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Clinical Investigation

Stereotactic Body Radiation Therapy for Mediastinal and Hilar Lymph Node Metastases

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Purpose: Stereotactic body radiation therapy (SBRT) to metastatic mediastinal and hilar lymphadenopathy (MHL) is challenging owing to the proximity of centrally located organs-at-risk. As limited data exist on the safety and efficacy of SBRT for MHL, a retrospective review of clinical outcomes was conducted from a large academic center.

Methods and Materials: Eligible patients received SBRT to MHL between 2014 to 2019 for the following indications: oligometastases, oligoprogression, or local control of a dominant area of progression. The primary endpoint was grade $\geq$3 toxicity (Common Terminology Criteria for Adverse Events, version 5.0). The cumulative incidence function evaluated local failure (LF) and starting or changing systemic therapy (SCST). Kaplan-Meier methodology estimated progression-free survival (PFS) and overall survival (OS).

Results: Fifty-two patients (84 metastases) were included. Median follow-up was 20 months. Primary cancer sites included kidney (53.8%), lung (13.4%), breast (7.7%), and other (25.1%). Indications for SBRT were oligoprogression (n = 35; 67.3%), oligometastases (n = 10; 19.2%), or local failure of a dominant area of progression (n = 7; 13.5%). The majority (n = 31; 59.6%) received SBRT to a single lymph node metastasis. Median SBRT dose was 35 Gy (range, 30-50 Gy) with a median biologically effective dose of 59.5 Gy (range, 48-100 Gy). All treatments were in 5 fractions. Seven grade $\geq$3 toxicities were experienced by 6 patients (11.5%) and were mostly transient (5/7; 71%). There was a single (1.9%) grade 5 toxicity (radiation pneumonitis). The cumulative incidence of LF was 9.0% at 2 years. The cumulative incidence of SCST was 33.2% and 57.1% at 1 and 2 years, respectively. Median PFS was 4.0 months (95% confidence interval, 2.8-7.3) and median OS was 31.7 months (95% confidence interval, 23.8-87.5).

Conclusions: In one of the largest single institutional series of SBRT for MHL, moderate rates of grade $\geq$3 toxicity were observed, although the majority were transient. This treatment resulted in low LF rates and potentially delayed SCST for many patients. © 2020 Elsevier Inc. All rights reserved.

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Introduction

Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiation therapy, permits the delivery of highly conformal and condensed courses of radiation with high biologically effective dose.[1] SBRT is the standard of care for early-stage, medically inoperable, non-small cell lung cancer (NSCLC), as it is more convenient and improves local control (LC) and overall survival (OS) compared with conventionally fractionated radiation therapy (CFRT).[2,3] Initial reports of severe toxicity after SBRT to central lung tumors raised safety concerns with high SBRT doses for tumors within 2 cm of the proximal bronchial tree (PBT).[4,5] However, a recent phase I or II study designed to determine the maximal tolerated 5-fraction SBRT dose for central NSCLC, found acceptable rates of toxicity in the modern era and provided a framework for appropriate SBRT planning and delivery in this setting.[6]

A higher risk scenario is the use of SBRT for "ultracentral" thoracic tumors. Generally, ultracentral refers to either gross tumor volume (GTV) abutment or planning target volume (PTV) abutment or overlap with mediastinal organs at risk (OARs), such as the PBT, esophagus, or great vessels.[7] Although prospective evaluation of SBRT dose fractionation schemes for ultracentral NSCLC is ongoing,[8] several institutional series have reported instances of treatment-related morbidity (including esophageal stricture, bronchial obstruction, fistula formation, and hemorrhage) and, in rare scenarios, mortality.[9] On the basis of these developments, ultracentral SBRT for metastatic mediastinal and hilar lymphadenopathy (MHL) has emerged as an option. The inclusion of lymph nodes with ultracentral lung targets, however, has been found to be associated with higher rates of serious SBRT-associated toxicity.[10] Therefore, when SBRT is considered for MHL, lower prescription doses compared with parenchymal lung targets are typically used. Although there is limited data describing MHL SBRT, it may hold merit as patients are often ineligible for other local therapies, such as resection, chemoradiotherapy, or protracted courses of CFRT. A limited number of relatively small, retrospective series of SBRT for MHL demonstrate effective LC and variable rates of grade $\geq$3 toxicity ranging from 0% to 15%.[11-16]

Achieving LC with SBRT is often desired in managing MHL, as the unabated compression or invasion of airways, great vessels, heart, or the esophagus by progressive tumors may cause symptomatic complications. Additional benefits may arise in patients with oligometastases (OM), oligoprogression (OP), or dominant areas of progression (DAP). In these populations, SBRT may prolong progression-free survival (PFS)[17-19] and overall survival OS,[17,20] and potentially allow for delays in starting or changing systemic therapy (SCST).[21,22] In the latter scenario, extended breaks from systemic therapy (ST) may improve quality of life while preserving next-line ST options for further disease progression.[21-24] Given the paucity of data on the safety and clinical outcomes of SBRT for MHL, this study was conducted to assess our institution's experience. We hypothesized that SBRT would be well tolerated, provide high rates of LC, and allow for delays in SCST.

Methods and Materials

Patient selection

This retrospective study was approved by the local institutional research ethics board. Consecutive patients treated with 5-fraction SBRT (with a total dose of at least 30 Gy) to metastatic MHL between January 2014 and July 2019 were identified from a prospectively maintained database. Patients eligible for retrospective analysis had a previously confirmed histopathologic diagnosis of a nonhematologic primary malignancy and at least 3 months of post-SBRT follow-up. Biopsy or fine-needle aspiration of targeted metastases was not required before SBRT delivery. SBRT use was as per institutional guidelines for the following indications: (1) OM (defined as $\leq$5 total metastases); (2) OP (defined as $\leq$5 progressive metastases in the context of otherwise stable metastatic disease); and (3) DAP (defined as a clinical situation where SBRT was recommended for LC of a progressive metastasis given its potential for symptomatic progression or rapid pace of growth).[25] At our institution, SBRT for MHL is used specifically as a strategy to prevent the compression of airways or great vessels, or to delay SCST. The decision to use SBRT rather than conventional low dose palliative radiation therapy often came from a desire to provide longer-term LC in patients who demonstrated a more indolent disease course previously. Typically, these patients were not symptomatic from their MHL.

Treatment characteristics

Patients were immobilized using a chest board, Elekta BlueBAG vacuum cushion system (Elekta, Stockholm, Sweden), and an abdominal compression plate. Nearly all patients were positioned with their arms above their heads; however, if an upper mediastinal lymph node was targeted, a thermoplastic head and shoulder mask was used (Orfit Industries NV, Wijnegem, Belgium) in the arms-down position. Four-dimensional computed tomography (CT) simulation was performed and images were binned by respiratory phase. Intravenous contrast with CT simulation was preferred; however, its use was ultimately at the discretion of the treating radiation oncologist (RO). The GTV was contoured using the 0-phase (peak inspiratory) and 50-phase (peak expiratory) image sets. GTV contours were combined to form an internal target volume (ITV) and an isotropic expansion of 5 mm was applied to create a PTV. Clinical target volume expansions for microscopic disease or elective nodal irradiation were not used. If mono-

isocentric irradiation of an adjacent parenchymal lung metastasis was performed synchronously, target volumes were contoured in an identical fashion as for lymph nodes, except that maximum intensity projection data sets may have also been used to contour parenchymal lung tumors.

Radiation planning was performed using CT average data sets with coverage objectives aiming to achieve ITV V100% ≥99% and PTV V95% ≥99%. Dose distributions were optimized for conformality while attempting to limit heterogeneity as much as possible within the PTV (Fig. 1). A point D_{max} ≤120% was the upper limit of what was acceptable, but most plans were optimized to have a point D_{max} ≤105% to 110%. In general, homogenous plans were desired to prevent "hot spots" near critical OARs. Undercoverage of the ITV or PTV was acceptable if dose-limits to OARs were exceeded. Normal tissue contouring and dose constraints were based on the Radiation Therapy Oncology Group 0813 protocol.[6] The prescribed dose was determined by the treating RO. All treatment courses were completed in 5 fractions, every other day. All radiation plans and dose-volume parameters were peer-reviewed at weekly interdisciplinary quality assurance rounds. SBRT was delivered using volumetric modulated arc therapy with Elekta Synergy (Elekta AB, Stockholm, Sweden) linear accelerators. Treatments were performed using daily cone beam CT image guidance and a 6 degrees of freedom HexaPOD robotic couch (Elekta AB) for positional correction.

In general, patients were advised to stop any nonhormonal ST before SBRT initiation to avoid potential side effects from concurrent therapy. To facilitate this, attempts were made to deliver SBRT during planned breaks between cycles of ST. The timing of ST reinitiation after SBRT was at the discretion of the patient's medical oncologist after discussion with the treating RO. ST was considered to be any oral or IV chemotherapy, immunotherapy, novel biological therapy (eg, tyrosine kinase inhibitors, mTOR inhibitors, or interleukin therapy) or hormonal therapy (eg, tamoxifen, aromatase inhibitors, or androgen deprivation therapy).

Endpoints and statistical analysis

Patients were followed with diagnostic CT imaging every 2 to 6 months after MHL SBRT completion. Time zero (t_0) for all endpoints was the date of initial MHL SBRT completion. Follow-up time was measured from t_0 to last known status. The primary endpoint was the incidence of grade ≥3 acute (≤3 months post-SBRT) and late (>3 months post-SBRT) toxicities as evaluated by the Common Terminology Criteria for Adverse Events, version 5.0. Toxicity data were obtained retrospectively from physician and procedure notes available in the electronic medical record. All grade ≥3 toxicities were reviewed independently by a panel of 4 ROs (J.S., I.P., A.V.L., P.C.), with final scoring and attribution achieved by consensus. Grade ≥3 toxicities were scored according to the National Cancer Institute Guidelines for Adverse Event Reporting Requirements[26] as "possible," "probable," or "definite" with respect to attribution to the SBRT intervention. Descriptive analyses of demographic, dosimetric, and toxicity data were compiled as means with standard deviations, medians with interquartile range for continuous variables, and frequencies or proportions for categorical variables.

Secondary endpoints were the cumulative incidence of local failure (LF) and SCST, as well as PFS and OS. Local and distant failures were evaluated predominantly using CT-based imaging. Time to failure was measured from t_0 to the date of any diagnostic imaging demonstrating disease progression. LF was defined as disease progression within the PTV, most commonly called when the irradiated targets increased in size over at least 2 consecutive follow-up CT scans with backdating to the initial scan demonstrating progression. Alternatively, LF was called if there was unequivocal agreement between the reading radiologist and treating RO. In the rare scenario where a second scan was not done to confirm continued growth demonstrated previously, and if an opinion regarding a local failure was undocumented or disputed, retrospective evaluation of imaging was performed and scored according to the Response Evaluation Criteria in Solid Tumors, version 1.1.[27] Competing risk analysis[28] was performed per metastasis to estimate the cumulative incidence function (CIF) of LF.

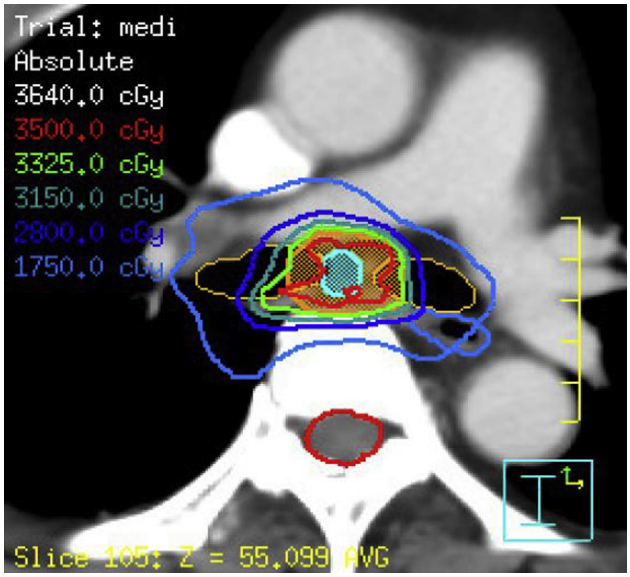

Fig. 1. An example dose distribution achieved in the treatment of a subcarinal lymph with stereotactic body radiation therapy to a dose of 35 Gy in 5 fractions. The internal target volume is delineated in cyan colorwash. The planning target volume is delineated in orange colorwash. Organs at-risk include the proximal bronchial tree (light orange), esophagus (light blue), and spinal canal (red). The great vessels are demonstrated with intravenous contrast (not contoured). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.10.004)

The competing event was death without LF, and patients lost to follow-up without LF were censored.

For SCST,[22] the CIF was estimated per patient, such that the primary event of interest was the act of starting or changing the ST strategy after t_0. Definitions of SCST were the following: (1) initiating ST in the first-line setting; (2) increasing the drug dosage for the current line of ST; (3) changing the current ST to a new line of treatment; or (4) reinitiating an existing line of ST after a planned "drug holiday." The competing event was death without SCST, and those lost to follow-up without SCST were censored. Gray's test subsequently evaluated the equality of the CIF for both LF and SCST by SBRT indication (OM, OP, or DAP).

PFS and OS were estimated using Kaplan-Meier methodology.[29] PFS was defined from t_0 to the date of any progression or death from any cause, with those lost to follow-up being censored. OS was defined from t_0 to the date of death from any cause, with those lost to follow-up being censored. The log-rank test was used to evaluate both PFS and OS by subgroups of SBRT indication (OM, OP, or DAP). All analyses were conducted using Statistical Analysis Software (SAS version 9.4, Cary, NC) and R package (v3.6.1).

Results

Fifty-two consecutive patients with a total of 84 mediastinal and hilar lymph node metastases received SBRT and were eligible for analysis. Patient and treatment characteristics are described in Tables 1 and 2, respectively. The median post-SBRT follow-up time was 20 months (interquartile range, 10-31 months). Twenty-one patients (n = 21/52; 40%) received SBRT to more than one site of metastatic MHL, and of those, 20 (20/21; 95%) were treated using a mono-isocentric radiation plan. An adjacent parenchymal lung metastasis was encompassed in the radiation plan of 11 patients (n = 11/52; 21%) undergoing SBRT to MHL. One patient underwent SBRT for metastases located in the hilar or subcarinal and paraesophageal nodal stations using 2 isocenters (2 separate plans) on alternating days. Two patients (n = 2/52; 4%) received SBRT to a second nodal region for a metachronous recurrence of MHL after initial SBRT.

Toxicity

Six of 52 patients (11.5%) experienced a total of 7 grade ≥3 toxicities (Table 3). One (1.9%) probable treatment-related death (grade 5 radiation pneumonitis) occurred in a patient undergoing mono-isocentric MHL SBRT to 4 separate targets: 2 right-sided hilar lymph node metastases, a subcarinal lymph node metastasis, and a parenchymal lung metastasis. One acute grade ≥3 toxicity was noted (acute esophagitis), with the remainder being late and occurring >3 months after SBRT completion. The majority (n = 5/7; 71%) of the observed grade ≥3 toxicities were transient in nature and resolved by the next follow-up visit after appropriate management. Three out of 7 grade ≥3 toxicities (n = 3/7; 43%) were due to an ipsilateral post-obstructive lobar pneumonia adjacent to a site of previous MHL SBRT. Of the 32 patients receiving nonhormonal ST before treatment, 91% (n = 29) stopped their systemic therapy before starting SBRT. None of the patients experiencing a grade ≥3 toxicity underwent concurrent ST.

Local failure

In total, 6 of 52 patients (11.5%) experienced a LF. The cumulative incidence of LF were as follows: 6 months (3.6%), 1 year (6.2%), 2 years (9.0%), and 3 years (13.3%; Fig. 2). Gray's test for equality of the CIF indicated no significant difference (P = .1155) between SBRT indication and the CIF of LF.

Starting or changing systemic therapy

In total, approximately half of all patients (n = 27/52; 51.9%) required a change in their ST strategy at any time point after completion of MHL SBRT. Of those, 22 (n = 22/27; 81.5%) changed their initial ST to a subsequent line of treatment, and 5 (n = 5/27; 18.5%) initiated ST in the first line setting after MHL SBRT. The median number of lines of systemic therapy before MHL SBRT was 1 (range, 0-4). The median number of previous lines of systemic therapy by SBRT indication was 0 (OM), 1 (OP), and 2 (DAP). The cumulative incidence of SCST were as follows: 6 months (15.4%), 1 year (33.2%), 2 years (57.1%), and 3 years (57.1%; Fig. 3). Gray's test for equality of the CIF indicated a trend between SBRT indication and SCST, although this was not statistically significant (P = .0567). In general, patients with OM and OP were more likely to require changes in their ST strategy. By SBRT indication, rates of SCST were as follows: at 6 months 0% (DAP), 10% (OM), and 20% (OP); at 1-year, 0% (DAP), 30% (OM), and 40.7% (OP); and at 2-years, 19.1% (DAP), 45% (OM), and 69% (OP).

Progression-free survival and overall survival

Forty-five out of the 52 patients (87%) progressed in any fashion (local or distant) at any time point after completion of MHL SBRT. At the time of initial progression for these 45 patients, 3 (n = 3/45; 7%) failed both locally and distantly, and all others (42/45; 93%) failed distantly alone. The actuarial median PFS was 4.0 months (95% CI, 2.8-7.3). PFS rates were as follows: 1 year (23.6%) and 2 years (11.6%). The actuarial median PFS by SBRT indication was 2.7 months (DAP), 4.5 months (OP), and 6 months (OM). Although a trend was apparent, the log-rank test did not demonstrate a statistically significant difference in PFS by SBRT indication (P = .1897). The actuarial median OS

Table 1 Patient characteristics

Characteristic	No. of patients, n = 52	%
Age at time of SBRT (y), median (range)	65 (43-85)	
Sex		
Male	13	25.0
Female	39	75.0
ECOG performance status		
0	29	55.8
1	23	44.2
Primary cancer site		
Kidney	28	53.8
Lung	7	13.4
Breast	4	7.7
Head/neck	3	5.8
Colon	3	5.8
Prostate	3	5.8
Other	4	7.7
Time to metastatic disease (mo), median (range)	14 (0-308)	
SBRT indication		
Oligoprogression	35	67.3
Oligometastases	10	19.2
Dominant area of progression	7	13.5
No. of mediastinal or hilar lymph node metastases targeted with SBRT		
1	31	59.6
2	13	25.0
3	7	13.5
4	1	1.9
Received synchronous SBRT to an adjacent lung metastasis	11	21.2
No. of lines of systemic therapy prior to MHL SBRT, median (range)	1 (0-4)	
Prior palliative-intent systemic therapy?		
No	17	32.7
Yes	35	67.3
If yes, last systemic therapy prior to MHL SBRT		
Tyrosine kinase inhibitor	12	23.1
Immunotherapy	11	21.2
Intravenous/oral chemotherapy	7	13.5
Hormonal therapy	3	5.8
Other biological therapy	2	3.8
Prior locally ablative metastasis-directed therapy?*		
No	24	46.2
Yes	28	53.8
Prior thoracic SBRT?		
No	40	76.9
Yes	12	23.1
Prior conventional thoracic radiation therapy?		
No	43	82.7
Yes	9	17.3
SBRT/SRS for any distant failure after MHL SBRT?		
No	24	46.2
Yes	28	53.8

Abbreviations: ECOG = Eastern Cooperative Oncology Group; MHL = mediastinal and hilar lymphadenopathy; SBRT = stereotactic body radiation therapy; SRS = stereotactic radiosurgery.

* Includes surgery, SBRT, stereotactic radiosurgery, chemoradiation, conventionally fractionated radiation therapy, or radiofrequency ablation.

was 31.7 months (95% CI, 23.8-87.5). OS rates were as follows: 1 year (84.2%), 2 years (63.8%), and 3 years (44.6%; Fig. 4).

Discussion

Mediastinal and hilar lymph node metastases are commonplace in both thoracic and extrathoracic malignancies and are associated with poor survival.[30] Historically, ST was the mainstay of treatment for MHL, with radiation therapy limited to the palliative setting for symptom control. Emerging randomized evidence, however, has suggested that locally ablative therapies, such as SBRT, can improve clinical outcomes in patients with limited metastatic disease.[17-20] There is also a desire for many clinicians to delay starting or changing an individual patient's ST strategy, in which case SBRT may act as another "line" of treatment.[21] Radiographic progression within MHL is often a concern for medical oncologists given that proximal airways and great vessels are in close proximity and would often trigger a change in ST strategy if local therapy was not offered. Furthermore, given that courses of SBRT are generally completed in less than 2 weeks, time off of ST is shorter in duration than if patients undergo other locally ablative therapies, such as resection or protracted courses of CFRT or chemoradiotherapy. For these reasons, in addition to the recent results of Radiation Therapy Oncology Group 0813 demonstrating an acceptable 7.2% risk of dose-limiting toxicity for centrally located lung tumors, interest in SBRT for MHL is growing.[11-16,31]

Our report is one of the largest single institutional series of SBRT for the management of mediastinal and hilar lymph node metastases. The primary objective of our study was to estimate the incidence of severe toxicity occurring in

Table 2 Treatment characteristics

Characteristic	No. (%) of lesions n = 84
Location of MHL treated with SBRT	
Hilar	29 (34.5)
Lower paratracheal	21 (25.0)
Subcarinal	18 (21.4)
Upper paratracheal	5 (6.0)
Paraortic	4 (4.8)
Paraesophageal	3 (3.6)
Aortopulmonary window	2 (2.4)
Interlobar	2 (2.4)
Prescribed SBRT dose in 5 fractions	
30 Gy	24 (28.6)
32.5 Gy	2 (2.4)
35 Gy	33 (39.3)
37.5 Gy	1 (1.2)
40 Gy	13 (15.5)
45 Gy	9 (10.7)
50 Gy	2 (2.4)
SBRT dose (Gy), median	35
BED_{10} (Gy), median (range)	59.5 (49-100)
BED_3 (Gy), median (range)	116.7 (90-216.7)
Maximum lesion size (cm), median (range)	2.0 (0.8-8.0)
PTV/dosimetric characteristics	
PTV (mL), median (range)	57.5 (11.3-771.1)
PTV D_{max} (%), median (range)	108 (103-132)
Conformality index,* median (range)	1.13 (1.12-1.29)
D_{max} (Gy) to central organs at risk, median (range)	
Proximal bronchial tree	36.5 (0.5-52.4)
Esophagus	31.7 (6.9-43.0)
Heart	34.6 (0.2-52.4)
Great vessels	36.7 (1.1-51.9)

Abbreviations: BED_{10} = biologically effective dose assuming an alpha/beta ratio of 10; BED_3 = biologically effective dose assuming an alpha/beta ratio of 3; D_{max} = maximum dose; MHL = mediastinal and hilar lymphadenopathy; PTV = planning target volume; SBRT = stereotactic body radiation therapy.

* Defined as the ratio of the volume encompassed by the 95% prescription isodose line and the PTV for a single target.

a population receiving SBRT to ultracentral nodal targets. We found that the incidence of grade ≥3 toxicities was 11.5% (n = 6/52), which is similar to other series of SBRT for ultracentral lung and lymph node targets.[9-16,31] Treatment-related mortality was 1.9%, with a single death secondary to radiation pneumonitis occurring in a patient undergoing mono-isocentric SBRT to multiple lesions, including an adjacent 5 cm lung metastasis. Reassuringly, most of the grade ≥3 toxicities (n = 5/7; 71%) were transient and resolved after appropriate management, with no long-term sequelae observed. Treatment also provided durable and excellent rates of LC, with a cumulative incidence of LF of only 9% at 2 years. The cumulative incidence of SCST was 57.1% at 2 years, suggesting that a significant proportion of patients did not require a change in their ST strategy after completion of MHL SBRT.

Although difficult to compare the results of a heterogeneous group of retrospective studies (with variable patient populations and treatment regimens), our findings are generally comparable with other series reporting on ultracentral lymph node and lung SBRT. In the largest known series of SBRT for MHL, Wang et al retrospectively assessed 85 patients (62% NSCLC) and found the incidence of grade ≥3 toxicity to be 7%, with grade 5 events occurring in 3.5% (n = 3/85) of patients.[12] All of the 3 treatment-related deaths occurred in patients who developed esophageal fistulae in regions where subcarinal nodal targets were reirradiated with SBRT.[12] The lower risk of mortality in our series may be explained by the absence of patients undergoing overlapping SBRT to a previously irradiated volume. Significant caution should be undertaken when treating subcarinal lymph nodes with SBRT, as the presence of multiple adjacent critical OARs (particularly the esophagus and PBT) may amplify the risk for treatment-related complications (Fig. 1). For SBRT to MHL, strategies, such as limiting PTV heterogeneity to a D_{max} ≤110% to 120%,[10,32] reducing circumferential high-dose irradiation of the esophagus and PBT, and strict adherence to established dose constraints[6,33] should be used. Other series report more favorable toxicity profiles for MHL SBRT. For example, a recent systematic review of 196 patients in 4 retrospective series found that SBRT to MHL was associated with a pooled grade ≥3 toxicity rate of 6%, although with a near-identical mortality rate of 2%.[31] Furthermore, in a multicenter analysis of 76 Italian patients, Franceschini et al reported a grade ≥3 toxicity rate of only 1.3% and no treatment-related deaths.[16] One noteworthy difference between the Italian study and our series, however, is that only 20% of patients underwent SBRT to ≥1 lymph node metastasis, compared with 40% (n = 21/52) in our series. Additionally, 21% (n = 11/52) in our series received synchronous SBRT to an adjacent lung metastasis. The higher rate of grade ≥3 toxicities in our study may, therefore, be secondary to the inclusion of multiple targets and larger resultant PTVs, which exposes a greater volume of OARs to higher radiation doses and has been demonstrated to increase the risk for SBRT-related toxicity with ultracentral tumors.[10,32] At our institution, all attempts are made to stop any nonhormonal ST agents before SBRT, as fatal toxicities (eg, pulmonary hemorrhage) have been reported, especially with tyrosine kinase inhibitors and antivascular endothelial growth factor therapy.[9,34,35] Despite these findings, the optimal timing of SBRT around ST schedules remains unknown. Fortunately, none of the patients in our cohort experienced fatal complications related to the PBT, esophagus, heart, or great vessels, likely due to the lower SBRT doses used (compared with typical SBRT doses used for lung tumors) and no reirradiation cases. Half of patients (n = 3/52;

Table 3 Characteristics of patients experiencing grade ≥3 toxicity

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Clinical scenario	65M with oligoprogressive RCC on sunitinib	62M with oligoprogressive RCC on observation	69F with oligoprogressive breast cancer on intravenous FEC-D chemotherapy	62M with oligoprogressive RCC on sunitinib	69M with oligoprogressive RCC on observation	79F with oligoprog ressive RCC on cabozan tanib
No. of lymph nodes targeted	1	1	2	3	3	3
Location of lymph node(s) targeted (IALCS lymph node station)	10R	10R	11R, 11R	7, 10L, 10R	7, 8, 10R	7, 10R, 10R
Parenchymal lung metastasis encompassed within the MHL SBRT PTV? (maximum dimension, location)	No	No	No	Yes (7.9 cm, left lower lobe)	No	Yes (5.0 cm, right lower lobe)
PTV	58.5 mL	30.1 mL	61.7 mL	476.9 mL	105.5 mL	368.1 mL
Prescription dose in 5 fractions	40 Gy	50 Gy	35 Gy	30 Gy	35 Gy	30 Gy
Toxicity	Grade 3 lung infection	Grade 3 lung infection	Grade 3 lung infection	Grade 3 acute esophagitis and grade 3 bronchopleural fistula	Grade 4 upper gastrointestinal hemorrhage	Grade 5 radiation pneumonitis
Time from SBRT completion to toxicity	337 d	1155 d	106 d	7 d (acute esophagitis) and 501 d (bronchopleural fistula)	212 d	153 d
Transient toxicity?	Yes	Yes	Yes	Yes (acute esophagitis); no (bronchopleural fistula)	Yes	No
Prior overlapping CFRT or SBRT?	No	No	No	No	No	No
Systemic therapy stopped prior to SBRT?	Yes	N/A	Yes	Yes	N/A	Yes
PTV D_{max}	108%	104%	108%	108%	105%	115%
Proximal bronchial tree D_{max}	41.5 Gy	51.2 Gy	36.5 Gy	31.6 Gy	36.5 Gy	31.5 Gy
Esophagus D_{max}	14.5 Gy	24.7 Gy	35.9 Gy	31.7 Gy	35.6 Gy	30.9 Gy
Heart D_{max}	41.1 Gy	50.9 Gy	36.8 Gy	32.0 Gy	36.3 Gy	32.5 Gy
Great vessels D_{max}	42.8 Gy	51.9 Gy	37.5 Gy	31.9 Gy	36.1 Gy	32.1 Gy
Lung V13.5 Gy	387.5 mL	177.2 mL	360.6 mL	723.1 mL	211.6 mL	706.3 mL
Panel consensus on attribution of SBRT to the observed grade ≥3 toxicity	Probable	Probable	Possible	Definite (acute esophagitis); possible (bronchopleural fistula)	Definite	Probable

Abbreviations: CFRT = conventionally fractionated radiation therapy; D_{max} = maximum dose; FEC-D = 5-fluorouracil, epirubicin, cyclophosphamide, and docetaxel; IASLC = International Association for the Study of Lung Cancer; MHL = mediastinal and hilar lymphadenopathy; PTV = planning target volume; RCC = renal cell carcinoma; SBRT = stereotactic body radiation therapy.

5.8%) experiencing a grade ≥3 toxicity developed an ipsilateral lobar pneumonia after SBRT to an adjacent hilar lymph node metastasis. Reports of radiation-induced organizing pneumonia (RIOP) after lung SBRT are not uncommon, occurring with an incidence of up to 8.2% at 2 years with varying latency (sometimes years) after treatment.[36,37] The cause of RIOP is unknown and may be caused by pulmonary infections, inflammation, or radiation-induced lung injury.[37] It is unclear if patients in our series developed RIOP or simply a community acquired pneumonia after lung SBRT. Regardless, symptoms were generally mild, and patients were treated with IV antibiotics without recurrence or long-term complications.

Despite the relatively modest median SBRT dose used (35 Gy; biologically effective $dose_{10}$ = 59.5 Gy), LC rates compare favorably against other series of MHL SBRT, with the cumulative incidence of LF at 2- and 3-years found to be 9% and 13.3%, respectively. An important consideration is that our series contained many patients at high risk for disease progression, such as those who received SBRT for OP or a DAP (n = 42/52; 81%). For these indications, the intent of SBRT was to delay changes in the ST strategy, or to optimize LC of a DAP in an area that could cause problems if the metastasis continued to grow. Although not definitely demonstrated in our series, patients receiving SBRT for OP and DAP have been found be at higher risk for systemic progression than those with OM.[22] It is not surprising, therefore, that we found a similar trend, although this was not found to be statistically significant in our series. The median PFS for our cohort was somewhat limited at 4 months, although this is comparable to other series investigating SBRT in oligoprogressive cancers.[22,38] Although distant progression was common, more than half (n = 28/52; 54%) of patients received further SBRT or SRS after initial MHL SBRT, indicating that the salvage of distant failures was feasible and may have additional delayed SCST. In fact, we found that 2 out of 3 patients (66.8%) at 1 year, and a large proportion (42.9%) of patients at 2 years, did not require a change in their ST strategy after MHL SBRT. Although not statistically significant (P = .0567), a trend was noted between SBRT indication and the cumulative incidence of SCST. It was observed that patients treated for a DAP were less likely to require a change in their ST strategy. For example, at 2 years post-MHL SBRT, 19.1% of patients with a DAP required a change in their ST strategy, compared with 45% with OM and 69% with OP. Patients treated for a DAP underwent more lines of ST before MHL SBRT and likely had fewer further ST options than those with OM or OP. For such patients, optimizing local control of progressing MHL may have been the main clinical benefit.

There may be several potential benefits of delaying SCST with SBRT: (1) prolonged breaks from ST may allow for quality of life preservation; (2) targeting progressive drug-resistant clones may allow current lines of ST to continue and prevent or delay the need to start subsequent (and potentially more toxic) lines of treatment; and (3) the use of locally ablative therapies at time of disease progression may be more cost-effective than the historical strategy of changing to next line ST.[21] Nevertheless, the decision to change the ST strategy for an individual patient is based on several patient, disease, and treatment related factors, which are admittedly outside of the scope of this retrospective review. As this topic remains an area of active

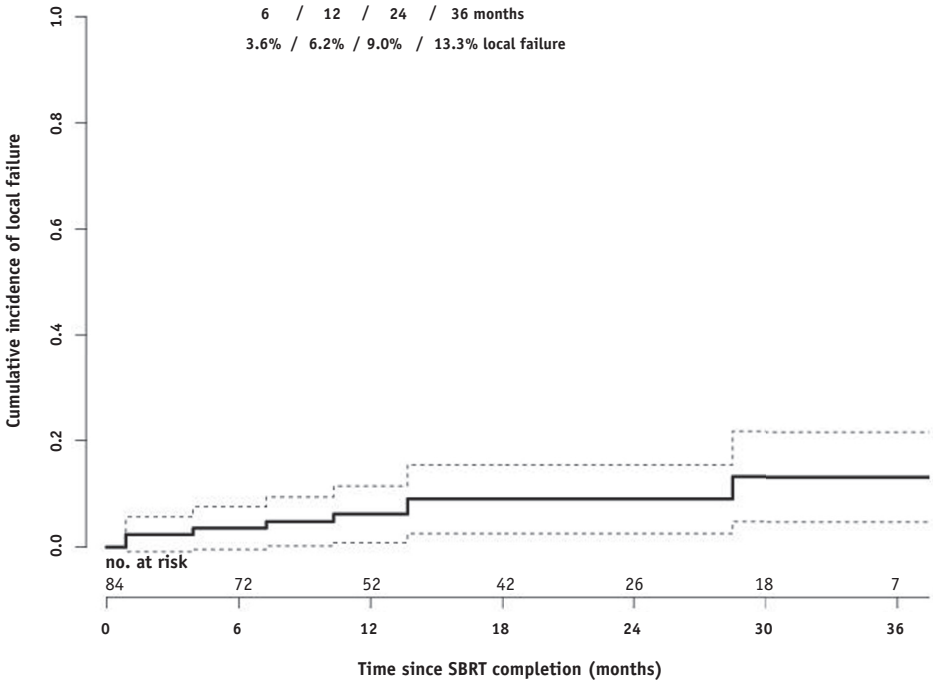

Fig. 2. The cumulative incidence of local failure for mediastinal and hilar lymph node metastases treated with stereotactic body radiation therapy. Dashed lines indicate the 95% confidence interval.

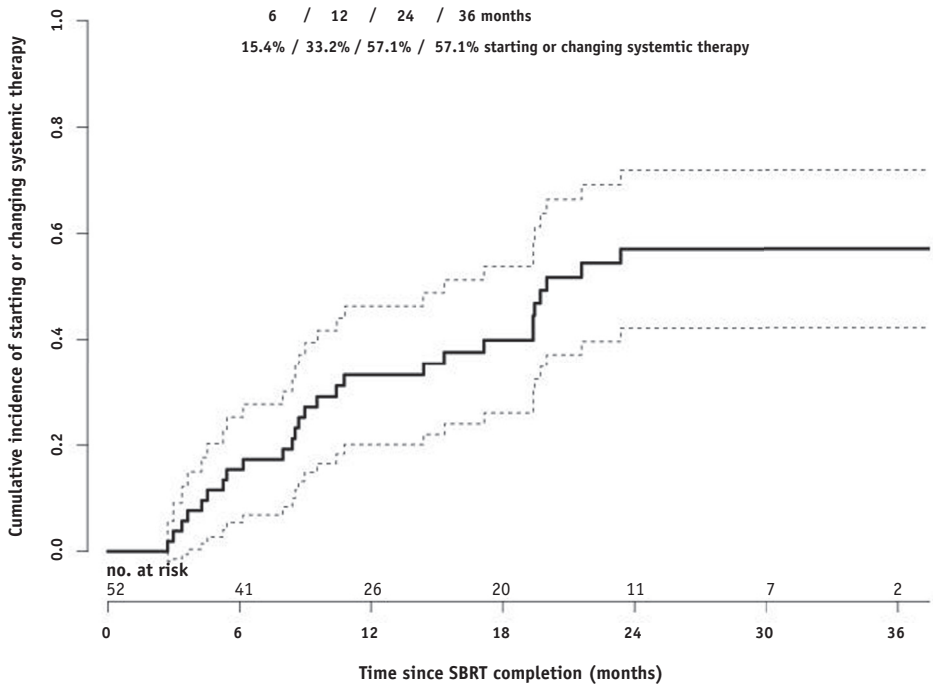

Fig. 3. The cumulative incidence of starting or changing systemic therapy after stereotactic body radiation therapy for mediastinal and hilar lymph node metastases. Dashed lines indicate the 95% confidence interval.

investigation,[39] we await the results of currently accruing, histology-specific, prospective studies (ClinicalTrials.gov ID: NCT02019576, NCT02756793, NCT03256981, and NCT03644303), which will shed light on the potential clinical benefits of SBRT for oligoprogressive cancers.

There are several limitations to this study, chiefly its retrospective nature (which limits the ability to draw conclusions on the causal effect of SBRT on clinical outcomes), relatively small sample size, and heterogeneous patient population (particularly with respect to primary site, treatment history, SBRT indications, SBRT dose prescriptions, and varying ST regimens). More than half of the included patients had a diagnosis of renal cell carcinoma, which may limit the applicability of our results to other

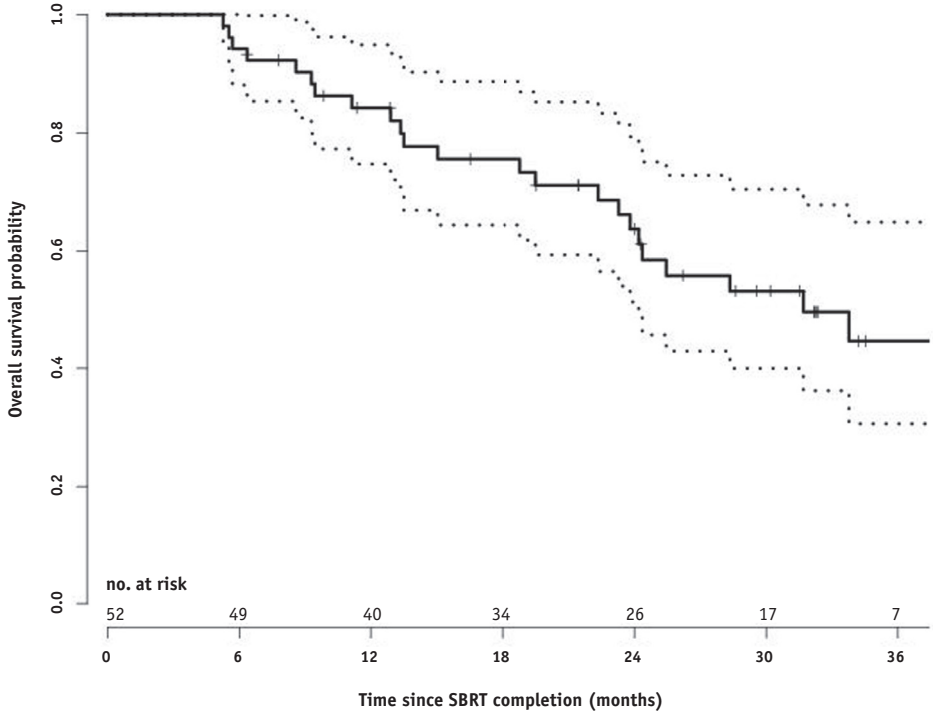

Fig. 4. Overall survival for patients undergoing stereotactic body radiation therapy for mediastinal and hilar lymph node metastases. Dashed lines indicate the 95% confidence interval.

populations. The retrospective extraction of patient data from medical charts and relatively short median follow-up time may have resulted in the underreporting of serious toxicities.

Conclusions

SBRT to mediastinal and hilar lymph node metastases is feasible and the risk for serious toxicity appears to be acceptable in the modern era. The majority of grade $\geq$3 toxicities were transient and did not result in any long-term treatment-related complications. Local failures were rare (9% cumulative incidence at 2 years) and many patients did not require a change in their ST strategy after MHL SBRT. We recommend that patients undergoing SBRT to MHL be treated with strict adherence to dose constraints presented in evidence-based protocols and guidelines.[6,8,33] Dosimetric strategies, such as potential undercoverage of target volumes adjacent to critical OARs and delivering more homogeneous SBRT plans, should be used to mitigate the risk of severe toxicity. Prospective evaluation of mediastinal and hilar SBRT is warranted.

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