Focused Versus Conventional Radiotherapy in Spinal Oncology: Is There any Difference in Fusion Rates and Pseudoarthrosis?

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Research Article

Keywords: Focused radiotherapy, conventional radiotherapy, external beam radiation, stereotactic body radiotherapy, pseudoarthrosis, non-union

Posted Date: October 29th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-973693/v1>

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Abstract

Introduction

Radiotherapy is considered standard of care for adjuvant peri-operative treatment of many spinal tumors, including those with instrumented fusion. Unfortunately, radiation treatment has been linked to increased risk of pseudoarthrosis. Newer focused radiotherapy strategies with enhanced conformality could offer improved fusion rates for these patients, but this has not been confirmed.

Methods

We performed a retrospective analysis of patients at three tertiary care academic institutions with primary and secondary spinal malignancies that underwent resection, instrumented fusion, and peri-operative radiotherapy. Two board certified neuro-radiologists used the Lenke fusion score to grade fusion status at 6 and 12-months after surgery. Secondary outcomes included clinical pseudoarthrosis, wound complications, and the effect of radiation timing, radiobiological dose delivered, the use of photons versus protons, tumor type, tumor location, and use of autograft on fusion outcomes.

Results

After review of 1252 spinal tumor patients, there were 60 patients with at least 6 months follow-up that were included in our analyses. Twenty-five of these patients received focused radiotherapy, 20 patients received conventional radiotherapy, and 15 patients were treated with protons. There was no significant difference between the groups for covariates such as smoking status, obesity, diabetes, intraoperative use of autograft, and use of peri-operative chemotherapy. There was a significantly higher rate of fusion for patients treated with focused radiotherapy compared to those treated with conventional radiotherapy at 6-months (64.0% versus 30.0%, Odds ratio: 4.15, **p=0.036**) and 12-months (80.0% versus 42.1%, OR: 5.50, **p=0.022**). There was a significantly higher rate of clinical pseudoarthrosis in the conventional radiotherapy cohort compared to patients in the focused radiotherapy cohort (19.1% versus 0%, **p=0.037**). There was no difference in fusion outcomes for any of the secondary outcomes except for use of autograft. The use of intra-operative autograft was associated with an improved fusion at 12-months (66.7% versus 37.5%, OR: 3.33, **p=0.043**).

Conclusion

Focused radiotherapy may be associated with an improved rate of fusion and clinical pseudoarthrosis when compared to conventional radiation delivery strategies in patients with spinal tumors. Use of autograft at the time of surgery may be associated with improved 12-month fusion rates. Further large-scale prospective and randomized controlled studies are needed to better stratify the effects of radiation delivery modality in these patients.

Introduction

Radiotherapy is an integral component of conventional treatment strategies for primary and secondary tumors of the spinal cord and column. The past decade has seen a significant advancement in the available technologies for delivery of radiation. [1][2, 3] This includes stereotactic body radiotherapy (SBRT) and proton-based radiation, which have both seen a surge in applications for various spinal pathologies. [4][5][6] Despite the necessity of radiation therapy in combination with surgery for adjuvant treatment of many spine tumors, radiation inhibits bone formation and therefore leads to increased risk of instrumentation failure and non-union. [7] Preclinical studies have shown that ionizing radiation induced double stranded DNA breaks have a direct effect on bone forming osteoblasts. [8] Interestingly, low dose radiation promotes osteogenesis, but high dose radiation, as is required for tumor control, inhibits bone growth. [8][9] Ionizing radiation enacts its effects on bone growth through various mechanisms, including cell cycle arrest, inhibiting collagen formation, regulation of vascular endothelial growth factor, and inhibition of osteoblast proliferation. [8][9][10, 11]

There is a paucity of literature describing the fusion outcomes for patients with spinal tumors, as most of these patients have metastatic disease and historically succumbed to their primary disease prior to the time that their fusion should be solid. [12] Due to tremendous advancements in targeted therapies and surgical strategies, patients live longer with their cancers, increasing the importance of preserving quality of life in these patients after their surgery. [13][14] Non-union can lead to debilitating pain, need for further surgery, and decreased quality of life for patients following instrumentation. The rates of pseudoarthrosis range from 5-35% following spinal instrumentation, with these rates being higher for those requiring radiation, so any efforts to enhance the likelihood of fusion for these patients will be of great benefit to them. [15][16][17]

The primary aim of this study is to assess the 6 and 12-month fusion rates in patients who underwent surgical resection with instrumentation for their spinal tumors and received radiotherapy with either conventional or focused delivery strategies. Secondary aims

were to assess the impact of radiation timing, number of fractions, dose, use of photons or protons, and use of autograft on fusion rates. We hypothesize that fusion rates will be improved in those patients treated with focused radiation delivery strategies.

Methods

Patient Population

The authors performed a retrospective analysis of patients at each of the three sites of our tertiary care academic institution from January 2013 to October 2020. This study was approved by the institutional IRB committee (IRB# 18-003951). The inclusion criteria were as follows: 1) adult patients with resection of a primary or secondary tumor of the spinal cord or column, 2) patients with instrumented fusion using rods and screws after their surgical resection, and 3) patients who received radiation treatment either before or after their surgical procedure. The exclusion criteria were as follows: 1) patients with less than 6-months of radiographic and clinical follow-up, 2) patients who received instrumentation using carbon-based hardware, 3) patients who received cement augmentation with their instrumentation. The purpose of this manuscript was not to assess the efficacy of newer instrumentation techniques such as fenestrated polymethylmethacrylate (PMMA)–augmented pedicle screw fixation, or carbon-based hardware, therefore we excluded these patients, as they would likely confound the results. We collected patient-specific variables such as age, sex, pathology diagnosis, smoking status at the time of surgery, post-operative wound issues, BMI, and diabetic status.

Radiation Treatment

We collected variables related to the radiotherapy including delivery modality, number of fractions, timing of radiation, and radiation dosage. Radiation modalities were grouped to consider the conformality of the radiotherapy as a potential predictor of the rate of fusion. “Focused radiation” was defined as those treatment plans that received greater than 5Gy per fraction using technology to maximize the conformality with steep dose gradients. This included intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) plans (Figure 1). [18, 19] Conventional radiation was defined as 3-dimensional external beam radiotherapy treatment plans (less than 5Gy per fraction, including plans with 8 Gy in 1 fraction), which did not use IMRT. [20] Proton-based radiation was considered in a separate group, due to inherent differences in treatment planning and underlying radiobiology. [21] We assessed the radiobiological effect by calculating the biologically effective dose (BED) for each patient and then compared patients above and below the median BED.

Outcomes

The primary outcome was fusion status as determined by two board-certified neuro-radiologists using X-ray and CT images. Each radiologist was blinded to the radiation status of the cohort, and they assessed each patient separately and discussed the discrepancies. The Lenke fusion scale was used to assess fusion at 6 and 12-months after placement of instrumentation. [22] The neuro-radiologists each assessed the fusion across the posterior elements on imaging since not every patient will have an interbody graft. Patients were classified in binary groups as fused with Lenke grade A or B, or non-fused with a Lenke grade of C or D (Figure 2). Secondary outcomes included the rate of clinically significant pseudoarthrosis, defined as those patients with radiographic evidence of pseudoarthrosis, who demonstrated new onset of pain and/or weakness which was attributed to their non-union. We compared data regarding post-operative wound complications for the groups. We analyzed the effect radiation timing (pre- versus post-operative & within 1-month of surgery versus > 1-month from surgery), dose (above versus below median BED), photons versus protons, primary versus secondary tumors, and use of intra-operative autograft on fusion outcomes.

Statistical Analysis

Statistical analyses were performed using the Fisher exact test, Student t-test, and Mann–Whitney U test for categorical, parametric continuous, and nonparametric continuous variables, respectively. Odds ratios were calculated based on effect sizes and Baptista-Pike was used to determine exact and mid confidence intervals. Analyses were performed using GraphPad Prism 9.1.0, GraphPad Software, San Diego, California USA.

Results

Patient demographics

We reviewed of 1252 patients with spinal tumors treated at our institutions within the time frame, resulting in 60 patients with at least 6-months of follow-up (mean follow-up: 33 months; standard deviation: 25.3 months) that were included in our analyses (Figure 3). Thirty-seven (61.6%) of these patients were male, with a mean age of 63.6 years and a mean follow-up time of 33 months (SD 25.3 months)

(Table 1). Twenty-five of these patients received focused radiotherapy modalities including SBRT (n=17) and IMRT (n=8). Twenty patients received conventional radiation delivery modalities, and 15 patients received proton-based radiotherapy. The cohorts were well-matched with no significant difference between them for confounders such as smoking status (p=0.309), obesity (p=0.515), diabetes (p=0.365), tumor type (p=>0.999), intraoperative use of autograft (p=>0.999), and use of peri-operative chemotherapy drugs such as nivolumab, ipilimumab, imatinib, cisplatin, and paclitaxel (p=>0.999). There were also similar numbers of levels fused with an average of 5.2 levels per patient in the focused radiotherapy 5.5 levels per patients in the conventional radiotherapy group (p=0.602). There was a trend towards a higher incidence of local recurrence in the conventional radiotherapy group at the time of fusion assessment (8.3 versus 35%, p=0.057). There were 34 patients with metastatic disease, 15 patients with chordoma, 2 patients with sarcoma, 2 patients with plasmacytoma, 2 patients with lymphoma, 2 patients with spinal cord gliomas, 1 patient with chondrosarcoma, 1 patient with melanocytoma, and 1 patient with atypical meningioma.

Effect of Radiotherapy Delivery Technique

There was a significantly higher rate of fusion for patients with focused radiotherapy compared to those with conventional radiotherapy at 6-months (64.0% versus 30.0%, OR: 4.15, **p=0.036**) 12-months (80.0% versus 42.1%, OR: 5.50, **p=0.022**) (Table 2). There was a near significant increase in the incidence of clinically significant pseudoarthrosis in the conventional radiation cohort (19.1% versus 0%, **p=0.036**), although only one patient required revision surgery for pseudoarthrosis (Table 3). There was no significant difference in the incidence of peri-operative wound healing complications between patients treated with focused radiotherapy and those treated with conventional radiotherapy (16.0% versus 5.0%, p=0.727). There were 88% of patients with CT scans available for review, with the remaining 12% of patients being evaluated using x-ray imaging.

Table 1. Characteristics of Patients with Spinal Tumor Resection and Instrumentation with Radiotherapy									
	Median Age (years)	M: F	Smoker	Obesity	Diabetes	Use of Autograft	Use of Chemotherapy	Wound Complications	Clinically Significant Pseudoarthrosis
All Patients (n=60)	63.6	37:23	6.7%, (n=4)	31.7% (n=19)	23.3% (n=14)	46.4% (n=26) ^a	26.7% (n=16)	15.0%, (n=9)	8.3% (n=5)
Focused Radiotherapy (n=25)	65.1	13:12	4.0% (n=1)	24.0% (n=6)	29.0% (n=8)	45.8% (n=11) ^b	32.0% (n=8)	16.0%, (n=4)	0.0% (n=0)
Conventional Radiotherapy (n=20)	60.6	15:5	15.0% (n=3)	35.0% (n=7)	17.2% (n=2)	41.2% (n=7) ^c	24.1% (n=7)	5.0% (n=1)	15.0% (n=3)
Proton-based Radiotherapy (15)	65.1	9:6	0% (n=0)	40.0% (n=6)	26.7% (n=4)	41.2% (n=8)	13.3% (n=2)	20.0% (n=3)	13.3% (n=2)*
^a Data missing for 4 patients, ^b Data missing for 1 patient, ^c Data missing for 3 patients									
* One patient required reoperation for pseudoarthrosis									

Table 2. Primary and Secondary Outcomes for Patients with Spinal Tumor Resection and Instrumentation with Radiotherapy						
	6-Month Fusion Rate	Odds Ratio (CI)		12-Month Fusion Rate	Odds Ratio (CI)	
Focused Versus Conventional	Focused: 64.0%, Conventional: 30.0%	4.15 (1.10 - 12.71)	p=0.036	Focused: 80.0%, Conventional: 42.1%	5.50 (1.34 to 18.83)	p=0.022
Preoperative Radiation Versus Postoperative Radiation	Preoperative: 42.9%, Postoperative: 45.7%	0.89 (0.25 - 2.77)	p=>0.999	Preoperative: 50.0%, Postoperative: 57.1%	0.75 (0.20 - 2.88)	p=0.734
High Versus Low BED Dosage	High BED: 52.2%, Low BED: 42.1%	1.44 (0.49 - 4.04)	p=0.585	High BED: 68.2%, Low BED: 56.3%	1.67 (0.40 - 5.72)	p=0.5105
Timing of Radiation	≤ 1 month: 42.9%, > 1 month: 48.4%	0.80 (0.27 - 2.46)	p=0.781	≤ 1 month: 63.2%, > 1 month: 48.3%	1.84(0.54 - 6.03)	p=0.382
Proton Versus Photon	Protons: 33.3%, Photons: 56.1%	0.39 (0.12 - 1.44)	p=0.227	Protons: 35.7%, Photons: 64.1%	0.31 (0.09 - 1.03)	p=0.115
Primary versus secondary tumors	Primary: 40.0% Secondary: 48.6%	0.63 (0.22 - 1.78)	p=0.439	Primary: 43.5% Secondary: 62.1%	0.47 (0.17 - 1.42)	p=0.264
Intraoperative Use of Autograft	Use of autograft: 50.0%, No autograft: 39.3%	1.55 (0.56 - 4.47)	p=0.591	Use of autograft: 66.7%, No autograft: 37.5%	3.33 (1.01 - 10.95)	p=0.043
BED: biologically effective dose						

Table 3 Clinical Pseudoarthrosis in patients with Spinal Tumor Resection and Instrumentation with Radiotherapy

Patient	Age/Sex	Radiation Modality	Presentation	Outcome
Patient 1	54/M	Conventional radiotherapy	Worsening pain with screw fracture	Conservative management
Patient 2	79/M	Conventional radiotherapy	Worsening pain with radiographic non-union	Conservative management
Patient 3	43/M	Conventional radiotherapy	Worsening pain with radiographic non-union	Conservative management
Patient 4	73/M	Conventional radiotherapy	Worsening pain with broken rod	Revision surgery
Patient 5	78/M	Proton radiotherapy	Worsening pain with screw fracture	Conservative management

Effect of Radiotherapy Timing, Dose, and Photons versus Protons

There was no significant difference in fusion outcomes for patients who received pre-operative radiotherapy (23% of patients, n=14), compared to those who received post-operative radiotherapy at 6-months (42.9% versus 45.7%, OR: 0.89, p=>0.999) and 12-months (50.0% versus 57.1%, OR: 0.65, p=0.734). There was no significant difference in fusion rates between those patients treated with radiotherapy within 1-month of surgery (40%, n=24) and those treated more than 1-month from their surgery at 6-months (42.9% versus 48.4%, OR: 0.80, p=0.781) and 12-months (63.2% versus 48.3%, OR: 1.84, p=0.382). There was no significant difference in 6-month (52.6% versus 31.8%, OR: 2.38, p=0.178) and 12-month (64.5% versus 42.9%, OR: 2.42, p=0.160) fusion rates for patients who received 40Gy or less (63% of patients, n=38) of total radiation as compared to those who received a higher dose. Whether photons or protons were used did not significantly impact fusion outcomes at 6-months (33.3% versus 56.1%, OR: 0.39, p=0.227), and 12-months (35.7% versus 64.1%, OR: 0.31, p=0.115).

Effect of Bone Graft and Tumor Type/Location

There were 28 (46.7%) patients who had use of intraoperative autograft during their surgery (45.8% of focused cohort, 41.2% of conventional cohort, $p=0.59$). All patients in the non-autograft group had intraoperative use of some form of allograft. Autograft modalities included iliac crest, femoral bone graft, and local bone not involved with tumor. At 6-months, there was no significant difference in the groups, with a 50.0% fusion rate for those with use of autograft, and 39.3% fusion rate for those without autograft (OR: 1.55, $p=0.420$). At 12-months, there was a significantly higher rate of fusion for those patients who had use of autograft at the time of surgery (66.7% versus 37.5%, OR: 3.33, **$p=0.043$**). There were 25 (41.7%) patients with primary tumors of the spinal cord or column and 35 (58.3%) patients with secondary tumors of the spinal column. There was no significant difference between the groups for fusion rate at 6-months (40.0% versus 48.6%, OR: 0.63, $p=0.439$) and 12-months (43.5% versus 62.1%, OR: 0.47, $p=0.264$). There were 22 patients with cervical tumors, 23 patients with thoracic tumors, and 15 patients. There was no significant difference between the groups for 6-month ($p=0.529$) and 12-month fusion ($p=0.423$), but the rate of fusion at 12-months was 66.7% for patients with lumbar spine tumors, and 50% for those with cervical tumors and 50% for those with thoracic tumors.

Discussion

Our study shows that focused radiotherapy may be associated with improved fusion rates following resection and instrumentation in patients with spinal tumors when compared to conventional radiotherapy delivery modalities. Two prior studies attempted to answer this question, however they were both inadequately powered, highlighting the difficulty of answering this question for patients with spinal tumors such as metastasis, as these patients historically do not survive long enough to collect meaningful fusion data. [23][24] Improved survival outcomes due to recent advances in targeted therapies have allowed assessment of fusion status to be a feasible outcome. Our study also reveals that intraoperative use of autograft is associated with higher 12-month fusion rates for spinal tumor patients who receive peri-operative radiotherapy in conjunction with resection and instrumentation.

The theoretical benefit of focused radiotherapy lies in the delivering a higher treatment dose to a more precise location to maximize treatment effect at the surgical bed while limiting toxicity to the spinal cord, abdominal viscera, surrounding bone, and instrumentation hardware. [25][26] Our study found a significantly higher rate of fusion for patients with focused radiotherapy at 6-months (64.0% versus 30.0%, OR: 4.15, **$p=0.036$**) and 12-months (80.0% versus 42.1%, OR: 5.50, **$p=0.022$**) compared to those who received radiation via a conventional delivery modality, indicating that the decreased radiation spillover into the surrounding bone is beneficial for fusion. A potential confounder was local spread of tumor into the fusion bed, as there was a near significant difference in the incidence of local recurrence at the time of fusion assessment (8.3 versus 35%, $p=0.057$). While local recurrence was not an endpoint of this study, this appears to be an additional benefit of focused radiotherapy over conventional. While this may possibly play a small role in fusion, review of the imaging showed most cases of tumor progression to be ventral to the posterior elements, where fusion was assessed. Other factors such as the number of levels fused and chest wall resection have been found to play a role in hardware failure, but our study was well match with groups having similar numbers of levels fused. [27] A higher dose of radiation should theoretically have a more pronounced deleterious effect on bone growth and therefore a higher risk of non-union. A previous study indicated that more than 40Gy delivered to the surgical bed of an anterior reconstruction appeared to increase the risk of pseudoarthrosis. [28] We compared patients with a higher radiobiological dose of radiotherapy to those with a lower radiobiological dose, but there was no significant difference in fusion among the groups ($p=0.160$). We found a higher incidence of clinically significant pseudoarthrosis in patients who received conventional radiotherapy when compared to those with conventional radiotherapy (19.1% versus 0%, **$p=0.037$**). Although only one patient required re-operation, there is significant pain, disability, and loss of work associated with post-operative pseudoarthrosis. [29, 30]

Expert opinion recommends at least one week between surgery and radiation to minimize the risk of wound healing complications, but there was insufficient literature to make recommendations for the timing of surgery as it relates to fusion. [12] Our study revealed no significant difference in the rate of fusion for those treated with radiotherapy within 1-month of surgery and those treated more than 1-month from their surgery at 6-months (≤ 1 month: 42.9%, > 1 month: 48.4%, OR: 0.80, $p=0.781$) and 12-months (≤ 1 month: 64.5%, > 1 month: 42.9%, OR: 2.42, $p=0.160$). Interestingly, the fusion rate at 6-months was nearly identical for the group treated within 1-month, but the fusion rate at 12-months was slightly higher for the patients treated within 1-month of surgery. This indicates that receiving radiotherapy within 1-month of surgery does not appear to have a deleterious effect on fusion rates. Some studies have found no significant benefit of protons over photons for tumor control when the treatment dose is identical. [31] However, protons allow for delivery of a higher dose of radiation with a more rapid drop-off at the treatment field margins, causing less damage to unintended surrounding structures and therefore improved outcomes. [32][33] Our study did not note any difference in fusion outcomes for patients treated with photons compared to those treated with protons.

There is a wide array of bone graft products, with varying osteo-inductive, osteo-conductive, and osteo-genic properties which may help increase the likelihood for achieving a solid fusion. However, there is a contraindication for use of products like rhBMP in cancer patients

because of a possible association between rhBMP and cancer, effectively eliminating its use in spine tumor patients. [34][35][36] Inability to use these types of products compounded with the use of peri-operative radiation explains the difficulty with obtaining a bony fusion in this patient population. Our study found a higher 12-month fusion rate when autografts such as iliac crest and femoral bone grafts were used compared to patients who received allograft and synthetic bone products (66.7% versus 37.5%, OR: 3.33, **p=0.043**). This finding appears to be consistent with the available evidence for non-neoplastic cases, as some studies found a better fusion rate when using autograft compared to synthetic allograft bone. [37–39][40][41]

Limitations

The question of fusion outcomes after spinal tumor resection and radiotherapy has historically been challenging to answer due to many inherent limitations of this patient population. Secondary tumors of the spinal column are the most common, and these patients often succumb to their systemic disease burden within a year of surgery. This limited the available data, as most of the patients who received radiation after resection of their spinal tumors died prior to the typical time frame one would expect to see fusion. This limited the ability to assess long term fusion, which would be most ideal. Our study started with over 1,200 potential patients, but after exclusion, there were 60 patients remaining. Another limitation of this study was our inability to factor in how much of the area of intended arthrodesis was included in the radiation treatment field. For multi-level posterior constructs, most of the instrumentation field will likely be out of the treatment field, but we were unable to account for this. We would ideally use CT imaging to assess fusion in all patients, but only x-ray imaging was available for 12% (n=7) of patients. There was also a fair amount of heterogeneity for the patients included. Patients with resection of a primary bone tumor such as chordoma may have a large bony gap making fusion much more challenging. Many of the chordoma patients received proton radiotherapy, and therefore were not included in the primary analysis. Also, there was no difference between the groups for the incidence of primary tumors ($p>0.999$). Despite these limitations, this appears to be the best available data to support one method of peri-operative radiotherapy over another. A strength of this study is the external validity, being comprised of patients from tertiary care institutions in three different geographical regions of the United States.

Conclusions

Based on our comparison of peri-operative focused radiotherapy and conventional radiotherapy for treatment of spinal tumor patients with surgical resection and instrumentation, focused radiotherapy appears to have a better fusion rate at 12-months as well as lower incidence of clinical pseudoarthrosis. Although no definitive recommendations can be made for the ideal timing of peri-operative radiotherapy, the use of radiotherapy within a month of surgery does not appear to have a significant deleterious effect on fusion. Surgeons should consider use of autograft when instrumenting spinal tumor patients who will receive peri-operative radiotherapy, as this may increase the likelihood for a solid fusion.

Declarations

Funding: O.O.A. is supported by Neurosurgery Research and Education Foundation Funding, but this funding is not directly related to this project.

Conflict of Interest: All authors report they have no conflicts of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. IRB approval was obtained for this study.

Statements and Declarations: Authors report no financial competing interests. O.O.A. is supported by Neurosurgery Research and Education Foundation Funding.

Author contributions: OOA: writing manuscript, data collection, statistical analysis, reviewed final, GD: writing manuscript, data collection, statistical analysis AG: data collection, JM: data collection, SS: data collection, critically revised manuscript, RK: figure preparation, critically revised manuscript, DT: critically revised manuscript, JS: critically revised manuscript, KM: critically revised manuscript, SV: critically revised manuscript, DB: data collection, MC: critically revised manuscript, MB: critically revised manuscript, JM: critically revised manuscript, MK: critically revised manuscript, AQ: critically revised manuscript, KA: critically revised manuscript, study supervision

Data availability statement: Not applicable, electronic medical record data is protected by institution

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Figures

Figure 1

Planning computed tomography (CT) demonstrating treatment fields for patients with spinal tumors and instrumentation. A) Treatment fields for a 76-year-old man with metastatic renal cell carcinoma who underwent a C6-T4 instrumented fusion and resection of his tumor followed by 30Gray of stereotactic body radiotherapy (SBRT) in 3 fractions. Treatment demonstrated ranging from at least 100% of the prescription dose in red to 80% of the prescription dose in blue. At 12-months the patient had evidence of Lenke grade B fusion. B) Treatment fields for a 79-year-old man with metastatic hepatocellular carcinoma who underwent a T11-L2 instrumented fusion and resection of his tumor followed by 8Gy of conventional external beam radiotherapy in 1 fraction. Treatment demonstrated ranging from at

least 100% of the prescription dose in red to 80% of the prescription dose in blue. The patient had a wound dehiscence requiring return to the operating room and a Lenke grade C fusion at 12-months.

Figure 2

Sagittal CT scans showing fusion Grades according to the Lenke Classification. A) Grade A: solid fusion with bilateral solid stout fusion present; B) Grade B: probably solid fusion with unilateral stout fusion mass and contralateral thin fusion mass; C) Grade C: probably not solidly fused with a thin unilateral fusion mass and probable pseudarthrosis on the contralateral side; D) Grade D: definitely not solidly fused with thin fusion masses bilaterally with obvious pseudarthrosis or bone graft dissolution bilaterally.

Figure 3

Flow diagram of included patients with spinal tumor resection included in our analysis.