CLINICAL INVESTIGATION

A multi-institutional analysis of outcomes following stereotactic body radiation therapy for management of metastases from squamous cell carcinomas of the head and neck

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ABSTRACT

Background: There is limited data on clinical outcomes following SBRT for patients with metastatic head and neck squamous cell carcinoma (mHNC).

Method: An international SBRT registry was utilized to identify patients. LC and OS were evaluated with the Kaplan-Meier method and a Cox-proportional hazards model for multivariate analysis (MVA) to assess potential prognostic factors.

Results: We identified 81 patients with 98 lesions treated with SBRT. Areas treated included the lung (53.0%), non-regional lymph nodes (16.0%), and spine (12.3%). OS rates at 1 year and 2 years were 66.4% and 43.1%, respectively. Utilizing KPS, spinal disease, and GTV, 1-year OS estimates were 90.9%, 70.4%, 54.5%, and 25% for patients with 0-3 of these factors, respectively (p = 0.002). One-year and 2-year LC rates were both 93.3%. Roughly 17% of patients reported toxicities (none Grade 3+).

Conclusion: SBRT resulted in promising LC for mHNC patients. Spinal disease, GTV, and KPS should be considered in selecting patients with mHNC that may benefit from SBRT.

Keywords: Stereotactic body radiation therapy, ablation, oligometastasis, registry, overall survival, local control

INTRODUCTION

Head and neck squamous cell carcinoma (HNC) is a locally aggressive malignancy with a tendency to metastasize to pulmonary, hepatic, and osseous sites in roughly 20-30% of cases (depending on the extent of nodal disease at diagnosis) [1-2]. Historically, median overall survival (OS) for patients with metastatic HNC (mHNC) has been quite poor at roughly 10 months with platinum-based systemic therapy and cetuximab [3]. More recently, the addition of immunotherapy has been noted to significantly improve OS, though prognosis is still quite poor with a median OS of approximately 15 months [4]. Generally, the role of radiation therapy in the setting of mHNC has been palliative in nature with prior studies noting durable pain responses following hypofractionated regimens [5].

However, there has been a paradigm shift over the past few years in the management of patients with oligometastatic disease either at initial presentation or at the time of recurrence [6]. Notably, stereotactic body radiation therapy (SBRT) has recently emerged as an effective and well-tolerated treatment modality for local ablation of metastatic lesions generally delivered in 1-5 fractions. Recent randomized clinical trials have noted significant OS benefits with the addition of SBRT to systemic therapy for patients with oligometastatic disease; however, only approximately 10% of patients had mHNC [7]. Currently, there is a lack of significant prospective evidence on the potential benefit of SBRT for patients with mHNC [8-9].

As the role of SBRT in the management of patients with mHNC continues to grow, further data is needed to guide optimal patient selection. The RSSearch Patient Registry (RSSPR) is a multi-institutional, international database with clinical information for patients treated with SBRT at both academic and community-based radiotherapy centers. With information on close to 30,000 patients, the RSSPR has previously been utilized to examine outcomes for numerous types of malignancies treated with SBRT [10-12]. With the RSSPR, we aimed to examine OS, local control (LC), and treatment-related toxicities for patients with mHNC treated with SBRT and evaluate potential prognostic factors associated with favorable OS.

MATERIALS AND METHODS

The methodology employed in prior analyses of the RSSPR has previously been discussed [10-12]. Regarding the registry, in brief, all international radiotherapy centers treating patients with SBRT are able to join the Registry and prospectively enroll patients after obtain-ing local Institutional Review Board/Ethics Committee (IRB/EC) approval. Informed consent is required to be obtained from all patients prior to inclusion in the registry. Radiotherapy planning was performed per individual institution guidelines using inverse planning on the MultiPlanSystem® (Accuray Incorporated, Sunnyvale, CA). All patients included for analysis were treated using the CyberKnife® Radiosurgery System.

We examined the registry for adult patients with mHNC treated with SBRT from the inception of the registry to February 2020. To be included in this study, information was required to be available on age, Karnofsky Performance Score (KPS), lesion location and treated gross tumor volume (GTV), primary tumor location, OS, prescription dose, and fractionation schedules. LC was examined by either positron-emission tomography (PET)/computed tomography (CT), magnetic resonance imaging (MRI), or CT alone per individual institutional preference. Treatment-related toxicities were graded based on Common Terminology Criteria for Adverse Events (CTCAE) guidelines.

Descriptive analysis was utilized to provide statistical summaries of relevant patient, treatment, and lesion characteristics. The Kaplan-Meier method with time-to-event analysis and the log-rank t-test was employed to evaluate potential prognostic factors of LC and OS (including age, doses and fractionation employed, initial KPS, GTV, tumor and primary cancer location, and biologically equivalent dose (BED)). A Cox-proportional hazards model was utilized for multivariate analysis (MVA) with a forward entry parsimonious method for independent variable selection including variables noted to approach significance ($p<0.10$) on univariate analysis (UVA). Dose escalation was defined as $BED_{10} \geq 90 \ Gy_{10}$ based on the median BED of the cohort and $\geq 100 \ Gy_{10}$ based on prior studies noting a LC benefit for primary lung cancers treated with BEDs $\geq 100 \ Gy_{10}$ and lung metastases comprising the greatest proportion of lesions treated [13]. The linear quadratic model was utilized to determine respective BEDs with an assumed alpha-beta ratio of 10. Dose escalation was also examined based on the dose per fraction, with a cutoff of 10 Gy as well as 12 Gy examined based on the median dose per fraction. Potential correlations between toxicity and dose escalation was analyzed via logistic regression.

RESULTS

Patient, treatment, and lesion characteristics

A summary of the cohort's demographic data, radiotherapy planning, and lesion characteristics can be found

Table 1. Summary of patient and lesion characteristics and radiotherapy planning

Variable	
Gender	56 male patients
	25 female patients
Median Age (years) (range)	68 (18 – 101)
Race	*Caucasian* – 72 patients
	African-American – 4 patients
	Other/Unknown – 5 patients
Median Initial KPS (range)	90% (40%-100%)
Median Initial GTV (cc) (range)	25 (1.20 - 70)
Primary Site	*Oral Cavity* – 33 patients
	Oropharynx – 20 patients
	Larynx – 19 patients
	Hypopharynx – 6 patients
	Nasopharynx – 3 patients
Location of Treated Metastasis	*Lung* – 43 patients
	Non-regional mediastinal lymph nodes – 12 patients
	Spine/Vertebral Body– 10 patients
	Liver and Intrahepatic Bile Ducts – 3 patients
	Floor of mouth – 3 patients
	Non-spinal bone metastases – 2 patients
	Heart, Mediastinum, and Pleura – 2 patients
	Oropharynx – 2 patients
	Non-regional para-aortic lymph node – 1 patient
	Other Distant Metastatic Site– 3 patients
Median number of fractions (range)	5 (1 – 5)
Median dose per fraction (Gy) (range)	10 (6-22)
Median Prescription Dose (Gy) (range)	*1 fraction* (n = 2): 22 (20-24)
	3 fractions (n = 23): 50 (21 – 60)
	4 fractions (n = 13): 48 (40 – 60)
	5 fractions (n = 43): 37.5 (30 – 60)
Median BED$_{10}$ (Gy$_{10}$) (range)	*Entire cohort* (n = 81): 92.2 (35.7–180)
	1 fraction (n = 2): 60.4 (50.4–70.4)
	3 fractions (n = 23): 133.33 (35.7–180)
	4 fractions (n = 13): 105.6 (80–150)
	5 fractions (n = 43): 65.63 (48–132)
Treatment response at last radiographic follow-up (n = 49) (patients)	*Complete Response:* 18.4% (9 patients)
	Partial Response: 20.4% (10 patients)
	Stable Disease: 20.4% (10 patients)
	LC with Distant Metastasis: 32.7% (16 patients)
	Local Failure Alone: 2.0% (1 patient)
	Local Failure and Metastasis: 6.1% (3 patients)
Median time to local progression (n = 4) (months) (range)	18.7 (6.3– 25.6)

in **Table 1**. A total of 81 patients met inclusion criteria with 98 lesions treated (49 lesions had LC information). The median age of patients was 68 years (range: 18-101). Roughly 90% of patients in the cohort were of Caucasian ethnicity with a median pre-treatment KPS of 90% (range: 40-100%). Regarding primary sites, 33, 20, and

19 patients had primary cancers of the oral cavity, oropharynx, and larynx, respectively. Commonly treated areas included the lung (43 patients), non-regional lymph nodes (13 patients), and osseous disease of the spine (10 patients). Median GTV was 25.0 cc (range: 1.20-70.1). **Table 1** also describes radiographic responses at patients' last follow-up, with most patients noted to have LC of the treated metastatic site after SBRT (91.8%).

The median prescription dose was 45 Gy (range: 20-60 Gy) and the median number of fractions was fractions (range: 1-5 fractions). The median BED_{10} was 92.2 Gy_{10} (range: 35.7–180), and the median dose per fraction of 10 Gy (range: 6-22 Gy). Two patients were treated with 1 fraction (median prescription dose: 22 Gy (range: 20-24 Gy)), 23 patients were treated with 3 fractions (median prescription dose: 50 Gy (range: 21-60 Gy)), 13 patients were treated with 4 fractions (median prescription dose: 48 Gy (range: 40-60 Gy)), and 43 patients were treated with 5 fractions (median prescription dose: 37.5 Gy (range: 30-60 Gy)).

Overall Survival

In Table 2, one can find examination of correlations between OS and potential prognostic factors. Following SBRT, 1-year and 2-year OS rates were 66.4% (95% CI: 53.4-76.4%) and 43.1% (95% CI: 30.3-55.2%), respectively. Both initial KPS and GTV were significantly correlated with OS on UVA. Patients with KPS ≥ 90% had a higher 1-year OS compared to those with a KPS of < 90% (88.0% vs. 41.0%; $p = 0.02$). Those with GTVs treated with SBRT that were ≥25cc also had lower 1-year OS compared to those with GTVs < 25 cc (81.9% vs. 61.4%; p=0.02; **Figure 1**). With regards to treated locations, patients that had spinal metastases treated with SBRT had lower 1-year OS spinal metastases (67.3% vs. 60.0%; p=0.11) as did those with non-regional lymph node metastases (71.4% vs 43.3%; $p = 0.06$) that were not statistically significantly different.

Based on the results of UVA, treated metastasis location (either spinal or non-regional lymph nodes), KPS, and GTV were included for MVA. Following MVA, only the presence of spinal metastatic disease maintained statistical significance (hazard ratio (HR) = 2.00 (95% CI: 1.03-3.80); p=0.04). Other factors examined including GTV (HR = 1.83 (95% CI: 0.87-3.89); p = 0.11), KPS (HR = 1.45 (95% CI: 0.78-2.71; p = 0.24), and presence of non-regional lymph node metastases (HR = 1.49 (95% CI: 0.65-3.42); p = 0.35) were not statistically significantly correlated with OS. When examining the prognostic significance of spinal metastases, KPS < 90%, and GTV ≥ 25 cc, patients with combined scores of 0 (no spinal disease, KPS ≥ 90%, GTV < 25cc), 1 (spinal disease, KPS < 90%, or GTV ≥ 25 cc),

Table 2. Kaplan-Meier Analysis of potential prognostic factors for OS following SBRT

| Variable	No. Patients	1-year OS Rate (95% CI)	Median OS (months)	p-value
BED$_{10}$				
< 90 Gy$_{10}$	33	65.9% (46.9-79.5%)	21.4	0.44
≥ 90 Gy$_{10}$	48	66.9% (48.6-80.0%)	21.1	
< 100 Gy$_{10}$	34	63.9% (45.2-77.7%)	21.4	0.33
≥ 100 Gy$_{10}$	47	69.1% (50.7-81.8%)	21.4	
Dose per fraction				
< 10 Gy	26	61.1% (39.7-76.9%)	22.2	0.55
10-12 Gy	23	73.7% (47.7-88.2%)	22.6	
> 12 Gy	32	66.9% (43.8-82.2%)	17	
Primary Location				
Oral Cavity	33	62.0% (41.8-76.9%)	18.2	0.28
Oropharynx	20	67.1% (40.7-83.8%)	15.9	0.78
Larynx	19	66.3% (39.3-83.4%)	21.4	0.71
Lesion Location				
Lung	43	69.3% (50.0–82.3%)	26.6	0.09
Non-Regional Lymph Nodes	13	43.3% (16.3–67.9%)	10.93	0.06
Spine/ Vertebral Body	10	60.0% (25.3–82.7%)	18.2	0.11
Age				0.77
< 70 years	42	65.9% (47.6–79.1%)	23.1	
≥ 70 years	39	67.3% (48.4–80.5%)	15.9	
GTV				0.02
< 25 cc	18	81.9% (53.8–93.8%)	35	
≥ 25 cc	63	61.4% (46.5–73.4%)	15.9	
Initial KPS				0.02
< 90%	28	44.0% (24.1-62.2%)	8.7	
≥ 90%	53	80.0% (63.3-88.6%)	25.7	
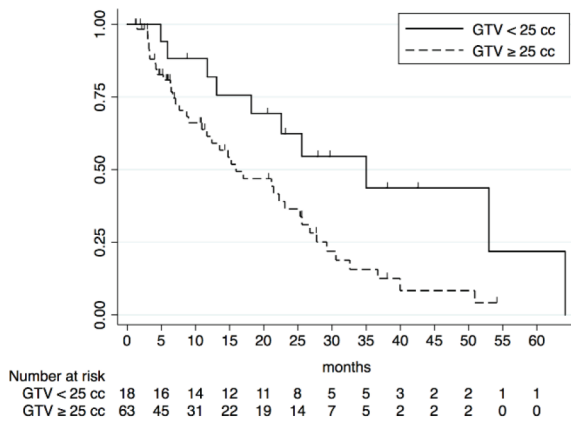
Figure 1. Kaplan-Meier curves examining OS based on treated gross tumor volume (GTV).
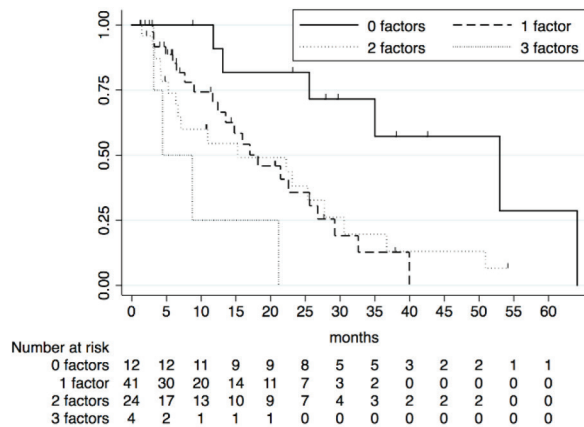

Figure 2. Kaplan-Meier curves examining OS based on initial patient Karnofsky Performance Score (KPS), treated gross tumor volume (GTV), and presence of spinal metastatic disease.

Table 3. Kaplan-Meier Analysis of potential prognostic factors for LC following SBRT

Variable	No. Lesions	1-year LC rate (95%CI)	p-value
BED_{10}			
< 90 Gy_{10}	18	100% (N/A)	0.09
≥ 90 Gy_{10}	31	88.0% (59.4-96.9%)	
< 100 Gy_{10}	19	100% (N/A)	0.09
≥ 100 Gy_{10}	30	88.0% (59.4-96.9%)	
Dose per fraction			
< 10 Gy	16	100% (N/A)	0.22
10-12 Gy	17	82.5% (46.1-95.3%)	
> 12 Gy	16	100% (71.9-99.4%)	
Primary Location			
Oral Cavity	15	83.3% (27.3-97.5%)	0.90
Oropharynx	20	93.4% (63.2-99.1%)	0.75
Larynx	13	100% (N/A)	0.89
Lesion Location			
Lung	28	88.9% (61.8-97.2%)	0.11
Non-Regional Lymph Nodes	8	100% (N/A)	0.44
Spine/Vertebral Body	3	100% (N/A)	0.72
Age			0.33
< 70 years	26	87.7% (58.1-96.9%)	
≥ 70 years	23	100% (N/A)	
GTV			0.74
< 25 cc	14	88.9% (43.3-98.4%)	
≥ 25 cc	35	96.2% (75.7–99.5%)	
Initial KPS			0.76
< 90%	19	91.7% (53.9-98.8%)	
≥ 90%	30	94.7% (68.1-99.2%)	

2 (2 of the noted factors), or 3 (3 of the noted factors) had 1-year OS rates of 90.9%, 70.4%, 54.5%, and 25% (**Figure 2**; $p = 0.002$), respectively.

Examination of potential correlation between radiation therapy planning and OS can also be seen in **Table 2.** No significant difference in median OS was noted between patients treated to a $BED_{10} ≥ 90$ Gy_{10} (21.1 vs. 21.4 months; $p = 0.44$) or a $BED_{10} ≥ 100$ Gy_{10} (21.4 months in both arms; $p = 0.33$). Similarly, no difference in OS was noted with dose escalation between examinations of < 10 Gy, 10-12 Gy, and > 12 Gy ($p = 0.55$).

Local Control

Table 3 shows analysis of potential correlations between variables of interest and LC. Both 1-year and

2-year LC rates were 93.3% (95% CI: 75.4-99.3%), and the 3-year LC rate was 76.4% (95% CI: 44.7-91.4%) (**Figure 3**). Treated metastases from oral cavity primaries had a 1-year LC of 83.3% vs. 96.0% ($p= 0.90$) with comparable 1-year LC rates between treated metastases from larynx (100%) and oropharyngeal (93.4%) primaries. GTV was not associated with LC following SBRT with 1-year LC of 96.2% in patients with treated GTVs ≥ 25cc compared to 88.9% for those with treated GTVs < 25 cc ($p = 0.74$). Pulmonary metastases treated with SBRT had a 1-year LC rate of 88.9% vs. 100% for non-pulmonary metastases that was not significantly different on UVA ($p = 0.11$).

With regards to the impact of radiation therapy planning, we did not identify a correlation between either prescription dose dose or fractionation schedule and LC. No statistically significant dose response was noted
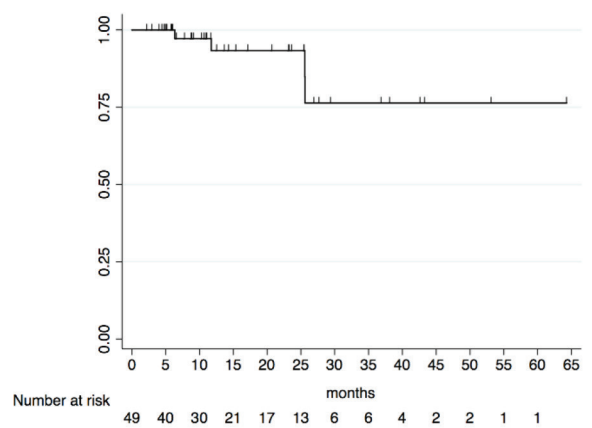
Figure 3. Kaplan-Meier curve examining LC following SBRT.

for BED_{10} at dose cutoffs of either 90 Gy_{10} or 100 Gy_{10} on UVA (100% vs. 88.1% and $p = 0.09$ for both dose examinations). Similarly, dose per fraction at cutoffs of < 10 Gy, 10-12 Gy, or > 12 Gy were not correlated with 1-year LC ($p = 0.22$). As no potential prognostic factors of LC were noted on UVA, an MVA analysis was not pursued with respect to LC.

Toxicities

Incidences of acute and late toxicities were relatively low at 17.3% (14 patients). Roughly 80% and 20% were acute and late toxicities, respectfully. All toxicities were either Grade 1-2 (64.3% were Grade 1 (9 patients) and 35.8% were Grade 2 (5 patients)). With regards to Grade 2 toxicities, the majority were fatigue (3/5) with one case of Grade 2 nausea following treatment of a non-regional lymph node metastasis. Dose escalation was not significantly correlated with toxicity incidence with either BED_{10} at cutoffs of 90 Gy_{10} ($p = 0.48$) or 100 Gy_{10} ($p = 0.57$) or higher doses per fraction at cutoffs of 10 Gy ($p = 0.64$) or 12 Gy ($p = 0.53$).

DISCUSSION

Currently, mHNC is associated with a poor prognosis despite recent advancements such as the addition of immunotherapy to the backbone of management [4]. However, for patients with limited disease burden at either initial presentation or at time of recurrence, SBRT may allow for more durable responses with first-line systemic therapy and potentially prolong OS based on recent studies [7]. To our knowledge, this cohort represents the largest multi-institutional experience

reported on SBRT specifically for patients with mHNC. LC was excellent and exceeded 90% at one and two years. Notably, a subset of patients with favorable KPS, smaller irradiated metastatic lesions, and lack of spinal osseous metastatic disease had quite favorable 1-year OS of roughly 70-90%. These results suggest in line with prior literature that carefully selected patients may derive significant benefit from aggressive ablative therapies of metastatic deposits in addition to standard-of-care systemic therapy.

Prior experiences examining outcomes specific to patients with mHNC following SBRT have noted similar outcomes to our findings (**Appendix 1**). Bonomo et al. have reported their experience for 27 patients with limited pulmonary metastases (1-5 lesions in the lung) treated with SBRT, with roughly 80% of patients having oligometastatic disease. The median time to progression was 10 months following SBRT, and primary tumor size was correlated with time to progression. Similar to our analysis, SBRT was well-tolerated with approximately 15% of patients having Grade 1 or Grade 2 toxicities [14]. Another analysis of patients with mHNC with pulmonary metastatic disease treated with SBRT noted excellent 2-year LC and 2-year OS of 94.4% and 61.6%, respectively, with no Grade 3 toxicities [18]. Regarding patients strictly with oligometastatic disease, Franzese et al. noted 1-year and 2-year LC rates of 83.1% and 70.2%, respectively, following SBRT to 71 lesions among 48 patients and 1-year and 2-year OS rates of 81.0% and 67.1% with non-lung metastases and poorer performance status associated with poorer OS. Bates et al. noted somewhat poorer results in a more favorable population of 27 patients with oligometastatic mHNC with 60 lesions treated with SBRT. Following SBRT, lower 2-year LC rates (57%) were noted with a more rapid median time to progression (0.5 years) and a 2-year OS rate of 43% [20].

Only one prospective trial has been reported examining the role of SBRT in the management of patients with mHNC [8]. McBride et al. conducted a randomized trial of unselected mHNC patients to examine whether SBRT to 27 Gy/3 fractions in combination with nivolumab led to an abscopal effect or a decrease in the size of a non-radiated lesion following ablation of another metastatic site. As such, it was required that patients had at least two lesions that could be radiographically followed after SBRT to assess for radiographic response. Patients were randomized to nivolumab alone (30 patients) or nivolumab and SBRT (32 patients). Similar to our analysis, the most common metastatic sites treated with SBRT were the lung (58.1%), lymph nodes (16.1%), and bone (12.9%). No difference was noted in the response rate of non-radiated lesions either with or without SBRT. Following the addition of SBRT to nivolumab, neither an OS benefit nor a longer duration of response was noted

with a significant increase in incidence of Grade 3-5 toxicities.

A number of prospective studies are currently underway examining the combination of immunotherapy and SBRT. Bahig et al. have previously published their Phase I/II protocol with an aim to enroll 35 patients with 2-10 extracranial metastases that will be treated with both durvalumab and tremilimumab in addition to SBRT to 2-5 metastases in between cycles 2 and 3 of immunotherapy with a primary endpoint of progression-free survival [9]. Also, KEYNOTE-717 will be examining in a randomized fashion the potential benefit of the addition of SBRT (36 Gy/3 fractions to 1-3 metastatic lesions) to pembrolizumab with systemic therapy started on the final day of SBRT with an accrual goal of 130 patients and primary endpoint of objective response rate.

Other studies have aimed to better define subsets of patients with mHNC with favorable OS to better inform clinical trial design. An analysis by Fleming et al. identified 82 patients with human papilloma virus (HPV)-associated oropharyngeal mHNC. Pulmonary metastases were the most common site among patients (74%) followed by bone (28%), and liver (12%). Similar to findings for patients with locoregionally advanced oropharyngeal HNC, smoking status was significantly associated with OS with never-smokers having a median OS of 37.6 months compared to 11.2 months in patients with a smoking history (p=0.006). In addition, the number of metastatic lesions also correlated with OS. Patients with one metastasis had a median OS of 41.2 months compared to 17.2 months for patients with 2-4 metastases and 10.8 months for patients with 5 or greater metastases[15]. These findings, in addition to those noted in our study of GTV, KPS, and spinal metastatic disease, merit consideration in future trial design to guide optimal patient selection for SBRT.

Also when considering SBRT in the management of patients with oligometastatic is the question of both cost and benefit for both the patient as well as the healthcare system. Prior cost-effectiveness and quality-adjusted analyses have noted a benefit to the addition of SBRT to systemic therapy both from health sector and societal perspectives [16]. Particularly with respect to pulmonary oligometastases, the recently reported randomized SAFFRON II study that compared 28 Gy/1 fraction to 48 Gy/4 fractions noted no significant difference in Grade 3 toxicities between either arm [17]. Our series did not show differences in LC between different SBRT fractionation schedules, and longer term follow-up from SAFFRON II with respect to durable LC as well as late toxicities will inform the optimal fractionation schedule for treatment of pulmonary metastases.

There are notable limitations to this study which merit attention. First, the relatively small sample size of our study limits the generalizability of our findings. No information was available in the registry regarding the extent of disease at the time SBRT was offered (i.e. oligometastatic or polymetastatic and volume of disease), HPV and smoking status, time from initial primary treatment to metastatic recurrence, whether patients had synchronous or metachronous metastatic disease at the time of SBRT and whether such sites were considered oligoprogessive or oligorecurrent, whether patients were treated for symptoms (i.e palliative intent SBRT to osseous disease for pain) or for durable LC, and which systemic treatments had been utilized prior to, during, or following SBRT. We also did not have robust information on whether patients had primary disease treated in addition to metastatic sites at time of diagnosis. Also, dosimetric information of interest such as prescription isodose line, volume of the GTV receiving certain doses, and mean dose to the GTV were unavailable, which limited dosimetric evaluations of LC. Also, there is the potential for improper reporting of data given the retrospective nature of our study. Finally, given variable and non-uniform follow-up across different institutions, there is a risk of a lower estimate of toxicity incidence following SBRT.

CONCLUSION

Favorable patient outcomes and low toxicity rates were noted following SBRT for patients with mHNC. Spinal osseous metastases, larger treated metastases, and lower performance statuses were correlated with poorer OS. No significant LC benefit was found with dose escalation. Prospective randomized clinical trials are warranted to further elucidate the role of SBRT for patients with mHNC, with this analysis suggesting the significance of non-spinal metastases, smaller GTVs, and patients with excellent performance status as a more favorable cohort of mHNC patients that warrant consideration in future trial design.

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Ethics

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained for all patients that participated in the RSSearch Patient Registry.

Author contributions

Conception and design: Raj Singh, Joanne Davis, Shiyu Song, Sanjeev Sharma, John Austin Vargo
Data collection: Jan Jenkins, Joanne Davis
Data analysis and interpretation: Raj Singh, John Austin Vargo
Manuscript writing: Raj Singh
Final approval of manuscript: Joanne Davis, Shiyu Song, Sanjeev Sharma, John Austin Vargo

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Appendix 1. Summary of prior experiences of SBRT for mHNC

Study	Number of Patients (Lesions)	Dose/ Fractiona-tion	Sites Treated and GTV	LC	OS	Toxicity	Notes
Bonomo, et al.[14]	27 (28)	25%: 54 Gy/ 3 fractions 17.6%: 55 Gy/ 5 fractions 14.3%: 50 Gy/ 5 fractions 2 lesions treated with 15 fractions	Pulmonary only metastases Median GTV: 22.7cc	3-month response rate: 75%	Median OS: 47 months	No Grade 3 or greater acute or late toxicities	Pulmonary-only oligometastases (1-5 sites) Median time to disease progression: 10 months
Pasalic, et al.[18]	82 (107) 64% were SCCs	73.8%: 50 Gy/4 fractions 19.6%: 70 Gy/10 fractions	Pulmonary only metastases Median GTV: 3.6cc	2-year: 94%	2-year: 62% (72% oligometastatic; 44% polymetastatic)	No Grade 3 or greater acute or late toxicities	Oligometastatic or polymetastatic included
Franzese, et al.[20]	48 (71) 26/48 patients had SCC	Median dose: 48 Gy/4 fractions Range: 21-75 Gy/3-8 fractions	59.1% were lung metastases	1-year: 83.1% 2-year: 70.2%	1-year: 81% 2-year: 67.1%	No Grade 3 or greater acute or late toxicities	Oligometastatic disease (1-5 sites total) in a maximum of 2 organs
Bates, et al.[20]	27 (60)	Majority treated to 50 Gy/5 fractions	44/60 pulmonary metastases 60% with lesion volumes < 5cc	1-year: 75% 2-year: 57%	1-year: 78.1% 2-year: 43%	N/A	Oligometastatic disease (1-5 sites total) Median time to disease progression: 6 months
McBride, et al.[8]	30 (53): Nivolumab alone 32 (47): Nivolumab and SBRT	27 Gy/ 3 fractions	SBRT arm: Lung: 17 Liver: 10 Lymph Node: 9 Other: 9 Bone: 2	N/A	1-year: Nivolumab alone: 50.2% Nivolumab and SBRT: 54.4%	Grade 3-5 toxicities: 13.3% (nivolumab alone) vs. 9.7% (nivolumab and SBRT)	Objective response rate of *non-irradiated* lesions: 34.5% vs. 29.0%