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Short-Interval Retreatment with Stereotactic Body Radiotherapy (SBRT) for Pediatric Neuroblastoma Resulting in Severe Myositis

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Abstract

We report a severe and not previously reported toxicity after short-interval retreatment with stereotactic body radiotherapy (SBRT) in a pediatric patient with neuroblastoma. This patient experienced Grade III radiation myositis (RM) after treatment with conventional radiation therapy followed by high-dose SBRT for persistent disease a short interval after the initial RT course. While SBRT shows outstanding rates of local control in adult disease, data in pediatric cancers is extremely limited. In this report, we discuss the rationale of SBRT in this patient's multimodality neuroblastoma treatment, management of the toxicity, and future perspectives on the use of SBRT in pediatric cancer.

Keywords

neuroblastoma; stereotactic body radiotherapy; SBRT; myositis

Case Description

This report details a child with *MYCN*-amplified stage 4 neuroblastoma whose post-relapse treatment included stereotactic body radiotherapy (SBRT). When diagnosed in 2013 at age 3 years, he received dose-intensive induction with cyclophosphamide, doxorubicin, vincristine, cisplatin, and etoposide.[1] He then had primary adrenal tumor resection, 3F8 anti-GD₂ monoclonal antibody immunotherapy, and intensity-modulated RT (IMRT) 21Gy in 14 fractions to the post-operative bed.[2–4] Progressive disease in the left femur and right scapula identified by MIBG scan were irradiated with 30Gy in 10 fractions in July and September 2014, respectively. Subsequent chemotherapy included cyclophosphamide, topotecan, irinotecan, temozolomide, ifosfamide, carboplatin, and etoposide. Follow-up MIBG and MRI scans showed persistent uptake and increased disease in the left femur and

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

right scapula, determined to represent persistent disease. Both sites were treated with 27 Gy in 3 fractions of SBRT completed October 2014, adhering to all departmental guidelines regarding organs-at-risk, including the brachial plexus. SBRT was utilized in this unique situation to control local disease, avoid further chemotherapy, and prevent use of morbid surgical resection. Dose and fractionation were based on a previous institutional re-irradiation protocol and current department practice for re-irradiation for osseous lesions in adults. In November, imaging studies showed substantial improvement in both sites and he then resumed chemotherapy.

Three months after SBRT, the patient experienced acute, severe right shoulder pain associated with refusal to move the right arm and holding it in a sling position. There was muscle weakness independent of pain. Shoulder radiograph showed no fracture. Right shoulder MRI showed extensive edema and high signal in the right shoulder musculature, particularly subscapularis (Figure 1A). He was started on oral ibuprofen 180mg BID, and escalated to fentanyl patch 12mcg with oxycodone liquid and hydromorphone rescue. Five days after right shoulder pain onset, he reported severe left thigh pain with gait abnormality and refusal to walk. Exam revealed muscle weakness and edema of the thigh and knee along with a stiff-legged gait resulting in limp. Femur radiograph showed no fracture. He was diagnosed with Grade III myositis as per Common Terminology Criteria for Adverse Events scale (CTCAE v4.0). Given worsening pain, he was given intravenous dexamethasone 4mg followed by oral prednisone 3mg/kg (50mg) for 5 days. There was moderate symptomatic relief after steroid use with increasing right arm and left leg use. His disability and pain slowly improved over 3 months with continued pain control using NSAIDs and rehabilitation. Subsequent MIBG and MRI imaging revealed continued controlled disease in both treated sites.

Discussion

RT plays a significant role in treating neuroblastoma, a small, round, blue cell tumor of the sympathetic nervous system affecting approximately 750 children annually in the United States, with 90% less than 5 years old at diagnosis.[5] Nearly 60% have metastases at presentation, and the 5-year survival for the high-risk group is approximately 40%.[6] Patients with high-risk disease receive consolidative RT to the primary site tumor bed and persistent MIBG-avid metastatic sites after induction chemotherapy as neuroblastoma is generally known to be a radiosensitive disease.[7] This dose is often 21Gy, but can range from 20–36Gy depending on treatment intent and level of residual disease. [2, 8] Immunotherapy including anti-GD₂ agents such as 3F8 and ch14.18 then follow.[9]

SBRT represents a significant innovation in clinical oncology, allowing delivery of ablative RT with relative sparing of high-dose to normal tissue.[10] SBRT can definitively treat adult tumors, such as lung, pancreas, liver, and prostate cancers, and ablate bone metastases. Local control exceeds 90% in spine and lung lesions.[11] In palliation of even previously radiated or radioresistant bone metastases, SBRT can provide durable pain control.[12] However, there is no routine indication or recommendation for SBRT in pediatrics outside of clinical trials.

This patient experienced SBRT-associated Grade III toxicity, not previously reported in children. SBRT in pediatrics is limited given concerns for significant early toxicity and potential late effects. The sole series reporting toxicity after SBRT in pediatric tumors involved 14 children and young adults with metastatic or recurrent Ewing sarcoma or osteosarcoma.[13] Two-year local control was 85%. A 17-year-old patient experienced grade 2 myositis in the right iliac wing 2 months after 50Gy in 5 fractions of SBRT and concurrent chemotherapy. A 23-year-old patient experienced grade 3 sacral plexopathy after 60Gy in 10 fractions. Both had prior in-field conventional RT.

The differential diagnosis in this patient includes trauma, infective myositis, disease progression, inflammatory myopathy, and RM. Factors supporting radiation as the cause include clinical symptoms, timing, MRI changes corresponding to the high-dose region (Figure 1B), and improvement with anti-inflammatory medications.

RM is associated with large fraction size and total dose, often >55–63Gy total dose conventionally fractionated RT.[14] Acute toxicity is augmented by concurrent chemotherapy. Muscle edema peaks at 12–18 months, due to acute and subacute inflammation and vascular injury. T2-weighted MRI shows muscle edema with increased interstitial fluid content and otherwise normal anatomy.[15] Muscle damage and myonecrosis may lead to late fibrosis and functional loss.[16]

Management involves symptom control and early rehabilitation interventions. Biopsy is not indicated unless clinical suspicion of auto-immune myopathy, or other pathology. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce muscle edema and inflammatory pain, adding steroids and opiates for inadequate relief. Early rehabilitation may help restore range of motion, strength, and functional use of the affected body part once pain is controlled. However, there are no known proven interventions to prevent or reverse late muscle fibrosis.

The major contributing factor for this severity of toxicity was a short time (1 month for the right scapula and 3 months for the left femur) between completion of conventional RT and SBRT. The effect of RT was likely cumulative with very high biologically equivalent dose treatment leading to more significant and potentially earlier toxicity. SBRT use is independently associated with chest wall myositis in lung and liver disease.[17] Furthermore a larger volume receiving high-dose RT has already been shown to be associated with chest wall toxicity in lung SBRT, and conventionally fractionated treatment in sarcoma. Although this relationship is not yet characterized in children, the treatment volume in our patient was exceptional in this patient to encompass both gross disease and margin for microscopic extension.[17–19] Although he did not receive concurrent chemotherapy, the patient received significant systemic therapy before and after RT. Given scant data on pediatric SBRT, there is an unclear biologic effect of high-dose radiation in developing muscle in children. The ablative nature of SBRT may have augmented toxicity due to ongoing muscle growth and rapid cell proliferation, compared to developed adult muscle.

We turned to SBRT in a desperate effort to control focal disease resistant to conventional RT, where alternative therapeutic options would have been significant and morbid resection of

both metastatic sites (e.g. distal femur resection and scapula resection) or further dose-intensive chemotherapy. SBRT offers outstanding local control and palliation in many adult diseases. Findings in ongoing phase II studies are pending ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01763970), number NCT01763970). Pediatric SBRT can offer excellent local control in oligometastatic disease, in the re-treatment setting when salvage surgery may be morbid, or when additional chemotherapy may not be tolerated or effective. While SBRT was very effective in this patient to control disease and we recommend further research into pediatric indications, we advise caution when considering short-interval, high-dose, and large-volume re-treatment.

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Abbreviation

SBRT	Stereotactic Body Radiotherapy
IMRT	Intensity Modulated Radiation Therapy
CTCAE	Common Terminology Criteria for Adverse Events
NSAID	Non-Steroidal Anti-inflammatory Drug
Gy	Gray
RM	Radiation Myositis

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Figure 1. Axial T2-weighted MR imaging shows a characteristic hyperintensity with otherwise normal tissue architecture, indicative of muscle edema. The muscle edema closely corresponds to the high-dose radiation region.