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CLINICAL INVESTIGATION

Pulmonary Stereotactic Body Radiation Therapy of Oligometastatic Head-and-Neck Squamous Cell Carcinoma: A Multicenter Retrospective Study

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Purpose: The value of stereotactic body radiation therapy (SBRT) in patients with oligometastatic head-and-neck squamous cell carcinoma (HNSCC) remains unclear, as existing evidence is primarily derived from retrospective single-center analyses with small patient cohorts. This study aimed to evaluate the outcomes of pulmonary SBRT in patients with oligometastatic HNSCC and to identify factors associated with survival.

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Methods and Materials: This trinational multicenter cohort study, including 16 centers from Germany, Austria, and Switzerland, retrospectively analyzed patients with oligometastatic HNSCC undergoing SBRT for pulmonary metastases between 2010 and 2023. The primary outcome was overall survival (OS). Secondary outcomes included progression-free survival and incidence of local failures.

Results: A total of 178 patients with 284 irradiated lung metastases were analyzed. The most common primary HNSCC subsites were oropharyngeal (n = 71), laryngeal (n = 37), and hypopharyngeal (n = 31). Lung metastases were treated with a median biologically effective dose ($BED_{\alpha/\beta = 10\ Gy}$) of 105 Gy (IQR, 84-113) at the planning target volume periphery. After a median follow-up of 40 months (95% CI, 34-46), the median OS and progression-free survival were 33 months (95% CI, 26-40) and 9 months (95% CI, 7-11), respectively. The 1-year cumulative incidence of local failures was 5.5% (95% CI, 3.2-8.8). One patient (0.6%) developed acute grade 3 dysphagia, and among 146 patients assessed for chronic toxicities, 2 (1.4%) experienced grade 3 events, with no grade 4-5 toxicities. On multivariable analysis, older (>65 years) patients (hazard ratio [HR], 1.59; 95% CI, 1.02-2.49; $P = .040$) and females (HR, 1.76; 95% CI, 1.04-2.99; $P = .035$) exhibited worse OS, whereas longer time between HNSCC diagnosis and first SBRT was associated with longer OS (HR, 0.99; 95% CI, 0.99-1.00; $P = .045$).

Conclusion: SBRT for pulmonary metastases achieves excellent local control with minimal toxicity in patients with oligometastatic HNSCC. Prospective trials are needed to determine the optimal timing for integrating SBRT with systemic treatment.

Introduction

With about 900,000 newly diagnosed patients annually worldwide, head-and-neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy.[1] Although local and locoregional failures are the most common forms of relapse in HNSCC, approximately 10% to 15% of patients experience distant metastases, with pulmonary metastases being the most frequent site of metastatic spread.[2-4] Notably, about 40% of these cases are classified as oligometastatic, characterized by a limited number of metastases, typically defined as up to 3 or 5 metastases.[5,6] Patients with oligometastatic HNSCC have a better prognosis compared with those with polymetastatic disease.[7-9] Currently, systemic therapy with immuno- and/or chemotherapy is the standard of care for patients with metastatic HNSCC.[10] Oligometastatic disease presents a unique therapeutic opportunity, where curative strategies with local ablative treatments can be employed to potentially improve patient outcomes.[11-14] For instance, the SABR-COMET trial demonstrated that stereotactic body radiation therapy (SBRT) significantly improves overall survival (OS) and progression-free survival (PFS) in patients with oligometastatic cancer compared with standard of care systemic treatment.[11,15] Within the context of oligometastatic disease, SBRT holds promise due to its ability to precisely deliver high-dose irradiation and spare organs at risk.[16-18] However, previous retrospective studies on SBRT for oligometastatic HNSCC were small, with a median of 32 patients (range, 6-81).[19] To date, only 1 randomized phase 2 trial, the GORTEC 2014-04 OMET trial (Stereotactic Radiotherapy Combined With Chemotherapy or Not for Treatment of Oligometastases in HNSCC), has exclusively included patients with oligometastatic HNSCC; however, it did not meet its initial recruitment target (n = 69 patients were randomized) and did not evaluate the combination of SBRT with first-line immunotherapy.[20] Despite these limitations, this trial demonstrated that SBRT alone in patients with oligometastatic HNSCC provides comparable survival outcomes with the combination of chemotherapy (EXTREME regimen) and SBRT, with significantly less quality of life deterioration and fewer severe toxicities in the SBRT-alone arm.

Prospective phase 2 basket trials, such as SABR-COMET and SABR-5, only included a small proportion of patients with HNSCC, eg, 10% in the SABR-COMET trial.[11,21] Given the small patient numbers in previous retrospective and prospective studies, multicenter analyses are required to identify prognostic factors for improved survival and to optimize the selection of patients with oligometastatic HNSCC for metastasis-directed therapy (MDT) such as SBRT. Additionally, local control rates after SBRT for pulmonary oligometastases from HNSCC varied widely across

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Ethics approval: The study was approved by the local institutional review board in advance (431/23-ek).

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Data Sharing Statement: Deidentified patient data are available for noncommercial purposes after approval of a scientific proposal to the corresponding author and after completion of a data transfer agreement.

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studies,[22-28] making multicenter analysis essential to accurately determine local control rates and compare them with other MDTs, such as metastasectomy and radiofrequency ablation. We, therefore, aimed to analyze the oncological outcomes of patients with oligometastatic HNSCC undergoing SBRT for lung metastases within a large international multicenter cohort study.

Methods and Materials

Study design

In a collaborative effort between the German Society for Radiation Oncology (DEGRO) working group "Radiosurgery and Stereotactic Radiotherapy" and the Young DEGRO, we conducted an international multicenter cohort study with 16 centers in Germany, Austria, and Switzerland. The study was approved by the local ethics committee of the Faculty of Medicine, Leipzig University (431/23-ek), and by each participating center's ethics committee. The study adhered to the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.

Patient population

Inclusion criteria were (1) HNSCC of the oral cavity, pharynx (naso-, oro-, or hypopharynx), or larynx; (2) SBRT for at least 1 pulmonary metastasis between January 1, 2010, and December 31, 2023; and (3) up to 5 metastatic lesions in a maximum of 3 organ systems at the time of SBRT. Patients were excluded if they had (1) nonsquamous cell histology; (2) prior pulmonary metastasectomy of the SBRT-treated lesion; or (3) in-field reirradiation with SBRT. Histologic confirmation of the SBRT-treated lung metastases was not required if multidisciplinary tumor boards deemed the lesion likely HNSCC-derived. The seventh edition of the TNM classification by the Union for International Cancer Control was used. The age-adjusted Charlson Comorbidity Index (aaCCI) was calculated as previously reported,[29] excluding metastasized HNSCC from the score. Oligometastatic disease was subclassified based on the classification system by the European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer.[30] Evaluation of local control regarding SBRT-treated lung metastases was performed based on histologic assessment or follow-up imaging with CT or PET-CT. The follow-up schedule after pulmonary SBRT in each of the 16 participating centers is indicated in Table E1. Given the poor positive predictive value of the Response Evaluation Criteria in Solid Tumors for diagnosing local recurrence after pulmonary SBRT,[31] confirmation of local recurrences was obtained either through histologic validation or by identifying high-risk CT features or continuous lesion enlargement accompanied by a positive F-18 fluorodeoxyglucose (FDG)-PET signal.[32,33] These radiological characteristics were assessed and diagnosed by board-certified radiologists or nuclear medicine specialists. Distant progression was defined as the development of new metastases or the progression of the primary tumor site or previously existing metastases. The biologically effective dose (BED) was calculated using the formula $BED = n \times d \times \left(1 + \frac{d}{\frac{\alpha}{\beta}}\right)$ with n = number of fractions, d = dose per fraction, and $\frac{\alpha}{\beta}$ = 10 Gy.[34] High-grade SBRT-related toxicities were recorded according to the Common Terminology Criteria for Adverse Events version 5.0. Toxicities were classified as acute if they occurred within the first 90 days after the initiation of SBRT, and as chronic if they developed thereafter.

Statistical analysis

OS was calculated from the start of the first SBRT for pulmonary metastasis until death from any cause, whereas PFS was computed from the same point until death or oncological progression, based on Response Evaluation Criteria in Solid Tumors 1.1. For OS, patients were censored at the last known date alive, and for PFS, at the last oncological consultation without progression. To calculate local failure incidence after SBRT, censoring occurred at the last chest imaging (CT or PET-CT). Median follow-up was determined using the reverse Kaplan-Meier method. Kaplan-Meier analyses with log-rank tests were conducted for OS and PFS, and cumulative incidence of local and distant failures was calculated with death as a competing event. To identify prognostic factors for OS and PFS, multivariable Cox proportional hazard regression was performed, including all variables potentially linked to survival based on literature. Missing data (aaCCI [n = 1], smoking status [n = 15], peri-treatment immune checkpoint inhibitor use [n = 4], and peri-treatment chemotherapy [n = 8]) were handled using multiple imputation (5 imputations). Hazard Ratios (HR) with 95% confidence intervals (95% CI) were reported for survival, calculated in months. Fine-Gray subdistribution hazard regression was performed to examine the association between a BED ≥100 Gy at the planning target volume (PTV) isodose and local failure incidence.

Statistical analyses were performed using IBM SPSS Statistics version 29 (IBM Corp.) and Stata version 17 (StataCorp LLC), whereas graphs were created with GraphPad Prism version 9 (GraphPad Software Inc.) and Stata. All tests and CIs were 2-sided, with statistical significance set at $\alpha = .05$.

Results

Characteristics of the study cohort

A total of 178 patients with 284 irradiated lung metastases met the inclusion criteria and were analyzed. Patient and treatment characteristics are shown in Table 1. The median age of the patients was 66 years (IQR, 59-72), with the

Table 1 Baseline characteristics of patients with oligometastatic head-and-neck squamous cell carcinoma (HNSCC) undergoing stereotactic body radiation therapy (SBRT) for lung metastases (n = 178 patients with 284 treated lesions)

Characteristic	N (%)
Patient characteristics	
Total (N)	178 (100)
Age at start of SBRT, median (IQR) (y)	66 (59-72)
Sex	
Female	37 (20.8)
Male	141 (79.2)
ECOG	
0	55 (30.9)
1	86 (48.3)
2	36 (20.2)
3	1 (0.6)
aaCCI, median (IQR)	4 (2-6)
Smoking	
Never smoker	29 (16.3)
Former smoker	93 (52.2)
Active smoker	41 (23.0)
Unknown	15 (8.4)
Primary cancer localization	
Oral cavity	29 (16.3)
Nasopharynx	8 (4.5)
Oropharynx	71 (39.9)
Hypopharynx	31 (17.4)
Larynx	37 (20.8)
Oro-/hypopharynx	2 (1.1)
p16 status	
p16-positive	27 (15.2)
p16-negative	60 (33.7)
Unknown	91 (51.1)
p16 status of oropharynx carcinomas	71 (100)
p16-positive	19 (26.8)
p16-negative	32 (45.1)
Unknown	20 (28.2)
UICC stage at first diagnosis	
I	12 (6.7)
II	7 (3.0)
III	29 (16.3)
IV	130 (73.0)
Previous radiation therapy of primary tumor	
No previous radiation therapy	13 (7.3)
Previous radiation therapy	165 (92.7)
Previous systemic treatment before SBRT including systemic treatment during curative radiation therapy	
No previous systemic treatment	42 (23.6)
Previous systemic treatment	136 (76.4)
Immune checkpoint inhibitor treatment within 60 d before or after the first SBRT	
Yes	12 (6.7)
No	162 (91.0)
Unknown	4 (2.2)
Chemotherapy administration within 30 d before or after the first SBRT	
Yes	20 (11.2)
No	150 (84.3)
Unknown	8 (4.5)
No. of metastases at SBRT, including treated metastasis	
1	100 (56.2)
2	50 (28.1)
3	18 (10.1)
4	7 (3.9)
5	3 (1.7)
No. of affected organs at the time of SBRT	
1	166 (93.3)
2	12 (6.7)
Histological confirmation	
Histological confirmation of HNSCC metastasis in at least 1 pulmonary lesion	87 (48.9)
No histological confirmation of HNSCC metastasis in a pulmonary lesion	91 (51.1)
Type of oligometastatic disease	
De-novo oligometastatic disease	163 (91.6)
Repeat oligometastatic disease	13 (7.3)
Induced oligometastatic disease	2 (1.1)
Time between initial diagnosis and first SBRT, median (IQR) (mo)	19 (9-33)
Lesion characteristics	
Total (N)	284 (100)
Histological confirmation	
Histological confirmation of SBRT-treated lung lesion	93 (32.7)
No histological confirmation of SBRT-treated lung lesion, but histological confirmation of ≥1 other lung lesion	49 (17.3)
	142 (50.0)

Table 1 (*Continued*)

Characteristic	N (%)
No histological confirmation of any lung lesions	
No. of fractions, median (IQR)	5 (3-8)
Single dose (PTV encompassing), median (IQR) (Gy)	11 (7-15)
Total dose (PTV encompassing), median (IQR) (Gy)	45 (41-54)
Dose inhomogeneity (PTV periphery dose/maximum dose), median (IQR) (%)	65 (65-80)
BED at PTV periphery, median (IQR) (Gy)	105 (84-113)

If patients were treated with more than 1 course of SBRT, patient characteristics refer to the time of first SBRT. The seventh edition of the TNM classification by the UICC was used in this study. The BED was calculated using the formula $BED = n \times d \times \left(1 + \frac{d}{\frac{\alpha}{\beta}}\right)$ with n = number of fractions, d = dose per fraction, and $\frac{\alpha}{\beta}$ = 10 Gy. The aaCCI was unknown in 1 patient. Percentages may not sum to 100% due to rounding.

Abbreviations: aaCCI = age-adjusted Charlson Comorbidity Index; BED = biologically effective dose; ECOG = Eastern Cooperative Oncology Group; PTV = planning target volume; SBRT = stereotactic body radiation therapy; UICC = Union for International Cancer Control.

majority of patients being male (141 [79.2%]). Most patients had an Eastern Cooperative Oncology Group (ECOG) status of 1 (86 [48.3%]), and median aaCCI was 4 (IQR, 2-6). The most common primary tumor localizations were the oropharynx (71 [39.9%]), larynx (37 [20.8%]), hypopharynx (31 [17.4%]), oral cavity (29 [16.3%]), nasopharynx (8 [4.5%]), and multilevel oro-/hypopharynx (2 [1.1%]). Of the 71 patients with oropharyngeal cancer, p16 status was known in 51 patients, of whom 19 (37.3%) had p16-positive cancer. In the total cohort, 27 patients (15.2%) had a p16-positive HNSCC. Most patients (165 [92.7%]) had received previous radiation therapy for the primary cancer before pulmonary SBRT. The median number of metastases at the time of first pulmonary SBRT was 1 (IQR, 1-2). Metachronous oligorecurrence (113 [63.5%]), de-novo oligometastatic disease (44 [24.7%]), and repeat oligorecurrence (8 [4.5%]) were the most common types of oligometastatic disease at the time of first SBRT. Details of the oligometastatic disease types are shown in Table E2. Twelve patients (6.7%) underwent immune checkpoint inhibitor administration within 60 days before or after the first pulmonary SBRT, and 20 patients (11.2%) were treated with chemotherapy within 30 days before or after the first SBRT. The median time between initial diagnosis of HNSCC and first pulmonary SBRT was 19 months (IQR, 9-33). Pulmonary lesions were treated with a median total dose of 45 Gy (IQR, 41-54) at the PTV encompassing isodose, delivered in a median of 5 fractions (IQR, 3-8) with a median of 11 Gy (IQR, 7-15) per fraction. The median BED at the PTV encompassing isodose was 105 Gy (IQR, 84-113); the median PTV inhomogeneity (PTV periphery dose/maximum dose) amounted to 65% (IQR, 65-80).

SBRT-related toxicities

SBRT-related grade 3 to 5 acute and chronic toxicities are summarized in Table 2. A total of 177 patients (99.4%) did not develop any high-grade SBRT-related acute toxicities, whereas 1 patient (0.6%) experienced grade 3 dysphagia, which was presumably related to the prior radiation therapy to the primary site. Of the 146 patients eligible for the assessment of chronic toxicities, 2 patients (1.4%) developed grade 3 toxicities (thoracic pain and pneumonitis; the latter occurred in a patient treated with adjuvant nivolumab after SBRT). No grade 4 or 5 toxicities were reported.

Oncological outcomes

Ninety-six patients (53.9%) died during the follow-up period after SBRT. After a median follow-up time of 40 months (95% CI, 34-46), the median OS was 33 months (95% CI, 26-40) (Fig. 1). The 1-, 2-, and 3-year OS were 75.8% (95% CI, 69.4-82.7), 57.7% (95% CI, 50.3-66.2), and 47.9 (95% CI, 40.2-57.2), respectively. One hundred patients (56.2%) developed new metastases or progression of the primary cancer after SBRT. The median PFS was 9 months (95% CI, 7-11), with 1-, 2-, and 3-year PFS being 44.1% (95% CI, 37.1-52.5), 32.9% (95% CI, 26.2-41.2), and 27.6% (95% CI, 21.1-36.0), respectively. Of the 284 lung metastases treated with SBRT, 15 (5.3%) developed local recurrence after a median time of 8 months (IQR, 1-10). Details of these recurrent lesions, including the methods used to confirm local recurrence, are provided in Table E3. The 1- and 2-year cumulative incidence of local failures was 5.5% (95% CI, 3.2-8.8) and 6.8% (95% CI, 4.1-11.3), respectively (Fig. E1). A BED ≥100 Gy at the PTV encompassing isodose was associated with a lower hazard of local failures (sHR, 0.17; 95% CI, 0.05-0.61; P = .006) in our cohort (Fig. E2). Prior histological confirmation of the treated lesion was not found to have an impact on the incidence of local failures (Fig. E3). The 1- and 2-year incidence rates of distant failures

Table 2 High-grade acute and chronic toxicities possibly related to SBRT

	N (%)
Acute toxicities	
No acute grade 3-5 toxicity	177 (99.4)
Grade 3 acute toxicity	1 (0.6)
Chronic toxicities	146 (100)
No chronic grade 3-5 toxicity	144 (98.6)
Grade 3 chronic toxicity	2 (1.4)

Toxicities were recorded according to the Common Terminology Criteria for Adverse Events version 5.0.

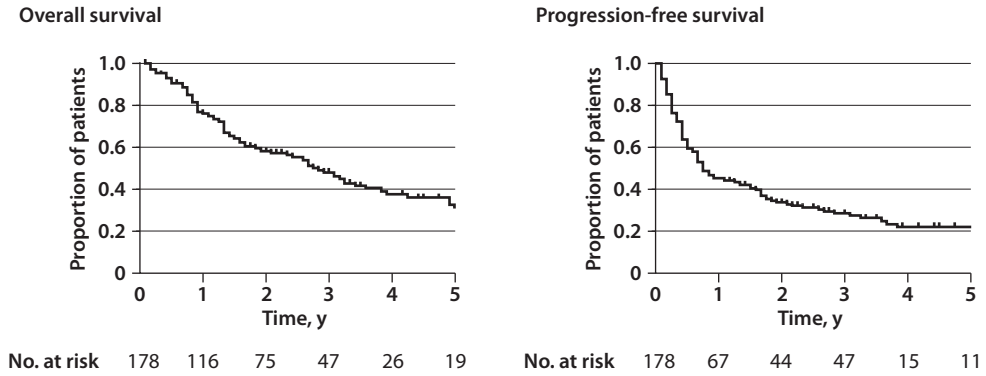

Fig. 1. Overall survival and progression-free survival in patients with oligometastatic head-and-neck squamous cell carcinoma undergoing pulmonary stereotactic body radiation therapy. Overall survival and progression-free survival are presented in years according to Kaplan-Meier analyses. Median follow-up time was 40 months (95% CI, 34-46).

after the first SBRT were 47.8% (95% CI, 39.6-55.6) and 57.2% (95% CI, 48.6-64.8), respectively.

Prognostic variables associated with survival

Kaplan-Meier analyses for OS, stratified by the number of metastases, affected organs, and time from diagnosis to SBRT, are shown in Figure 2. Figure E4 shows the survival outcomes depending on the type of oligometastatic disease, whereas Figure E5 displays OS stratified by prior histological confirmation of treated pulmonary lesions. The multivariable analysis identified several factors associated with OS (Table 3). Elderly patients (>65 years) had a higher hazard of death (HR, 1.59; 95% CI, 1.02-2.49; P = .040), and female sex was independently associated with reduced OS (HR, 1.76; 95% CI, 1.04-2.99; P = .035). A longer time between diagnosis and SBRT was linked to a lower hazard of death (HR, 0.99; 95% CI, 0.98-1.00; P = .045). ECOG status, comorbidity, smoking, primary tumor site, p16 status, number of metastases, affected organs, peri-treatment immune checkpoint inhibitor or chemotherapy administration, oligometastatic type, and BED were not significantly associated with OS. The only significant variable, that was associated with PFS, was the number of affected organs (HR, 2.93; 95% CI, 1.27-6.80; P = .012) (Table E4).

Discussion

To the best of our knowledge, this international multicenter study presents the largest analysis of patients with oligometastatic HNSCC undergoing pulmonary SBRT. SBRT for pulmonary metastases demonstrated excellent local control with minimal toxicity, and a distinct subset of patients achieved durable disease control and long-term survival.

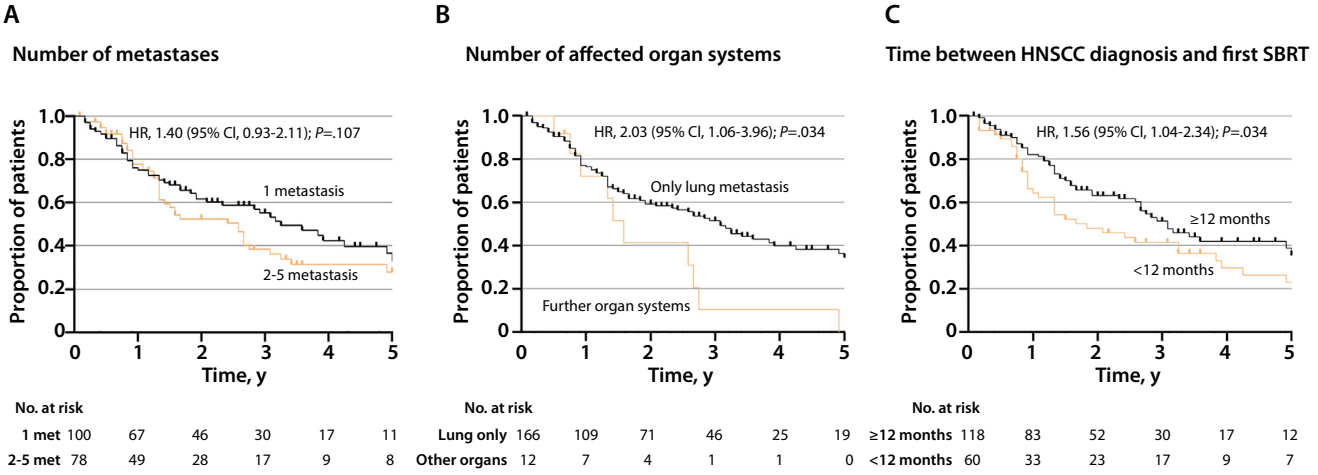

Fig. 2. Overall survival in patients with oligometastatic head-and-neck squamous cell carcinoma undergoing pulmonary stereotactic body radiation therapy (SBRT) stratified for different clinical variables. Number of metastases at the time of first SBRT (A), number of affected organs at the time of first SBRT (B), and time interval between first diagnosis of head-and-neck squamous cell carcinoma and time of first pulmonary SBRT (C). Hazard ratios with 95% CI are reported for survival times, calculated in months.

Table 3 Multivariable Cox proportional hazard regression analysis for overall survival in patients with oligometastatic head-and-neck squamous cell carcinoma (HNSCC) undergoing pulmonary stereotactic body radiation therapy (SBRT)

Characteristic	HR (95% CI)	*P*
Age (y)		
≤65	Reference	
>65	1.59 (1.02-2.49)	.040
Sex		
Male	Reference	
Female	1.76 (1.04-2.99)	.035
ECOG status		
0	Reference	
1	1.27 (0.78-2.05)	.338
2-3	1.37 (0.68-2.74)	.379
aaCCI	1.03 (0.94-1.14)	.517
Smoking		
Never smoker	Reference	
Former or active smoker	1.28 (0.67-2.44)	.454
Primary localization		
Oropharynx	Reference	
Oral cavity	1.26 (0.61-2.61)	.527
Nasopharynx	1.49 (0.51-4.40)	.468
Hypopharynx	1.77 (0.95-3.30)	.073
Larynx	0.95 (0.52-1.74)	.860
Oro-/hypopharynx (multilevel)	NA*	NA*
p16 status		
Positive	Reference	
Negative/unknown	1.25 (0.60-2.58)	.548
Immune checkpoint inhibitor treatment within 60 d before or after the first SBRT		
Yes	Reference	
No	1.09 (0.34-3.50)	.882
Chemotherapy administration within 30 d before or after the first SBRT		
Yes	Reference	
No	0.56 (0.25-1.26)	.159
No. of metastases at the time of first SBRT	1.07 (0.82-1.38)	.633
No. of affected organs at the time of first SBRT		
1	Reference	
2	2.28 (0.92-5.66)	.076
Type of oligometastatic disease		
De-novo oligometastatic disease	Reference	
Repeat oligometastatic disease	0.85 (0.33-2.21)	.744
Induced oligometastatic disease	6.76 (0.66-69.00)	.107
BED at PTV periphery of the first SBRT (Gy)	0.99 (0.98-1.00)	.162
Time between initial diagnosis and first SBRT (mo)	0.99 (0.98-1.00)	.045

Abbreviations: aaCCI = age-adjusted Charlson Comorbidity Index; BED = biologically effective dose; ECOG = Eastern Cooperative Oncology Group; PTV = planning target volume.

* Because there were no events in the 2 patients with multilevel oro-/hypopharynx cancer, no HR could be calculated.

The 1- and 2-year OS rates of 75.8% and 57.7% observed in this multicenter analysis are comparable with the recently published results from a meta-analysis regarding patients with oligometastatic HNSCC in which 1- and 2-year OS rates were 80.1% and 60.7%, respectively.[19] The median OS in our cohort was 33 months, which is considerably better than after palliative chemoimmunotherapy as reported in the Keynote-048 trial (median OS of 13.6 months in the CPS ≥1 population[10]), but presumably attributed to selection biases.

The median PFS of 9 months in our cohort is comparable with previous studies regarding oligometastatic HNSCC, eg, 10 months in the study by Bonomo et al[35], 9.6 months in the study by Mohamed et al[25], and 9.3 months in the study by Franzese et al.[36] The OMET trial from the GORTEC group, which randomized between SBRT alone versus SBRT plus chemotherapy, reported a 1-year OS of 85.6% (95% CI, 74.7-98.1) in the chemo-SBRT arm versus 85.3% (95% CI, 74.2-98.1) in the SBRT-alone arm.[20] Median PFS was 12.9 months (95%CI, 7.5-17.3) in the chemo-SBRT arm and 7.4 months (95% CI, 4.2-15.6) in the SBRT-alone arm, which is comparable with the median PFS of 9 months (95% CI, 7-11) in our study.[20] Local control rates were 80.0% in the chemo-SBRT arm and 82.4% in the SABR-alone arm of the OMET trial; however, direct comparisons with our study are challenging, as the OMET trial did not specifically focus on pulmonary oligometastases, even though the vast majority (82.6%) had lung-only metastases at the time of SBRT.

Although a key limitation of SBRT is the lack of tissue availability for molecular analyses if no prior biopsy has been performed, SBRT has several benefits: it is noninvasive, does not require anesthesia, can be performed on an outpatient basis, is also possible for patients with limited lung capacity, has been shown to maintain or even improve quality of life, and can often be administered concurrently with systemic therapies—advantages that are more challenging with metastasectomy due to the recovery period required after surgery.[37]

Considering the oncological outcomes after metastasectomy of pulmonary metastases in patients with HNSCC,[38,39] our results seem to be comparable. In the systematic review by Young et al,[39] 13 studies with 403 patients were included evaluating the efficacy of pulmonary metastasectomy in patients with HNSCC and metachronous pulmonary metastases. The 5-year OS amounted to 29.1% after pulmonary metastasectomy, which is almost identical to the 5-year OS of 30.5% in our cohort. It must be noted that our cohort comprises both synchronous and metachronous lung metastases, whereas the systematic review of Young et al[39] only included metachronous lung metastases. The systematic review by Schlachtenberger et al[38] identified 15 studies on pulmonary metastasectomy in patients with head-and-neck cancer. The included studies reported median survival rates ranging from 10 to 77 months after pulmonary metastasectomy, with 5-year OS rates between 21% and 59%. Notably, the 3 largest studies reported 5-year OS rates between 21% and 36%, so that again the survival outcomes after pulmonary SBRT appear comparable with the outcomes reported for patients receiving pulmonary metastasectomy.

Positive tumoral p16 expression is known to be prognostic in patients with oropharyngeal carcinoma undergoing both curative treatment and palliative systemic treatment. However, little is known about its prognostic value in patients with oligometastatic HNSCC. Although we could not identify a prognostic role of the p16 status in both the univariable and multivariable analyses, Modesto et al[40] reported within a cohort of 186 patients with oropharyngeal squamous cell carcinoma and distant metastases that patients with p16-positive cancers had significantly longer 2-year OS compared with patients with p16-negative cancers (75% vs 15%). Wright et al[41] showed in a retrospective observational cohort study that MDT was associated with improved survival in patients with oligometastatic human papillomavirus (HPV)-associated oropharyngeal carcinoma when compared with systemic therapy alone (median OS not reached vs 40.7 months, $P = 0.004$).

The 1-year cumulative incidence of local failure after SBRT in our cohort was 5.5%, which aligns well with the outcomes generally observed after SBRT for pulmonary (oligo)metastases.[42-45] In the systematic review by Mayinger et al,[46] which included 35 studies encompassing over 3600 patients and 4650 lung metastases from different primary carcinomas, the median local control rate at 1 year was 90%, with acute toxicity ≥grade 3 occurring in only 0.5% of patients. In line with previous studies regarding lung metastases from other primary cancers, a BED ≥100 Gy at the PTV encompassing isodose was associated with higher local control rates.[47] While achieving high local control rates with SBRT, we also observed a very low incidence of SBRT-related toxicities in our cohort, suggesting that SBRT can be conducted safely in patients with oligometastatic HNSCC. These findings are consistent with the meta-analysis by Mutsaers et al,[19] where no grade 4 or 5 toxicities were reported, and grade 3 toxicities remained uniformly below 5%. In the OMET phase 2 trial, rates of severe treatment-related toxicities were 8.8% in the SBRT-alone group, with no grade 5 toxicities.[20]

The proportion of patients with HNSCC in previous trials and registry studies that evaluated the role of SBRT in patients with oligometastatic disease was low.[48] For instance, although the SABR-COMET randomized phase 2 trial showed significant survival benefits and a favorable toxicity profile for SBRT in patients with oligometastatic disease, only about 10% of the patients had HNSCC.[11] A prospective registry study conducted in the United Kingdom involving 1422 patients who received SBRT for 3 or fewer metachronous metastases did not include any patients with HNSCC.[49] Even though the evidence for MDT in patients with oligometastatic HNSCC is limited, international guidelines recommend MDT in this scenario. The current National Comprehensive Cancer Network (NCCN) guideline states that "locoregional treatment (eg, surgery, radiotherapy, ablative therapies) may be used for oligometastatic disease,"[50] whereas the EHNS-ESMO-ESTRO guideline recommends consideration of MDT (surgery of radiation therapy) for treatment with curative intention "in selected patients with oligometastatic disease" (Level of evidence II, grade of recommendation C).[51] The GORTEC group also offered recommendations for the optimal treatment of patients with oligometastatic HNSCC, but emphasized that data on the ideal sequencing of systemic therapies and MDT, including SBRT, remain insufficient.[52,53] Several prospective trials are currently attempting to define treatment strategies for oligometastatic HNSCC. For instance, the OligoRARE (Stereotactic Body Radiotherapy in Patients With Rare Oligometastatic Cancers, NCT04498767) trial is assessing standard of care with or without SBRT across various cancers, including HNSCC. The PROLoNg (Pembrolizumab and Radiotherapy for OLigometastatic Squamous Cell Carcinoma of the Head and Neck, NCT05815927) trial is a randomized phase 3 trial, which is going to evaluate the effect of adding SBRT to pembrolizumab in patients with oligometastatic HNSCC and a CPS ≥1. A currently recruiting ECOG-ACRIN phase 3 trial (NCT05721755) compares consolidative radiation therapy with pembrolizumab versus pembrolizumab alone after chemoimmunotherapy in oligometastatic HNSCC.

Limitations

The study's retrospective nature introduces potential biases, such as selection bias, and limits the ability to establish causality. The multicenter design, although enhancing the generalizability of the findings, also introduces variability in treatment protocols, imaging techniques, and follow-up procedures across different institutions. Histological confirmation of all treated lung metastases was not mandatory, and therefore, it cannot be completely ruled out that second primary lung carcinoma was among the SBRT-treated lesions. Because of the extended timeframe of this analysis, which collected between 2010 and 2023, the reporting of multiparametric dose prescriptions in accordance with the

International Commission on Radiation Units and Measurements Report 91 was not feasible for all treated lesions, and therefore, detailed dosimetric data regarding SBRT were not available for all lesions.[54,55] Even though the median follow-up time of 40 months was sufficient to observe potential long-term toxicities, the retrospective design and the lack of a centralized toxicity review may have led to underreporting of SBRT-related toxicities, especially of chronic toxicities, in our study. In this context, we did not analyze SBRT-related grade 1-2 toxicities, such as fatigue and nausea, which, despite their lower severity, can still significantly impact patients' quality of life.[56,57] Furthermore, our analysis lacks a control group, such as oligometastatic HNSCC patients treated exclusively with systemic therapy, which prevents us from definitively determining the oncological impact of SBRT on survival compared with systemic treatments like immunotherapy or chemoimmunotherapy. Finally, our multiple regression analysis demonstrates a relatively low event-per-variable ratio, warranting cautious interpretation of these results, which should be considered primarily hypothesis-generating.

Conclusions

SBRT of pulmonary metastases demonstrates excellent local control with minimal high-grade toxicities in patients with oligometastatic HNSCC. Certain patient groups may achieve durable survival after SBRT. Prospective multicenter trials will be essential to identify the patient groups that benefit most from SBRT and for determining the optimal timing to integrate SBRT with other oncologic treatments in patients with oligometastatic HNSCC.

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