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VARIABILITY IN CLINICAL TARGET VOLUME DELINEATION FOR INTENSITY MODULATED RADIOTHERAPY IN THREE CHALLENGING CERVIX CANCER SCENARIOS

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Abstract

Purpose/Objective(s)—The purpose of this study was to assess variability in contouring the gross tumor volume (GTV) and clinical target volume (CTV) of three clinical cervix cancer cases

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by a cohort of international experts in the field, in preparation for the development of an online teaching atlas.

Methods and Materials—Twelve international experts participated. Three clinical scenarios: node positivity (PLN), retroverted uterus (RV) and parametrial invasion (PI) were used. Sagittal and axial MR images of the clinical cases were downloaded to participants' treatment planning systems for contouring. The GTV/cervix/uterus/parametria/vagina and nodal CTV were contoured. Contours' consensus was assessed for sensitivity/specificity using an expectation maximization algorithm called Simultaneous Truth and Performance Level Estimation (STAPLE) and overall experts' agreement was summarized by kappa statistics.

Results—Agreement for GTV in the three clinical cases was high (STAPLE sensitivity 0.54–0.92; specificity 0.97–0.98; kappa measure for PLN, RV and PI was 0.86, 0.76 and 0.42; $p < 0.0001$).

Moderate to substantial agreement was seen for nodal CTV (kappa statistics for PLN, RV and PI was 0.65, 0.58 and 0.62; $p < 0.0001$), uterus (kappa for PLN, RV and PI was 0.45, 0.74 and 0.77; $p < 0.0001$) and parametria (kappa for PLN, RV and PI was 0.49, 0.62 and 0.50; $p < 0.0001$).

Contouring heterogeneity was greatest for the cervix (kappa measure for PLN, RV and PI was 0.15, 0.4 and 0.24; $p < 0.0001$) and vagina (kappa for PLN, RV and PI was 0.47, 0.36 and 0.46; $p < 0.0001$), reflecting difficulties in determining the interface between GTV and these tissues.

Conclusion—Kappa statistics of the different CTV components generally demonstrated moderate to substantial agreement among international experts in the field of gynecological radiotherapy. Further planning target volume (PTV) margins accounting for organ motion and set-up errors are a necessary addition to the CTV.

Keywords

Intensity-modulated radiotherapy; cervix cancer; guidelines; CTV

INTRODUCTION

As the use of highly conformal radiotherapy techniques such as intensity modulated radiotherapy (IMRT) and volumetric arc therapy continues to increase within the radiation oncology community^{1–8}, concerns have been raised regarding adequate expertise in target delineation and the risk of geographical target miss due to either inaccurate contouring or a lack of understanding about the consequences of inter- and intra-fraction organ motion that can occur during highly conformal radiation treatment.

The technological drive from 2-dimensional radiotherapy planning to 3-dimensional volumetric planning requires a paradigm shift in the way clinical target volumes (CTV) are generated (fields versus volumes). It is important to ensure that use of more conformal treatment volumes does not compromise patient outcomes through inadequate contouring or poor target delineation. Additionally, the critical issue of dose coverage in mobile targets involved with gross disease may necessitate irradiation of more normal tissue than traditionally spared with IMRT in the postoperative setting.

The aim of this paper is to highlight some challenging cases in cervix cancer where CTV delineation for the purposes of IMRT, is not without controversy. The three cervix cancer cases used in this project were intended to populate an online Radiation Therapy Oncology Group (RTOG) GYN atlas for the purposes of providing guidance in CTV delineation in various challenging clinical scenarios.

METHODS & MATERIALS

Twelve international experts in the field of gynecological radiotherapy participated in this project. A number of them were part of the GYN IMRT consortium, which helped develop consensus guidelines in CTV delineation for cervix cancer for IMRT⁹. Three clinical cervix cancer scenarios were used for this contouring exercise, representing scenarios of node positivity (PLN), retroverted uterus (RV) and parametrial invasion (PI). Participants were provided with magnetic resonance images (MRI) of the clinical cases (Figure 1a–f) in addition to a brief clinical description of the case, including diagnostic imaging findings and relevant examination under anesthesia (EUA) findings. While images from the RV case had been used to illustrate the variability in CTV definitions in the consensus guidelines paper⁹, none of the participants had seen or contoured the CTV using that dataset prior to this study. Participants were asked to contour the gross tumor volume (GTV)/cervix/uterus/parametria/vagina⁹ and nodal CTV¹⁰ as per published guidelines. The MRI acquisition protocol consisted of axial and sagittal T2-weighted fast spin echo (FSE) images on a standard diagnostic MR couch. The slice thickness was 4mm, with a gap thickness of 1mm for both the axial and sagittal scans. Matrix size was 320×256 and field of view was 22cm. The sagittal images were fat suppressed T2-weighted FSE for the PI & PLN cases (Figure 1b and f). Participants were provided with both the axial and true sagittal MRI scans, however most treatment planning systems (TPS) will only accept axial images. While true sagittal scans are usually better quality than reconstructed sagittal images, there would be no way to directly fuse the axial and sagittal scans together within the TPS thus the sagittal scans were viewed separately and used to as an adjunct to the contouring.

Contours were assessed for sensitivity and specificity using an expectation maximization algorithm called Simultaneous Truth and Performance Level Estimation (STAPLE) and overall agreement was summarized by kappa statistics as per previous publication⁹. Generalized kappa statistics were used to correct for contour agreement which occurred by chance alone. Values between +1 (perfect agreement) to 0 (no agreement above chance) and –1 (complete disagreement) were generated for each of the CTV components¹¹. A Kappa value between 0.41–0.60 corresponds to a moderate level agreement, 0.61–0.80 substantial and above 0.8–1.0 perfect.

Ninety-five percent agreement contours were then generated. The conformity index, defined as the ratio of the average volume to the encompassing volume, was also calculated for each of the structures contoured. When these contours were reviewed, areas of poor agreement were highlighted for further discussion.

The three clinical scenarios were as follows:

1. Involved Pelvic Lymph Node (PLN)

50yo diagnosed with FIGO 3B SCC cervix.

On EUA the tumor is 5cm in maximum diameter, firm & necrotic. Invasion of the anterior upper 2/3 of vagina is seen. There is left parametrial involvement out to the pelvic sidewall. The right parametrium is nodular but not to sidewall and there were no palpable pelvic lymph nodes.

Diagnostic MRI reveals a 5cm × 6cm × 6.7cm tumor replacing the whole cervix. Invasion of the lower uterine segment and anterior upper 2/3 of vagina is noted without definite bladder or rectal invasion. There is loss of cervical stroma in keeping with parametrial extension but pelvic sidewalls are clear. There are bilateral internal iliac lymph nodes, the left measuring 2.4cm × 2.2cm and the right measuring 2.3cm × 2cm. A left ovarian cyst measuring 2.3cm × 1.7cm is also noted.

Representative images (Figure 1a–b)

2. *Retroverted Uterus (RV)*

63yo presents with FIGO 1B SCC cervix

On EUA the tumor is just over 4cm in diameter, confined to the cervix with no vaginal, parametrial or uterosacral involvement.

Diagnostic MRI shows a 4cm × 3.5cm × 3cm mass involving predominantly the anterior cervix. There is non-visualization of the normal cervical stroma, indicating early right parametrial invasion. No vaginal, bladder or rectal involvement is noted, and there is no hydroureter. A 6mm right external iliac lymph node is seen of indeterminate significance.

Representative images (Figure 1c–d)

3. *Parametrial Invasion (PI)*

31yo diagnosed with bulky FIGO 1B SCC cervix

On EUA there is an exophytic tumor involving whole cervix, measuring 5cm × 5cm × 2cm. The fornices, vagina and parametria are all clear.

Diagnostic MRI reveals an irregular cervical mass extending along the left lateral margin of the cervix, measuring 3.1cm × 2.2cm × 2.1cm. There is left parametrial invasion but no extension to the pelvic sidewall, nor invasion of vagina, bladder or rectum. No hydroureter is seen. The right ovary is normal in appearance, and the left ovary has a 1.5cm hemorrhagic cyst but is otherwise normal. A left external iliac lymph node measures 1cm, and a right external iliac lymph node measures 0.8cm, both being suspicious for involvement.

Representative images (Figure 1e–f)

RESULTS

Agreement for GTV in the three clinical cases was moderate to high (STAPLE sensitivity 0.54–0.92; specificity 0.97–0.98; kappa statistics for PLN, RV and PI were 0.87, 0.77 and 0.45; $p < 0.0001$). Table 1.

Moderate to substantial agreement was seen for nodal CTV (kappa measure for PLN, RV and PI was 0.67, 0.62 and 0.64; $p < 0.0001$) (Figure 2), uterus (kappa for PLN, RV and PI was 0.50, 0.79 and 0.81; $p < 0.0001$) and parametria (kappa for PLN, RV and PI was 0.46, 0.61 and 0.48; $p < 0.0001$) (Figure 3).

Contouring heterogeneity was greatest for the cervix (kappa measure for PLN, RV and PI was 0.15, 0.45 and 0.33; $p < 0.0001$) and vagina (kappa for PLN, RV and PI was 0.49, 0.36 and 0.48; $p < 0.0001$), reflecting difficulties in determining the interface between GTV and these tissues. Instructions to the participants was to “contour the cervix, if seen”, which was a subjective determination. Of the twelve participants, 42%, 82% and 83% were able to identify the cervix in the respective cases. The conformity index ranged from 0.25 to 0.69. The greatest concordance was seen for GTV and uterus. Table 1. Representative axial images from all three cases demonstrating the STAPLE 95% agreement volumes are shown in Figure 4. The CTV would include the nodal CTV, GTV, uterus, parametria, cervix and vagina.

DISCUSSION

The aim of this project was to test the robustness of the previously published cervix IMRT contouring guidelines in its applicability to more challenging cervix cancer scenarios as described in the Methods section. In general, contouring agreement among participants for the GTV, nodal CTV and uterus was high. Heterogeneity was highest for the cervix contour, in part due to the subjective nature of its identification as well as ambiguity about whether it should be contoured as an encompassing structure. This is reflected in the Kappa results for GTV in the PI case (kappa = 0.45), as there was marked overlap between what was contoured as “cervix” versus “GTV”. (Figure 5a and b respectively) It could be argued that identification of the cervix is largely academic as it would almost certainly be included within the tumor CTV. The same could be said for the vagina contour. While a number of GYN IMRT consortium members also took part in this project, it became apparent that, even among experts, inclusion of the mesorectum in the parametrial volume for the PLN case remains contentious (Figure 6a–f). This highlights some of the difficulties with applying IMRT to this tumor site. It could be argued that with traditional 3-dimensional conformal radiotherapy fields, the CTV would have included much of the tissues anterior to the presacral curve (given the extensive pelvic lymph node involvement and large primary tumor). Added to that, the margins for PTV and subsequent field edges, it is likely that the entire mesorectum would have received a reasonably high dose. However, in the setting of IMRT contouring, there was a tendency for the majority of the participants to exclude the mesorectum. This was actively debated among participants as to whether the mesorectum should or should not be explicitly included. Agreement on clear indications for inclusion of the mesorectum within the parametrial volume included:

1. Uterosacral ligament involvement either clinically or radiologically
2. Infiltration of the mesorectal fascia on MRI
3. Mesorectal nodes of ≥ 5 mm diameter on MRI

While there were no reported cases of isolated failures in the caudal extent of the mesorectum, it should be noted that there are no large patterns of failure studies in the current era of IMRT to draw upon¹².

The issue of appropriate planning target volume (PTV) margins for this tumor site remains challenging. It is clearly recognized that the CTVs designated in this study would still require additional margins to account for day-to-day variations in organ motion and set-up uncertainties. The fact that the cervix and uterus are mobile structures varying in position both during and between daily fractions only adds to the difficulty in applying constrained IMRT beams for definitive management of this patient population. Complicating this is the highly individualized tumor regression that occurs during treatment, which in turn can influence tumor and normal tissue coverage^{13–17}. While several groups have investigated inter-fraction motion for this tumor site using 3-dimensional imaging and proposed a variety of margin recipes, it remains to be seen whether a class solution PTV margin is appropriate^{13, 18–21}. More individualized PTV margin strategies such as creating an internal target volume (ITV) using a bladder full/bladder empty technique or selecting from a library of plans based on the different bladder volumes have also been investigated²². While adaptive radiotherapy techniques would be the ideal solution to this problem (such as repeated imaging and re-planning based on individualized patient anatomy and tumor response), the time, labor and resources required to realize this lies beyond the scope of most radiotherapy centers⁴.

The development of consensus contouring guidelines for cervix cancer IMRT was in response to the burgeoning use of IMRT for this tumor site and an acknowledgement of the dangers associated with incorrect target delineation and its consequences for the patient. The guidelines were acknowledged to be a work in progress and likely to require modification and updating as further clinical details emerged with time.

The strength of this work lies in the combined expertise of numerous experts in the field across several countries who have contributed to the guidelines and the delineation of these cases.

The application and use of the contouring guidelines within the wider radiation oncology community has yet to be formally investigated. It is anticipated that refinement of the guidelines with further iterations is likely. Development of an interactive on-line teaching atlas, providing feedback would have value. Radiation oncologists are not formally trained in the interpretation of MRI but as technological advances proceed and imaging for radiotherapy planning becomes increasingly sophisticated, tools to help clinicians up-skill in the face of such advances are valuable.

Similarly, efforts to optimize the MR image quality obtained for radiotherapy planning is substantially more complex than for CT. Issues such as the most appropriate sequences to

use, trade-off between image acquisition time versus the degradation of image quality due to patient/organ motion; signal-to-noise ratio; geometric distortion effects; use of IV contrast and antiperistaltic agents etc. are all important factors. Ideally, patients should be scanned in the same position they would be for their planning CT, including the usual immobilization devices, flat table top and laser localizers to ensure reproducible set up. MRI vendors have recognized this need and oncology specific packages have become more widely available.

CONCLUSION

Definitive treatment of cervix cancer with IMRT or other highly conformal treatment strategies poses challenges. Practitioners should be cognizant of the risks of geographical target miss, both in the planning stages when contouring target volumes and in the treatment stages when soft tissue image verification is mandated if highly conformal radiotherapy is being used. As the CTV only accounts for regions of gross and subclinical disease, additional margins to account for organ motion and set-up uncertainties remain an essential component of the final treatment volume.

The 95% agreement contours for these three clinical cases would help form the basis for the “gold standard” contours in the teaching atlas. This comprehensive magnetic resonance imaging (MRI) atlas would then be available on-line through the NRG Oncology Group website (formerly RTOG/Gynecologic Oncology Group (GOG)/National Surgical Adjuvant Breast and Bowel Project (NSABP)). The creation of an interactive online teaching atlas, providing immediate feedback to the users on consensus CTV contours for a variety of cervix cancer scenarios, will provide a valuable knowledge translation tool for clinicians treating this site.

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Figure 1.

Representative T2 weighted axial & sagittal MRI images of Pelvic Lymph Node (PLN) case (a–b); Retroverted Uterus (RV) case (c–d) and Parametrial Invasion (PI) case (e–f)

Figure 2.

Representative T2 weighted axial images from Pelvic Lymph Node (PLN) case (a–b), Retroverted Uterus (RV) case (c–d) and Parametrial Invasion (PI) case (e–f). Different line colors represent different participants' nodal CTV contours. STAPLE consensus contour (red) overlaid

Figure 3. Representative T2 weighted axial images from Pelvic Lymph Node (PLN) case (a–b), Retroverted Uterus (RV) case (c–d) and Parametrial Invasion (PI) case (e–f). Different line colors represent different participants' parametrial contours. STAPLE consensus contour (red) overlaid.

Figure 4. Representative T2 weighted axial images from pelvic lymph node (PLN) case (a); retroverted uterus (RV) case (b) and parametrial invasion (PI) case with STAPLE 95% agreement contours overlaid. Nodal CTV (light blue); parametria (green); GTV (red); cervix (pink); uterus (orange).

Figure 5.

T2 weighted axial images from Parametrial Invasion (PI) case demonstrating overlap between “cervix” contours (a) versus “GTV” contours (b). STAPLE 95% agreement consensus contour (red) overlaid. Different line colors represent each observer - five of the 12 observers contoured the “cervix”; all 12 contoured the “GTV”.

Figure 6.
a)–f). T2 weighted axial images from Pelvic Lymph Node (PLN) case demonstrating participant's parametria contours with STAPLE consensus contour (red) overlaid.

Table 1

STAPLE estimates on inter-observer agreement sensitivity, agreement specificity & Kappa measures for each clinical case scenario. Summarized volume measurements and conformity index (CI) for contoured structures for each clinical scenario. Pelvic Lymph Node case (PLN); Retroverted uterus case (RV); Parametrial invasion case (PI); Maximum(Max); Minimum (Min); Average (Avg).

Structure	STAPLE	PLN	RV	PI
GTV	No. Experts	12	11	12
	Sensitivity	0.91±0.04	0.86±0.11	0.54±0.25
	Specificity	0.99±0.01	0.97±0.03	0.97±0.04
	Kappa Measure * (p-value)	0.87 (<0.0001)	0.77 (<0.0001)	0.45 (<0.0001)
	Max/Min Avg (cm ³)	229.7/176 202.3	27.7/13.8 20.8	60.4/13.5 29.5
	Union (cm ³)	295.01	33.74	75.67
	CI	0.69	0.62	0.39
Nodal CTV	No. Experts	12	11	12
	Sensitivity	0.72±0.13	0.64±0.15	0.71±0.16
	Specificity	0.99±0.02	0.99±0.01	0.98±0.03
	Kappa Measure * (p-value)	0.67 (<0.0001)	0.62 (<0.0001)	0.64 (<0.0001)
	Max/Min Avg (cm ³)	503.6/173.3 297.1	393.3/130.3 237.2	536.8/115.8 278.0
	Union (cm ³)	608.02	524.13	624.63
	CI	0.49	0.45	0.45
Uterus	No. Experts	12	11	12
	Sensitivity	0.84±0.10	0.82±0.10	0.89±0.06
	Specificity	0.94±0.01	0.99±0.01	0.98±0.02
	Kappa Measure * (p-value)	0.50 (<0.0001)	0.79 (<0.0001)	0.81 (<0.0001)
	Max/Min Avg (cm ³)	295.2/47.2 117.5	69.6/42.8 57.2	187.7/115.8 142.9
	Union (cm ³)	329.55	92.7	226.34
	CI	0.36	0.62	0.63
Parametria	No. Experts	12	11	12
	Sensitivity	0.54±0.26	0.66±0.12	0.54±0.20
	Specificity	0.99±0.01	0.99±0.01	0.98±0.02
	Kappa Measure * (p-value)	0.46 (<0.0001)	0.61 (<0.0001)	0.48 (<0.0001)
	Max/Min Avg (cm ³)	353.5/36.8 183.7	180.1/94.6 125.1	324.6/67.1 160.7
	Union (cm ³)	512.98	300.4	489.46
	CI	0.36	0.42	0.33

Structure	STAPLE	PLN	RV	PI
Cervix	No. Experts	5	9	10
	Sensitivity	0.42±0.52	0.67±0.32	0.54±0.38
	Specificity	0.97±0.03	0.95±0.06	0.94±0.04
	Kappa Measure* (p-value)	0.15 (<0.0001)	0.45 (<0.0001)	0.33 (<0.0001)
	Max/Min Avg (cm ³)	191.8/5.9 82.0	49.9/8.5 28.7	63.3/5.5 36.6
	Union (cm ³)	211.81	59.9	93.24
	CI	0.39	0.48	0.39
Vagina	No. Experts	12	11	12
	Sensitivity	0.52±0.20	0.54±0.24	0.58±0.22
	Specificity	0.99±0.01	0.96±0.07	0.98±0.03
	Kappa Measure* (p-value)	0.49 (<0.0001)	0.36 (<0.0001)	0.48 (<0.0001)
	Max/Min Avg (cm ³)	52.7/6.6 28.0	59.0/4.1 17.8	31.5/7.3 16.7
	Union (cm ³)	86.21	70.46	50.53
	CI	0.32	0.25	0.33

* Corrected for chance