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Survival analysis of patients with metastatic head and neck squamous cell carcinoma treated with metastasis-directed radiotherapy and immunotherapy

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Abstract

Objective Immunotherapy combined with chemotherapy is currently the first-line treatment for metastatic head and neck squamous cell carcinoma (HNSCC). This study aims to evaluate whether adding metastasis-directed radiotherapy (MDRT) to immunotherapy and chemotherapy could improve the survival rate of patients with metastatic HNSCC.

Materials and methods A retrospective analysis was conducted on patients with HNSCC who developed distant metastases after curative treatment. Systemic treatment was determined by the multidisciplinary team, with a programmed cell death-1 (PD-1) inhibitor combined with chemotherapy as the primary approach. The feasibility of radiotherapy was evaluated by clinical and imaging examinations. Stereotactic body radiotherapy (SBRT) was used to deliver different doses according to the number and location of metastatic lesions. Kaplan–Meier method was used to estimate survival, and Cox regression analysis was performed to evaluate the association between clinical factors and survival outcomes.

Results From January 2018 to June 2023, a total of 94 patients with 164 metastatic sites were included for the analysis. The most common primary tumor was the nasopharynx (77.7%), with the lung being the most frequent site of metastasis (46.8%), followed by bone (37.2%). Radiotherapy was administered to 276 metastatic lesions, with a median dose of 52.3 Gy (range: 24–60 Gy). The median overall survival (OS) was 43.0 months (range: 20.2–65.8). The OS rates at 2 and 5 years were 70.1% (95% CI, 59.7–80.5%) and 30.1% (95%CI 11.7–48.5%), respectively. Univariate and multivariate analysis showed that the number of metastases and the location of the primary tumor were significantly associated with OS.

Conclusions In patients with metastatic HNSCC, MDRT combined with immunotherapy and chemotherapy can effectively improve local control and OS. These findings warrant further validation through prospective clinical trials:

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Keywords Metastatic, Head and neck squamous cell carcinoma, Metastasis-directed radiotherapy, MDRT, PD-1 inhibitors

Head and neck cancer is a common cancer type, comprising approximately 3–5% of all cancer diagnoses worldwide [1]. Despite a 5-year survival rate ranging of 50 to 65%, a significant number of patients experience recurrence after treatment, with up to 15% developing distant metastases [2]. Before the advent of immunotherapy, the most effective systemic therapy offered a median overall survival (OS) of only 10 months for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) [3]. In 2016, the first immune checkpoint inhibitor, targeting programmed cell death protein 1 (anti-PD-1), was approved for managing recurrent or metastatic HNSCC. The phase III KEYNOTE-048 trial [4] demonstrated that pembrolizumab significantly extended OS in patients with R/M HNSCC, increasing it from 10.7 to 13 months. However, the immune response rate remained below 20% [5]. It's worth noting that the volume and extent of metastatic lesions are key prognostic indicators [6].

Radiotherapy has garnered widespread recognition as an integral facet of curative treatment across many types of cancer. Nevertheless, for patients with metastatic cancer, radiotherapy principally serves to alleviate disease-associated symptoms. The first prospective study [7] investigated the potential of localized radiotherapy in augmenting survival in the treatment of metastatic disease, revealing that select individuals with oligometastatic disease could potentially derive benefit from this therapeutic regimen. Subsequently, accumulating evidence suggests that radiotherapy may enhance progression-free survival and OS in certain patients with metastatic disease. A randomized phase II study [8] on radiotherapy for all active metastases following successful induction chemotherapy in metastatic non-small cell lung carcinoma demonstrated superior outcomes with combined local treatments compared to systemic therapy alone. Prospective studies have explored the potential of local therapy in treating metastatic disease, particularly for those with a minimal metastatic burden [9, 10]. A similar trial of metastasis-directed radiotherapy (MDRT) for patients with head and neck cancer with a limited metastatic burden has also shown a significant improvement in survival [11]. Local control strategies for metastatic diseases, particularly for patients with limited metastases, are evolving.

Currently, metastatic head and neck cancer has entered the immune era, with the multiple interactions between immunotherapy and radiotherapy being increasingly recognized [12]. However, the role of MDRT in systemic therapy remains unclear. Therefore, we reviewed patients with metastatic HNSCC who had failed first-line treatment at our center and analyzed the survival outcomes of those who received MDRT.

Materials and methods

According to a retrospective study protocol approved by the Institutional Ethics Committee (SCCHEC-02–2020-018), patients with metastatic HNSCC who had failed curative first-line treatment in Sichuan Cancer Hospital between January 2018 to June 2023 were eligible for inclusion. All the patients signed the informed consent. Primary tumor sites included the nasopharynx (NPC), oropharynx, oral cavity, larynx and hypopharynx. Metastatic sites were identified through biopsy or imaging and reviewed by a multidisciplinary team (MDT). All patients received immunotherapy with anti-PD-1, and concurrent chemotherapy was considered acceptable based on MDT recommendations. Metastatic lesions were treated with stereotactic radiotherapy (SBRT) or hypofractionated intensity-modulated radiotherapy (≤ 60 Gy). Exclusion criteria included: patients with untreated primary metastases, those with simple recurrence, and those receiving palliative radiotherapy for bone metastases only.

Follow-up after radiotherapy

After completion of radiotherapy for local disease, patients were evaluated every 2 to 3 months during the first-year post-treatment, and then every 4 to 6 months thereafter. Each follow-up included a physical assessment and imaging with CT or MRI. Toxicity data were recorded according to the National Cancer Institute's CTCAE v5.0 criteria.

Statistical analysis

All analyses were performed with SPSS 25.0 software (SPSS Inc. Chicago, IL, USA). The primary end point of the study was OS, defined as the time from the occurrence of distant metastases to death. OS was analyzed using Kaplan-Meier method. Metastases were classified according to the number of lesions and affected organs as follows: 1, 2–5, more than 5, single organ, and multiple organs. Univariate analysis was performed with the log-rank test, while Cox proportional hazards regression was used to estimate hazard ratios (HR). Cox regression analysis was performed to evaluate the association between clinical factors and survival. Two-sided p-values < 0.05 were considered statistically significant. The R statistical software version 4.4.0 was utilized for calculate the number at risk under the survival curve (R Project, http://www.R-project.org/).

Table 1 The characteristics and metastasis details of the patients

Characteristic		*N* (%)
Age at DM, years	Median (range)	49.6 (20–81)
Sex	Male	72 (76.6)
	Female	22 (23.4)
KPS at DM	Median (range)	80 (60–100)
Primary tumor location	Nasopharynx	73 (77.7)
	Oral cavity	7 (7.4)
	Oropharynx	4 (4.3)
	Larynx	3 (3.2)
	Hypopharynx	7 (7.4)
Sites of metastasis	Lung	44 (46.8)
	Liver	29 (30.9)
	Bone	35 (37.2)
	Brain	4 (4.3)
	Other	52 (55.3)
No. of metastasis	1	45 (47.9)
	2–5	33 (25.1)
	5+	16 (17.0)

N number, DM distant metastases, KPS Karnofsky performance status

Table 2 Treatment's details

Treatment		*N* (%)
PD-1 inhibitors	Pembrolizumab	14 (14.9)
	Camrelizumab	12 (12.8)
	Tislelizumab	12 (12.8)
	Sintilimab	15 (16.0)
	Toripalimab	41 (43.6)
Cycles of PD-1 inhibitors	Median (range)	10 (1–44)
Chemotherapy	Yes	90 (95.7)
	No	4 (4.3)
Cycles of chemotherapy	Median (range)	4 (1–8)
Radiotherapy	SBRT	187 (67.8)
	Hypofractionated	89 (32.2)
Dose of radiotherapy	Median (range)	52.3 Gy (24–60 Gy)

Results

From January 2018 to June 2023, a total of 94 patients with 164 metastatic sites were included in the retrospective analysis. The characteristics and details of the patients' metastases are shown in Table 1. The median age was 49.6 years (range: 20–81 years), and most patients were males (76.6%). The most common primary tumor was the nasopharynx (77.7%). The lung was the most frequent site of metastases (46.8%), followed by bone (37.2%). Forty-five patients (47.9%) had a solitary metastasis, 33 patients (25.1%) had 2–5 metastases and 16 patients (17.0%) had 5 or more metastases.

All patients received treatment with PD-1 inhibitors (including pembrolizumab, camrelizumab, tislelizumab, sintilimab, toripalimab), with 90 cases of patients with chemotherapy. The chemotherapy regimen was based on gemcitabine combined with platinum. Radiotherapy was administered to a total of 276 metastatic lesions with a median dose of 52.3 Gy (range: 24–60 Gy). Details of treatment are shown in Table 2.

The median follow-up was 18.0 months (range: 1–84 months). The OS rates at 2 and 5 years were 70.1% (95%CI 59.7–80.5%) and 30.1% (95%CI 11.7–48.5%), respectively (Fig. 1). The median OS was 43.0 months (rang 20.2–65.8). Univariate analysis showed that age, sex, KPS, the number of metastatic organs, and chemotherapy were not associated with OS, while the number of metastatic lesions was significantly associated with OS (HR 2.01, 95%CI 1.24–3.25; $p = 0.005$). The location of the primary tumor (nasopharyngeal vs. non-nasopharyngeal) was also associated with OS (HR 2.05, 95%CI 0.97–4.37; $p = 0.054$) (Fig. 2). Multivariate analysis confirmed that the number of metastases and the location of the primary tumor remained significant factors for OS (Table 3).

Discussion

The management of patients with metastatic cancer is evolving rapidly. With the advent of novel systemic therapeutic, such as immunotherapy and targeted drugs, the prognosis and tolerability of treatment have significantly improved. At the same time, the role of local interventions, particularly radiotherapy, in the treatment of metastatic disease is also swiftly evolving. Supporting this shifts, several prospective trials have demonstrated that local treatment of oligometastases not only prolongs disease progression but also delays the need of systemic therapy, potentially improving overall survival [9, 13–17]. A comprehensive retrospective analysis, including long-term follow-up of HNSCC cases, indicates potential therapeutic benefits for locally advanced metastatic disease. Median subsequent metastasis-free survival and 5-year survival after local therapy ($n = 30$) were estimated at 26.4 months (95% CI: 9.8–54.0) and 31%, (95% CI: 15–48%), respectively. However, these studies primarily focus on individuals affected by oligo-metastatic conditions. The role of incorporating local radiotherapy in combination with immunotherapy for patients with multi-metastatic cases remains to be clarified. This study retrospectively analyzed patients with HNSCC who had received immunotherapy combined with MDRT in our center. The results showed a median overall survival of 43 months, with a 2-year OS rate was 70.1%, which was significantly higher than the current guideline recommended regimen of chemotherapy plus immunotherapy [4]. In the subgroup of patients with non-nasopharyngeal squamous cell carcinoma of the head and neck, the 2-year overall survival rate of 56.3% was also higher than that observed in KEYNOTE-048 [18]. These results suggest that MDRT may provide a survival benefit for patients with metastatic HNSCC in the immunotherapy era.

Several studies have suggested that patients with oligometastatic disease may achieved long-term survival with

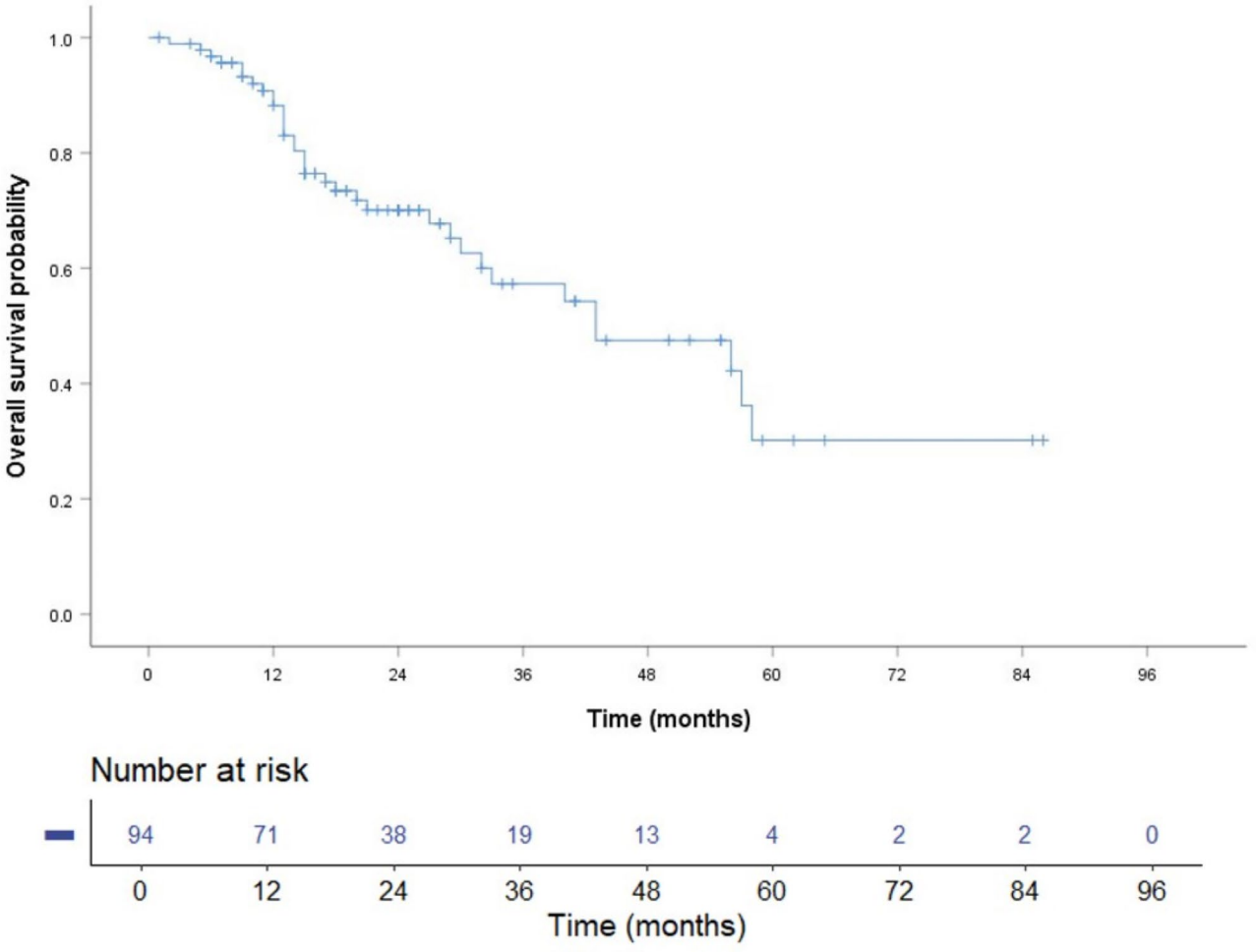

Fig. 1 Kaplan–Meier curve for overall survival of all patients

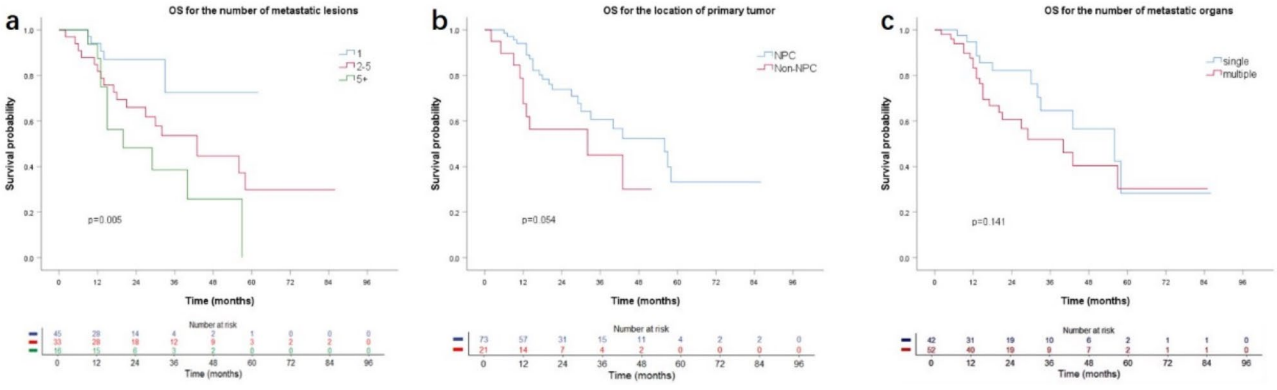

Fig. 2 Kaplan–Meier curves for overall survival based on (**a**) the number of metastatic lesions, (**b**) the location of the primary tumor, (**c**) the number of organs involved with metastases

local radiotherapy combined with systemic therapy [13, 15, 19]. SABR-COMET trial demonstrated an 8-year OS of approximately 40% (versus 6% with systemic therapy alone) and a PFS of 20% in patients with colorectal liver metastases treated with ablation or resection [14] 。 In our study, patients with a single metastasis had significantly better OS compared to those with two or more metastases in univariable analyses. In addition, the median 2-year OS of patients with 2–5 metastases treated with MDRT reached 66.0%, enabling some patients to achieve long-term disease-free survival. Therefore, we believe that patients with multiple metastases may still

Table 3 Univariate and multivariate analysis for overall survival

	Group	*N*	HR	95% CI	*p*-value
Univariate analysis					
Age(year)	< 50	52	1.40	0.71–2.79	0.332
	≥ 50	42			
Sex	Male	72	1.06	0.49–2.27	0.887
	Female	22			
KPS	< 80	33	0.58	0.29–1.15	0.116
	≥ 80	61			
Primary tumor location	NPC	73	2.05	0.97–4.37	**0.054**
	HNC	21			
Sites of metastasis	Single	52	1.68	0.83–3.40	0.141
	Multiple	42			
No. of metastasis	1	45	2.01	1.24–3.25	**0.005**
	2–5	33			
	5+	16			
Chemotherapy	Yes	90	0.70	0.17–2.95	0.624
	No	4			
Multivariate analysis					
Primary tumor location			3.26	1.44–7.37	**0.005**
No. of metastasis			2.48	1.47–4.18	**0.001**

N number, HR hazard ratio, CI confidence interval, KPS Karnofsky performance status, NPC nasopharynx carcinoma, HNC head neck cancer

benefit from MDRT. However, in the analysis based on the number of metastatic sites, there was no significant association between single-site and multi-site metastases and OS, which may be due to the presence of multiple metastases within a single site in some patients.

Most patients in our study received local SBRT. With advances in image-guided radiotherapy, SBRT has become an excellent option for managing oligometastatic disease in certain sites, such as lung, liver, and bone [20]. This approach is efficient, noninvasive and well tolerated. SBRT improves local lesion control and could enhance immune activation [21]. Therefore, combing of SBRT with PD-1/PD-L1 inhibitors is more likely to provide survival benefits. A phase I/II clinical trial showed the efficacy of durvalumab combined with tremelimumab and SBRT in patients with oligometastatic HNSCC, showing an ORR of 64.3% and a median PFS of 7.2 months. These remarkable outcomes are presumably attributable to the integration of SBRT within immunotherapy that served to either stimulate the immune system or eliminate slow-responding or immunotherapy-resistant lesions [22]. Nonetheless, findings from a subsequent phase II randomized study [23] indicated no enhancement in therapeutic responses or abscopal effects when SBRT was added to nivolumab in unselected patients with metastatic HNSCC. The good survival outcomes in oligometastatic patients treated with SBRT in this study suggest that further randomized clinical trials are needed, focusing on patients' metastatic status.

Our study has some limitations. The main factors included its retrospective nature, insufficient sample size, and the unclear PD-1 expression status of the patients. Moreover, the substantial heterogeneity in radiotherapy response may have influenced the treatment outcomes. Finally, the follow-up time of this study was relatively short due to the clinical application of immunotherapy.

Conclusion

In the era of immunotherapy, MDRT combination therapy offers an opportunity for long-term survival in patients with metastatic HNSCC, especially those with oligometastatic disease. Further randomized clinical trials are needed to evaluate the value of MDRT in metastatic HNSCC.

Abbreviations

HNSCC	Head and neck squamous cell carcinoma
MDRT	Metastasis-directed radiotherapy
PD-1	Programmed cell death-1
SBRT	Stereotactic radiotherapy
OS	Overall survival
MDT	Multidisciplinary team
DM	Distant metastases

Author contributions

Peng Xu, Mei Feng, Jinyi Lang contributed to the conception of the study; Shuo Wang, Jie Zhou, Yecai Huang, Shun Lu performed the experiment; Peng Xu, Zhengyi Tang, Dongmei Liu contributed significantly to analysis and manuscript preparation; Peng Xu, Jie Zhou, Lucia Clara Orlandini performed the data analyses and wrote the manuscript; Jie Zhou, Shun Lu helped perform the analysis with constructive discussions.All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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