Efficacy of local therapy to metastatic foci in nasopharyngeal carcinoma: large-cohort strictly-matched retrospective study

Meng-Xia Zhang*, Ting Liu*, Rui You*, Xiong Zou*, Yong-Long Liu*, Xi Ding, Chong-Yang Duan, Han-Shi Xu, You-Ping Liu, Rou Jiang, Zhi-Qiang Wang, Chao Lin, Yu-Long Xie, Si-Yuan Chen, Yan-Feng Ouyang, Ruo-Qi Xie, Yi-Jun Hua, Rui Sun, Pei-Yu Huang, Shun-Lan Wang and Ming-Yuan Chen

Abstract

Background: Studies of local therapy (LT) to metastatic foci from nasopharyngeal carcinoma (NPC) are inconsistent and controversial. Here, we aimed to explore the survival benefit of LT directed at metastatic foci from NPC.

Methods: A retrospective analysis was conducted in NPC patients with liver, lung, and/or bone metastases. The postmetastatic overall survival (OS) rate was analyzed using the Kaplan–Meier method and compared by the log-rank test. Multivariate analysis was performed using the Cox hazard model. Subgroup analyses evaluating the effect of LT were performed for prespecified covariates. Propensity score matching was applied to homogenize the compared arms.

Results: Overall, 2041 of 2962 patients were eligible for analysis. At a median follow-up of 43.4 months, the 5-year OS improved by an absolute difference of 14.6%, from 46.2% in the LT group *versus* 31.6% in the non-LT group, which led to a hazard ratio of 0.634 for death ($p < 0.001$). Matched-pair analyses confirmed that LT was associated with improved OS ($p = 0.003$), and the survival benefits of LT remained consistent in the subcohorts of liver and lung metastasis ($p = 0.009$ and $p = 0.007$, respectively) but not of bone metastasis (BoM; $p = 0.614$). Radiotherapy was predominantly used for BoM and biological effective dose (BED) >60 Gy was found to yield more survival benefit than that of BED ≤ 60 Gy.

Conclusions: The addition of LT directed at metastasis has demonstrated an improvement to OS compared with non-LT group in the present matched-pair study, especially for patients with liver and/or lung metastases.

Keywords: distant metastasis, local therapy, nasopharyngeal carcinoma, propensity score matching, survival

Introduction

Nasopharyngeal carcinoma (NPC) is rare in Western countries but is prevalent in China and Southeast Asia. NPC is distinct from other head and neck cancers due to its high rates of distant metastasis, including synchronous metastasis (smNPC, metastasis at initial diagnosis) and metachronous metastasis (mmNPC, metastasis over 6 months after radical chemoradiotherapy).[1–3] The incidences of smNPC and mmNPC have been reported to be 4%−10% and 15%–30%, respectively.[4–6] When metastasis occurs, the survival outcomes of patients are unsatisfactory with a median overall survival (OS) of 12–30 months after multidisciplinary therapies.[1,7]

Aiming to explore the most effective regimen for metastatic NPC (mNPC) and to improve survival outcome of patients, a variety of strategies, including systemic chemotherapy, immunotherapy,

Correspondence to:
Ming-Yuan Chen
Department of
Nasopharyngeal
Carcinoma, Sun Yat-sen
University Cancer Center,
651 Dongfeng East Road,
Guangzhou 510060, China

Sun Yat-sen University
Cancer Center, State Key
Laboratory of Oncology in
South China, Collaborative
Innovation Center
for Cancer Medicine,
Guangdong Key Laboratory
of Nasopharyngeal
Carcinoma Diagnosis
and Therapy, Guangzhou,
China

Nasopharyngeal Cancer
Center, The First Hospital
of Nanchang (NanChang
Hospital, Sun Yat-sen
University), Nanchang,
China
**chmingy@mail.sysu.
edu.cn**

**Meng-Xia Zhang
Ting Liu
Rui You
Xiong Zou
Yong-Long Liu
Xi Ding
Han-Shi Xu
Chao Lin
Si-Yuan Chen
Yan-Feng Ouyang
Ruo-Qi Xie
Yi-Jun Hua
Rui Sun
Pei-Yu Huang**
Department of
Nasopharyngeal
Carcinoma, Sun Yat-sen
University Cancer Center,
Guangzhou, China

Sun Yat-sen University
Cancer Center State Key
Laboratory of Oncology in
South China, Collaborative
Innovation Center
for Cancer Medicine,
Guangdong Key Laboratory
of Nasopharyngeal
Carcinoma Diagnosis
and Therapy, Guangzhou,
China

You-Ping Liu
Yu-Long Xie
Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China

Sun Yat-sen University Cancer Center State Key Laboratory of Oncology in South China

Collaborative Innovation Center for Cancer Medicine

Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China Nasopharyngeal Cancer Center, The First Hospital of Nanchang (NanChang Hospital, Sun Yat-sen University), Nanchang, China

Chong-Yang Duan
Department of Biostatistics, School of Public Health, Southern Medical University, Guangzhou, China

Rou Jiang
Cancer Prevention Center, Sun Yat-sen University Cancer Center, Guangzhou, China

Zhi-Qiang Wang
Department of Radiation Oncology, First Affiliated Hospital of Kunming Medical University, No.1 School of Clinical Medicine, Kunming Medical University, Kunming, Yunnan, China

Shun-Lan Wang
Department of Otolaryngology, The first Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China

*These authors contributed equally.

targeted therapy, treatment of *in situ* primary tumors and local therapy (LT) to metastatic foci, have been utilized over the past decade.[8–10] To date, systematic chemotherapy remains the mainstay of treatment for mNPC.[11] Zhang *et al.*[12] established gemcitabine and cisplatin doublet chemotherapy as the standard first-line treatment for patients with recurrent or metastatic NPC. Immunotherapy based on immune checkpoint inhibitors shows promising efficacy both in first-line and in the following lines of treatment for mNPC.[13–18] Studies have reported that the addition of targeted therapy (cetuximab) to chemotherapy is associated with an improvement in survival in patients with recurrent or metastatic NPC.[19–22] However, significant toxicities of targeted therapy, such as hemorrhagic events, leucopenia, and hand–foot–skin reactions, cannot be ignored.[22–25] Prospective randomized phase III trials will be necessary to validate the efficacy of targeted therapy. In addition to systematic therapy, treatment of *in situ* primary tumors is also important. The results from a multicenter, randomized phase III clinical trial suggest that definitive radiotherapy (RT) for the primary nasopharynx and cervical lymph nodes as well as systematic chemotherapy significantly improve survival in smNPC patients who are sensitive to induction chemotherapy.[26]

As for LT to metastasis, its therapeutic effect in mNPC remains inconsistent and controversial. Several retrospective studies found that LT, such as surgery or radiofrequency ablation (RFA) for liver metastasis (LiM)[27] or lung metastasis (LuM)[28] and RT for bone metastasis (BoM),[29] may provide additional survival benefits for patients. Liang *et al.*[30] analyzed 448 mmNPC patients and found that LT to metastasis could benefit patients' survival. In contrast, a multicenter population study of three cohorts containing 977 smNPC patients has demonstrated that LT is not associated with better survival in patients undergoing systemic chemotherapy and radical RT for primary tumors even for patients with oligometastasis and without liver involvement.[31] However, due to limited sample sizes, no propensity score matching was applied or inadequate confounding variables were matched to achieve a balanced exposure groups at baseline in these retrospective studies. Herein, we conducted this study with a large cohort ($n = 2041$) of mNPC patients (synchronous and metachronous) and long-term follow-up (median: 43.4 months) and adopted a PSM method to strictly homogenize

the compared arms, aiming to explore the survival benefit of LT for mNPC patients.

Materials and methods

Study population

Consecutive mNPC patients at Sun Yat-Sen University Cancer Center (SYSUCC) between January 2006 and December 2020 were recruited. Tumors were restaged according to the eighth edition of the TNM staging system by the Union for International Cancer Control/American Joint Committee on Cancer.[32] The inclusion criteria were as follows: (a) histologically confirmed NPC; (b) Karnofsky performance status (KPS) score ⩾70; (c) smNPC or mmNPC; (d) LiM, LuM, and/or BoM, single, or combined metastasis; (e) treatment-naive for metastatic disease at diagnosis; and (f) with complete medical record. The exclusion criteria were as follows: (a) previously suffering from or concomitant other malignancies; (b) combined with other metastatic sites (spleen, adrenal gland, brain, etc.); (c) combined with tumor recurrence; and (d) follow-up time <1 month.

Data collection and definition

The following data were collected: (a) patient demographics, including sex, age at the initial diagnosis of NPC, KPS score, and Epstein–Barr virus (EBV) DNA count before treatment for metastases (pre-EBV DNA); (b) tumor characteristics, including pathological type, T/N/M stage, and metastatic sequence (synchronous or metachronous); (c) treatment characteristics, including chemotherapy, immunotherapy, targeted therapy, RT for primary tumor, and LT for DM; and (d) survival status and time point. The definition of metastasis has been previously reported.[33] Briefly, suspicious lesions detected by conventional work-up or positron emission tomography/computed tomography (PET/CT) were identified as metastasis only when additional examinations [CT, magnetic resonance imaging (MRI), or biopsy] confirmed the diagnosis.

Treatment

The treatment regimens were extracted directly from the electronic medical records. Chemotherapy was nearly exclusively cisplatin-based with the combination of one or two of the following drugs:
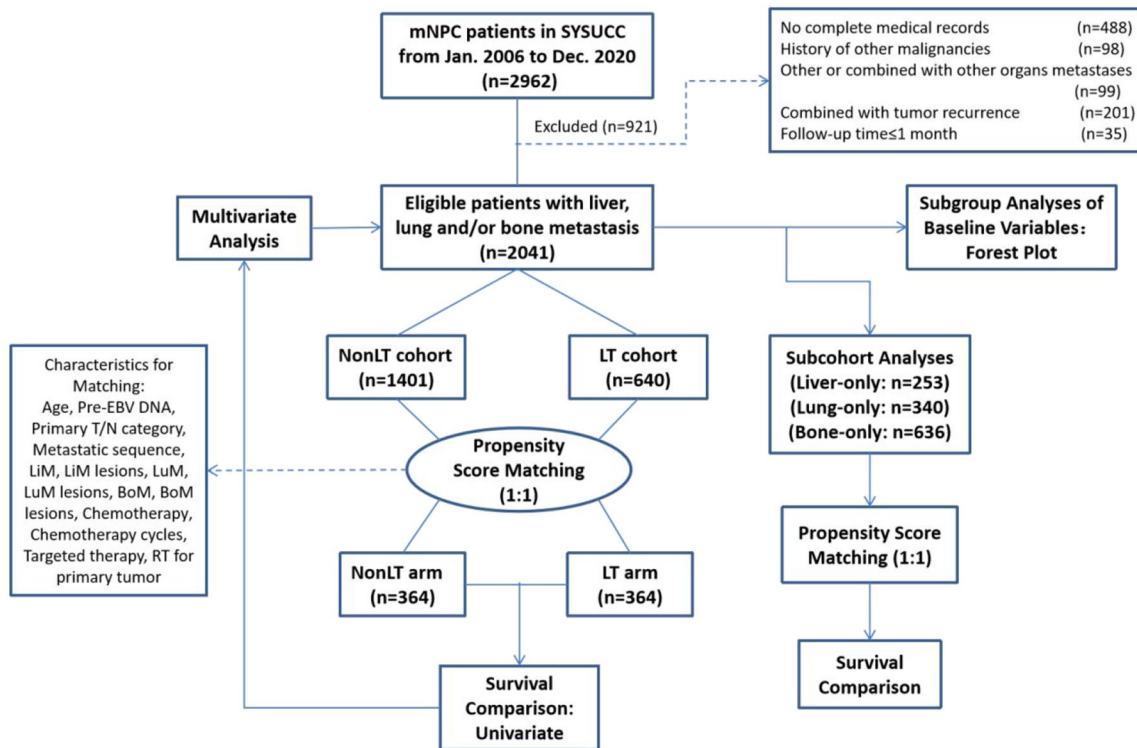
Figure 1. Flowchart for patient selection, matched cohorts generation and survival comparison.
BoM, bone metastasis; LiM, liver metastasis; LT, local therapy; LuM, lung metastasis; mNPC, metastatic nasopharyngeal carcinoma; RT, radiotherapy; SYSUCC, Sun Yat-sen University Cancer Center.

fluorouracil, paclitaxel, gemcitabine, navelbine, or others. Targeted therapy included anti-epidermal growth factor receptor agents (cetuximab or nimo-tuzumab), single target angiogenesis inhibitor (bevacizumab) and multitarget angiogenesis inhibitors (apatinib, famitinib, or anlotinib). Immunotherapy mainly included immune check-point inhibitors (antibodies against CTLA-4, PD-1, or PD-L1 inhibitor). LT to metastatic liver included surgery, RT, RFA, transcatheter hepatic artery chemoembolization (TACE), and particle implantation. LT to metastatic lungs included surgery, RT, RFA, and particle implantation. LT to metastatic bones included surgery, RT, RFA, and radionuclide therapy.

Endpoints and statistical analysis

Baseline characteristics were converted into binary variables and are presented as numbers with per-centages. The best cutoff value of biological effec-tive dose (BED) was selected from median, receiver operating characteristic (ROC) curve, and minimum p-value method based on R package of ggrisk. The distributional differences of categorical variables were compared using the chi-square test or Fisher's exact test. OS was defined as the time from the diagnosis of metastasis to the time of death due to any cause or the last follow-up. The cumulative survival rates were estimated using the Kaplan–Meier method and were compared using the log-rank test. The median follow-up duration was calculated by the reverse Kaplan–Meier method. To explore independent prognostic fac-tors, baseline characteristics with statistical signifi-cance ($p < 0.05$) under univariate analyses were included in a Cox proportional hazards model as confounding factors. Matched cohorts were gener-ated via a 1:1 PSM method with a stringent caliper of 0.01. Several rounds of matching were con-ducted until all parameters were balanced. Statistical analyses were conducted using R 4.0.3 and SPSS version 26.0 (Chicago, IL, USA). Statistical significance was defined as a two-sided p value of less than 0.05.

Results

Patient characteristics

A flow diagram of this study is presented in Figure 1. Totally, 2041 of 2962 patients who met all

criteria were enrolled in the final analyses. The median age was 44.0 years (Interquartile range, IQR: 37.0–52.0). Male predominance (81.2%) was found. Patients had a good KPS of ≥90 in 90.2% of cases. The pathological subtype of non-keratinizing undifferentiated NPC (type III) accounted for 97.8% of cases. According to the initial diagnosis, patients had a T4 tumor in 30.3% of cases and N3 lymph node involvement in 40.3% of cases. A total of 1102 patients had mmNPC, and 939 patients had smNPC. Half of the patients (50.2%) had a pre-EBV DNA count $\geq 10^4$ copies/mL (the cutoff value was referred to a previous report[34]). Bone was the most frequent metastatic site ($n = 1341$, 65.7%) followed by the liver ($n = 908$, 44.5%) and lung ($n = 833$, 40.8%) (Table 1).

Regarding the treatment characteristics, 1873 (91.8%), 490 (24.0%), and 530 (26.0%) patients underwent chemotherapy, targeted therapy, and immunotherapy, respectively. Chemotherapy was nearly exclusively cisplatin-based with 1149 (56.3%) patients who received six cycles or more (median: 6, range: 1–22). 91.7% of patients received RT for primary tumor (median dose: 7000 cGy, range: 5000–7976 cGy). A total of 640 (31.4%) patients received LT to metastatic foci. Specifically, 235, 144, and 305 patients underwent LT for metastatic liver, lung, and bone, respectively. The most frequently used LT method for LiM was RFA followed by RT and surgery. The top three LT methods used for LuM were surgery, RT, and RFA. For BoM, RT was predominantly used as the LT method (Table 1).

Survival benefit of LT in the entire population

In the entire cohort, 640 (31.4%) patients received LT. Before matching, significant differences were detected for age, pre-EBV DNA and other variables ($p < 0.05$ for all) (Table 2). As shown in Figure 2(a), a statistically associated difference was observed at 1, 3, and 5 years for OS rates (91.7 *versus* 85.6%, 61.2 *versus* 47.8% and 46.2 *versus* 31.6%, respectively; all $p < 0.001$) between patients with and without LT. After PSM, 364 patients who underwent LT were matched with 364 patients who lacked LT (all $p > 0.1$; Table 2). Compared to patients who did not receive LT, LT did improve the survival of mNPC patients ($p = 0.003$; Figure 2(b)). Multivariate analyses confirmed LT as an independent favorable predictor of OS (hazard ratio,

HR = 0.634, and 95% CI = 0.531–0.757% CI; $p < 0.001$) (Table 3).

Association between LT and OS by subgroup analyses

Subgroup comparisons for OS of mNPC patients with or without LT demonstrated that LT was associated with improved OS in nearly all subgroups, except for the subgroup of patients without chemotherapy (HR = 0.646, $p = 0.108$). Significant interactions were detected for metastatic sequence and LT, which indicates that patients with mmNPC may benefit more from LT than those with smNPC (HR: 0.639 *versus* 0.777, $p = 0.045$) (Figure 3).

The efficacy of LT for patients with liver-only, lung-only, and bone-only metastasis

As LT efficacy was confirmed in the unselected patients with mNPC, we further conducted sub-cohort analysis in patient with liver-only ($n = 253$), lung-only ($n = 340$), and bone-only ($n = 636$) metastasis to evaluate the survival benefit of LT. Baseline characteristics between patients with or without LT before and after matching were listed in Supplemental Tables 1–3. Based on matched-pair analyses, LT to LiM or LuM was shown to improve survival of patients with liver-only and lung-only metastasis ($p = 0.009$ and $p = 0.007$, respectively; Figure 4(a) and (b)) and were confirmed by multivariate analyses in the unmatched cohorts (Figure 4(d)). However, LT to BoM failed to benefit patients with bone-only metastasis ($p = 0.614$; Figure 4(c) and (d)).

Treatment outcomes of different radiation dose prescriptions and no RT in patient with BoM

Since RT was the primarily used LT to BoM, we further compared the survival outcomes brought by different radiation doses among patients with BoM. Dose prescriptions were converted to BEDs, and a BED of 60 Gy was selected as the best cutoff value for separating patient outcomes (Figure 5(a)). In the subcohort of bone-only metastasis, 150 patients who have detailed RT record and 451 patients who did not receive RT for BoM were enrolled for analysis. Pairwise comparisons demonstrated that the OS rate was significantly higher in high BED (>60 Gy) group than those without RT ($p = 0.033$), whereas there was no survival benefit observed in low BED

Table 1. Baseline patient demographics, tumor characteristics, and treatment characteristics.

Characteristics	No. (%)
All	2041 (100)
Sex	
Female	383 (18.8)
Male	1658 (81.2)
Age	
<45	1035 (50.7)
≥45	1006 (49.3)
KPS score	
<90	199 (9.8)
≥90	1842 (90.2)
Pathology[a]	
Type I-II	44 (2.2)
Type III	1997 (97.8)
Pre-EBV DNA	
$<10^4$	1016 (49.8)
$\geq 10^4$	1025 (50.2)
Primary T category	
T1-3	1423 (69.7)
T4	618 (30.3)
Primary N category	
N0-2	1218 (59.7)
N3	823 (40.3)
Metastatic sequence	
Metachronous	1102 (54.0)
Synchronous	939 (46.0)
Primary overall stage	
I	1 (0.1)
II	64 (3.1)
III	441 (21.6)
IVA	596 (29.2)
IVB	939 (46.0)
Metastatic site	
Liver-only	253(12.4)
Lung-only	340(16.7)

(Continued)

Table 1. (Continued)

Characteristics	No. (%)
Bone-only	636(31.2)
Liver + lung	107(5.2)
Liver + bone	319(15.6)
Lung + bone	157(7.7)
Liver + lung+bone	229(11.2)
LiM	
No	1133 (55.5)
Yes	908 (44.5)
Liver-combined	655 (72.1)
Liver-only	253 (27.9)
LiM lesions (*n* = 908)	
Single	256 (28.2)
Multiple	652 (71.8)
LuM lesions (*n* = 833)	
Single	168 (20.2)
Multiple	665 (79.8)
BoM	
No	700 (34.3)
Yes	1341 (65.7)
Bone-combined	705 (52.6)
Bone-only	636 (47.4)
BoM lesions (*n* = 1341)	
Single	301 (22.4)
Multiple	1040 (77.6)
Chemotherapy	
No	168 (8.2)
Yes	1873 (91.8)
LuM	
No	1208 (59.2)
Yes	833 (40.8)
Lung-combined	493 (59.2)
Lung-only	340 (40.8)
Chemotherapy cycles	
<6	892 (43.7)

(Continued)

Table 1. (Continued)

Characteristics	No. (%)
≥6	1149 (56.3)
Targeted therapy	
No	1551 (76.0)
Yes	490 (24.0)
Immunotherapy	
No	1511 (74.0)
Yes	530 (26.0)
RT for primary tumor	
No	169 (8.3)
Yes	1872 (91.7)
LT for DM	
No	1401 (68.6)
Yes	640 (31.4)
LT for LiM (n = 235)	
Surgery	26(10.7)
RT	41 (16.7)
RFA	140 (60.1)
Combined[b]	23 (9.9)
Others[c]	6 (2.6)
LT for LuM (n = 144)	
Surgery	55 (38.5)
RT	53 (35.7)
RFA	27 (18.8)
Combined[d]	9 (7.0)
LT for BoM (n = 305)	
RT	284 (95.4)
Others[e]	21 (1.3)

BoM, bone metastasis; DM, distant metastasis; KPS, Karnofsky performance status; LiM, liver metastasis; LuM, lung metastasis; LT, local therapy; RFA, radiofrequency ablation; RT, radiotherapy.
[a]Type I: keratinizing; type II: nonkeratinizing differentiated; type III: Nonkeratinizing undifferentiated.
[b]Surgery + RT or surgery + RFA or RT + RFA.
[c]Others included transcatheter hepatic artery chemoembolization (TACE) and particle implantation.
[d]Surgery + RT or surgery + RFA or RT + RFA or RFA + particle implantation;
[e]Others included surgery, radionuclide therapy, and RFA.

(≤60 Gy) group when compared to non-RT group (p = 0.893) (Figure 5(b), Supplemental Table 4). We further conducted matched-pair analyses between different BED groups and non-RT group to confirm the above results. After matching (Supplemental Table 5), high BED group (>60 Gy), but not low BED group (≤60 Gy) was beneficial as LT to BoM for survival when compared to patients without RT (p = 0.004 and p = 0.716, respectively; Figure 5(c) and (d)).

Discussion

To the best of our knowledge, this retrospective study evaluating the efficacy of LT for LiM/LuM/BoM in mNPC patients had the largest sample size to date. Our study substantiated several noteworthy findings. First, LT resulted in a significant OS advantage for mNPC patients based on strict matched-pair analysis. Second, subgroup analyses revealed that LT remained a significant favorable prognosticator in nearly all subgroups. Third, in subcohort analyses, the addition of LT could benefit patients with liver and/or lung metastases but not with BoM. Last, RT with high BED (>60 Gy) for BoM was found to yield more survival benefit for patients with BoM than that of low BED (≤60 Gy).

The optimal strategy for mNPC is to eradicate all detectable and invisible tumors through the combination of systemic and local treatment. Systemic therapies are effective in controlling microscopic diseases, but their impact on macroscopic diseases may be limited. In contrast, local therapies may provide ideal local control for macroscopic lesions. Curative LT to metastatic foci has been reported to improve survival among patients with lung, liver, breast, and prostate cancer.[35,36] For NPC, success of LT has been confirmed in patients with limited metastases.[37] In the present study, we demonstrated that LT was associated with better survival of mNPC patients, owing to its potential effect on reducing tumor burden and preventing further dissemination of metastases. Subgroup analysis demonstrated that LT did not benefit patients without chemotherapy, which indicates that LT may not confer survival benefit when the microscopic metastases are not eliminated simultaneously. Additionally, our data showed that patients with mmNPC benefited more from LT than those with smNPC. One

Table 2. Baseline characteristics between patients with and without LT before and after matching in the entire cohort.

Characteristics	Before matching			After matching		
	Non-LT (*n* = 1401)	LT (*n* = 640)	*p* Value	Non-LT (*n* = 364)	LT (*n* = 364)	*p* Value
Sex			0.146			1.000
Female	251	132		75	75	
Male	1150	508		289	289	
Age			0.001			0.650
<45	676	359		216	222	
≥45	725	281		148	142	
KPS score			0.822			0.590
<90	138	61		28	32	
≥90	1263	579		336	332	
Pathology			0.768			1.000
Type III	1370	627		364	364	
Type *I* + II	31	13		0	0	
Pre-EBV DNA			<0.001			0.286
<10^4	639	377		232	218	
≥10^4	762	263		132	146	
Primary *T* category			0.289			0.750
T1-3	987	436		247	251	
T4	414	204		117	113	
Primary *N* category			<0.001			0.480
N0-2	798	420		246	237	
N3	603	219		118	127	
Metastatic sequence			<0.001			0.875
Metachronous	711	391		241	243	
Synchronous	690	249		123	121	
LiM			0.001			0.940
No	813	320		208	209	
Yes	588	320		156	155	
LiM lesions			<0.001			0.858
No	813	320		208	209	
Single	125	131		39	43	

(Continued)

Table 2. (Continued)

Characteristics	Before matching			After matching		
	Non-LT (*n* = 1401)	LT (*n* = 640)	*p* Value	Non-LT (*n* = 364)	LT (*n* = 364)	*p* Value
Multiple	463	189		117	112	
LuM			0.062			0.941
No	810	398		200	199	
Yes	591	242		164	165	
LuM lesions			<0.001			0.184
No	810	398		200	199	
Single	99	69		29	43	
Multiple	492	173		135	122	
BoM			0.004			0.643
No	452	248		133	127	
Yes	949	392		231	237	
BoM lesions			<0.001			0.889
No	452	248		133	127	
Single	184	117		47	47	
Multiple	765	275		184	190	
Chemotherapy			<0.001			0.885
No	73	95		25	26	
Yes	1328	545		339	338	
Chemotherapy cycles			<0.001			0.824
<6	556	336		169	172	
≥6	845	304		195	192	
Targeted therapy			0.086			0.797
No	1080	471		272	275	
Yes	321	169		92	89	
Immunotherapy			0.601			0.330
No	1042	469		250	262	
Yes	359	171		114	102	
RT for primary tumor			<0.001			1.000
No	161	8		0	0	
Yes	1240	632		364	364	

BoM, bone metastasis; KPS, Karnofsky performance status; LiM, liver metastasis; LuM, lung metastasis; LT, local therapy; RT, radiotherapy.
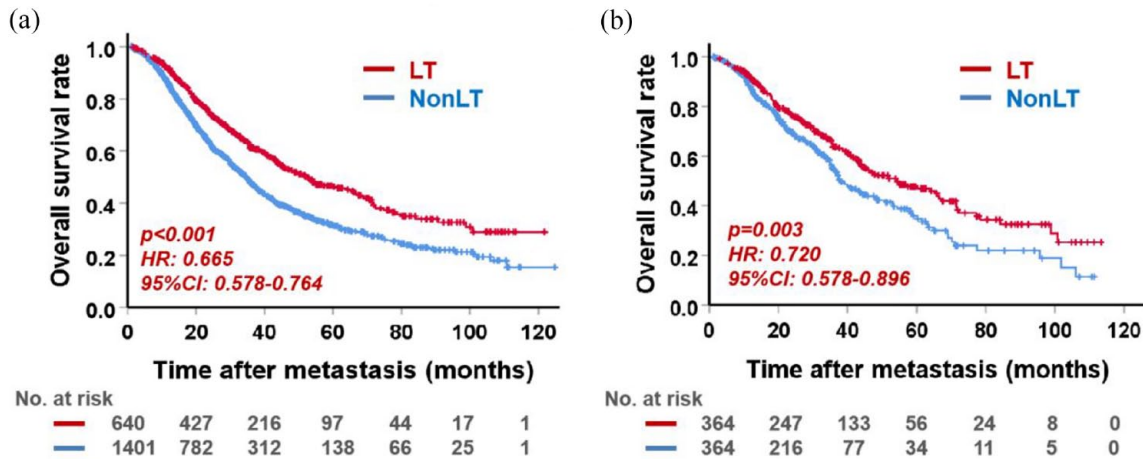
Figure 2. Overall survival rates of mNPC patients who received either LT or did not receive LT for metastatic sites before (a) and after (b) matching. LT: local therapy.

Table 3. Prognostic factors in the unselected population by univariate and multivariate analyses.

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Sex (Female *versus* Male)	1.055 (0.898–1.241)	0.514	–	–
Age (≥45 *versus* <45)	1.305 (1.152–1.477)	<0.001	1.272 (1.121–1.444)	<0.001
KPS score (≥90 *versus* <90)	0.749 (0.614–0.913)	0.004	–	–
Pathology (I–II *versus* III)	0.972 (0.642–1.471)	0.892	–	–
Pre-EBV DNA (≥10^4 *versus*<10^4)	1.749 (1.539–1.987)	<0.001	1.470 (1.283–1.685)	<0.001
Primary T category (T4 *versus* T1–3)	1.105 (0.964–1.267)	0.150	1.197 (1.043–1.374)	0.010
Primary N category (N3 *versus* N0-2)	1.316 (1.160–1.492)	<0.001	1.198 (1.052–1.364)	0.007
Metastatic sequence (SM *versus* MM)	0.874 (0.772–0.990)	0.034	0.655 (0.569–0.755)	<0.001
LiM (Yes *versus* No)	1.816 (1.602–2.058)	<0.001	1.951 (1.709–2.228)	<0.001
LuM (Yes *versus* No)	0.996 (0.879–1.129)	0.953	1.205 (1.053–1.378)	0.007
BoM (Yes *versus* No)	1.338 (1.166–1.535)	<0.001	1.453 (1.249–1.691)	<0.001
Chemotherapy (Yes *versus* No)	0.837 (0.664–1.055)	0.132	0.744 (0.584–0.948)	0.017
Targeted therapy (Yes *versus* No)	0.940 (0.812–1.089)	0.411	-	-
Immunotherapy (Yes *versus* No)	0.654 (0.558–0.767)	<0.001	0.542 (0.458–0.640)	<0.001
RT for primary tumor (Yes *versus* No)	0.559 (0.458–0.682)	<0.001	0.609 (0.490–0.757)	<0.001
LT for DM (Yes *versus* No)	0.665 (0.578–0.764)	<0.001	0.693 (0.599–0.802)	<0.001

HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; SM, synchronous metastasis; MM, metachronous metastasis; LiM, liver metastasis; LuM, lung metastasis; BoM, bone metastasis; LT, local therapy; RT, radiotherapy; DM, distant metastasis.
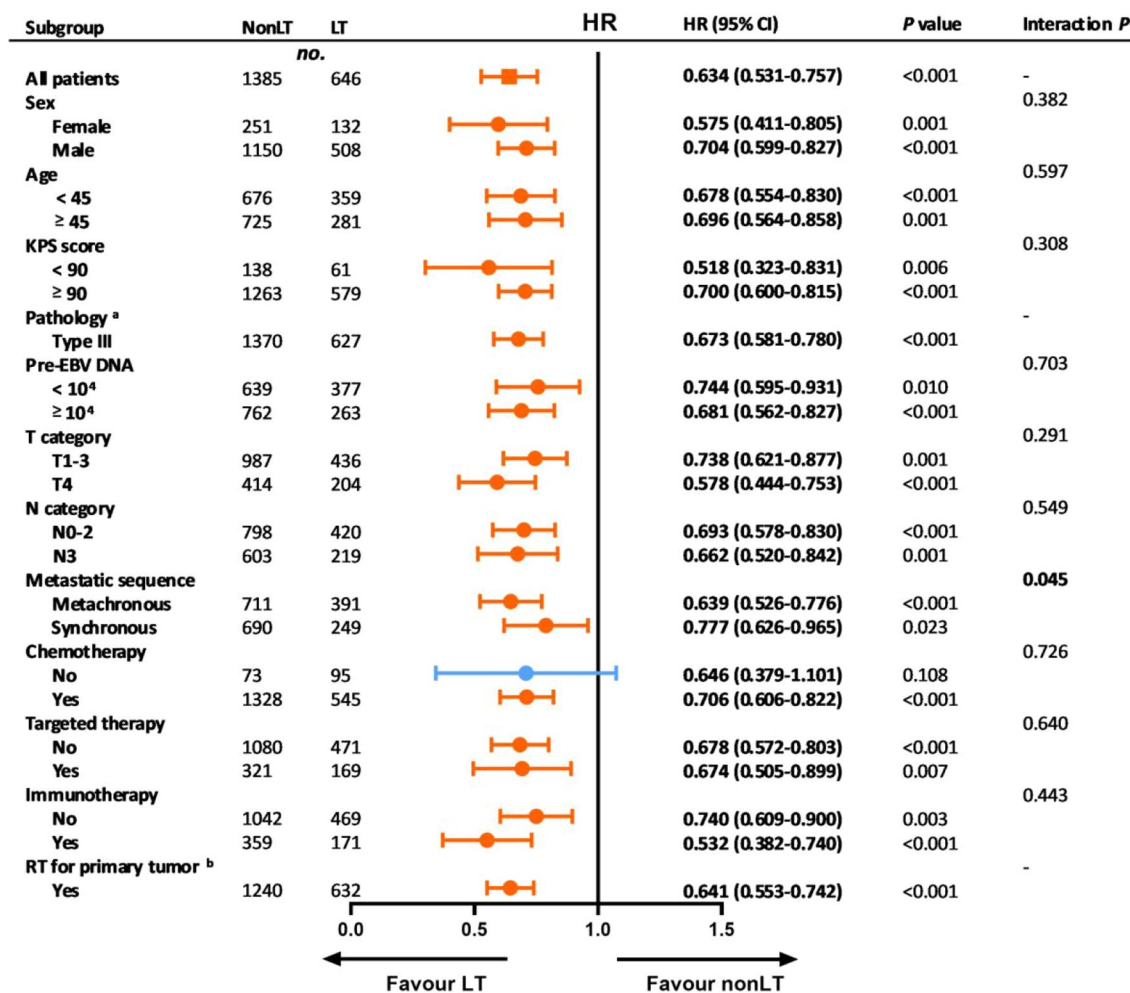
Subgroup	NonLT	LT	HR	HR (95% CI)	P value	Interaction P
	no.					
All patients	1385	646		0.634 (0.531–0.757)	<0.001	-
Sex						0.382
Female	251	132		0.575 (0.411–0.805)	0.001	
Male	1150	508		0.704 (0.599–0.827)	<0.001	
Age						0.597
< 45	676	359		0.678 (0.554–0.830)	<0.001	
≥ 45	725	281		0.696 (0.564–0.858)	0.001	
KPS score						0.308
< 90	138	61		0.518 (0.323–0.831)	0.006	
≥ 90	1263	579		0.700 (0.600–0.815)	<0.001	
Pathology [a]						-
Type III	1370	627		0.673 (0.581–0.780)	<0.001	
Pre-EBV DNA						0.703
< 10^4	639	377		0.744 (0.595–0.931)	0.010	
≥ 10^4	762	263		0.681 (0.562–0.827)	<0.001	
T category						0.291
T1–3	987	436		0.738 (0.621–0.877)	0.001	
T4	414	204		0.578 (0.444–0.753)	<0.001	
N category						0.549
N0–2	798	420		0.693 (0.578–0.830)	<0.001	
N3	603	219		0.662 (0.520–0.842)	0.001	
Metastatic sequence						0.045
Metachronous	711	391		0.639 (0.526–0.776)	<0.001	
Synchronous	690	249		0.777 (0.626–0.965)	0.023	
Chemotherapy						0.726
No	73	95		0.646 (0.379–1.101)	0.108	
Yes	1328	545		0.706 (0.606–0.822)	<0.001	
Targeted therapy						0.640
No	1080	471		0.678 (0.572–0.803)	<0.001	
Yes	321	169		0.674 (0.505–0.899)	0.007	
Immunotherapy						0.443
No	1042	469		0.740 (0.609–0.900)	0.003	
Yes	359	171		0.532 (0.382–0.740)	<0.001	
RT for primary tumor [b]						-
Yes	1240	632		0.641 (0.553–0.742)	<0.001	

0.0   0.5   1.0   1.5

← Favour LT   Favour nonLT →

Figure 3. Forest plot of the association between LT and overall survival by subgroup based on multivariate analyses.
CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status; LT, local therapy; RT, radiotherapy.
[a]A total of 1997 cases of pathological type III were analyzed.
[b]A total of 1872 cases that received RT for primary tumor were analyzed.

potential explanation is that for mmNPC, LT of metastatic sites is mostly implemented after the treatment of primary tumors (≥6 months). The patient's physical condition has recovered and has good tolerance to LT. As for smNPC (metastasis at initial diagnosis), patient may receive chemotherapy and LT for primary tumors first. On this basis, adding LT to metastatic sites may increase the risk of severe treatment toxicities, thus to reduce survival benefit. Currently, there is no relevant literature report, which is worthy of further exploration and verification.

LiM are commonly regarded as an incurable disease and portend an inferior prognosis compared to bone or LuM, and the treatment has largely been palliative.[38,39] With the advancements in imaging methods, systemic treatment and local therapies (including surgery, RT, and locally ablative techniques) over the past decades, evidence has been provided for a more aggressive treatment for LiM. Successful treatment experience has been achieved with hepatectomy in colorectal cancer with LiM, and previous studies on surgical resection for patients with noncolorectal hepatic metastases have shown encouraging results with median postoperative follow-up or OS periods of 23.5–49 months.[40–42] For NPC, literature regarding surgical treatment of LiM is rare. Delis *et al.*[43] reported a patient with a solitary LiM from NPC who underwent segmentectomy and no recurrence was noted during the
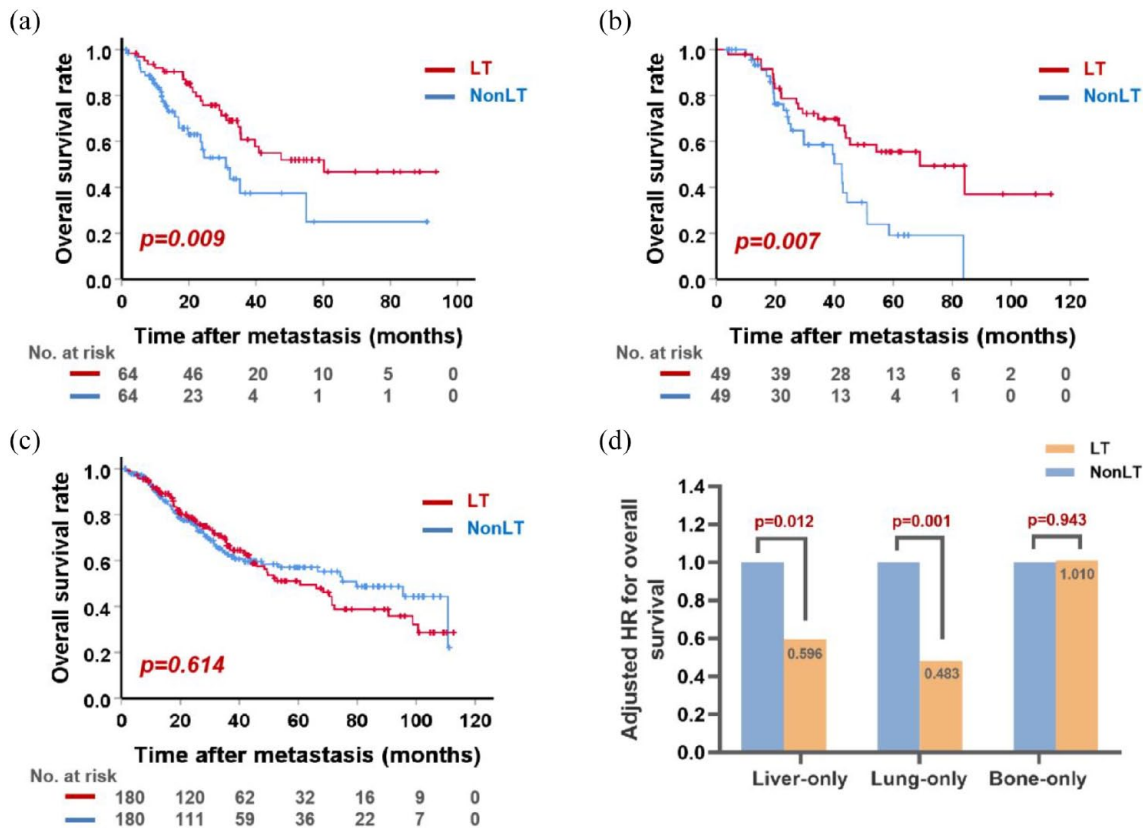
Figure 4. Comparison of overall survival (OS) in mNPC patients in the local therapy (LT) for liver-only (a), lung-only (b), or bone-only (c) metastasis and non-LT groups after matching. (d) Adjusted hazard ratios (HRs) for OS stratified by LT in subcohorts of liver-only, lung-only, and bone-only metastasis. The group with non-LT was the reference group (HR = 1). The adjusted variables were age, pre-EBV DNA, metastatic sequence, LiM lesions, chemotherapy, targeted therapy, immunotherapy, and RT for primary tumor for liver-only metastasis subcohort. The adjusted variables were age, KPS score, pre-EBV DNA, LuM lesions, chemotherapy, immunotherapy, and RT for primary tumor for lung-only metastasis subcohort. The adjusted variables were age, KPS score, pre-EBV DNA, primary *N* category, metastatic sequence, BoM lesions, and RT for primary tumor for bone-only metastasis subcohort.
BoM, bone metastasis; KPS, Karnofsky performance status; LiM, liver metastasis; LuM, lung metastasis; LT, local therapy.

6-month follow-up after resection. Another case study reported two patients with metachronous LiM from NPC who underwent metastasectomy had a mean postoperative survival period of 58.0 months.[44] Hung raises the point that LiMs present an invasive outgrowth pattern due to the deficiency of hepatic capsule and blood supply.[41] Thus, metastasectomy has a role in curbing the further spread of tumor.

Apart from surgical management, nonsurgical LT options, such as RFA, RT, and TACE, are available for LiM. CT-guided RFA can be administered with high technical efficiency and may prolong survival in selected NPC patients.[28,45,46] RFA for treating NPC patients with 1–3 LiMs prolongs survival compared to those who only receive chemotherapy

(median OS: 48.1 *versus* 25.9 months).[47] Peng *et al.*[48] reported the effectiveness of TACE for NPC patients with LiM, and they suggested that it can be optional for suitable patients because it may control intrahepatic lesions and prolong survival. The advantage of RT, especially stereotactic body radiation therapy, is that its effectiveness is not impaired by intravascular blood flow or bile accumulation in the gallbladder. Furthermore, external irradiation can reach any tumor locations of liver, such as the subphrenic area. NPC patients with LuM are historically regarded as a distinct group with favorable prognosis.[39,49] In a case–control study that matched 55 and 22 patients who underwent surgery and nonsurgery for LuM, patients who underwent pulmonary surgery had a better postmetastatic survival (PMS) than those without surgery (5-year PMS:
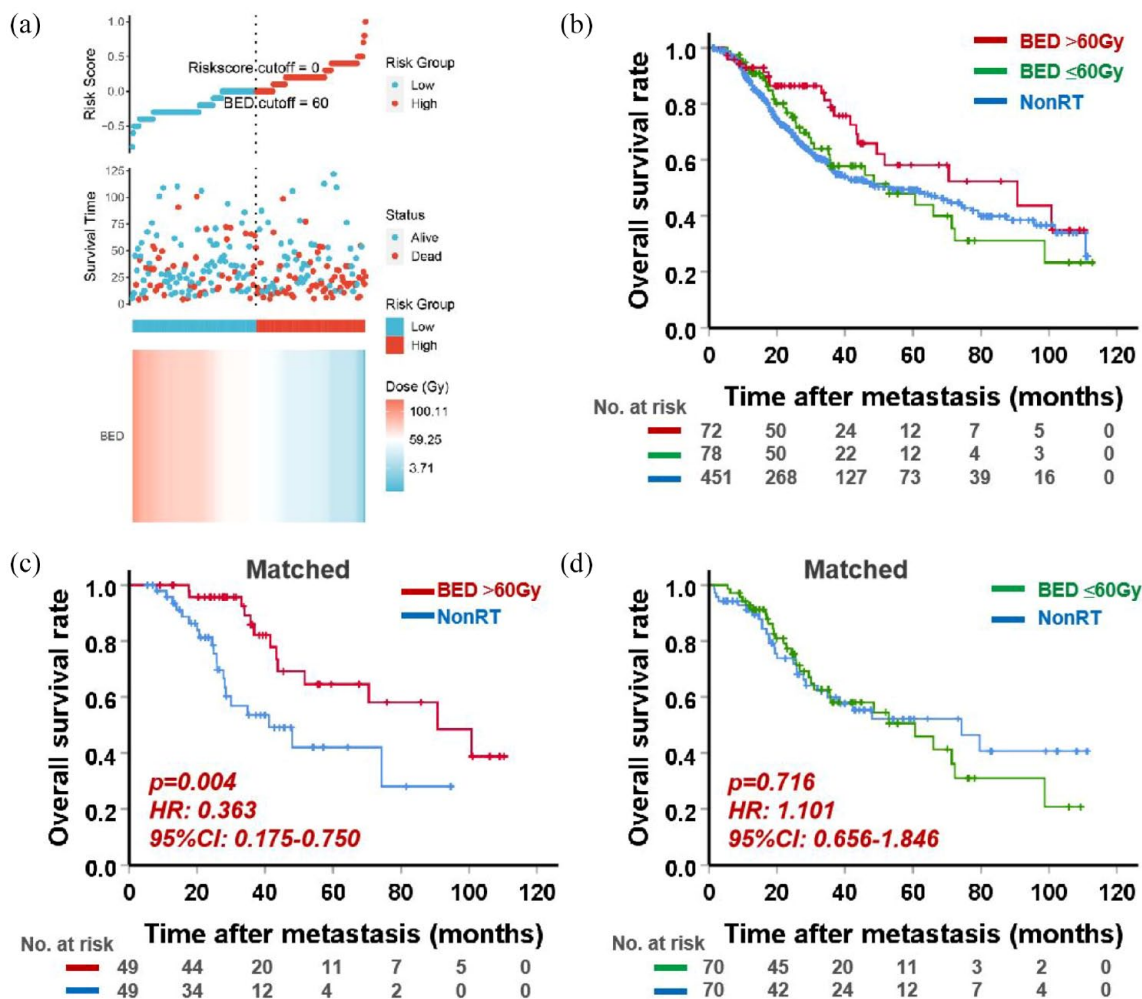
Figure 5. Comparison of survival outcomes brought by different radiation doses and non-RT. (a) The best cutoff value of BED was selected. (b) Survival comparison of patients who received BED > 60 Gy, BED ≤ 60 Gy or non-RT for bone metastasis. (c and d) Survival outcomes were compared in BED > 60Gy and BED ≤ 60 Gy groups with non-RT group after matching.
BED, biological effective dose, RT, radiotherapy.

75.53 *versus* 47.81%, *p* = 0.005).[50] A study by Ma *et al.*[51] included 105 patients with solitary LuM from NPC who received surgery ± chemotherapy, RT ± chemotherapy or chemotherapy alone, surgery ± chemotherapy, and RT ± chemotherapy showed better OS than chemotherapy alone (82.4 *versus* 49.6 *versus* 29 months, *p* < 0.001). Surgical resection has also been shown to be superior to chemotherapy for LuM from NPC in selected series. Cheng *et al.*[52] reported a 2-year OS of 80% in 12 patients who underwent surgical resection and only 24.1% in 65 patients who underwent only chemotherapy.

For unresectable LuM, RFA and RT are two alternative therapies for patients with well-controlled primary disease. In a study by Pan *et al.*,[28] there were no significant differences between the survival probability of patients with RFA (*n* = 10) and surgery for LuM (*n* = 27). Therefore, patients who have unresectable tumors, have contraindications to surgery or are unwilling to receive surgery could be recommended to receive RFA treatment. Regarding RT for LuM, Wu *et al.*[53] reported that stereotactic RT is an effective and safe treatment for LuM and that BED ≥ 75 Gy has a better local control on LuM.

Although improved survival was detected in patients who received LT for LiM and/or LuM, this survival benefit was not observed in patients with BoM. In a study by Shen *et al.*,[29] local RT

combined with chemotherapy was associated with longer survival of NPC patients with solitary BoM than those who received chemotherapy alone (5-year OS: 57.3 *versus* 11.2%). Nevertheless, this impact was not significant for patients with multiple bone metastases.[29] Although RT is the primary treatment method for BoM, consensus regarding the optimal dose prescription is lacking. Most patients were reported to receive 30–60 Gy doses for BoM.[54–58] A previous study has noted that aggressive RT (Equivalent Dose in 2 Gy/fractions, EQD2 ≥ 60 Gy) does not present survival benefits for patients with synchronous BoM based on systemic chemotherapy and radical RT for primary tumor.[31] Conversely, a study showed that patients who received intensive RT (60–75 Gy/30–35 fractions) to bone metastatic sites had improved survival; the study concluded that for patients with a long-term predicted life expectancy and treatment goals, radical RT to BoM should be considered.[59] Fukushima *et al.*[60] reported that intensive LT is beneficial not only for patients with solitary BoM but also for those with multiple bone metastases. Our results demonstrated that patients who received BED > 60 Gy, but not BED ≤ 60 Gy, resulted in better survival outcomes than those who did not receive RT to BoM. In our subcohort, more than half of patients received BED ≤ 60 Gy, which may be a potential explanation for the negative results obtained by LT for BoM.

Collectively, we demonstrated that LT could benefit patients with mNPC, especially for liver and/or LuM. Aggressive RT may be beneficial in the management of BoM. Further prospective randomized trials are warranted to confirm the results. What remain to be determined is the optimal candidates for LT to metastatic foci and which treatment paradigm is the most suitable and effective for specific metastasis.

Limitations

First, the patient selection may be biased due to the retrospective nature of this study. Nevertheless, matched-pair analysis was performed based on a large-scale population. Second, we failed to include more potential prognostic factors, such as metastatic lesion site/size, posttreatment EBV-DNA, and others, due to the lack of medical records or the difficulty of unifying data collection standards. Third, this was a single-center study derived from a high prevalence area.

Declarations

Author contribution(s)
Meng-Xia Zhang: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Ting Liu: Data curation; Methodology; Writing – original draft.

Rui You: Conceptualization; Methodology; Writing – review & editing.

Xiong Zou: Formal analysis; Writing – review & editing.

Yong-Long Liu: Data curation; Methodology; Writing – review & editing.

Xi Ding: Methodology; Writing – original draft.

Chong-Yang Duan: Methodology; Writing – review & editing.

Han-Shi Xu: Methodology; Writing – review & editing.

You-Ping Liu: Methodology; Writing – review & editing.

Rou Jiang: Supervision; Writing – review & editing.

Zhi-Qiang Wang: Formal analysis; Writing – review & editing.

Chao Lin: Formal analysis; Writing – original draft.

Yu-Long Xie: Formal analysis; Writing – review & editing.

Si-Yuan Chen: Data curation; Writing – original draft.

Yan-Feng Ouyang: Data curation; Writing – original draft.

Ruo-Qi Xie: Data curation; Software.

Yi-Jun Hua: Project administration; Writing – review & editing.

Rui Sun: Project administration; Writing – review & editing.

Supplemental material
Supplemental material for this article is available online.

References

1. Chen YP, Chan ATC, Le QT, *et al*. Nasopharyngeal carcinoma. *Lancet* 2019; 394: 64–80.

2. Chinese Journal of Cancer. The 150 most important questions in cancer research and clinical oncology series: questions 6-14. *Chin J Cancer* 2017; 36: 33.

3. Zhang LL, Xu F, He WT, *et al*. Development and validation of a prognostic nomogram for the pre-treatment prediction of early metachronous metastasis in endemic nasopharyngeal carcinoma: a big-data intelligence platform-based analysis. *Ther Adv Med Oncol* 2020; 12: 1758835920978132.

4. Lee AWM, Ma BBY, Ng WT, *et al*. Management of nasopharyngeal carcinoma: current practice and future perspective. *J Clin Oncol* 2015; 33: 3356–3364.

5. Lee AWM, Ng WT, Chan LK, *et al*. The strength/weakness of the AJCC/UICC staging system (7th edition) for nasopharyngeal cancer and suggestions for future improvement. *Oral Oncol* 2012; 48: 1007–1013.

6. Yi JL, Gao L, Huang XD, *et al*. Nasopharyngeal carcinoma treated by radical radiotherapy alone: ten-year experience of a single institution. *Int J Radiat Oncol Biol Phys* 2006; 65: 161–168.

7. Loong HH, Ma BB and Chan AT. Update on the management and therapeutic monitoring of advanced nasopharyngeal cancer. *Hematol Oncol Clin North Am* 2008; 22: 1267–1278.

8. Tan WL, Tan EH, Lim DW, *et al*. Advances in systemic treatment for nasopharyngeal carcinoma. *Chin Clin Oncol* 2016; 5: 21.

9. Jain A, Chia WK and Toh HC. Immunotherapy for nasopharyngeal cancer-a review. *Chin Clin Oncol* 2016; 5: 22.

10. Lee V, Kwong D, Leung TW, *et al*. Palliative systemic therapy for recurrent or metastatic nasopharyngeal carcinoma – how far have we achieved? *Crit Rev Oncol/Hematol* 2017; 114: 13–23.

11. Colevas AD, Yom SS, Pfister DG, *et al*. NCCN guidelines insights: Head and neck cancers, version 1.2018. *J Natl Compr Cancer Netw* 2018; 16: 479–490.

12. Zhang L, Huang Y, Hong S, *et al*. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet* 2016; 388: 1883–1892.

13. Fang W, Yang Y, Ma Y, *et al*. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, phase 1 trials. *Lancet Oncol* 2018; 19: 1338–1350.

14. Yang Y, Qu S, Li J, *et al*. Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2021; 22: 1162–1174.

15. Mai HQ, Chen QY, Chen D, *et al*. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. *Nat Med* 2021; 27: 1536–1543.

16. Lv JW, Li JY, Luo LN, *et al*. Comparative safety and efficacy of anti-PD-1 monotherapy, chemotherapy alone, and their combination therapy in advanced nasopharyngeal carcinoma: findings from recent advances in landmark trials. *J Immunother Cancer* 2019; 7: 159.

17. Ma BBY, Lim WT, Goh BC, *et al*. Antitumor activity of nivolumab in recurrent and metastatic nasopharyngeal carcinoma: an international, Multicenter Study of the Mayo Clinic Phase 2 Consortium (NCI-9742). *J Clin Oncol* 2018; 36: 1412–1418.

18. Hsu C, Lee SH, Ejadi S, *et al*. Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1–positive nasopharyngeal carcinoma: results of the KEYNOTE-028 study. *J Clin Oncol* 2017; 35: 4050–4056.

19. Zhang M, Huang H, Li X, *et al*. Long-term survival of patients with chemotherapy-naïve metastatic nasopharyngeal carcinoma receiving cetuximab plus docetaxel and cisplatin regimen. *Front Oncol* 2020; 10: 1011.

20. Zhao C, Miao J, Shen G, *et al*. Anti-epidermal growth factor receptor (EGFR) monoclonal antibody combined with cisplatin and 5-fluorouracil in patients with metastatic nasopharyngeal carcinoma after radical radiotherapy: a multicentre, open-label, phase II clinical trial. *Ann Oncol* 2019; 30: 637–643.

21. Xia WX, Liang H, Lv X, *et al*. Combining cetuximab with chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma: a propensity score analysis. *Oral Oncol* 2017; 67: 167–174.

22. Chan AT, Hsu MM, Goh BC, *et al*. Multicenter, phase II study of cetuximab in combination with carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol* 2005; 23: 3568–3576.

23. Chua DT, Wei WI, Wong MP, *et al*. Phase II study of gefitinib for the treatment of recurrent and metastatic nasopharyngeal carcinoma. *Head Neck* 2008; 30: 863–867.

24. Ma B, Hui EP, King A, *et al*. A phase II study of patients with metastatic or locoregionally recurrent nasopharyngeal carcinoma and evaluation of plasma Epstein-barr virus DNA as a biomarker of efficacy. *Cancer Chemother Pharmacol* 2008; 62: 59–64.

25. You B, Le Tourneau C, Chen EX, *et al*. A Phase II trial of erlotinib as maintenance treatment after gemcitabine plus platinum-based chemotherapy in patients with recurrent and/or metastatic nasopharyngeal carcinoma. *Am J Clin Oncol* 2012; 35: 255–260.

26. You R, Liu YP, Huang PY, *et al*. Efficacy and safety of locoregional radiotherapy with chemotherapy vs chemotherapy alone in De novo metastatic nasopharyngeal carcinoma: A multicenter phase 3 Randomized Clinical Trial. *JAMA Oncol* 2020; 6: 1345–1352.

27. Li W, Bai Y, Wu M, *et al*. Combined CT-guided radiofrequency ablation with systemic chemotherapy improves the survival for nasopharyngeal carcinoma with oligometastasis in liver: propensity score matching analysis. *Oncotarget* 2017; 8: 52132–52141.

28. Pan CC, Wu PH, Yu JR, *et al*. Comparative survival analysis in patients with pulmonary metastases from nasopharyngeal carcinoma treated with radiofrequency ablation. *Eur J Radiol* 2012; 81: e473–e477.

29. Shen L, Dong J, Li S, *et al*. M1 stage subdivision and treatment outcome of patients with bone-only metastasis of nasopharyngeal carcinoma. *Oncologist* 2015; 20: 291–298.

30. Liang YJ, Sun XS, Yang ZC, *et al*. Effect of local treatment for metastasis and its sequence with chemotherapy on prognosis of post-treatment metastatic nasopharyngeal carcinoma patients. *Oral Oncol* 2019; 92: 40–45.

31. Zou X, You R, Liu H, *et al*. Establishment and validation of M1 stage subdivisions for de novo metastatic nasopharyngeal carcinoma to better predict prognosis and guide treatment. *Eur J Cancer* 2017; 77: 117–126.

32. Amin MB, Greene FL, Edge SB, *et al*. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to

cancer staging. *CA Cancer J Clin* 2017; 67: 93–99.

33. Tang LQ, Chen QY, Fan W, *et al*. Prospective study of tailoring whole-body dual-modality [18F] fluorodeoxyglucose positron emission tomography/computed tomography with plasma Epstein-barr virus DNA for detecting distant metastasis in endemic nasopharyngeal carcinoma at initial staging. *J Clin Oncol* 2013; 31: 2861–2869.

34. You R, Liu YP, Lin M, *et al*. Relationship of circulating tumor cells and Epstein-barr virus DNA to progression-free survival and overall survival in metastatic nasopharyngeal carcinoma patients. *Int J Cancer* 2019; 145: 2873–2883.

35. Huang F, Wu G and Yang K. Oligometastasis and oligo-recurrence: more than a mirage. *Radiat Oncol* 2014; 9: 230.

36. Moreno AJ, Albiach CF, Soria RM, *et al*. Oligometastases in prostate cancer: restaging stage IV cancers and new radiotherapy options. *Radiat Oncol* 2014; 9: 258.

37. Chan OS and Ngan RK. Individualized treatment in stage IVC nasopharyngeal carcinoma. *Oral Oncol* 2014; 50: 791–797.

38. Fandi A, Bachouchi M, Azli N, *et al*. Long-term disease-free survivors in metastatic undifferentiated carcinoma of nasopharyngeal type. *J Clin Oncol* 2000; 18: 1324–1330.

39. Pan C, He N, Zhao M, *et al*. Subdividing the M1 stage of liver metastasis for nasopharyngeal carcinoma to better predict metastatic survival. *Med Oncol* 2011; 28: 1349–1355.

40. Teo MC, Tan YM, Chung AY, *et al*. Metastectomy for non-colorectal, non-neuroendocrine liver secondaries. *ANZ J Surg* 2006; 76: 575–578.

41. Weitz J, Blumgart LH, Fong Y, *et al*. Partial hepatectomy for metastases from noncolorectal, nonneuroendocrine carcinoma. *Ann Surg* 2005; 241: 269–276.

42. Groeschl RT, Nachmany I, Steel JL, *et al*. Hepatectomy for noncolorectal non-neuroendocrine metastatic cancer: a multi-institutional analysis. *J Am Coll Surg* 2012; 214: 769–777.

43. Delis S, Biliatis I and Bourli A. Surgical resection of a solitary liver metastasis from nasopharyngeal carcinoma: a case report. *Hepatobiliary Pancreat Dis Int* 2006; 5: 610–612.

44. Lim SJ, Iyer NG, Ooi LL, *et al*. Metastasectomy for metachronous pulmonary and hepatic metastases from nasopharyngeal carcinoma: report of 6 cases and review of the literature. *Head Neck* 2016; 38: E37–E40.

45. Jin Y, Cai YC, Cao Y, *et al*. Radiofrequency ablation combined with systemic chemotherapy in nasopharyngeal carcinoma liver metastases improves response to treatment and survival outcomes. *J Surg Oncol* 2012; 106: 322–326.

46. Tian YM, Zeng L, Wang FH, *et al*. Prognostic factors in nasopharyngeal carcinoma with synchronous liver metastasis: a retrospective study for the management of treatment. *Radiat Oncol* 2013; 8: 272.

47. Pan C, Wu P, Yu J, *et al*. CT-guided radiofrequency ablation prolonged metastatic survival in patients with liver metastases from nasopharyngeal carcinoma. *Int J Hyperthermia* 2011; 27: 549–554.

48. Peng C, Zhou C, Li G, *et al*. Hepatic artery infusion pump for nasopharyngeal carcinoma with liver metastasis. *Clin Exp Metastasis* 2020; 37: 333–339.

49. Hui EP, Leung SF and Au JS. Lung metastasis alone in nasopharyngeal carcinoma: a relatively favorable prognostic group. A study by the Hong Kong Nasopharyngeal Carcinoma Study Group. *Cancer* 2004; 101: 300–306.

50. Zhao ZR, Liu DH, Wang YZ, *et al*. Pulmonary metastasectomy in patients with lung metastases from nasopharyngeal carcinoma. *Ann Surg Oncol* 2021; 28: 4542–4550.

51. Ma J, Wen ZS, Lin P, *et al*. The results and prognosis of different treatment modalities for solitary metastatic lung tumor from nasopharyngeal carcinoma: a retrospective study of 105 cases. *Chin J Cancer* 2010; 29: 787–795.

52. Cheng LC, Sham JS, Chiu CS, *et al*. Surgical resection of pulmonary metastases from nasopharyngeal carcinoma. *Aust N Z J Surg* 1996; 66: 71–73.

53. Wu SX, Deng ML, Bao Y, *et al*. [Therapeutic analysis of stereotactic radiotherapy for 39 patients with lung metastasis]. *Ai zheng = Aizheng = Chin J Cancer* 2006; 25: 880–884.

54. Howell DD, James JL, Hartsell WF, *et al*. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97-14. *Cancer* 2013; 119: 888–896.

55. Chow E, Harris K, Fan G, *et al*. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007; 25: 1423–1436.

56. Khot A, Love C, Garg MK, *et al*. Long-term disease control in a patient with recurrent

bone-only oligometastatic nasopharyngeal carcinoma. *J Clin Oncol* 2016; 34: e25–e26.

57. Setton J, Wolden S, Caria N, *et al.* Definitive treatment of metastatic nasopharyngeal carcinoma: Report of 5 cases with review of literature. *Head Neck* 2012; 34: 753–757.

58. Lim A, Corry J, Lau E, *et al.* Prolonged remission in a patient with nasopharyngeal carcinoma with a solitary bone metastasis. *J Clin Oncol* 2011; 29: e135–e137.

59. Li XY, Jia GD, Sun XS, *et al.* Intensive local radiotherapy is associated with better local control and prolonged survival in bone-metastatic nasopharyngeal carcinoma patients. *Front Oncol* 2020; 10: 378.

60. Fukushima H, Hozumi T, Goto T, *et al.* Prognostic significance of intensive local therapy to bone lesions in renal cell carcinoma patients with bone metastasis. *Clin Exp Metastasis* 2016; 33: 699–705.

Visit SAGE journals online
journals.sagepub.com/
home/tam

⑤SAGE journals