Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 2, pp. 348–355, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.10.075

CLINICAL INVESTIGATION **Cervix**

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY FOR THE DEFINITIVE TREATMENT OF CERVIX CANCER

Karen Lim, M.B.B.S.,* William Small, Jr., M.D.,† Lorraine Portelance, M.D.,‡ Carien Creutzberg, M.D., Ph.D.,§ Ina M. Jürgenliemk-Schulz, M.D., Ph.D.,‖ Arno Mundt, M.D.,¶ Loren K. Mell, M.D.,¶ Nina Mayr, M.D.,** Akila Viswanathan, M.D.,†† Anuja Jhingran, M.D.,‡‡ Beth Erickson, M.D.,§§ Jennifer De Los Santos, M.D.,‖‖ David Gaffney, M.D., Ph.D.,¶¶ Catheryn Yashar, M.D.,¶ Sushil Beriwal, M.D.,*** Aaron Wolfson, M.D.,††† Alexandra Taylor, F.R.C.R.,‡‡‡ Walter Bosch, Ph.D.,§§§ Issam El Naqa, Ph.D.,§§§ and Anthony Fyles, M.D. * for the Gyn IMRT Consortium.

*Radiation Medicine Program, Princess Margaret Hospital/ Ontario Cancer Institute, University Health Network, Toronto, Ontario, Canada; †Department of Radiation Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois; ‡Department of Radiation Oncology, McGill University Health Center, Montreal, Quebec, Canada; §Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands; ‖Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands; ¶Department of Radiation Oncology, University of California, San Diego, School of Medicine, La Jolla, California; **Department of Radiation Medicine, Ohio State University, Columbus, Ohio; †† Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; ‡‡Department of Radiation Oncology, M.D. Anderson Cancer Center, Houston, Texas; §§Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin; ‖‖Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, Alabama; ¶¶Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah; ***Department of Radiation Oncology, Magee-Women's Hospital of University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; †††Department of Radiation Oncology, University of Miami Miller School of Medicine, Miami, Florida; ‡‡‡Department of Radiotherapy, Hammersmith Hospital, London, United Kingdom; and §§§Washington University School of Medicine, St. Louis, Missouri

Purpose: Accurate target definition is vitally important for definitive treatment of cervix cancer with intensity-modulated radiotherapy (IMRT), yet a definition of clinical target volume (CTV) remains variable within the literature. The aim of this study was to develop a consensus CTV definition in preparation for a Phase 2 clinical trial being planned by the Radiation Therapy Oncology Group.

Methods and Materials: A guidelines consensus working group meeting was convened in June 2008 for the purposes of developing target definition guidelines for IMRT for the intact cervix. A draft document of recommendations for CTV definition was created and used to aid in contouring a clinical case. The clinical case was then analyzed for consistency and clarity of target delineation using an expectation maximization algorithm for simultaneous truth and performance level estimation (STAPLE), with kappa statistics as a measure of agreement between participants.

Results: Nineteen experts in gynecological radiation oncology generated contours on axial magnetic resonance images of the pelvis. Substantial STAPLE agreement sensitivity and specificity values were seen for gross tumor volume (GTV) delineation (0.84 and 0.96, respectively) with a kappa statistic of 0.68 ($p < 0.0001$). Agreement for delineation of cervix, uterus, vagina, and parametria was moderate.

Conclusions: This report provides guidelines for CTV definition in the definitive cervix cancer setting for the purposes of IMRT, building on previously published guidelines for IMRT in the postoperative setting. © **2011 Elsevier Inc.**

Intensity-modulated radiotherapy, Cervical cancer, Guidelines, CTV.

Reprint requests to: Anthony Fyles, MD, FRCPC, Radiation Medicine Program, Princess Margaret Hospital, 610 University Ave., Toronto, Ontario, Canada M5G 2M9. Tel: (416) 946-6522; Fax: (416) 946-2111; E-mail: Anthony.Fyles@rmp.uhn.on.ca

Conflict of interest: none.

Acknowledgment—The names of the radiation oncologists who contributed to this work as members of the Gyn IMRT Consortium are listed in the Addendum to this article.

Received Oct 30, 2009, and in revised form Oct 30, 2009. Accepted for publication Oct 30, 2009.

INTRODUCTION

Intensity-modulated radiotherapy (IMRT) is being increasingly explored as a means to reduce normal tissue toxicity in cervix cancer with or without treatment intensification (such as extended-field radiotherapy or concomitant boost) (1–6). Reductions in acute and late toxicities with the use of IMRT have been reported in conjunction with low rates of in-field failures(2, 3, 7). Accurate target definition is vitally important to ensure the target is not under-treated and to limit the dose to surrounding normal tissues. There are published guidelines on clinical target volume (CTV) definitions for a number of tumor sites including the postoperative gynecological and prostatectomy setting (8, 9). However, CTV definitions for IMRT for the radical treatment of cervix cancer remain variable within the literature(2, 3, 5, 6, 10). The amount of organ motion, tumor regression, and deformation that cervix cancer patients demonstrate is more substantial than in prostate cancer (11–18). These complex intrapelvic organ dynamics imply greater caution when highly conformal radiotherapy (such as IMRT) is used for this site than for prostate cancer. In order for IMRT to be delivered safely, adequate planning tumor volume (PTV) margins are necessary to account for CTV motion.

The aim of this report is to provide consensus guidelines for defining CTV for the intact cervix in order to achieve safe clinical IMRT practice in preparation for a planned Radiation Therapy Oncology Group (RTOG) Phase 2 clinical trial. These guidelines would supplement currently published consensus guidelines on postoperative IMRT for endometrial and cervix cancer (9).

METHODS AND MATERIALS

A proposal for a prospective RTOG trial evaluating the role of IMRT in the definitive cervix cancer setting was the impetus behind the development of these guidelines. Representatives from the following groups participated in the Gyn IMRT Consortium: RTOG; National Cancer Institute of Canada; Japan Clinical Oncology Group; and European Society of Therapeutic Radiology and Oncology.

An electronic survey among Consortium members was undertaken prior to the June 2008 RTOG meeting to determine patterns of practice for delivering IMRT in cases of definitive cervix cancer. The survey explored the current prevalence of IMRT usage in definitive cervix cancer treatment; imaging modalities used for target delineation; CTV definition; planning margins; and prescriptions and target verification during treatment. Specific questions detailing the more controversial aspects of CTV definition were also explored, including the amount of uterus to include in the CTV, how to define the parametrium, and how much vagina to treat. At the meeting, current data on organ motion, tumor regression, and examples of current IMRT practice were reviewed.

Following the review, a draft document describing contouring boundaries for CTV structures was circulated. Consortium members were provided with magnetic resonance (MR) images (axial and sagittal T_2-weighted views) and axial computed tomography (CT) images from a clinical case and asked to contour the gross tumor volume (GTV) of cervix (if seen), uterus, vagina, and parametrium on the axial MR images, using these guidelines. It was assumed that the ''true'' CTV existed within the collection of contours generated by the Consortium members. An expectation–maximization algorithm for simultaneous truth and performance level estimation (STAPLE) was used to determine an estimation of this ''true'' CTV contour. Sensitivity and specificity were then calculated for each CTV component, using the estimated ''true'' CTV (8, 19). Generalized kappa statistics were used to correct for contour agreement which occurred by chance alone. Values ranging from +1 (perfect agreement) to 0 (no agreement above chance) and −1 (complete disagreement) were generated for each of the CTV components (20).

Agreement contours of 95% were also generated, representing volumes where consensus was reached. These contours were reviewed at a second RTOG meeting in June 2009, and areas of controversy or discordance in the contours were discussed and resolved.

A teaching atlas was also felt to be a valuable addition to the guidelines. Consortium members were asked to contour several cases representing different clinical scenarios. The 95% agreement contours would then form the basis for the ''gold standard'' contours in the teaching atlas. This comprehensive MR imaging atlas would be available online at the RTOG website.

RESULTS

A total of 16 members from the Consortium were surveyed, with a response rate of 75% (12/16). There was general consensus on the structures to be included in the CTV (such as GTV, cervix, uterus, parametria, vagina, and regional lymph nodes) but less agreement regarding the definition of these structures for the purposes of contouring. All respondents agreed that the lateral boundary of parametria should be at the pelvic sidewall and that the medial boundary of parametria should abut the GTV, cervix, uterus, and vagina. The superior and inferior boundaries of the parametria were more varied (Fig. 1). The amount of normal tissues (such as the uterus and vagina) to include in the CTV also differed. Forty-two percent of survey respondents felt that it was not always necessary to include the entire uterus in the CTV. Reasons for this included the observation that isolated uterine recurrences are rare and the fundus is not always included in patients with small, cervix-confined tumors and large fibroid uteri. The length of the normal vagina included in the CTV varied from 1.5 cm to the bottom of the pubic symphysis (approximately 4 cm below tumor). CT was the most prevalent imaging modality used to determine the tumor CTV (91%), though most respondents used multiple imaging modalities (MRI, 55%; positron emissions tomography, 46%). PTV margins for tumor CTV and nodal CTV ranged from 1 to 5 cm and 0.5 to 1 cm, respectively. Based on these findings, some guidelines for target delineation were felt to be important in achieving consistent, safe standards of practice.

Nineteen experts in the field of gynecological radiation oncology used the draft guidelines to contour a clinical case. These Consortium members demonstrated high specificity but lower sensitivity, particularly in relation to the parametrial contours (Table 1). Substantial STAPLE agreement sensitivity and specificity values were seen for GTV delineation (0.84 and 0.96, respectively), with a kappa statistic of 0.68 ($p < 0.0001$). Kappa values for cervix, uterus, vagina, and parametria indicated moderate agreement (0.42–0.57).

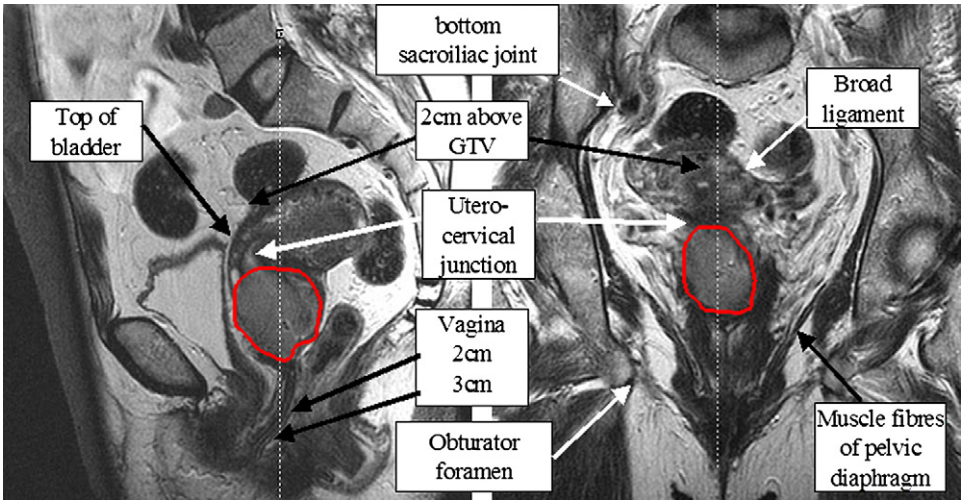

Fig. 1. Sagittal and coronal T_2-weighted MR images of a patient showing the different definitions of superior and inferior parametrial boundaries from survey respondents. Red contour = GTV.

On the whole, the 95% agreement contours were felt to be quite consistent with the intention of the guideline document (Fig. 2). Areas of controversy included anatomical boundaries for the parametrial tissue, the volume of uterus to include in the CTV, the length of normal vagina to treat, PTV margin recommendations, and the use of bladder and/or bowel preparation. The majority of these issues were resolved during the June 2009 meeting, and the finalized document was circulated for comment prior to publication.

Consensus guidelines for delineation of CTV for IMRT for the intact cervix

This document is not meant to be prescriptive since clinical judgment remains an important aspect of determining extent of disease. There are also aspects of the CTV and suggested minimum PTV margins which remain areas of active research. Further refinement of these areas is likely as data regarding patterns of failure in cervix cancer patients treated with nonconventional pelvic fields accrues.

Simulation

While the majority of survey respondents used CT as a clinical imaging modality, this was in the context of generous PTV margins and relatively large field sizes. In the setting of more conformal treatment, MR imaging was strongly recommended by the group to aid in target delineation due to the difficulty in distinguishing soft tissue components on CT. Either a diagnostic MR scan or an MR simulation scan (with the patient in the same treatment position) were recommended if resources allowed. Fusion of the T_2-weighted axial MR images to the planning CT was recommended. Ideally, the MR image would occur close to the time of planning to minimize discrepancies in organ positioning.

The use of patient immobilization at planning and during treatment is necessary to help minimize set-up error.

CTV components

It was agreed that the CTV should include the GTV, cervix (if not already encompassed by the GTV), uterus, parametria, ovaries, and vaginal tissues. The rationale for the inclusion of

Table 1. Agreement among consortium members

Structure	Sensitivity (avg. ± SD)	Specificity (avg. ± SD)	Kappa measure*
GTV	0.84 ± 0.14	0.96 ± 0.04	0.68†
Cervix	0.55 ± 0.24	0.98 ± 0.03	0.42†
Uterus	0.68 ± 0.22	0.97 ± 0.03	0.57†
Vagina	0.58 ± 0.13	0.99 ± 0.01	0.53†
Parametria	0.48 ± 0.27	0.99 ± 0.02	0.42†

Abbreviations: SD = standard deviation.
* Corrected for chance.
† p value of <0.001.

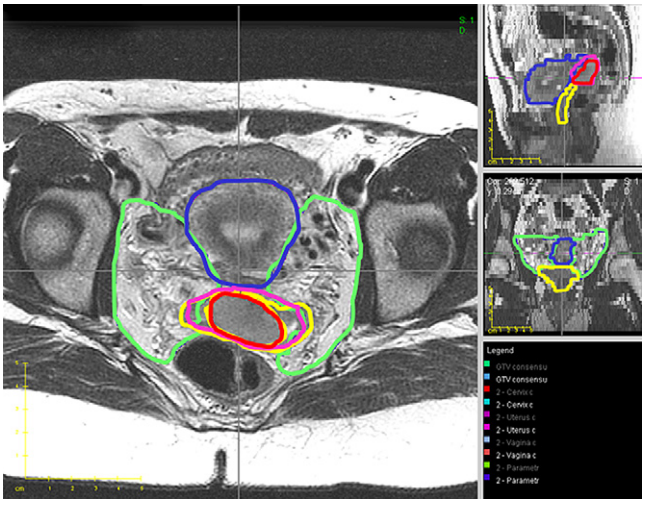

Fig. 2. Axial and reconstructed sagittal and coronal views of T_2-weighted MR images from a clinical contouring case showing 95% agreement contours for GTV (red), cervix (pink), vagina (yellow), parametria (green), and uterus (blue).

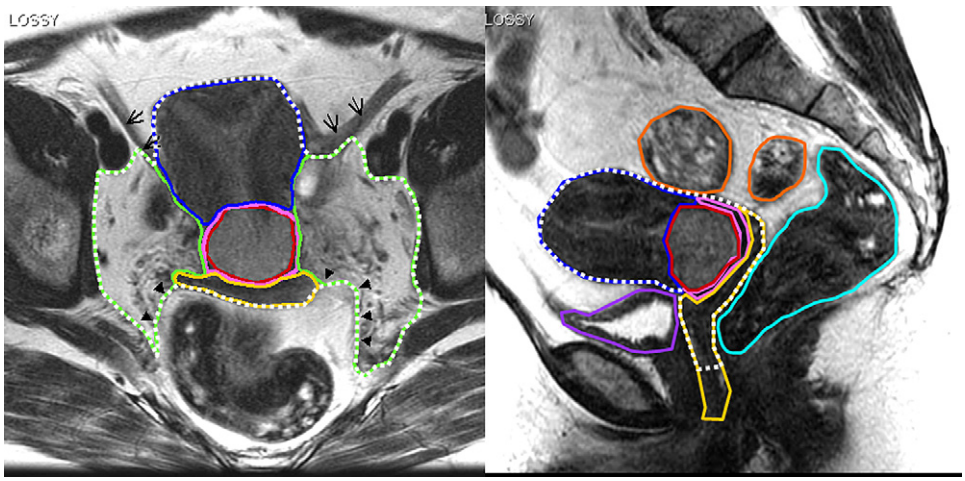

Fig. 3. T_2-weighted MR axial (left) and sagittal (right) images of one patient demonstrating GTV (red), cervix (pink), uterus (blue), vagina (yellow), parametrium (green), bladder (purple), rectum (light blue), and sigmoid (orange). Arrow heads refer to uterosacral ligaments and mesorectal fascia. Arrows refer to the broad ligament and top of the fallopian tube. Dashed white lines represent the CTV.

these structures is extrapolated from the surgical management of cervix cancer (21–23). Details for the extent of uterus, parametria, and vagina to be included in the CTV are shown in Fig. 3 and Table 2 and Supplementary Fig. E1 to E4.

Uterus

The group consensus was that the entire uterus should be included in the CTV for the following reasons. The uterus and cervix are embryologically one unit with interconnected lymphatics and no clear separating fascial plane (24). Second, determination of myometrial invasion radiologically or clinically can be difficult. While published outcomes of radical trachelectomy for early-stage disease have demonstrated overall recurrence rates of less than 5% and mortality rates of less than 3% (25), uterine recurrences have been reported (2%), although the exact location of these recurrences (fundal vs. corpus) have not been stated (26–28). Recurrence rates after radical trachelectomy have been substantially higher (up to 10%) for patients with tumor sizes greater than 2 cm (more comparable to a radiotherapy patient cohort) or with the presence of lymph–vascular invasion (25, 29). The possibility of excluding the uterine fundus in selected cases may be revisited in the future, once more data have been collected.

Table 2. CTV components

GTV	Entire GTV; intermediate/high signal seen on T_2-weighted MR images
Cervix	Entire cervix; if not already included within GTV contour
Uterus	Entire uterus
Parametrium	Entire parametrium, including ovaries; include entire mesorectum if uterosacral ligament involved
Vagina	Minimal or no vaginal extension: upper half of the vagina Upper vaginal involvement: upper two-thirds of the vagina Extensive vaginal involvement: entire vagina

Parametria

Explicit boundaries defining the extent of parametrial tissue have been lacking within the radiotherapy literature. Efforts were made to reach a consensus on the anatomical boundaries of this tissue space. The parametrial tissue is encompassed by the broad ligament but is not always well demarcated on axial imaging. The boundaries of the parametrium are described in Table 3. The superior boundaries of the parametria are at the top of the fallopian tube, and contours should stop once loops of bowel are seen next to the uterus as this is clearly above the broad ligament. For the very anteverted uterus, particularly where the fundus lies below the cervix, the parametrial volume should stop once the cervix is seen. Inferiorly, the parametrial tissue finish at the muscles of the pelvic floor (Fig. 4). Anteriorly, the parametrial boundary lies at the posterior wall of the bladder. In patients with a very small bladder (which lies deep in the pelvis), it was decided to set the anterior parametrial boundary in line with the posterior border of the external iliac

Table 3. Anatomical boundaries of parametria

Location	Anatomic structures
Anteriorly	Posterior wall of bladder or posterior border of external iliac vessel
Posteriorly	Uterosacral ligaments and mesorectal fascia
Laterally	Medial edge of internal obturator muscle/ ischial ramus bilaterally
Superiorly	Top of fallopian tube/ broad ligament. Depending on degree of uterus flexion, this may also form the anterior boundary of parametrial tissue.
Inferiorly	Urogenital diaphragm

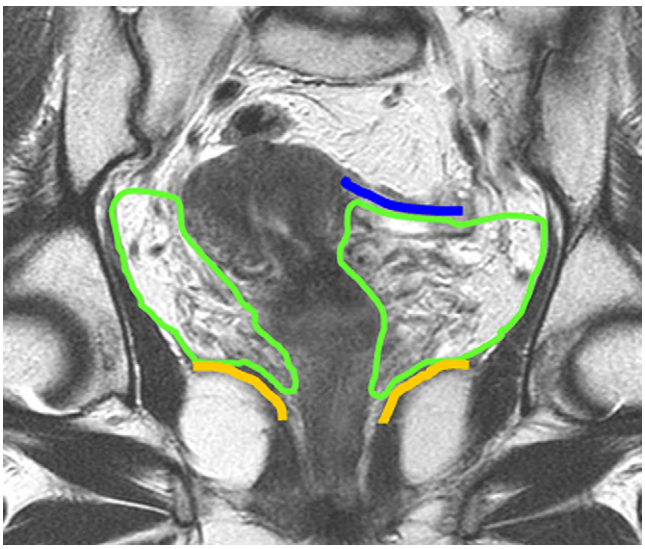

Fig. 4. Coronal T_2-weighted MR image of a patient with a relatively upright uterus, demonstrating the superior and inferior boundaries of parametria. Top of broad ligament (blue), pelvic diaphragm (yellow), parametria (green).

vessels. Posteriorly, the parametrial tissue is bounded by the mesorectal fascia and uterosacral ligaments. Care must be taken to include the entire uterosacral ligaments if they are either clinically or radiologically involved with disease. If this is the case, an argument can be made to include the entire mesorectum as pararectal lymph nodes would also be at risk. In that case, parametrial volumes would extend up to the rectal contour (Fig. 5). Patients with Federation Internationale de Gynecologie et d'Obstetrique (FIGO) stage 3B or greater disease and those with extensive nodal involvement should also have the entire mesorectum included in the parametrial volume. Laterally, the parametrial volume should extend to the pelvic sidewall (excluding bone and muscle). It is acknowledged that there would be some overlap of this volume with the nodal CTV, particularly along the obturator strip. The pelvic sidewall was considered a more consistent and reproducible boundary and any overlap between the two volumes could be dealt with during treatment planning. (Fig. 6)

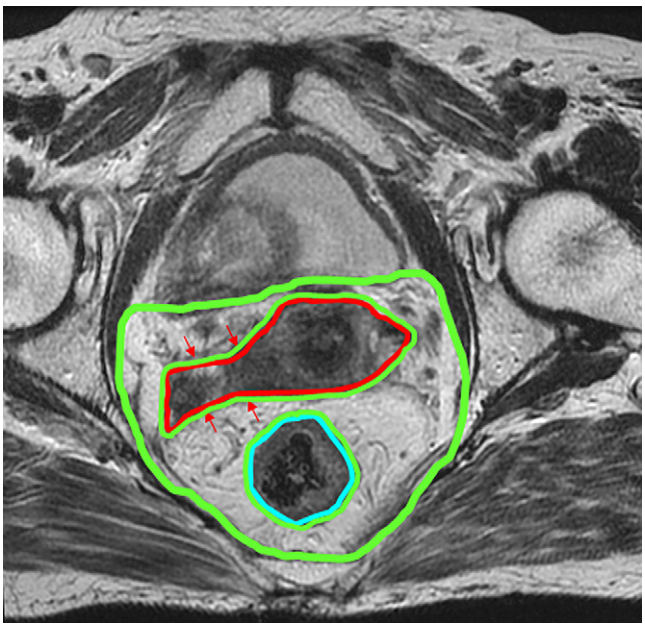

Fig. 5. Axial T_2-weighted MR image of a patient showing the GTV (red contour), modified parametrium (green), and rectum (light blue); red arrows indicate right proximal uterosacral ligament invasion.

Vagina

For tumors with minor or no extension into the vaginal fornices, the upper half of the vagina should be included in the CTV. For those tumors with upper vaginal involvement, the upper two-thirds of the vagina should be treated. Those tumors with extensive involvement should have the entire vagina encompassed in the CTV. This would be in conjunction with clinical judgment as vulva and perineum would not be included unless they were grossly involved (Fig. 3).

Nodal CTV

The nodal CTV must include involved nodes and relevant draining nodal groups (common, internal, and external iliac and obturator and presacral lymph nodes). Inclusion of para-aortic lymph nodes will depend on the extent of disease and results of staging investigations. Details of nodal CTV delineation will not be addressed in this document as a number of guidelines already exist (9, 30, 31).

Organs at risk

While the majority of published literature for IMRT for this site report contouring of normal structures such as pelvic

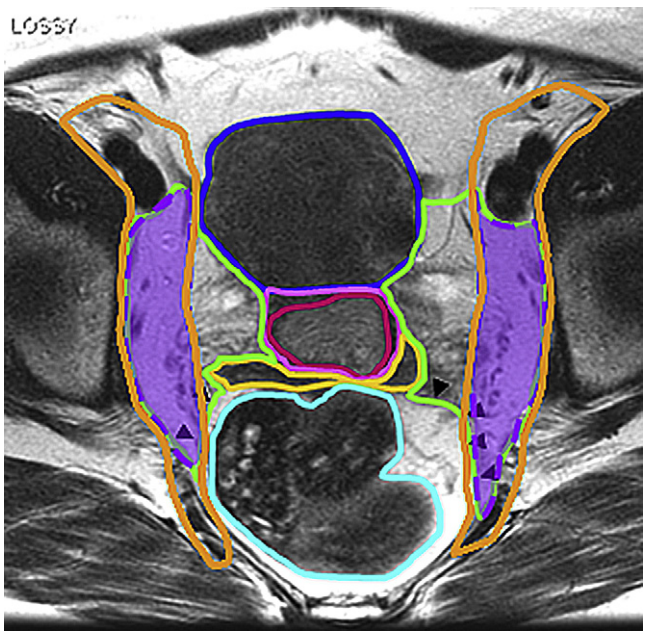

Fig. 6. Axial T_2-weighted MR image showing overlap (purple-shaded region) between nodal clinical target volume (orange contour) and lateral portion of parametrial volume (green contour).

bone marrow, femoral heads, bladder, rectum, and bowel, the exact definition of how some of these organs were contoured remains vague. While bladder is straightforward, the extent of rectum and bowel contoured can substantially influence planning dose constraints and subsequent reported outcomes. The controversies regarding organ at risk (OAR) definition and delineation for IMRT in this setting are beyond the scope of this report.

PTV margins and image guidance

The survey of patterns of practice indicated that PTV margins varied among Consortium members, largely as a function of data available for organ motion for this site. A number of groups have published CTV-PTV margin recommendations which have ranged from 0.6 to 4 cm, depending on their methodology for assessing organ motion (11, 12, 14, 18, 32, 33). The combination of unpredictable organ motion and substantial tumor regression resulted in conservative margin recommendations by the Consortium. Margins of 1.5 to 2 cm around the CTV were recommended if good quality daily soft tissue verification was available during treatment. A PTV margin of 7 mm around the nodal CTV was agreed upon in line with previous recommendations in the postoperative cervix cancer setting (*e.g.*, RTOG protocol 0418). If bone matching alone was being used, more generous margins would be necessary, due to the uncertainty of tumor CTV position in relation to nodal CTV position. The use of IMRT without any form of daily soft tissue verification risks geographical target miss and should be approached with caution. Even the use of fiducial markers is not always reliable as they may shift over the course of treatment.

DISCUSSION

Traditional whole-pelvis radiotherapy fields based on bony landmarks encompasses targets within the pelvis with little sparing of OAR. The benefit of these large treatment volumes is that geographical miss is minimized. In the era of more conformal treatment, where target delineation becomes critical, one of the major difficulties with pelvic IMRT for the radical treatment of cervix cancer lies in the definition of the CTV components. While there is general agreement on what constitutes the CTV, defining these different components becomes more problematic. Explicit radiological boundaries of pelvic targets such as parametrial tissue are lacking, and there are few data to guide our choice as to the extent of uterus and vagina that should be included in the CTV.

It is evident from the clinical contouring case that while experts in the field were reasonably certain about what should not be in the CTV (high specificity values [Table 1]), the sensitivity was less, reflecting the difficulty in determining the interface between the different CTV components. The moderate agreement (as evidenced by the Kappa measures from Table 1) for cervix, uterus, vagina, and parametrial contours reflects some of the problems inherent with contouring for this particular clinical case, where the extreme anteversion of the uterus made identifying various CTV components challenging (Fig. 2).

These CTV components are subject to organ motion, deformation, and tumor regression, resulting in highly individualized and unpredictable organ dynamics (12, 13, 16, 18, 33). For IMRT to be given safely for the intact cervix, daily soft tissue image-guided verification is required to prevent geographical miss. The potential differential in motion between the tumor CTV (which is relatively mobile) and the nodal CTV (which remains largely fixed to bone) means a combined CTV encompassing both would require generous margins since any isocenter shift to cover one component could compromise coverage of the other component (Fig. 7). Minimizing the motion of the tumor CTV through bladder and bowel preparations might help, though the highly

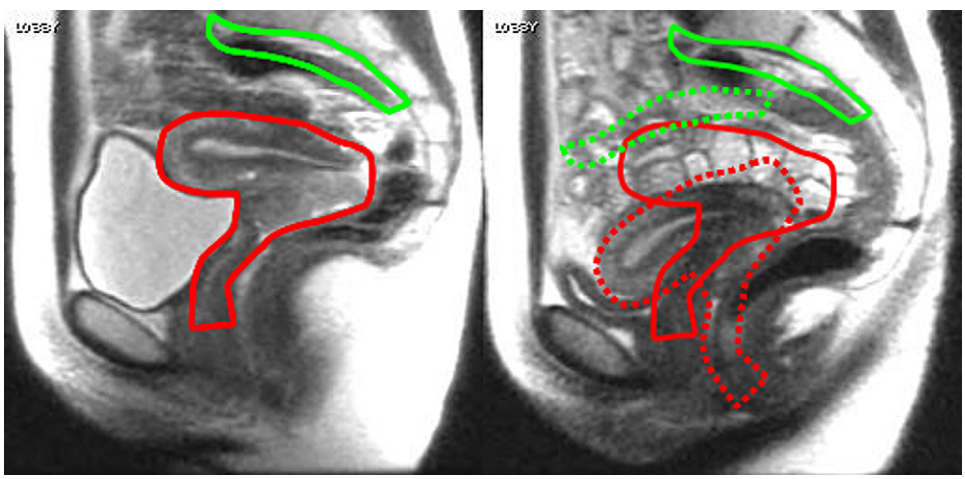

Fig. 7. Sagittal T_2-weighted MR images obtained 1 week apart from the same patient, demonstrating the marked difference between uterus and cervix positions, with altered bladder filling. Primary tumor CTV (red contour) and nodal CTV (green) contours overlaid. Solid lines represent targets at week 1, dashed lines represent the targets at week 2 if a direct translational shift is made to compensate for the change in the primary tumor CTV position. Nodal CTV and portions of tumor CTV in week 2 are missed.

individualized nature of the organ motion and tumor regression means that this is not a safeguard against significant shifts in target position. As a consequence, margin recommendations are difficult and any class solution would need to be generous in order to encompass unpredictable outliers. With PTV margins of 1.5 to 2 cm, OAR sparing with IMRT becomes more difficult. While planning and clinical studies have all shown that there is indeed some OAR sparing using IMRT, even with generous margins, the toxicity experienced by patients can be variable (2, 10, 34).

Integrated boost strategies for primary cervical tumors should be approached with caution as the large PTV margins currently required to compensate for organ motion are also likely to result in increased doses being delivered to surrounding normal tissues, thereby increasing toxicity.

While the potential for normal-tissue sparing is one of the motivations behind the move toward IMRT for this site, achieving good target coverage remains the primary objective. Further refinement of PTV margins will continue to evolve as the results of ongoing research mature.

CONCLUSIONS

This is the first consensus document attempting to clarify target definitions for whole-pelvis IMRT for the intact cervix. It was felt that clear target definition guidelines would be useful in achieving consistency across different treatment centers. This report does not attempt to address issues of minimizing organ motion or adaptation to organ motion or tumor regression. The value of this document lies in providing groundwork for safe practice, building on previously published guidelines for IMRT in the postoperative setting, and for future trials of IMRT in cervix cancer.

REFERENCES

1. Ahmed RS, Kim RY, Duan J, *et al*. IMRT dose escalation for positive para-aortic lymph nodes in patients with locally advanced cervical cancer while reducing dose to bone marrow and other organs at risk. *Int J Radiat Oncol Biol Phys* 2004; 60:505–512.
2. Beriwal S, Gan GN, Heron DE, *et al*. Early clinical outcome with concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2007;68:166–171.
3. Gerszten K, Colonello K, Heron DE, *et al*. Feasibility of concurrent cisplatin and extended field radiation therapy (EFRT) using intensity-modulated radiotherapy (IMRT) for carcinoma of the cervix. *Gynecol Oncol* 2006;102:182–188.
4. Mell LK, Kochanski JD, Roeske JC, *et al*. Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;66:1356–1365.
5. Portelance L, Chao KS, Grigsby PW, *et al*. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys* 2001; 51:261–266.
6. van de Bunt L, van der Heide UA, Ketelaars M, *et al*. Conventional, conformal, and intensity-modulated radiation therapy treatment planning of external beam radiotherapy for cervical cancer: The impact of tumor regression. *Int J Radiat Oncol Biol Phys* 2006;64:189–196.
7. Salama JK, Mundt AJ, Roeske J, *et al*. Preliminary outcome and toxicity report of extended-field, intensity-modulated radiation therapy for gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2006;65:1170–1176.
8. Michalski JM, Lawton C, El Naqa I, *et al*. Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2010. In press.
9. Small W Jr., Mell LK, Anderson P, *et al*. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;71: 428–434.
10. Mundt A, Mell L, Roeske J. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 2003;56:1354–1360.
11. Buchali A, Koswig S, Dinges S, *et al*. Impact of the filling status of the bladder and rectum on their integral dose distribution and the movement of the uterus in the treatment planning of gynaecological cancer. *Radiother Oncol* 1999;52:29–34.
12. Chan P, Dinniwell R, Haider MA, *et al*. Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: A cinematic-MRI point-of-interest study. *Int J Radiat Oncol Biol Phys* 2008;70: 1507–1515.
13. Huh SJ, Park W, Han Y. Interfractional variation in position of the uterus during radical radiotherapy for cervical cancer. *Radiother Oncol* 2004;71:73–79.
14. Kaatee RS, Olofsen MJ, Verstraate MB, *et al*. Detection of organ movement in cervix cancer patients using a fluoroscopic electronic portal imaging device and radiopaque markers. *Int J Radiat Oncol Biol Phys* 2002;54:576–583.
15. Lee CM, Shrieve DC, Gaffney DK. Rapid involution and mobility of carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2004;58:625–630.
16. Lim KSH, Kelly V, Stewart J, *et al*. Whole pelvis IMRT for cervix cancer: What gets missed & why? *Int J Radiat Oncol Biol Phys* 2008;72:S112–S112.
17. Mayr NA, Yuh WT, Taoka T, *et al*. Serial therapy-induced changes in tumor shape in cervical cancer and their impact on assessing tumor volume and treatment response. *AJR Am J Roentgenol* 2006;187:65–72.
18. van de Bunt L, Jurgenliemk-Schulz IM, de Kort GA, *et al*. Motion and deformation of the target volumes during IMRT for cervical cancer: What margins do we need? *Radiother Oncol* 2008;88:233–240.
19. El Naqa I, Michalski JM, Lawton C, *et al*. Investigation of statistical methods to analyze target volume definition among experts in radiotherapy treatment planning. *Radiother Oncol* 2007;84:S126.
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–174.
21. Meigs JV, Dresser R. Carcinoma of the cervix treated by the roentgen ray and radium. *Ann Surg* 1937;106:653–667.
22. Querleu D, Morrow CP. Classification of radical hysterectomy. *Lancet Oncol* 2008;9:297–303.
23. Wertheim E. The extended abdominal operation for carcinoma uteri. *Am J Obstet Gynecol* 66:167–232, 1912
24. Höckel M, Horn L-C, Fritsch H. Association between the mesenchymal compartment of uterovaginal organogenesis and local

tumour spread in stage IB-IIB cervical carcinoma: a prospective study. *Lancet Onco* 2005;6:751–756.
25. Plante M. Vaginal radical trachelectomy: An update. *Gynecol Oncol* 2008;111:S105–S110.
26. Bali A, Weekes A, Van Trappen P, *et al*. Central pelvic recurrence 7 years after radical vaginal trachelectomy. *Gynecol Oncol* 2005;96:854–856.
27. Diaz JP, Sonoda Y, Leitao MM, *et al*. Oncologic outcome of fertility-sparing radical trachelectomy versus radical hysterectomy for stage IB1 cervical carcinoma. *Gynecol Oncol* 2008; 111:255–260.
28. Hertel H, Köhler C, Grund D, *et al*. Radical vaginal trachelectomy (RVT) combined with laparoscopic pelvic lymphadenectomy: Prospective multicenter study of 100 patients with early cervical cancer. *Gynecol Oncol* 2006;103:506–511.
29. Nishio H, Fujii T, Kameyama K, *et al*. Abdominal radical trachelectomy as a fertility-sparing procedure in women with early-stage cervical cancer in a series of 61 women. *Gynecol Oncol* 2009;115:51–55.
30. Dinniwell R, Chan P, Czarnota G, *et al*. Pelvic lymph node topography for radiotherapy treatment planning from ferumoxtran-10 contrast-enhanced magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2009;74:844–851.
31. Taylor A, Rockall AG, Reznek RH, *et al*. Mapping pelvic lymph nodes: Guidelines for delineation in intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63:1604–1612.
32. Beadle BM, Jhingran A, Salehpour M, *et al*. Cervix regression and motion during the course of external beam chemoradiation for cervical cancer. *Int J Radiat Oncol Biol Phys* 2009;73:235–241.
33. Taylor A, Powell MEB. An assessment of interfractional uterine and cervical motion: Implications for radiotherapy target volume definition in gynaecological cancer. *Radiother Oncol* 2008;88:250–257.
34. Roeske JC, Bonta D, Mell LK, *et al*. A dosimetric analysis of acute gastrointestinal toxicity in women receiving intensity-modulated whole-pelvic radiation therapy. *Radiother Oncol* 2003;69:201–207.

ADDENDUM

The following radiation oncologists contributed to this work as members of the Gyn IMRT Consortium: Anamaria Yeung, M.D., and Robert Amdur, M.D. (Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL); Ivy Petersen, M.D. (Department of Radiation Oncology, Mayo Clinic, Rochester, MN); Penny Anderson, M.D. (Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA); Melanie Powell, M.D., F.R.C.R. (Department of Radiotherapy, St Bartholomew's Hospital, London, UK); Mahesh Varia, M.D. (Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC); Tracey Schefter, M.D. (Department of Radiation Oncology, University of Colorado, Aurora, CO); Satoshi Ishikura, M.D., Ph.D. (Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan); Gillian Thomas, M.D. (Odette Cancer Centre, Sunnybrook Health Sciences Centre and Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada).