

Remineralization in a Case of Spinal Metastasis Following Radiation Treatment with CyberKnife Stereotactic Radiosurgery

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Abstract

In evaluating the outcomes of stereotactic radiosurgery (SRS) in the treatment of spinal metastases, authors have looked primarily at endpoints of pain relief and tumor growth suppression. The question of structural stability has been raised, but the pattern of bone remineralization has not been investigated in detail. With traditional radiation, both tumor control and pain relief are modest, and resulting bone remineralization can reach 80% with responsive tumors. SRS offers higher rates of both tumor growth control and pain relief (88%), even for radioresistant tumors, but the protection from vertebral fracture is not improved when there is more than 40% of the vertebra involved. We report a case of a partially collapsed C2 vertebral body affected by multiple myeloma, which was surgically stabilized and treated with CyberKnife SRS. Upon a 12-month follow-up period including CT imaging, remineralization of the vertebral body was observed starting at three months post-SRS that significantly progressed during the 12-month follow-up period. Final radiographic evaluation showed almost complete restoration of the structure of the vertebral body and the associated bone densities with significantly increased stability. This pattern of remineralization is contrasted with reported results of traditional radiation therapy, and its implications for stabilization are noted.

Categories: Radiation Oncology, Neurosurgery

Keywords: srs, remineralization, stabilization, vertebra

Introduction

There are over 700,000 new cases of cancer in the U.S. every year, and 35% will experience metastases to the spine [1] that will cause pain and may threaten cord function by either direct compression of the cord or by indirect bony collapse with compression. When cord compression presents, decompressing surgery often remains the first step in management, followed by radiation. In the cases of a metastasis without cord compression, radiation is often chosen for the pain relief and tumor control. Results in terms of tumor control and fracture prevention from traditional radiation have been modest with the greatest limitation imposed by the cord tolerance dose [2].

There have been several reports on the pattern of bone response to traditional radiation treatments in cancer patients (Table 1). The earliest is Munzebach, et al. who studied 13 patients (75% with breast cancer) receiving a standard fractionated dose of 40 Gy over four wks. With alpha/beta = 10 Gy, which is used throughout this publication, the Biological Equivalent Dose (BED) was 48 Gy [3]. Dual energy CT was used to quantitate the calcium changes. They

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found that immediately following radiation, 50% showed less than 20% increase in calcification, while the remaining showed up to a 60% increase, all occurring in areas not affected by tumor, i.e., the periphery of osteolytic changes. Three out of six patients who showed remineralization were studied at four weeks post-treatment and half showed no progression in remineralization, while three progressed slightly. The resulting bone pattern was always abnormal (Figure 1). The remineralization progressed from the periphery to the center of the metastatic lesion. They found no explanation of this pattern, in either tumor type or amount of radiation given, and concluded that radiotherapy does not in every case lead to the desired result of remineralization to prevent fracture of the vertebral body.

Author	Number patients/ Diagn.	Fractionation used	Outcomes
Crone-Munzebach (1987) [3]	12 Pts, 9 Breast CA No change in vert. height of vertebral body.	2.5 cGy/8 Fx BED 25 Gy	6/12 showed some remineralization at the periphery adjacent to tumor with 50% further increases at four wks post-treatment.
Koswig (1999) [6]	107 Pts with Breast, Lung, prostate and lung	8 Gy x 1 vs 3 Gy x 10 BED 14.4 Gy vs 39 Gy	Complete pain response 33% vs 31%. Remineralization 25% vs 73%.
Reinbold (1989) [5]	19 Pts Only osteolytic lesions.	2 Gy x 20 Fx BED 48 Gy	13/19 showed complete pain relief, with 17% decrease immediately in bone density followed by 34% increase at three months with peripheral bone also increasing at both intervals. Non-responders showed an initial drop (2%) in density and slight gain of 6% at three months. Surrounding bone increased slightly in all cases. Final trabecular pattern is always abnormal.
Wachenfeld (1996) [4]	14 Pts with Breast CA Osteolytic and osteoblastic lesions	2 Gy x 15 Fx BED 36 Gy	Osteolytic lesions showed no change immediately after radiation, with increase at six wks and three mo. Chemotherapy showed remineralization.

TABLE 1: Reports on remineralization after radiation for spine metastases

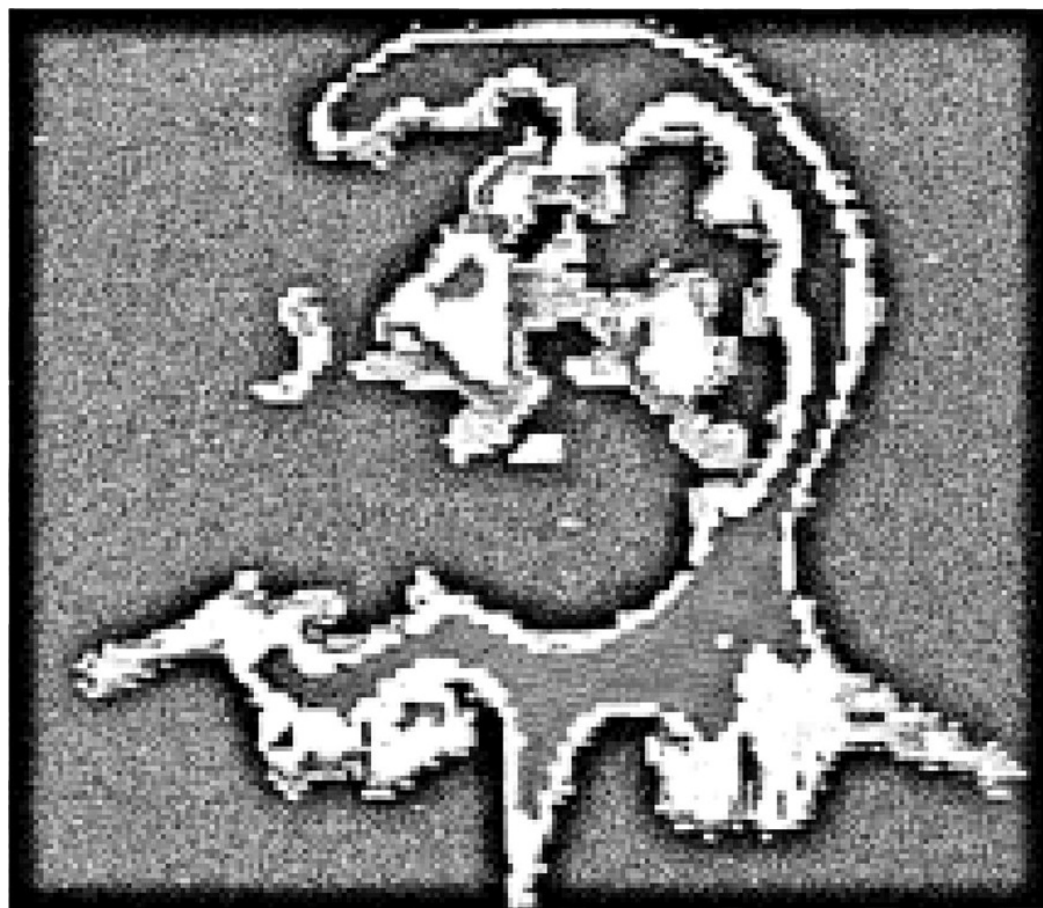


FIGURE 1: Vertebral Body Structural Deficiencies due to Osteolysis

A similar response pattern was reported by Wachenfeld [4] who looked at 14 patients with breast cancer receiving 30 Gy in 15 fx with a BED of 36 Gy. Patients were evaluated by CT with 10 mm thick slices of the affected vertebra using a quantitative CT measurement system. They found no change in mineral density at the conclusion of therapy, followed by a 30% increase at four weeks and 50% by three months for osteolytic lesions; the reverse occurred for osteoblastic lesions. They urged chemotherapy as an additional means of increasing bone density for stability. Rolf-Dieter Reinbold [5], also using quantitative CT of 8 mm sections in the midplane of the vertebra, studied 19 patients receiving 40 Gy over four weeks with a BED of 48 Gy. Sixty-six percent had good pain relief, considered a positive response to radiation, and this group showed a 20% drop in remineralization upon completion of radiation, followed at three months by an increase to over 60% of original bone density. In non-responding patients (33%), there was no change at completion of radiation and a slight rise of 20% at three months. Both groups showed an initial decrease in bone density immediately after therapy, and as well, the normal uninvolved bone showed increased density following radiotherapy. In explaining the increase in density in normal bone following therapy, Reinbold suggested that osteoblasts were stimulated by radiation accounting for the remineralization in successfully responding tumors. He also concluded that the final pattern of remineralization of lytic areas were rarely normal in appearance. In contrast to these reports of standard fractionation schemas, Koswig, et al. [6] compared the variation in remineralization in accepted hypofractionation and single fraction schemas, 10 x 3 Gy and 1 x 8 Gy. The results for both pain control and remineralization were followed over the following 30 months. Pain control was complete in 33% of patients using either schema, and reached full response by 30

days. Remineralization decreased for both groups at one month, while at six months there was a significantly higher remineralization for the 10 fraction group reaching 80% above baseline vs. only 20% for the single fraction group. In reporting responses by tumor type, they found that the responses were uniform for the single fraction group, whereas with 10 fractions, the patients with breast and prostate cancer reached 60-80% improvement, while the remaining lung and renal cases remained below 40% improvement. Comparing the fractionation schemas of 1 x 8 Gy (BED of 14.4 Gy) and 10 x 3 Gy (BED of 39 Gy) yields the following results: For patients in the single fraction group, the pain responses were complete in only 33% and the remineralization rate was poor. For patients in the 10 fraction group pain control and remineralization were better, especially for breast and prostate cancer reaching 60-80% improvement in remineralization. These results offered evidence that the responses of both pain relief and remineralization was proportionately related to the BED.

Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) are new approaches offering radiation doses that, unlike traditional radiation therapy, have the ablative capability for even radio-resistant cancers [7-8]. The ability to deliver high doses, while sparing the adjacent spinal cord, make it ideal for metastatic lesions to the spine, especially when they have received prior full standard doses. With higher tumor ablation rates, one might expect a correspondingly higher rate of remineralization with fewer instability crises than with conventional radiation.

Case Presentation

A 62-year-old female with multiple myeloma, i.e., plasmacytoma located at C2, presented with neck pain and evidence of pathological fracture of the posterior wall, and for that reason underwent immediate posterior stabilization of the occiput to C5 (Figure 2). Two weeks after surgery, she underwent CyberKnife SRS treatment in one session that lasted 135 minutes. A total of 18 Gy was delivered to the 77% isodose volume to a maximum total dose of 23.38 Gy that closely conformed to the target surface (Figure 3). The inverse treatment plan directed 231 beams, which rendered coverage of 94.13% of the planning target volume (PTV) and coverage of 97.4% of the gross tumor volume (GTV). The circular beams all measured 10 mm in diameter. The dose rate was set at 600 MU/min. GTV and PTV had a volume of 12.32 cm³ and 13.83 cm³, respectively.

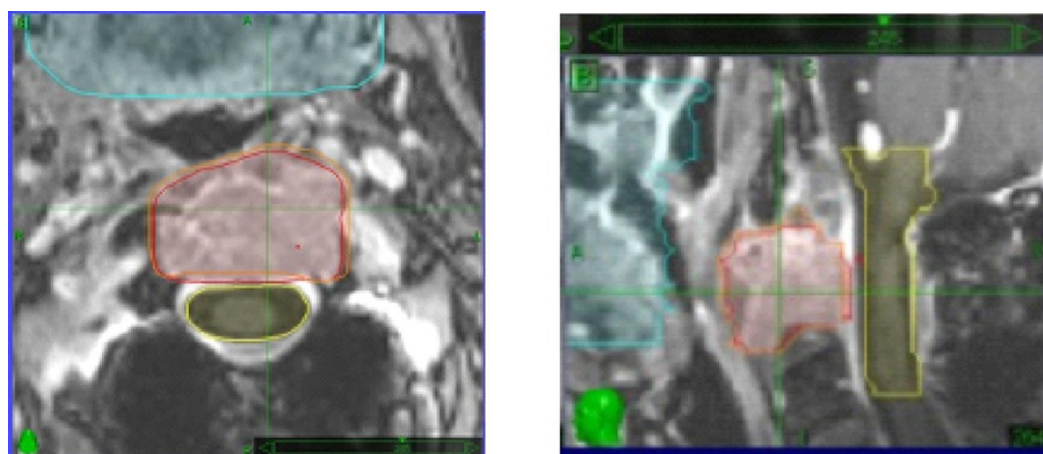


FIGURE 2: C2 Tumor, PreOp; PTV (Red) and Cord (Yellow)

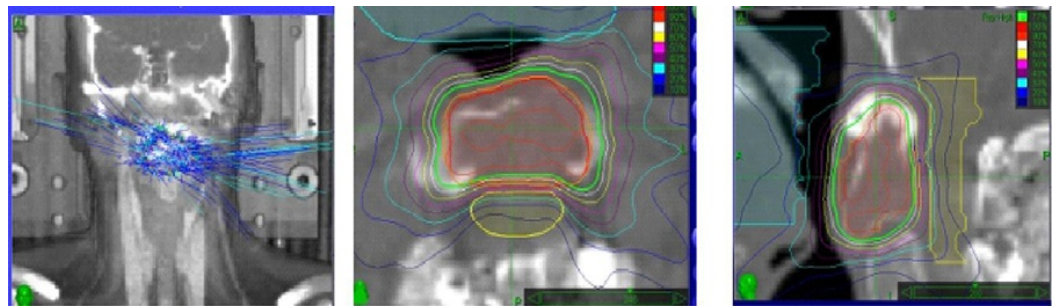


FIGURE 3: CK Treatment Plan; Left: CK Beam Configuration; Center: Axial View PTV (Red), 77% Isodose Line (Green); Right: Spinal Canal (Yellow)

Concomitant chemotherapy was not used as part of the treatment. The patient experienced no postoperative complications. Postoperative whole body PET-CT imaging revealed no significant new abnormalities to suggest interval progression of disease when compared to preoperative studies. The sequential CT scans of C2 revealed complete tumor ablation (Figure 4). Bone remineralization of the C2 vertebra progressed slowly with remineralization of the cortex seen at three months, followed by nearly complete body remineralization over next nine month follow-up period. The pattern of remineralization appeared to mimic the original trabecular pattern throughout the vertebrae. The posterior fusion progressed normally.

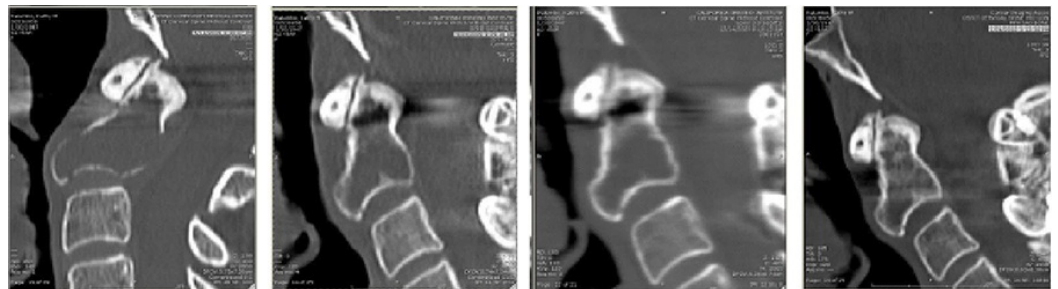


FIGURE 4: 1. Pre-Instrumentation and SRS; 2. Post-SRS at three months; 3. Post-SRS at six months; 4. Post-SRS at 12 months.

Complete tumor ablation was achieved and sustained after 12 months in this C2 vertebra. The cortical bone showed early repair by three months. This was followed by a gradual remineralization throughout the vertebral body, achieving a near normal trabecular pattern by 12 months. The patient did not receive chemotherapy or bisphosphonates.

Discussion

The advent of SRS and SBRT offers an improved approach to radiation treatment of spine metastases, while the goals of durable pain control and tumor suppression can be met with cord sparing. Using the results of traditional radiation treatment as a measure, we might expect this improved ablation with SRS and SBRT to translate into a better rate of remineralization. The current literature supports this. Gerszten, et al. reporting their series of 339 patients with spine

metastases treated with CyberKnife SBRT [9] used a maximum intra-tumoral dose ranging from 12.5 to 25 Gy (mean 20 Gy), showed long-term (five to 35 months) pain management with 86% of the patients, long-term tumor control in 90% of the lesions treated with SRS as a primary treatment modality and in 88% of lesions treated for radiographic tumor progression. They reported an overall tumor control rate of 90%. Specifically excluded from this treatment were all cases with demonstrated vertebral instability and all patients who had prior full standard radiation. Gertzen does not comment on the postoperative appearance of the treated vertebral lesions nor does he state that subsequent vertebral body instability did not occur.

In a separate prospective program, Gerszten, et al. [10] addressed patients whose spine metastases presented with either compromised canals or with vertebral fractures. Vertebroplasty was used to treat the instability followed 12 days later by SRS. In these 26 patients, pain control with vertebroplasty was excellent, and tumor control with SRS was excellent, except for two patients. One patient with a primary ocular melanoma had poor pain control and progressive instability requiring subsequent open decompression and stabilization. Gerszten stated that the inability to control the cancer cells prevented the fracture from healing. The second patient had a cholangiocarcinoma and reported poor pain control and subsequent hip fracture that prevented further evaluation or treatments. The effect of bone healing was not otherwise commented upon perhaps because of the vertebroplasty changes.

Several reports of other SRS and SBRT systems have discussed post-treatment incidence of vertebral fractures. Chang, et al. [2] used a near-simultaneous computed tomography-guided SBRT, in 63 patients. Thirty-two patients were treated with 6 Gy for five fractions to a total dose of 30 Gy with a BED of 48 Gy; a second group of patients received 9 Gy in three fractions. SBRT was considered for definitive treatment in 60% of the patients. A 77% control rate was reported, and one case of vertebral body collapse requiring stabilization. They attribute the failure rate to: 1) the failure to adequately extend the radiation field posteriorly beyond the area of visible tumor to include the pedicles and posterior elements, and 2) the under-dosing of the epidural space in an attempt to limit the spinal cord dose. Laufer, et al. [11] reported results with single fraction image-guided IMRT delivering 8-24 Gy, with median dose 24 Gy, for spinal metastases in 63 patients, with 90% local control rate, but with 39% developing progressive vertebral fractures which occurred only in areas of lytic lesions involving more than 20% of the vertebral body. Thirty percent of patients had initial baseline fractures. In comparing pretreated vertebral body tumor involvement to subsequent post-treatment risk of vertebral collapse, it was found that the risk with 40%, 60%, and 80% involvement was 14x, 24x, and 85x higher than with 20% involvement. The conclusion would seem to be that radiation alone could not be relied upon to prevent collapses. This seems intuitive since it takes time for remineralization to occur, and if during that time period stresses are greater than residual bone could support, then instability would be expected.

Furthermore, it has been shown that above a delivered dose of 20 Gy to the vertebral body, bone necrosis can be introduced that would prevent timely remineralization. In the case presented here, the prescription dose of 18 Gy was below that threshold, and therefore, bone necrosis could be prevented.

Conclusions

If SRS and SBRT are capable of ablating cancer with 85-100% efficiency, as has been reported [12-13], we should expect to see remineralization occurring concurrently with eventual reconstitution of the spine's stability. Our case report suggests that this can be an achievable outcome. In cases with extensive vertebral involvement, prophylactic stabilization or concurrent use of external bracing remains advisable, given the slow nature of the remineralization process.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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