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International Journal of Radiation Oncology biology • physics

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Scientific Letter

Safety, Efficacy, and Patterns of Failure After Single-Fraction Stereotactic Body Radiation Therapy (SBRT) for Oligometastases

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Received Jun 27, 2020. Accepted for publication Oct 9, 2020.

Purpose: Fewer attendances for radiation therapy results in increased efficiency and less foot traffic within a radiation therapy department. We investigated outcomes after single-fraction (SF) stereotactic body radiation therapy (SBRT) in patients with oligometastatic disease.

Methods and Materials: Between February 2010 and June 2019, patients who received SF SBRT to 1 to 5 sites of oligometastatic disease were included in this retrospective study. The primary objective was to describe patterns of first failure after SBRT. Secondary objectives included overall survival (OS), progression-free survival (PFS), high-grade treatment-related toxicity (Common Terminology Criteria for Adverse Events grade $\geq$3), and freedom from systemic therapy (FFST).

Results: In total, 371 patients with 494 extracranial oligometastases received SF SBRT ranging from 16 Gy to 28 Gy. The most common primary malignancies were prostate (n = 107), lung (n = 63), kidney (n = 52), gastrointestinal (n = 51), and breast cancers (n = 42). The median follow-up was 3.1 years. The 1-, 3-, and 5-year OS was 93%, 69%, and 55%, respectively; PFS was 48%, 19%, and 14%, respectively; and FFST was 70%, 43%, and 35%, respectively. Twelve patients (3%) developed grade 3 to 4 treatment-related toxicity, with no grade 5 toxicity. As the first site of failure, the cumulative incidence of local failure (irrespective of other failures) at 1, 3 and 5 years was 4%, 8%, and 8%, respectively; locoregional relapse at the primary was 10%, 18%, and 18%, respectively; and distant failure was 45%, 66%, and 70%, respectively.

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Disclosures: D.B. reports personal fees from AstraZeneca outside the submitted work. M.B. reports personal fees from Regeneron Pharmaceuticals outside the submitted work. N.H. reports grants from Varian Medical Systems outside the submitted work. T.K. reports other from the University of Wollongong outside the submitted work. S.S. reports various financial relationships (outside the submitted work) with Varian Medical Systems, AstraZeneca, and BMS and supported by an National Health and Medical Research Council (NHMRC) fellowship GNT1122347 and Peter MacCallum Cancer Centre Discovery Fellowship.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Supplementary material for this article can be found at https://doi.org/10.1016/j.ijrobp.2020.10.011.

Acknowledgments—The authors thank Melissa Bruce for input into manuscript preparation and submission and Gaudreault Mathieu for assistance with data acquisition.

Int J Radiation Oncol Biol Phys, Vol. 109, No. 3, pp. 756–763, 2021
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2020.10.011

Conclusions: SF SBRT is safe and effective, and a significant proportion of patients remain FFST for several years after therapy. This approach could be considered in resource-constrained or bundled-payment environments. Locoregional failure of the primary site is the second most common pattern of failure, suggesting a role for optimization of primary control during metastasis-directed therapy.

Introduction

The COVID-19 pandemic has necessitated a sharp focus on delivering radiation therapy more efficiently in a resource-constrained environment. Efforts to limit traffic within a radiation therapy department have encouraged shortening of treatment courses.[1,2] A recent European Society for Radiotherapy and Oncology/American Society for Radiation Oncology consensus statement showed strong consensus (90%) support for single-fraction (SF) 30 to 34 Gy for stage I non-small cell lung cancer if choosing increased hypofractionation during the pandemic.[3] Although SF stereotactic body radiation therapy (SBRT) for primary non-small cell lung cancer has randomized phase 2 evidence to support consensus,[4,5] evidence on choice of fractionation schedules for oligometastatic disease is lacking. However, if proven to be safe and effective, SF SBRT for oligometastatic disease may be particularly attractive during this pandemic, and possibly beyond, especially in resource-constrained or bundled-payment environments. The purpose of this study is to assess clinical outcomes secondary to SF SBRT to 1 to 5 sites in patients with oligometastatic disease. In particular, this study focuses on patterns of failure to inform strategies to optimize outcomes after SF SBRT to oligometastatic disease.

Methods and Materials

This retrospective study received institutional ethics board approval and assessed patients treated between February 2010 and June 2019 at the Peter MacCallum Cancer Centre. Eligible patients had solid-organ malignancies with metastatic disease, were aged $\geq$18 years, and were treated with SF SBRT to 1 to 5 sites of disease. This research followed the STROBE guideline for reporting of cohort studies.

Technical aspects of treatment delivery have been previously described.[6] Briefly, for tumors moving with respiration, a 4-dimensional computed tomography (CT) scan was acquired for treatment planning, which was used to define an internal target volume (ITV). Otherwise, a 3-dimensional CT was acquired for treatment planning, on which a gross tumor volume (GTV) was delineated. The clinical target volume (CTV) was considered equivalent to the GTV. A 5-mm GTV, CTV, or ITV to planning target volume (PTV) margin was used for all treatments. Vertebral body metastases CTV definition, PTV margin, and dose prescription were as previously published.[7] Treatment plans were performed using either Elekta XiO, BrainLab iPlan, or Varian Eclipse treatment planning systems. Treatment planning processes included noncoplanar 3-dimensional CT, dynamic conformal arc therapy, intensity modulated radiation therapy, or volumetric modulated arc therapy. Dose calculation was performed with convolution/superposition, analytical anisotropic algorithm, or AcurosXB reporting dose to medium. Treatment was typically prescribed such that 99% of the PTV received the prescription dose, with the near maximum between 125% and 140% of the prescription dose. PTV coverage was compromised to comply with maximum dose constraints to adjacent critical organs. Dose constraints have previously been published[8-10] and are summarized in Table E1. Patients were treated on a Varian Clinac iX or TrueBeam with either a millennium or HD120 MLC (Varian Medical Systems, Palo Alto, CA). Image guidance was performed using cone beam CT, matching to the GTV/CTV/ITV with translation corrections only. For bone and vertebral body lesions, stereoscopic x-rays were used in addition to cone beam CT, with translation and rotation corrections applied.

Prior treatment for metastatic disease was not an exclusion criterion. Consecutive patients were included. during the study period the most common reasons for receipt of multifraction SBRT was reirradiation SBRT, spinal lesions with spinal instability neoplastic score score $>$7, and liver metastases. Patients who had distant progression after SBRT with 1 to 5 metastases were routinely considered for further salvage SBRT. Patients with unknown primary malignancy or intracranial disease only were excluded. The primary objective was to describe patterns of first failure after SBRT. Secondary objectives were to assess patterns of failure after salvage therapy, overall survival (OS), progression-free survival (PFS), widespread failure-free survival (WFFS), high-grade treatment-related toxicity (Common Terminology Criteria for Adverse Events 4.0), and time to initiation of systemic therapy. Routine follow-up included the use of conventional imaging (CT with or without whole body bone scan). For patients with a limited pattern of oligorecurrent disease, a positron emission tomography scan was performed before consideration of salvage therapies. Widespread failure was defined as the development of $>$5 concomitant metastatic lesions. The landmark start date for all time-to-event endpoints was the date of commencement of the first SBRT.

The pattern of first failure is defined as the cumulative incidence of the first failure, considering each failure separately, and was classified as local, locoregional (LR) of primary, or distant (and any combination of those failures). LR of primary is a failure in the primary site or in the

regional draining lymph nodes related to the primary. For example, LR in the context of prostate cancer was defined as noninguinal pelvic lymph nodes below the bifurcation, and LR in the context of lung cancer was defined as mediastinal or ipsilateral supraclavicular lymph nodes. Attribution of local failure was clinician defined and based on imaging findings with or without biopsy confirmation. Patients with prostate cancer and biochemical progression without radiologic progression were censored at the date of biochemical progression for all analyses of recurrence. The Kaplan-Meier method was used to describe the time-to-event curves. Cumulative incidence curves assuming competing risks were provided to describe the pattern of first failure. A sensitivity analysis was performed assessing the cohort excluding patients with prostate cancer, second including only patients with prostate cancer, and again including only patients with lung cancer. All statistical analyses were performed in R (R version 3.6.1).

Results

Patient and lesion characteristics

In total, 371 consecutive patients had 494 oligometastases treated with SF SBRT. The most common primary malignancies were prostate (29%), lung (17%), nonprostate genitourinary (14%), gastrointestinal (14%), and breast (11%) (Table 1). Sixty-four percent (n = 238) had adenocarcinoma. For prior treatments, 96% received definitive treatment of the primary (eg, surgery or radiation therapy); 33% had prior adjuvant or concurrent systemic therapy with the primary intervention, 24% had prior systemic therapy directed at metastatic disease, and 33% had systemic therapy at the time of SBRT. Twenty-eight percent received prior metastasis-directed therapy. At the time of SBRT, 96% had 1 to 3 active metastases. Of 494 lesions, 38% were in lung, 28% in bone, 16% in spine, and 11% in lymph nodes. Of the lung metastases, 10 (6%) were centrally located, and 157 (94%) were peripherally located. The prescription dose ranged from 16 Gy to 28 Gy and the most common prescription was 20 Gy (58%). The mean (±standard deviation) metastasis size (maximal axial tumor dimension) was 20.4 mm (±14.7 mm). Additional information about target characteristics and dose selection are in Table E2. In general, target dose selection was 16 Gy to 18 Gy for complex bone or central lung, 20 Gy to 24 Gy for bone or soft tissue, and 26 Gy to 28 Gy for adrenal and peripheral lung.

Outcomes

The median follow-up time was 3.1 years. Time to event outcomes are described in Table 2. Median OS was 5.4 years, and 5-year OS was 55% (95% confidence interval [CI], 48-62) for the entire cohort. Median PFS after SBRT was 1 year, with a 5-year PFS rate of 14% (95% CI, 9-20). Median widespread failure-free survival was 2 years. Of the 252 patients who were not on systemic therapy at the time of SBRT, median time to initiation of systemic therapy was 2.1 years, and 35% (95% CI, 26-43) were free from systemic therapy at 5 years. Figure 1 depicts Kaplan-Meier estimates for survival outcomes of interest.

Because prostate cancer can progress biochemically without radiologic confirmation, and thus systemic hormonal manipulation can be initiated before radiologic progression, a sensitivity analysis was performed excluding prostate primaries. In this subset, OS, PFS, and WFFS at 5 years was 43%, 12%, and 22%, respectively. The median OS, PFS, and WFFS were lower at 4 years, 0.8 years, and 1.6 years, respectively. The median freedom from systemic therapy of patients excluding those with prostate cancer was higher at 3.5 years. Analysis of the prostate cancer–only subset of patients revealed OS, PFS, and WFFS at 5 years was 78%, 19%, and 30%, respectively. For the subset including only patients with lung cancer (the second largest primary malignancy group), the OS, PFS, and WFFS at 5 years was 27%, 0%, and 11%, respectively.

Patterns of failure

Patterns of first failure are summarized in Table 3. Distant failures were the most dominant pattern of first failure after SBRT. The cumulative incidence of distant failure as the first site at 5 years (irrespective of other failures) was 70%, followed by LR relapse to the primary (18%) and local failure of the SBRT target (8%; Fig. 2).

After disease progression, 102 patients had salvage treatment consisting of high-dose radiation therapy alone (n = 46), surgery alone (n = 15), the combination of surgery and high-dose RT (n = 9), or other (n = 32 [palliative radiation therapy n = 27, thermal ablation n = 5]). The treatment approach for each lesion was independently formulated based on tumor location when multiple courses of SBRT were prescribed. The cumulative incidence of first failure at 1 year according to salvage treatment at progression is shown in Table 4. Thirty patients had local progression. Of these, 7 received salvage local therapy (5 had surgery, 1 had thermal ablation, and 1 had intracranial radiosurgery). No repeat SBRT after initial failure of SBRT was prescribed.

Treatment toxicity

Sixty-one percent (n = 228) of the patients did not report treatment-related toxicity. A total of 12 patients (3%) developed grade 3 or 4 treatment-related toxicity. One patient developed unexplained severe dyspnea without radiographic evidence of pneumonitis 1 month after SBRT to 4 peripheral lung metastases. One patient developed L5-S1 radiculopathy manifesting as foot-drop 43 months after 20 Gy in 1 fraction to an L5 spine metastasis from sarcoma. The remaining high-grade toxicities were symptomatic

Table 1 Baseline characteristics of the patients included for analysis

Characteristic	Total (n = 371)
Sex, n (%)	
Male	245 (66%)
Female	126 (34%)
Age at SBRT treatment, y	
Median (range)	67 (23-95)
Primary site of histologic origin, n (%)	
Bone and soft tissue	28 (8%)
Breast	42 (11%)
Gastrointestinal	51 (14%)
Genitourinary (nonprostate)	52 (14%)
Prostate	107 (29%)
Lung	63 (17%)
Skin	21 (6%)
Other	7 (2%)
PET screened pre-SBRT, n (%)	
Yes	328 (88%)
No	43 (12%)
Histology of primary, n (%)	
Adenocarcinoma	238 (64%)
Clear cell carcinoma	40 (11%)
Sarcoma	27 (7%)
Squamous cell carcinoma	20 (5%)
Other	46 (12%)
Type of metastasis, n (%)	
Metachronous	280 (75%)
Synchronous	91 (25%)
Radical treatment of primary, n (%)	
Yes	356 (96%)
No	15 (4%)
Surgery to primary, n (%)	
Yes	284 (77%)
No	87 (23%)
RT to primary, n (%)	
No	175 (47%)
Yes	196 (53%)
No. of prior lines of systemic therapy for metastases n (%)	
0	282 (76%)
1	68 (18%)
2	12 (3%)
>2	9 (2%)
Prior metastasis-directed therapy, n (%)	
Yes	105 (28%)
No	266 (72%)
ECOG performance status at time of SBRT, n (%)	
0	248 (68%)
1	100 (28%)
2	14 (4%)
3	1 (0%)
Missing	8
Total no. of metastasis treated with SBRT, n (%)	
1	273 (74%)
2	70 (19%)
3	19 (5%)
4	7 (2%)
5	2 (1%)
Total no. of known metastases, n (%)	
1	179 (48%)
2	82 (22%)
3	53 (14%)
4	30 (8%)
5	20 (5%)
6	4 (1%)
7	1 (1%)
8	1 (1%)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PET = positron emission tomography; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

Table 2 Kaplan-Meier estimates and 95% confidence intervals at specific time points for OS, PFS, WFFS, and FFST

Year	OS	PFS	WFFS	FFST
1	93 (90-95)	48 (43-53)	67 (62-72)	70 (63-75)
2	80 (75-84)	29 (24-34)	50 (44-56)	51 (44-57)
3	69 (63-74)	19 (15-24)	39 (33-44)	43 (36-50)
4	60 (53-66)	18 (13-23)	32 (26-38)	40 (32-47)
5	55 (48-62)	14 (9-20)	24 (17-31)	35 (26-43)
Median (y)	5.4 (4.7-NE)	1.0 (0.8-1.2)	2.0 (1.6-2.5)	2.1 (1.8-3.5)

Abbreviations: FFST = freedom from systemic therapy; NE = not evaluable; OS = overall survival; PFS = progression-free survival; WFFS = widespread failure-free survival.

fractures from treatment of bone (n = 6) or spine (n = 4) lesions. Of these 10, 4 had prior local treatments to the same site, either with surgery or radiation therapy. No treatment-related death (grade 5) was observed.

Discussion

A cornerstone recommendation for radiation therapy during the COVID-19 pandemic has been the rationalization of fractionation schedules.[1,2,11] Our study findings suggest that SF SBRT for oligometastatic disease can be delivered with high local control and low toxicity. Moreover, we observed a median time to onset of systemic therapy of 2.1 years, demonstrating another potential advantage of SBRT: the potential to delay initiation or switching of immunosuppressive systemic therapies. Moving beyond the pandemic, these findings may support the use of shortened courses of SBRT for patients with oligometastatic disease in bundled-payment or low-resource environments.

The recently reported SABR-COMET randomized trial[12] demonstrated a benefit with the addition of fractionated SBRT to standard of care in patients with 1 to 5 oligometastases. This difference was seen in both 5-year PFS (0% vs 17.3%, $P = .001$) and OS (17.7% vs 42.3%, $P = .005$); these improvements are comparable to our

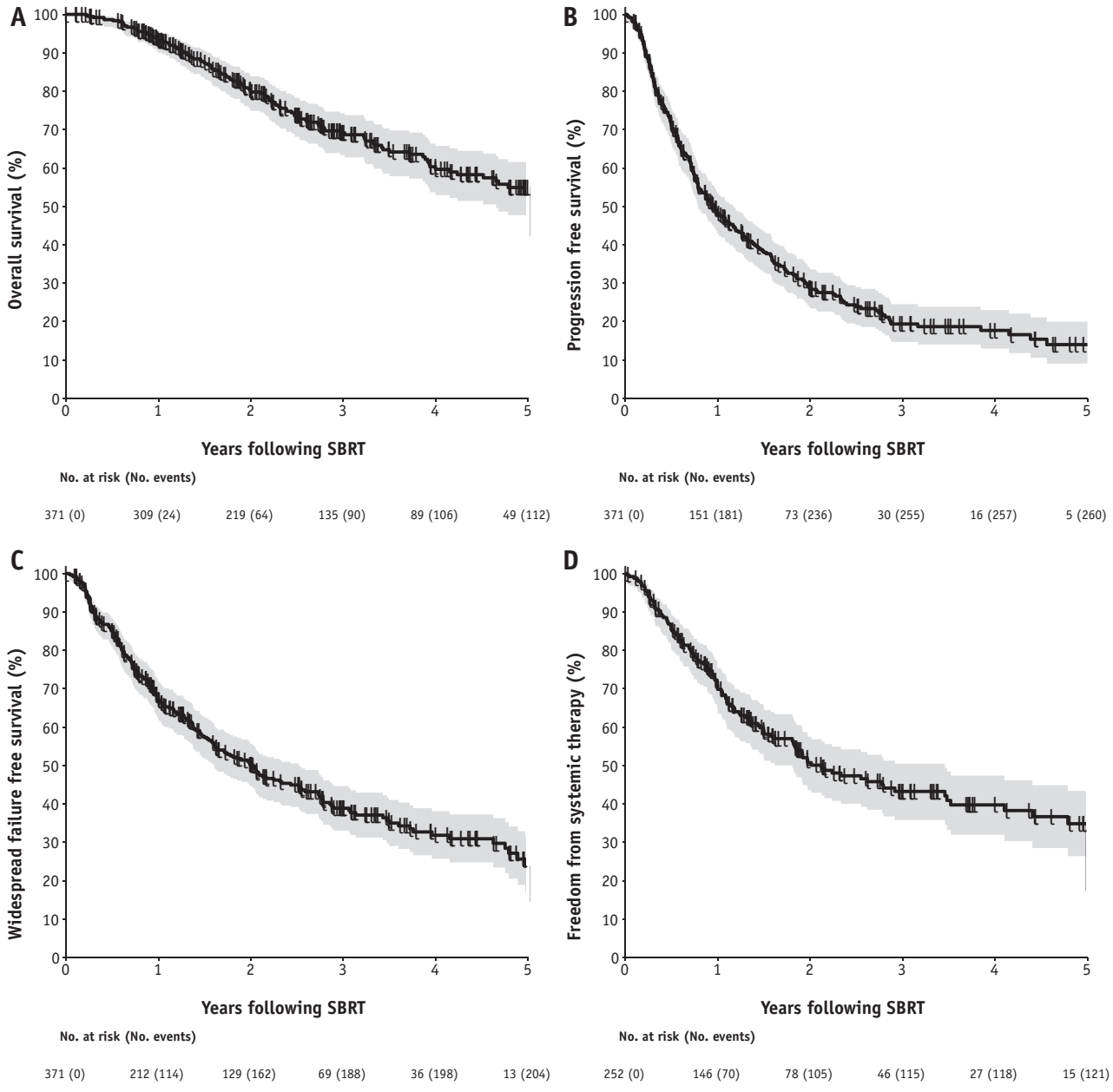

Fig. 1. Oncologic outcomes for the single-fraction cohort: (A) overall survival, (B) progression-free survival, (C) widespread failure-free survival, and (D) freedom from systemic therapy in subset who did not have systemic therapy at time of SBRT. Gray shaded area indicates 95% confidence interval; numbers below each graph highlight the number of patients at risk for each year after stereotactic body radiation therapy treatment.

observed 5-year OS (55%) and PFS (14%). In particular, these long-term PFS outcomes are consistent across the literature.[13-16] Our cohort had a similar proportion of breast and prostate cancer (40% in current study vs 41% in SABR-COMET), as well as 1 to 3 active metastatic sites (96% current study vs 94% in SABR-COMET). A notable difference was the toxicity rates, with 3 deaths noted in SABR-COMET (albeit the attribution of toxicity to SBRT was arguably quite conservative). Although one possible hypothesis is that SF SBRT is less toxic than the fractionated schedules used in SABR-COMET, it is more likely that either toxicity was underreported owing to the retrospective nature of this analysis or that the small number of deaths in SABR-COMET was a chance finding. The toxicity of single-fraction versus multifraction SBRT for oligometastatic disease is presently being prospectively evaluated in the TransTasman Radiation Oncology Group (TROG) 13.01 SAFRON II clinical trial.[10] Other notable randomized trials currently supporting the role of SBRT as consolidation therapy in oligometastatic disease include the studies by Gomez et al[17] and Iyengar et al[18] in the context of lung cancer. In these early terminated studies of 49 and

Table 3 Patterns of first failure

Event	Year 1	Year 2	Year 3	Year 4	Year 5
Local*	2 (1-4)	4 (2-6)	5 (3-9)	5 (3-9)	5 (3-9)
Local + distant*	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)
LR to primary*	5 (3-7)	7 (5-10)	8 (5-11)	8 (5-11)	8 (5-11)
LR to primary + distant*	5 (3-8)	8 (5-11)	10 (7-14)	10 (7-14)	10 (7-14)
Distant*	37 (32-42)	49 (43-54)	54 (48-59)	55 (49-60)	57 (50-64)
Death*	1 (0-2)	2 (1-4)	2 (1-4)	2 (1-4)	3 (1-6)
Any local (± distant)†	4 (2-6)	6 (4-9)	8 (5-11)	8 (5-11)	8 (5-11)
Any LR to primary (± distant)†	10 (7-14)	15 (11-19)	18 (13-22)	18 (14-23)	18 (14-23)
Any distant (± Local or LR to primary)†	45 (39-50)	59 (53-64)	66 (60-71)	67 (61-73)	70 (63-76)

Abbreviations: CI = confidence interval; LR = locoregional.
* Cumulative incidences of individual failure categories. Data presented as cumulative incidence estimates, % (95% CI).
† Incidence of any local, LR, or distant failure (irrespective of other failures). Data presented as cumulative incidence estimates, % (95% CI).

29 patients, metastasis-directed therapy was used after initial induction systemic therapy. The median PFS of the control and experimental arm was 4.4 months versus 14.2 months ($P = .02$), and 3.5 months versus 9.7 months ($P = .01$), respectively.

Interestingly, we found that LR relapse in the primary was the second most common pattern of failure, after distant recurrence. Primary failures are rarely reported in studies describing outcomes after local oligometastases management, in which failure in the primary is commonly classified as a distant failure. The reason may be the questionable clinical significance, particularly in the setting of widespread metastatic disease. Although distant relapses predominate in the oligometastatic setting, it appears that primary relapses remain unavoidable. Chance et al[19] reported that 3 of 43 patients' primary site failed after SBRT to adrenal metastases (7% failure rate). Yoshida et al[20] reported that 9 of 27 patients developed eventual primary relapse in the prostate (33% failure rate) after metastasis-directed therapy. Focusing on the primary is increasingly relevant because emerging evidence suggests that local treatment of primary disease confers survival benefits in the metastatic setting.[11,21] Most notably, in the STAMPEDE trial,[21] patients with low-volume metastatic prostate cancer had significantly improved survival after receipt of prostate radiation therapy (HR 0.68). In our study, we observed an 18% risk of first failure being LR to the primary at 5 years, which suggests that there may be a role of optimizing control of the primary when planning metastasis-directed therapy.

The classic phenotype of isolated oligometastatic disease potentially amenable to curative local treatment is, unfortunately, the exception rather than the rule in the published literature. At 5 years, only a small minority (14%) would be free from any progression[12] and only 18% to 26% free from widespread metastasis in 5 years.[13,14] This is consistent with our observations, in which 5-year

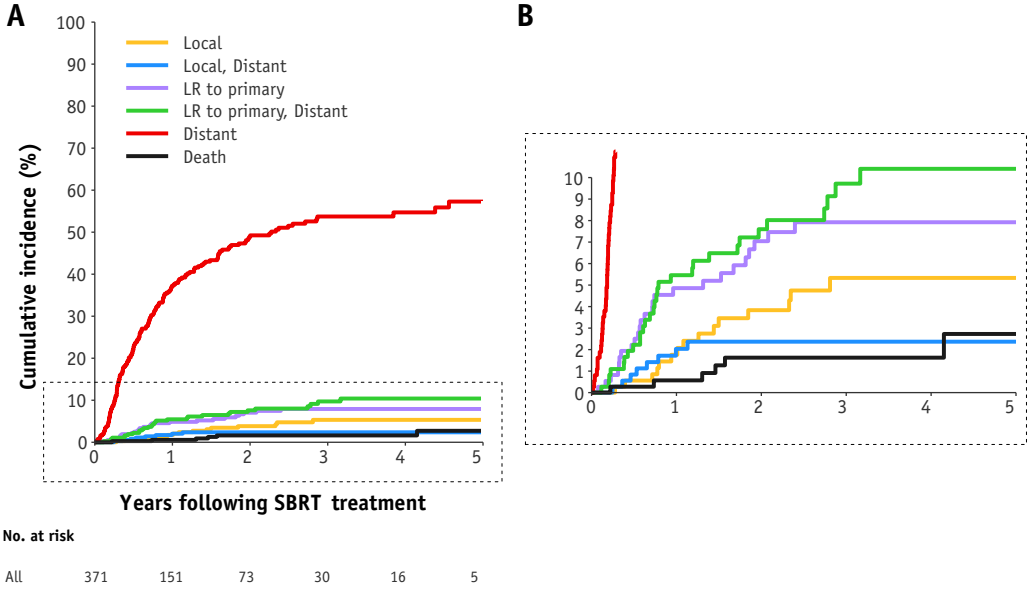

Fig. 2. Cumulative incidence of first failure. (A) All patterns of failure inclusive of distant failure; numbers below the graph highlight the number of patients at risk for each year after stereotactic body radiation therapy. (B) Subset of (A) that highlights patterns of failure exclusive of distant failure. *Abbreviation:* LR = locoregional.

Table 4 Cumulative incidence % (95% CI) of first failure at 1 year after salvage treatment, by salvage treatment type

Salvage treatment	Local	Local + distant	LR to primary	LR to primary + distant	Distant	Death
High-dose RT (n = 46)	5 (1-14)	7 (2-18)	0 (0-0)	7 (2-18)	41 (26-56)	2 (0-11)
Surgery (n = 24)	0 (0-0)	4 (0-19)	5 (0-20)	5 (0-20)	48 (25-67)	5 (0-20)
Other (n = 32)	7 (1-20)	3 (0-15)	4 (0-18)	3 (0-15)	43 (25-60)	20 (8-36)

Abbreviations: CI = confidence interval; LR = locoregional; RT = radiation therapy.

PFS and WFFS were 14% and 24%, respectively. Therefore, despite local efficacy, distant failure is common after SBRT in this cohort, which raises the question: Is SBRT a worthwhile intervention in the first instance? Perhaps an aspect that encourages a trial of the approach is the palatable adverse event profile of SF SBRT. We reported a relatively low rate of grade 3 to 4 toxicity (n = 12, 3%). In the context of a median time to initiation of systemic therapy of 2.1 years in the entire cohort, and 3.5 years in the cohort excluding prostate cancer patients, there is considerable potential for SBRT to preserve quality of life for clinically meaningful periods of time. There is also consistent reporting of a small minority of patients who remain disease free for years after SBRT, and when this outcome is realized and contextualized against the small impost of a single outpatient visit for treatment, SF SBRT may become a reasonably attractive proposition.

This study was limited by its retrospective nature and the inherent biases, including retrospective reporting of toxicity. Toxicity outcomes secondary to SBRT were difficult to differentiate from those secondary to medical comorbidities or other treatment modalities. Attribution of local failure can be challenging and sometimes overestimated on radiology after SBRT and is a known limitation of patterns-of-failure analyses. Heterogeneity in the patient cohort limits interpretation of histology-specific outcomes. Although we included consecutive patients, these findings are from a single institution and are not externally validated.

Conclusion

SF SBRT is safe and effective, and a significant proportion of patients remain free from systemic therapy for several years after SBRT. After distant failure, LR failure of the primary site is the second most common pattern of failure, suggesting that we should consider whether primary control is adequate at the time of embarking on metastasis-directed therapy.

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