Method of Computing Direction-dependent Margins for the Development of Consensus Contouring Guidelines

Liam S. P. Lawrence  
University of Toronto  https://orcid.org/0000-0003-2070-8308

Lee Chin  
Sunnybrook Health Sciences Centre

Rachel W. Chan  
Sunnybrook Research Institute

Timothy K. Nguyen  
London Health Sciences Centre

Arjun Sahgal  
Sunnybrook Health Sciences Centre

Chia-Lin Tseng  
Sunnybrook Health Sciences Centre

Angus Z. Lau  (✉ angus.lau@sri.utoronto.ca)  
Sunnybrook Research Institute

Research Article

**Keywords:** Consensus contouring, clinical target volume margins, interobserver variability, stereotactic body radiotherapy

**Posted Date:** February 25th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-249434/v1

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

**Version of Record:** A version of this preprint was published at Radiation Oncology on April 13th, 2021. See the published version at https://doi.org/10.1186/s13014-021-01799-1.
Title: Method of computing direction-dependent margins for the development of consensus contouring guidelines

Authors and affiliations: Liam S. P. Lawrence, MASc, a Lee Chin, PhD, MCCPM, b,c Rachel W. Chan, PhD, d Timothy K. Nguyen, MD, e Arjun Sahgal, MD, c Chia-Lin Tseng, MD, c Angus Z. Lau, PhD d

a) Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada
b) Department of Medical Physics, Odette Cancer Centre, Toronto, Ontario, Canada
c) Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
d) Department of Physical Sciences, Sunnybrook Research Institute, Toronto, Ontario, Canada
e) Department of Radiation Oncology, London Health Sciences Centre, Western University, London, Ontario, Canada

Corresponding author: Angus Z. Lau
Telephone number: 416-480-6100
Mailing address: M7-601, 2075 Bayview Avenue, Toronto, ON Canada M4N 3M5
Email: angus.lau@sri.utoronto.ca
Abstract

Background: Clinical target volume (CTV) contouring guidelines are frequently developed through studies in which experts contour the CTV for a representative set of cases for a given treatment site and the consensus CTVs are analyzed to generate margin recommendations. Measures of interobserver variability are used to quantify agreement between experts. In cases where an isotropic margin is not appropriate, however, there is no standard method to compute margins in specified directions that represent possible routes of tumor spread. Moreover, interobserver variability metrics are often measures of volume overlap that do not account for the dependence of disagreement on direction. To aid in the development of consensus contouring guidelines, this study demonstrates a novel method of quantifying CTV margins and interobserver variability in clinician-specified directions.

Methods: The proposed algorithm was applied to 11 cases of non-spine bone metastases to compute the consensus CTV margin in each direction of intraosseous and extraosseous disease. The median over all cases for each route of spread yielded the recommended margins. The disagreement between experts on the CTV margin was quantified by computing the median of the coefficients of variation for intraosseous and extraosseous margins.

Results: The recommended intraosseous and extraosseous margins were 7.0 mm and 8.0 mm, respectively. The median coefficient of variation quantifying the margin disagreement between experts was 0.59 and 0.48 for intraosseous and extraosseous disease.
Conclusions: The proposed algorithm permits the generation of margin recommendations in relation to adjacent anatomy and quantifies interobserver variability in specified directions. This method can be applied to future consensus CTV contouring studies.

Keywords
Consensus contouring, clinical target volume margins, interobserver variability, stereotactic body radiotherapy

List of Abbreviations
CT = computed tomography
CTV = clinical target volume
GTV = gross tumor volume
MRI = magnetic resonance imaging
SBRT = stereotactic body radiotherapy
STAPLE = simultaneous truth and performance level estimation

Background
Conformal radiotherapy techniques, including stereotactic radiosurgery and stereotactic body radiotherapy (SBRT), are increasingly being delivered for most malignancies. Consistent and accurate delineation of the clinical target volume (CTV) is essential for ensuring treatment efficacy and meaningful interpretation of dosimetric and clinical outcomes in clinical trials. The
CTV is defined as an additional margin to the gross tumor volume (GTV), the demonstrable extent of the tumor, to encompass microscopic disease. Ideally, CTV margin recommendations are informed by pathological evaluation of microscopic tumor extension (1–3) and examination of patterns of disease recurrence. In the absence of such data, expert consensus can provide guidance. Over the last decade, a number of consensus contouring studies to formulate guidelines have emerged for various disease sites (4–12).

In these studies, experts are typically provided with patient images and asked to contour the CTV given a reference GTV. Measures of inter-observer variability are used to determine the agreement between experts (13). A consensus CTV is often created from a collection of expert contours by applying the simultaneous truth and performance level estimation (STAPLE) algorithm (14). Consensus contouring recommendations typically include CTV margins based, in part, on the STAPLE consensus CTV. In clinical contouring practice, the GTV would be expanded isotropically or anisotropically along the Cartesian axes using these margins.

However, tumor spread can vary in extent in arbitrary directions because of anatomic barriers, anisotropic tissue structure, or preferential migration within the tissue of origin (15). Future treatment planning systems should implement expansion in arbitrary directions using anisotropic margins for better conformation to the disease volume. For this purpose, a method of analyzing expert contours to generate margin recommendations in specified directions that represent potential routes of tumor spread is needed. Such analysis would also benefit from a metric for quantifying interobserver variability in specified directions to assess disagreement on the
appropriate margin. Common measures of interobserver variability like the Dice coefficient and the kappa statistic (17) are based on volume overlap and therefore do not capture the dependence of disagreement on direction. Existing algorithms that could be applied for computation of anisotropic margins and contour variability rely on approximately spherical volumes (18,19), which may not be a valid assumption, or do not make use of specified directions (20–22).

This study proposes a novel method to compute consensus CTV margins and margin variability in directions chosen based on clinical assessment of potential routes of spread and anatomical barriers. For generating clinical contouring recommendations, the consensus CTV margin is computed for specified routes of spread in multiple cases, then a margin recommendation is made based on a summary statistic across all cases. For demonstration, the method is applied to 11 cases of non-spine bone metastases, where margins are expected to be anisotropic, to determine separate intraosseous and extraosseous margins.

**Methods and Materials**

**Metrics**

The upcoming metric definitions rely on a quantity called the *directional margin* \( M(d) \), where \( d \) is any clinically relevant direction in 3D. The directional margin is computed from a GTV and a CTV in two steps. First, a set of \( N \) expansion vectors \( \{ v_i \}_{i=1}^N \) are identified: these vectors are oriented parallel to \( d \) and extend from the GTV surface to the CTV surface without intersecting
the interior of the GTV. Second, the directional margin is defined as the median of the lengths of
the expansion vectors: $M(d) = MEDIAN(\{||v_i||\}_{i=1}^N)$, where $|| \cdot ||$ is the Euclidean norm. This
procedure is illustrated in Figure 1. The diagram shows 2D contours for demonstration, but the
algorithm can be applied to any contiguous 3D volume. Pseudocode is shown in an additional file
(see Additional file 1).

The consensus CTV margin is the directional margin of the GTV to the consensus CTV. The margin
deviation is the coefficient of variation of the directional margins from the GTV to each expert
CTV. For $K$ expert CTVs and a set of directional margins $\{M(d)_j\}_{j=1}^K$ in direction $d$, $CV(d) =$
$STD(\{M(d)_j\}_{j=1}^K)/MEAN(\{M(d)_j\}_{j=1}^K)$ is the margin deviation.

**Application to Clinical Cases**

The method was applied to 11 clinical cases, chosen specifically to represent a wide range of
sites, and taken from a study on international practice patterns for the use of SBRT to treat non-
spine bone metastases (16). Each of nine radiation oncologists delineated the CTV contour, based
on the provided GTV contour and the simulation CT and MRI scans. The contours were defined
in the CT space (in-plane pixel size: 1.17 x 1.17 mm; slice thickness: 1-3 mm). Using all CTV
contours, a consensus contour was computed using the STAPLE algorithm and approved by all
radiation oncologists for use in making contouring recommendations (16).
For each case, directions of intraosseous and extraosseous extension were identified by two co-authors ([TKN] and [CLT]), both radiation oncologists. In each direction, the consensus margin was computed using the GTV and the consensus CTV, while the margin deviation was computed using the GTV and the individual participant CTVs. Computations were done using MATLAB (version R2016b, The Mathworks, Inc.). The median consensus margin and margin deviation for intraosseous and extraosseous extension were computed across all cases.

Results

For illustration, Figure 2 shows the consensus margin and margin deviation in each clinician-specified direction for a pubic symphysis case. This case showed no extraosseous extension. Figure 3 shows the consensus margins and margin deviations over all 11 cases. The median consensus margins were 7.0 mm (intraosseous) and 8.0 mm (extraosseous); the median margin deviations were 0.59 (intraosseous) and 0.48 (extraosseous).

Discussion

The purpose of the directional margin algorithm is to quantify CTV expansions by direction for the development of contouring guidelines. The advantage of applying this algorithm over computing an isotropic margin is that the extent of tumor spread may depend on direction because of anatomical barriers or the nature of surrounding tissue. In an application to multiple cases of non-spine bone metastases the proposed method yielded separate estimates of intraosseous and extraosseous extension, which would not have been possible by computing an
isotropic margin. This data can inform the development of subsequent consensus contouring recommendations. Since routes of spread will typically vary in different directions, anisotropic CTV expansions in arbitrary directions should be a feature of future treatment planning systems.

The agreement between experts on the appropriate margin for a given route of spread can be quantified using the margin deviation. The range of the margin deviation will need to be characterized in more subjects so that outliers can be identified in future studies on contouring variability that employ this technique.

One of the strengths of the proposed method is the ability to account for complex geometries, since the lengths of all expansion vectors are incorporated (Figure 4(A)). The primary limitation of this method is that it does not account for the fact that only a subset of the GTV surface is relevant for margin computation when barriers to tumor spread are present in the specified direction (Figure 4(B)). The method can be generalized by segmenting anatomical barriers and excluding inappropriate vectors. This strategy could be facilitated by recent advances in automated segmentation for CTV delineation (15,23).

Conclusions

This report described and demonstrated a novel method to compute CTV margins and margin disagreement between expert contours in any number of specified clinically relevant directions. The proposed approach allows for the generation of margin recommendations in relation to adjacent anatomy. The method was applied to 11 cases of non-spine bone metastases to
compute recommended intraosseous and extraosseous margins. The margin disagreement was also quantified. The method can be applied in future consensus contouring studies.

References

1. Teh BS, Bastasch MD, Wheeler TM, Mai W-Y, Frolov A, Uhl BM, et al. IMRT for prostate cancer: Defining target volume based on correlated pathologic volume of disease. Int J Radiat Oncol Biol Phys. 2003;56(1):184–91.

2. Wang W, Feng X, Zhang T, Jin J, Wang S, Liu Y, et al. Prospective evaluation of microscopic extension using whole-mount preparation in patients with hepatocellular carcinoma: Definition of clinical target volume for radiotherapy. Radiat Oncol. 2010;5(73).

3. Jenkins P, Anjarwalla S, Gilbert H, Kinder R. Defining the clinical target volume for bladder cancer radiotherapy treatment planning. Int J Radiat Oncol Biol Phys. 2009;75(5):1379–84.

4. Soliman H, Ruschin M, Angelov L, Brown PD, Chiang VLS, Kirkpatrick JP, et al. Consensus contouring guidelines for postoperative completely resected cavity stereotactic radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys. 2018;100(2):436–42.

5. Cox BW, Spratt DE, Lovelock M, Bilsky MH, Lis E, Ryu S, et al. International spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. Int J Radiat Oncol Biol Phys. 2012;83(5):e597–605.
6. Redmond KJ, Robertson S, Lo SS, Soltys SG, Ryu S, McNutt T, et al. Consensus contouring guidelines for postoperative stereotactic body radiation therapy for metastatic solid tumor malignancies to the spine. Int J Radiat Oncol Biol Phys. 2017;97(1):64–74.

7. Dunne EM, Sahgal A, Lo SS, Bergman A, Kosztyla R, Dea N, et al. International consensus recommendations for target volume delineation specific to sacral metastases and spinal stereotactic body radiation therapy (SBRT). Radiother Oncol. 2020;145:21–9.

8. Lim K, Small W, Portelance L, Creutzberg C, Jürgenliemk-Schulz IM, Mundt A, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. Int J Radiat Oncol Biol Phys. 2011;79(2):348–55.

9. Myerson RJ, Garofalo MC, El Naqa I, Abrams RA, Apte A, Bosch WR, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: A Radiation Therapy Oncology Group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys. 2009;74(3):824–30.

10. Wu AJ, Bosch WR, Chang DT, Hong TS, Jabbour SK, Kleinberg LR, et al. Expert consensus contouring guidelines for intensity modulated radiation therapy in esophageal and gastroesophageal junction cancer. Int J Radiat Oncol Biol Phys. 2015;92(4):911–20.

11. Leung E, D'Souza D, Bachand F, Han K, Alfieri J, Huang F, et al. MRI-based interstitial brachytherapy for vaginal tumors: A multi-institutional study on practice patterns, contouring, and consensus definitions of target volumes. Brachytherapy. 2019;18(5):598–605.
12. Tseng C-L, Stewart J, Whitfield G, Verhoeff JJC, Bovi J, Soliman H, et al. Glioma consensus contouring recommendations from a MR-Linac International Consortium Research Group and evaluation of a CT-MRI and MRI-only workflow. J Neurooncol [Internet]. 2020 Aug 29 [cited 2020 Aug 31]; Available from: http://link.springer.com/10.1007/s11060-020-03605-6

13. Vinod SK, Jameson MG, Min M, Holloway LC. Uncertainties in volume delineation in radiation oncology: A systematic review and recommendations for future studies. Radiother Oncol. 2016;121:169–79.

14. 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(7):903–21.

15. Unkelbach J, Bortfeld T, Cardenas CE, Gregoire V, Hager W, Heijmen B, et al. The role of computational methods for automating and improving clinical target volume definition. Radiother Oncol. 2020 Dec;153:15–25.

16. Nguyen TK, Sahgal A, Dagan R, Eppinga W, Guckenberger M, Kim JH, et al. Stereotactic Body Radiation Therapy for Nonspine Bone Metastases: International Practice Patterns to Guide Treatment Planning. Pract Radiat Oncol. 2020;10(6):e452–60.

17. Allozi R, Li XA, White J, Apte A, Tai A, Michalski JM, et al. Tools for consensus analysis of experts’ contours for radiotherapy structure definitions. Radiother Oncol. 2010 Dec;97(3):572–8.
18. Rasch C, Barillot I, Remeijer P, Touw A, van Herk M, Lebesque JV. Definition of the prostate in CT and MRI: a multi-observer study. Int J Radiat Oncol. 1999;43(1):57–66.

19. Song WY, Chiu B, Bauman GS, Lock M, Rodrigues G, Ash R, et al. Prostate contouring uncertainty in megavoltage computed tomography images acquired with a helical tomotherapy unit during image-guided radiation therapy. Int J Radiat Oncol Biol Phys. 2006;65(2):595–607.

20. Deurloo KEI, Steenbakkers RJHM, Zijp LJ, de Bois JA, Nowak PJCM, Rasch CRN, et al. Quantification of shape variation of prostate and seminal vesicles during external beam radiotherapy. Int J Radiat Oncol Biol Phys. 2005;61(1):228–38.

21. Jansen EPM, Nijkamp J, Gubanski M, Lind PARM, Verheij M. Interobserver variation of clinical target volume delineation in gastric cancer. Int J Radiat Oncol Biol Phys. 2010;77(4):1166–70.

22. Weiss E, Wu J, Sleeman W, Bryant J, Mitra P, Myers M, et al. Clinical Evaluation of Soft Tissue Organ Boundary Visualization on Cone-Beam Computed Tomographic Imaging. Int J Radiat Oncol Biol Phys. 2010 Nov 1;78(3):929–36.

23. Shusharina N, Söderberg J, Edmunds D, Löfman F, Shih H, Bortfeld T. Automated delineation of the clinical target volume using anatomically constrained 3D expansion of the gross tumor volume. Radiother Oncol. 2020 May;146:37–43.
Figure Captions

Figure 1 – Diagram for directional margin explanation: (A) and (B) show coronal and axial views of the GTV (green) and CTV (red). In blue and orange are the expansion vectors in the anatomical right (R) and left (L) directions respectively. The dimensions are shown along the axes. (C): The vector lengths collected over the surface of the GTV. Computing the medians yields an expansion of 7.0 mm in the R direction and 2.0 mm in the L direction.

Figure 2 – Consensus margin and margin deviation for a metastasis in the pubic symphysis: CT and overlaid contours for a patient with a metastasis in the pubic symphysis. The GTV and STAPLE CTV are the solid green and red contours respectively; the expert contours are dotted. The relevant directions, indicated by the vectors, are termed superior-anterior (SA), inferior-posterior (IP), superior-right (SR), and posterior-right (PR). The text annotations report the consensus margin (mm) followed by the margin deviation (dimensionless) associated with the same-color direction.

Figure 3 – Comparison of intraosseous and extraosseous consensus margins and margin deviations: (A) and (B) show boxplots of the consensus CTV margins and margin deviations over all 11 cases of non-spine bone metastases. The points of a given color are the metrics in each direction for a specific case.

Figure 4 – Cases for discussion of strengths and limitations of method: (A): The GTV (green) and STAPLE CTV (red) for an acetabular metastasis. The cyan vectors in the inferior direction show variation in length, accounted for by the proposed algorithm. (B): The GTV (green) and STAPLE
CTV (red) for a metastasis in the iliac crest, with the cyan vectors indicating a potential direction of intraosseous extension. Some of the vectors lie outside of the bone.

Declarations

Ethics approval and consent to participate
This study was approved by the Sunnybrook institutional research ethics board.

Consent for publication
Not applicable.

Availability of data and materials
The datasets analyzed during the current study are available from the authors on reasonable request.

Competing interests
CLT has received travel accommodations/expenses and honoraria for past educational seminars from Elekta and belongs to the Elekta MR-Linac Research Consortium. AS has been an advisor/consultant with Abbvie, Merck, Roche, Varian (Medical Advisory Group), Elekta (Gamma Knife Icon), BrainLAB, and VieCure (Medical Advisor Board); ex officio Board Member to
International Stereotactic Radiosurgery Society (ISRS); received honorarium for past educational seminars with Elekta AB, Accuray Inc, Varian (CNS Teaching Faculty), BrainLAB, and Medtronic Kyphon; research grant with Elekta AB; and travel accommodations/expenses by Elekta, Varian, and BrainLAB. AS also belongs to the Elekta MR-Linac Research Consortium, Elekta Spine, Oligometastases and Linac Based SRS Consortia.

Funding

This research received support from the Natural Sciences and Engineering Research Council (NSERC) (RGPIN-2017-06596, CRD 507521-16). NSERC did not play a role in the design of the study, nor in the collection, analysis, and interpretation of data, nor in writing the manuscript.

Authors’ contributions

LSPL contributed to the formal analysis, methodology, software, and visualization. LC, RWC, and AZL contributed to the methodology and supervision. AZL also contributed to funding acquisition. TKN and CLT contributed to the formal analysis and methodology. AS contributed to conceptualization, funding acquisition, and resources. All authors contributed to writing, reviewing, and editing the manuscript.

Acknowledgements

Not applicable.
Additional files

Additional file 1:

Extension: .pdf
Title: Directional margin algorithm pseudocode
Description: Pseudocode for the directional margin algorithm, which forms the basis of the proposed method
Figure 1

Diagram for directional margin explanation: (A) and (B) show coronal and axial views of the GTV (green) and CTV (red). In blue and orange are the expansion vectors in the anatomical right (R) and left (L) directions respectively. The dimensions are shown along the axes. (C): The vector lengths collected over the surface of the GTV. Computing the medians yields an expansion of 7.0 mm in the R direction and 2.0 mm in the L direction.
Figure 2

Consensus margin and margin deviation for a metastasis in the pubic symphysis: CT and overlaid contours for a patient with a metastasis in the pubic symphysis. The GTV and STAPLE CTV are the solid green and red contours respectively; the expert contours are dotted. The relevant directions, indicated by the vectors, are termed superior-anterior (SA), inferior-posterior (IP), superior-right (SR), and posterior-right (PR). The text annotations report the consensus margin (mm) followed by the margin deviation (dimensionless) associated with the same-color direction.
Figure 3

Comparison of intraosseous and extraosseous consensus margins and margin deviations: (A) and (B) show boxplots of the consensus CTV margins and margin deviations over all 11 cases of non-spine bone metastases. The points of a given color are the metrics in each direction for a specific case.
Figure 4

Cases for discussion of strengths and limitations of method: (A): The GTV (green) and STAPLE CTV (red) for an acetabular metastasis. The cyan vectors in the inferior direction show variation in length, accounted for by the proposed algorithm. (B): The GTV (green) and STAPLE CTV (red) for a metastasis in the iliac crest, with the cyan vectors indicating a potential direction of intraosseous extension. Some of the vectors lie outside of the bone.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.pdf