# Optimizing the Treatment Mode for De Novo Metastatic Nasopharyngeal Carcinoma With Bone-only Metastasis

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**Research Article**

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# Abstract

**Purpose:** No standard radiotherapy regimens was established in the treatment of de novo metastatic nasopharyngeal carcinoma (mNPC) with bone-only metastasis. The current study aimed to investigate the efficacy of palliative chemotherapy (PCT) plus locoregional radiotherapy (LLRT) with or without local radiotherapy (RT) to bone metastatic lesions in mNPC, and identify the optimal candidates.

**Methods:** We retrospectively analyzed 141 de novo mNPC patients with bone-only metastasis who received at least two cycles of PCT with or without LLRT and RT to bone metastasis. The difference in survival was evaluated by the log-rank test. Univariable and multivariable analysis was made by Cox regression.

**Results:** Patients who received PCT plus LLRT had significantly longer overall survival (OS) (45.0 months vs 13.5 months, HR = 0.30 , $p$ = 0.001) and progression-free survival (PFS) (29.0 months vs 11.0 months, HR = 0.34, $p$ = 0.014), especially in patients who had less than 3 metastatic bone lesions. Multivariate analysis confirmed that LRRT, more chemotherapy cycles (≥ 4) and limited number of bone metastasis (≤ 3) were favorable prognostic factors for OS. Subgroup analysis revealed that RT to metastatic bones had a tendency to prolong the survival time in the unselected population who received PCT plus LLRT ($p$ > 0.05), while further data suggested that RT to metastatic bones dramatically improve OS (72.0 months vs 26.0 months, $p$ = 0.002) and PFS (60.0 months vs 20.0 months, $p$ = 0.006) for mNPC with less than 3 metastatic bone lesions.

**Conclusions:** LLRT and RT to bone metastatic lesions followed by PCT in de novo mNPC with bone-only metastasis significantly prolonged survival in patients with less than 3 metastatic bone lesions.


# Introduction

Nasopharyngeal carcinoma is an endemic malignancy in southern China, with an incidence of up to 30 cases per 100000 person-years[1], and approximately 4–10% of those patients were metastatic NPC (mNPC) at diagnosis [2]. mNPC is a heterogeneous entity that ranges from a single metastasis to multiple organ metastases. Bone metastasis is the mostly common invaded organ, accounting for over 60% of all metastatic sites and favoring longer survival[3]. To date, mNPC were generally considered incurable and there is no optional treatment. Palliative chemotherapy (PCT) is the primary treatment, locoregional radiation therapy (LLRT) is strongly recommended in chemotherapy-sensitive patients with mNPC [4, 5]. While radiotherapy (RT) to metastatic bones is only widely administrated for relieving pain and improving quality of life in de novo mNPC with bone metastasis.

Nowadays, increasing studies had reported that NPC patients with solitary bone metastasis, or even with recurrent bone-only oligometastatic could have a long-term disease control and a better survival [6, 7]. Moreover, emerging evidences have suggested a vital role of local radiotherapy in de novo mNPC with bone-only metastasis, giving a fascinating insight into the management of bone metastatic mNPC [8–11]. However, the potential benefit of combine PCT plus LLRT with or without RT to metastatic bones in

mNPC remains controversial. No general consensus was established and no standard regimens was strongly recommended [2, 4].

In the present study, we retrospectively analyzed 141 de novo mNPC with bone-only metastasis between June 2007 and December 2017 at our cancer center, and explored the clinical significance of different practice strategy in de novo mNPC with different patterns of bone metastasis (metastatic bone sites ≤ 3 and > 3), and aimed to optimize the treatment regimens and found the most potential candidates.

# Materials And Methods

### Patients

141 patients with mNPC who were admitted to Fujian Cancer Hospital between June 2007 and December 2017. Inclusion criteria were as follows: (I) patients were newly and histologically diagnosed with mNPC; (II) mNPC with bone-only metastasis. Exclusion criteria were as follows: (I) patients with NPC developed multiple organ metastases; (II) patients who were previously treated; (III) patients who were lost in the follow up; (IV) patients had less than two cycle of chemotherapy. Re-staging of all patients was done according to the 8th edition of American Joint Committee on Cancer (AJCC) / Union for International Cancer Control (UICC). Our study was approved by the Ethics Committee of Fujian Medical University Cancer Hospital, Fuzhou, China. Written informed consent was obtained from all patients.

### Treatment

All patients received platinum-based systematic chemotherapy. Chemotherapy regimens, including gemcitabine, paclitaxel or docetaxel plus platinum, were administered every 3–4 weeks. LRRT to nasopharynx and neck was conducted by two-dimensional radiotherapy (2DRT) or intensity modulated radiotherapy (IMRT), which was described as previous[12]. The patterns of radiotherapy to metastatic bone were heterogeneous. 40 Gy with 20 fractions or 30Gy with 10 fractions were most commonly used, and few patients received 50 Gy using 25 fractions or 60-70 Gy.

### Follow-up

Evaluation of tumor response, including computed tomography (CT), magnetic resonance imaging, emission computed tomography or positron emission tomography CT, was selectively conducted after every two or three cycles of chemo therapy. After all therapeutic process, patients were evaluated every 3 months for the first 2 years, every 6 months from year 3–5, and then every 12 months. The overall survival (OS) was measured from the date of diagnosis to the date of death from any cause. The progression-free survival (PFS) was measured from the date of diagnosis to the time of treatment failure.

### Statistical analysis

All statistical analyses were performed using the soft-ware SPSS version 24.0 and Graph Pad Prism 8. The Cox regression model was used for the univariate analysis and multivariate analysis. The propensity score matching (PSM) analysis was used to reduce the data bias and the confounding variable. Kaplan–Meier analysis and log-rank method were used to compare survival difference. *p* values < 0.05 were considered statistically significant, and all p values were two sided.

## Results

# Patient characteristics

A total of 141 de novo mNPC patients with bone-only metastasis who were treated with PCT with or without LLRT and RT to metastatic bones between January 2007 and December 2017 were eligible for our study (Fig. 1).

The median age was 46.1 years (range 17–73 years). With a median follow-up time of 71.5 months (95% CI, 57.6–85.4 months). The median OS was 38.0 months (95% CI, 24.4–51.6 months), and the 1-, 3- and 5- year survival rate was 100%, 88.7% and 82.2% respectively (Fig. 2).

The comparison of patients' characteristics between PCT plus LLRT and PCT alone were shown in (Table 1).

Table 1
Characteristics of 141 de novo mNPC with Bone-only metastasis

| Characteristics | PCT plus LLRT No (%)(n = 131) | PCT alone No (%)(n = 10) | *p* |
|---|---|---|---|
| Age(y) | | | 0.502 |
| ≤ 50 | 84 (64.1) | 8 (80.0) | |
| > 50 | 47 (35.9) | 2 (20.0) | |
| Sex | | | 0.815 |
| Female | 107 (81.7) | 9 (90.0) | |
| Male | 24 (18.3) | 1 (10.0) | |
| T stage | | | 0.104 |
| T1-2 | 39 (29.8) | 6 (60.0) | |
| T3-4 | 92 (70.2) | 4 (40.0) | |
| N stage | | | 0.907 |
| N0-1 | 22 (16.7) | 1 (10.0) | |
| N2-3 | 110 (83.3) | 9 (90.0) | |
| ECOG score | | | 1.000 |
| 0 | 118 (90.1) | 9 (90.0) | |
| 1 | 13 (9.9) | 1 (10.0) | |
| Chemo cycles | | | 0.417 |
| < 4 | 42 (30.5) | 5 (50.0) | |
| ≥ 4 | 77 (60.0) | 5 (50.0) | |
| No. of bone metastasis | | | 0.480 |
| ≤ 3 | 44 (33.6) | 5 (50.0) | |
| > 3 | 87 (66.4) | 5 (50.0) | |
| RT to bone metastasis | | | 0.419 |
| No | 81 (61.8) | 8 (80.0) | |
| Yes | 50 (38.2) | 2 (20.0) | |

PCT palliative chemotherapy, LLRT locoregional radiotherapy, ECOG Eastern Cooperative Oncology Group, Chemo Chemotherapy, RT radiotherapy.

Majority of NPC patients received PCT plus LLRT (92.9%), among them, 44 patients had less than 3 bone metastatic lesions. 37.9% of all populations received RT to bone metastasis in PCT plus LLRT group.

## Efficacy Of Additional Llrt

Kaplan-Meier curves showed that median OS in the PCT plus LLRT group was significantly longer than the PCT alone group (45.0 months vs 13.5 months; $p = 0.001$) (Fig. 3a), as well as PFS (29.0 months vs 11.0 months; $p = 0.014$) (Fig. 3b). In order to confirm whether LRRT can benefit all patients who received PCT plus LLRT, we conducted a subgroup analysis based on the number of bone metastasis. Patients who had less than 3 bone metastatic lesions were closely associated with longer median OS than those who had more than 3 bone metastatic lesions (63.5 months vs 24.0 months; $p < 0.001$) (Fig. 3c), which was also tanable in term of the median PFS (48.0 months vs 16.0 months; $p = 0.010$) (Fig. 3d).

Univariate and Multivariate analysis further confirmed LRRT was an independent prognostic factor in OS for de novo mNPC patients (Table 2). In addition, Multivariate analysis also suggested that more chemotherapy cycles ($\geq 4$) and limited bone metastasis predict better survival outcome.

Table 2
Univariable and Multivariate analysis for PFS and OS in 141 de novo mNPC patients

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| | HR (95% CI) | *p* | HR (95% CI) | *p* |
| **Progress-free survival** | | | | |
| Age (≤ 50 vs > 50) | 1.030 (0.655–1.620) | 0.898 | | |
| Sex (Female vs Male) | 0.931 (0.532–1.629) | 0.801 | | |
| Chemotherapy cycles (< 4 vs ≥ 4) | 0.325 (0.208–0.507) | < 0.001 | 0.363 (0.230–0.573) | < 0.001 |
| Locoregional radiation therapy (No vs Yes) | 0.479 (0.230–0.999) | 0.050 | 0.712 (0.338–1.501) | 0.187 |
| No. of bone metastasis (≤ 3 vs > 3) | 0.517 (0.333–0.802) | 0.003 | 0.597 (0.383–0.930) | 0.023 |
| **Overall Survival** | | | | |
| Age (≤ 50 vs > 50) | 1.404 (0.904–2.181) | 0.131 | | |
| Sex (Female vs Male) | 0.993 (0.575–1.715) | 0.981 | | |
| Chemotherapy cycles (< 4 vs ≥ 4) | 0.298 (0.193–0.460) | < 0.001 | 0.337(0.217–0.523) | < 0.001 |
| Locoregional radiation therapy (No vs Yes) | 0.335 (0.166–0.676) | 0.002 | 0.439 (0.216–0.891) | 0.023 |
| No. of bone metastasis (≤ 3 vs > 3) | 0.473 (0.305–0.732) | 0.001 | 0.536 (0.345–0.832) | 0.005 |

### Efficacy of additional RT to metastatic bones in patients received PCT plus LLRT

To explore whether RT to metastatic bones would generate actual benefits in de novo mNPC patients who had already received PCT plus LLRT, Kaplan-Meier analysis was conducted. The data revealed that despite the trend of benefit, RT to metastatic bones had no statistical significance in OS (60.0 months vs 38.0 months, $p = 0.492$) (Fig. 4a) and PFS (37.0 months vs 25.0 months, $p = 0.503$) (Fig. 4b ).

To eliminate the unbalanced factors between the above two groups, propensity score matching (PSM) (1:1) with a nearest neighbor was performed (Additional file 1: Table S1).

The Kaplan–Meier demonstrated that RT to metastatic bones was not closely associated with better OS and PFS ($p>0.05$) (Additional file 2: Figure S1).

In order to screen the dominant population of RT to metastatic bones, subgroup analysis in 50 patients who received PCT plus LLRT and RT to metastatic bones was done. Patients was stratified by number of metastatic bone sites (≤ 3 group and > 3 group), as we had found number of bone metastasis was an independent prognostic factor in OS and PFS. Interestingly, Kaplan-Meier analysis showed that RT to metastatic bones had significantly longer median OS (72.0 months vs 26.0 months, $p = 0.002$) (Fig. 4c) and PFS (60.0 months vs 20.0 months, $p = 0.006$) (Fig. 4d).

# Discussion

Treatment of mNPC was a major challenge for radiotherapy physician. The skeleton was the most common site of distant metastasis in NPC, whereas the optimal therapeutic strategy has remained largely undefined. Our study showed that compared to PCT alone, combination of PCT and LLRT could improve OS and PFS in de novo mNPC with bone-only metastasis, especially in patients with limited metastatic bone sites (≤ 3). Moreover, LLRT and number of bone metastasis (≤ 3) were favorable independently factor for OS. For patients receiving PCT plus LLRT, there was no significant benefit from RT to metastatic bones in unselected patients. Subgroup analysis further confirmed that RT for metastatic bones only improve OS and PFS for mNPC with less than 3 metastatic bone lesions.

Local radiotherapy in mNPC is becoming hot-button issues. Rusthoven et al. reported that compared to chemotherapy alone, local radiotherapy combined with chemotherapy was associated with improved OS (median OS 21.4 vs 15.5 months, 5-year OS 28% vs 10%), resulting in a 39% reduction of death risk[13]. Similar findings were also found in some retrospective studies[14–20]. Up to now, there are only one multicenter phase 3 randomized clinical trial investigated the efficacy of LLRT in de novo mNPC. The trial demonstrated that PCT plus LLRT can significantly prolong OS of chemotherapy-sensitive mNPC patients. The 2-year survival rate was 76.4% in PCT plus LRRT group versus 54.5% in the PCT alone group ( HR = 0.42) [5]. As to mNPC with bone-only metastasis, Shen et al found that compared with chemotherapy or radiotherapy alone, combined chemoradiotherapy could significantly benefit patients with single bone metastasis (HR = 0.21). In additional, spinal metastasis and more than 3 bone metastasis sites are unfavorable elements for OS [21]. Consistent with above studies, our study also highlight the significance of LLRT in de novo mNPC with bone-only metastasis. Our study suggest that patients receiving PCT plus LLRT had over three times OS than PCT alone (45.0 months vs 13.5 months), and longer OS was remarkably observed in patients who had less than 3 bone ( median OS = 63.5 months). While our results were somewhat different from Shen' study, our study suggested that less chemotherapy cycles (< 4 ), no locoregional radiation therapy and larger number of bone metastasis (> 3) were associated with worse OS. Taken together, LLRT should be considered after PCT in clinical practice of mNPC in future, especially for mNPC patients with bone-only metastasis. More randomized clinical trials are warranted.

For mNPC patients with bone-only metastasis, who will benefit from RT to metastatic bones has not yet been well characterized. Li et al reported that patients who received intensive local radiotherapy to bone lesions had longer OS (HR = 0.63) and PFS (HR = 0.80), and the post-treatment EBV DNA level and radical

radiation dose were independent prognostic factors for OS [9]. However, our study indicated that for patients receiving PCT plus LLRT, the benefit from RT to metastatic bones was only seen in mNPC with less than 3 metastatic bone lesions, not in patients without selection. Of note, patients receiving PCT plus LLRT and RT to metastatic bones lives the longest survival. Therefore, for mNPC with less than 3 metastatic bone lesions, radical radiotherapy to metastatic bone would be strongly preferred as patients may have a long-term survival.

Since there is no consensus on who should receive LLRT and / or RT to metastatic sizes after first-line PCT, prognostic models and risk stratifications guiding the subdivisions of mNPC patients based on clinical features, therapeutic response and blood biomarkers had been widely researched to identify the optimal candidates [3, 14, 17, 19, 22–25], as well as in mNPC with bone-only metastasis[6, 9–11, 21, 26]. Li et al suggested that instead of high-risk mNPC, low-risk patients experienced significant survival benefits from definitive radiation therapy in addition to palliative chemotherapy (PCT) based on 5 prognostic factors, including response of metastases to chemotherapy, number of metastatic sites, liver metastasis, serum lactate dehydrogenase and posttreatment EBV-DNA [22]. Zou et al reported PCT combined with LLRT may benefit mNPC patients without liver involvement liver involvement [3]. Xu et al found that additional LRRT after PCT may only improve OS for oligometastatic patients, rather than polymetastatic disease [23]. Similar findings were also seen in other studies [15, 24]. With respect to the mNPC with bone-only metastasis, chen et al. develop a prognostic score and divided patients into low and high risk groups based on age, N, anemia, bone metastasis free interval, without radiotherapy to primary sites and without radiotherapy to first metastasis sites [26]. Sun et al. subdivide mNPC with bone-only metastasis based on EBV DNA after PCT and the number of metastatic lesions[10]. Our study classified mNPC into two group through number of bone metastatic lesions, proving a simple and feasible way to predict survival and guide clinical practice. In summary, looking for reliable and valuable biomarkers is vital to aid doctors in selecting the most suitable patients for individualized and comprehensive therapy.

The study had sone limitations. Firstly, our study is retrospective study in single-center. Secondly, our simple sizes are relatively small, which might affect statistical performance even when PSM was performed. Thirdly, EBV DNA and other blood biomarkers were not assessed in our study. Further prospective trails are needed in the future to guide the management of de novo mNPC with bone-only metastasis.

# Conclusions

These findings suggest that PCT plus LLRT and RT to metastatic bones really remarkably improves survival in de novo mNPC with limited number of bone metastasis ($n \leq 3$). Our study supports an aggressive interventions for selective mNPC patients with bone-only metastasis. Prospective clinical trials are expected to confirm these results and to find the optimal population.

# Abbreviations

RT: radiation therapy; LRRT: locoregional radiation therapy; mNPC:metastatic nasopharyngeal carcinoma; PCT: palliative chemotherapy; IMRT: intensity-modulated radiotherapy; OS: Overall survival; PFS: progression-free survival; PSM: Propensity score-matched; ECOG: Eastern Cooperative Oncology Group; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; HR: Hazard ratios; CI: confidence interval; EBV: Epstein-Barr virus.

# Declarations

### Ethical approval and consent to participate

This study was approved by the Ethics Committee of Fujian Medical University Cancer Hospital, Fuzhou, China.

### Consent for publication

Not applicable.

### Availability of data and material

The datasets generated and/or analyzed in our study are available from the corresponding author.

### Competing interests

The authors declare that they have no competing interests.

### Ethical statement and consent to participate

The study protocol was designed in accordance with the guidelines outlined in the Declaration of Helsinki. All information was retrospectively extracted in the context of compliance with the relevant regulations and protection of patients' privacy. This study was approved by the Ethical Review Committee of Fujian Cancer Hospital (No. SQ2019-031-01). All of the participants signed an informed consent form.

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### Authors' contributions

All authors helped to perform the research; LC participated in manuscript writing and data analysis; PJJ, LSJ and LC participated in study concept and study design. LS and ZLL participated in data collection. All authors approved the final manuscript.

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# Figures

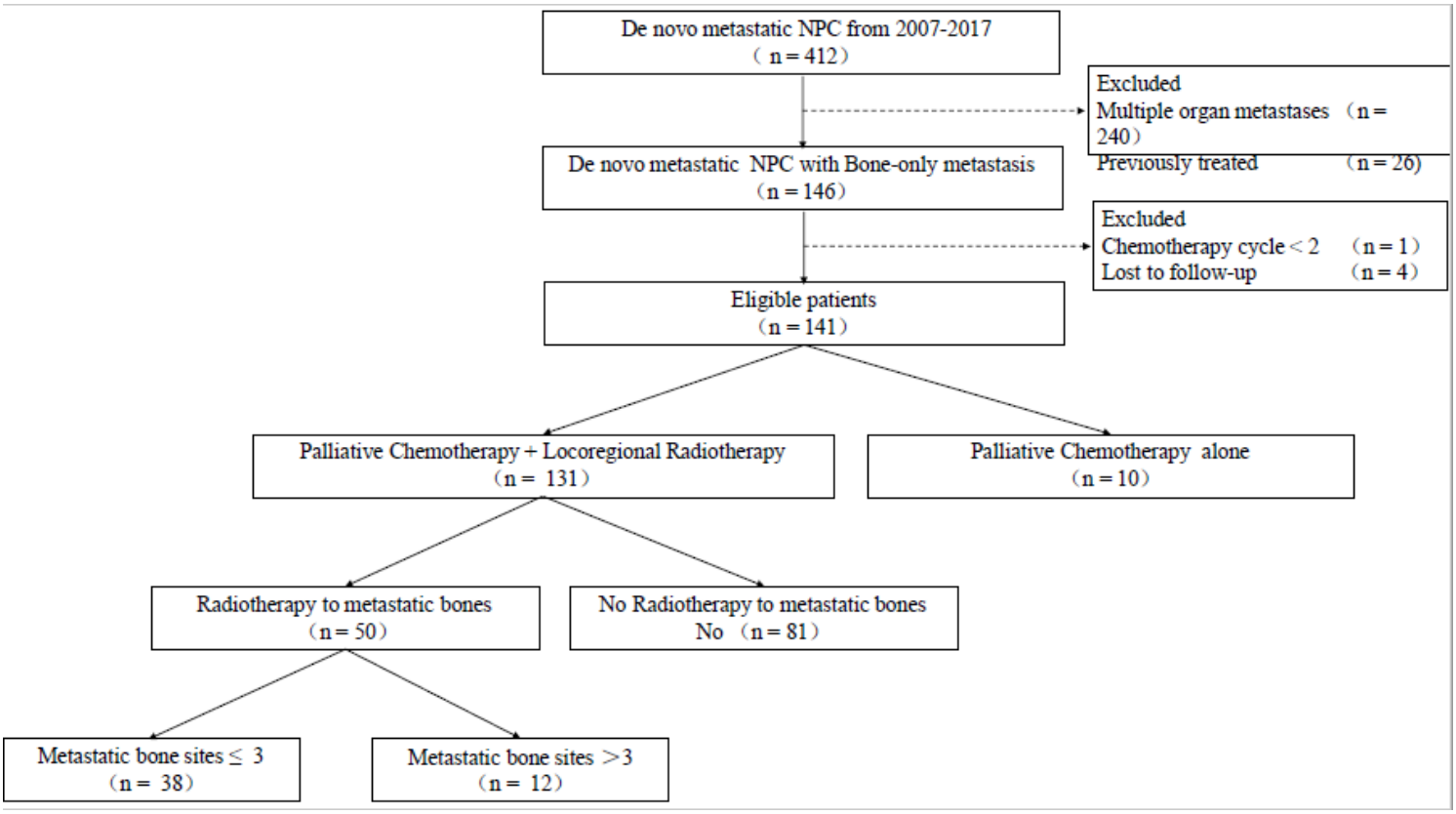



**Figure 1**

Flow diagram of study selection process.

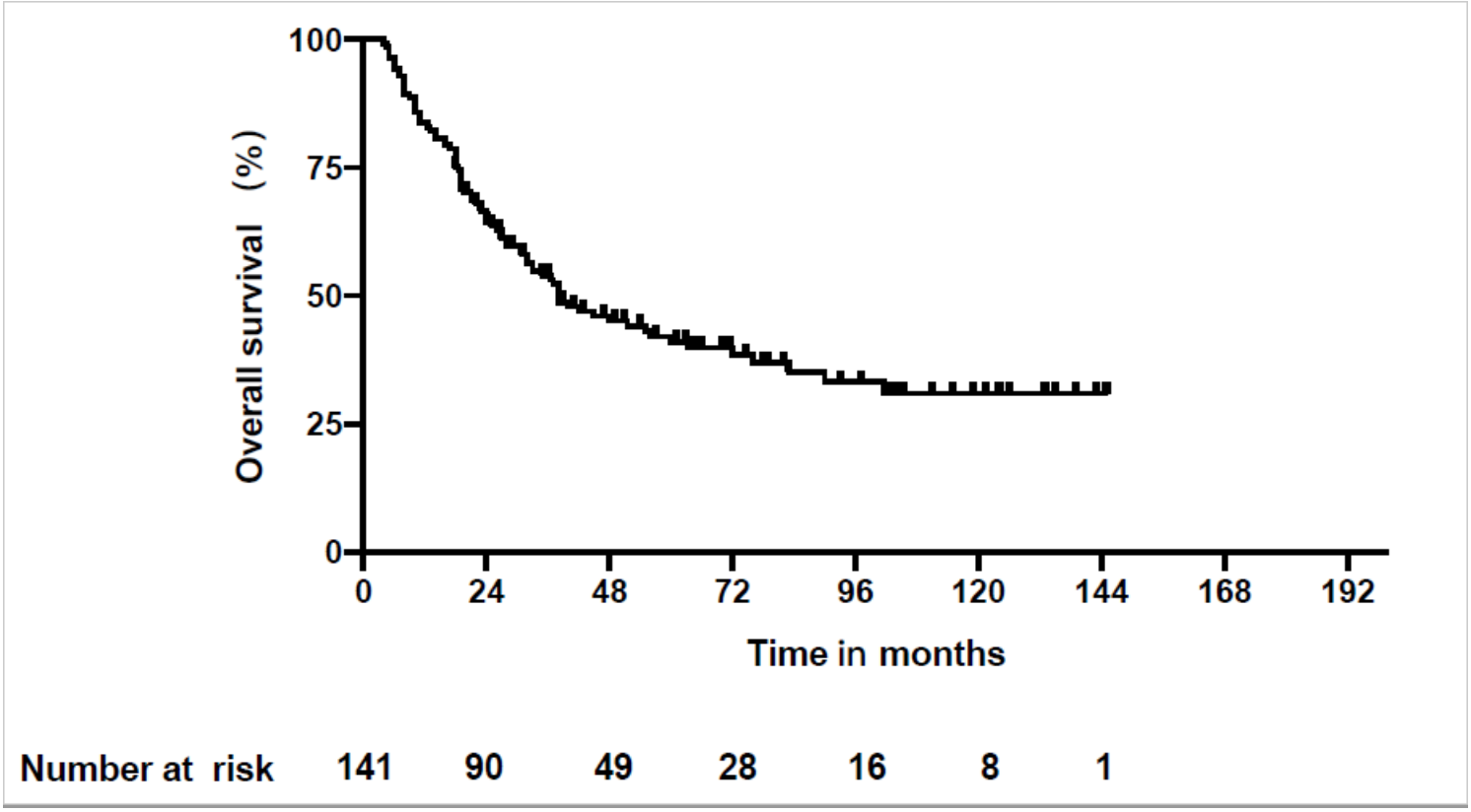
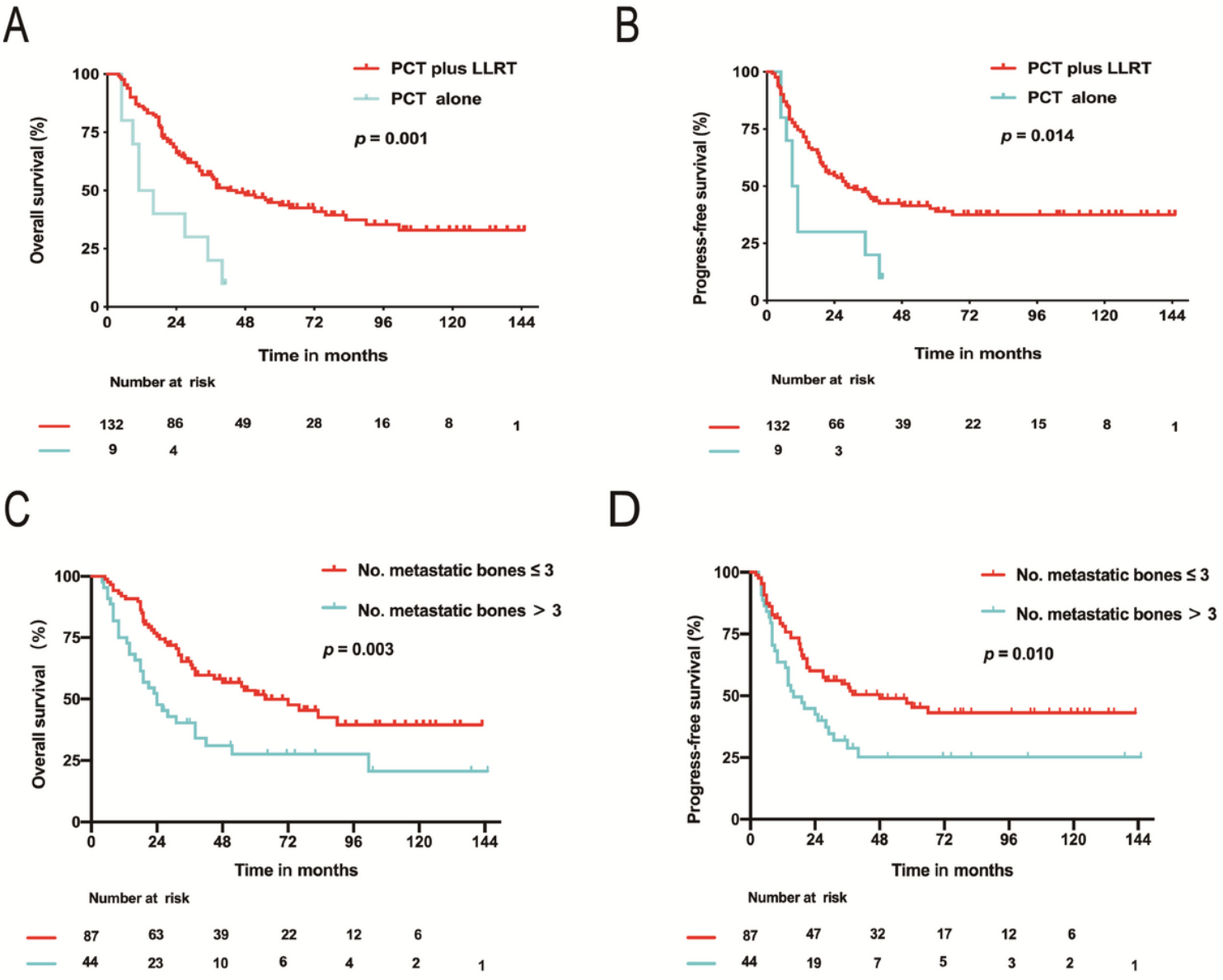



**Figure 2**

Kaplan–Meier curves of OS in 141 de novo mNPC patients with bone-only metastasis




## Figure 3

Kaplan–Meier curves for OS (a) and PFS (b) of 141 de novo mNPC patients receiving at least two cycles palliative chemotherapy (PCT); Kaplan–Meier curves according to No. of metastatic bones for OS (c) and PFS (d) of 131 de novo mNPC patients with bone-only metastasis receiving PCT and locoregional radiation therapy (LLRT).

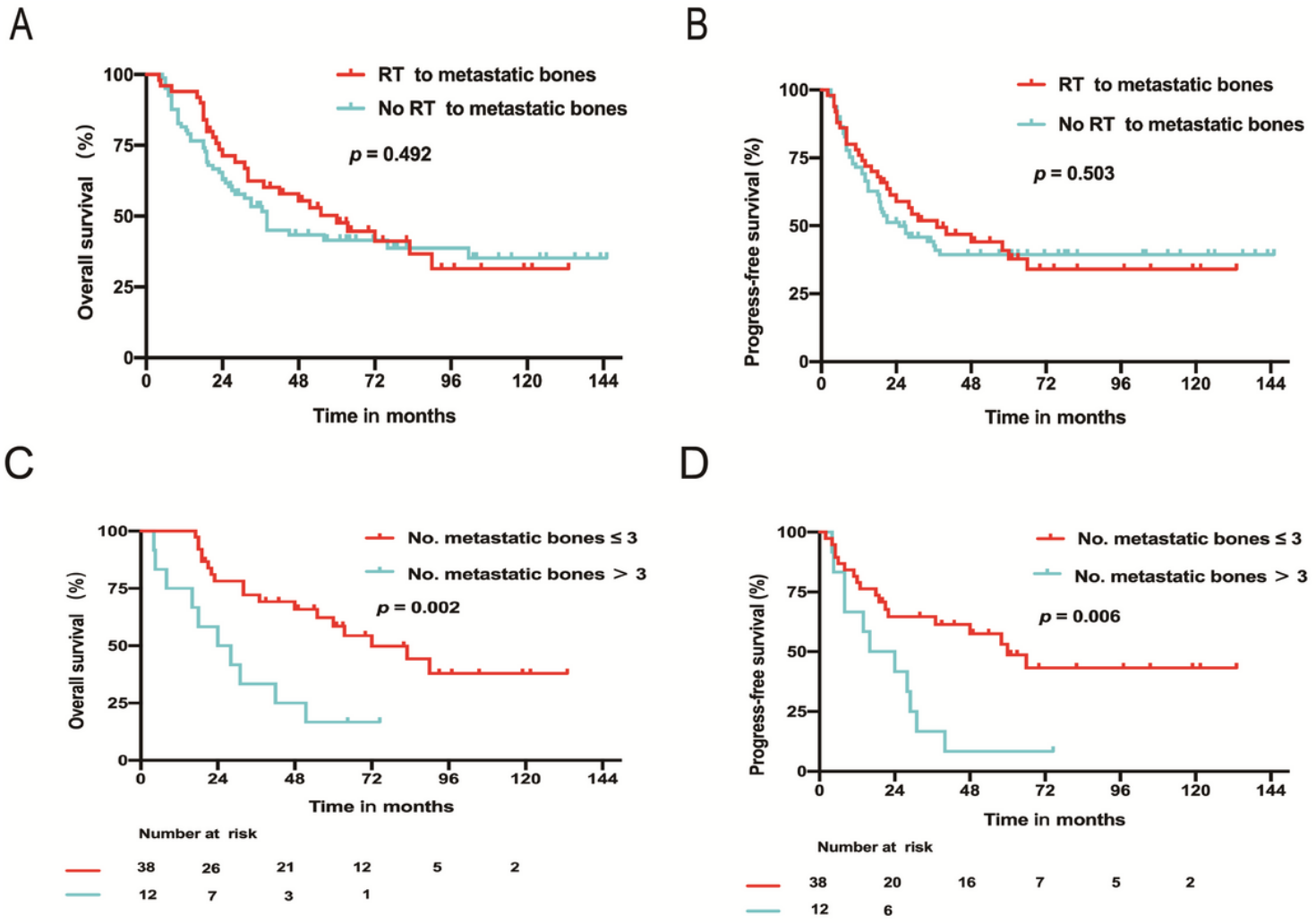



**Figure 4**

Kaplan–Meier curves for OS (a) and PFS (b) of 131 de novo mNPC patients based on whether patients received RT to metastatic bones or not; Kaplan–Meier curves according to No. of metastatic bones for OS (c) and PFS (d) of 50 de novo mNPC patients receiving PCT plus LLRT and RT to metastatic bones.

# Supplementary Files

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- TableS1.docx
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