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Review Article

Stereotactic Body Radiation Therapy for Pulmonary Oligometastasis from Head and Neck Cancer: The Potential Survival Benefits from PD-1 Inhibitors

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Abstract

Objective: Stereotactic body radiotherapy is suitable for most pulmonary oligometastasis, but there is little data that reported the different values of SBRT combined with systemic therapy between NP and non-NP cancers.

Method: This was a retrospective study on patients with pulmonary oligometastatic HNC treated with SBRT at Zhejiang Cancer Hospital.

Main Results: A total of 43 patients with 65 pulmonary metastatic lesions were included in the study.24 cases originated from NP cancer, and 19 originated from non-NP cancer. The median follow-up time was 29.7 months. The 1-year local control rate was 95.4%, and 3-year PFS and OS2 were 68.7% and 46.0% in the whole group. Subgroup analysis showed local control rates were 95.1% and 95.8% in the NP group and non-NP group (p=1.000). Median PFS times were 47.0 months and 13.3months (p=0.006), and 3-year OS2 was 87.1% and 47.9% in the two groups (p=0.011). Primary tumor location, time to metastasis, number of pulmonary lesions, BED, and systemic therapy were found to be significant predictors for PFS and (or) OS2 in univariate analysis. Systemic therapy and the number of pulmonary lesions were maintained in Cox regression analysis. No SBRT-related toxicity above grade 3 was observed.

Conclusion: SBRT is an effective and tolerable therapy for patients with pulmonary oligometastasis from HNC. On the basis of systemic treatment, radical curative-intent with SBRT could be achieved in selected HNC patients.

Keywords: Cancer; Head and Neck; Oligometastasis; Pulmonary Metastasis; Stereotactic Body Radiotherapy

Introduction

In general, patients with distant metastases are considered to have a short life expectancy and poor prognosis [7,17], and the main treatment scheme for these patients is systemic chemotherapy, targeted therapy and/or immunotherapy [4,9,29]. However, it has been observed that some patients with limited metastases have a good chance of long-term survival. In 1995, Hellman and Weichselbaum coined the term "oligometastasis" to describe the state of having metastases to 2 or fewer organs and having fewer than 5 metastatic lesions [31], and in the update in 2011, local methods combined with systemic treatment were recommended to achieve curative-intent in oligometastatic tumors [31].

The lung is one of the main organs of metastases from head and neck cancers [14], and pulmonary metastasectomy and Stereotactic Body Radiation Treatment (SBRT) are two curative-intent local methods forpulmonary oligometastasis (Vengaloor et al., 2019). Shiono reported 114 patients underwent resection of pulmonary metastases from head and neck squamous cell carcinomas, and the 5-year Overall Survival (OS) rate after pulmonary metastasectomy was 26.5% [23]. SBRT was originally applied as a supplement to surgeryfor patients who couldn't tolerate surgical resection [26]. In recent years, a large number of clinical studies have confirmed SBRT is a safe and effective method for treating pulmonary oligometastasis derived from different tumors, such as lung cancer, liver cancer, breast cancer, and malignant melanoma [1,12,27,30]. As a non-invasive treatment, SBRT has evolved as an ideal method for local curative treatment in pulmonary oligometastasis to date [18].

PD-1 inhibitors had been recommended as preferred systemic treatment for metastatic HNC. Compared with pulmonary metastasectomy, synergistic effect between SBRT and PD-1 has been confirmed by laboratory and clinical evidence. SBRT can lead to an increase in immunogenicity by inducing immunogenic cell death, triggering the release of tumor-derived antigens and attracting CD8+ T cells to the tumor microenvironment. However, the pulmonary oligometastases had been regarded as the value of the synergistic effect in have not been established, therefore, we conducted this study to evaluate the differences. Data from all patients treated with pulmonary SBRT were reviewed, then cases with pulmonary oligometastatic disease originated from HNC were collected and the treatment results were assessed.

Material and Methods

Patients

This was a retrospective study on patients with pulmonary

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oligometastasis treated with SBRT at Zhejiang Cancer Hospital. Data for all patients diagnosed with HNC who received pulmonary SBRT in this institution between January 1st 2014 and March 31st 2021 were reviewed. Patients whose primary pathological type was not squamous cell carcinoma were excluded in the first round. In the second round, patients whose pulmonary disease was diagnosed as a second primary cancer were excluded. Last, patients whose metastatic state did not meet the criteria of pulmonary oligometastasis were excluded, and the remaining patients were included in this study. The criteria for pulmonary oligometastsis were defined as up to 5 pulmonary metastases on the most recent chest imaging prior to the SBRT start date and no active extra-thoracic disease. All patients were divided into two groups according to Nasopharyngeal (NP) and Non-Nasopharyngeal (non-NP) origin.

This study was approved by the Ethics Committee in Research of Zhejiang Cancer Hospital. There was no informed consent because it was retrospective research and would not harm the study's subjects.

SBRT Procedure

Radiotherapy for pulmonary metastasis was delivered according to the SBRT technical criterion in this institution using a conventional linear accelerator (Elekta, Stockholm, Sweden or Varian, Palo Alto, California, USA) through Volumetric Modulated Arc Therapy (VMAT) or Rapid Arc. The patients were fixed in the supine position with a customized immobilization device and then underwent a 4D-CT simulation scan (Philips, Amsterdam, Netherlands). The time phase interval of respiration during 4D-CT scanning was 10%, with 10 images of the respiratory time phase on each layer. The scan encompassed the upper margin of the second cervical spine up to the lower margin of the second lumbar spine with a 3-5-mm layer thickness. All the images were transferred to the treatment planning system (Ray Station Launcher 4.5.1, Stockholm, Sweden), the Gross Tumor Volume (GTV) was contoured phase-by-phase in reference to the chest CT or PET/CT, the GTVs of different inspiratory and expiratory states were fused to form the inner target area (ITV), and the 5-8-mmarea was expanded to form the Planned Target Volume (PTV) on the basis of the ITV [6]. Moreover, Organs at Risk (OAR) including the spinal cord, bilateral pulmonary, trachea, chest wall, brachial plexus, heart, and esophagus were contoured. The fractional dose and number were determined according to the diameter and location of pulmonary disease. Normally, the prescription dose was 48-64 Gy in 8-10 fractions for central lesions and 48-60 Gy in 4-5 fractions for peripherallesions. The Biologically Effective Dose (BED) derived from the linear quadratic model was used to compare the effect of fractionated radiation.

Follow-up and Data Acquisition

During follow-up, chest CT scans and/or PET/CT scans were performed at 3-6-month intervals. Local Control (LC) was defined as tumor controlled within the scope of the PTV, including local tumor disappearance (Complete Response, CR), shrinking (Partial Response, PR) or no change (Stable Disease, SD). Progression-Free Survival (PFS) was defined as the interval between the first day after SBRT and any form of tumor progression or death. Overall Survival (OS) was defined as the interval between tumor diagnosis and death from any cause. There were two OS calculations: OS1 was calculated from the first diagnosis of the primary tumor, and OS2 was calculated from the first diagnosis of pulmonary oligometastasis. The SBRT-related side effects were evaluated using common terminology criteria for adverse events reporting, version 3.0.

Statistics Analysis

Categorical variables were compared using the chi-squared test or Fisher's exact test. Continuous variables were analyzed using aT test. Cumulative survival rates were estimated by the Kaplan-Meier method. Univariate analysis and Cox regression analysis were performed to identify independent prognostic factors. A 2-sided p value less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (version 17.0, Chicago, Illinois, USA).

Results

Patient Inclusion and Exclusion

From January 2014 to March 2021, 83 patients who were diagnosed with HNC and received pulmonary SBRT entered screening. Of these 83 patients, 11 were excluded due to non-squamous cell carcinoma, including adenocarcinoma (n=5), Adenoid cystic carcinoma (n=4) and small cell carcinoma (n=2). Of the 72 patients with squamous cell carcinoma, 17 were excluded because the pulmonary lesion was diagnosed as a second primary cancer. Then, 12 patients who did notmeet the criteria of pulmonary oligometastasis were excluded, including extensive metastasis (n=5) and oligometastasis to other organs (n=7). Eventually, 43 patients with head and neck squamous cell carcinoma received SBRT for only pulmonary oligometastatic lesions were enrolled in this retrospectivestudy: 24 with NP cancer and 19 with non-NP cancer. A flow diagram of the study selection is shown in (Figure 1).

Patient Characteristics

The data of these 43 patients with pulmonary oligometastasis from HNC were collected, including 24 cases originated from then asopharynx and 19did not originate from the nasopharynx (non-nasopharynx):hypopharynx, 6 cases; oropharynx, 6 cases; larynx, 3 cases; oral cavity, 3 cases; and nasal cavity, 1 case. A total of 65 pulmonary lesions were treated by SBRT on account of 4 patients with 3 pulmonary metastases simultaneously, 9 patients with 2

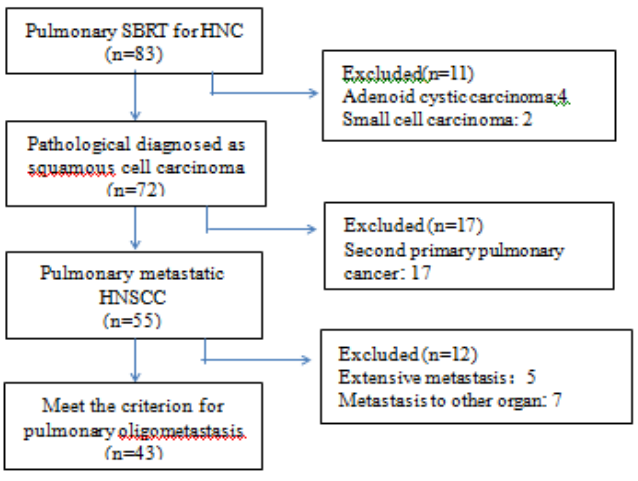

Figure 1: Flow diagram of study selection.

Table 1: Clinical characteristics of 43 patients with pulmonary oligometastasis from HNC.

	NP group (n)	non-NP Group(n)	p value
Sex			
male	17	16	
female	7	3	0.504
Age			
mean	52.6 years	63.1years	0.000
ECOG PS			
0-1	23	17	
2	1	2	0.575
T classification			
T1-2	8	3	
T3-4	16	16	0.338
N classification			
N0-1	12	5	
N2-3	12	14	0.115
Tumor stage			
N0-1	5	1	
N2-3	19	18	0.205
PD-1 inhibitors			
Yes	14	7	
No	10	12	0.161
Chemotherapy			
Yes	18	10	
No	6	9	0.126

pulmonary metastases simultaneously, and 30 patients with one pulmonary metastasis, of which 5 patients with SBRT to a new pulmonary metastasis after the first course of SBRT. Calculated from the first course of SBRT to March 31th, 2022, the median follow-up time was 29.7months (range, 7-79 months), and the follow-up rate was 100%. Among all patients, 3 cases of nasopharyngeal carcinoma had metastasis at initial diagnosis, and the other 40 cases had metastasis after the treatment of primary tumors. The treatment for the primary disease was radical cure: 3 cases received surgery only, 29 cases received radical radiotherapy or chemoradiotherapy, and 11 cases received surgery combined with adjuvant radiotherapy or chemoradiotherapy. Twenty-eight patients received systemic chemotherapy after pulmonary oligometastasis, including TP by 13 patients, GP by 7 patients, FP by 5 patients, and single platin or taxal by 3 patients. Twenty-one patients received PD-1 inhibitors after pulmonary oligometastasis, of which, PD-1 inhibitors alone for 9 patients and PD-1 inhibitors combined with systemic therapy for 12 patients. The clinical and pulmonary characteristics of these patients are summarized in (Tables 1-2).

Local Control and Survival

A total of 65 pulmonary lesions were treated with SBRT in 43 patients. The longest LC time was 79 months at the end of the follow-up time, and the median LC time was not reached. There were 25 CRs, 31 PRs, 6 SDs, and 3 PDs in the 65 lesions at 1 year, and the 1-year LC rate was 95.4%. Stratified according to the primary disease, the1-year LC rate of the NP and non-NP groups were 95.1% (39/41) vs. 95.8% (23/24), respectively (Fisher's Exact Test, p=1.000).The Biological Equivalent Dose (BED) was calculated in each lesion. BED was lower than 100Gy in 5 lesions, of which, 2 PRs,1 SD and 2 PDs, the 1-year LC rate of the BED < 100Gy and BED >100 Gy were 60% (3/5) vs. 98.3% (59/60) (Fisher's Exact Test, p=0.014).

Table 2: Characteristics of pulmonary oligometastatic disease.

	NP group	non-NP group	p value
Time to metastasis*			
Median (range)	24.0 (0-90.9) months	7.6 (1.5-46.9) months	
Mean	27.1 months	11.7 months	0.017
Number of metastasis#			
Median(range)	1(1-3)	1(1-3)	
mean	1.50±0.78	1.53±0.77	0.913
Largest diameter#			
Median(range)	1.50 (0.4-4.6)cm	1.7 (0.8-2.5)cm	
Mean	1.49cm	1.48 cm	0.961
BED#			
<100Gy	1	4	
≥100Gy	37	28	0.156
Post-metastatic system treatment*			
no	1	1	
yes	11	11	1.000

*: forty-three patients with pulmonary oligometastases were counted, #: sixty-five lesions were counted.

There were 22 cases of new progression occurred in the whole cohort, 9 of which appeared within 1 year after SBRT. The new lesions included 10 cases of pulmonary metastasis, 7 cases of liver metastasis, 5 cases of bone metastasis, 2 cases of mediastinal lymph node metastasis, 2 cases of retroperitoneal lymph node metastasis, 1 case of brain metastasis, and 5 cases of primary recurrence. The median PFS was 30.2 months (95% CI: 6.1,54.3), and the 3-year PFS was 46.0%. Subgroup analysis showed that the median PFS times were 47.0 months (95% CI: 28.8,65.1) in the NP group and 13.3 months (95% CI: 5.9,20.7) in the non-NP group ($\chi 2$=7.581, p=0.006). At the time of the last follow-up, 13 patients died of tumor progression: 4 in the NP group and 9 in the non-NP group. The 3-year OS1 and OS2 were 78.9% and 68.7% respectively. After stratification according to the primary disease, the 3-year OS1 was 94.7% and 60.9% (p=0.006), and the 3-year OS2 was 87.1% and 47.9% (p=0.011) in the NP group and the non-NP group, respectively. The specific survival curves were shown in (Figure 2).

The univariate analysis of these patients was shown in (Table 3). Primary tumor location, time to metastasis, number of pulmonary lesions, BED of SBRT, and systemic therapy (chemotherapy or PD-1 inhibitors) were found to be significant predictors for PFS and (or) OS2. Patients with NP origin had a better survival than those with non-NP origin (mean PFS time 47.6 vs. 17.4 months, P=0.011. mean OS2 time64.6 vs. 34.3 months, p=0.011). And that patients with SBRT combined with systemic therapy had a better survival than those without chemotherapy or PD-1 inhibitors. However, the

Table 3: Univariate analysis of Survival in the total cohort.

	PFS			OS2		
	Mean±SD (months)	χ^2	p value	Mean±SD (months)	χ^2	p value
Age (years)						
≤60	44.4±7.4	2.289	0.130	59.6±6.2	3.360	0.067
>60	21.3±3.6			42.1±8.8		
Gender						
Male	35.8±7.7	0.084	0.772	54.2±6.4	0.047	0.829
Female	31.4±6.7			40.5±6.3		
T classification						
T1-2	49.1±11.2	0.889	0.346	64.5±8.6	1.580	0.209
T3-4	27.2±3.5			47.3±6.0		
N classification						
N0-1	38.8±6.3	2.591	0.107	58.3±6.4	2.118	0.146
N2-3	30.5±6.9			49.9±7.2		
Tumor stage						
N0-1	42.8±10.8	0.995	0.318	54.7±6.8	1.158	0.282
N2-3	34.5±6.0			51.5±5.9		
Primary tumor						
Nasopharynx	47.6±7.6	6.539	0.011	64.6±6.0	6.424	0.011
Non-nasopharynx	17.4±2.7			34.3±5.2		
Time to metastasis						
≤12 months	17.9±3.3	6.406	0.011	33.7±4.9	8.081	0.004
>12 months	47.3±7.6			64.9±6.0		
Number of metastasis						
Single	39.4±5.0	7.286	0.007	51.7±3.9	5.711	0.017
Multiple	20.4±6.7			39.8±8.1		
Largest diameter						
<2cm	40.8±6.6	0.131	0.717	56.3±6.2	0.713	0.398
≥2cm	28.1±5.8			46.0±9.2		
BED						
<100Gy	14.9±5.4	3.378	0.066	24.1±5.9	4.021	0.045
≥100Gy	39.9±6.1			56.9±5.4		
Systemic chemotherapy						
Yes	46.5±7.8	7.134	0.008	62.4±6.3	5.108	0.024
No	19.7±5.2			39.7±7.4		
PD-1 inhibitors						
Yes	49.1±7.7	6.318	0.012	67.8±5.6	8.522	0.004
No	18.1±2.9			34.0±4.6		

advantages of systemic therapy were maintained in Cox regression analysis, but the difference between NP cancer and non-NP cancer was not observed. The forest plots of Cox regression analysis were shown in (Figure 3).

Toxicity

During follow-up, only moderate SBRT-related toxicities were observed, including 2cases of radiation-related esophagitis and 1 case of radiation-related pneumofibrosis with no symptoms in the NP group, and2 cases of moderate radiation pneumonitis with dry cough in the non-NP group. The incidence rates of radiation-related injury were12.5% and10.5% in the NP and non-NP groups, respectively (p=1.0). In all, there were no severe SBRT-related toxicities above grade 3, and all patients tolerated the radiation treatment well.

Thinking of more than half of the patients had received systemic therapy, we analyzed the treatment related adverse events (TRAEs), the most frequently reported events were fatigue, nausea and vomiting, and myelosuppression. There was no systemic treatment delayed because of SBRT, and SBRT didn't increase the probability and intensity of systemic treatment related AEs.

Discussion

The lung is one of the most common metastatic sites in HNC. Compared with liver metastasis, HNC patients with pulmonary metastasis had better therapeutic efficacy, especially in patients with pulmonary oligometastatic cancer [19]. Some studies have found that local radiotherapy combined with systematic treatment can cure some pulmonary oligometastatic HNC and the radiation dose was related to the prognosis [25]. At an earlier time, we reviewed the clinical data of 51 patients with pulmonary oligometastasis from NP cancer treated with systemic chemotherapy combined with conventional radiotherapy. The 2-year PFS rate and 3-year OS rate after pulmonary metastasis in patients with curative dose (≥60Gy) were better than those in patients with palliative dose(<60Gy) (57.1% vs. 25.8%, p=0.002 and 89.3% vs. 72.7%, p=0.003) [25].

The superiority of SBRT is that it can focus radiation dose on target volume, so the prescription dose can be boosted highly, which would increase the objective response of pulmonary lesions theoretically. There have been many studies in support of SBRT with high BED in patients with metastatic disease [8]. Improved LC was observed for lung metastases that received SBRT doses of BED ≥100Gy with 3-year LC rate of 77.1% compared to 45% for lung metastases treated with BED < 100Gy (p = 0.01) [21]. Similar results occurred in other cancers. Sun et al. reported a retrospective study about 108 small hepatic cell cancer patients who were treated with SBRT. They observed that OS, PFS and Distant Metastasis Free Survival (DMFS) were significantly higher in the BED ≥ 100Gy group than in the BED < 100Gy group (OS: p = 0.020; PFS: p = 0.017; DMFS: p = 0.012) [24]. In our study, benefit from high-dose exposure to SBRT, the 3-year PFS was 46.0% and 3-year OS2 was 68.7% in the whole group. Furthermore, the patients who received SBRT with BED ≥ 100 Gy had better LC rate and OS2 than those with BED < 100Gy. The results further verified the relationship between the prescription radiation dose and curative effect.

Despite of good local control, 22 cases of new progression occurred during the follow-up time, 9 of which appeared within 1 year after SBRT. We speculated that was associated with the criterion of oligometastasis only based on radiological evaluation. Given the limitations of available molecular analyses in distinguishing the oligometastasis from the initial stage of extensive metastasis, systemic therapy, including chemotherapy and immunotherapy, may remedy the deficiency of local treatment. The univariate and multivariate analysis showed that patients with SBRT combined with systemic therapy had better PFS and OS2 than those without chemotherapy

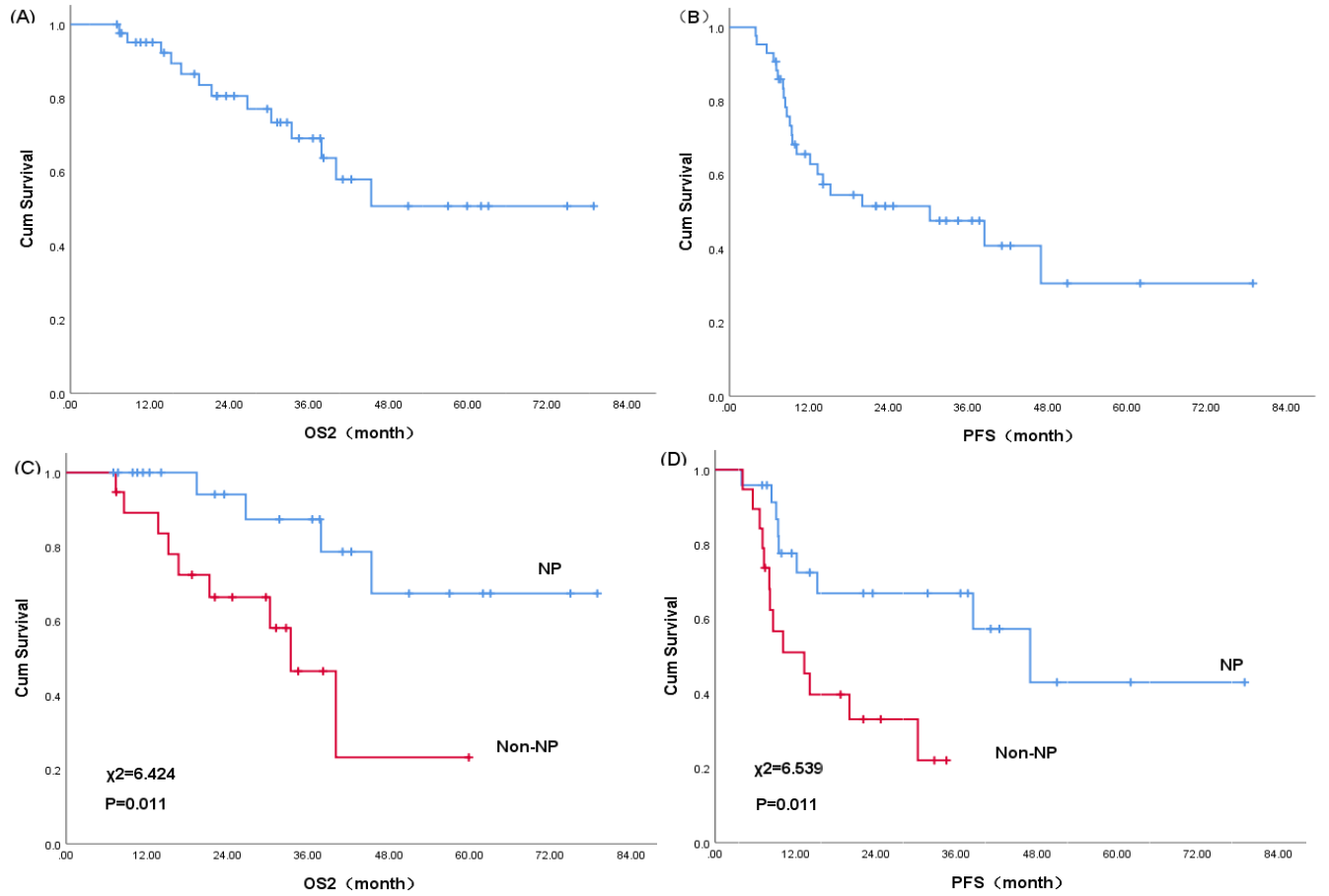

Figure 2: Survival curves of patients with pulmonary oligometastases from HNC: A. Overall survival rate after pulmonary metastasis; B. Progression-free survival rate after pulmonary metastasis; C. Overall survival rate after pulmonary metastasis stratificated by primary disease; D. Progression-free survival rate after pulmonary metastasis stratificated by primary disease.

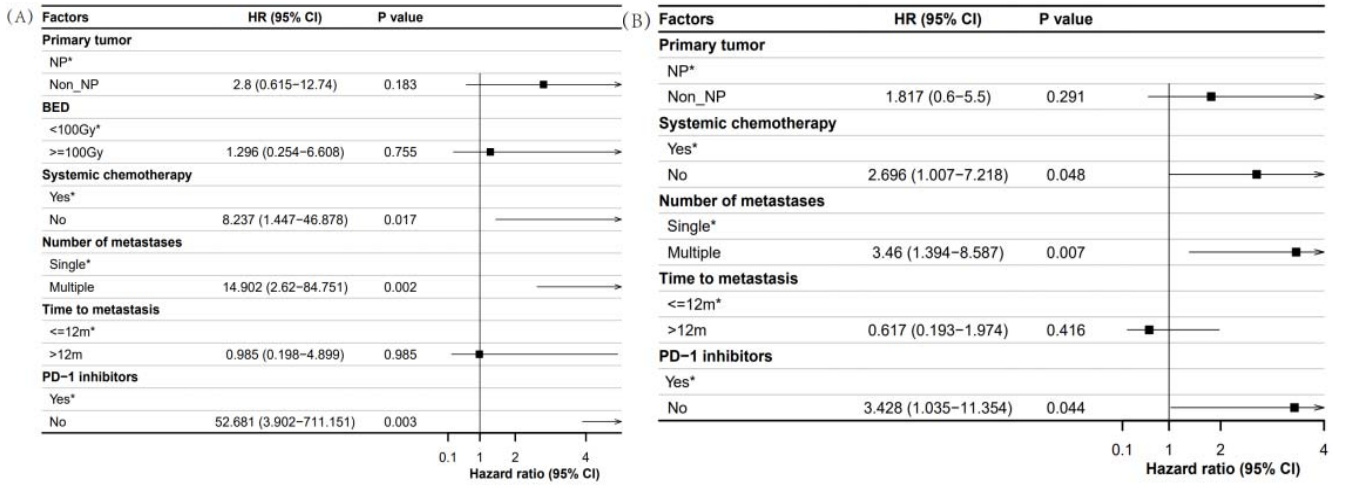

Figure 3: Forest plots of the Cox regression analysis: A. Overall survival rate after pulmonary metastasis; B. Progression-free survival rate after pulmonary metastasis; C. Overall survival rate after pulmonary metastasis stratificated by primary disease; D. Progression-free survival rate after pulmonary metastasis stratificated by primary disease.

or PD-1 inhibitors in the study. Synergistic effects of SBRT and immunotherapy have been supported by many laboratory researches, such as systemic anti-tumor immunity generated by abnormal proteins caused by radiotherapy irradiation [16], or elimination of damaged tumor cells mediated by broken double-stranded DNA (dsDNA) produced by irradiated tumor cells [22]. Pan observed that

SBRT extended the clinical benefit of PD-1 inhibitors in refractory recurrent/metastatic NP cancer [13]. But Nancy collected 62 patients with metastatic HNC, who were randomly assigned to nivolumab or nivolumab plus SBRT. There was no statistically significant difference in ORR, OS and PFS between arms [15]. Bahig designed a phase I/II single arm study that Durvalumab and tremelimumab combined with SBRT were given to treat HNC patients with 2–10 extracranial metastatic lesions [3]. This study is still on progress, and we look forward to the research results.

HNC is a heterogenous group of malignant tumors and different the raputic effects have been found with different tissue origination [17]. Pasalic et al. applied SBRT for metastatic HNC, they found OS in oligometastatic non-squamous HNC and HNSCC were 100% and 66% (P =0.03) [20]. Thinking of differences in biological behavior, we generally distinguished NP cancers from other head and neck squamous cell carcinomas (non-NP cancers). In our study, we observed SBRT could achieve good local control for pulmonary metastasis originated from both NP and non-NP cancer, and the 1-year local control rates of the two groups were 95.1% and 95.8%, respectively. As for overall survival, OS2 and PFS reflect the value of post-metastatic treatment more directly than OS1, and we found the differences in OS2 and PFS were significant. The median PFS was 47.0 months in the NP group and 13.3 months in the non-NP group, the results showed the patients with non-NP origin were more inclined to disease progress after SBRT. From this point of view, potent systemic treatment, including chemotherapy combined with immunotherapy, might be more important in non-NP cancers. This need to be verified by more real-world data and prospective controlled studies.

Regardless, it is essential to address several limitations of this current study. First, this was a retrospective study, the intrinsic selection bias maybe responsible for the observed differences in outcome. Second, the relatively small sample size of the patient cohort might weaken the effectiveness of the statistical analysis. Additionally, differentiating oligometastasis from initial stage of extensive metastasis was difficult only from a radiological standpoint. Therefore, this study was not necessarily representative of the general situation of patients with pulmonary oligometastatic disease.

Conclusions

The results of the retrospective study suggest that SBRT is an effective and tolerable therapy for patients with pulmonary oligometastasis from HNC. On the basis of systemic treatment, radical curative-intent with SBRT could be achieved in selected HNC patients. These findings provide a worthy alternative for patients with pulmonary oligometastatic HNC. We recommend that SBRT be further explored in the randomized controlled trial context to clarify which subgroups of patients is most likely benefit from this local ablative therapy in the oligometastatic setting.

Acknowledgments

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