Stereotactic body radiation therapy (SBRT) has emerged as a highly effective treatment modality for obtaining durable local control of a variety of primary cancers, including early-stage lung cancer and metastatic lesions in both bone and soft tissues. The delivery of a high biologically effective dose (BED) by administering large radiation doses in a few fractions is especially attractive for the treatment of tumors with a radioresistant histology and also for tumors that have been previously irradiated. However, when treating spinal tumors, ensuring dose conformity to tight volumes with a steep dose gradient is critical to preventing toxicity in adjacent normal structures, such as the spinal cord and cauda equina.1 Local control of spine and paraspinal tumors treated with SBRT is high, and generally greater than 80% local control is achieved in most series.1,11,14,15,19,27 Many patients who undergo SBRT to the spine (also known as spine stereotactic radiosurgery) have limited metastatic disease and/or excellent performance status. Because patients with metastatic disease are living longer due to advances in available sys-
Radiation myositis is a complication of radiotherapy that was initially described in 1959. To date, most of the available clinical evidence in the literature has reported radiation myositis in the setting of conventional external-beam radiotherapy. A high incidence of chest wall pain and rib fracture is a known complication following lung SBRT and has been reported to correlate with dose-volume parameters. A case report noted radiation-induced myositis following lung SBRT that radiographically mimicked chest wall tumor invasion. This highlights the importance of recognizing the radiographic sequelae of postradiation changes in the muscle and soft tissues. Radiographically, vasculitis and muscle injury from radiation may appear on MRI as muscle edema, which is characterized by increased signal intensity on T2-weighted images that correlates with the radiation field; these findings should be differentiated from residual or recurrent tumor. Myositis has also been reported to occur and result in severe pain in patients who received SBRT to the appendicular skeleton. To the best of our knowledge, myositis following spine SBRT has not been reported in the literature. In this clinical series, we describe 11 patients who developed radiation-induced myositis following spine SBRT.

**Methods**

**Patient Selection**

A total of 667 patients received 891 SBRT treatments to the spine from 2011 to 2016 at Memorial Sloan Kettering Cancer Center. Institutional board review approval was obtained. Patient, tumor, and treatment information were collected. Eleven patients were identified as having radiographic evidence of myositis following spine SBRT. Patients with myositis initially presented with symptomatic myofascial back pain localized to the irradiated fields, which was further evaluated with MRI. Myositis was diagnosed based on radiographic MRI evidence of the features of muscle volume loss, T2-weighted hyperintensity in the radiation field, and irregular muscle enhancement on T1-weighted postcontrast imaging. All identified myositis cases were further reviewed by a single radiologist (E.L.) to determine the dates of radiographic onset, peak myositis, and myositis resolution. Myositis volumes were contoured by a single physician (N.A.L.) at the time of peak myositis on MRI, and radiation dose parameters were calculated, including the contoured volume of myositis and the mean dose. Based on an estimated α/β ratio of 4 for muscle, BED and equivalent dose in 2-Gy fractions (EQD2) were also accounted for to account for the different fractionation schemes included. Myositis was graded according to clinical symptoms using the Common Terminology Criteria for Adverse Events (CTCAE; version 4.03). For all patients, information was collected on the radiation dose, radiation fraction schedule, and receipt of anti–vascular endothelial growth factor (VEGF) therapy within 90 days before or after SBRT.

**Radiation Treatment**

Patients underwent simulation for radiation planning; 2-mm-thick CT images were obtained. Myelography or MRI fusion was performed to delineate spinal cord anatomy and tumor volume. Patients were immobilized with a patient-customized cradle for both SBRT simulation and therapy. Treatment planning was performed with either Top Module (in-house software at Memorial Sloan Kettering Cancer Center) or Eclipse (Varian Medical Systems) with inverse treatment planning. The gross tumor volume (GTV) was outlined according to the CT and MRI images after review by a radiation oncologist and neurosurgeon. According to consensus guidelines, the clinical target volume encompassed the GTV as well as the adjacent bone. The planning target volume was a 2-mm expansion from the clinical target volume but excluded the thecal sac and the esophagus if it was not abutting the GTV. The prescribed dose to the planning target volume was either 24 Gy in 1 fraction or 27 Gy in 3 fractions, and the dose was prescribed to the 100% isodose line as allowed by the dose constraints to the spinal cord. Treatment was delivered with a linear accelerator using 6-mV and/or 15-mV photons. Cone-beam CT was performed to verify patient positioning prior to treatment. Following treatment, patients were monitored with serial MRI beginning approximately 8 weeks after treatment.

**Statistical Analysis**

The cumulative incidence of myositis was calculated using the Kaplan-Meier log-rank method, as well as the rates of myositis by fractionation schedule and the receipt of anti-VEGF treatment within 90 days of SBRT. Univariate statistical analyses were performed to evaluate the relationships between the radiation fractionation schedule and myositis and between anti-VEGF therapy and myositis using Cox modeling. IBM SPSS Statistics software (version 2015) was used for all analyses.

**Results**

**Summary of Cases**

Eleven patients who developed postradiation myositis were identified; a summary of the clinical characteristics is shown in Table 1. Eight patients (73%) were treated with a 24-Gy dose administered in a single fraction, and 3 patients were treated to a 27-Gy dose administered over 3 fractions. The median patient age was 57 years (range 25–83 years). The majority of patients were female (64%). The most common tumor histology was renal cell carcinoma (36%) followed by sarcoma (27%). The most common radiation site was the lumbar spine (82%), while the thoracic spine represented the remaining sites (18%) and included either a single level or multiple adjacent levels. Of note, all 11 patients had stable disease within the radiation field at the time of the last MRI session.

Table 2 shows the collected parameters by individual patient. Patients in cases 4 and 8 had undergone prior radiation within or abutting the currently reported radiation field. Of the 11 patients with myositis reported in this case series, the radiation treatment plans of 9 patients were available for contouring the volume of muscle at the peak of radiographic myositis. The median volume of myositis was 49 cm³ (range 13–146 cm³). The median of the mean...
dose administered to muscle with myositis was 17.5 Gy (range 9.2–26.1 Gy). The median BED was 82.7 Gy (range 30.3–126.7 Gy), and median EQD2 was 55.1 Gy (range 20.2–84.5 Gy). A total of 5 patients (45%) received anti-VEGF therapy at any time. At least 6 patients were not receiving any systemic therapy at the time of myositis.

The clinical symptoms reported by patients with myositis included pain, muscle spasms, weakness, and numbness associated with the location of myositis that was identified radiographically. The majority of patients (9 patients; 82%) were clinically symptomatic; only 2 patients (18%) did not report any clinical symptoms that appeared to correlate with the location of myositis. The majority of myositis cases were CTCAE grade 0 or 1 (64%); 2 patients experienced grade 2 toxicity and 2 patients experienced grade 3 toxicity. The median time to the development of the clinical symptoms of myositis was 1.4 months (range 0.2–6.1 months). Treatment of symptoms included analgesics and steroids in all symptomatic patients.

The median time to the development of radiographic evidence of myositis was 4.7 months (range 2.0–9.7 months), and radiographic changes predominately included T2 hyperintensity on MRI. There was also radiographic evidence of necrosis associated with myositis in 5 of 11 patients. Three patients underwent biopsy; no patient had tumor recurrence, but fibrotic and skeletal muscle necrosis was evident.

The cumulative incidence of myositis for all treatments (n = 891) was 1.9% at 12 months. The rate of myositis was 3.7% in patients who received 24 Gy in 1 fraction of SBRT (n = 309) versus 0.7% in the patients who received 27 Gy in 3 fractions of SBRT (n = 582) at 12 months (p = 0.015). On the univariate analysis, single-fraction SBRT was associated with increased risk of developing myositis compared with 3-fraction SBRT (HR 4.5, 95% CI 1.2–16.9; p = 0.027).

Two hundred thirty-one patients (34.6%) received anti-VEGF therapy at any time, and anti-VEGF therapy was administered within 90 days of spine SBRT for a total of 187 spine SBRT treatments. On the univariate analysis, receipt of anti-VEGF therapy within 90 days of SBRT was not significantly associated with increased risk of developing myositis (HR 2.2, 95% CI 0.6–7.1; p = 0.2).

<table>
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<tr>
<th>Patient Characteristics</th>
<th>Radiation</th>
<th>Myositis</th>
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<th>Radiographic Evidence</th>
<th>Systemic Therapy</th>
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NA = not applicable; RT = radiation therapy; U = unavailable.
Representative Case

Case 2

A 57-year-old woman with no significant medical history presented with a 2-month history of low-back pain. Pain was exacerbated by moving from sitting to standing or lying to sitting. She underwent conservative management with physical therapy, but pain did not improve and worsened to the point that she was almost bedridden. She also reported right-leg paresthesia but denied any weakness or changes in bowel or bladder function. MRI of the spine was performed and demonstrated diffuse marrow abnormality in the L-3 vertebral body with a moderate compression fracture and expansion into the ventral epidural space, as well as several lesions in additional vertebrae (Fig. 1A). Further workup with CT of the body showed a left renal lesion and additional osseous lesions. Neurological examination findings were unremarkable. The patient underwent kyphoplasty and biopsy of the L-3 vertebral body, and pathology revealed renal cell carcinoma. After kyphoplasty, her back pain significantly improved. She then underwent spine SBRT to the L-3 vertebral body at a dose of 24 Gy in a single fraction (Fig. 2). Radiation treatment was performed as detailed in Methods. The patient experienced no acute radiation toxicity. One month after radiation treatment, she began systemic therapy with pazopanib and also received denosumab.

Six months after radiation treatment, the patient developed pain in the lumbar spine that radiated into the groin and anterior left thigh, with left hip flexion limited by pain. Spine MRI performed at that time showed irregular enhancement in the left psoas muscle and the erector spinae muscles (Fig. 1B). The diagnosis was uncertain, and a biopsy sample was obtained to rule out tumor or abscess. Pathology revealed skeletal muscle with extensive necrosis and patchy acute and chronic inflammation with no evidence of tumor or infectious process (Fig. 3). The patient’s symptoms were treated with methylprednisolone and morphine, and both her pain and weakness resolved over 2 months. Around this time, her systemic therapy was changed from pazopanib to axitinib due to decreased blood counts. At the most recent follow-up performed 2.5 years after administration of radiation to the L-3 vertebral body, MRI continued to show volume loss of the left psoas muscle with vague residual enhancement (Fig. 1F).

Discussion

We have presented a series of 11 patients who experienced myositis after spine SBRT. Myositis is an infrequent delayed complication of high-dose spine radiosurgery that to our knowledge has not been previously described. Most of the patients in this series improved with steroid therapy. The muscles affected by myositis correlated with the radiation treatment ports in all cases.

Gillette et al. reviewed evidence of late radiation injury to muscle in 1995 after the Late Effects Consensus Conference of the Radiation Therapy Oncology Group/
European Organization for Research and Treatment of Cancer, and they reviewed studies that demonstrated focal muscle degeneration, loss of capillaries, and increase in collagen at 2–4 months following a single dose of 20 Gy with recovery or improvement noted after 1 year. Histological studies revealed decreased collagen replacement and recovery of capillary networks at 1 year. In our case series, the median time to the development of clinical symptoms from myositis was 1.4 months, and the median time to radiographic evidence of myositis was 4.7 months. This timing is comparable to that in the studies reported by Phillip et al.

Interestingly, 45% of the myositis cases presented in this series were in patients who received anti-VEGF therapy. However, the univariate analysis did not demonstrate an increased risk of myositis development in patients who received anti-VEGF therapy within 90 days of SBRT. Nonetheless, our study presents only a small sample size of myositis cases, and this relationship needs to be prospectively validated in a larger series to assess whether potential radiation recall is associated with anti-VEGF therapy and affects this condition. Prior studies have suggested that progressive muscle injury is caused by ischemia from vessel injury as well as radiation-induced inflammation. Specifically, for radiation administered to the periaortic region as a single dose with intraoperative high dose-rate brachytherapy, the dose that caused a 50% decrease in psoas muscle fibers at 2 years was 21 Gy, and the median effective dose for severe vascular injury at 2 years was 19 Gy. In our representative case, the patient was noted to have volume loss in the left psoas muscle at 2.5 years after radiotherapy (Fig. 1F). For single-fraction intraoperative radiation, Gillette et al. concluded that significant soft-tissue complications occurred after administration of doses of 10–20 Gy but single-fraction radiation offered the benefit of a reduced at-risk volume.

While the observed rate of myositis was significantly higher in the patients who received 24 Gy in 1 fraction of SBRT than in the patients who received 27 Gy in 3 fractions of SBRT, the incidence of myositis is still relatively low and we caution that the potential complications of lowering EQD2 or fractionation may compromise tumor control.

The literature review also reveals various reports of radiation recall myositis. The radiation recall phenomenon is defined as acute inflammation in previously irradiated tissues, and this typically occurs weeks to months following radiotherapy and is thought to be induced by subsequent cytotoxic therapy. Gemcitabine, carboplatin, paclitaxel, and other chemotherapeutic agents have been associated with radiation myositis. Molecular targeted therapies have also been implicated in radiation recall, as have antibiotic agents. However, it should be noted that the cases presented in this series are not consistent with the radiation recall phenomenon in which acute radiation toxicity is later recalled following drug administration. Rather, we described an independent and delayed effect of high-dose stereotactic radiation.

Conclusions

Radiation-induced myositis is a rare delayed complication after spine SBRT. Treatment with steroids and analgesics results in adequate pain control. Knowledge of this
adverse effect is important for clinicians so they can recognize and treat myositis and include it in the differential diagnosis. Although further investigation is warranted, single-fraction schedules may be associated with an increased risk of myositis secondary to spine SBRT.

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References


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