Scientific Article

Stereotactic Body Radiation Therapy and Concurrent Targeted Therapy for Lung Metastases in Pediatric Sarcoma

Riley M. Goldsmith, BS,[a,1] Jessica L. Xing, MD,[b,1] Cory W. Heal, MD,[b] Michelina C. De La Maza, MD,[c] and Baldassarre Stea, MD, PhD[b,]*

[a]College of Medicine, University of Arizona, Tucson; [b]Department of Radiation Oncology, College of Medicine, University of Arizona, Tucson; and [c]Department of Pediatrics, Division of Hematology Oncology, College of Medicine, University of Arizona, Tucson

Purpose: The purpose of this investigation was to evaluate the efficacy and safety of stereotactic body radiation therapy (SBRT) for pulmonary metastases from pediatric sarcomas.

Methods and Materials: This study was a single institutional retrospective chart review including patients younger than 21 years of age at diagnosis who had received SBRT for pulmonary metastasis from metastatic sarcoma. Our current electronic record system was queried for all eligible patients. Primary endpoint was tumor response as defined by Respone Evaluation Criteria in Solid Tumors 1.1 criteria. Secondarily, we analyzed factors that affected tumor response as well as toxicity of treatment. Median dose was 50 Gy ranging from 30 to 60 Gy in 5 fractions to the planning tumor volume.

Results: There were 7 patients, ranging in age from 6 to 21 years with a total of 14 pulmonary lesions treated with SBRT. Median and mean follow-up times for the 7 patients were 10.6 months and 15.9 months, respectively. The complete response rate was 50%, partial response 21%, stable disease 21%, and progressive disease 7%. Four of the 7 patients were treated with concurrent systemic therapy, 3 of which were targeted oral therapies. Additionally, we observed that patients who were on targeted therapy such as regorafenib or pazopanib seemed to have better local control compared with patients without targeted therapy.

Conclusions: With an overall response rate of 92%, SBRT provided a noninvasive effective palliative treatment option with few side effects in this small retrospective study of 7 patients. A larger prospective clinical trial is warranted to evaluate the role of SBRT in the treatment of unresectable metastatic pediatric sarcomas.

Introduction

The lungs are one of the most common sites of metastatic disease for pediatric bone and soft tissue sarcomas. Advances in both systemic therapy and radiation therapy have changed the management for pulmonary metastases.

Sarcomas are considered rare among all human malignancies but are the second most prevalent type of solid tumors in the pediatric population.[1] Osteosarcoma (OS)

is a rare, primary malignant bone tumor that accounts for only 3% of all childhood cancers. Patients with metastatic OS have a 3-year survival rate of 20% to 45%, with pulmonary metastases being the most common site of spread.[2] Pulmonary metastases are commonly treated with wedge resection for peripheral lesions and the 5-year survival for patients with solitary pulmonary metastases is roughly 30%.[3] Ewing sarcoma (ES) is the second most common primary bone tumor seen in children and adolescents,[4] and 47.1% of distant metastases occur in the lungs.[5] Patients with ES with pulmonary metastasis alone have a 3-year event free survival of 29% to 52%.[6] Rhabdomyosarcoma is the most common soft tissue sarcoma in children, and 47% of distant metastases are pulmonary.[7] A retrospective study conducted in children with stage 4 rhabdomyosarcoma reported a 5-year overall survival for isolated pulmonary metastasis of 43%.[8] Finally, synovial sarcoma is the most common nonrhabdomyosarcomatous soft tissue sarcoma of childhood.[9] A European retrospective study with 258 patients with synovial sarcoma under the age of 21 concluded that 5.8% of cases had distant metastasis with 86% being pulmonary.[10]

Compared with conventional radiation therapy, stereotactic body radiation therapy (SBRT) uses highly conformal dose distributions to deliver large doses of radiation in a hypofractionated course of radiation therapy usually in 1 to 5 treatments. This allows for increasing biologically effective doses while shortening treatment times compared with conventional radiation therapy. This treatment modality represents a noninvasive alternative to metastasectomy, as an ablative dose is used to provide local tumor control. There are limited studies comparing tumor response and survival of pediatric patients treated with metastasectomy versus SBRT. A study conducted by Yu and colleagues did not show a statistically significant difference between the 2 treatment options for OS patients.[11] Additional studies are needed to comment directly regarding the efficacy of SBRT versus metastasectomy in the setting of solitary metastases. In the setting of diffuse metastatic disease, however, SBRT can be of value for delaying disease progression and its associated symptoms particularly for patients with nonresectable disease.

Systemically, tyrosine kinase inhibitors, such as regorafenib or pazopanib, are currently used in the treatment of recurrent sarcomas or in metastatic disease progression setting. These agents can be safely used concurrently with radiation therapy and may even have a synergistic effect.[12] Recent studies demonstrate that regorafenib may provide benefits to certain nonadipocytic sarcoma histology.[13] In the 'Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma' (REGOSARC) trial, patients with nonadipocytic sarcoma treated with regorafenib compared with placebo demonstrated improved progression-free survival (PFS).[13] In the 'Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma' (REGOBONE) trial, disease progression was delayed in recurrent, progressive and metastatic osteosarcoma patients who had failed prior chemotherapy treatments.[14] Additionally, the 'Randomized double-blind phase II study of regorafenib in patients with metastatic osteosarcoma' (SARC024) trial demonstrated that regorafenib significantly improves PFS in patients with progressive metastatic osteosarcoma who had received at least one prior treatment.[15] Patients in the SARC024 trial receiving regorafenib had a PFS of 3.6 months compared with 1.7 months for the placebo group.[15] As for pazopanib, another multikinase inhibitor, the Pallette phase 3 clinical trial reported that this agent showed superior PFS compared with placebo in patients with metastatic nonadipocytic soft tissue sarcoma.[16] Another retrospective analysis reviewed 15 OS patients with a median age of 25 who were treated with pazopanib. Results showed that 60% of patients demonstrated either a stable disease or partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[17] Here, we endeavored to analyze our experience using SBRT for pediatric patients with lung metastases occurring after failure of systemic therapy or after previous metastasectomy. Some of these patient were treated with concurrent multikinase inhibitors.

Methods and Materials

This was a retrospective study, approved by the local Institutional Review Board. Seven pediatric patients were found to have been treated with SBRT over the period of 2016 to 2022. All 7 patients had been treated with palliative intent for their pulmonary metastases from pediatric sarcomas as they either had systemic disease progression or had failed primary chemotherapy and were being treated on second- or third-line systemic agent with the goal of prolonging life but not curative intent. Patients had to be 21 years old or younger at the onset of diagnosis and received SBRT with 5 or fewer fractions. All patients were treated on a Varian TrueBeam linear accelerator equipped with a robotic couch. Volumetric modulated arc therapy plans were generated using the RayStation planning system version 10. All patients underwent 4-dimensional computed tomography (CT) during treatment simulation with respiratory management during treatment. A 5 mm margin was used around the internal gross target volumes to derive the planning treatment volume. In all but one patient, there was no prior wedge resection or lobectomy and only one patient had a central lesion, defined as a zone within 2 cm of the tracheo-bronchial tree and major pulmonary vessels. Doses of 6 to 12 Gy were delivered every other day for a total of 5 days (total dose range, 30-60 Gy). Standard SBRT constraints were used during treatment planning derived from the American Association of Physicists in Medicine Task Group 101 report.[18] All SBRT treatment plans met the

constraints for the normal lung, heart, and esophagus. Of note, all treatment plans met constraints for lung-GTV of CV12.5 Gy >1500 [cc] and V13.5 Gy < 37[%].

Measurements of pretreatment volumes were obtained from the simulation CT scan in the lung window. Post-treatment measurements of tumor size were done with the measuring tool on Philips PACS Software in the lung window. From these data points, we were then able to determine the best tumor response to SBRT using the RECIST 1.1 criteria.[19] Complete response (CR) was defined as the disappearance of the target lesion. PR was defined as at least a 30% decrease in the diameter of the target lesion. Progressive disease (PD) was defined as at least a 20% increase in the diameter of the target lesion. Stable disease was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Concurrent therapy was designated as any systemic therapy given concurrently or within 1 month of SBRT treatment initiation or completion. Additionally, we reviewed the maximum standardized uptake values (SUV) from all available pre- and posttreatment positron emission tomography(PET)-CT scans when available to evaluate metabolic response. Statistical analysis was performed using RStudio. The Kaplan-Meier clustered survival analysis was used to derive local recurrence-free survival probabilities.

Results

There were 7 pediatric patients harboring 14 pulmonary sarcoma metastases in this study (2 males and 5 females); additional clinical details are included in Table 1. Three out of the 7 patients were still alive at the time of data analysis. Median patient age at the start of treatment was 15 years. Although all patients were treated with "palliative" intent due to presence of other metastatic sites or failure to respond to primary therapy, some were treated for salvage after surgery and with the intent of prolonging life as long as possible. Primary tumor histology included osteosarcoma (9 lesions), ES (2 lesions), embryonal rhabdomyosarcoma (2 lesions), and synovial sarcoma (1 lesion). All the lesions were peripheral except for one located in the hilum. Only one patient had had a surgical intervention before radiation therapy treatment. In this patient, the lesion recurred after wedge resection and had a CR after SBRT therapy. Only 1 of the 7 patients had received previous whole lung radiation therapy. Median SBRT dose was 50 Gy, ranging from 30 to 60 Gy, delivered in 5 fractions, every other day. Median follow-up time was 12.7 months and mean follow-up time was 15.9 months. We defined mean follow-up time as the mean time between the day of first radiation therapy treatment to the last clinic follow-up visit. Average and median time to lung progression after SBRT was 9.5 and 4 months, respectively (Table 1). Additional pertinent patient demographics as well as tumor response and postradiation events can be found in Table 2.

Results for best overall response is as follows: complete response rate was 50%, partial response 21%, stable disease 21%, and progressive disease 7%. An example of a complete response on CT imaging can be found in Fig. 1. Only one patient demonstrated a local failure, defined as recurrence of the tumor after achieving a CR. Time to local failure for this patient was 6.6 months. However, this single lesion that was considered PD by RECIST criteria, was not metabolically active on PET CT imaging. The 3-year local recurrence-free survival for the entire group was 80% using the Kaplan-Meier survival estimator

Table 1   Clinical details for the 7 patients treated in this series

Patient no.	Sarcoma type	Primary site	Extent of disease at diagnosis	Response to initial therapy at primary site at the time of SBRT	Courses of SBRT to pulmonary sites	Time to progression in lung after SBRT (mo)
1	Osteosarcoma	Left distal femur	Localized	CR	4	4.8
2	Osteosarcoma	Left distal femur	Localized	CR	3	4.0
3	Telangiectatic Osteosarcoma	Left distal femur	Metastatic lung disease and lymphadenopathy	CR	2	1.6
4	Ewing	Right 4th metatarsal	Localized	CR	1	11.8
5	Embryonal rhabdomyosarcoma	Coccyx	Localized	SD	2	37.0
6	Ewing	Left forearm	Localized	CR	1	1.8
7	Synovial sarcoma	Right calf	Metastatic lung disease	CR	1	5.6

Abbreviations: CR = complete response; SBRT = stereotactic body radiation therapy; SD = stable disease.

Table 2　Patient demographics, treatment parameters, tumor response and postradiation events

Pt no.	Histology	Pt age	Concurrent systemic therapy	Location	Tumor diameter (cm)	SBRT dose (Gy)	Local failure (time from SBRT (days)	Best overall response	Late toxicity onset (days)	TTR from CR (days)
1	Osteosarcoma	13	None	Anterior RML	1.11	50	No	SD	None	N/A
1	Osteosarcoma	13	None	Lateral LLL	0.7	50	No	PD	None	N/A
1	Osteosarcoma	14	None	Right oblique fissure	2.8	52	No	PR	None	N/A
1	Osteosarcoma	15	None	Right juxta-pleural nodule	1.43	50	No	PR	None	N/A
2	Osteosarcoma	20	Regorafenib	LLL	2.62	55	No	CR	None	N/A
2	Osteosarcoma	20	Regorafenib	LUL	1.84	55	No	CR	None	N/A
2	Osteosarcoma	20	Regorafenib	RLL	3.33	55	No	CR	None	N/A
3	Telangiectatic osteosarcoma	17	Pazopanib	LLL	2.61	45	No	SD	None	N/A
3	Telangiectatic osteosarcoma	17	Pazopanib	RUL	2.01	50	No	SD	None	N/A
4	Ewing	21	Vincristine, cyclo-phosphamide topotecan	LLL	1.99	50	No	PR	Pulmonary fibrosis (63)	N/A
5	Embryonal rhabdo-myosarcoma	6	None	LLL	2.08	40	No	CR	None	N/A
5	Embryonal rhabdo-myosarcoma	6	None	Hilum	1.22	30	No	CR	None	N/A
6	Ewing	18	None	RLL	0.73	50	253	CR	None	199
7	Synovial Sarcoma	14	Pazopanib	RUL	1.87	60	No	CR	None	N/A

Abbreviations: CR = complete response; LLL = left lower lobe; LUL = left upper lobe; PR = partial response; PD = progressive disease; PT = patient; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SBRT = stereotactic body radiation therapy; SD = stable disease; TTR = time to recurrence.
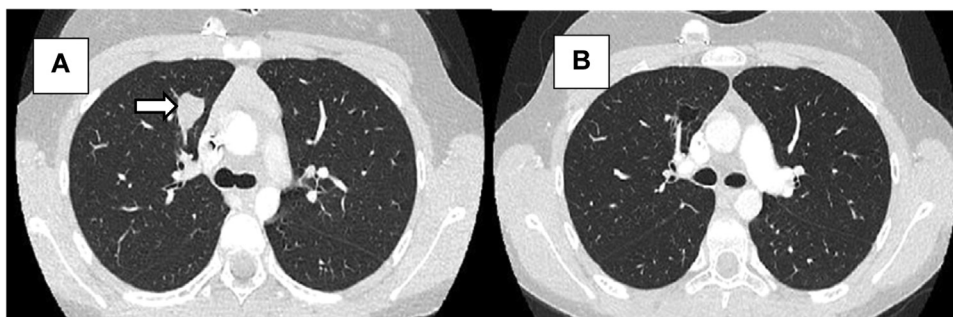
Figure 1 Axial computed tomography of a patient who achieved a complete response. (A) Before and (B) after stereotactic body radiation therapy treatment to the pulmonary nodule (arrow). Patient was treated concurrently with pazopanib.

(Fig. 2). There were no acute adverse events noted related to lung radiation therapy treatment including no cases of radiation pneumonitis. There was one instance of a mild late toxicity, grade 2 pulmonary fibrosis, occurring 4 months after the end of treatment (see Table 2). Patient was asymptomatic from fibrosis seen on CT. Of note, neither critical volume constraint (CV12.5 Gy = 2263.4 cc) nor volume constraints (V13.5 Gy = 7.87%) were out of range in the patient's final treatment plan. No other treatment-related toxicities were documented in the remaining patients.

Additionally, 4 out of 7 patients were treated with concurrent systemic therapy. We defined concurrent therapy as being administered within 1 month of SBRT or simultaneiusly. Two patients were treated with pazopanib, one patient with regorafenib and one patient with a combination therapy of vincristine, cyclophosphamide, and topotecan. Of note, no patients treated with concurrent chemotherapy or targeted therapy had progression of disease locally in the radiation treatment field. Patients who received concurrent therapy seemed to have a high CR rate, but this was not statistically significant using binary

logistic regression analysis (odds ratio, 1.78; 95% CI, 0.215%-16.4%; $P = .594$).

Discussion

This retrospective study, although small, suggests that SBRT is a safe and effective treatment option for the management of pulmonary sarcoma metastases in pediatric patients. Additionally, the absence of progressive disease in lesions treated with SBRT while receiving systemic therapy indicates that concurrent therapy may further improve local control due a synergistic effect. Compared with other forms of conventional treatment such as surgery, SBRT offers a less invasive treatment modality for these aggressive, often radioresistant, tumors. However, careful patient selection is paramount as SBRT may not be appropriate for all patients due to potential high risk of toxicity in certain circumstances, especially if performed concomitantly with certain systemic agents. For example, ultracentral tumors, which are defined as those abutting the proximal bronchial tree, esophagus, or other
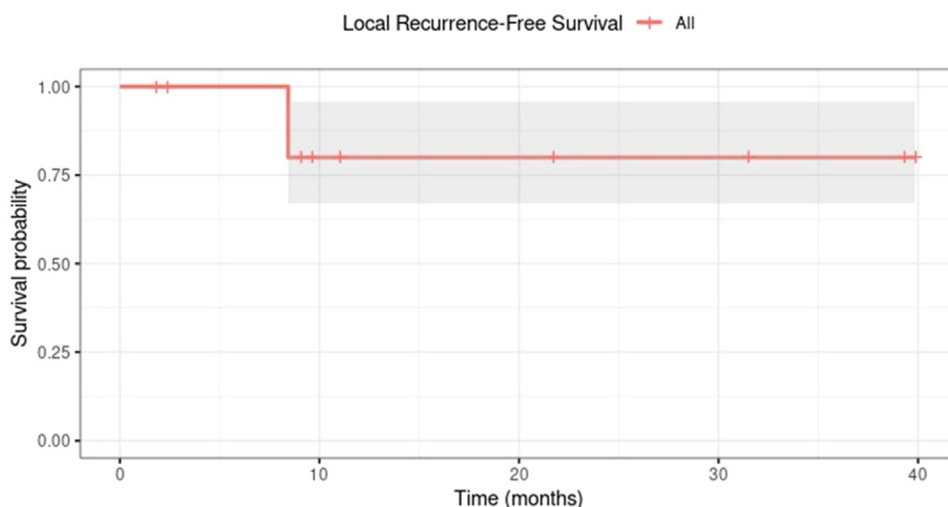

Figure 2 Kaplan-Meier plot for local recurrence-free survival for 6 months was 100%. 1 year = 80%; 3 year = 80%.

mediastinal structures, can have high risk of toxicity and severe morbidity when SBRT is performed in combination with antiangiogenic agents, such as bevacizumab, pazopanib or ramucirumab.[20]

ES is generally considered a radiation sensitive histology. The standard treatment for de novo ES presenting with metastases to the lungs is chemotherapy with surgical resection and whole lung irradiation (WLI).[21] In the setting of relapse with isolated metastasis to the lungs, second-line chemotherapy with or without WLI is also considered a good treatment option. The dose used for WLI (15-18 Gy in 10-12 fractions) is sufficient to sterilize microscopic disease but usually not sufficient for gross disease. In our small study, there were 2 patients with ES lung metastases, and although the lesions treated with SBRT responded well to the treatment, both patients recurred with additional lung metastases at 1.8 and 11.8 months after the initial SBRT treatment, raising the question of whether WLI after SBRT might have prevented or delayed further lung metastases. However, a previous study of WLI from Germany noted no improvement in overall survival, although there was marginal improvement in the control of pulmonary disease and PFS ($P = .18$) when TLI was done after achieving a complete remission to second line chemotherapy.[22] Although WLI is usually well tolerated, cases of severe pneumonitis after WLI are reported to be around 1.8%, and grade ≥3 acute lung toxicity rates range between 0% to 12.2%.[23] Our patients had failed first-line chemotherapy, and they were receiving second- or third-line treatment but had not achieved a second remission (Table 2). They had oligo-progressive disease and therefore metastatic site irradiation (SBRT) was chosen; this approach improved time to relapse and progression free survival, without exposing the patient to the added toxicity of TLI. SBRT will likely reshape the treatment paradigm of relapsed ES.[24]

In eligible patients, pulmonary metastases from osteosarcoma are usually treated with thoracotomy and lobectomy/metastasectomy.[25] Osteosarcoma is considered radioresistant to conventionally fractionated radiation therapy; thus, radiation is largely regarded as a palliative treatment option in this disease. One study comparing the efficacy of metastasectomy versus chemotherapy in adult patients with resectable lung masses found significantly improved overall survival in patients treated surgically.[26] In our study, there were 9 osteosarcoma lesions and remarkably all achieved a CR after SBRT. Additional research is required to directly compare the effectiveness of SBRT versus metastasectomy in pediatric sarcomas with pulmonary metastases. Indeed, there are now prospective clinical trials being conducted studying the role of SBRT in pediatric pulmonary metastasis from sarcoma. A phase 1/2 trial analyzed the safety profile and secondarily, local control, in pulmonary metastases treated with SBRT. Results showed that 87.5% of the 7 lesions treated with SBRT at 6 weeks post radiation therapy achieved

partial response with 30 Gy delivered in 3 fractions.[27] The results of our investigation using 50 Gy in 5 fractions compare well with those reported in the previous study.

In this study, we defined local control by the RECIST 1.1 criteria and best overall response was the optimal response when comparing the first post radiation CT with the most recent axial CT. There are inherent limitations when using RECIST 1.1 to evaluate local control. Measurements of axial tumor diameter may subtly vary between reviewers and timing between the first post radiation CT and final post radiation CT was not standard for all patients. In a prospective trial, patients would undergo imaging at uniform intervals.

We were also able to track the metabolic response for 9 out of the 14 lesions through the analysis of PET CT scans. We compared preradiation PET CT images and SUV reports to the latest available postradiation PET CT data. PET CT was useful in evaluating tumor response in addition to CT follow-up. There was a decrease in maximal SUV in 8 of the 9 lesions compared with preradiation PET-CT. Additionally, it is interesting to note that in the only case of PD (based on CT scan), the reported final SUV on PET was 1.2, raising the possibility that the PD noted on the CT scan may have been a case of radiation fibrosis. In one study, a SUV of greater than 2.5 in pulmonary lesions was considered malignant and indicative of a true positive in 71% of patients.[28] PET CT provides additional information regarding tumor response according to RECIST 1.1 guidelines.

Although the local control of the lesions targeted with SBRT appears to be quite good (Fig. 2), all patients eventually progressed with new lung lesions at a median time of 4 months (Table 1), likely because these patients were being treated with less effective second- or third-line systemic agents. There is no known role of WLI for osteosarcoma or nonrhabdomyosarcoma metastases.

Finally, while the small number of patients in our retrospective review limits statistically significant results, it provides additional support to the use of SBRT in the context of pulmonary metastases, when surgical resection may be challenging or not indicated. We would like to note that 4 of the 7 CR were obtained while patients were taking the targeted drugs pazopanib and regorafenib suggesting an additive or synergistic effect between these drugs and high dose radiation. Additional studies with larger patient populations will be needed to further explore these early but encouraging results.

Conclusion

With an overall response rate of 92% (including stable disease), this small retrospective study suggests that SBRT provides a noninvasive, effective, and well-tolerated temporizing treatment option for pediatric patients with metastatic sarcomas to the lungs. The relationship between increasingly advanced treatment

modalities and patient life expectancy necessitates careful management of metastases to maintain quality of life. As such, the data reported helps to further explore new ways to treat metastatic disease more effectively in patients with relapsed sarcomas. Our data also suggest that concurrent targeted therapy and SBRT may be generally safe in pediatric patients with pulmonary metastases from sarcoma.

Disclosures

Acknowledgments

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