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Consensus Contouring Guidelines for Post-Operative Stereotactic Body Radiation Therapy (SBRT) for Metastatic Solid Tumor Malignancies to the Spine

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Abstract

Objective—Although post-operative stereotactic body radiotherapy (SBRT) for spinal metastases is increasingly performed, few guidelines exist. We sought to develop consensus contouring guidelines to promote safe and effective clinical practice.

Methods—Ten spine SBRT specialists representing 10 international centers independently contoured the CTV, PTV, spinal cord, and spinal cord PRV for 10 representative clinical scenarios in post-operative spine SBRT for metastatic solid tumor malignancies. Contours were imported into Computational Environment for Radiotherapy Research. Agreement between physicians was calculated with an expectation minimization algorithm using Simultaneous Truth and Performance Level Estimation (STAPLE) with kappa statistics. Target volume definition guidelines were established by finding optimized confidence level consensus contours using histogram agreement analyses.

Results—Nine expert radiation oncologists and 1 neurosurgeon completed contours for all 10 cases. The mean sensitivity and specificity were 0.79 (range: 0.71 - 0.89) and 0.94 (range: 0.90 - 0.99) for the clinical target volume (CTV) and 0.79 (range: 0.70 - 0.95) and 0.92 (range: 0.87 - 0.99) for the planning target volume (PTV), respectively. Mean kappa agreement, which demonstrates the probability that contours agree by chance alone, was 0.58 (range: 0.43 - 0.70) for CTV and 0.58 (range: 0.37 - 0.76) for PTV (p<0.001 for all cases). Optimized consensus contours were established for all patients with 80% confidence interval. Recommendations for CTV include treatment of the entire pre-operative extent of bony and epidural disease, plus immediately adjacent bony anatomic compartments at risk of microscopic disease extension. In particular, a "donut-shaped" CTV was consistently applied in cases of pre-operative circumferential epidural extension regardless of extent of residual epidural extension. Otherwise more conformal anatomic based CTV were determined and described. Spinal instrumentation was consistently excluded from the CTV.

Conclusions—We provide consensus contouring guidelines for common scenarios in postoperative SBRT for spinal metastases. These consensus guidelines are subject to clinical validation.

Keywords

Post-operative spine stereotactic body radiation therapy (SBRT); contouring; spine metastases; stereotactic radiosurgery

Introduction

Surgery is a critical therapeutic modality in the management of complex spinal metastases. For patients with symptomatic single spinal level malignant epidural spinal cord compression (MESCC), surgical decompression followed by conventional radiotherapy (RT) has been proven to be superior with respect to ambulatory function as compared to RT alone (1). A more modern, although not randomized, prospective study also suggests a significant benefit in quality of life in those patients with MESCC treated with surgery plus RT (2). The surgical intent is circumferential decompression with stabilization of the vertebral column. Frank mechanical instability, impending instability or MESCC are other typical surgical

indications. Regardless of the type of surgery, adjuvant conventional external beam RT is delivered with the intent of tumor control and most typically, a regimen of 30 Gy in 10 fractions is used. As patients with metastatic disease live longer due to more effective systemic therapy, the complexity of spinal metastases management to will only continue to

Spine SBRT was developed with the intent to deliver a higher biologically equivalent dose in a hypo-fractionated treatment schedule as compared to conventional RT. The intent was to maximize both local and pain control as conventional RT is associated with sub-optimal results. Although no randomized controlled trials have been published to confirm the benefit of SBRT over conventional RT, an increasing body of literature demonstrates excellent local control following SBRT for both radio-sensitive and radio-resistant primary tumors with rates of in-field failure less than 20 percent with median FU ranging from 6–21 months (3–8). As the technique has matured, its application to the post-operative patient is emerging. (7, 9–16). Historically, post-operative RT has been associated with local control rates ranging from 4–79% (17–22), and the current, albeit few, post-operative spine SBRT series suggest rates of approximately 70–100% (7, 9–13, 19, 20, 23–27).

evolve in both surgical and RT domains. One such development in spine RT has been the transition from conventional RT to the use of stereotactic body radiotherapy (SBRT).

The practice of post-operative spine SBRT is unique compared to intact metastases as considerations must be made specific to the pre-operative tumor location, residual disease, spinal hardware and more specifically the epidural space. It has been shown that the most common pattern of failure following SBRT in both intact and post-operative patients is within the epidural space (9, 11, 13), as such in both the surgical and RT domains there is increasing attention to the management of epidural disease. This is highlighted by the increasing adoption of separation surgery where the intent is to decompress, downgrade the epidural disease, and minimize tumor debulking as this surgical approach is coupled to postoperative spine SBRT as the modality to render tumor control (11, 13, 23, 24). The consequence of epidural failure cannot be underscored as there is potential for neurologic compromise, re-operation, and deterioration in quality of life. Therefore, the potential for geographic miss due to the conformality of spine SBRT should be minimized. The success of prior contouring guidelines for spine SBRT (28) for intact spinal metastases prompted this current effort aiming at consensus contouring guidelines for representative post-operative cases based on the pre-operative and post-operative imaging amongst experts in the field. We propose uniform reproducible guidelines but future prospective evaluation is required to evaluate the impact on clinical outcomes.

Methods

Nine spine radiation oncologists and 1 neurosurgeon with a collective experience of greater than 1400 post-operative spine SBRT cases participated in the project which was IRB approved by the coordinating center. Providers were selected from programs with large clinical and academic experience in spine SBRT techniques. Ten cases from real patients treated at a single institution were identified and reviewed by the participants. Clinical scenarios were designed to represent a diverse spectrum of pre-operative tumor locations

with varying degrees and anatomic locations of epidural involvement and para-spinal extension.

For each of the 10 cases, physicians were given a synopsis of clinical scenario including the patient's age, oncologic history, neurologic exam, details regarding the surgical approach, technique and findings as well as applicable pre- and post-operative radiographic results such as the extent of bony and epidural involvement. Patients were simulated in site specific custom immobilization. A complete set of anonymized co-registered datasets including pre-operative MRI, post-operative MRI, CT simulation, and CT myelogram when necessary for spinal cord delineation were provided in DICOM format. Physicians were told that all patients would be treated with SBRT and were asked to independently delineate the clinical target volume (CTV), planning target volume (PTV), and the spinal cord avoidance structure on the axial treatment planning simulation CT scan with 1 mm slices.

Finalized structures were returned to the coordinating center in DICOM format and imported into a commercial treatment planning system for initial review. All contours for each patient were then exported to the Computational Environment for Radiotherapy Research (29) for analysis. Agreement between physician contours was calculated quantitatively using kappa statistics, which correct for the probability that contours agree by chance alone. Interpretation of kappa results are as follows (29): <0 poor agreement; 0.01–0.20 slight agreement; 0.21–0.40 fair agreement; 0.41–0.60 moderate agreement; 0.61–0.80 substantial agreement; 0.81–1.00, almost perfect agreement. Statistical significance was assessed based on the standard error of the kappa statistic, with *p*-values < 0.01 reflecting a significant difference between observed agreement and chance agreement. Final consensus contours were generated with an expectation minimization algorithm using Simultaneous Truth and Performance Level Estimation (STAPLE) (31–32).

In this algorithm, the consensus contour is estimated by iteratively optimizing measures of sensitivity and specificity. Sensitivity reflects the probability that a voxel in the consensus contour is also in each of the expert contours, whereas specificity reflects the probability that a voxel outside the consensus contour is also outside one or more expert contours. Final consensus contours were generated based on an 80% confidence level, consistent with similar work by Cox et al (28).

Anatomic descriptions of consensus contours were developed using the International Spine Radiosurgery Consortium (ISRC) anatomic classification system previously utilized in the development of consensus contouring guidelines for intact vertebrae (28). Figure 1 outlines this system in which each vertebral level is divided into 6 sectors including the body (sector 1), left pedicle (sector 2), left transverse process and lamina (sector 3), spinous process (sector 4), right transverse process and lamina (sector 5), and right pedicle (sector 6).

Results

Radiographic characteristics of each case are shown in Table 1, with anatomic descriptions and representative pre-operative axial MRI, pre-operative sagittal MRI, post-operative axial CT myelogram or T2 weighted MRI, and axial T1 post gadolinium MRI images presented

for each case. Two cases involved the cervical spine, 7 involved the thoracic spine, and 1 involved the lumbar spine. Nine of the patients had MESCC pre-operatively and 1 patient had a vertebral body fracture without epidural extension of tumor which had undergone vertebroplasty. Ten physicians submitted contours for all 10 cases the CTV, PTV, spinal cord, and spinal cord planning risk volume.

CTV and PTV delineation

Table 2 shows the CTV and PTV contour agreement according to the STAPLE analysis. For the CTV, there was a high level of agreement between contouring physicians with a mean sensitivity of 0.79 (range: 0.71 - 0.89) and mean specificity of 0.94 (range: 0.90 - 0.99) for the CTV. The mean kappa agreement for the CTV was 0.58 (range: 0.43 - 0.70) for CTV and was statistically with p<0.001 for all cases. Similarly, for the PTV the mean sensitivity was 0.94 (range: 0.90 - 0.99) and the mean specificity was 0.92 (range: 0.87 - 0.99). The mean kappa agreement for the PTV was 0.58 (range: 0.37 - 0.76) and the agreement was again statistically significant with p<0.001 for all cases. The lowest kappa scores, representing the most variability between contours were for cases 7 and 10. Table 3 shows the simulation MRI with individual contours represented by thin lines and the 80% consensus contours as they apply to the ISRC anatomic classification system. Axial pre-operative MRI images and axial post-operative images are also shown for each patient.

Evaluation of the CTV 80% consensus contours suggests coverage is driven by the preoperative sites of osseous and epidural disease, irrespective of the extent of surgical resection. The CTV generally includes not only the sites of gross residual disease on postoperative CT and MRI, but also the regions that were involved pre-operatively based CT and MRI. There is consistent inclusion of adjacent anatomic compartments at risk of microscopic disease extension. Table 4 describes the post-operative CTV based on preoperatively bony and epidural involvement using the ISRC anatomic classification as a framework. PTV expansions varied between institutions ranging from no expansion to an approximately 2.5 mm expansion. The cord avoidance structure was consistently subtracted out from the final PTV for treatment planning. Surgical instrumentation and incision do not need to be included unless believed to be specifically at risk of tumor involvement. Table 5 summarizes the overall consensus contouring guidelines for GTV, CTV and PTV.

Discussion

Spine SBRT is being increasingly practiced in both community and academic centers, with more recent applications to the post-operative setting (7, 9–16). The historical standard of care has been large, aggressive surgery (often corpectomy) followed by palliative doses of radiation therapy. However, the development of SBRT now allows dose escalation and delivery of ablative radiation doses with excellent local control when SBRT is utilized as the sole modality of treatment (3–8). Furthermore, innovations in surgical techniques include minimally invasive surgical interventions designed to decompress the spinal cord and stabilize the vertebral column with substantially shorter recovery periods and more rapid return to systemic therapy than traditional aggressive surgical interventions (11, 13, 23, 24).

Therefore, the emerging treatment paradigm of limited surgical intervention followed by aggressive SBRT allows the benefit of surgical intervention and preservation of neurologic function to a broader group of metastatic patients.

Although consensus guidelines have been established for contouring intact vertebral bodies (28), there are presently no recommendations specific to the post-operative patient. The need for such guidelines is of paramount importance given developments in spinal surgery that depend on the SBRT to locally control the disease so that surgical morbidity can be reduced by focusing on epidural decompression and stabilization without performing a vertebrectomy. Our study has successfully established consensus in contouring common post-operative spinal metastases cases based on *both* the pre- and post-operative disease locations according to the ISRC template with high sensitivity and specificity (Table 2 and 3). The significance in the Kappa statistics confirms non-random agreement between the contouring physicians. The automated STAPLE segmentation evaluation limits human associated inter- and intra-observer errors. The similarity between the contouring guidelines for both intact and post-operative spine SBRT should be noted. Specifically, these guidelines are consistent with the previously published definitive guidelines to include the involved and adjacent ISRC sites, but utilize the extent of preoperative tumor involvement and take into account anatomic changes from surgery. The most variability between physician contours were found in cases 7 and 10. This appears to be due to variability in the subclinical bony coverage in case 7 and para-spinal extension margin in case 10. The recommendations presented in this manuscript are supported by a recent pattern of failure analysis (33) specific to post-operative spine SBRT failures and epidural disease. The methodology consisted of examining the location of epidural disease on the pre-operative and postoperative MRI, and the relationship to where epidural disease progression was observed according to the 6 sectors previously described by the ISRC. The investigators confirmed that the site at the highest risk of local failure following post-operative spine SBRT is within the epidural space (9, 33). The pre-operative epidural disease location was observed to be a significant predictor of location of progression as opposed to the post-operative location of residual epidural disease. This led the investigators to conclude that the CTV must include the anatomy involved based on the pre-operative MRI and post-operative MRI. This finding is in agreement with the contouring guidelines proposed in this study. The study by Chan et al. also observed that patients with pre-operative anterior epidural disease (sectors 1, 6, and 2) alone rarely recurred in the region of the posterior elements (sector 4). However, they did occasionally develop recurrences in the postero-lateral epidural space (sectors 3 and 5), suggesting that if the epidural disease is discrete and centralized, a donut distribution is not required. By contrast, patients with pre-operative circumferential epidural disease involvement were at risk of failure in any sector despite surgical clearance, suggesting that a circumferential donut CTV is necessary in these patients. The consensus contours in this study are in agreement with these findings.

It is important to note that there are several limitations of this study. First, while the selected cases were chosen to encompass a wide range of clinical scenarios, they may not be directly applicable to all situations and cannot replace clinical expertise and unique patient specific decision making. Second, while these consensus guidelines are consistent with the aforementioned patterns of failure analysis (33), they are ultimately based on clinical

practice patterns of experienced providers and have not been validated. Finally, the cases selected for this contouring exercise were all radiation naïve and management in the setting of re-irradiation has not yet been addressed. It should be noted that this manuscript is not intended to a comprehensive summary of the literature, but reference is provided for a recently published critical review (34).

Conclusions

Our study represents a novel and important contribution to assist in the safe and effective delineation of the CTV in the post-operative spine SBRT patient. Our future research will focus on clinical validation.

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Summary

We sought to develop consensus contouring guidelines to promote safe and effective practice of SBRT for spinal metastases in the post-operative setting. Ten spine specialists from 10 international centers independently contoured target volumes for 10 common clinical scenarios. Agreement between physicians was calculated quantitatively with an expectation minimization algorithm using Simultaneous Truth and Performance Level Estimation (STAPLE) with kappa statistics. This manuscript summarizes and presents the consensus contours.



Figure 1.

International Spine Radiosurgery Consortium anatomic classification system for consensus target volumes for spine radiosurgery (28). Reprinted with permission from Elsevier.

	Post-operative axial T1 post MRI	A BAR	Con	
	Post-operative axial CT myelogram or T2 MRI			
-operative SBRT consensus contours for spine metastases.	Pre-operative sagittal MRI			THE.
	Pre-operative axial MRI		- AN	
Summary of cases for post-	Anatomic description	Case 1: T5 level. Pre-operative circumferential epidural disease with no residual epidural disease post- operatively. Pre-operative bony involvement includes the body, bilateral pedicles, bilateral transverse processes, bilateral laminae, and spinous process.	Case 2: T4 level. Pre-operative circumferential epidural disease with focal residual anterior epidural disease post- operatively. Pre-operative bony involvement includes the body, bilateral pedicles, bilateral transverse processes, bilateral laminae, and spinous process.	Case 3: T6 level. Pre-operative circumferential epidural disease with residual near circumferential epidural disease post-operatively. Pre- operative bony involvement includes the body, bilateral pedicles, bilateral transverse processes, and bilateral laminae.

Table 1

Post-operative axial T1 post MRI			
Post-operative axial CT myelogram or T2 MRI			
Pre-operative sagittal MRI			
Pre-operative axial MRI			
Anatomic description	Case 4:C2 level. Pre-operative anterior and right lateral epidural disease status post atabilization and biopsy. Post- operative residual antero- lateral epidural disease. Pre- operative bony involvement includes the body, odontoid, right pedicle, and right transverse process.	Case 5: LI level. Pre-operative anterior epidural disease. No residual epidural disease post- operatively. Pre-operative bony involvement includes the body and bilateral pedicles.	Case 6: T11 level. Pre- operative anterior and left lateral epidural disease. Post- operative residual antero- lateral epidural disease. Pre- operative bony involvement includes the body and left pedicle.

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perative axial T1 post MRI	0		
st-operative axial CT myelogram or Post-o MRI			0
Pre-operative sagittal MRI P(T)	TIT		R IA
Pre-operative axial MRI			
Anatomic description	Case 7:73 level. Pre-operative posterior epidural disease. No residual epidural disease post- operatively. Pre-operative bony involvement inculdes the spinous process, bilateral laminae, and bilateral transverse processes.	Case 8: C4 level. Pre-operative anterior, right lateral and posterior epidural disease. No residual epidural disease post- operatively. Pre-operative bony involvement includes the body, right pedicle, right transverse process, right lamina, and spinous process.	Case 9:T9 level. Pre-operative vertebral body fracture without epidural disease status post vertebroplasty. No residual epidural disease post- operatively. Pre-operative bony involvement in the body.

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Post-operative axial T1 post MRI	
Post-operative axial CT myelogram or T2 MRI	
Pre-operative sagittal MRI	
Pre-operative axial MRI	
Anatomic description	Case 10: T11 level. Pre- operatively anterior and left lateral epidural disease with extensive paraspinal extension. Post-operative paraspinal antero- lateral epidural disease. Pre- operative bony involvement includes the body, left pedicle, left transverse process, and left lamina.

Table 2

Absolute kappa agreement, sensitivity and specificity for CTV target delineation between participating spinal oncology specialists based on the STAPLE analysis.

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		CTV				<u>PTV</u>		
Ca	use Mean sensitivity (average +/- SD)	Mean specificity (average +/- SD)	Kappa measure	P value	Mean sensitivity (average +/- SD)	Mean specificity (average +/- SD)	Kappa measure	P value
	1 0.74 +/- 0.22	0.95 +/- 0.07	0.57	<0.001	0.74 +/- 0.20	0.96 +/- 0.06	0.59	<0.001
	2 0.76 +/- 0.23	0.93 +/- 0.09	0.52	<0.001	0.75 +/- 0.24	0.92 +/- 0.12	0.53	<0.001
	3 0.77 +/- 0.26	0.99 +/- 0.02	0.70	<0.001	0.70 +/- 0.24	0.99 +/- 0.02	0.66	<0.001
	4 0.86 +/- 0.16	0.91 +/- 0.12	0.63	<0.001	0.87 +/- 0.12	0.88 +/- 0.19	0.60	<0.001
	5 0.86 +/- 0.16	0.94 +/- 0.07	0.67	<0.001	0.86 +/- 0.12	0.93 +/- 0.10	0.67	<0.001
	6 0.78 +/- 0.28	0.95 +/- 0.05	0.60	<0.001	0.77 +/- 0.22	0.94 + - 0.10	0.59	<0.001
	7 0.71 +/- 0.29	0.93 +/- 0.12	0.43	<0.001	0.71 +/- 0.29	0.90 +/- 0.15	0.37	<0.001
	8 0.75 +/- 0.16	0.93 +/- 0.09	0.52	<0.001	0.78 +/- 0.16	0.91 + - 0.14	0.51	<0.001
	9 0.89 +/- 0.20	0.93 +/- 0.07	0.70	<0.001	0.95 +/- 0.04	0.90 + - 0.11	0.76	<0.001
	10 0.77 +/- 0.30	0.90 +/- 0.15	0.46	<0.001	0.80 + - 0.20	0.87 + - 0.18	0.47	<0.001

Table 3

Consensus CTV contours for post-operative SBRT for spine metastases. Consensus contours are shown in bold red and individual contours are shown in

	Schematic diagram	K	K	K
	Simulation MRI with individual and consensus CTV contour			
	Post-operative axial CT myelogram or T2 MRI			
	Pre-operative axial MRI			
unique colors.	Patient number	-	7	ſ

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Schematic diagram	
Simulation MRI with individual and consensus CTV contour	
Post-operative axial CT myelogram or T2 MRI	
Pre-operative axial MRI	
Patient number	01

Table 4

Guidelines for CTV contouring for post-operative SBRT for spine metastases based on pre-operative epidural involvement, and both pre-operative and post-operative bony involvement.

ative CTV description	ential treatment including the pre-operative body, bilater ilateral transverse processes, bilateral laminae, and spinc	ive body	ive body plus ipsilateral pedicle +/- lamina	ive body plus ipsilateral pedicle, ipsilateral transverse d ipsilateral lamina	ive body plus ipsilateral pedicle, bilateral transverse pro- minae, and spinous process	ive spinous process, bilateral laminae and bilateral trans	olus coverage of the entire pre-operative extent of para-si
Post-oper	Circumfer pedicles, l process	Pre-opera	Pre-opera	Pre-opera process ar	Pre-opera bilateral Ia	Pre-opera processes	As above
<u>Post-operative ISRC</u> bony CTV recommendation	1,2,3,4,5,6	1	1,2	1,2,3	1, 3, 4, 5, 6 + / - 2	3,4,5	As above
<u>Pre-operative ISRC</u> <u>bony anatomic</u> <u>involvement</u>	1-3, 5-6, +/-4	1	1	1,2	1,4,5,6	4	As above
<u>Pre-operative epidural involvement</u>	Circumferential epidural disease	Anterior epidural involvement in region of central body	Anterior epidural involvement in lateral region of body	Epidural involvement anteriorly in the region of the body and unilaterally in the region of pedicle	Epidural involvement anteriorly in the region of the body, unilaterally in the region of pedicle, and posteriorly in the region of the spinous process	Posterior epidural involvement in region of spinous process	Any of the above plus extensive para-spinal extension

Table 5

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Summary of GTV, CTV and PTV contouring guidelines for post-operative spine SBRT for spinal metastases.

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