Central nervous system radiation therapy is commonly used in the treatment of both primary and metastatic tumors of the brain and spine. For example, postoperative radiotherapy has been frequently incorporated in the management of high-grade gliomas since a survival benefit was established in the late 1970s by Walker et al. Furthermore, chemoradiation therapy has become the standard of care for the treatment of glioblastoma.

Pseudoprogression is loosely defined as the subacute (up to 6 months) occurrence of increased contrast enhancement on posttreatment MRI that subsequently subsides without further treatment and does not represent progressive disease. According to a comprehensive review by Kruser et al., 18%–20% of all patients with high-grade gliomas experience a clinical course and/or pathological analysis consistent with pseudoprogression. Hence, pseudoprogression of gliomas in the setting of radiotherapy with or without chemotherapy is a perplexing and important treatment factor for the managing clinician.

Tumor pseudoprogression of spinal metastasis after radiosurgery: a novel concept and case reports

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Radiosurgery for primary and metastatic tumors of the central nervous system is increasing in utility and intensity. Known complications in the brain include radiation necrosis and the well-documented phenomenon of pseudoprogression. Known complications of radiosurgery to spinal column tumors include radiation myelopathy and delayed vertebral compression fractures; however, the concept of pseudoprogression of spinal column tumors has not been previously described. The authors review 2 cases of spinal metastasis treated with stereotactic radiosurgery (SRS) and attempt to define the concept of spine tumor pseudoprogression.

Two patients who had undergone SRS to the spine for metastatic disease presented in early follow-up (3 and 7 weeks) with symptomatic complaints consisting of axial pain, radicular pain, or evidence of cord compression. In both patients, MRI revealed evidence of tumor enlargement. In one patient, the lesion had grown by 9 mm and 7.7 mm in the axial and sagittal planes, respectively. In the other patient, the tumor growth resulted in a 5-mm decrease in spinal canal diameter with epidural compression and right foraminal encroachment. Because of the absence of progressive neurological deficit, myelopathy, mechanical symptomatology of instability, or vertebral compression fracture, the first patient was treated expectantly with a corticosteroid taper and had improvement of symptoms at 1 month and near-total radiographic resolution of the tumor. In the second patient, worsening symptoms suggested a need for surgical intervention to address presumed radiosurgical failure and tumor progression. During surgery, only necrotic tumor cells were observed, without viable tumor. Follow-up imaging over 1 year showed ongoing local control.

To their knowledge, the authors report the first description of pseudoprogression involving spinal column metastasis in the literature and aim to alert the treating physician to this clinical situation. Unlike brain tumor pseudoprogression, spine tumor pseudoprogression is a relatively early posttreatment phenomenon, measured in days to 2 months. The authors believe that the acute inflammatory response associated with tumor necrosis and disruption of the tumor capillary integrity caused by radiotherapy is an important component in the development of pseudoprogression. Future studies will be fundamental in assigning clinical significance, defining the incidence and predictors, and affecting future management of this phenomenon.

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after radiotherapy of other brain lesions such as vestibular schwannoma; however, to our knowledge, the manifestation of this phenomenon within the spine has not been reported. Spinal stereotactic radiosurgery (SRS) is an emerging treatment for patients with spinal metastases. Therefore, in practice, certain patients require SRS to the tumor or tumor bed after resection of metastatic tumors. Commonly, albeit not well characterized, patients complain in follow-up examination of a flare of pain that manifests after radiotherapy. Some cases may even show evidence radiographically corresponding to their clinical symptoms. In general, the pain experienced by these patients responds dramatically to a corticosteroid taper, but in rare instances it may require surgical intervention. Here, we review 2 cases in which radiotherapy for spinal metastasis resulted in symptomatic and radiographic pseudoprogression of disease. We will also introduce the concept of “spine tumor pseudoprogression” in reference to osseous tumor metastasis and attempt to further define this entity.

Case Reports

Case 1: Clinical and Radiographic Pseudoprogression

A 57-year-old woman with known renal cell carcinoma presented with increasing mechanical neck pain with radiation into the right suboccipital region. Her pain worsened with rotation to the right. She exhibited neither neurological deficit nor evidence of myelopathy. Computed tomography and MRI demonstrated a right occipital condyle and anterior ring of C-1 metastasis with epidural involvement but no spinal cord compression (Fig. 1A). Given the patient's mechanical symptoms, she underwent an occipitocervical fusion with planned postoperative adjuvant SRS to the metastasis. Approximately 3 weeks after successful surgical fixation, her mechanical pain had largely subsided, and the tumor was treated with 22 Gy to the 80% isodose line in a single fraction using a CyberKnife (Accuray) linear accelerator (Fig. 2).

The patient returned for follow-up 3 weeks after radiosurgery with a marked flare of nonmechanical pain, worse at night, with radiation into the right suboccipital region. Again, she exhibited neither neurological deficit nor myelopathy. MRI revealed evidence of tumor enlargement in the axial and sagittal planes by 9 mm and 7.7 mm, respectively (Fig. 1B). At that time, the patient was treated with a corticosteroid taper in the following manner: dexamethasone 2 mg by mouth 3 times daily for 7 days followed by 2 mg twice a day for 3 days, then 1 mg twice a day for 2 days, and finally 1 mg daily for 2 days. She had marked improvement of her symptoms upon initial dosing and resolution at 1 month. Subsequent imaging revealed near-total radiographic resolution of tumor (Fig. 1C).

Case 2: Clinical, Radiographic, and Histological Confirmation of Pseudoprogression

A 77-year-old man with known metastatic melanoma presented with increasing mechanical back pain and bilateral L-4 radiculopathies. CT and MRI demonstrated osseous lesions involving L-3 with epidural compression and, to a lesser extent, L-1 with no epidural compression (Fig. 3A and B). The initial treatment strategy was an L2–4 posterior instrumented fusion with decompression followed by postoperative adjuvant radiosurgery to the L-3 vertebral body. This is in accordance with the treatment strategy referred to as “separation surgery.” Given the limited osseous disease in L-1, the surgeon (J.W.) believed that this disease could be treated in the same postoperative adjuvant session to avoid a longer segment fusion. Therefore, approximately 3 weeks after surgery, L-1 and L-3 were both treated with 22 Gy to the 80% isodose line in a single fraction using a Trilogy linear accelerator (Varian Medical Systems) (Fig. 4).

At 4 weeks postradiosurgery, the patient was largely pain free and had returned to normal activities; however, at 7 weeks, he reported a marked flare of nonmechanical axial back pain, thigh pain, and a new-onset right iliopsoas weakness. MRI revealed radiographic enlargement of the L-1 lesion that resulted in a 5-mm decrease in spinal canal diameter with epidural compression and right foraminal encroachment (Fig. 3C and D). There was no evidence of pathological fracture. Given the worsening pain and new neurological deficit, the decision was made to proceed to surgery for extension of his fusion and resection of L-1.

**FIG. 1.** Case 1. **A:** Pretreatment axial T1-weighted MR image with contrast enhancement demonstrating right occipital condyle and right anterior C-1 ring metastasis measuring 36.5 mm in the axial plane. Note the effacement of subarachnoid space and displacement of vertebral artery but no cord compression. **B:** Axial T1-weighted MR image with contrast enhancement obtained 32 days after treatment, demonstrating enlargement of tumor (46.5 mm) with increased effacement of subarachnoid space, further displacement of the vertebral artery, and mild deformation of the spinal cord. **C:** Axial T1-weighted MRI with contrast enhancement obtained at 4 months posttreatment, showing marked resolution of contrast enhancement and tumor volume.
metastasis. At the time of preoperative planning, the medical team believed that this represented a failure of radiosurgery and tumor progression.

Total laminectomy, epidural tumor resection, and L-1 vertebrectomy were performed via a bilateral transpedicular approach (Fig. 5 left). Notably, the diseased vertebral body and the epidural mass were not vascular as would be expected for a melanoma metastasis. Multiple permanent sections of both the osseous lesion and the epidural lesion revealed only necrotic tumor cells without viable tumor (Fig. 6). Subsequent imaging continued to show local control of tumor at both L-1 and L-3 more than 1 year later (Fig. 5 right).

Discussion

The spine is the most common site for bony metastasis. The goals of intervention for spinal metastasis typically include local disease control, pain relief, maintenance of neurological integrity, and avoidance of spinal instability. Radiotherapy is the mainstay of treatment, with surgery indicated for instability, urgent decompression, pain relief, and tumor biopsy. Additionally, SRS has been shown to be beneficial for both primary and salvage treatment of metastatic disease, for radioresistant metastasis such as renal cell or melanoma, and also for treatment after spinal decompression and stabilization surgery. Ideally, SRS delivers high doses of radiation to the tumor while minimizing the effect to healthy tissues.

Surgical patients receiving adjuvant SRS often present on follow-up examinations with symptomatic complaints consisting of axial pain, radicular pain, or some evidence of cord compression. Like cranial symptoms involving acute radiation injury, spine manifestations are usually transient, reversible, and alleviated with steroids. The cases reviewed here appear to be the first written accounts of what we have deemed to be spine tumor pseudoprogression within the vertebral column.

As described earlier, pseudoprogression is the subacute, postradiotherapy reaction that mimics tumor progression with increased contrast enhancement and edema but ultimately stabilizes or regresses without further mediation. Moreover, pseudoprogression represents treatment effects rather than treatment failure. It is theorized to exist on a continuum of posttreatment radiation effects that proceed from pseudoprogression to radiotherapy necrosis. The incorporation of a time delineation has arbitrarily been included on this spectrum. Pseudoprogression is considered an early effect, occurring from 4 weeks up to 6 months, and radiotherapy necrosis is said to be a late effect that occurs from 6 months up to years after treatment. Currently, the definition of pseudoprogression includes a time delineation.
progression relies solely on the clinical course, with image findings in the absence of intervention. The diagnosis of radiotherapy necrosis is largely dependent on histopathological evidence.

Spine tumor pseudoprogression involving spinal column metastasis seems to have some inherently different qualities with respect to pseudoprogression of brain tumors. First, several sources indicate that symptomatic patients and those with accompanied neurological deterioration are more likely to have early progressive disease rather than pseudoprogression. In the senior author's (J.W.) experience, worsening or new-onset pain of nonmechanical quality in patients after spinal SRS may not be unusual, even in patients without progressive disease. The cases reported here are examples of this instance. Second, the mechanism with which pseudoprogression in the brain occurs has been attributed to vasodilation, disruption of the blood-brain barrier, and edema. This transient process is made evident radiographically when increased permeability and leakage of gadolinium enters through the damaged blood-brain barrier in the irradiated region as well as the capillary bed of the tumor. Furthermore, Hoffman et al. described early radiotherapy reactions to correspond to the turnover of myelin. This, in addition to the presence of necrosis and vascular endothelial proliferation on tissue samples of radiated tumors, has led others to postulate that oligodendrocytes are the targets of early radiotherapy reactions. The histopathological sample of our patient who underwent re-resection for symptomatically enlarging tumors (Case 2) showed only necrotic tumor cells with obliteration of the tumor's vasculature. Reasonably, the different innate qualities of bone and neural tissues should produce varying behaviors at a cellular level when confronted with high doses of radiation. At the very least, the comparison of the reviewed patient's tissue pathology to reports of brain tumor pseudoprogression leads us to favor vascular disruption, tumor capillary permeability, and the resultant edema of the epidural and osseous tumor as highly significant factors driving early radiotherapy effects and development of pseudoprogression. If it is indeed vasogenic edema leading to the clinical and radiographic manifestation of spine tumor pseudoprogression, this could explain the patient's dramatic response to corticosteroid administration.

It is possible that the incidence of spine tumor pseudoprogression directly correlates with increasing radiation dose used in spinal SRS for treatment of metastasis. Currently, the major complications of spinal SRS include radiation myelopathy and vertebral compression fracture. For brain tumors, the primary risk factor for radiation necrosis is total radiation dose, with necrosis rarely occurring at a total dose less than 50 Gy. Similarly, Sahgal et al. showed a dose-dependent increase in vertebral compression fracture. When the dose was increased from ≤ 19 to 20–23 Gy/fraction and then ≥ 24 Gy/fraction, the 1-year incidence of vertebral compression fracture increased from 10% to 19% and 39%, respectively. Appropriately, a threshold of ≥ 20 Gy is supported.
Both patients examined here received 22 Gy, indicating that this moderately higher dose of radiation may be associated with so-called spine tumor pseudoprogression. In the future, prospective studies could provide some utility in further defining this association.

Sometimes it becomes clinically relevant to evaluate the patient radiographically. In these instances, increased contrast enhancement and increased signal on T2-weighted MRI can regularly be seen to correlate with the flare of pain described by the symptomatic patient. Unfortunately, while multiple imaging modalities have been retrospectively reviewed to differentiate pseudoprogression from early progressive disease, no technique has emerged to reliably distinguish the two. Young et al. studied 321 patients by analyzing 11 MRI features on initial postradiotherapy MRI in an effort to compare differences, if any, when a final diagnosis of pseudoprogression or early progressive disease was made. They found subependymal enhancement to be the sole predictor of early progression (p = 0.001). Regardless, conventional MRI appears to be an inadequate method for distinguishing these entities in the central nervous system, and the results reported by Young et al. are certainly not applicable in reference to the comparison of pseudoprogression versus early progressive disease within the spinal column. Future evaluation of this disease entity by PET-CT or dynamic contrast-enhanced MRI may prove useful in assessing pseudoprogression versus true tumor progression.

Periodically, surgical intervention becomes necessary when there is concern for true disease progression, mechanical pain secondary to instability or fracture progression, and when patient symptoms become intractable to medical management alone. With unreliable neuroimaging to distinguish pseudoprogression from actual disease progression, this disease process should be regarded as a diagnosis of exclusion after surgically urgent causes, such as hemorrhage or spinal instability, have been ruled out. Ultimately, the decision to proceed with surgery remains highly focused on preservation of neurological function, pain management for palliation of uncontrolled disease, local disease control, and spinal stability.

Conclusions

We report the first description of spine tumor pseudoprogression involving spinal metastasis in the literature, although it may be more prevalent when correlated clinically. Spinal column tumor pseudoprogression is both a clinical and a radiographic phenomenon, defined as postradiotherapy pain exacerbation accompanied by the suggestion of enlargement of the osseous tumor radiographically. Although the concept of spine tumor pseudoprogression stems from pseudoprogression of brain tumors postradiotherapy, there appear to be some inherent differences. Nevertheless, we believe that the inflammatory response, disruption of the tumor capillary integrity, and the development of edema caused by radiotherapy is an important component in the development of spine tumor pseudoprogression.

It is our aim that introduction of “spine tumor pseudoprogression” will alert the treating physician to the clinical situation. It may include the onset of new neurological deficit that may require surgical intervention, as in Case 2. Therefore, spine tumor pseudoprogression should be treated as a diagnosis of exclusion and can be managed expectantly with steroid taper when new neurological deficit or signs and symptoms of instability are not present, as in Case 1. In all cases, appropriate tumor surveillance imaging is recommended to assess for tumor response to SRS. With the introduction of this concept, future prospective studies may demonstrate a dose-dependent risk of pseudoprogression associated with SRS, and radiographic attributes from PET-CT or dynamic contrast-enhanced MRI may be identified to distinguish pseudoprogression from true tumor progression. These studies will be fundamental in assigning clinical significance and effecting future management of this phenomenon.

References


**Author Contributions**
Conception and design: Weaver. Acquisition of data: both authors. Analysis and interpretation of data: Taylor. Drafting the article: Taylor. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Weaver. Study supervision: Weaver.

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**Pseudoprogression of spinal metastasis after radiosurgery**

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