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Outcomes for oligometastatic head and neck cancer treated with stereotactic body radiotherapy: Results from an international multi-institutional consortium

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Abstract

Background: We report the results of an international multi-institutional cohort of oligometastatic (OMD) head and neck cancer (HNC) patients treated with SBRT.

Methods: Patients with OMD HNC (≤5 metastases) treated with SBRT between 2008 and 2016 at six institutions were included. Treated metastasis control (TMC), progression-free survival (PFS), and overall survival (OS) were analyzed by multivariable analysis (MVA).

Results: Forty-two patients with 84 HNC oligometastases were analyzed. The TMC rate at 1 and 2 years were 80% and 66%, with a median time to recurrence of 10.1 months. The median PFS and OS were 4.7 and 23.3 months. MVA identified a PTV point maximum (BED)10 > 100 Gy as a predictor of improved TMC (HR = 0.31, $p = 0.034$), and a cumulative PTV > 48 cc as having worse PFS (HR = 2.99, $p < 0.001$).

Conclusion: Favorable TMC and OS was observed in OMD HNCs treated with SBRT.

KEYWORDS

oligometastatic: head and neck cancer, radiation oncology, SABR, SBRT

1 | INTRODUCTION

Head and neck cancers (HNCs) are a heterogeneous group of malignancies, comprised primarily of squamous cell carcinoma (>90%) of the upper aerodigestive tract.[1] Despite significant improvements in locoregional control and advances in systemic treatments, distant metastases (DM) occur in approximately 15% of patients with a median survival of 10 month.[2–4] Interestingly, patients with oligometastatic disease (OMD) across multiple cancer types, in which a limited number of metastases (generally defined as 1–5) can be targeted with definitive ablative treatment, have also been identified as having improved outcomes.[5] While further randomized evidence

is accruing, studies suggest that aggressive ablative treatment may delay progression, prolong survival, and in select cases, potentially cure patients with limited metastatic bulk.[6]

Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), is characterized by the conformal delivery of high doses of ionizing radiation in a small number of fractions with relative sparing of normal tissues.[7] SBRT has been increasingly used in both radical and palliative settings due to high rates of local control, acceptable toxicity profile, and expedient delivery schedules. Treatment of OMD with SBRT has shown a potential to improve disease control, and potentially survival, in early phase clinical trials largely focused on lung and prostate cancer.[8–10] OMD outcomes in HNCs are, however, less clearly defined and debate remains regarding the therapeutic benefit, and toxicity of metastasis-directed treatments. For instance, in a meta-analysis of retrospective studies of HNC patients treated with metastectomy for pulmonary DM, surgical resection resulted in a 5-year OS of 29%.[11] Similarly, the phase II SABR-COMET trial of 99 patients (10% HNCs) with 1–5 metastases showed improved OS in favor of local ablation (42% vs. 17%).[12,13] While these treatments have shown promise in treating OMD, they are not without potential drawbacks. For one, most studies are retrospective with only a small number of prospective studies. Confounding factors, such as the use of different SBRT systems, use of other local or systemic treatments, variations in the number and types of metastases, and inclusion of different tumor types, also make it difficult to compare studies. Second, metastectomy and SBRT carry the risk of complications, such as bleeding, infection, organ damage, and even death. In addition, these treatments can be costly, and in the case of metastectomy may require a significant recovery period. There is also some debate about the optimal timing of metastasis-directed treatments particularly as it relates to the sequencing of systemic and local treatments.

The lack of multicenter studies in OMD research, coupled with inconsistent treatments, outcomes, and heterogeneous patient populations, suggest the need for greater international collaboration to validate the benefit of SBRT in this population. In recent years, the Consortium for Oligometastasis Research (CORE) has pooled data from six large SBRT centers and demonstrated favorable OS in 1033 OMD cancer patients treated with SBRT.[14] In this subset analysis of the CORE database, we aimed to report the clinical characteristics, treatment patterns, and survival outcomes of HNC patients with OMD treated with SBRT.

2 | METHODS

2.1 | Study design and population

This is a multi-institutional retrospective study of patients with HNC from the Consortium for Oligometastasis Research (CORE). The CORE consortium was established from six institutions with a strong experience in SBRT and were selected based on their willingness to collaborate and ability to provide a sufficient sample size of OMD patients treated with SBRT. The CORE database comprises 1033 patients (≥18 years old) with biopsy-proven oligometastatic (5 or less extracranial metastases) cancer. All patients were treated with SBRT to at least one OMD site between January 1, 2008 and December 31, 2016, while those with brain metastases at baseline were excluded. All HNC patients within the overall cohort were included in the analysis, and every patient, received curative treatment for their primary disease. Patients with synchronous metastases received curative treatment prior to OMD directed SBRT. Patient clinical data and radiation treatment parameters were obtained though retrospective chart review following REB approval at each participating institution: Odette Cancer Centre (Toronto, Canada), University of Turin (Turin, Italy), Princess Alexandra Hospital (Brisbane, Australia), University of Florida Health Proton Therapy Institute (Florida, USA), Johns Hopkins University (Maryland, USA), and University Hospitals Seidman Cancer Center (Ohio, USA).

2.2 | Treatment and follow-up

All patients were treated with SBRT to at least one site of OMD. SBRT protocols used by each participating institution with regards to simulation, immobilization, image guidance, and gross tumor volume expansions have been previously described by our group.[15] ITVs were defined using 4D-CT for lung and liver metastases in order to account for physiological motion and were generated as follows: GTVp_inhale + GTVp_exhale = ITV. The choice of dose fractionation was based on institutional practices that also considers specific patient and tumor factors at the discretion of the treating oncologist. Tables detailing the treatment techniques, dose/fractionation, and gating/tracking used for each site treated are presented in Tables S2–S4, Supporting Information). All RT prescription doses were transformed to biologically effective dose (BED) in order to estimate tumor effect using the equation $\mathrm{BED} = nD\,[1 + D/(\alpha/\beta)]$, where n is the number of fractions, D is dose per fraction, and $\alpha/\beta = 10$. Toxicity from SBRT is reported based on the

National Cancer Institute Common Terminology for Adverse Events (CTCAE, version 4). Only grade 3 toxicity and higher was collected to ensure a more consistent and reliable assessment of treatment outcomes. Multidisciplinary follow-up generally included computed tomography (CT) scan of the head and neck, chest, and abdomen acquired at regular intervals as per institutional guidelines. Additional imaging and interventions were obtained based on patient symptoms.

2.3 | Study outcomes

Our outcomes of interest include treated metastasis control (TMC), widespread progression (WSP), progression-free survival (PFS), and overall survival (OS). WSP was defined as developing greater than five new sites of extracranial metastases or malignant effusions. The follow-up interval was defined starting from the date of SBRT treatment. The endpoints for our outcomes of interest were as follows: (1) TMC: date of recurrence at the SBRT site or death or last follow-up, (2) WSP: date of recurrence with greater than five new sites of metastases, (3) PFS: date of any progression (local, oligo- or widespread progression) or time of death, (4) OS: date of death or last follow-up.

2.4 | Statistical analysis

Patient and treatment characteristics are presented as continuous variables (median and range), or categorical variables (frequency). Competing risk analysis was used to estimate the actuarial cumulative incidence of treated metastasis recurrence, and WSP over time using death as any cause as a competing risk factor. OS and PFS were analyzed using the Kaplan–Meier method. Univariable analysis (UVA) with the Fine and Gray method was used to investigate the relationship between clinical factors and our outcomes of interest. Variables with a p-value <0.10 were entered into a multivariable analysis (MVA) and only those with a p-value <0.05 were retained in the final model through backward selection. The relationship between BED and PTV was investigated using spearman correlation.

3 | RESULTS

3.1 | Patient and treatment characteristics

Overall, 42 patients with 84 treated oligometastases were included in the analysis. The median follow-up was 18.2 months (range: 0.6–77.2 months). The median age at

TABLE 1 Patient level characteristics ($n = 42$)

Variable number (%)	
Age at SBRT, mean (SD)	**61.2 (13.5)**
Sex	
Male	35 (83.3)
Female	7 (16.7)
Primary site	
Oropharynx	18 (42.9)
Larynx	9 (21.4)
Nasopharynx	5 (11.9)
Oral cavity	4 (9.5)
Hypopharynx	4 (9.5)
Unknown primary	2 (4.8)
T stage	
T1	3 (7.1)
T2	9 (21.4)
T3	9 (21.4)
T4	17 (40.5)
Unknown	4 (9.5)
N stage	
N0	6 (14.3)
N1	2 (4.8)
N2	29 (69.0)
N3	4 (9.5)
Unknown	1 (2.4)
Total metastases	
1	23 (54.8)
2	10 (23.8)
3	5 (11.9)
4	3 (7.1)
5	1 (2.4)
Site of metastases	
Liver	2 (4.8)
Lymph node	2 (4.8)
Lung	21 (50.0)
Lung and liver	1 (2.4)
Lung and lymph node	1 (2.4)
Nonspine bone	3 (7.1)
Spine bone	10 (23.8)
Spine and nonspine bone	2 (4.8)
Timing of metastases	
Metachronous ≥24 months	24 (57.1)
Metachronous <24 months	7 (16.7)
Synchronous	11 (26.2)

(Continues)

TABLE 1 (Continued)

Variable number (%)	
Age at SBRT, mean (SD)	**61.2 (13.5)**
Pre-SBRT systemic treatment	
Cytotoxic chemotherapy	3 (7.1)
Immunotherapy	1 (2.4)
Multiple	1 (2.4)
None	37 (88.1)
Radiation parameters	
BED, mean (SD)	86.56 Gy (21.77)
ITV/GTV volume, mean (SD)*	27.28 cc (60.83)
PTV volume, mean (SD)	79.89 cc (111.67)
ITV/GTV BED, mean (SD)	107.08 Gy (26.13)
PTV BED, mean (SD)	88.49 Gy (25.97)

*SD: standard deviation

TABLE 2 Lesion level characteristics ($n = 84$)

Variable	Number (%)
Primary site[a]	
Oropharynx	41 (48.8)
Larynx	18 (21.4)
Nasopharynx	6 (7.1)
Oral cavity	5 (6.0)
Hypopharynx	10 (11.9)
Unknown primary	4 (4.8)
Site of metastases	
Liver	3 (3.6)
Lymph node/soft tissue	8 (9.5)
Lung	51 (60.7)
Nonspine bone	6 (7.1)
Spine bone	16 (19.0)
Timing of metastases	
Metachronous ≥24 months	56 (66.7)
Metachronous <24 months	12 (14.3)
Synchronous	16 (19.0)
SBRT fractionation	
20–28 Gy/1	2 (2.4)
24–28 Gy/3–5	4 (4.8)
24–31 Gy/2	5 (6.0)
30–35 Gy/3–5	13 (15.5)
40–45 Gy/4–5	1 (1.2)
50 Gy/10	11 (13.1)
50 Gy/5	48 (57.1)
Radiation parameters	
BED, mean (SD)	87.92 Gy (21.10)
ITV/GTV volume, mean (SD)[a]	14.02 cc (40.51)
PTV volume, mean (SD)	48.26 cc (75.84)
ITV/GTV BED, mean (SD)	51.83 Gy (9.28)
PTV BED, mean (SD)	48.26 Gy (75.84)

[a]Volume of irradiated GTV (or ITV if applicable in the case of liver and lung metastases) presented as mean with standard deviation.

treatment was 64 years, and 83% of the cohort were male. The most common primary site was oropharynx (43%, $n = 18$), and the majority of patients presented with either one or two metastases (78.6%). Information on HPV status was not available. The most common sites treated with SBRT were lung (60.7%) and bone (26.1%) metastases. Eleven patients (26.2%) presented with M1 disease at the time of initial diagnosis, 24 (57%) presented with OMD within 24 months of diagnosis, and 7 (16.7%) presented with OMD 24 months after initial diagnosis. Out of the 42 patients in our study, 37 (88%) were systemic therapy naive with SBRT delivered as a first line treatment. Only three patients received concomitant systemic treatment during SBRT: two patients were treated with cytotoxic chemotherapy while one patient received immunotherapy. SBRT dose and fractionation ranged from 20 in 1 fraction to 50 Gy in 5–10 fractions. The median biologic effective dose (BED)10 was 100 Gy. A summary of patient and lesion level characteristics are provided in Tables 1 and 2.

3.2 | Treated metastasis control and progression-free survival

Among 76 evaluable lesions (8 had missing data), TMC rates at 1 and 2 years were 80% and 66%, respectively (Figure 1). The median time to treated metastasis recurrence at lesion level among those who recur was 10.1 months (95% CI 7.5–14.6) as compared to 14.9 months at patient level (95% CI 10.4–14.8) (Figure S1). The median PFS, on the other hand, was only 4.7 months (95% CI 3.7–4.7) (Figure 2). BED and PTV volumes were significantly negatively correlated with each 1 cc increase in PTV size changing BED by −0.09 (−0.03 to −0.15, $p < 0.001$). MVA identified a planning target volume (PTV) BED10 > 100 Gy as a significant predictor of improved TMC (HR = 0.31, $p = 0.034$), while a cumulative PTV > 48 cc was associated with a worse PFS (HR = 2.99, $p < 0.001$) (Table 3). The timing of OMD (i.e., synchronous vs. metachronous) and number of OMD lesions were not associated with any of our outcomes of interest. The results of the UVA and MVA analysis are summarized in Table 3.

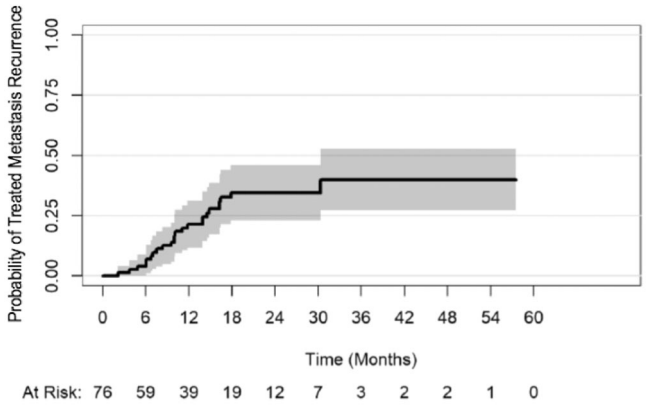

FIGURE 1 Treated metastasis control in OMD HNC lesions treated with SBRT ($n = 76$)

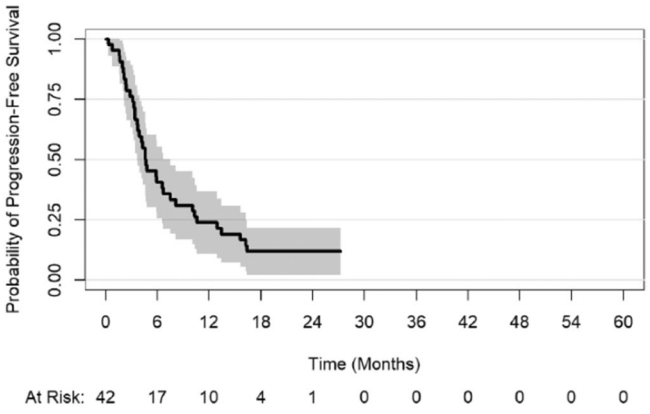

FIGURE 2 Progression-free survival in OMD HNC patients treated with SBRT ($n = 42$)

3.3 | Widespread progression survival and overall survival

The median OS in the cohort was 23.3 months (95% CI 15.2–23.3). The 1- and 3-year OS rates were 75.6% (95% CI 62.5–88.7) and 29.0% (95% CI 10.3–47.8), respectively (Figure 3). In MVA, there were no significant predictors of OS. The rates of developing WSP at 12 and 24 months were 31.7% and 48.3%, respectively (Figure 4). The median time to WSP in those who developed WSP was 10.3 months (95% CI 7.7–12.2). There were no factors identified impacting WSP, including timing and number of OMD lesions (Table S5).

3.4 | Salvage treatments

Of the 11 patients with synchronous OMD, 7 (64%) had primary site and or regional recurrences. Six were treated with surgical salvage and one with systemic therapy. Out of 25 patients with treated metastasis recurrence events, only three patients were treated with repeat SBRT (two spine, one nonspine bone), while three received conventional RT. Salvage systemic therapy with cytotoxic chemotherapy ($n = 4$) and immunotherapy ($n = 5$) was much more common. A breakdown of salvage treatments by metastatic site is presented in Table S6.

3.5 | Toxicity

Severe toxicity was rare. One patient developed a grade 3 brachial plexus injury after spine SBRT, and another a grade 3 pneumonitis after lung SBRT.

4 | DISCUSSION

In this study, we demonstrate that oligometastatic HNC patients treated with SBRT have favorable treated metastasis control (TMC) and overall survival (OS), and experience a low risk of late adverse events. The TMC rate at 1 and 2 years were 80% and 66%, respectively. Our outcomes are comparable to other heterogeneous series of OMD in HNC treated with SBRT as shown in Table S1.[16–25] We also demonstrate that a BED over >100 Gy is associated with improved TMC. In addition, a lower disease burden at baseline, with a combined PTV < 48 cc, was also associated with a reduced risk of PFS. However, PFS remains short with a median of only 4.7 months. Despite short PFS, median OS was nearly 2 years. This may reflect the efficacy of subsequent "salvage" options including systemic therapy or further SBRT.

The impact of SBRT on survival outcomes in OMD has been described across a variety of histologies and treatment sites, which have demonstrated a dose and volume response to treatment.[26-32] However, most of these studies only included a limited subset of HNC patients, and generally did not report their outcomes separately for this subgroup of patients.[12,25,31,32] In addition, the highly selected inclusion criteria may not reflect real world practice patterns and outcomes. Thus, results from these studies may not be generalizable to HNC patients and highlights ongoing uncertainty regarding the differential benefit of SBRT across cancer types (CURB, NRG BR002).[33,34] Overall, these recent randomized trials suggest that the use of SBRT may not confer a significant benefit in all patients with oligometastatic/oligoprogression and that further research is needed to fully understand the role of SBRT in this patient population and to identify potential subgroups of patients who may benefit from this treatment approach.

While SBRT has been championed in recent years due to its relative convenience and clinical success,

TABLE 3 Results of univariable and multivariable analyses for treated metastasis control, progression-free survival, and overall survival

	Univariable		Multivariable	
Variables	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Treated metastasis recurrence				
Primary site		0.144		
Oropharynx	1			
Larynx	0.9 (0.3–2.5)	0.85		
Nasopharynx	**1.9×10^{-6} (5.4×10^{-7} to 6.8×10^{-6})**	**<0.001**		
Oral cavity	2.0 (0.2–19.3)	0.55		
Hypopharynx	1.5 (0.5–5.1)	0.47		
Unknown primary	3.2 (0.2–46.2)	0.39		
Site of metastases		0.33		
Lung	1			
Lymph node/soft tissue	1.0 (0.l–9.7)	0.99		
Nonspine bone	1.9 (0.5–6.4)	0.33		
Spine bone	1.0 (0.3–3.3)	0.96		
Other	**5.8×10^{-6} (1.6×10^{-6} to 2.1×10^{-5})**	**<0.001**		
Number of metastases		0.66		
1 metastasis	1			
2 metastases	0.79 (0.2–2.5)	0.68		
>2 metastases	0.89 (0.9–2.6)	0.83		
Timing of metastases		0.82		
Metachronous ≤24 months	1			
Metachronous >24 months	0.87 (0.2–3.0)	0.83		
Synchronous	0.95 (0.2–3.5)	0.94		
ITV-GTV volume quartile[a]		0.06		
1	1			
2	0.55 (0.2–1.6)	0.28		
3	0.82 (0.3–2.0)	0.68		
4	**2.69 (1.1–6.6)**	**0.03**		
PTV volume quartile		**0.02**		
1	1			
2	1.2 (0.4–3.2)	0.71		
3	**2.38 (1.1–5.6)**	**0.04**		
4	**4.03 (1.6–10.2)**	**0.003**		
Pre-SBRT systemic treatment		0.49		
No	1			
Yes	0.54 (0.1–3.1)			
Radiation parameters				
ITV/GTV max BED > median	**0.31 (0.1–0.9)**	**0.03**	**0.31 (0.1–0.9)**	**0.03**
PTV-max BED > median	0.87 (0.4–1.9)	0.74		
ITV/GTV-mean BED > median	0.61 (0.2–1.7)	0.33		
PTV-mean BED > median	0.78 (0.3–2.0)	0.61		
Progression-free survival				
Primary site		**0.04**		

TABLE 3 (Continued)

	Univariable		Multivariable	
Variables	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Oropharynx	1			
Larynx	0.94 (0.5–1.9)	0.87		
Nasopharynx	0.25 (0.04–1.4)	0.12		
Oral cavity	**3.43 (1.3–9.2)**	**0.01**		
Hypopharynx	**2.03 (0.9–4.2)**	**0.06**		
Unknown primary	**2.88 (0.9–8.7)**	**0.06**		
Site of metastases		0.54		
Lung	1			
Lymph node/soft tissue	2.1 (1.0–4.4)	0.99		
Nonspine bone	1.8 (0.8–3.9)	0.17		
Spine bone	1.8 (0.7–4.4)	0.21		
Other	1.2 (0.2–6.3)	0.81		
Number of metastases		0.80		
1 metastasis	1			
2 metastases	1.18 (0.6–2.2)			
>2 metastases	1.31 (0.5–3.2)			
Timing of metastases		0.94		
Metachronous ≤24 months	1			
Metachronous >24 months	0.93 (0.3–2.5)			
Synchronous	0.88 (0.4–1.9)			
ITV-GTV volume quartile		**0.04**		
1	1			
2	0.55 (0.2–1.6)	0.28		
3	0.82 (0.3–2.0)	0.68		
4	**2.69 (1.1–6.6)**	**0.03**		
PTV volume quartile		**0.02**		
1	**1**		1	
2	1.2 (0.4–3.2)	0.71	1.2 (0.4–3.2)	0.71
3	**2.38 (1.1–5.6)**	**0.04**	**2.38 (1.0–5.6)**	**0.04**
4	**4.03 (1.6–10.2)**	**0.003**	**4.0 (1.6–10.2)**	**0.003**
Pre-SBRT systemic treatment				
No	1	0.67		
Yes	0.79 (0.3–2.3)			
Radiation parameters				
ITV/GTV max BED > median	0.79 (0.4–1.6)	0.53		
PTV-max BED > median	**0.55 (0.3–1.0)**	**0.07**		
ITV/GTV-mean BED > median	0.68 (0.3–1.4)	0.31		
PTV-mean BED > median	0.81 (0.4–1.5)	0.52		
Overall survival				
Primary site		**0.06**		
Oropharynx	1			
Larynx	1.11 (0.4–3.0)	0.84		

(Continues)

TABLE 3 (Continued)

	Univariable		Multivariable	
Variables	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Nasopharynx	0.28 (0.03–2.4)	0.24		
Oral cavity	**6.15 (2.3–16.7)**	**0.003**		
Hypopharynx	1.71 (0.4–6.5)	0.43		
Unknown primary	1.94 (0.3–10.6)	0.45		
Site of metastases		0.54		
Lung	1			
Lymph node/soft tissue	2.1 (1.0–4.4)	0.99		
Nonspine bone	1.8 (0.8–3.9)	0.17		
Spine bone	1.8 (0.7–4.4)	0.21		
Other	1.2 (0.2–6.3)	0.81		
Number of metastases		0.70		
1 metastasis	1			
2 metastases	1.11 (0.4–2.7)			
>2 metastases	1.51 (0.6–3.7)			
Timing of metastases		0.90		
Metachronous ≤24 months	1			
Metachronous >24 months	1.31 (0.38–4.52)			
Synchronous	1.06 (0.39–2.9)			
ITV-GTV volume quartile		0.14		
1	1			
2	0.46 (0.1–1.8)	0.27		
3	0.89 (0.3–2.3)	0.80		
4	2.37 (0.6–9.0)	0.21		
PTV volume quartile		0.31		
1	1			
2	1.83 (0.6–5.3)	0.27		
3	1.53 (0.5–4.7)	0.46		
4	2.9 (0.8–9.9)	0.09		
Pre-SBRT systemic treatment				
No	1	0.59		
Yes	1.69 (0.5–5.9)			
Radiation parameters				
ITV/GTV max BED > median	1.84 (0.7–4.6)	0.19		
PTV-max BED > median	1.32 (0.6–2.9)	0.48		
ITV/GTV-mean BED > median	1.86 (0.7–4.5)	0.17		
PTV-mean BED > median	1.51 (0.7–3.3)	0.31		

Note: Bold indicates $p < 0.05$.

[a]Volume of irradiated GTV (or ITV if applicable in the case of liver and lung metastases) presented as quartiles.

surgery has also been studied in this population. For instance, a systematic review and meta-analysis of 13 studies comprising 403 HNC patients treated with pulmonary metastectomy for metachronous OMD showed an excellent 5 year OS of 29.1%.[11] Consistent with these results, Wedman et al. demonstrated a 5-survival rate of 59% in HNC patients treated with metastectomy as compared to 4% in the nonmetastectomy group.[34] Thus, while

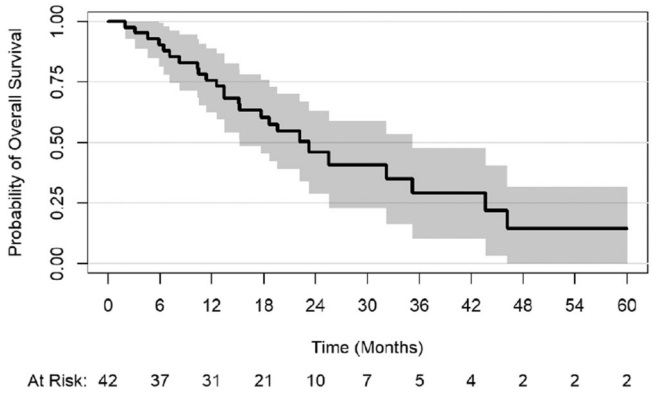

FIGURE 3 Overall survival in OMD HNC patients treated with SBRT ($n = 42$)

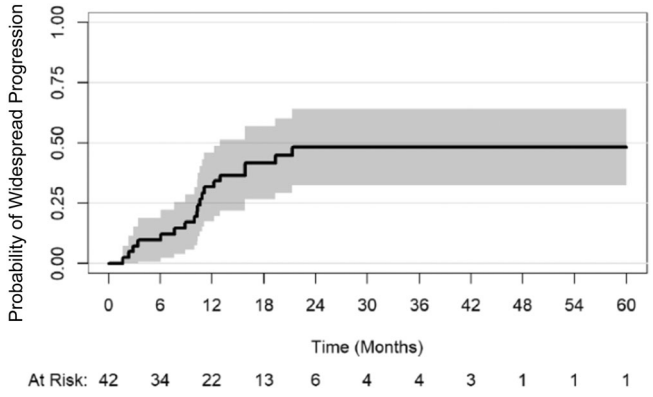

FIGURE 4 Widespread progression in OMD HNC patients treated with SBRT ($n = 42$)

metastectomy appears to improve outcomes in HNC patients with OMD, surgery is likely to be best suited for a patient population with a limited number of metastases and good performance status. In contrast, SBRT offers several inherent advantages, including patient convenience, lower risk of morbidity in patients with advanced age and comorbidities, lack of surgical recovery time, and ability to target multiple sites of disease. In addition, emerging data suggests comparable results to invasive surgery. For instance, Pasalic et al. demonstrated that SBRT for HNC patients results in a 2-year OS comparable to pulmonary metastasectomy.[22] While there are no randomized controlled trials that have compared outcomes between SBRT and metastasectomy in HNC patients, optimal management of HNC patient with OMD ought to include a multi-disciplinary approach weighing performance status, patient preference, co-morbidities, prior treatments, burden and location of disease, and histology.

Risk factors associated with poor outcomes in HNC patients treated with either surgery or SBRT for OMD include but are not limited to patient age, sex, oral cavity or sinonasal primary, tumor volume, incomplete resection of pulmonary nodules, BED of metastasis-directed SBRT, number of metastases, and absence of bone or brain metastases.[19,22,23,33–41] For instance, in studies by Shiono and Nibu et al., patients with oral cavity cancer treated with metastectomy had a worse 5-year OS as compared with other sites (9.2% vs. 32.4% and 15.4% vs. 45.2%, respectively).[37,39] Multiple studies have also demonstrated improved outcomes in HNC patients with single metastases as compared to those with polymetastatic disease (>5 metastases).[36] In addition, a BED >100 Gy ($a/b = 10$) was shown to correlate with TMC in a study of 51 patients treated with SABR for pulmonary metastases.[23]

In our analysis, we confirm the robustness and clinical relevance of the aforementioned risk factors by demonstrating that a BED over >100 Gy and a lower disease burden at baseline, with a combined PTV < 48 cc, were associated with improved TMC and PFS, respectively. It is possible that the slightly lower rates of TMC observed in our cohort reflects the multiplicity of histologies and metastatic sites analyzed along with their varying degrees of radio-sensitivity. As standard of care treatments produce varying outcomes in the curative nonmetastatic HNC setting, the potential benefits of SBRT in the oligometastatic setting may differ among the HN subsites. The type of radiation used and response to subsequent salvage treatment may also contribute to differences in TMC rates. Future studies should identify patient subgroups that are likely to benefit most from SBRT, taking into account factors such as tumor histology, location and size, and prior treatments received.

In the setting of synchronous disease, radical treatment of primary site has been shown to confer a survival benefit in OMD nasopharyngeal cancer, at the cost of increased toxicity.[42] Furthermore, much of the data supporting oncologic advantages of ablative treatments to date have required controlled primary disease.[43-46] While no randomized evidence exists to support the aggressive treatment of primary disease in other subsites, the potential morbidity and mortality of poorly controlled primary disease likely plays a role in HNC patients with OMD.

Compared to previous studies, our analysis benefits from availability of radiation treatment parameters (e.g., RT dose, PTV size) and associated clinical outcomes. However, our study had several limitations including a low sample size as well as incomplete documentation of clinical variables and heterogeneous HNC populations. Differences in referral patterns and treatment preferences could have also resulted in selection bias, while variability in diagnostic tests, treatment techniques and follow-up period between treating centers introduces additional uncertainty. The high proportion of lung metastases in our series, with limited pathologic

confirmation in a population with overlapping risk factors also raises the question of whether some of these lesions are truly HNC OMD, or a new lung primary. In addition, SBRT treatment standards may have evolved through the follow-up period. We also did not consider molecular markers or genetic alterations such as HPV status which may impact outcomes in HNC. Finally, our study was limited by the scope of our toxicity reporting with only grade 3 and higher adverse events collected. More mature follow-up is also required to fully assess the risk of severe late toxicity post-SBRT.

In summary, we show that SBRT is an effective and well-tolerated treatment in OMD HNC patients with a relatively favorable TMC and OS. However, the poor PFS observed suggests the need for more effective systemic treatments to control distant failure.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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