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Scientific Article

Efficacy and Safety of Stereotactic Body Radiation Therapy for Pediatric Malignancies: The LITE-SABR Systematic Review and Meta-Analysis

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Abstract

Purpose: Limited data are currently available on clinical outcomes after stereotactic body radiation therapy (SBRT) for pediatric and adolescent and young adult (AYA) patients with cancer. We aimed to perform a systematic review and study-level meta-analysis to characterize associated local control (LC), progression-free survival (PFS), overall survival, and toxicity after SBRT.

Methods and Materials: Relevant studies were queried using a Population, Intervention, Control, Outcomes, Study Design (PICOS)/Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)/Meta-analysis of Observational Studies in Epidemiology (MOOSE) selection criteria. Primary outcomes were 1-year and 2-year LC as well as incidence of acute and late grade 3 to 5 toxicities, with secondary outcomes of 1-year overall survival and 1-year PFS. Outcome effect sizes were estimated with weighted random effects meta-analyses. Mixed-effects weighted regression models were performed to examine potential correlations between biologically effective dose (BED_{10}), LC, and toxicity incidence.

Results: Across 9 published studies, we identified 142 pediatric and AYA patients with 217 lesions that were treated with SBRT. Estimated 1-year and 2-year LC rates were 83.5% (95% confidence interval, 70.9%-96.2%) and 74.0% (95% CI, 64.6%-83.4%), respectively, with an estimated acute and late grade 3 to 5 toxicity rate of 2.9% (95% CI, 0.4%-5.4%; all grade 3). The estimated 1-year OS and PFS rates were 75.4% (95% CI, 54.5%-96.3%) and 27.1% (95% CI, 17.3%-37.0%), respectively. On meta-regression, higher

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BED_{10} was correlated with improved 2-year LC with every 10 Gy_{10} increase in BED_{10} associated with a 5% improvement in 2-year LC ($P = .02$) in sarcoma-predominant cohorts.

Conclusions: SBRT provided durable LC for pediatric and AYA patients with cancer with minimal severe toxicities. Dose escalation may result in improved LC for sarcoma-predominant cohorts without a subsequent increase in toxicity. However, further investigations with patient-level data and prospective inquiries are indicated to better define the role of SBRT based on patient and tumor-specific characteristics.

Introduction

Cancer in pediatric and adolescent and young adult (AYA) patients is a significant source of morbidity and mortality.[1] Metastatic disease is particularly associated with poor outcomes across a variety of primary histologies highlighting the need for new therapeutic approaches.[2-4] The role of radiation therapy (RT) is quite varied in the setting of metastatic disease in pediatric patients and ranges from whole lung irradiation for pulmonary metastases in select histologies such as Ewing sarcoma, rhabdomyosarcoma, and Wilms tumor, palliative (RT) for symptomatic osseous metastatic disease, or more definitive approaches to all initially involved metastatic sites in patients who have responded well to systemic therapy.

For patients with oligometastatic disease or locally recurrent disease, surgical resection/metastasectomy may be used with the goal of long-term cure, although not all patients are surgical candidates.[5] Stereotactic body radiation therapy (SBRT) provides a noninvasive alternative to resection/metastasectomy that delivers ablative and highly conformal doses of radiation therapy in 1 to 5 fractions. This approach has the potential benefit of providing superior local control (LC) to conventional RT for histologies thought to be radioresistant (notably sarcoma), given the higher biologically effective doses (BEDs) delivered. Due its steep dose fall-off, SBRT also has improved normal tissue sparing compared with conventional RT, which is particularly relevant in the pediatric population to minimize the risk of associated chronic morbidity secondary to late toxicities.

Notably, SBRT is increasingly used for adults with oligometastatic disease, with evidence suggesting improved OS with aggressive local ablative therapy in addition to palliative systemic therapy.[6] SBRT has also been shown to provide improved palliation of spinal metastatic disease compared with conventional RT in the adult population.[7] Although a number of prospective and retrospective experiences have reported on the use of SBRT for pediatric and AYA patients, each is limited by number of patients and lesions treated with larger multi-institutional trials pending analysis.[8-10] As such, we aimed to perform a systematic review and study-level meta-analysis of available data in the literature to characterize both the safety and efficacy of SBRT for the pediatric and AYA population.

Methods and Materials

Literature selection

We searched PubMed, Embase, and the Cochrane Library for published experiences reporting on clinical outcomes after SBRT for pediatric malignancies up to July 1, 2021. The Population, Intervention, Control, Outcomes, Study Design (PICOS) method (Table E1) was used to design criteria for inclusion.[11-13] To further define search methods and implementation of the study, both the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) selection algorithm (Fig. E1) in addition to PRISMA (Fig. E2) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist guidelines (Fig. E3) were followed.[14,15]

For identification of relevant studies, different combinations of the following search terms were used: stereotactic body radiation therapy, stereotactic ablative radiation therapy, SBRT, SABR, pediatric, AYA, Ewing's sarcoma, osteosarcoma, metastasis, paraspinal, lung, pulmonary, bone, local control, overall survival, progression-free survival, and toxicity. We also reviewed related articles in addition to citations of the initially identified manuscripts.

Relevant inclusion criteria used following our initial search were (1) pediatric or AYA patients 39 years of age or younger; (2) information on 1 of the primary outcomes (LC or grade 3-5 toxicity rates); (3) patients treated with SBRT (defined as at least 5 Gy/fraction delivered in 1-5 fractions); and (4) experiences with either ≥5 patients or ≥10 lesions with information on 1 of the primary outcomes. Exclusion criteria included (1) studies without information on either LC or grade 3 to 5 toxicities; (2) studies that included nonpediatric or AYA patients or without outcomes specific to these subgroups; (3) patients not treated with SBRT or without information specific to patients who received SBRT; (4) works involving patients included in more than 1 study; (5) works with <5 patients or <10 lesions without information on 1 of the primary outcomes; (6) studies involving nonhuman subjects; (7) works not published in English; and (8) unfinished manuscripts.

Ethics

The procedures followed for the purposes of this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Helsinki Declaration (1964, amended in 1975, 1983, 1989, 1996, and 2000) of the World Medical Association.

Data extraction

Independent authors (R.S., A.V.) conducted and reviewed extraction of relevant data from each study that included the primary and secondary outcomes in addition to descriptive analysis of study, patient, and treatment data. For studies that met inclusion criteria and had missing data relating to primary or secondary outcomes, we reached out to authors for missing data. For studies by Tinkle et al and Lazarev et al, patient-level data were obtained after we reached out to the respective first authors for subgroups of their respective patient cohorts treated with SBRT (defined as at least 5 Gy/fraction and delivered in 1-5 fractions); otherwise, study-level data were used.[10,16]

Outcome measures

The primary outcomes of the study were 1-year and 2-year LC rates as well as acute and late grade 3 to 5 toxicities after SBRT, with secondary outcomes of 1-year progression-free survival (PFS) and 1-year OS from date of radiation. Acute toxicities were defined as those occurring within 3 months of SBRT and late toxicities as those occurring at least 3 months after completion of SBRT. When specified, the majority of articles used Common Terminology Criteria for Adverse Events for grading of toxicities. Across all studies, LC was generally defined as having radiographic stable disease or a partial or complete response after SBRT of the primary irradiated lesion, with some studies specifically employing the Response Evaluation Criteria in Solid Tumors (RECIST). When possible, patients treated specifically with palliative intent were excluded (ie, Brown et al), although in the majority of studies this was not specified.

Statistical analysis

For all statistical analyses, the Meta-Analysis for R (metafor) package version 2.0-0 of RStudio, version 1.1.383, was used.[17,18] The DerSimonian and Laird method was followed to determine variances with proportions for primary and secondary outcomes calculated for each study.[19] Relevant effect sizes for both primary and secondary outcomes were calculated with a weighted random effects model dependent on respective sample sizes and forest plots were generated for both primary and secondary outcomes.[20,21] Heterogeneity for all outcomes were assessed with the I^2 statistic and Cochran Q test.[22,23] Egger's test was utilized to assess for publication bias.[24]

To examine potential correlations between BED, assuming an alpha-beta ratio of 10 for LC and early toxicity and an alpha-beta ratio of 3 for late toxicity, and to explore potential heterogeneity in these outcomes, we used mixed-effects meta-regression models using an ordinary least squares approach to estimate weighted linear relationships.[25] For studies that used a variety of dose/fractionation/schemes, we calculated a median BED across all fractionation schedules employed for each study. Relevant weighting for each study for the meta-estimate was determined by taking the number of patients/lesions treated and dividing this by the total number of patients across all included published experiences.[20] We then summarized the results by slopes representing expected changes in either LC or toxicity per 10 unit change in BED. As the cohort of Lazarev et al included a majority of patients with neuroblastoma (that is considered quite radiosensitive compared with other studies comprising sarcoma primaries, that are considered to be more radioresistant), we also performed a subgroup analysis for examination of LC excluding Lazarev et al.[16]

Results

Characteristics of studies included for quantitative analysis

Among 9 published studies meeting inclusion criteria, we identified 142 pediatric and AYA patients with cancer with 217 lesions treated with SBRT.[8-10,16,26-30] Studies were published from 2014 to 2021 with patients from the United States, United Kingdom, and France. Table 1 shows respective data on both primary and secondary outcomes for each study as well as other relevant information regarding patient age, extent of follow-up, primary cancer histologies, primary lesion locations, and dose and fractionation schemes. Median patient age was 15 years (range, 3-28.7). The most common primary histologies were osteosarcoma (45 patients; 31.6%), Ewing sarcoma (43 patients; 30.2%), soft-tissue sarcoma (20 patients; 14.1%), and neuroblastoma (10 patients; 7.0%). The most common locations of treated lesions when specified were spine/paraspinal (83/217 lesions; 38.2%), nonspinal bone (72/217; 33.2%), and lung (53/217; 24.4%). The median dose and fractionation was 35 Gy (range, 12-60 Gy) and 5 (range, 1-5), respectively, without information on isodose prescription available. The median follow-up was 19.2 months (range, 3-76.8 months).

Table 1 Studies examining clinical outcomes after SBRT for pediatric malignancies

Study	Patients (lesions)	Median age (y) (range)	Median follow-up (range)	Histology	Sites of treated lesions	Median target size (range)	Mean/median prescription dose (range)	LC rate (95% CI)	PFS and OS rate (95% CI)	Acute and late toxicities and additional comments
Elledge et al (2021)[9]	14 (37) All patients with metastases from pediatric sarcomas 8 received SBRT to all metastases and 6 to a portion of metastases Prospective multi-institutional phase 2	17 (4-25)	6.8 mo (1.1-36.2 mo)	Ewing sarcoma: 7 patients Osteosarcoma: 4 patients High-grade soft-tissue sarcoma: 3 patients	Spine: 21 lesions Extremities: 9 lesions Pelvis: 6 lesions Skull: 1 lesion Median number of treated lesions: 3 (1-5)	Median maximal dimension: 2.0 cm (0.7-3.3 cm)	All patients treated to 40 Gy/5 fractions	6-mo LC: 89% (43%-98%) 1-y LC: 82.5% 2-y LC: 82.5%	1-y PFS: 29% (9%-52%) 1-y OS: 84% (49%-96%) Median OS: 24 mo	2/14 patients (14.3%) with grade 3 toxicities; 1 case of esophagitis and 1 case of osteoporosis 12/16 total toxicities reported among 9 patients were grade 1 No cases of reirradiation
Tinkle et al (2021)[10] (numbers specific to patients who received SBRT)	40 (76) 30/40 (75%) and 6/40 (15%) with multiple and solitary metastases, respectively 4/40 (10%) with solitary local recurrence Retrospective multi-institutional	16.7 (5.5-25.9)	13.2 mo (0.5-63.3 mo)	Nonrhabdomyosarcoma soft tissue sarcoma: 12 patients Ewing sarcoma: 11 patients Osteosarcoma: 9 patients Rhabdomyosarcoma: 4 patients Other: 4 patients	Spine: 20 lesions Lung: 13 lesions Pelvis/sacrum: 13 lesions Ribs: 7 lesions Shoulder: 3 lesions Other: 20 lesions	Median target volume: 28.7 cc (1.4-313 cc)	MPD: 35 Gy/5 fractions Dose range: 12-40 Gy Fraction range: 1-5	1-y LC: 74% (61.2%-83.4%) 2-y LC: 69% (54.4%-79.5%)	1-y PFS: 23% (9.1%-36.9%) 1-y OS: 78% (58.4%-88.6%)	2/40 patients (5%) with late grade 3 toxicities (osteonecrosis and radiation pneumonitis) 6/40 patients (15%) treated with SBRT as reirradiation
Lazarev et al (2018)[16] (numbers specific to patients who	19 (19) 3/19 patients with localized/recurrent disease; 6/19 patients treated with	12 (4-18)	18.3 mo (2.27-44.7 mo)	Neuroblastoma: 10 patients Osteosarcoma: 5 patients Ewing sarcoma: 3 patients	Axial bone: 9 lesions Appendicular bone: 6 lesions Head and neck: 2 lesions	Median maximal dimension: 4.0 cm (1.4-17.8 cm)	MPD: 30 Gy/5 fractions Dose range: 24-40 Gy Fraction range: 3-5	1-y LC: 82.5% (54.7%-94.0%) 2-y LC: 82.5% (54.7%-	1-y PFS: 34% (14%-55.3%) 1-y OS: 62.4%	3/19 patients (15.8%) with late grade 3 toxicities (peripheral sensory neuropathy, myositis, and

(*continued on next page*)

Table 1 (*Continued*)

Study	Patients (lesions)	Median age (y) (range)	Median follow-up (range)	Histology	Sites of treated lesions	Median target size (range)	Mean/median prescription dose (range)	LC rate (95% CI)	PFS and OS rate (95% CI)	Acute and late toxicities and additional comments
received SBRT)	palliative intent Retrospective			Other: 1 patient	Thoracic: 2 lesions			94.0%)	(36.7%-80.0%)	radiation enteritis resulting in SBO requiring surgery) 5/19 patients (26.3%) treated with SBRT as reirradiation
Parsai et al (2021)[27]	31 (88) All patients with metastases from pediatric sarcomas 57 lesions with radiographic follow-up >3 mo Retrospective	17.9 (4.1-29.3)	7.4 mo (0.2-31.4 mo)	Osteosarcoma: 14 patients Ewing sarcoma: 8 patients Rhabdomyosarcoma: 2 patients Synovial sarcoma: 2 patients Clear cell sarcoma: 2 patients Other: 7 patients	Spine: 24 lesions Extremity: 18 lesions Other: 16 lesions Pulmonary: 16 lesions Soft tissue: 13 lesions Liver: 1 lesion Median number of lesions treated: 2 (1-14)	Median PTV: 39 cc (3-806 cc)	MPD: 30 Gy/5 fractions Dose range: 16-60 Gy Fraction range: 1-5	1-y LC: 83.1% 2-y LC: 65.8%	6-mo OS: 73.4% 1-y OS: 46.9%	No acute grade 3 toxicities or greater 1/31 patients (3.2%) with late grade 3 toxicity in reirradiated field (SBO after SBRT to 18 Gy/1 fraction to a lumbar spine lesion requiring surgery)
Brown et al (2014)[26]	8 (19) 13/14 patients (total cohort) with metastases from pediatric sarcoma; 1 patient with recurrent localized disease Retrospective	24 (4.9-33.4)	19.2 mo (0.04-48 mo)	Osteosarcoma: 5 patients Ewing sarcoma: 3 patients	Osseous: 13 lesions Pulmonary/mediastinal: 6 lesions	N/A	MPD: 40 Gy/5 fractions Dose range: 16-50 Gy Fraction range: 1-5	2-y LC: 85% (among 14 lesions treated with definitive/ curative intent)	1-y OS: 62.5%	No acute or late grade 3 for patients treated with SBRT 1 patient with grade 3 neuropathy treated with 60 Gy/10 fractions 5 and 8 additional patients/lesions

(*continued on next page*)

Table 1 (*Continued*)

Study	Patients (lesions)	Median age (y) (range)	Median follow-up (range)	Histology	Sites of treated lesions	Median target size (range)	Mean/median prescription dose (range)	LC rate (95% CI)	PFS and OS rate (95% CI)	Acute and late toxicities and additional comments
	27 total patients; 14 treated with curative intent; 13 with palliative									treated with 10 fractions; 1 patient aged 66.4 y and 1 aged 63.4 y
Di Perri et al (2021)[29]	16 (16) Prospective multi-institutional	12 (3-20) (entire cohort)	All completed a 2-y follow-up	Osteosarcoma: 7 patients Ewing sarcoma: 4 patients Rhabdomyosarcoma: 1 patient Sarcoma: 1 patient Melanoma: 1 patient Other: 2 patients	Lung: 5 patients Paraspinal: 11 patients	N/A	Dose range: Overall: 25-50 Gy Lung: 40-50 Gy Paraspinal: 24.3-35 Gy Fraction range: 3-5	N/A	N/A	No acute or late grade ≥3 toxicities attributable to SBRT 5/16 (31.3%) patients with paraspinal disease treated in reirradiation setting
Chandy et al (2020)[28]	6 (6) 3 treated for local recurrence; 2 for metachronous metastases; 1 for a synchronous metastasis Retrospective	15 (5-20) (entire cohort)	3.4 y (0.28-6.4 y) (entire cohort)	Ewing sarcoma: 3 patients Neuroblastoma: 2 patients Paraganglioma: 1 patient	All sites either vertebral or paravertebral	N/A	MPD: 27 Gy/3 fractions Dose range: 27-30 Gy Fraction range: 3-5 fractions	2-y LC: 50%	Median OS: 58.4 mo (33.8-82.9 mo) Mean distant PFS: 44.1 mo (28.3-60.0 mo)	No acute or late grade ≥3 toxicities attributable to SBRT
Liu et al (2020)[8]	5 (8) All treated for pulmonary metastases Prospective phase 1/2 dose escalation	13 (7-21)	2.1 y (1.4-2.5 y)	Ewing sarcoma: 3 patients Osteosarcoma: 1 patient Anaplastic chordoma: 1 patient	All pulmonary metastases	N/A	All treated to 30 Gy/3 fractions	2-y LC: 60%	2-y distant-free survival: 40%	No acute or late grade ≥3 toxicities attributable to SBRT

(*continued on next page*)

Table 1 (*Continued*)

Study	Patients (lesions)	Median age (y) (range)	Median follow-up (range)	Histology	Sites of treated lesions	Median target size (range)	Mean/median prescription dose (range)	LC rate (95% CI)	PFS and OS rate (95% CI)	Acute and late toxicities and additional comments
Deck et al (2019)[30]	3 (12) All treated for pulmonary metastases Retrospective	11 (9-21)	2.9 y (1.9-4.0 y)	Rhabdoid tumor: 1 patient Ewing sarcoma: 1 patient Wilms tumor: 1 patient	All pulmonary metastases	PTV: 2.6-17.1 cc	Dose range: 37.5-50 Gy Fraction range: 3-5 fractions	No local failures with minimum of 1.9-y follow-up	1 patient died of disease at 4 y after SBRT; 2 other patients alive at 1.9 and 2.9 y after SBRT	No acute or late grade ≥3 toxicities attributable to SBRT

Abbreviations: LC = local control; MPD = median prescription dose; N/A = not applicable; OS = overall survival; PFS = progression-free survival; PTV = planning target volume; SBO = small bowel obstruction; SBRT = stereotactic body radiation therapy.

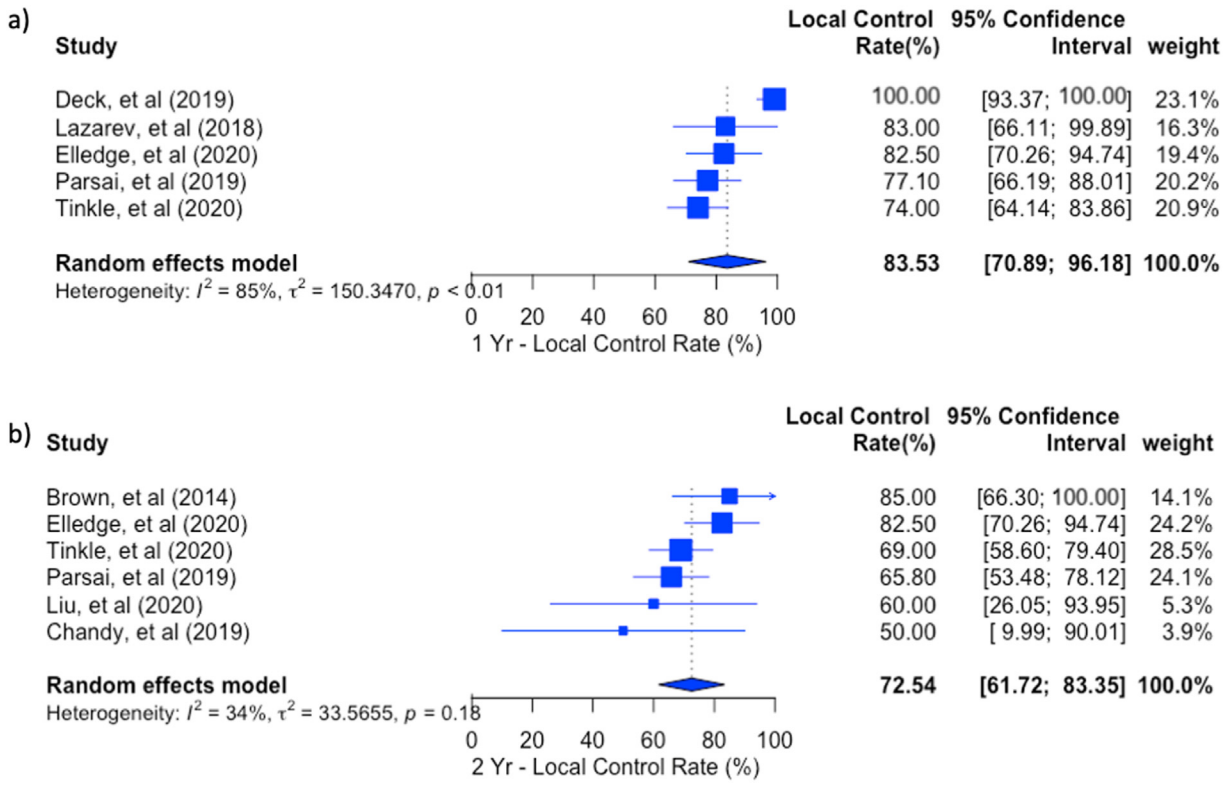

Figure 1 Forest plots examining 1-year local control (A) and 2-year local control (B) after stereotactic body radiation therapy.

Local control

Across 6 studies, 209 lesions had available information on 1-year LC.[8-10,16,27,30] The estimated pooled 1-year LC rate after SBRT was 83.5% (95% confidence interval [CI], 70.9%-96.2%; Fig. 1A). Significant heterogeneity was noted with respect to 1-year LC. No correlation was noted between BED_{10} and 1-year LC. There was no evidence of publication bias.

Across 7 studies, 217 lesions had available information on 2-year LC.[8-10,16,26,27,30] The estimated pooled 2-year LC rate after SBRT was 74.0% (95% CI, 64.6%-83.4%; Fig. 1B). There was no evidence of significant heterogeneity with respect to 2-year LC. On initial meta-regression, BED_{10} was not found to be associated with 2-year LC (P = .27). However, on subgroup analysis of sarcoma-predominant studies, BED_{10} was found to be correlated with 2-year LC with a roughly 5% increase in 2-year LC estimated for every 10 Gy increase in BED_{10} (P = .02; Fig. 2). There was no evidence of publication bias.

Overall survival and progression-free survival

Across 7 studies, 111 patients had available information on 1-year OS.[8-10,16,26,27,30] The estimated pooled 1-year OS rate was 75.4% (95% CI, 54.5%-96.3%; Fig. 3A). Significant heterogeneity was noted with respect to 1-year OS. There was no evidence of publication bias.

Across 4 studies, 78 patients had available information on 1-year PFS.[8-10,16] The estimated pooled 1-year PFS rate was 27.1% (95% CI, 17.3-37.0%; Fig. 3B). There was no evidence of significant heterogeneity with respect to 1-year PFS. There was no evidence of publication bias.

Toxicity

Across 9 studies, 142 patients had available information on acute and late grade 3 to 5 toxicities.[8-10,16,26-30] The estimated pooled acute and late grade 3 to 5 toxicity rate was 2.9% (95% CI, 0.4%-5.4%; Fig. 4). Notably, all incidences were grade 3 toxicities (Table 1). There was no evidence of significant heterogeneity with respect to acute and late grade 3 to 5 toxicities. No correlation was noted between BED_{10} and acute toxicity after meta-regression (P = .32) or BED_3 and late toxicity (P = .43). There was no evidence of publication bias.

Discussion

For adult patients with oligometastatic cancer, significant investigation is currently underway regarding the potential role of SBRT in multimodality and aggressive therapeutic approaches with the goal of achieving long-

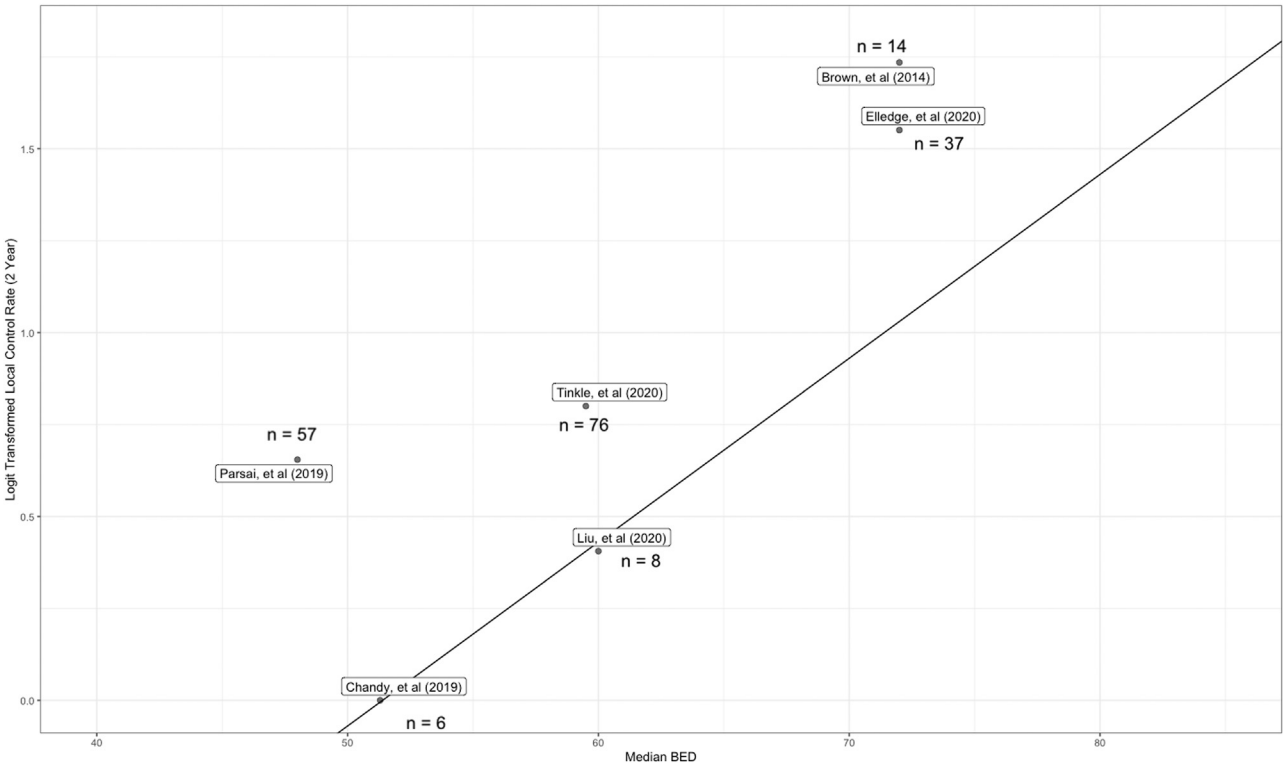

Figure 2 Meta-regression examining correlation between biologically effective dose and 2-year local control.

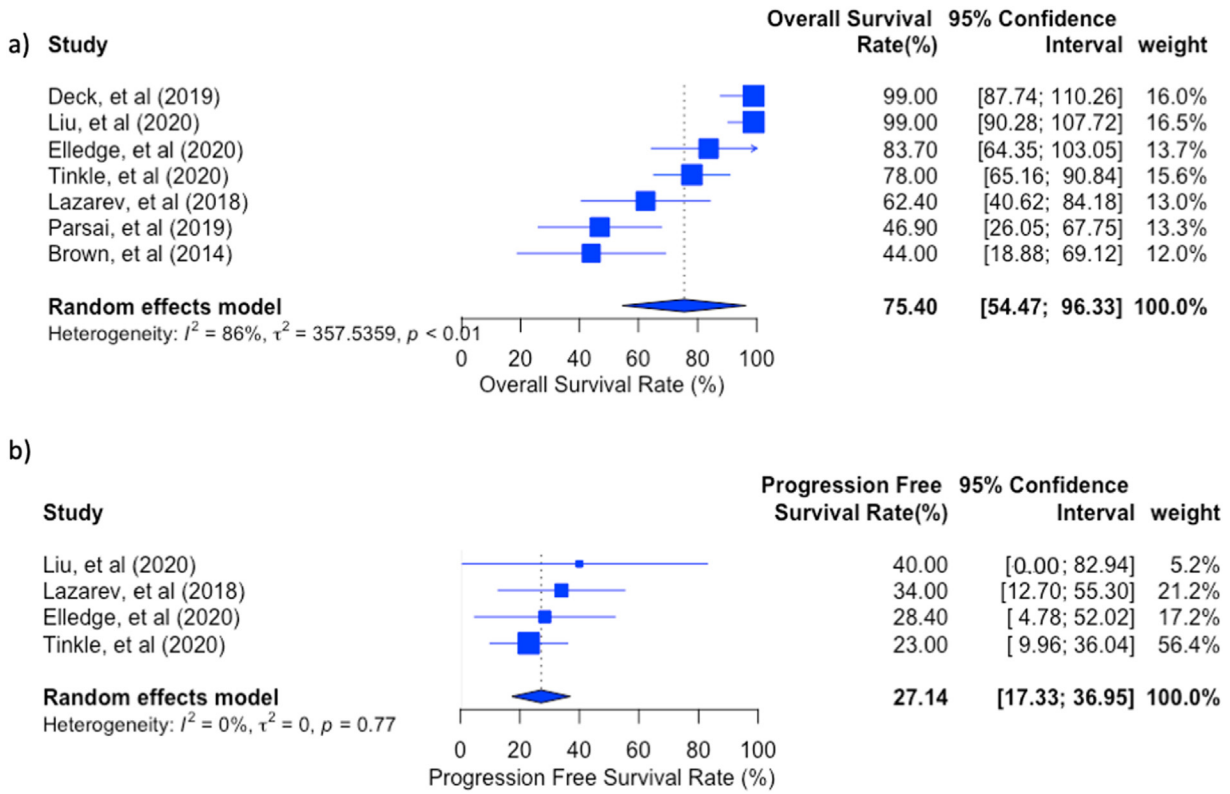

Figure 3 Forest plots examining 1-year overall survival (A) and 1-year progression-free survival (B) after stereotactic body radiation therapy.

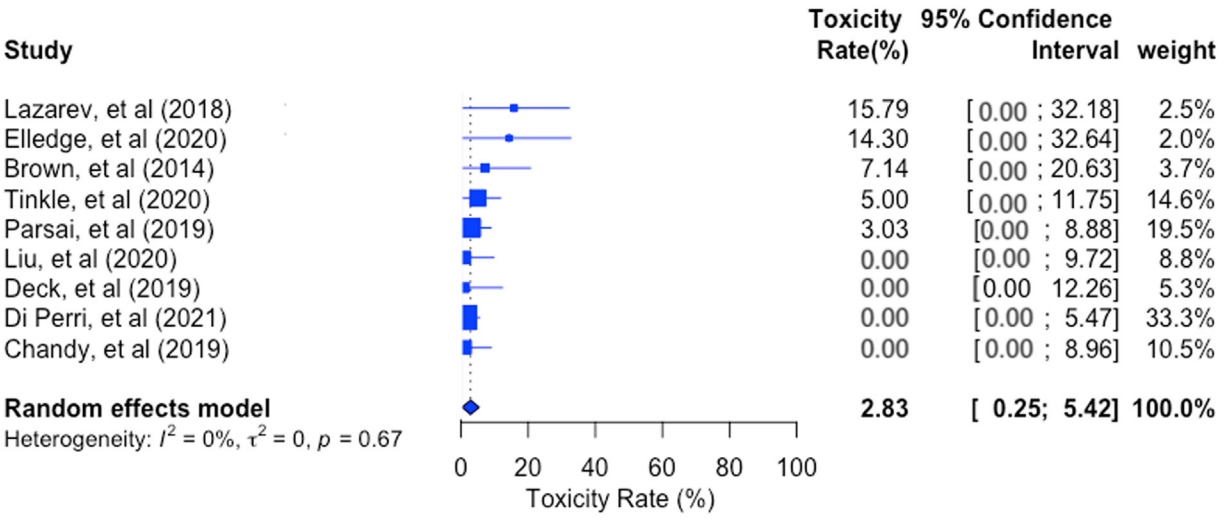

Figure 4 Forest plot examining acute and late grade 3 to 5 toxicities after stereotactic body radiation therapy.

term cure given promising results thus far.[6,31] SBRT has also been shown to be superior to conventional RT with the goal of palliation of symptomatic spinal metastases for adult patients with metastatic disease.[7] In the context of pediatric and AYA patients with cancer, SBRT also offers many therapeutic advantages, including the ability to potentially provide durable LC even for radioresistant histologies with ablative doses, a shorter and more convenient fractionation schedule that allows for prompt reinitiation of systemic therapy, and more conformal treatment to minimize late toxicities in long-term survivors. Our findings suggest that SBRT provides durable LC with minimal acute and/or late severe toxicities for pediatric and AYA patients with cancer. Notably, dose escalation was also found to be associated with improved LC, potentially owing to a high proportion of radioresistant histologies such as osteosarcoma and soft-tissue sarcomas comprising the cohort.

A number of studies included in our analysis aimed to determine the optimal dose and fractionation schedule for SBRT. The first reported series on SBRT for metastatic osteosarcoma and Ewing sarcoma by Brown et al treated 14 cases with curative/definitive intent to a median dose of 40 Gy/5 fractions (BED_{10} = 72.0 Gy; range, 30-60 Gy in 3-10 fractions). The 2 local failures noted were lesions from metastatic osteosarcoma treated to 30 Gy/3 fractions (BED_{10} = 60.0 Gy).[26] A recently published series by Parsai et al treated 31 patients with 88 lesions with SBRT to a median dose of 30 Gy/5 fractions (BED_{10} = 48.0 Gy).[27] Of the 57 lesions with LC data, they noted 10 total local failures with 9 of 10 of these observed in patients treated to <40 Gy in 5 fractions; as such, it is noted that the group's practice changed thereafter to treat to at least 40 Gy/5 fractions. Both of these series' findings suggest a potential dose-response, potentially owing to radioresistant histologies, and that SBRT with a BED_{10} of 72.0 Gy or higher (correlating to 40 Gy/5 fractions) may provide the most durable LC, which has implications both in palliative settings for symptom relief as well as curative settings for disease control. Similarly, our analysis noted a dose-response with every 10 Gy increase in BED_{10} associated with a roughly 5% increase in 2-year LC in sarcoma-predominant cohorts. However, the goal of treatment (curative vs palliative), lesion location, whether SBRT is being offered in the reirradiation setting, and primary histology all merit consideration in selection of dose/fractionation schedule.

Thus far, 2 prospective trials [8,10] and 1 prospective multi-institutional cohort study[9] have been published on clinical outcomes for pediatric and AYA patients treated with SBRT. Liu et al reported the results of a single-institution phase 1/2 dose-escalation study of 5 patients (3 with Ewing sarcoma, 1 with osteosarcoma, and 1 with anaplastic chordoma) with 8 pulmonary metastases (all with lesions <3 cm without receipt of prior pulmonary RT) treated at a prespecified dose level 2 of 30 Gy/3 fractions. Partial responses were noted in 7 of 8 lesions treated at 6 weeks after SBRT with a 2-year LC rate of 60% and no grade 3 or greater toxicities.[8] The first reported multi-institutional phase 2 trial by Elledge et al reported on outcomes for 14 patients with metastatic sarcoma with 37 bone metastases treated with SBRT to 40 Gy/5 fractions.[9] The reported 1-year and 2-year LC rates were quite favorable at 82.5% with 2 grade 3 toxicities reported (esophagitis and osteoporosis of the distal radius) with no significant difference in pain scores noted from baseline to 1-month follow-up. Notably, a post hoc analysis compared patients who received SBRT to all known sites of disease to those who received SBRT to only to a limited number of sites and found improved median PFS (9.3 vs 3.7 months) and median OS (not reached vs 12.7 months) potentially suggesting that aggressive local ablative therapies should be pursued to all sites of metastatic disease when feasible in patients. Of note, both Lansky

performance status (90-100) and age (<17) were associated with improved PFS and OS and merit consideration in guiding patient selection for aggressive local ablative therapies. Di Perri et al also have published toxicity results in their multi-institutional prospectively followed cohort of 16 pediatric patients treated with SBRT with no acute or late grade 3 toxicities noted.[29]

Of note, evidence specific to Ewing sarcoma does suggest a clinical benefit to aggressive local therapy. Secondary analysis of the EURO-EWING 99 trial revealed superior 3-year event-free survival in patients who received local therapy (either surgery or RT) to the primary site as well as metastatic sites (39%) versus local therapy to only the primary or metastatic sites (19%) versus no local therapy (14%).[32] Notably, patients who received multimodality therapy for local treatment (surgery and RT) had quite favorable 3-year EFS (59%) versus surgery alone (33%), RT alone (35%), or no local therapy (16%). The data suggest that in carefully selected patients with metastatic Ewing sarcoma that multisite ablative therapies merit consideration. The recently closed Children's Oncology Group (COG) AEWS1221 (NCT02306161) trial examined the feasibility of SBRT for treatment of pulmonary and bone metastases in combination with an IGF-1R monoclonal antibody, ganitumab, for patients with newly diagnosed metastatic Ewing sarcoma and we anxiously await the analysis. The ganitumab arm was closed early due to lack of benefit with additional toxicity noted. Similarly, analyses of MMT4-89 and MMT4-91 on metastatic rhabdomyosarcoma have similarly noted the prognostic significance of number of total metastases and involved organs/sites with patients with 0 to 1 versus 2 or greater unfavorable characteristics (with others being primary site location, bone or bone marrow involvement, and patient age) having significantly different 5-year OS rates of 47% and 9%, respectively.[33]

There are significant limitations to this analysis given the inherent issues with study-level data, the rarity of pediatric cancers and relatively recent incorporation of SBRT into clinical practice, and limited follow-up given the poor prognosis of many patients with metastatic disease. The total number of patients and lesions incorporated in our analysis was fairly low across mainly retrospective experiences (with the exception of Elledge et al), leading to a higher likelihood of bias in our effects estimates related to the results of larger series. However, our analysis is the largest study thus far on clinical outcomes of SBRT for pediatric and AYA patients with cancer. Our analysis did not use patient-level data, which limits our ability to analyze outcomes with respect to patient performance status, age (particularly the proportion of pediatrics vs AYA), lesion location, extent of metastatic disease (or whether patients were treated for local recurrence), size of lesions treated, dose and fractionation, primary lesion histology, receipt of systemic therapy, whether SBRT was administered in the reirradiation setting, and other relevant clinical factors. Of note is the heterogeneity across histologies in our study, as one might expect more favorable responses at more moderate prescription doses for neuroblastoma and rhabdomyosarcoma versus nonrhabdomyosarcoma soft tissue sarcomas, as an appropriate balance between LC and toxicity risk is key particularly in the metastatic setting. Roughly 45% of patients included were considered radioresistant histologies (ie, osteosarcoma and nonrhabdomyosarcoma soft tissue sarcomas) and 30% were Ewing sarcoma, with a small proportion (7%) being neuroblastoma and even less having rhabdomyosarcoma. We did perform a subgroup analysis for 2-year LC for sarcoma-predominant histologies to attempt to characterize a histology-specific dose-response within the limitations of a study-level meta-analysis. The range of ages in our cohort is also a limitation that should be noted given variable differences in toxicities expected across variable age groups. As patients were included from a variety of institutions and as SBRT was used in palliative settings, clinical follow-up was nonuniform and limits analysis of LC and may also underestimate the incidence of severe and late toxicities. This has particular implications for the late toxicity estimate, where characterizing long-term toxicity for survivors of pediatric and AYA cancers is paramount. There also was heterogeneity in both dose/fractionation selection as well as histologies included given few reports on this topic that limits generalizability of our findings. For the purposes of meta-regressions examining correlations between BED, LC, and toxicity, we were limited to using median BED for series that used a variety of dose/fractionation schemes.

Conclusion

Based on the results of this study-level meta-analysis, SBRT in pediatric and AYA patients was found to result in durable LC with minimal short-term significant toxicities and favorable 1-year OS. A dose-response was noted for sarcoma-predominant cohorts with every 10 Gy increase in BED_{10} associated with a roughly 5% increase in 2-year LC without a subsequent increase in toxicity, likely owing to the high proportion of nonrhabdomyosarcoma soft tissue sarcomas in our analysis (roughly 75%). However, this study should be seen as hypothesis-generating for further patient-level inquiries given the limitations of a study-level meta-analysis limited by significant heterogeneity across a variety of patient, tumor, and treatment characteristics. Our aim is to leverage these findings into further inquiries by pooling data across a variety of institutions to individualize dose/fractionation schema based on histology as well as tumor location given prior large studies that have noted the effect of tumor location (ie, soft tissue vs bone) on LC. We also hope with longer follow-up of the identified cohorts to better characterize patients who achieved durable LC. In addition, further

prospective trials are warranted to guide choice of dose/fractionation schema (which may be histology dependent), the timing of SBRT in combination with systemic therapy and/or surgery, and optimal patient selection for consideration of local ablative therapy.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101123.

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