoperative sarcopenia determinants in pancreatic cancer patients. *Clin Nutr* 2017; **36**: 1649-1653 [PMID: [27789123](https://pubmed.ncbi.nlm.nih.gov/27789123/) DOI: [10.1016/j.clnu.2016.10.014](https://doi.org/10.1016/j.clnu.2016.10.014)]
 - 117 **Ozola Zalite I**, Zykus R, Francisco Gonzalez M, Saygili F, Pukitis A, Gaujoux S, Charnley RM, Lyadov V. Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: a systematic review. *Pancreatol* 2015; **15**: 19-24 [PMID: [25524484](https://pubmed.ncbi.nlm.nih.gov/25524484/) DOI: [10.1016/j.pan.2014.11.006](https://doi.org/10.1016/j.pan.2014.11.006)]
 - 118 **Prado CM**, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008; **9**: 629-635 [PMID: [18539529](https://pubmed.ncbi.nlm.nih.gov/18539529/) DOI: [10.1016/S1470-2045\(08\)70153-0](https://doi.org/10.1016/S1470-2045(08)70153-0)]
 - 119 **Schmocker RK**, Vanness DJ, Greenberg CC, Havlena JA, LoConte NK, Weiss JM, Neuman HB, Levenson G, Smith MA, Winslow ER. Utilization of preoperative endoscopic ultrasound for pancreatic adenocarcinoma. *HPB (Oxford)* 2017; **19**: 465-472 [PMID: [28237627](https://pubmed.ncbi.nlm.nih.gov/28237627/) DOI: [10.1016/j.hpb.2017.01.017](https://doi.org/10.1016/j.hpb.2017.01.017)]
 - 120 **Hartwig W**, Schneider L, Diener MK, Bergmann F, Büchler MW, Werner J. Preoperative tissue diagnosis for tumours of the pancreas. *Br J Surg* 2009; **96**: 5-20 [PMID: [19016272](https://pubmed.ncbi.nlm.nih.gov/19016272/) DOI: [10.1016/j.brs.2008.11.007](https://doi.org/10.1016/j.brs.2008.11.007)]

- 10.1002/bjs.6407]
- 121 **Lee TH**, Cho YD, Cha SW, Cho JY, Jang JY, Jeong SW, Choi HJ, Moon JH. Endoscopic ultrasound elastography for the pancreas in Korea: a preliminary single center study. *Clin Endosc* 2013; **46**: 172-177 [PMID: 23614128 DOI: 10.5946/ce.2013.46.2.172]
 - 122 **Chantarojanasiri T**, Kongkam P. Endoscopic ultrasound elastography for solid pancreatic lesions. *World J Gastrointest Endosc* 2017; **9**: 506-513 [PMID: 29085561 DOI: 10.4253/wjge.v9.i10.506]
 - 123 **Okasha H**, Elkholy S, El-Sayed R, Wifi MN, El-Nady M, El-Nabawi W, El-Dayem WA, Radwan MI, Farag A, El-Sherif Y, Al-Gemeie E, Salman A, El-Sherbiny M, El-Mazny A, Mahdy RE. Real time endoscopic ultrasound elastography and strain ratio in the diagnosis of solid pancreatic lesions. *World J Gastroenterol* 2017; **23**: 5962-5968 [PMID: 28932088 DOI: 10.3748/wjg.v23.i32.5962]
 - 124 **Niederau C**, Grendell JH. Diagnosis of pancreatic carcinoma. Imaging techniques and tumor markers. *Pancreas* 1992; **7**: 66-86 [PMID: 1557348 DOI: 10.1097/00006676-199201000-00011]
 - 125 **Vozzo CF**, Sanaka MR. Endoscopic Management of Pancreaticobiliary Disease. *Surg Clin North Am* 2020; **100**: 1151-1168 [PMID: 33128885 DOI: 10.1016/j.suc.2020.08.006]
 - 126 **Alauddin MM**, De Palatis L. Current and Future Trends in Early Detection of Pancreatic Cancer: Molecular Targets and PET Probes. *Curr Med Chem* 2015; **22**: 3370-3389 [PMID: 26295468 DOI: 10.2174/0929867322666150821094015]
 - 127 **Moradi F**, Iagaru A. The Role of Positron Emission Tomography in Pancreatic Cancer and Gallbladder Cancer. *Semin Nucl Med* 2020; **50**: 434-446 [PMID: 32768007 DOI: 10.1053/j.semnuclmed.2020.04.002]
 - 128 **Li XX**, Liu NB, Zhu L, Yuan XK, Yang CW, Ren P, Gong LL, Zhao LJ, Xu WG, Wang P. Consequences of additional use of contrast-enhanced (18)F-FDG PET/CT in target volume delineation and dose distribution for pancreatic cancer. *Br J Radiol* 2015; **88**: 20140590 [PMID: 25939819 DOI: 10.1259/bjr.20140590]
 - 129 **Wang L**, Dong P, Wang WG, Tian BL. Positron emission tomography modalities prevent futile radical resection of pancreatic cancer: A meta-analysis. *Int J Surg* 2017; **46**: 119-125 [PMID: 28890410 DOI: 10.1016/j.ijso.2017.09.003]
 - 130 **Santhosh S**, Mittal BR, Bhasin DK, Rana SS, Gupta R, Das A, Nada R. Fluorodeoxyglucose-positron emission tomography/computed tomography performs better than contrast-enhanced computed tomography for metastasis evaluation in the initial staging of pancreatic adenocarcinoma. *Ann Nucl Med* 2017; **31**: 575-581 [PMID: 28689356 DOI: 10.1007/s12149-017-1193-0]
 - 131 **Daamen LA**, Groot VP, Goense L, Wessels FJ, Borel Rinkes IH, Intven MPW, van Santvoort HC, Molenaar IQ. The diagnostic performance of CT vs FDG PET-CT for the detection of recurrent pancreatic cancer: a systematic review and meta-analysis. *Eur J Radiol* 2018; **106**: 128-136 [PMID: 30150034 DOI: 10.1016/j.ejrad.2018.07.010]
 - 132 **England CG**, Hernandez R, Eddine SB, Cai W. Molecular Imaging of Pancreatic Cancer with Antibodies. *Mol Pharm* 2016; **13**: 8-24 [PMID: 26620581 DOI: 10.1021/acs.molpharmaceut.5b00626]
 - 133 **Feng X**, Wang Y, Lu D, Xu X, Zhou X, Zhang H, Zhang T, Zhu H, Yang Z, Wang F, Li N, Liu Z. Clinical Translation of a ⁶⁸Ga-Labeled Integrin $\alpha_v\beta_6$ -Targeting Cyclic Radiotracer for PET Imaging of Pancreatic Cancer. *J Nucl Med* 2020; **61**: 1461-1467 [PMID: 32086242 DOI: 10.2967/jnumed.119.237347]
 - 134 **Serrao EM**, Kettunen MI, Rodrigues TB, Dzien P, Wright AJ, Gopinathan A, Gallagher FA, Lewis DY, Frese KK, Almeida J, Howat WJ, Tuveson DA, Brindle KM. MRI with hyperpolarised [1-¹³C]pyruvate detects advanced pancreatic preneoplasia prior to invasive disease in a mouse model. *Gut* 2016; **65**: 465-475 [PMID: 26347531 DOI: 10.1136/gutjnl-2015-310114]
 - 135 **Mayo SC**, Austin DF, Sheppard BC, Mori M, Shipley DK, Billingsley KG. Evolving preoperative evaluation of patients with pancreatic cancer: does laparoscopy have a role in the current era? *J Am Coll Surg* 2009; **208**: 87-95 [PMID: 19228509 DOI: 10.1016/j.jamcollsurg.2008.10.014]
 - 136 **Allen VB**, Gurusamy KS, Takwoingi Y, Kalia A, Davidson BR. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. *Cochrane Database Syst Rev* 2016; **7**: CD009323 [PMID: 27383694 DOI: 10.1002/14651858.CD009323.pub3]
 - 137 **Pisters PW**, Lee JE, Vauthey JN, Charnsangavej C, Evans DB. Laparoscopy in the staging of pancreatic cancer. *Br J Surg* 2001; **88**: 325-337 [PMID: 11260096 DOI: 10.1046/j.1365-2168.2001.01695.x]
 - 138 **Fong ZV**, Alvino DML, Fernández-Del Castillo C, Mehtsun WT, Pergolini I, Warshaw AL, Chang DC, Lillemoe KD, Ferrone CR. Reappraisal of Staging Laparoscopy for Patients with Pancreatic Adenocarcinoma: A Contemporary Analysis of 1001 Patients. *Ann Surg Oncol* 2017; **24**: 3203-3211 [PMID: 28718038 DOI: 10.1245/s10434-017-5973-5]
 - 139 **Karachristos A**, Scarmeas N, Hoffman JP. CA 19-9 Levels predict results of staging laparoscopy in pancreatic cancer. *J Gastrointest Surg* 2005; **9**: 1286-1292 [PMID: 16332484 DOI: 10.1016/j.gassur.2005.06.008]
 - 140 **Wang KX**, Ben QW, Jin ZD, Du YQ, Zou DW, Liao Z, Li ZS. Assessment of morbidity and mortality associated with EUS-guided FNA: a systematic review. *Gastrointest Endosc* 2011; **73**: 283-290 [PMID: 21295642 DOI: 10.1016/j.gie.2010.10.045]
 - 141 **Yane K**, Kuwatani M, Yoshida M, Goto T, Matsumoto R, Ihara H, Okuda T, Taya Y, Ehira N, Kudo T, Adachi T, Eto K, Onodera M, Sano I, Nojima M, Katanuma A. Non-negligible rate of needle tract seeding after endoscopic ultrasound-guided fine-needle aspiration for patients undergoing distal

- pancreatectomy for pancreatic cancer. *Dig Endosc* 2020; **32**: 801-811 [PMID: 31876309 DOI: 10.1111/den.13615]
- 142 **Zhang L**, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. *World J Gastroenterol* 2018; **24**: 2047-2060 [PMID: 29785074 DOI: 10.3748/wjg.v24.i19.2047]
- 143 **Clarke DL**, Clarke BA, Thomson SR, Garden OJ, Lazarus NG. The role of preoperative biopsy in pancreatic cancer. *HPB (Oxford)* 2004; **6**: 144-153 [PMID: 18333068 DOI: 10.1080/13651820410030862]
- 144 **Pezzilli R**. Asymptomatic lesions of the pancreas: an overview. *J Gastroenterol Hepatol Res* 2014; **3**: 1216-1219
- 145 **Tanaka M**, Fernández-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, Salvia R, Shimizu Y, Tada M, Wolfgang CL. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology* 2017; **17**: 738-753 [PMID: 28735806 DOI: 10.1016/j.pan.2017.07.007]
- 146 **van Roessel S**, Kasumova GG, Verheij J, Najarian RM, Maggino L, de Pastena M, Malleo G, Marchegiani G, Salvia R, Ng SC, de Geus SW, Lof S, Giovannazzo F, van Dam JL, Kent TS, Busch OR, van Eijck CH, Koerkamp BG, Abu Hilal M, Bassi C, Tseng JF, Besselink MG. International Validation of the Eighth Edition of the American Joint Committee on Cancer (AJCC) TNM Staging System in Patients With Resected Pancreatic Cancer. *JAMA Surg* 2018; **153**: e183617 [PMID: 30285076 DOI: 10.1001/jamasurg.2018.3617]
- 147 **Bockhorn M**, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, Asbun HJ, Bassi C, Büchler M, Charnley RM, Conlon K, Cruz LF, Dervenis C, Fingerhut A, Friess H, Gouma DJ, Hartwig W, Lillemo K, Montorsi M, Neoptolemos JP, Shrikhande SV, Takaori K, Traverso W, Vashist YK, Vollmer C, Yeo CJ, Izbicki JR; International Study Group of Pancreatic Surgery. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014; **155**: 977-988 [PMID: 24856119 DOI: 10.1016/j.surg.2014.02.001]
- 148 **Isaji S**, Mizuno S, Windsor JA, Bassi C, Fernández-Del Castillo C, Hackert T, Hayasaki A, Katz MHG, Kim SW, Kishiwada M, Kitagawa H, Michalski CW, Wolfgang CL. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. *Pancreatology* 2018; **18**: 2-11 [PMID: 29191513 DOI: 10.1016/j.pan.2017.11.011]
- 149 **Brown JA**, Zenati MS, Simmons RL, Al Abbas AI, Chopra A, Smith K, Lee KKW, Hogg ME, Zeh HJ, Panizza A, Zureikat AH. Long-Term Surgical Complications After Pancreatoduodenectomy: Incidence, Outcomes, and Risk Factors. *J Gastrointest Surg* 2020; **24**: 1581-1589 [PMID: 32410174 DOI: 10.1007/s11605-020-04641-3]
- 150 **Seiler CA**, Wagner M, Bachmann T, Redaelli CA, Schmied B, Uhl W, Friess H, Büchler MW. Randomized clinical trial of pylorus-preserving duodenopancreatectomy vs classical Whipple resection-long term results. *Br J Surg* 2005; **92**: 547-556 [PMID: 15800958 DOI: 10.1002/bjs.4881]
- 151 **Hüttner FJ**, Fitzmaurice C, Schwarzer G, Seiler CM, Antes G, Büchler MW, Diener MK. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) vs pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. *Cochrane Database Syst Rev* 2016; **2**: CD006053 [PMID: 26905229 DOI: 10.1002/14651858.CD006053.pub6]
- 152 **Karim SAM**, Abdulla KS, Abdulkarim QH, Rahim FH. The outcomes and complications of pancreaticoduodenectomy (Whipple procedure): Cross sectional study. *Int J Surg* 2018; **52**: 383-387 [PMID: 29438817 DOI: 10.1016/j.ijssu.2018.01.041]
- 153 **Mora-Oliver I**, Garcés-Albir M, Dorcaratto D, Muñoz-Fornier E, Izquierdo Moreno A, Carbonell-Aliaga MP, Sabater L. Pancreatoduodenectomy with artery-first approach. *Minerva Chir* 2019; **74**: 226-236 [PMID: 30600965 DOI: 10.23736/S0026-4733.18.07944-0]
- 154 **Li Z**, Wei A, Xia N, Zheng L, Yang D, Ye J, Xiong J, Hu W. Blumgart anastomosis reduces the incidence of pancreatic fistula after pancreaticoduodenectomy: a systematic review and meta-analysis. *Sci Rep* 2020; **10**: 17896 [PMID: 33087777 DOI: 10.1038/s41598-020-74812-4]
- 155 **Ricci C**, Ingaldi C, Alberici L, Pagano N, Mosconi C, Marasco G, Minni F, Casadei R. Blumgart Anastomosis After Pancreaticoduodenectomy. A Comprehensive Systematic Review, Meta-Analysis, and Meta-Regression. *World J Surg* 2021; **45**: 1929-1939 [PMID: 33721074 DOI: 10.1007/s00268-021-06039-x]
- 156 **Fang Y**, Gurusamy KS, Wang Q, Davidson BR, Lin H, Xie X, Wang C. Meta-analysis of randomized clinical trials on safety and efficacy of biliary drainage before surgery for obstructive jaundice. *Br J Surg* 2013; **100**: 1589-1596 [PMID: 24264780 DOI: 10.1002/bjs.9260]
- 157 **Schorn S**, Vogel T, Demir IE, Demir E, Safak O, Friess H, Ceyhan GO. Do somatostatin analogues have the same impact on postoperative morbidity and pancreatic fistula in patients after pancreaticoduodenectomy and distal pancreatectomy? *Pancreatology* 2020; **20**: 1770-1778 [PMID: 33121847 DOI: 10.1016/j.pan.2020.10.043]
- 158 **Ammori BJ**, Ayiomamitis GD. Laparoscopic pancreaticoduodenectomy and distal pancreatectomy: a UK experience and a systematic review of the literature. *Surg Endosc* 2011; **25**: 2084-2099 [PMID: 21298539 DOI: 10.1007/s00464-010-1538-4]
- 159 **Mehrabi A**, Hafezi M, Arvin J, Esmailzadeh M, Garoussi C, Emami G, Kössler-Ebs J, Müller-Stich BP, Büchler MW, Hackert T, Diener MK. A systematic review and meta-analysis of laparoscopic vs open distal pancreatectomy for benign and malignant lesions of the pancreas: it's time to randomize. *Surgery* 2015; **157**: 45-55 [PMID: 25482464 DOI: 10.1016/j.surg.2014.06.081]
- 160 **Pierce RA**, Spittler JA, Hawkins WG, Strasberg SM, Linehan DC, Halpin VJ, Eagon JC, Brunt LM,

- Frisella MM, Matthews BD. Outcomes analysis of laparoscopic resection of pancreatic neoplasms. *Surg Endosc* 2007; **21**: 579-586 [PMID: [17180287](#) DOI: [10.1007/s00464-006-9022-x](#)]
- 161 **Petrucciani N**, Nigri G, Debs T, Giannini G, Sborlini E, Antolino L, Aurello P, D'Angelo F, Gugenheim J, Ramacciato G. Frozen section analysis of the pancreatic margin during pancreaticoduodenectomy for cancer: Does extending the resection to obtain a secondary R0 provide a survival benefit? *Pancreatol* 2016; **16**: 1037-1043 [PMID: [27697467](#) DOI: [10.1016/j.pan.2016.09.004](#)]
- 162 **Winter JM**, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg* 2006; **10**: 1199-210; discussion 1210 [PMID: [17114007](#) DOI: [10.1016/j.gassur.2006.08.018](#)]
- 163 **Schmidt CM**, Glant J, Winter JM, Kennard J, Dixon J, Zhao Q, Howard TJ, Madura JA, Nakeeb A, Pitt HA, Cameron JL, Yeo CJ, Lillemoe KD. Total pancreatectomy (R0 resection) improves survival over subtotal pancreatectomy in isolated neck margin positive pancreatic adenocarcinoma. *Surgery* 2007; **142**: 572-8; discussion 578 [PMID: [17950350](#) DOI: [10.1016/j.surg.2007.07.016](#)]
- 164 **Karpoff HM**, Klimstra DS, Brennan MF, Conlon KC. Results of total pancreatectomy for adenocarcinoma of the pancreas. *Arch Surg* 2001; **136**: 44-7; discussion 48 [PMID: [11146775](#) DOI: [10.1001/archsurg.136.1.44](#)]
- 165 **Scholten L**, Stoop TF, Del Chiaro M, Busch OR, van Eijck C, Molenaar IQ, de Vries JH, Besselink MG; Dutch Pancreatic Cancer Group. Systematic review of functional outcome and quality of life after total pancreatectomy. *Br J Surg* 2019; **106**: 1735-1746 [PMID: [31502658](#) DOI: [10.1002/bjs.11296](#)]
- 166 **Tomlinson JS**, Jain S, Bentrem DJ, Sekeris EG, Maggard MA, Hines OJ, Reber HA, Ko CY. Accuracy of staging node-negative pancreas cancer: a potential quality measure. *Arch Surg* 2007; **142**: 767-723; discussion 773 [PMID: [17709731](#) DOI: [10.1001/archsurg.142.8.767](#)]
- 167 **Tol JA**, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, Andrén-Sandberg A, Asbun HJ, Bockhorn M, Büchler MW, Conlon KC, Fernández-Cruz L, Fingerhut A, Friess H, Hartwig W, Izbicki JR, Lillemoe KD, Milicevic MN, Neoptolemos JP, Shrikhande SV, Vollmer CM, Yeo CJ, Charnley RM; International Study Group on Pancreatic Surgery. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). *Surgery* 2014; **156**: 591-600 [PMID: [25061003](#) DOI: [10.1016/j.surg.2014.06.016](#)]
- 168 **Sun J**, Yang Y, Wang X, Yu Z, Zhang T, Song J, Zhao H, Wen J, Du Y, Lau WY, Zhang Y. Meta-analysis of the efficacies of extended and standard pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas. *World J Surg* 2014; **38**: 2708-2715 [PMID: [24912627](#) DOI: [10.1007/s00268-014-2633-9](#)]
- 169 **Zgliczynski S**, Gietka-Czernel M, Gorowski T, Bednarski A, Chomicki O, Jastrzebska W, Makowska A, Niegowska E, Pucilowska J, Soszynski P. Results of 131I therapy for 2,000 thyrotoxic patients: do the effects depend on the dose? *Exp Clin Endocrinol* 1991; **97**: 286-291 [PMID: [1915646](#) DOI: [10.1245/s10434-008-0281-8](#)]
- 170 **Gurusamy KS**, Kumar S, Davidson BR, Fusai G. Resection vs other treatments for locally advanced pancreatic cancer. *Cochrane Database Syst Rev* 2014; CD010244 [PMID: [24578248](#) DOI: [10.1002/14651858.CD010244.pub2](#)]
- 171 **Yamada S**, Fujii T, Sugimoto H, Nomoto S, Takeda S, Kodera Y, Nakao A. Aggressive surgery for borderline resectable pancreatic cancer: evaluation of National Comprehensive Cancer Network guidelines. *Pancreas* 2013; **42**: 1004-1010 [PMID: [23532000](#) DOI: [10.1097/MPA.0b013e31827b2d7c](#)]
- 172 **Mollberg N**, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Büchler MW, Weitz J. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011; **254**: 882-893 [PMID: [22064622](#) DOI: [10.1097/SLA.0b013e31823ac299](#)]
- 173 **Wang S**, Shi N, You L, Dai M, Zhao Y. Minimally invasive surgical approach vs open procedure for pancreaticoduodenectomy: A systematic review and meta-analysis. *Medicine (Baltimore)* 2017; **96**: e8619 [PMID: [29390259](#) DOI: [10.1097/MD.00000000000008619](#)]
- 174 **Palanivelu C**, Senthilnathan P, Sabnis SC, Babu NS, Srivatsan Gurumurthy S, Anand Vijai N, Nalankilli VP, Praveen Raj P, Parthasarathy R, Rajapandian S. Randomized clinical trial of laparoscopic vs open pancreatoduodenectomy for periampullary tumours. *Br J Surg* 2017; **104**: 1443-1450 [PMID: [28895142](#) DOI: [10.1002/bjs.10662](#)]
- 175 **Poves I**, Burdío F, Morató O, Iglesias M, Radosevic A, Ilzarbe L, Visa L, Grande L. Comparison of Perioperative Outcomes Between Laparoscopic and Open Approach for Pancreatoduodenectomy: The PADULAP Randomized Controlled Trial. *Ann Surg* 2018; **268**: 731-739 [PMID: [30138162](#) DOI: [10.1097/SLA.0000000000002893](#)]
- 176 **Croome KP**, Farnell MB, Que FG, Reid-Lombardo KM, Truty MJ, Nagorney DM, Kendrick ML. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? *Ann Surg* 2014; **260**: 633-8; discussion 638 [PMID: [25203880](#) DOI: [10.1097/SLA.0000000000000937](#)]
- 177 **Boone BA**, Zenati M, Hogg ME, Steve J, Moser AJ, Bartlett DL, Zeh HJ, Zureikat AH. Assessment of quality outcomes for robotic pancreaticoduodenectomy: identification of the learning curve. *JAMA Surg* 2015; **150**: 416-422 [PMID: [25761143](#) DOI: [10.1001/jamasurg.2015.17](#)]
- 178 **Wang SE**, Shyr BU, Chen SC, Shyr YM. Comparison between robotic and open

- pancreaticoduodenectomy with modified Blumgart pancreaticojejunostomy: A propensity score-matched study. *Surgery* 2018; **164**: 1162-1167 [PMID: 30093277 DOI: 10.1016/j.surg.2018.06.031]
- 179 **Zureikat AH**, Postlewait LM, Liu Y, Gillespie TW, Weber SM, Abbott DE, Ahmad SA, Maithel SK, Hogg ME, Zenati M, Cho CS, Salem A, Xia B, Steve J, Nguyen TK, Keshava HB, Chalikhonda S, Walsh RM, Talamonti MS, Stocker SJ, Bentrem DJ, Lumpkin S, Kim HJ, Zeh HJ 3rd, Kooby DA. A Multi-institutional Comparison of Perioperative Outcomes of Robotic and Open Pancreaticoduodenectomy. *Ann Surg* 2016; **264**: 640-649 [PMID: 27433907 DOI: 10.1097/SLA.0000000000001869]
- 180 **Nassour I**, Tohme S, Hoehn R, Adam MA, Zureikat AH, Alessandro P. Safety and oncologic efficacy of robotic compared to open pancreaticoduodenectomy after neoadjuvant chemotherapy for pancreatic cancer. *Surg Endosc* 2021; **35**: 2248-2254 [PMID: 32440928 DOI: 10.1007/s00464-020-07638-w]
- 181 **Baimas-George M**, Watson M, Murphy KJ, Iannitti D, Baker E, Ocuin L, Vrochides D, Martinie JB. Robotic pancreaticoduodenectomy may offer improved oncologic outcomes over open surgery: a propensity-matched single-institution study. *Surg Endosc* 2020; **34**: 3644-3649 [PMID: 32328825 DOI: 10.1007/s00464-020-07564-x]
- 182 **Mizrahi JD**, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet* 2020; **395**: 2008-2020 [PMID: 32593337 DOI: 10.1016/S0140-6736(20)30974-0]
- 183 **Perri G**, Prakash L, Qiao W, Varadhachary GR, Wolff R, Fogelman D, Overman M, Pant S, Javle M, Koay EJ, Herman J, Kim M, Ikoma N, Tzeng CW, Lee JE, Katz MHG. Postoperative Chemotherapy Benefits Patients Who Received Preoperative Therapy and Pancreatectomy for Pancreatic Adenocarcinoma. *Ann Surg* 2020; **271**: 996-1002 [PMID: 31895709 DOI: 10.1097/SLA.0000000000003763]
- 184 **Müller PC**, Frey MC, Ruzza CM, Nickel F, Jost C, Gwerder C, Hackert T, Z'graggen K, Kessler U. Neoadjuvant Chemotherapy in Pancreatic Cancer: An Appraisal of the Current High-Level Evidence. *Pharmacology* 2021; **106**: 143-153 [PMID: 32966993 DOI: 10.1159/000510343]
- 185 **Neoptolemos JP**, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW; European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350**: 1200-1210 [PMID: 15028824 DOI: 10.1056/NEJMoa032295]
- 186 **Oettle H**, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zülke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013; **310**: 1473-1481 [PMID: 24104372 DOI: 10.1001/jama.2013.279201]
- 187 **Neoptolemos JP**, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW; European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; **304**: 1073-1081 [PMID: 20823433 DOI: 10.1001/jama.2010.1275]
- 188 **Neoptolemos JP**, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, Faluy O, O'Reilly DA, Cunningham D, Wadsley J, Darby S, Meyer T, Gillmore R, Anthoney A, Lind P, Glimelius B, Falk S, Izbicki JR, Middleton GW, Cummins S, Ross PJ, Wasan H, McDonald A, Crosby T, Ma YT, Patel K, Sherriff D, Soomal R, Borg D, Sothi S, Hammel P, Hackert T, Jackson R, Büchler MW; European Study Group for Pancreatic Cancer. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017; **389**: 1011-1024 [PMID: 28129987 DOI: 10.1016/S0140-6736(16)32409-6]
- 189 **Conroy T**, Hammel P, Hebban M, Ben Abdelghani M, Wei AC, Raoul JL, Choné L, Francois E, Artru P, Biagi JJ, Lecomte T, Assenat E, Faroux R, Ychou M, Volet J, Sauvanet A, Breysacher G, Di Fiore F, Cripps C, Kavan P, Texereau P, Bouhier-Leporrier K, Khemissa-Akouz F, Legoux JL, Juzyna B, Gourgou S, O'Callaghan CJ, Jouffroy-Zeller C, Rat P, Malka D, Castan F, Bachet JB; Canadian Cancer Trials Group and the Unicancer-GI-PRODIGE Group. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *N Engl J Med* 2018; **379**: 2395-2406 [PMID: 30575490 DOI: 10.1056/NEJMoa1809775]
- 190 **Parmar A**, Chaves-Porras J, Saluja R, Perry K, Rahmadian AP, Santos SD, Ko YJ, Berry S, Doherty M, Chan KKW. Adjuvant treatment for resected pancreatic adenocarcinoma: A systematic review and network meta-analysis. *Crit Rev Oncol Hematol* 2020; **145**: 102817 [PMID: 31955005 DOI: 10.1016/j.critrevonc.2019.102817]
- 191 **Galvano A**, Castiglia M, Rizzo S, Silvestri N, Brunetti O, Vaccaro G, Gristina V, Barraco N, Bono M, Guercio G, Graceffa G, Fulfaro F, Gori S, Bazan V, Russo A. Moving the Target on the Optimal Adjuvant Strategy for Resected Pancreatic Cancers: A Systematic Review with Meta-Analysis. *Cancers (Basel)* 2020; **12** [PMID: 32110977 DOI: 10.3390/cancers12030534]
- 192 **Raufi AG**, Breakstone R, Leonard K, Charpentier K, Beard R, Renaud J, Cavanaugh L, Sturtevant A, MacKinnon K, Almhanna K, Olszewski A, Safran HP. Adjuvant FOLFOX+Nab-Paclitaxel (FOLFOX-A) for Pancreatic Cancer: A Brown University Oncology Research Group Phase II Study

- (BrUOG295). *Am J Clin Oncol* 2020; **43**: 857-860 [PMID: 32976178 DOI: 10.1097/COC.0000000000000762]
- 193 **Kamarajah SK**, Bundred JR, Alrawashdeh W, Manas D, White SA. A systematic review and network meta-analysis of phase III randomised controlled trials for adjuvant therapy following resection of pancreatic ductal adenocarcinoma (PDAC). *HPB (Oxford)* 2020; **22**: 649-659 [PMID: 31894014 DOI: 10.1016/j.hpb.2019.12.001]
- 194 **Ma SJ**, Oladeru OT, Miccio JA, Iovoli AJ, Hermann GM, Singh AK. Association of Timing of Adjuvant Therapy With Survival in Patients With Resected Stage I to II Pancreatic Cancer. *JAMA Netw Open* 2019; **2**: e199126 [PMID: 31411712 DOI: 10.1001/jamanetworkopen.2019.9126]
- 195 **You MS**, Ryu JK, Huh G, Chun JW, Paik WH, Lee SH, Kim YT. Comparison of efficacy between adjuvant chemotherapy and chemoradiation therapy for pancreatic cancer: AJCC stage-based approach. *World J Clin Oncol* 2020; **11**: 747-760 [PMID: 33033696 DOI: 10.5306/wjco.v11.i9.747]
- 196 **Janssen QP**, O'Reilly EM, van Eijck CHJ, Groot Koerkamp B. Neoadjuvant Treatment in Patients With Resectable and Borderline Resectable Pancreatic Cancer. *Front Oncol* 2020; **10**: 41 [PMID: 32083002 DOI: 10.3389/fonc.2020.00041]
- 197 **Murphy JE**, Wo JY, Ryan DP, Jiang W, Yeap BY, Drapek LC, Blaszkowsky LS, Kwak EL, Allen JN, Clark JW, Faris JE, Zhu AX, Goyal L, Lillmoie KD, DeLaney TF, Fernández-Del Castillo C, Ferrone CR, Hong TS. Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma: A Phase 2 Clinical Trial. *JAMA Oncol* 2018; **4**: 963-969 [PMID: 29800971 DOI: 10.1001/jamaoncol.2018.0329]
- 198 **van Roessel S**, van Veldhuisen E, Klompmaker S, Janssen QP, Abu Hilal M, Alseidi A, Balduzzi A, Balzano G, Bassi C, Berrevoet F, Bonds M, Busch OR, Butturini G, Del Chiaro M, Conlon KC, Falconi M, Frigerio I, Fusai GK, Gagnière J, Griffin O, Hackert T, Halimi A, Klaiber U, Labori KJ, Malleo G, Marino MV, Mortensen MB, Nikov A, Lesurtel M, Keck T, Kleeff J, Pandé R, Pfeiffer P, Pietrasz D, Roberts KJ, Sa Cunha A, Salvia R, Strobel O, Tarvainen T, Bossuyt PM, van Laarhoven HWM, Wilmink JW, Groot Koerkamp B, Besselink MG; European-African Hepato-Pancreato-Biliary Association. Evaluation of Adjuvant Chemotherapy in Patients With Resected Pancreatic Cancer After Neoadjuvant FOLFIRINOX Treatment. *JAMA Oncol* 2020; **6**: 1733-1740 [PMID: 32910170 DOI: 10.1001/jamaoncol.2020.3537]
- 199 **Yoo C**, Hwang I, Song TJ, Lee SS, Jeong JH, Park DH, Seo DW, Lee SK, Kim MH, Byun JH, Park JH, Hwang DW, Song KB, Lee JH, Lee W, Chang HM, Kim KP, Kim SC, Ryoo BY. FOLFIRINOX in borderline resectable and locally advanced unresectable pancreatic adenocarcinoma. *Ther Adv Med Oncol* 2020; **12**: 1758835920953294 [PMID: 32983266 DOI: 10.1177/1758835920953294]
- 200 **Oba A**, Ho F, Bao QR, Al-Musawi MH, Schulick RD, Del Chiaro M. Neoadjuvant Treatment in Pancreatic Cancer. *Front Oncol* 2020; **10**: 245 [PMID: 32185128 DOI: 10.3389/fonc.2020.00245]
- 201 **Giovinazzo F**, Soggiu F, Jang JY, Versteijne E, van Tienhoven G, van Eijck CH, Han Y, Choi SH, Kang CM, Zalupski M, Ahmad H, Yentz S, Helton S, Rose JB, Takishita C, Nagakawa Y, Abu Hilal M. Gemcitabine-Based Neoadjuvant Treatment in Borderline Resectable Pancreatic Ductal Adenocarcinoma: A Meta-Analysis of Individual Patient Data. *Front Oncol* 2020; **10**: 1112 [PMID: 32850319 DOI: 10.3389/fonc.2020.01112]
- 202 **Versteijne E**, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, Buijssen J, Busch OR, Creemers GM, van Dam RM, Eskens FALM, Festen S, de Groot JWB, Groot Koerkamp B, de Hingh IH, Homs MYV, van Hooft JE, Kerver ED, Luelmo SAC, Neelis KJ, Nuytens J, Paardekooper GMRM, Patijn GA, van der Sangen MJC, de Vos-Geelen J, Wilmink JW, Zwinderman AH, Punt CJ, van Eijck CH, van Tienhoven G; Dutch Pancreatic Cancer Group. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol* 2020; **38**: 1763-1773 [PMID: 32105518 DOI: 10.1200/JCO.19.02274]
- 203 **Cloyd JM**, Chen HC, Wang X, Tzeng CD, Kim MP, Aloia TA, Vauthey JN, Lee JE, Katz MHG. Chemotherapy Versus Chemoradiation as Preoperative Therapy for Resectable Pancreatic Ductal Adenocarcinoma: A Propensity Score Adjusted Analysis. *Pancreas* 2019; **48**: 216-222 [PMID: 30629022 DOI: 10.1097/MPA.0000000000001231]
- 204 **Grossberg AJ**, Chu LC, Deig CR, Fishman EK, Hwang WL, Maitra A, Marks DL, Mehta A, Nabavizadeh N, Simeone DM, Weekes CD, Thomas CR Jr. Multidisciplinary standards of care and recent progress in pancreatic ductal adenocarcinoma. *CA Cancer J Clin* 2020; **70**: 375-403 [PMID: 32683683 DOI: 10.3322/caac.21626]
- 205 **Ghaneh P**, Palmer DH, Cicconi S, Halloran C, Psarelli EE, Rawcliffe CL, Sripatham R, Mukherjee S, Wadsley J, Al-Mukhtar A, Jiao LR, Wasan HS, Carter R, Graham JS, Ammad F, Evans J, Tjaden C, Hackert T, Buchler MW, Neoptolemos JP; European Study Group for Pancreatic Cancer (ESPAC). ESPAC-5F: four-arm, prospective, multicenter, international randomized phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or MFFX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer. *J Clin Oncol* 2020; **38** (15_Suppl): 4505 [DOI: 10.1200/JCO.2020.38.15_suppl.4505]
- 206 **Gamboia AC**, Rupji M, Switchenko JM, Lee RM, Turgeon MK, Meyer BI, Russell MC, Cardona K, Kooby DA, Maithel SK, Shah MM. Optimal timing and treatment strategy for pancreatic cancer. *J Surg Oncol* 2020; **122**: 457-468 [PMID: 32470166 DOI: 10.1002/jso.25976]
- 207 **Sohal D**, Duong MT, Ahmad SA, Gandhi N, Beg MS. SWOG S1505: Results of perioperative chemotherapy (peri-op CTx) with mFFX vs gemcitabine/nab-paclitaxel (Gem/nabP) for resectable pancreatic ductal adenocarcinoma (PRA). *J Clin Oncol* 2020; **38** (15_Suppl): 4504

- 208 **Motoi F**, Unno M. Adjuvant and neoadjuvant treatment for pancreatic adenocarcinoma. *Jpn J Clin Oncol* 2020; **50**: 483-489 [PMID: 32083290 DOI: 10.1093/jjco/hyaa018]
- 209 **Labori KJ**, Lassen K, Hoem D, Grønbech JE, Søreide JA, Mortensen K, Smaaland R, Sorbye H, Verbeke C, Dueland S. Neoadjuvant chemotherapy vs surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) - study protocol for a national multicentre randomized controlled trial. *BMC Surg* 2017; **17**: 94 [PMID: 28841916 DOI: 10.1186/s12893-017-0291-1]
- 210 **Schwarz L**, Vernerey D, Bachet JB, Tuech JJ, Portales F, Michel P, Cunha AS. Resectable pancreatic adenocarcinoma neo-adjuvant FOLF(IRIN)OX-based chemotherapy - a multicenter, non-comparative, randomized, phase II trial (PANACHE01-PRODIGE48 study). *BMC Cancer* 2018; **18**: 762 [PMID: 30041614 DOI: 10.1186/s12885-018-4663-4]
- 211 **Ettrich TJ**, Berger AW, Perkhof L, Daum S, König A, Dickhut A, Wittel U, Wille K, Geissler M, Algül H, Gallmeier E, Atzpodiën J, Kornmann M, Mucic R, Prasnikar N, Tannapfel A, Reinacher-Schick A, Uhl W, Seufferlein T. Neoadjuvant plus adjuvant or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer - the NEONAX trial (AIO-PAK-0313), a prospective, randomized, controlled, phase II study of the AIO pancreatic cancer group. *BMC Cancer* 2018; **18**: 1298 [PMID: 30594153 DOI: 10.1186/s12885-018-5183-y]
- 212 **Motoi F**, Kosuge T, Ueno H, Yamaue H, Satoi S, Sho M, Honda G, Matsumoto I, Wada K, Furuse J, Matsuyama Y, Unno M; Study Group of Preoperative Therapy for Pancreatic Cancer (Prep) and Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP). Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 vs upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). *Jpn J Clin Oncol* 2019; **49**: 190-194 [PMID: 30608598 DOI: 10.1093/jjco/hyy190]
- 213 **Okusaka T**, Nakamura M, Yoshida M, Kitano M, Uesaka K, Ito Y, Furuse J, Hanada K, Okazaki K; Committee for Revision of Clinical Guidelines for Pancreatic Cancer of the Japan Pancreas Society. Clinical Practice Guidelines for Pancreatic Cancer 2019 From the Japan Pancreas Society: A Synopsis. *Pancreas* 2020; **49**: 326-335 [PMID: 32132516 DOI: 10.1097/MPA.0000000000001513]
- 214 **Okusaka T**, Furuse J. Recent advances in chemotherapy for pancreatic cancer: evidence from Japan and recommendations in guidelines. *J Gastroenterol* 2020; **55**: 369-382 [PMID: 31997007 DOI: 10.1007/s00535-020-01666-y]
- 215 **UMIN-CTR Clinical Trial**. Randomized phase II/III study of gemcitabine and nab-paclitaxel therapy vs S-1 and concurrent radiotherapy as neoadjuvant treatment for Borderline resectable pancreatic cancer. [cited 21 Dec 2019]. In: UMIN-CTR Clinical Trial [Internet]. Available from: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000030821
- 216 **Sahni S**, Nahm C, Krisp C, Molloy MP, Mehta S, Maloney S, Itchins M, Pavlakis N, Clarke S, Chan D, Gill AJ, Howell VM, Samra J, Mittal A. Identification of Novel Biomarkers in Pancreatic Tumor Tissue to Predict Response to Neoadjuvant Chemotherapy. *Front Oncol* 2020; **10**: 237 [PMID: 32195182 DOI: 10.3389/fonc.2020.00237]
- 217 **Hammel P**, Lacy J, Portales F, Sobrero AF, Pazo Cid RA, Mozo JLM, Terrebbonne E, Dowden SD, Li JS, Ong TJ, Nydam T, Philip PA. Phase II LAPACT trial of nab-paclitaxel (nab-P) plus gemcitabine (G) for patients with locally advanced pancreatic cancer (LAPDAC). *J Clin Oncol* 2018; **36** (suppl 4): 204
- 218 **Marthey L**, Sa-Cunha A, Blanc JF, Gauthier M, Cuffe A, Francois E, Trouilloud I, Malka D, Bachet JB, Coriat R, Terrebbonne E, De La Fouchardière C, Manfredi S, Solub D, Lécaillon C, Thiot Bidault A, Carbonnel F, Taieb J. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. *Ann Surg Oncol* 2015; **22**: 295-301 [PMID: 25037971 DOI: 10.1245/s10434-014-3898-9]
- 219 **Weniger M**, Moir J, Damm M, Maggino L, Kordes M, Rosendahl J, Ceyhan GO, Schorn S; RESPECT-study group. Respect - A multicenter retrospective study on preoperative chemotherapy in locally advanced and borderline resectable pancreatic cancer. *Pancreatol* 2020; **20**: 1131-1138 [PMID: 32739267 DOI: 10.1016/j.pan.2020.06.012]
- 220 **Suker M**, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, El-Rayes BF, Wang-Gillam A, Lacy J, Hosein PJ, Moorcraft SY, Conroy T, Hohla F, Allen P, Taieb J, Hong TS, Shridhar R, Chau I, van Eijck CH, Koerkamp BG. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol* 2016; **17**: 801-810 [PMID: 27160474 DOI: 10.1016/S1470-2045(16)00172-8]
- 221 **Philip PA**, Lacy J, Portales F, Sobrero A, Pazo-Cid R, Manzano Mozo JL, Kim EJ, Dowden S, Zakari A, Borg C, Terrebbonne E, Rivera F, Sastre J, Bathini V, López-Trabada D, Asselah J, Saif MW, Shiansong Li J, Ong TJ, Nydam T, Hammel P. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. *Lancet Gastroenterol Hepatol* 2020; **5**: 285-294 [PMID: 31953079 DOI: 10.1016/S2468-1253(19)30327-9]
- 222 **Kunzmann V**, Algül H, Goekkurt E, Siegler GM, Martens UM, Waldschmidt D, Pelzer U, Hennes E, Fuchs M, Siveke J, Kullmann F, Boeck S, Ettrich TJ, Ferenczy P, Keller R, Germer C, Stein H, Hartlapp I, Klein I, Heinemann V. Conversion rate in locally advanced pancreatic cancer (LAPDAC) after nab-paclitaxel/gemcitabine- or MFFX-based induction chemotherapy (NEOLAP): final results of a multicenter randomised phase II AIO trial. *Ann Oncol* 2019; **30**: v253
- 223 **Wolfe AR**, Prabhakar D, Yildiz VO, Cloyd JM, Dillhoff M, Abushahin L, Alexandra Diaz D, Miller ED, Chen W, Frankel WL, Noonan A, Williams TM. Neoadjuvant-modified FOLFIRINOX vs nab-paclitaxel plus gemcitabine for borderline resectable or locally advanced pancreatic cancer patients

- who achieved surgical resection. *Cancer Med* 2020; **9**: 4711-4723 [PMID: [32415696](#) DOI: [10.1002/cam4.3075](#)]
- 224 **Hammel P**, Huguët F, van Laethem JL, Goldstein D, Glimelius B, Artru P, Borbath I, Bouché O, Shannon J, André T, Mineur L, Chibaudel B, Bonnetain F, Louvet C; LAP07 Trial Group. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. *JAMA* 2016; **315**: 1844-1853 [PMID: [27139057](#) DOI: [10.1001/jama.2016.4324](#)]
- 225 **Arcelli A**, Buwenge M, Macchia G, Bertini F, Guido A, Deodato F, Cilla S, Scotti V, Rosetto ME, Djan I, Parisi S, Mattiucci GC, Cellini F, Fiore M, Bonomo P, Belgioia L, Niespolo RM, Gabriele P, Di Marco M, Simoni N, Mazzarotto R, Morganti AG; AIRO (Italian Association of Radiation Oncology and Clinical Oncology) Gastrointestinal Study Group. Stereotactic body radiotherapy vs conventionally fractionated chemoradiation in locally advanced pancreatic cancer: A multicenter case-control study (PAULA-1). *Cancer Med* 2020; **9**: 7879-7887 [PMID: [32910549](#) DOI: [10.1002/cam4.3330](#)]
- 226 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX vs gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: [21561347](#) DOI: [10.1056/NEJMoa1011923](#)]
- 227 **Von Hoff DD**, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Taberner J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: [24131140](#) DOI: [10.1056/NEJMoa1304369](#)]
- 228 **Chan KKW**, Guo H, Cheng S, Beca JM, Redmond-Misner R, Isaranuwachai W, Qiao L, Earle C, Berry SR, Biagi JJ, Welch S, Meyers BM, Mittmann N, Coburn N, Arias J, Schwartz D, Dai WF, Gavura S, McLeod R, Kennedy ED. Real-world outcomes of FOLFIRINOX vs gemcitabine and nab-paclitaxel in advanced pancreatic cancer: A population-based propensity score-weighted analysis. *Cancer Med* 2020; **9**: 160-169 [PMID: [31724340](#) DOI: [10.1002/cam4.2705](#)]
- 229 **Wang Y**, Camateros P, Cheung WY. A Real-World Comparison of FOLFIRINOX, Gemcitabine Plus nab-Paclitaxel, and Gemcitabine in Advanced Pancreatic Cancers. *J Gastrointest Cancer* 2019; **50**: 62-68 [PMID: [29143916](#) DOI: [10.1007/s12029-017-0028-5](#)]
- 230 **Wang-Gillam A**, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, Macarulla T, Lee KH, Cunningham D, Blanc JF, Hubner RA, Chiu CF, Schwartzmann G, Siveke JT, Braiteh F, Moyo V, Belanger B, Dhindsa N, Bayever E, Von Hoff DD, Chen LT; NAPOLI-1 Study Group. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 2016; **387**: 545-557 [PMID: [26615328](#) DOI: [10.1016/S0140-6736\(15\)00986-1](#)]
- 231 **Golan T**, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, Park JO, Hochhauser D, Arnold D, Oh DY, Reinacher-Schick A, Tortora G, Algül H, O'Reilly EM, McGuinness D, Cui KY, Schlienger K, Locker GY, Kindler HL. Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer. *N Engl J Med* 2019; **381**: 317-327 [PMID: [31157963](#) DOI: [10.1056/NEJMoa1903387](#)]
- 232 **Alistar A**, Morris BB, Desnoyer R, Klepin HD, Hosseinzadeh K, Clark C, Cameron A, Leyendecker J, D'Agostino R Jr, Topaloglu U, Boteju LW, Boteju AR, Shorr R, Zachar Z, Bingham PM, Ahmed T, Crane S, Shah R, Migliano JJ, Pardee TS, Miller L, Hawkins G, Jin G, Zhang W, Pasche B. Safety and tolerability of the first-in-class agent CPI-613 in combination with modified FOLFIRINOX in patients with metastatic pancreatic cancer: a single-centre, open-label, dose-escalation, phase 1 trial. *Lancet Oncol* 2017; **18**: 770-778 [PMID: [28495639](#) DOI: [10.1016/S1470-2045\(17\)30314-5](#)]
- 233 **Jiang B**, Zhou L, Lu J, Wang Y, Liu C, You L, Guo J. Stroma-Targeting Therapy in Pancreatic Cancer: One Coin With Two Sides? *Front Oncol* 2020; **10**: 576399 [PMID: [33178608](#) DOI: [10.3389/fonc.2020.576399](#)]
- 234 **von Ahrens D**, Bhagat TD, Nagrath D, Maitra A, Verma A. The role of stromal cancer-associated fibroblasts in pancreatic cancer. *J Hematol Oncol* 2017; **10**: 76 [PMID: [28351381](#) DOI: [10.1186/s13045-017-0448-5](#)]
- 235 **Provenzano PP**, Hingorani SR. Hyaluronan, fluid pressure, and stromal resistance in pancreas cancer. *Br J Cancer* 2013; **108**: 1-8 [PMID: [23299539](#) DOI: [10.1038/bjc.2012.569](#)]
- 236 **Hingorani SR**, Zheng L, Bullock AJ, Seery TE, Harris WP, Sigal DS, Braiteh F, Ritch PS, Zalupski MM, Bahary N, Oberstein PE, Wang-Gillam A, Wu W, Chondros D, Jiang P, Khelifa S, Pu J, Aldrich C, Hendifar AE. HALO 202: Randomized Phase II Study of PEGPH20 Plus Nab-Paclitaxel/Gemcitabine Versus Nab-Paclitaxel/Gemcitabine in Patients With Untreated, Metastatic Pancreatic Ductal Adenocarcinoma. *J Clin Oncol* 2018; **36**: 359-366 [PMID: [29232172](#) DOI: [10.1200/JCO.2017.74.9564](#)]
- 237 **Catenacci DV**, Junttila MR, Karrison T, Bahary N, Horiba MN, Nattam SR, Marsh R, Wallace J, Kozloff M, Rajdev L, Cohen D, Wade J, Sleckman B, Lenz HJ, Stiff P, Kumar P, Xu P, Henderson L, Takebe N, Salgia R, Wang X, Stadler WM, de Sauvage FJ, Kindler HL. Randomized Phase Ib/II Study of Gemcitabine Plus Placebo or Vismodegib, a Hedgehog Pathway Inhibitor, in Patients With

- Metastatic Pancreatic Cancer. *J Clin Oncol* 2015; **33**: 4284-4292 [PMID: [26527777](#) DOI: [10.1200/JCO.2015.62.8719](#)]
- 238 **McCleary-Wheeler AL**, Carr RM, Palmer SR, Smyrk TC, Allred JB, Almada LL, Tolosa EJ, Lamberti MJ, Marks DL, Borad MJ, Molina JR, Qi Y, Lingle WL, Grothey A, Pitot HC, Jatoi A, Northfelt DW, Bryce AH, McWilliams RR, Okuno SH, Haluska P, Kim GP, Colon-Otero G, Lowe VJ, Callstrom MR, Ma WW, Bekaii-Saab T, Hung MC, Erlichman C, Fernandez-Zapico ME. Phase 1 trial of Vismodegib and Erlotinib combination in metastatic pancreatic cancer. *Pancreatology* 2020; **20**: 101-109 [PMID: [31787526](#) DOI: [10.1016/j.pan.2019.11.011](#)]
- 239 **Murphy JE**, Wo JY, Ryan DP, Clark JW, Jiang W, Yeap BY, Drapek LC, Ly L, Baglini CV, Blaszkowsky LS, Ferrone CR, Parikh AR, Weekes CD, Nipp RD, Kwak EL, Allen JN, Corcoran RB, Ting DT, Faris JE, Zhu AX, Goyal L, Berger DL, Qadan M, Lillemoe KD, Talele N, Jain RK, DeLaney TF, Duda DG, Boucher Y, Fernández-Del Castillo C, Hong TS. Total Neoadjuvant Therapy With FOLFIRINOX in Combination With Losartan Followed by Chemoradiotherapy for Locally Advanced Pancreatic Cancer: A Phase 2 Clinical Trial. *JAMA Oncol* 2019; **5**: 1020-1027 [PMID: [31145418](#) DOI: [10.1001/jamaoncol.2019.0892](#)]
- 240 **Dimcevski G**, Kotopoulos S, Bjånes T, Hoem D, Schjøtt J, Gjertsen BT, Biermann M, Molven A, Sorbye H, McCormack E, Postema M, Gilja OH. A human clinical trial using ultrasound and microbubbles to enhance gemcitabine treatment of inoperable pancreatic cancer. *J Control Release* 2016; **243**: 172-181 [PMID: [27744037](#) DOI: [10.1016/j.jconrel.2016.10.007](#)]
- 241 **Cooke VG**, LeBleu VS, Keskin D, Khan Z, O'Connell JT, Teng Y, Duncan MB, Xie L, Maeda G, Vong S, Sugimoto H, Rocha RM, Damascena A, Brentani RR, Kalluri R. Pericyte depletion results in hypoxia-associated epithelial-to-mesenchymal transition and metastasis mediated by met signaling pathway. *Cancer Cell* 2012; **21**: 66-81 [PMID: [22264789](#) DOI: [10.1016/j.ccr.2011.11.024](#)]
- 242 **Veenstra VL**, Damhofer H, Waasdorp C, van Rijssen LB, van de Vijver MJ, Dijk F, Wilmink HW, Besselink MG, Busch OR, Chang DK, Bailey PJ, Biankin AV, Kocher HM, Medema JP, Li JS, Jiang R, Pierce DW, van Laarhoven HWM, Bijlsma MF. ADAM12 is a circulating marker for stromal activation in pancreatic cancer and predicts response to chemotherapy. *Oncogenesis* 2018; **7**: 87 [PMID: [30442938](#) DOI: [10.1038/s41389-018-0096-9](#)]
- 243 **Griesmann H**, Drexel C, Milosevic N, Sipos B, Rosendahl J, Gress TM, Michl P. Pharmacological macrophage inhibition decreases metastasis formation in a genetic model of pancreatic cancer. *Gut* 2017; **66**: 1278-1285 [PMID: [27013602](#) DOI: [10.1136/gutjnl-2015-310049](#)]
- 244 **Morrison AH**, Byrne KT, Vonderheide RH. Immunotherapy and Prevention of Pancreatic Cancer. *Trends Cancer* 2018; **4**: 418-428 [PMID: [29860986](#) DOI: [10.1016/j.trecan.2018.04.001](#)]
- 245 **Royal RE**, Levy C, Turner K, Mathur A, Hughes M, Kammula US, Sherry RM, Topalian SL, Yang JC, Lowy I, Rosenberg SA. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother* 2010; **33**: 828-833 [PMID: [20842054](#) DOI: [10.1097/CJI.0b013e3181eccc14e](#)]
- 246 **Brahmer JR**, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthy S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012; **366**: 2455-2465 [PMID: [22658128](#) DOI: [10.1056/NEJMoa1200694](#)]
- 247 **O'Reilly EM**, Oh DY, Dhani N, Renouf DJ, Lee MA, Sun W, Fisher G, Hezel A, Chang SC, Vlahovic G, Takahashi O, Yang Y, Fitts D, Philip PA. Durvalumab With or Without Tremelimumab for Patients With Metastatic Pancreatic Ductal Adenocarcinoma: A Phase 2 Randomized Clinical Trial. *JAMA Oncol* 2019; **5**: 1431-1438 [PMID: [31318392](#) DOI: [10.1001/jamaoncol.2019.1588](#)]
- 248 **Tumeh PC**, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, Chmielowski B, Spasic M, Henry G, Ciobanu V, West AN, Carmona M, Kivork C, Seja E, Cherry G, Gutierrez AJ, Grogan TR, Mateus C, Tomasic G, Glaspy JA, Emerson RO, Robins H, Pierce RH, Elashoff DA, Robert C, Ribas A. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* 2014; **515**: 568-571 [PMID: [25428505](#) DOI: [10.1038/nature13954](#)]
- 249 **Humphris JL**, Patch AM, Nones K, Bailey PJ, Johns AL, McKay S, Chang DK, Miller DK, Pajic M, Kassahn KS, Quinn MC, Bruxner TJ, Christ AN, Harliwong I, Idrisoglu S, Manning S, Nourse C, Nourbakhsh E, Stone A, Wilson PJ, Anderson M, Fink JL, Holmes O, Kazakoff S, Leonard C, Newell F, Waddell N, Wood S, Mead RS, Xu Q, Wu J, Pinese M, Cowley MJ, Jones MD, Nagrial AM, Chin VT, Chantrill LA, Mawson A, Chou A, Scarlett CJ, Pinho AV, Rooman I, Giry-Laterriere M, Samra JS, Kench JG, Merrett ND, Toon CW, Epari K, Nguyen NQ, Barbour A, Zeps N, Jamieson NB, McKay CJ, Carter CR, Dickson EJ, Graham JS, Duthie F, Oien K, Hair J, Morton JP, Sansom OJ, Grützmann R, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Schulick RD, Wolfgang CL, Morgan RA, Lawlor RT, Rusev B, Corbo V, Salvia R, Cataldo I, Tortora G, Tempero MA; Australian Pancreatic Cancer Genome Initiative, Hofmann O, Eshleman JR, Pilarsky C, Scarpa A, Musgrove EA, Gill AJ, Pearson JV, Grimmond SM, Waddell N, Biankin AV. Hypermutation In Pancreatic Cancer. *Gastroenterology* 2017; **152**: 68-74.e2 [PMID: [27856273](#) DOI: [10.1053/j.gastro.2016.09.060](#)]
- 250 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl*

- J Med* 2015; **372**: 2509-2520 [PMID: 26028255 DOI: 10.1056/NEJMoa1500596]
- 251 **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: 28596308 DOI: 10.1126/science.aan6733]
- 252 **Wainberg ZA**, Hochster HS, Kim EJH, George B, Kalyan A, Chiorean EG, Waterhouse DM, Gutierrez M, Parikh AR, Jain R, Carrizosa DR, Soliman HH, Bhore R, Banerjee S, Lyons L, Louis CU, Ong TJ, O'Dwyer PJ. Phase I study of nivolumab (Nivo) + nab-paclitaxel (nab-P) + gemcitabine (Gem) in advanced pancreatic cancer (APDAC). *J Clin Oncol* 2019; **37**: 298
- 253 **Weiss GJ**, Blaydorn L, Beck J, Bornemann-Kolatzki K, Urnovitz H, Schütz E, Khemka V. Phase Ib/II study of gemcitabine, nab-paclitaxel, and pembrolizumab in metastatic pancreatic adenocarcinoma. *Invest New Drugs* 2018; **36**: 96-102 [PMID: 29119276 DOI: 10.1007/s10637-017-0525-1]
- 254 **National Institute of Public Health**. ONO-4538 Phase II Study (ONO-4538-83/TASUKI-83). [cited 21 Dec 2019]. In: National Institute of Public Health [Internet]. Available from: https://rctportal.niph.go.jp/en/detail?trial_id=JapicCTI-184230
- 255 **Wang-Gillam A**, O'Reilly EM, Bendell JC, Wainberg ZA, Borazanci EH, Bahary N, O'Hara MH, Beatty GL, Pant S, Cohen DJ, Leong S, Beg MS, Yu KH, Evans TRJ, Seufferlein T, Okusaka T, Phillips P, Liu X, Perna SK, Le DT. A randomized phase II study of cabiralizumab (cabira) + nivolumab (nivo) ± chemotherapy (chemo) in advanced pancreatic ductal adenocarcinoma (PDAC). *J Clin Oncol* 2019; **37**: TPS465
- 256 **Schizas D**, Charalampakis N, Kole C, Economopoulou P, Koustas E, Gkotsis E, Ziogas D, Psyri A, Karamouzis MV. Immunotherapy for pancreatic cancer: A 2020 update. *Cancer Treat Rev* 2020; **86**: 102016 [PMID: 32247999 DOI: 10.1016/j.ctrv.2020.102016]
- 257 **Le DT**, Picozzi VJ, Ko AH, Wainberg ZA, Kindler H, Wang-Gillam A, Oberstein P, Morse MA, Zeh HJ 3rd, Weekes C, Reid T, Borazanci E, Crocenzi T, LoConte NK, Musher B, Laheru D, Murphy A, Whiting C, Nair N, Enstrom A, Ferber S, Brockstedt DG, Jaffee EM. Results from a Phase IIb, Randomized, Multicenter Study of GVAX Pancreas and CRS-207 Compared with Chemotherapy in Adults with Previously Treated Metastatic Pancreatic Adenocarcinoma (ECLIPSE Study). *Clin Cancer Res* 2019; **25**: 5493-5502 [PMID: 31126960 DOI: 10.1158/1078-0432.CCR-18-2992]
- 258 **Asahara S**, Takeda K, Yamao K, Maguchi H, Yamaue H. Phase I/II clinical trial using HLA-A24-restricted peptide vaccine derived from KIF20A for patients with advanced pancreatic cancer. *J Transl Med* 2013; **11**: 291 [PMID: 24237633 DOI: 10.1186/1479-5876-11-291]
- 259 **Suzuki N**, Hazama S, Iguchi H, Uesugi K, Tanaka H, Hirakawa K, Aruga A, Hatori T, Ishizaki H, Umeda Y, Fujiwara T, Ikemoto T, Shimada M, Yoshimatsu K, Shimizu R, Hayashi H, Sakata K, Takenouchi H, Matsui H, Shindo Y, Iida M, Koki Y, Arima H, Furukawa H, Ueno T, Yoshino S, Nakamura Y, Oka M, Nagano H. Phase II clinical trial of peptide cocktail therapy for patients with advanced pancreatic cancer: VENUS-PC study. *Cancer Sci* 2017; **108**: 73-80 [PMID: 27783849 DOI: 10.1111/cas.13113]
- 260 **Miyazawa M**, Katsuda M, Maguchi H, Katanuma A, Ishii H, Ozaka M, Yamao K, Imaoka H, Kawai M, Hirono S, Okada KI, Yamaue H. Phase II clinical trial using novel peptide cocktail vaccine as a postoperative adjuvant treatment for surgically resected pancreatic cancer patients. *Int J Cancer* 2017; **140**: 973-982 [PMID: 27861852 DOI: 10.1002/ijc.30510]
- 261 **Wedén S**, Klemp M, Gladhaug IP, Møller M, Eriksen JA, Gaudernack G, Buanes T. Long-term follow-up of patients with resected pancreatic cancer following vaccination against mutant K-ras. *Int J Cancer* 2011; **128**: 1120-1128 [PMID: 20473937 DOI: 10.1002/ijc.25449]
- 262 **Toubaji A**, Achar M, Provenzano M, Herrin VE, Behrens R, Hamilton M, Bernstein S, Venzon D, Gause B, Marincola F, Khleif SN. Pilot study of mutant ras peptide-based vaccine as an adjuvant treatment in pancreatic and colorectal cancers. *Cancer Immunol Immunother* 2008; **57**: 1413-1420 [PMID: 18297281 DOI: 10.1007/s00262-008-0477-6]
- 263 **Abou-Alfa GK**, Chapman PB, Feilchenfeldt J, Brennan MF, Capanu M, Gansukh B, Jacobs G, Levin A, Neville D, Kelsen DP, O'Reilly EM. Targeting mutated K-ras in pancreatic adenocarcinoma using an adjuvant vaccine. *Am J Clin Oncol* 2011; **34**: 321-325 [PMID: 20686403 DOI: 10.1097/COC.0b013e3181e84b1f]
- 264 **Cohn A**, Morse MA, O'Neil B, Whiting S, Coeshott C, Ferraro J, Bellgrau D, Apelian D, Rodell TC. Whole Recombinant *Saccharomyces cerevisiae* Yeast Expressing Ras Mutations as Treatment for Patients With Solid Tumors Bearing Ras Mutations: Results From a Phase I Trial. *J Immunother* 2018; **41**: 141-150 [PMID: 29528991 DOI: 10.1097/CJI.0000000000000219]
- 265 **Katsuda M**, Miyazawa M, Kawai M, Hirono S, Okada KI, Shimizu A, Kitahata Y, Yamaue H. A phase III, double-blind, randomized clinical trial comparing S-1 in combination with DC vaccine loaded with WT1 peptides (TLP0-001) or placebo for the patients with advanced pancreatic cancer refractory to standard chemotherapy. *J Clin Oncol* 2017; **35**: TPS4153
- 266 **Katsuda M**, Miyazawa M, Ojima T, Katanuma A, Hakamada K, Sudo K, Asahara S, Endo I, Ueno M, Hara K, Yamada S, Fujii T, Sato S, Ioka T, Ohira M, Akahori T, Kitano M, Nagano H, Furukawa M, Adachi T, Yamaue H. A double-blind randomized comparative clinical trial to

- evaluate the safety and efficacy of dendritic cell vaccine loaded with WT1 peptides (TLP0-001) in combination with S-1 in patients with advanced pancreatic cancer refractory to standard chemotherapy. *Trials* 2019; **20**: 242 [PMID: [31029154](#) DOI: [10.1186/s13063-019-3332-5](#)]
- 267 **Liu J**, Zhong JF, Zhang X, Zhang C. Allogeneic CD19-CAR-T cell infusion after allogeneic hematopoietic stem cell transplantation in B cell malignancies. *J Hematol Oncol* 2017; **10**: 35 [PMID: [28143567](#) DOI: [10.1186/s13045-017-0405-3](#)]
- 268 **June CH**, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. *Science* 2018; **359**: 1361-1365 [PMID: [29567707](#) DOI: [10.1126/science.aar6711](#)]
- 269 **Wu J**, Cai J. Dilemma and Challenge of Immunotherapy for Pancreatic Cancer. *Dig Dis Sci* 2021; **66**: 359-368 [PMID: [32140943](#) DOI: [10.1007/s10620-020-06183-9](#)]
- 270 **Beatty GL**, O'Hara MH, Lacey SF, Torigian DA, Nazimuddin F, Chen F, Kulikovskaya IM, Soulen MC, McGarvey M, Nelson AM, Gladney WL, Levine BL, Melenhorst JJ, Plesa G, June CH. Activity of Mesothelin-Specific Chimeric Antigen Receptor T Cells Against Pancreatic Carcinoma Metastases in a Phase I Trial. *Gastroenterology* 2018; **155**: 29-32 [PMID: [29567081](#) DOI: [10.1053/j.gastro.2018.03.029](#)]
- 271 **Le DT**, Lutz E, Uram JN, Sugar EA, Onners B, Solt S, Zheng L, Diaz LA Jr, Donehower RC, Jaffee EM, Laheru DA. Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. *J Immunother* 2013; **36**: 382-389 [PMID: [23924790](#) DOI: [10.1097/CJI.0b013e31829fb7a2](#)]
- 272 **Chung V**, Kos FJ, Hardwick N, Yuan Y, Chao J, Li D, Waisman J, Li M, Zurcher K, Frankel P, Diamond DJ. Evaluation of safety and efficacy of p53MVA vaccine combined with pembrolizumab in patients with advanced solid cancers. *Clin Transl Oncol* 2019; **21**: 363-372 [PMID: [30094792](#) DOI: [10.1007/s12094-018-1932-2](#)]
- 273 **Wang-Gillam A**, Lockhart AC, Tan BR, Suresh R, Lim KH, Ratner L, Morton A, Huffman J, Marquez S, Boice N, DeNardo DG. Phase I study of defactinib combined with pembrolizumab and gemcitabine in patients with advanced cancer. *J Clin Oncol* 2018; **36**: 2561
- 274 **Reiss KA**, Mick R, O'Hara MH, Teitelbaum UR, Karasic TB, Schneider CJ, O'Dwyer PJ, Karlson D, Cowden S, Fuhrer MJ, Carpenter EL, Pantel AA, Makvandi M, Mankoff DA, Nathanson KL, Maxwell KN, Beatty GL, Domchek SM. A randomized phase II trial of niraparib plus either nivolumab or ipilimumab in patients with advanced pancreatic cancer whose cancer has not progressed on platinum-based therapy. *J Clin Oncol* 2019; **37**: TPS4161
- 275 **Desai J**, Kortmansky JS, Segal NH, Fakih M, Oh DY, Kim KP, Rahma OE, Ko AH, Chung HC, Alsina M, Yeh KH, Li S, Al-Sakaff NJA, Patel J, Barak H, Wang J, Zhang X, Bleul C, Cha E, Lee J. MORPHEUS: A phase Ib/II study platform evaluating the safety and clinical efficacy of cancer immunotherapy (CIT)—based combinations in gastrointestinal (GI) cancers. *J Clin Oncol* 2019; **37**: TPS467
- 276 **Rahal A**, Musher B. Oncolytic viral therapy for pancreatic cancer. *J Surg Oncol* 2017; **116**: 94-103 [PMID: [28407327](#) DOI: [10.1002/jso.24626](#)]
- 277 **Eissa IR**, Bustos-Villalobos I, Ichinose T, Matsumura S, Naoe Y, Miyajima N, Morimoto D, Mukoyama N, Zhiwen W, Tanaka M, Hasegawa H, Sumigama S, Aleksic B, Kodera Y, Kasuya H. The Current Status and Future Prospects of Oncolytic Viruses in Clinical Trials against Melanoma, Glioma, Pancreatic, and Breast Cancers. *Cancers (Basel)* 2018; **10** [PMID: [30261620](#) DOI: [10.3390/cancers10100356](#)]
- 278 **Chang KJ**, Senzer NN, Binmoeller K, Goldsweig H, Coffin R. Phase I dose-escalation study of talimogene laherparepvec (T-VEC) for advanced pancreatic cancer (ca). *J Clin Oncol* 2012; **30**: e14546
- 279 **Noonan AM**, Farren MR, Geyer SM, Huang Y, Tahiri S, Ahn D, Mikhail S, Ciombor KK, Pant S, Aparo S, Sexton J, Marshall JL, Mace TA, Wu CS, El-Rayes B, Timmers CD, Zwiebel J, Lesinski GB, Villalona-Calero MA, Bekaii-Saab TS. Randomized Phase 2 Trial of the Oncolytic Virus Pelareorep (Reolysin) in Upfront Treatment of Metastatic Pancreatic Adenocarcinoma. *Mol Ther* 2016; **24**: 1150-1158 [PMID: [27039845](#) DOI: [10.1038/mt.2016.66](#)]
- 280 **Mahalingam D**, Wilkinson GA, Eng KH, Fields P, Raber P, Moseley JL, Cheetham K, Coffey M, Nuovo G, Kalinski P, Zhang B, Arora SP, Fountzilias C. Pembrolizumab in Combination with the Oncolytic Virus Pelareorep and Chemotherapy in Patients with Advanced Pancreatic Adenocarcinoma: A Phase Ib Study. *Clin Cancer Res* 2020; **26**: 71-81 [PMID: [31694832](#) DOI: [10.1158/1078-0432.CCR-19-2078](#)]
- 281 **Haller SD**, Monaco ML, Essani K. The Present Status of Immuno-Oncolytic Viruses in the Treatment of Pancreatic Cancer. *Viruses* 2020; **12** [PMID: [33213031](#) DOI: [10.3390/v12111318](#)]
- 282 **Aguirre AJ**, Nowak JA, Camarda ND, Moffitt RA, Ghazani AA, Hazar-Rethinam M, Raghavan S, Kim J, Brais LK, Ragon D, Welch MW, Reilly E, McCabe D, Marini L, Anderka K, Helvie K, Oliver N, Babic A, Da Silva A, Nadres B, Van Seventer EE, Shahzade HA, St Pierre JP, Burke KP, Clancy T, Cleary JM, Doyle LA, Jajoo K, McCleary NJ, Meyerhardt JA, Murphy JE, Ng K, Patel AK, Perez K, Rosenthal MH, Rubinson DA, Ryou M, Shapiro GI, Sicinska E, Silverman SG, Nagy RJ, Lanman RB, Knoerzer D, Welsch DJ, Yurgelun MB, Fuchs CS, Garraway LA, Getz G, Hornick JL, Johnson BE, Kulke MH, Mayer RJ, Miller JW, Shyn PB, Tuveson DA, Wagle N, Yeh JJ, Hahn WC, Corcoran RB, Carter SL, Wolpin BM. Real-time Genomic Characterization of Advanced Pancreatic Cancer to Enable Precision Medicine. *Cancer Discov* 2018; **8**: 1096-1111 [PMID: [29903880](#) DOI: [10.1158/2159-8290.CD-18-0275](#)]
- 283 **Bernabe-Ramirez C**, Patel R, Chahal J, Saif MW. Treatment options in BRAF-mutant metastatic

- colorectal cancer. *Anticancer Drugs* 2020; **31**: 545-557 [PMID: 32304411 DOI: 10.1097/CAD.0000000000000940]
- 284 **O'Reilly EM**, Hechtman JF. Tumour response to TRK inhibition in a patient with pancreatic adenocarcinoma harbouring an NTRK gene fusion. *Ann Oncol* 2019; **30**: viii36-viii40 [PMID: 31605106 DOI: 10.1093/annonc/mdz385]
- 285 **Solomon JP**, Linkov I, Rosado A, Mullaney K, Rosen EY, Frosina D, Jungbluth AA, Zehir A, Benayed R, Drilon A, Hyman DM, Ladanyi M, Sireci AN, Hechtman JF. NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. *Mod Pathol* 2020; **33**: 38-46 [PMID: 31375766 DOI: 10.1038/s41379-019-0324-7]
- 286 **Aguirre AJ**. Oncogenic NRG1 Fusions: A New Hope for Targeted Therapy in Pancreatic Cancer. *Clin Cancer Res* 2019; **25**: 4589-4591 [PMID: 31164372 DOI: 10.1158/1078-0432.CCR-19-1280]
- 287 **Jones MR**, Williamson LM, Topham JT, Lee MKC, Goytain A, Ho J, Denroche RE, Jang G, Pleasance E, Shen Y, Karasinska JM, McGhie JP, Gill S, Lim HJ, Moore MJ, Wong HL, Ng T, Yip S, Zhang W, Sadeghi S, Reisle C, Mungall AJ, Mungall KL, Moore RA, Ma Y, Knox JJ, Gallinger S, Laskin J, Marra MA, Schaeffer DF, Jones SJM, Renouf DJ. *NRG1* Gene Fusions Are Recurrent, Clinically Actionable Gene Rearrangements in *KRAS* Wild-Type Pancreatic Ductal Adenocarcinoma. *Clin Cancer Res* 2019; **25**: 4674-4681 [PMID: 31068372 DOI: 10.1158/1078-0432.CCR-19-0191]
- 288 **Thompson ED**, Roberts NJ, Wood LD, Eshleman JR, Goggins MG, Kern SE, Klein AP, Hruban RH. The genetics of ductal adenocarcinoma of the pancreas in the year 2020: dramatic progress, but far to go. *Mod Pathol* 2020; **33**: 2544-2563 [PMID: 32704031 DOI: 10.1038/s41379-020-0629-6]
- 289 **Chantrill LA**, Nagrial AM, Watson C, Johns AL, Martyn-Smith M, Simpson S, Mead S, Jones MD, Samra JS, Gill AJ, Watson N, Chin VT, Humphris JL, Chou A, Brown B, Morey A, Pajic M, Grimmond SM, Chang DK, Thomas D, Sebastian L, Sjoquist K, Yip S, Pavlakis N, Asghari R, Harvey S, Grimison P, Simes J, Biankin AV; Australian Pancreatic Cancer Genome Initiative (APGI); Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) Trial Management Committee of the Australasian Gastrointestinal Trials Group (AGITG). Precision Medicine for Advanced Pancreas Cancer: The Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) Trial. *Clin Cancer Res* 2015; **21**: 2029-2037 [PMID: 25896973 DOI: 10.1158/1078-0432.CCR-15-0426]
- 290 **Kuo KK**, Hsiao PJ, Chang WT, Chuang SC, Yang YH, Wuputra K, Ku CC, Pan JB, Li CP, Kato K, Liu CJ, Wu DC, Yokoyama KK. Therapeutic Strategies Targeting Tumor Suppressor Genes in Pancreatic Cancer. *Cancers (Basel)* 2021; **13** [PMID: 34359820 DOI: 10.3390/cancers13153920]
- 291 **Yarchoan M**, Myzak MC, Johnson BA 3rd, De Jesus-Acosta A, Le DT, Jaffee EM, Azad NS, Donehower RC, Zheng L, Oberstein PE, Fine RL, Laheru DA, Goggins M. Olaparib in combination with irinotecan, cisplatin, and mitomycin C in patients with advanced pancreatic cancer. *Oncotarget* 2017; **8**: 44073-44081 [PMID: 28454122 DOI: 10.18632/oncotarget.17237]
- 292 **Aung KL**, Fischer SE, Denroche RE, Jang GH, Dodd A, Creighton S, Southwood B, Liang SB, Chadwick D, Zhang A, O'Kane GM, Albaba H, Moura S, Grant RC, Miller JK, Mbabaali F, Pasternack D, Lungu IM, Bartlett JMS, Ghai S, Lemire M, Holter S, Connor AA, Moffitt RA, Yeh JJ, Timms L, Krzyzanowski PM, Dhani N, Hedley D, Notta F, Wilson JM, Moore MJ, Gallinger S, Knox JJ. Genomics-Driven Precision Medicine for Advanced Pancreatic Cancer: Early Results from the COMPASS Trial. *Clin Cancer Res* 2018; **24**: 1344-1354 [PMID: 29288237 DOI: 10.1158/1078-0432.CCR-17-2994]
- 293 **Singhi AD**, George B, Greenbowe JR, Chung J, Suh J, Maitra A, Klempner SJ, Hendifar A, Milind JM, Golan T, Brand RE, Zureikat AH, Roy S, Schrock AB, Miller VA, Ross JS, Ali SM, Bahary N. Real-Time Targeted Genome Profile Analysis of Pancreatic Ductal Adenocarcinomas Identifies Genetic Alterations That Might Be Targeted With Existing Drugs or Used as Biomarkers. *Gastroenterology* 2019; **156**: 2242-2253.e4 [PMID: 30836094 DOI: 10.1053/j.gastro.2019.02.037]
- 294 **Luchini C**, Brosens LAA, Wood LD, Chatterjee D, Shin JI, Sciammarella C, Fiadone G, Malleo G, Salvia R, Kryklyva V, Piredda ML, Cheng L, Lawlor RT, Adsay V, Scarpa A. Comprehensive characterisation of pancreatic ductal adenocarcinoma with microsatellite instability: histology, molecular pathology and clinical implications. *Gut* 2021; **70**: 148-156 [PMID: 32350089 DOI: 10.1136/gutjnl-2020-320726]
- 295 **Choi M**, Kipps T, Kurzrock R. ATM Mutations in Cancer: Therapeutic Implications. *Mol Cancer Ther* 2016; **15**: 1781-1791 [PMID: 27413114 DOI: 10.1158/1535-7163.MCT-15-0945]
- 296 **Nanda N**, Roberts NJ. *ATM* Serine/Threonine Kinase and its Role in Pancreatic Risk. *Genes (Basel)* 2020; **11** [PMID: 31963441 DOI: 10.3390/genes11010108]
- 297 **Mukhopadhyay S**, Goswami D, Adisheshaiah PP, Burgan W, Yi M, Guerin TM, Kozlov SV, Nissley DV, McCormick F. Undermining Glutaminolysis Bolsters Chemotherapy While NRF2 Promotes Chemoresistance in *KRAS*-Driven Pancreatic Cancers. *Cancer Res* 2020; **80**: 1630-1643 [PMID: 31911550 DOI: 10.1158/0008-5472.CAN-19-1363]
- 298 **Janes MR**, Zhang J, Li LS, Hansen R, Peters U, Guo X, Chen Y, Babbar A, Firdaus SJ, Darjania L, Feng J, Chen JH, Li S, Long YO, Thach C, Liu Y, Zariw A, Ely T, Kucharski JM, Kessler LV, Wu T, Yu K, Wang Y, Yao Y, Deng X, Zarrinkar PP, Brehmer D, Dhanak D, Lorenzi MV, Hu-Lowe D, Patricelli MP, Ren P. Targeting *KRAS* Mutant Cancers with a Covalent G12C-Specific Inhibitor. *Cell* 2018; **172**: 578-589.e17 [PMID: 29373830 DOI: 10.1016/j.cell.2018.01.006]
- 299 **Nagasaka M**, Li Y, Sukari A, Ou SI, Al-Hallak MN, Azmi AS. *KRAS* G12C Game of Thrones, which direct *KRAS* inhibitor will claim the iron throne? *Cancer Treat Rev* 2020; **84**: 101974 [PMID:

32014824 DOI: [10.1016/j.ctrv.2020.101974](https://doi.org/10.1016/j.ctrv.2020.101974)]

- 300 **Jones S**, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Kamiyama H, Jimeno A, Hong SM, Fu B, Lin MT, Calhoun ES, Kamiyama M, Walter K, Nikolskaya T, Nikolsky Y, Hartigan J, Smith DR, Hidalgo M, Leach SD, Klein AP, Jaffee EM, Goggins M, Maitra A, Iacobuzio-Donahue C, Eshleman JR, Kern SE, Hruban RH, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 2008; **321**: 1801-1806 [PMID: [18772397](https://pubmed.ncbi.nlm.nih.gov/18772397/) DOI: [10.1126/science.1164368](https://doi.org/10.1126/science.1164368)]
- 301 **Waddell N**, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, Johns AL, Miller D, Nones K, Quek K, Quinn MC, Robertson AJ, Fadlullah MZ, Bruxner TJ, Christ AN, Harliwong I, Idrisoglu S, Manning S, Nourse C, Nourbakhsh E, Wani S, Wilson PJ, Markham E, Cloonan N, Anderson MJ, Fink JL, Holmes O, Kazakoff SH, Leonard C, Newell F, Poudel B, Song S, Taylor D, Waddell N, Wood S, Xu Q, Wu J, Pinese M, Cowley MJ, Lee HC, Jones MD, Nagrial AM, Humphris J, Chantrill LA, Chin V, Steinmann AM, Mawson A, Humphrey ES, Colvin EK, Chou A, Scarlett CJ, Pinho AV, Giry-Laterriere M, Rooman I, Samra JS, Kench JG, Pettitt JA, Merrett ND, Toon C, Epari K, Nguyen NQ, Barbour A, Zeps N, Jamieson NB, Graham JS, Niclou SP, Bjerkvig R, Grützmann R, Aust D, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Wolfgang CL, Morgan RA, Lawlor RT, Corbo V, Bassi C, Falconi M, Zamboni G, Tortora G, Tempero MA; Australian Pancreatic Cancer Genome Initiative, Gill AJ, Eshleman JR, Pilarsky C, Scarpa A, Musgrove EA, Pearson JV, Biankin AV, Grimmond SM. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 2015; **518**: 495-501 [PMID: [25719666](https://pubmed.ncbi.nlm.nih.gov/25719666/) DOI: [10.1038/nature14169](https://doi.org/10.1038/nature14169)]
- 302 **Cani PD**. Human gut microbiome: hopes, threats and promises. *Gut* 2018; **67**: 1716-1725 [PMID: [29934437](https://pubmed.ncbi.nlm.nih.gov/29934437/) DOI: [10.1136/gutjnl-2018-316723](https://doi.org/10.1136/gutjnl-2018-316723)]
- 303 **Maekawa T**, Fukaya R, Takamatsu S, Itoyama S, Fukuoka T, Yamada M, Hata T, Nagaoka S, Kawamoto K, Eguchi H, Murata K, Kumada T, Ito T, Tanemura M, Fujimoto K, Tomita Y, Tobe T, Kamada Y, Miyoshi E. Possible involvement of Enterococcus infection in the pathogenesis of chronic pancreatitis and cancer. *Biochem Biophys Res Commun* 2018; **506**: 962-969 [PMID: [30401562](https://pubmed.ncbi.nlm.nih.gov/30401562/) DOI: [10.1016/j.bbrc.2018.10.169](https://doi.org/10.1016/j.bbrc.2018.10.169)]
- 304 **Wang S**, Dong W, Liu L, Xu M, Wang Y, Liu T, Zhang Y, Wang B, Cao H. Interplay between bile acids and the gut microbiota promotes intestinal carcinogenesis. *Mol Carcinog* 2019; **58**: 1155-1167 [PMID: [30828892](https://pubmed.ncbi.nlm.nih.gov/30828892/) DOI: [10.1002/mc.22999](https://doi.org/10.1002/mc.22999)]
- 305 **Cognoux A**, Dalmasso G, Martinez R, Buc E, Delmas J, Gibold L, Sauvanet P, Darcha C, Déchelotte P, Bonnet M, Pezet D, Wodrich H, Darfeuille-Michaud A, Bonnet R. Bacterial genotoxin colibactin promotes colon tumour growth by inducing a senescence-associated secretory phenotype. *Gut* 2014; **63**: 1932-1942 [PMID: [24658599](https://pubmed.ncbi.nlm.nih.gov/24658599/) DOI: [10.1136/gutjnl-2013-305257](https://doi.org/10.1136/gutjnl-2013-305257)]
- 306 **Nougayrède JP**, Taieb F, De Rycke J, Oswald E. Cyclomodulins: bacterial effectors that modulate the eukaryotic cell cycle. *Trends Microbiol* 2005; **13**: 103-110 [PMID: [15737728](https://pubmed.ncbi.nlm.nih.gov/15737728/) DOI: [10.1016/j.tim.2005.01.002](https://doi.org/10.1016/j.tim.2005.01.002)]
- 307 **Bao Y**, Spiegelman D, Li R, Giovannucci E, Fuchs CS, Michaud DS. History of peptic ulcer disease and pancreatic cancer risk in men. *Gastroenterology* 2010; **138**: 541-549 [PMID: [19818786](https://pubmed.ncbi.nlm.nih.gov/19818786/) DOI: [10.1053/j.gastro.2009.09.059](https://doi.org/10.1053/j.gastro.2009.09.059)]
- 308 **Mitsuhashi K**, Noshio K, Sukawa Y, Matsunaga Y, Ito M, Kurihara H, Kanno S, Igarashi H, Naito T, Adachi Y, Tachibana M, Tanuma T, Maguchi H, Shinohara T, Hasegawa T, Imamura M, Kimura Y, Hirata K, Maruyama R, Suzuki H, Imai K, Yamamoto H, Shinomura Y. Association of Fusobacterium species in pancreatic cancer tissues with molecular features and prognosis. *Oncotarget* 2015; **6**: 7209-7220 [PMID: [25797243](https://pubmed.ncbi.nlm.nih.gov/25797243/) DOI: [10.18632/oncotarget.3109](https://doi.org/10.18632/oncotarget.3109)]
- 309 **Fan X**, Alekseyenko AV, Wu J, Peters BA, Jacobs EJ, Gapstur SM, Purdue MP, Abnet CC, Stolzenberg-Solomon R, Miller G, Ravel J, Hayes RB, Ahn J. Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. *Gut* 2018; **67**: 120-127 [PMID: [27742762](https://pubmed.ncbi.nlm.nih.gov/27742762/) DOI: [10.1136/gutjnl-2016-312580](https://doi.org/10.1136/gutjnl-2016-312580)]
- 310 **Li Q**, Jin M, Liu Y, Jin L. Gut Microbiota: Its Potential Roles in Pancreatic Cancer. *Front Cell Infect Microbiol* 2020; **10**: 572492 [PMID: [33117731](https://pubmed.ncbi.nlm.nih.gov/33117731/) DOI: [10.3389/fcimb.2020.572492](https://doi.org/10.3389/fcimb.2020.572492)]
- 311 **Chakladar J**, Kuo SZ, Castaneda G, Li WT, Gnanasekar A, Yu MA, Chang EY, Wang XQ, Ongkeko WM. The Pancreatic Microbiome is Associated with Carcinogenesis and Worse Prognosis in Males and Smokers. *Cancers (Basel)* 2020; **12** [PMID: [32962112](https://pubmed.ncbi.nlm.nih.gov/32962112/) DOI: [10.3390/cancers12092672](https://doi.org/10.3390/cancers12092672)]
- 312 **Rogers CJ**, Prabhu KS, Vijay-Kumar M. The microbiome and obesity-an established risk for certain types of cancer. *Cancer J* 2014; **20**: 176-180 [PMID: [24855004](https://pubmed.ncbi.nlm.nih.gov/24855004/) DOI: [10.1097/PPO.000000000000049](https://doi.org/10.1097/PPO.000000000000049)]
- 313 **Qin J**, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012; **490**: 55-60 [PMID: [23023125](https://pubmed.ncbi.nlm.nih.gov/23023125/) DOI: [10.1038/nature11450](https://doi.org/10.1038/nature11450)]
- 314 **Sousa T**, Paterson R, Moore V, Carlsson A, Abrahamsson B, Basit AW. The gastrointestinal microbiota as a site for the biotransformation of drugs. *Int J Pharm* 2008; **363**: 1-25 [PMID: [18682282](https://pubmed.ncbi.nlm.nih.gov/18682282/) DOI: [10.1016/j.ijpharm.2008.07.009](https://doi.org/10.1016/j.ijpharm.2008.07.009)]

- 315 **Iida N**, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, Molina DA, Salcedo R, Back T, Cramer S, Dai RM, Kiu H, Cardone M, Naik S, Patri AK, Wang E, Marincola FM, Frank KM, Belkaid Y, Trinchieri G, Goldszmid RS. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science* 2013; **342**: 967-970 [PMID: [24264989](#) DOI: [10.1126/science.1240527](#)]
- 316 **Vande Voorde J**, Sabuncuoğlu S, Noppen S, Hofer A, Ranjbarian F, Fieuws S, Balzarini J, Liekens S. Nucleoside-catabolizing enzymes in mycoplasma-infected tumor cell cultures compromise the cytostatic activity of the anticancer drug gemcitabine. *J Biol Chem* 2014; **289**: 13054-13065 [PMID: [24668817](#) DOI: [10.1074/jbc.M114.558924](#)]
- 317 **Pushalkar S**, Hundeyin M, Daley D, Zambirinis CP, Kurz E, Mishra A, Mohan N, Aykut B, Usyk M, Torres LE, Werba G, Zhang K, Guo Y, Li Q, Akkad N, Lall S, Wadowski B, Gutierrez J, Kochen Rossi JA, Herzog JW, Diskin B, Torres-Hernandez A, Leinwand J, Wang W, Taunk PS, Savadkar S, Janal M, Saxena A, Li X, Cohen D, Sartor RB, Saxena D, Miller G. The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression. *Cancer Discov* 2018; **8**: 403-416 [PMID: [29567829](#) DOI: [10.1158/2159-8290.CD-17-1134](#)]
- 318 **Geller LT**, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, Gavert N, Zwang Y, Cooper ZA, Shee K, Thaiss CA, Reuben A, Livny J, Avraham R, Frederick DT, Ligorio M, Chatman K, Johnston SE, Mosher CM, Brandis A, Fuks G, Gurbatri C, Gopalakrishnan V, Kim M, Hurd MW, Katz M, Fleming J, Maitra A, Smith DA, Skalak M, Bu J, Michaud M, Trauger SA, Barshack I, Golan T, Sandbank J, Flaherty KT, Mandinova A, Garrett WS, Thayer SP, Ferrone CR, Huttenhower C, Bhatia SN, Gevers D, Wargo JA, Golub TR, Straussman R. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. *Science* 2017; **357**: 1156-1160 [PMID: [28912244](#) DOI: [10.1126/science.aah5043](#)]
- 319 **Lehouritis P**, Cummins J, Stanton M, Murphy CT, McCarthy FO, Reid G, Urbaniak C, Byrne WL, Tangney M. Local bacteria affect the efficacy of chemotherapeutic drugs. *Sci Rep* 2015; **5**: 14554 [PMID: [26416623](#) DOI: [10.1038/srep14554](#)]
- 320 **Kamarajah SK**, Burns WR, Frankel TL, Cho CS, Nathan H. Validation of the American Joint Commission on Cancer (AJCC) 8th Edition Staging System for Patients with Pancreatic Adenocarcinoma: A Surveillance, Epidemiology and End Results (SEER) Analysis. *Ann Surg Oncol* 2017; **24**: 2023-2030 [PMID: [28213792](#) DOI: [10.1245/s10434-017-5810-x](#)]
- 321 **Raut CP**, Tseng JF, Sun CC, Wang H, Wolff RA, Crane CH, Hwang R, Vauthey JN, Abdalla EK, Lee JE, Pisters PW, Evans DB. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg* 2007; **246**: 52-60 [PMID: [17592291](#) DOI: [10.1097/01.sla.0000259391.84304.2b](#)]
- 322 **Crippa S**, Guarneri G, Belfiori G, Partelli S, Pagnanelli M, Gasparini G, Balzano G, Lena MS, Rubini C, Doglioni C, Zamboni G, Falconi M. Positive neck margin at frozen section analysis is a significant predictor of tumour recurrence and poor survival after pancreatoduodenectomy for pancreatic cancer. *Eur J Surg Oncol* 2020; **46**: 1524-1531 [PMID: [32098733](#) DOI: [10.1016/j.ejso.2020.02.013](#)]
- 323 **Meyer W**, Jurowich C, Reichel M, Steinhäuser B, Wunsch PH, Gebhardt C. Pathomorphological and histological prognostic factors in curatively resected ductal adenocarcinoma of the pancreas. *Surg Today* 2000; **30**: 582-587 [PMID: [10930222](#) DOI: [10.1007/s005950070096](#)]
- 324 **Sohn TA**, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, Sauter PK, Coleman J, Hruban RH, Lillemoe KD. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000; **4**: 567-579 [PMID: [11307091](#) DOI: [10.1016/s1091-255x\(00\)80105-5](#)]
- 325 **Chang DK**, Johns AL, Merrett ND, Gill AJ, Colvin EK, Scarlett CJ, Nguyen NQ, Leong RW, Cosman PH, Kelly MI, Sutherland RL, Henshall SM, Kench JG, Biankin AV. Margin clearance and outcome in resected pancreatic cancer. *J Clin Oncol* 2009; **27**: 2855-2862 [PMID: [19398572](#) DOI: [10.1200/JCO.2008.20.5104](#)]
- 326 **Helm J**, Centeno BA, Coppola D, Melis M, Lloyd M, Park JY, Chen DT, Malafa MP. Histologic characteristics enhance predictive value of American Joint Committee on Cancer staging in resectable pancreas cancer. *Cancer* 2009; **115**: 4080-4089 [PMID: [19626671](#) DOI: [10.1002/ncr.24503](#)]
- 327 **Kinsella TJ**, Seo Y, Willis J, Stellato TA, Siegel CT, Harpp D, Willson JK, Gibbons J, Sanabria JR, Hardacre JM, Schulak JP. The impact of resection margin status and postoperative CA19-9 Levels on survival and patterns of recurrence after postoperative high-dose radiotherapy with 5-FU-based concurrent chemotherapy for resectable pancreatic cancer. *Am J Clin Oncol* 2008; **31**: 446-453 [PMID: [18838880](#) DOI: [10.1097/COC.0b013e318168f6c4](#)]
- 328 **Pelucchi C**, Galeone C, Polesel J, Manzari M, Zucchetto A, Talamini R, Franceschi S, Negri E, La Vecchia C. Smoking and body mass index and survival in pancreatic cancer patients. *Pancreas* 2014; **43**: 47-52 [PMID: [24177141](#) DOI: [10.1097/MPA.0b013e3182a7c74b](#)]
- 329 **Yuan C**, Morales-Oyarvide V, Babic A, Clish CB, Kraft P, Bao Y, Qian ZR, Rubinson DA, Ng K, Giovannucci EL, Ogino S, Stampfer MJ, Gaziano JM, Sesso HD, Cochrane BB, Manson JE, Fuchs CS, Wolpin BM. Cigarette Smoking and Pancreatic Cancer Survival. *J Clin Oncol* 2017; **35**: 1822-1828 [PMID: [28358654](#) DOI: [10.1200/JCO.2016.71.2026](#)]
- 330 **Jiang P**, Zhang M, Gui L, Zhang K. Expression patterns and prognostic values of the *cyclin-dependent kinase 1* and *cyclin A2* gene cluster in pancreatic adenocarcinoma. *J Int Med Res* 2020; **48**: 300060520930113 [PMID: [33290118](#) DOI: [10.1177/0300060520930113](#)]

- 331 **Bailey P**, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, Miller DK, Christ AN, Bruxner TJ, Quinn MC, Nourse C, Murtaugh LC, Harliwong I, Idrisoglu S, Manning S, Nourbakhsh E, Wani S, Fink L, Holmes O, Chin V, Anderson MJ, Kazakoff S, Leonard C, Newell F, Waddell N, Wood S, Xu Q, Wilson PJ, Cloonan N, Kassahn KS, Taylor D, Quek K, Robertson A, Pantano L, Mincarelli L, Sanchez LN, Evers L, Wu J, Pinese M, Cowley MJ, Jones MD, Colvin EK, Nagrial AM, Humphrey ES, Chantrill LA, Mawson A, Humphris J, Chou A, Pajic M, Scarlett CJ, Pinho AV, Giry-Laterriere M, Rومان I, Samra JS, Kench JG, Lovell JA, Merrett ND, Toon CW, Epari K, Nguyen NQ, Barbour A, Zeps N, Moran-Jones K, Jamieson NB, Graham JS, Duthie F, Oien K, Hair J, Grützmann R, Maitra A, Iacobuzio-Donahue CA, Wolfgang CL, Morgan RA, Lawlor RT, Corbo V, Bassi C, Rusev B, Capelli P, Salvia R, Tortora G, Mukhopadhyay D, Petersen GM; Australian Pancreatic Cancer Genome Initiative, Munzy DM, Fisher WE, Karim SA, Eshleman JR, Hruban RH, Pilarsky C, Morton JP, Sansom OJ, Scarpa A, Musgrove EA, Bailey UM, Hofmann O, Sutherland RL, Wheeler DA, Gill AJ, Gibbs RA, Pearson JV, Waddell N, Biankin AV, Grimmond SM. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 2016; **531**: 47-52 [PMID: 26909576 DOI: 10.1038/nature16965]
- 332 **Li X**, Li Z, Zhu H, Yu X. Autophagy Regulatory Genes MET and RIPK2 Play a Prognostic Role in Pancreatic Ductal Adenocarcinoma: A Bioinformatic Analysis Based on GEO and TCGA. *Biomed Res Int* 2020; **2020**: 8537381 [PMID: 33204717 DOI: 10.1155/2020/8537381]
- 333 **Liu JQ**, Liao XW, Wang XK, Yang CK, Zhou X, Liu ZQ, Han QF, Fu TH, Zhu GZ, Han CY, Su H, Huang JL, Ruan GT, Yan L, Ye XP, Peng T. Prognostic value of Glypican family genes in early-stage pancreatic ductal adenocarcinoma after pancreaticoduodenectomy and possible mechanisms. *BMC Gastroenterol* 2020; **20**: 415 [PMID: 33302876 DOI: 10.1186/s12876-020-01560-0]
- 334 **Qian B**, Wei L, Yang Z, He Q, Chen H, Wang A, Yang D, Li Q, Li J, Zheng S, Fu W. Hic-5 in pancreatic stellate cells affects proliferation, apoptosis, migration, invasion of pancreatic cancer cells and postoperative survival time of pancreatic cancer. *Biomed Pharmacother* 2020; **121**: 109355 [PMID: 31683179 DOI: 10.1016/j.biopha.2019.109355]
- 335 **Song C**, Chen T, He L, Ma N, Li JA, Rong YF, Fang Y, Liu M, Xie D, Lou W. PRMT1 promotes pancreatic cancer growth and predicts poor prognosis. *Cell Oncol (Dordr)* 2020; **43**: 51-62 [PMID: 31520395 DOI: 10.1007/s13402-019-00435-1]
- 336 **Kurahara H**, Maemura K, Mataka Y, Tanoue K, Iino S, Kawasaki Y, Idichi T, Arigami T, Mori S, Shinden Y, Higashi M, Ueno S, Shinchi H, Natsugoe S. Lung recurrence and its therapeutic strategy in patients with pancreatic cancer. *Pancreatol* 2020; **20**: 89-94 [PMID: 31787525 DOI: 10.1016/j.pan.2019.11.015]
- 337 **Liu M**, Zhang Y, Yang J, Cui X, Zhou Z, Zhan H, Ding K, Tian X, Yang Z, Fung KA, Edil BH, Postier RG, Bronze MS, Fernandez-Zapico ME, Stemmler MP, Brabletz T, Li YP, Houchen CW, Li M. ZIP4 Increases Expression of Transcription Factor ZEB1 to Promote Integrin $\alpha 3 \beta 1$ Signaling and Inhibit Expression of the Gemcitabine Transporter ENT1 in Pancreatic Cancer Cells. *Gastroenterology* 2020; **158**: 679-692.e1 [PMID: 31711924 DOI: 10.1053/j.gastro.2019.10.038]
- 338 **Ou ZL**, Luo Z, Lu YB. Long non-coding RNA HULC as a diagnostic and prognostic marker of pancreatic cancer. *World J Gastroenterol* 2019; **25**: 6728-6742 [PMID: 31857775 DOI: 10.3748/wjg.v25.i46.6728]
- 339 **Fu Z**, Jiao Y, Li Y, Ji B, Jia B, Liu B. TYMS presents a novel biomarker for diagnosis and prognosis in patients with pancreatic cancer. *Medicine (Baltimore)* 2019; **98**: e18487 [PMID: 31861032 DOI: 10.1097/MD.00000000000018487]
- 340 **Bu F**, Zhu X, Yi X, Luo C, Lin K, Zhu J, Hu C, Liu Z, Zhao J, Huang C, Zhang W, Huang J. Expression Profile of GINS Complex Predicts the Prognosis of Pancreatic Cancer Patients. *Oncotargets Ther* 2020; **13**: 11433-11444 [PMID: 33192076 DOI: 10.2147/OTT.S275649]



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