Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2011 December 1; 81(5): e775–e780. doi:10.1016/j.ijrobp.2010.11.033.

Variation in the Gross Tumor Volume and Clinical Target Volume for Preoperative Radiotherapy of Primary Large High-Grade Soft Tissue Sarcoma of the Extremity Among RTOG Sarcoma Radiation Oncologists

Dian Wang^{*}, Walter Bosch[†], David G. Kirsch[‡], Rawan Al Lozi[†], Issam El Naqa[†], David Roberge[§], Steven Finkelstein[¶], Ivy Petersen^{§§}, Michael Haddock^{§§}, Yen-Lin E. Chen^{**}, Naoyuki G. Saito^{††}, Ying J. Hitchcock^{‡‡}, Aaron H. Wolfson^{¶¶}, and Thomas F. DeLaney^{**}

^{*}Medical College of Wisconsin, Milwaukee, WI

[†]Washington University, St Louis, MO

[‡]Duke University, Durham, NC

[§]McGill University Health Centre, Montreal, QC, Canada

^{§§}Mayo Clinic, Rochester, MN

[¶]Moffitt Cancer Center, Tampa, FL

^{**}Massachusetts General Hospital, Boston, MA

^{††}Roswell Park Cancer Institute, Buffalo, NY

^{‡‡}University of Utah, Salt Lake City, UT

^{¶¶}University of Miami Miller School of Medicine, Miami, FL

Abstract

Purpose/Objective(s)—To evaluate variability in the definition of preoperative radiotherapy gross tumor volume (GTV) and clinical target volume (CTV) delineated by sarcoma radiation oncologists.

Materials/Methods—Extremity sarcoma planning CT images along with the corresponding diagnostic MRI from 2 patients were distributed to 10 RTOG sarcoma radiation oncologists with instructions to define GTV and CTV, using standardized guidelines. The CT data with contours were then returned for central analysis. Contours representing statistically-corrected 95% (V95) and 100% (V100) agreement were computed for each structure.

Results—For the GTV, the minimum, maximum, mean (SD) volumes (mL) were 674, 798, 752±35 for the lower extremity case and 383, 543, 447±46 for the upper extremity case. The volume (cc) of the union, V95 and V100 were 882, 761, and 752 for the lower, and 587, 461, and

© 2010 Elsevier Inc. All rights reserved.

Reprint requests to: Dian Wang, MD., Ph.D., Department of Radiation Oncology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53045; Tel: (414) 805-4496; Fax: (414) 805-4369; dwang@mcw.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest: None

455 for the upper extremity, respectively. The overall GTV agreement was judged to be almost perfect in both lower and upper extremity cases [$\kappa = 0.9$ ($p < 0.0001$) and $\kappa = 0.86$ ($p < 0.0001$)]. For the CTV, the minimum, maximum, mean (SD) volumes (mL) were 1145, 1911, 1605 ± 211 for the lower extremity case and 637, 1246, 1006 ± 180 for the upper extremity case. The volume (cc) of the union, V95 and V100 were 2094, 1609, and 1593 for the lower, and 1533, 1020, and 965 for the upper extremity cases, respectively. The overall CTV agreement was judged to be almost perfect in the lower extremity case [$\kappa = 0.85$ ($p < 0.0001$)], but only substantial in the upper extremity case [$\kappa = 0.77$ ($p < 0.0001$)].

Conclusions—Almost perfect agreement existed in the GTV of these two representative cases. There was no significant disagreement in the CTV of the lower extremity, but variation in the CTV of upper extremity was seen, perhaps related to the positional differences between the planning CT and the diagnostic MRI.

Keywords

Sarcoma; target definition; radiotherapy

Introduction

Many studies have shown that the combination of preoperative radiotherapy and surgery is an effective strategy to treat many soft tissue sarcomas (STS) with high risk features (1-6). The advantages of preoperative radiation include the delivery of a lower radiation dose to a smaller target volume when compared with postoperative radiotherapy, which translates into fewer chronic side effects (subcutaneous fibrosis, lymphedema and joint stiffness) and better function of the extremity, as suggested by a prospective randomized trial of preoperative versus postoperative radiotherapy (6). Other potential advantages of preoperative radiotherapy include facilitating surgical resection through tumor shrinkage and reducing the risk of tumor cell seeding at the time of surgery (3-5). The main concern about preoperative radiotherapy has been centered on the risk of increasing the rate of delayed wound healing (1,2). In the above mentioned phase III prospective study, the rate of major wound complications increased from 17% to 35% with preoperative radiation therapy; these major wound complications were almost entirely limited to the lower extremity and were generally temporary and without significant, long-term effect on function (1,2).

Traditionally, large fields have been employed for conventional radiotherapy of extremity STS; of note, larger fields are considered to increase the risk for radiation-related toxicity (6). Recently, image-guided radiation treatment (IGRT) technologies such as image-guided intensity modulated radiotherapy (IG-IMRT) have emerged to treat varied malignancies including STS (7-11). IMRT is able to deliver a highly conformal dose to the gross disease planning target volume and high risk subclinical disease regions, while minimizing dose to selected, adjacent critical structures. It is conceivable that improved techniques of delivering radiotherapy (i.e., IGRT) that conform the high dose region to smaller, more accurately targeted volumes may further reduce radiation related toxicity. Currently, the National Cancer Institute (NCI) –funded Radiation Therapy Oncology Group (RTOG) is conducting a prospective clinical trial to investigate the impact of preoperative advanced image-guided radiation technology (IGRT) on the risk of radiation-related toxicities in patients with extremity STS. Target volumes such as gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV) are delineated according to strict guidelines in this study. A total dose of 50 Gy in 25 fractions was prescribed to 95% or more primary tumor PTV using either daily image-guided three dimensional conformal radiotherapy or intensity modulated radiotherapy. Here we conducted a comparative study of the delineated GTV and CTV in the treatment of extremity STS by multiple sarcoma radiation oncologists who

participated in this clinical study looking at the concordance among this group. With this analysis we aim to demonstrate that it will be possible to develop a consensus of GTV and CTV for future prospective studies of preoperative radiotherapy for STS.

Materials and Methods

This research was reviewed and approved by the Medical College of Wisconsin Human Research Protection Office and all collaborators completed training in both human research and patient privacy at their respective institutions. Treatment planning computed tomography (CT) scans along with the associated diagnostic MR images from 2 patients with soft tissue sarcoma who had undergone diagnostic core needle biopsies; one patient had a STS of the upper extremity and other a soft tissue sarcoma of lower extremity. The CT simulation data sets were obtained with patients in the supine position; the patient with upper extremity STS had her arm elevated (similar to the arm position for breast radiotherapy) and the other patient with lower extremity STS had the affected leg straight but the unaffected leg in frog leg position. The diagnostic MR data sets were obtained after the simulation CT scans with the patient in the supine position; the patient with upper extremity STS had the MR images of the affected arm with the arm lowered which was different from the position used for the CT simulation scan, while the patient with the lower extremity STS had the MR images of the affected leg in the same position used for the simulation CT. Both CT and MR data were anonymized and were made available for download from the Image-Guided Therapy QA Center website. Clinical synopses of each case and instructions for delineation of GTV and CTV were provided to a panel of participating physicians; these are summarized in Table 1 and Table 2.

Each participant was asked to use his or her institutional treatment planning system to define a GTV and CTV for each clinical case. The CTs with contours were then exported as DICOM data sets to the Imaging-Guided Therapy QA Center. Contours from each investigator were then imported to the Computerized Environment for Radiation Research, an open-source Matlab-based radiation therapy planning analysis tool (12). Contours were then compared for agreement by using Matlab statistical software package.

Several algorithms were used to measure the level of agreement between physicians. The commonly used apparent volume overlap was calculated as the average agreement probability by which a voxel is selected by the experts. This was corrected for agreement by chance by using generalized kappa statistics (13). Briefly, Kappa statistics assume values between +1 (perfect agreement) and 0 (no agreement above chance) and -1 (complete disagreement). According to Landis and Koch criteria, a kappa value of 0 is poor, 0.01-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, and 0.80-1.00 almost perfect (14).

An imputation method was utilized to analyze the contour data. This approach uses an expectation-maximization (EM) algorithm for simultaneous truth and performance level estimation to estimate the “true” GTV and CTV contours (STAPLE, 15). This iterative method calculates the expected value of the underlying probability distribution from a given dataset when the data are incomplete or have missing values and uses it to maximizes the conditional probability of the unknown, “true” GTV and CTV contours given the observed contours (16). From the estimated true GTV and CTV contours, we estimated the sensitivity and specificity that individual investigator's contours would determine anatomical sites that could contain gross and subclinical disease.

Results

Twelve radiation oncologists who enrolled patients into the current NCI/ROG IGRT sarcoma study (ROG 0630) were asked to participate; 10 returned contour data sets. Minimal variations in the GTV in both lower extremity and upper extremity cases were seen among the participating physicians; minimal variations were also noted in the lower extremity CTV, but more variability was seen for the upper extremity CTV among the participating physicians, as demonstrated in Figure 1 and Figure 2.

For GTV, the agreement of contours is quantitatively reported in Table 3. The minimum, maximum, mean (SD) volumes (mL) were 674, 798, 752 ± 35 for the lower extremity case and 383, 534, 447 ± 46 for the upper extremity case. The volume of the union of all GTV contours (mL) was 882 and 587 for lower extremity and upper extremity, respectively. According to kappa statistics, the overall agreement was judged to be almost perfect ($\kappa = 0.90$, $\kappa = 0.86$) for the lower extremity and the upper extremity sarcoma respectively ($p < 0.0001$ each). The estimated sensitivities and specificities from individual investigators' contours were 0.95 ± 0.04 and 0.98 ± 0.01 for lower extremity and 0.92 ± 0.06 and 0.98 ± 0.02 for upper extremity. This indicates higher agreement levels with increased volume as shown in Figure 1.

For CTV, the agreement of contours is quantitatively reported in Table 4. The minimum, maximum, mean (SD) volumes (mL) were 1145, 1911, 1605 ± 211 for the lower extremity case and 637, 1246, 1006 ± 180 for the upper extremity case. The volume of the union of all contours (mL) was 2094 and 1533 for lower extremity and upper extremity, respectively. According to kappa statistics, the overall agreement was judged to be almost perfect and substantial ($\kappa = 0.85$, $\kappa = 0.77$) for the lower extremity and the upper extremity sarcoma respectively ($p < 0.0001$ each). The estimated sensitivities and specificities from individual investigators' contours were 0.93 ± 0.09 and 0.97 ± 0.03 for the lower extremity sarcoma and 0.89 ± 0.11 and 0.96 ± 0.03 for the upper extremity sarcoma. Similarly, this indicates higher agreement levels with increased volume as shown in Figure 2.

Discussion and Conclusion

In the era of IGRT for extremity STS, it is imperative that the GTV and CTV are accurately defined to successfully implement advanced IGRT, especially IG-IMRT. The successful application of such advanced treatment delivery will potentially maintain high rates of local tumor control while reducing radiation-related toxicities when compared with the traditional "large-field" conventional radiotherapy (6,11). Results from our study including sarcoma radiation oncologists participating in ROG sarcoma IGRT study (protocol #0630) have shown "substantial agreement to almost perfect agreement" in the GTV and CTV of extremity sarcoma. This indicates that the GTV and CTV are largely agreed upon between this group of sarcoma radiation oncologists when a specific instruction was provided. Therefore, this analysis establishes that sarcoma radiation oncologist contour similar GTV and CTV, which is an important foundation to establish consensus recommendations for the GTV and CTV for IGRT for STS, which is one goal of the current prospective phase II clinical trial of pre-operative IGRT for extremity STS (ROG 0630).

Because MRI better delineates soft tissue compared to CT, MRI is often recommended to more accurately determine the radiation target through co-registration of the MRI with the planning CT images for sarcoma radiotherapy. Ideally, the patient's position for the planning CT is replicated for the MRI to optimize the quality of the co-registered images. However, the co-registration between MRI and CT may not always be achieved in daily clinical practice for many reasons. One of reasons is that the patient position for simulation CT may not be fit for MR scanner as seen in the case 2 with STS of upper extremity. Agreement

among the GTV of the upper extremity STS is almost perfect. However, variation exists in the CTV of upper extremity STS (Table 1 and Figure 1), which may be secondary to the positional differences between the planning CT and the diagnostic MRI. This variation in the CTV contour might be reduced if MRI images were repeated in the treatment position. However, this is often not practical as open MRIs may be required, repeat studies are costly and inconvenient, the radiotherapy immobilization devices may not be MRI-compatible, the pickup coils may interfere with the immobilization device and the treatment position chosen may simply not be feasible in any MRI. Another possibility to reduce this positional difference would be to compromise on the position used to treat the patient – with arms by the side or above the head. All together, appropriate setup and imaging are key important factors to accurately define the sarcoma targets for radiation and to avoid near-circumferential irradiation of limb for patients with upper limb sarcoma.

In summary, when given specific instructions and co-register MRI images, sarcoma radiation oncologists can reproducibly delineate clinical target volumes for soft tissue sarcoma. Consensus guidelines are feasible in this rare and anatomically complex tumor site.

Acknowledgments

This study is supported by ATC Grant U24 CA81647 from the NIH

Reference

1. Davis AM, O'Sullivan B, Bell RS, et al. Function and health status outcomes in a randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma. *J Clin Oncol.* 2002; 20:4472–4477. [PubMed: 12431971]
2. O'Sullivan MB, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomized trial. *Lancet.* 2002; 359:2235–2241. [PubMed: 12103287]
3. O'Sullivan B, Iain Ward I, Catton C. Recent advances in radiotherapy for soft tissue sarcoma. *Current Oncology Reports.* 2003; 5:274–281. [PubMed: 12781068]
4. Maples WJ, Buskirk SJ. Multimodality treatment of upper extremity bone and soft tissue sarcomas. *Hand Clinic.* 2004; 20:221–225.
5. Clarkson P, Ferguson PC. Primary multidisciplinary management of extremity soft tissue sarcomas. An excellent and in-depth overview of the most recent therapeutic approaches concerning ESTS. *Current Options Oncol.* 2004; 5:451–462.
6. Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol.* 2005; 75:48–53. [PubMed: 15948265]
7. Mackie TR, Kapatoes J, Ruchala K, et al. Image guidance for precise conformal radiotherapy. *Int J Radiat Oncol Biol Phys.* 2003; 56:89–105. [PubMed: 12694827]
8. Yan D, Lockman D, Martinez A, et al. Computed tomography guided management of interfractional patient variation. *Semin Radiat Oncol.* 2005; 15:168–79. [PubMed: 15983942]
9. Mackie TR, Balog J, Ruchala K, et al. Tomotherapy. *Semin Radiat Oncol.* 1999; 9:108–17. [PubMed: 10196402]
10. Mohan R, Zhang X, Wang H, et al. Use of deformed intensity distributions for on-line modification of image-guided IMRT to account for interfractional anatomic changes. *Int J Radiat Oncol Biol Phys.* 2005; 61:1258–66. [PubMed: 15752908]
11. O'Sullivan B, Ward I, Haycocks T, et al. Techniques to modulate radiotherapy toxicity and outcome in soft tissue sarcoma. *Curr Treat Options Oncol.* 2003; 4:453–464. [PubMed: 14585226]
12. Deasy JO, Blanco AI, Clark VH. CERR: A computational environment for radiotherapy research. *Med Phys.* 2003; 30:979–985. [PubMed: 12773007]
13. Fleiss, JL. Statistical methods for rates and proportions. 2nd ed.. Wiley; New York (NY): 1981.

14. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977; 33:159–174. [PubMed: 843571]
15. Warfield SK, Zou KH, Wells WM. Simultaneous truth and performance level estimation (STAPLE): An algorithm for the validation of image segmentation. *IEEE Trans Med Imaging*. 2004; 23:903–921. [PubMed: 15250643]
16. Dempster A, Laird N, Rubin D. Maximum likelihood from incomplete data via the EM algorithm. *J Royal Stat Soc Series B*. 1977; 39:1–38.

Figure 1.

Axial and sagittal computed tomography (CT) reconstructions demonstrating individual contours from 10 sarcoma radiation oncologists, as well as the 95% consensus contours, for GTV (upper) and CTV (lower) overlaid on the upper extremity sarcoma case CT data sets.

Figure 2.

Axial and sagittal computed tomography (CT) reconstructions demonstrating individual contours from 10 sarcoma radiation oncologists, as well as the 95% consensus contours, for GTV (upper) and CTV (lower) overlaid on the lower extremity sarcoma case CT data sets.

Table 1**Clinical synopses****Case 1 with soft tissue sarcoma of lower extremity**

55-year-old male with 16 cm mass in the posterior aspect of right distal thigh. The core needle biopsy of this lesion demonstrated a high-grade round cell liposarcoma. The clinical stage (AJCC) is III T2bN0M0G3

Description of the diagnostic MRI of right distal thigh: A large well circumscribed heterogeneous, multiloculated mass located within the posterior distal thigh. The tumor measures 14.8 cm in craniocaudad dimension, 7.8 cm in AP dimension, and 11.3 cm in maximal medial-lateral dimension. There is a small loculated component located at its midaspect, anterolaterally, which measures 2.4×1.2 cm. There is irregular and discontinuous enhancement lining this mass which appears slightly less intense and less nodular when compared to the prior study. There are multiple thin enhancing septae traversing this mass as well. Overall the enhancing component of this mass is estimated to represent less than 10% of the mass volume. The anterior margin of this mass abuts the posterior margin of the popliteus artery for several centimeters along its course. This mass abuts the posterior tibial and common peroneal nerves which are deviated laterally. This mass has a large area of contact with the semimembranosus muscle and focally abuts the semi tendinosis muscle. There is a distinct fat plane between this mass and the biceps femoris muscles.

There is mild increased signal within the inferior aspect of the vastus medialis muscle and a tiny amount of fluid along its medial margin. These findings have not significantly changed from prior study and are nonspecific. Incidental note is made of degenerative disease involving the patellofemoral joint.

The patient underwent a simulation CT scan in a supine position with right thigh (affected thigh) straight and left thigh (unaffected thigh) in frog leg position, and then MR of right thigh in the same position as for the simulation CT scan.

Case 2 with soft tissue sarcoma of upper extremity

74 year-old female with 15 cm mass in the anterior aspect of right arm. The core needle biopsy showed high-grade myxofibrosarcoma (myxoid MFH). Clinical stage (AJCC) is III T2bN0M0G3.

Descriptions of the diagnostic MRI of right arm: Within the long head of the biceps, there is a large heterogeneously enhancing mass. The tumor contacts the humerus but there is no underlying marrow change or cortical thinning. The tumor also extends up to the neurovascular bundle containing brachial arteries and veins as well as the median and ulnar nerves. None of these structures are definitively encased. There is some inter-digitation of tumor between these structures however.

The patient underwent a simulation CT scan in a supine position with right arm up supported on the alpha cradle immobilizer, however, MRI of right arm sarcoma was subsequently performed not in the same position as for simulation CT. This is because the patient's arm position was not fit for the MR scanner.

Table 2**Delineations of Gross Target Volume (GTV) and Clinical Target Volume (CTV)**

Delineations of GTV and CTV
Gross Tumor Volume (GTV): Gross tumor defined by MRI T1 plus contrast images (MRI with contrast is required). Fusion of MRI and CT is recommended to delineate the GTV for radiotherapy planning, but this is optional.
Clinical Target Volume (CTV) for Intermediate-to-High Grade Tumors ≥ 8 cm: Include gross tumor and clinical microscopic margins. Typically CTV = GTV and suspicious edema (defined by MRI T2 images) plus 3 cm margins in the longitudinal (proximal and distal) directions. If this causes the field to extend beyond the compartment, the field can be shortened to include the end of a compartment. The radial margin from the lesion should be 1.5 cm including any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.

Table 3

Summary of Gross Tumor Volume (GTV) statistics

	Lower extremity	Upper Extremity
Maximum volume (mL)	798.33	534.41
Minimum volume (mL)	673.58	383.28
Average volume (mL)	751.72	447.25
Medium volume (mL)	759.49	443.14
Standard volume (mL)	34.58	46.18
Intersection volume (mL)	600.25	311.10
Union volume (largest volume assuming outermost contours)	882.14	587.16
Agreement sensitivity (Mean $\pm$ SD)	0.95 $\pm$ 0.04	0.92 $\pm$ 0.06
Agreement specificity (Mean $\pm$ SD)	0.98 $\pm$ 0.01	0.98 $\pm$ 0.02
Overall Kappa (p value)	0.90 (<0.0001) "Almost Perfect"	0.86 (<0.0001) "Almost Perfect"

Table 4

Summary of Clinical Target Volume (CTV) statistics

	Lower extremity	Upper Extremity
Maximum volume (mL)	1911.49	1245.92
Minimum volume (mL)	1145.27	637.27
Average volume (mL)	1604.78	1005.57
Medium volume (mL)	1627.90	1067.40
Standard volume (mL)	210.95	180.45
Intersection volume (mL)	1101.76	543.31
Union volume (largest volume assuming outermost contours)	2093.72	1533.12
Agreement sensitivity (Mean $\pm$ SD)	0.93 $\pm$ 0.09	0.89 $\pm$ 0.11
Agreement specificity (Mean $\pm$ SD)	0.97 $\pm$ 0.03	0.96 $\pm$ 0.03
Overall Kappa (p value)	0.85 (<0.0001) "Almost Perfect"	0.77 (<0.0001) "Substantial"