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Effect of local treatment for metastasis and its sequence with chemotherapy on prognosis of post-treatment metastatic nasopharyngeal carcinoma patients

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ABSTRACT

Background: Distant metastasis after chemoradiotherapy remains the leading cause of death in NPC patients. But the effect of local treatment for metastatic sites and its sequence with chemotherapy on prognosis of them are poorly documented.
Methods: 448 post-treatment metastatic NPC patients were included in our retrospective study. And Cox regression and log-rank tests were applied to investigate the association between topical treatment and its sequence with chemotherapy and survival using the propensity score method (PSM) to adjust for gender, age, Tumor stage, Node stage, metastatic sites, diabetes and smoking with a 1:2 matching protocol.
Results: The 3-year OS was significantly higher in patients who received local treatment of distant metastasis compared with patients who did not (48.8% vs 33.8%, P = 0.001) in primary cohort. PSM identified 120 patients in the cohort with local treatment and 240 in that without and similar survival benefits were observed for the local treatment (3-year OS: 36.2% versus 48.8%, P = 0.011). Subgroup analyses indicated that there was no significant survival difference in patients with different treatment sequence.
Conclusions: In conclusion, post-treatment metastatic NPC patients could be beneficial from local treatment for metastasis but its sequence with palliative chemotherapy does not affect overall survival.

Introduction

The battle against nasopharyngeal carcinoma (NPC), an epidemic malignant tumor in southeastern Asia resulting in 50,800 deaths in 2012 worldwide, has won a lot of achievement since the usage of intensity-modulated radiotherapy (IMRT) [1]. Nowadays, radiotherapy is the fundamental treatment modality and concurrent chemoradiotherapy (CCRT) is recommended for locoregional advanced NPC according to the National Comprehensive Cancer Network (NCCN) Guidelines [2,3]. Despite the survival benefit obtained from modern treatment modalities and techniques, 20% to 30% of patients die of distant metastasis, locoregional relapse, or both. The distant metastasis remains the key challenge to treatment failure. Over 20% NPC patients will develop distant metastasis after systematic chemoradiotherapy [4], which has been a leading cause of death in patients with NPC and there is no effective treatment for such patients [5,6]. Optimal treatment strategy remains a subject of debate [7–9].

Unfortunately salvage treatment for those post-treatment metastasis NPC patients are undefined. According to 2018 NCCN Clinical Practice Guidelines and previous study, NPC patients with metastasis are recommended to receive platinum-based combination chemotherapy or concurrent chemo/radiotherapy [10,11]. It is uncertain whether those patients should be applied with strategies incorporating local treatment for metastasis. It is uncertain and hardly reported whether palliative chemotherapy (PCT) or combined PCT with local treatment is suitable for those metastatic NPC patients after systematic chemoradiotherapy.

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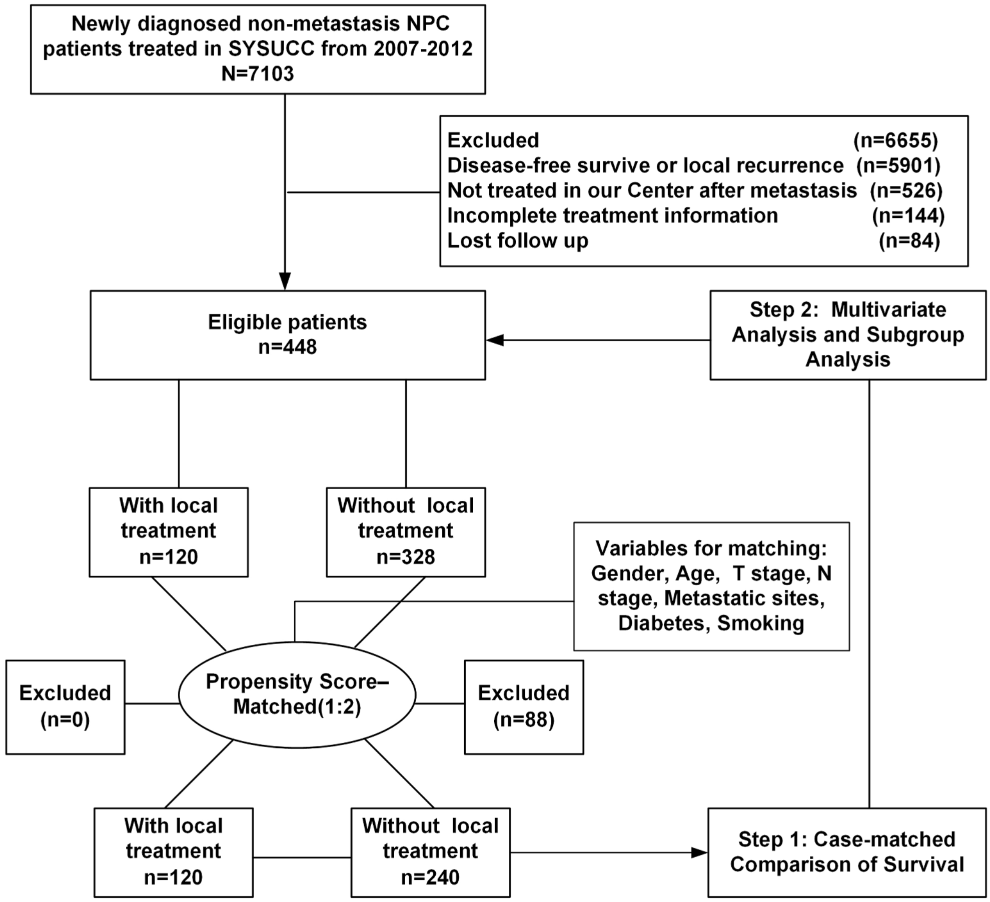


Fig. 1. Analysis flow chart.

Furthermore, data of the best time-point for local treatment are poorly documented. The sequence between topical treatment and chemotherapy remains largely unknown. Hence, we conducted a study involving 448 NPC patients who developed distant metastasis after initial treatment, with long-term follow-up, attempting to disclose the best strategy toward distant lesions.

Methods

Patients

The retrospective cohort study included 448 NPC patients who developed distant lesions after initial treatment at Sun Yat-sen University Cancer Center (Guangzhou, China) between 2007 and 2012. Our eligibility criteria included: M0 stage at the time of diagnosis; achieved CR after primary treatment; distant lesions occurred after initial treatment; no history of other malignancies; and histologically confirmed NPC. The exclusion criteria were as follows: metastasis at the time of diagnosis, recurrent metastatic NPC patients, patients with insufficient clinical data or lost follow up. The criteria of inclusion and exclusion in this study was described in the flow chart (Fig. 1).

Diagnosis and treatment

After primary therapy, most metastasis was suggested by the conventional work-up including chest x-ray/ computed tomography (CT), abdominal ultrasound, and skeletal scintigraphy [12]. Metastasis should be confirmed in imaging studies by at least one of the following evaluations: CT with contrast, magnetic resonance imaging (MRI) with contrast, Positron emission tomography–computed tomography (PET/CT) with consistent clinical procedures or biopsy results of distant metastatic lesions. RECIST 1.1 guidelines were used to evaluate the treatment outcomes. For those NPC patients with distant lesions occurred after initial treatment, cisplatin (20–30 mg/m^2 d1-3) combined with 5-fluorouracil (800–1000 mg/m^2 d1-d5) chemotherapy regimen was the most popular strategy. Other common palliative chemotherapy strategies included GP: cisplatin (20–30 mg/m^2 d1-3) with gemcitabine (800–1000 mg/m^2 d1,8), GX: gemcitabine (800–1000 mg/m^2 d1,8) with capecitabine (2 g/m^2 d1-d14), TPF: paclitaxel (135 mg/m^2 d1) or docetaxel (60–75 mg/m^2 d1) plus cisplatin (20–25 mg/m^2 d1-3) plus 5-fluorouracil (3–3.75 g/m^2, 120 h), and TP: docetaxel (75 mg/m^2 d1) or paclitaxel (175 mg/m^2 d1) plus cisplatin (20–25 mg/m^2 d1). Carboplatin and lobaplatin were also applied in platinum-based strategy. All regimens were administered every 3 weeks intravenously. Definitive radiotherapy targeting bone metastases using two-dimensional conventional radiotherapy (2D-CRT) or intensity-modulated radiotherapy (IMRT) was applied to some NPC patients. The accumulated radiation dose to the bone metastases was 30–45 Gy. The metastatic liver and lung tumor were eliminated mainly by surgical resection or ablation. Local treatments were generally applied to control local symptoms and eliminate metastases.

Follow-up and outcome

After salvage treatment patients were assessed every 3 months for the first 3 years and then every 6 months thereafter until death. Routine follow up included physical examination, nasopharyngoscopy, MRI with contrast of head and neck, chest X-ray or CT with contrast and abdominal ultrasound. Other examination such as PET/CT would be considered by physician. The primary endpoint in our study was overall survival (OS). OS was defined as the time from the date of metastasis to the date of death from any cause in our study.

Statistical analysis

Kaplan–Meier method and Cox proportional hazards models were applied to estimate the survival. Baseline characteristics were calculated by Chi-square test or continuity Chi-square test. Multivariable cox regression were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the correlations between characteristics and OS. Enter method was used in the multivariable cox regression. The propensity score for every patient in this study was calculated using multivariable logistic regression models given the following covariates: gender, age, Tumor stage, Node stage, metastatic sites, diabetes, smoking. The match was performed using a 1:2 matching protocol with a greedy-matching algorithm, and the caliper width is equal to 0.05 of the logit standard deviation of the propensity score. Statistical analyses were performed by Statistical Package for Social Sciences 24.0 (IBM Corporation, Armonk, NY, USA) and R (http://www.R-project.org). All statistical tests were two-tailed and $P < 0.05$ was considered to suggest statistical significance.

Result

Patient characteristics

From 2007 to 2012, we retrospectively involved 448 NPC patients who developed distant lesions after initial treatment. Clinical characteristics and treatment method were listed in Table 1. In details, 120 patients received local treatment of metastasis combined with PCT and 328 patients received PCT only. The male-to-female ratio was 4.3:1 and the average age of all patients was 43 years old. The characteristics in different treatment groups were in good balance excepted the metastatic sites. There was significantly higher proportion of multiple metastatic sites in patients without local treatment (40.0% versus 19.5%, P = 0.004). In order to reduce the potential confounding, we established the new cohort using propensity score matching (PSM) with the ratio of 1:2. For the matched analysis, 360 patients were identified. This analysis eliminated differences in all of the observed baseline characteristics in the larger cohort ($P > 0.05$) (Table 1).

Survival analysis

The median follow-up was 21.1 months (range = 1–142 months). 321 patients died during follow-up. The 1-year, 3-years and 5-years OS were 82.2%, 37.3% and 21.4% respectively. Grouped by treatment method, the 3-year OS was significantly higher in patients who received local treatment of distant metastasis compared with patients who did not (48.8%, 95% confidence interval [CI] 39.4–58.2% versus 33.8%, 95% CI 27.4–38.3%, P = 0.001) in primary cohort (Fig. 2A). Then, we recalculated the effects of the two treatment methods in PSM cohort, which revealed similar survival benefits for the local treatment (3-year OS: 36.2%, 95% CI 29.5–42.9% versus 48.8%, 95% CI 39.4–58.2%, P = 0.011) (Fig. 2B).

We carried out multivariate analyses that included sex (female or male), patient age (≤43 years or > 43), T stage, N stage, metastatic site (bone, lung, liver, distant nodal or multiple metastatic sites), and

Table 1
Clinical characteristics.

Characteristic	Primary chohrt			PSM cohort		
	No LT	LT	*P*-value	No LT	LT	*P*-value
Total	328	120		240	120	
Gender						
Female	62 (18.9%)	20 (16.7%)	0.679	41(17.1%)	20(16.7%)	1.000
Male	266 (81.1%)	100 (83.3%)		199(82.9%)41	100(83.3%)	
Age (years)						
≤43	166 (50.6%)	65 (54.2%)	0.523	127(52.9%)	65(54.2%)	0.911
> 43	162 (49.4%)	162 (45.8%)		113(47.1%)	55(45.8%)	
Diabetes						
No	315 (96.0%)	117 (97.5%)	0.575	233(97.1%)	117(97.5%)	1.000*
Yes	13 (4.0%)	3 (2.5%)		7(2.9%)	3(2.5%)	
Smoking						
No	184 (56.1%)	63 (52.5%)	0.520	127(52.9%)	63(52.5%)	1.000
Yes	144 (43.9%)	57 (47.5%)		113(47.1%)	57(47.5%)	
History of NPC						
No	295 (89.9%)	112 (93.3%)	0.355	222(92.5%)	112(93.3%)	0.833
Yes	33 (10.1%)	8 (6.7%)		18(7.5%)	8(6.7%)	
T stage						
T1	14 (4.3%)	6 (5.0%)	0.836	12(5.0%)	6(5.0%)	0.988
T2	47 (14.3%)	21 (17.5%)		39(16.3%)	2117.5(%)	
T3	163 (49.7%)	28 (47.5%) (23.573%)		114(47.5%)	57(47.5%)	
T4	104 (81.5%)	36 (76.7%)		75(31.1%)	36(30.0%)	
N stage						
N0	19 (5.8%)	7 (5.8%)	0.230	18(7.5%)	7(5.8%)	0.467
N1	86 (26.2%)	38 (31.7%)		62(25.8%)	38(31.7%)	
N2	145 (44.2%)	57 (47.5%)		111(46.3%)	57(47.5%)	
N3	78 (23.8%)	18 (15.0%)		49(20.4%)	18(15.0%)	
Metastatic sites						
Bone	67 (20.4%)	39 (32.5%)	0.004	61(25.4%)	39(32.5%)	0.075
Lung	74 (22.6%)	19 (15.8%)		63(26.3%)	19(15.8%)	
Liver	42 (12.8%)	25 (20.8%)		33(13.8%)	25(20.8%)	
Distant nodal	14 (4.0%)	5 (4.2%)		8(3.3%)	5(4.2%)	
Multiple sites	132 (40.2%)	32 (26.7%)		75(31.3%)	32(26.7%)	

Abbreviations: NPC = nasopharyngeal carcinoma; LT = local treatment.
P values were calculated by Chi-square test or continuity Chi-square test (*).

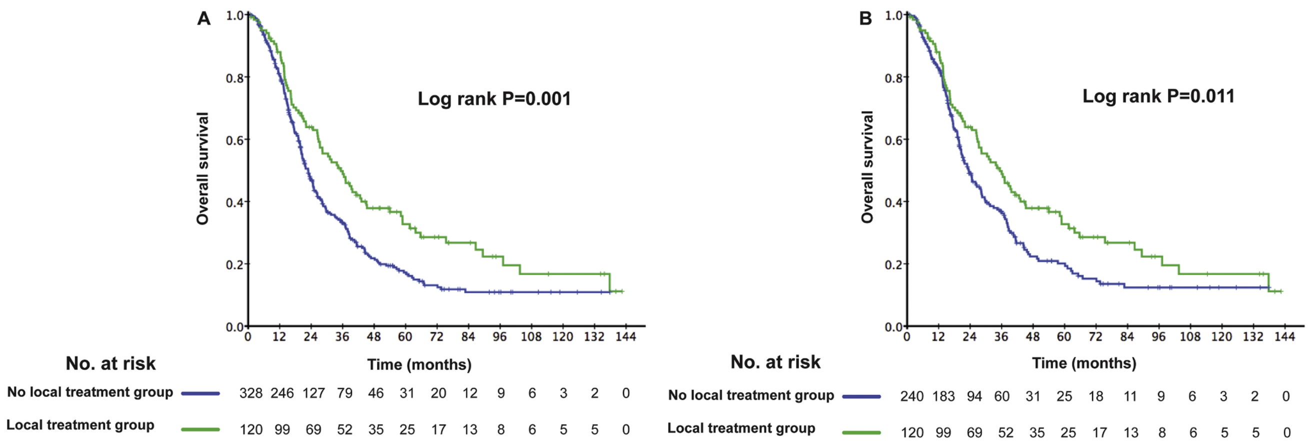


Fig. 2. Kaplan-Meier curves of overall survival in the (A) entire cohort; (B) PSM cohort.

Table 2
Multivariate analysis of OS.

	Primary cohort			PSM cohort		
Characteristic	HR	95% CI	P-value	HR	95% CI	P-value
Gender	0.67	0.50–0.91	0.011	0.71	0.50–1.01	0.056
Age (years)	1.35	1.08–1.70	0.009	1.31	1.01–1.71	0.041
Diabetes	1.36	0.76–2.44	0.305	1.26	0.61–2.62	0.535
Smoking	1.30	1.02–1.67	0.036	1.20	0.90–1.58	0.212
History of NPC	1.27	0.89–1.81	0.193	1.27	0.82–1.97	0.280
T stage						0.216
T2 vs. T1	0.79	0.45–1.38	0.409	0.83	0.45–1.51	0.534
T3 vs. T1	0.61	0.36–1.04	0.067	0.63	0.36–1.13	0.121
T4 vs. T1	0.60	0.35–1.04	0.068	0.61	0.34–1.11	0.106
N stage						0.693
N1 vs. N0	0.94	0.57–1.56	0.816	0.97	0.57–1.65	0.919
N2 vs. N0	0.97	0.59–1.59	0.904	1.02	0.61–1.70	0.952
N3 vs. N0	0.86	0.50–1.46	0.577	0.81	0.45–1.45	0.484
Metastatic site						0.021
Lung vs. Bone	0.67	0.47–0.97	0.033	0.67	0.45–0.98	0.039
Liver vs. Bone	1.08	0.75–1.57	0.683	1.05	0.71–1.56	0.792
Distant nodal vs. Bone	1.05	0.58–1.92	0.863	1.09	0.54–2.23	0.804
Multiple vs. Bone	1.32	0.99–1.77	0.063	1.28	0.92–1.78	0.144
Local treatment	0.66	0.51–0.86	0.002	0.69	0.53–0.91	0.009

Abbreviations: HR = hazard ratio; CI = confidence interval; NPC = nasopharyngeal carcinoma.
A Cox proportional hazard model was used to perform multivariate analyses. All variables were transformed into categorical variables. HRs were calculated for Gender (Male vs. Female); Age (years) (> 41 vs. ≤41); Diabetes (Yes vs. No); Smoking (Yes vs. No); History of NPC (Yes vs. No); Local treatment (Yes vs. No).

local treatment. Table 2 shows that a significant protective value was indicated for the application of local treatment in the multivariate model for OS (hazard ratio [HR] 0.66, 95% CI 0.51–0.86, P = 0.002) in primary cohort. In PSM cohort, the multivariate analysis was consistent with the result obtained from primary cohort (Table 2). (See Table 3.).

Subgroup analysis

According to the treatment sequence, we divided the patients with local treatment into two subgroups. One group included patients who received PCT first and then received local treatment of distant metastasis, while another group included patients who received local treatment first. Furthermore, we investigated whether the order of the treatment method influence the survival of these patients. As shown in Fig. 3, there was no significant survival difference in patients with different treatment sequence (3-year OS: 50.2% 95% CI 34.5–62.9% versus 45.0% 95% CI 31.3–58.7%, P = 0.894). In multivariable analysis, treatment sequence was not an independent prognostic factor for OS (PCT + local treatment vs. local treatment + PCT HR: 0.919, 95%CI: 0.712–1.184, P = 0.513).

Table 3
Multivariate analysis of OS in patients with local treatment.

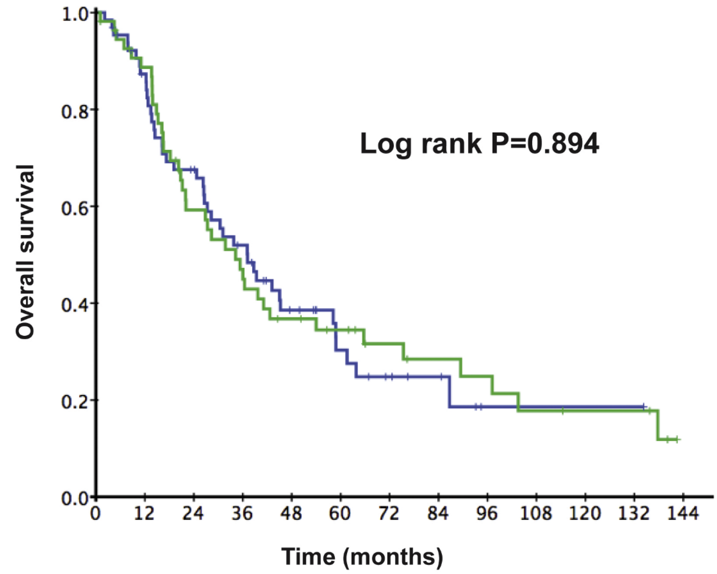
Characteristic	HR	95% CI	P-value
Gender	0.758	0.382–1.504	0.428
Age (years)	1.366	0.854–2.185	0.193
Diabetes	1.776	0.476–6.622	0.393
Smoking	1.707	0.661–1.732	0.783
History of NPC	1.459	0.621–3.425	0.386
T stage	0.641	0.375–1.097	0.105
N stage	1.013	0.609–1.686	0.960
Metastatic site			
Lung vs. Bone	0.577	0.248–1.345	0.203
Liver vs. Bone	1.472	0.759–2.854	0.252
Distant nodal vs. Bone	1.720	0.510–5.808	0.382
Multiple vs. Bone	1.126	0.596–2.129	0.715
Treatment sequence	0.919	0.712–1.184	0.513

Abbreviations: HR = hazard ratio; CI = confidence interval; NPC = nasopharyngeal carcinoma.
A Cox proportional hazard model was used to perform multivariate analyses. All variables were transformed into categorical variables. HRs were calculated for Gender (Male vs. Female); Age (years) (> 41 vs. ≤41); Diabetes (Yes vs. No); Smoking (Yes vs. No); History of NPC (Yes vs. No); T stage (T3-4 vs. T1-2); N stage (N2-3 vs. N0-1); Treatment sequence (PCT + local treatment vs. local treatment + PCT).

Discussion

To the best of our knowledge, our study is the first one to investigate the influence of local treatment for metastases and its sequence with chemotherapy on prognosis of post-treatment metastatic nasopharyngeal carcinoma patients. PSM was used to balance the characteristics between the local treatment group and non-local treatment group. This study provided several notable findings. Firstly, local treatment for metastases showed a significant survival benefit in post-treatment metastatic NPC patients. Secondly, there is no significant association between the sequence of topical treatment and chemotherapy and overall survival.

Distant metastasis remains the main cause of death in post-treatment NPC patients and common metastatic lesions include lung, liver, bone, distant lymph nodes or their combinations. The outcomes of these patients are very poor, with a median overall survival of about 22 months when using the first-line platinum-based chemotherapy [10]. Metastatic NPC is heterogeneous as the illness condition is



No. at risk

PCT + local treatment	65	53	40	29	18	11	7	5	1	1	1	1	1
Local treatment + PCT	55	46	29	23	17	14	10	8	7	5	4	4	0

Fig. 3. Kaplan-Meier curves of overall survival and different treatment sequence.

remarkably different among patients. Therefore, a few patients can achieve long-term survival despite of the unsatisfactory overall survival rate [13]. However, optimal treatment modalities are still not well-established. According to the NCCN guidelines, surgery or systemic therapy/radiotherapy are recommended for selected patients with limited metastases while most metastatic patients received platinum-based chemotherapy alone.

Treatment of metastatic NPC after treatment requires only attention to the site of metastasis, which is quite different from newly metastatic NPC patients, and limited metastasis has the opportunity to achieve long-term survivorship with topical treatment [13]. Therefore, the topical approach involving radiotherapy, surgery or ablative treatment to the oligometastasis may make a difference. Local treatment for metastases has been reported to prolong survival in metastatic NPC patients, including partial hepatectomy for liver metastases, radiofrequency ablation for lung metastases and radiotherapy for bone and distant lymph node metastases [14–18]. Huang et al conducted a cohort to investigate the effect of partial hepatectomy or transcatheter hepatic artery chemoembolization (TACE) on survival among NPC patients with liver metastases. He discovered that hepatectomy provided a significant survival benefit over TACE, with a 3-year overall survival rate of 64.2% for hepatectomy and 26.6% for TACE, which were both higher than those without liver local treatment [14,19]. Pan and colleagues investigated the effect of local pulmonary therapy including CT-guided pulmonary radiofrequency ablation (RFA) treatment and surgical resection on survival in NPC patients with pulmonary metastases. Patients with RFA treatment were demonstrated to have a significantly better overall survival than patients without RFA treatment (77.1 months vs 32.4 months, $p < 0.01$) while no statistically significant difference was found between RFA treatment and surgical resection of pulmonary metastases ($p = 0.75$) [17]. Furthermore, Shen et al gave evidence that combined chemoradiotherapy could significantly benefit to bone-only metastases NPC patients compared with chemotherapy alone with an HR of 0.21(95% CI: 0.09–0.50) [20]. Analogously, He et al reported that radiotherapy to the bone-only metastasis provided a benefit in overall survival in NPC patients in comparison with those without radiotherapy ($P < 0.001$) [18].

Consistently, in this study, local treatment for metastases was a prognostic parameter for longer survival for post-treatment metastatic nasopharyngeal carcinoma patients. Patients with the application of local treatment showed significantly higher OS compared with those without, with an HR of 0.69 (95% CI: 0.53–0.91) in the well-balanced PSM cohort, and similar benefit was observed in the primary cohort. Moreover, the sequence between topical treatment and PCT did not show significant impact on overall survival (HR: 0.919, 95%CI: 0.712–1.184, $P = 0.513$). Our findings suggested that metastatic NPC patients could be beneficial from topical treatment but its sequence with PCT does not affect overall survival, a result that may guide the clinical treatment.

Additionally, in this study, age and metastatic site were also found to be associated with OS in adjusted multivariate analysis in the well-balanced cohort. The old had worse OS is mainly driven by the higher incidence of comorbidities like community-acquired pneumonia and decreased physical function [21]. The OS of patients with lung metastasis alone was evidently higher than that with liver, bone, or distant lymph nodal only or multiple metastasis, which was in accordance with previous studies [22]. For patients with such favorable features like oligometastasis, there is progressively a strong advocacy for a curative approach to screen out who are effective for metastatic lesion treatment and perform topical palliative treatment that could achieve long-term survival.

However, this study has several potential limitations. Firstly, although we performed a propensity score matching analysis to eliminate selection biases, our retrospective study was not devoid of selection bias. Secondly, the treatment regimens were not uniform restricted by retrospective study. Last but not least, few patients had data of the level of plasma EBV DNA, C-reactive protein, lactate dehydrogenase at diagnosis of metastasis, therefore, treatment modality was not analyzed in conjunction with biomarkers.

Conclusion

In conclusion, post-treatment metastatic NPC patients could be beneficial from local treatment for metastasis but its sequence with palliative chemotherapy does not affect overall survival. In the future, a study with well-designed, multi-center, prospective randomized design in combination with biomarkers is needed to validate this conclusion.

Conflict of interest statement

The authors declare that they have no competing interests. None of the authors has any financial and personal relationships with other people or organizations that could inappropriately influence (bias) of this work.

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