Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 3, pp. 824–830, 2009

0360-3016/09/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2008.08.070

**CLINICAL INVESTIGATION** **Rectum**

# ELECTIVE CLINICAL TARGET VOLUMES FOR CONFORMAL THERAPY IN ANORECTAL CANCER: A RADIATION THERAPY ONCOLOGY GROUP CONSENSUS PANEL CONTOURING ATLAS

Robert J. Myerson, M.D., Ph.D.,* Michael C. Garofalo, M.D.,† Issam El Naqa, Ph.D.,* Ross A. Abrams, M.D.,‡ Aditya Apte, Ph.D.,* Walter R. Bosch, Ph.D.,* Prajnan Das, M.D.,§ Leonard L. Gunderson, M.D.,‖ Theodore S. Hong, M.D.,¶ J. J. John Kim, M.D.,# Christopher G. Willett, M.D.,** and Lisa A. Kachnic, M.D.††

*Department of Radiation Oncology, Washington University, St. Louis, MO; †Department of Radiation Oncology, University of Maryland Medical Center, Baltimore, MD; ‡Department of Radiation Oncology, Rush University Medical Center, Chicago, IL; §Department of Radiation Oncology, University of Texas, MD Anderson Cancer Center, Houston, TX; ‖Department of Radiation Oncology, Mayo Clinic, Scottsdale AZ; ¶Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA; #Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; **Department of Radiation Oncology, Duke University, Durham, NC; and ††Department of Radiation Oncology, Boston University Medical Center, Boston, MA

**Purpose:** To develop a Radiation Therapy Oncology Group (RTOG) atlas of the elective clinical target volume (CTV) definitions to be used for planning pelvic intensity-modulated radiotherapy (IMRT) for anal and rectal cancers.
**Methods and Materials:** The Gastrointestinal Committee of the RTOG established a task group (the nine physician co-authors) to develop this atlas. They responded to a questionnaire concerning three elective CTVs (CTVA: internal iliac, presacral, and perirectal nodal regions for both anal and rectal case planning; CTVB: external iliac nodal region for anal case planning and for selected rectal cases; CTVC: inguinal nodal region for anal case planning and for select rectal cases), and to outline these areas on individual computed tomographic images. The imaging files were shared via the Advanced Technology Consortium. A program developed by one of the co-authors (I.E.N.) used binomial maximum-likelihood estimates to generate a 95% group consensus contour. The computer-estimated consensus contours were then reviewed by the group and modified to provide a final contouring consensus atlas.
**Results:** The panel achieved consensus CTV definitions to be used as guidelines for the adjuvant therapy of rectal cancer and definitive therapy for anal cancer. The most important difference from similar atlases for gynecologic or genitourinary cancer is mesorectal coverage. Detailed target volume contouring guidelines and images are discussed.
**Conclusion:** This report serves as a template for the definition of the elective CTVs to be used in IMRT planning for anal and rectal cancers, as part of prospective RTOG trials. 

**Intensity-modulated radiotherapy, Conformal pelvic radiation, Anal cancer, Rectal cancer, Contouring guidelines.**

## INTRODUCTION

Intensity-modulated radiotherapy (IMRT) enables the delivery of complex radiation therapy (RT) plans that previously could not be accomplished with conventionally planned two- to four-field techniques or more sophisticated three-dimensional (3D) conformal RT (3D-CRT). The advent of IMRT provides an opportunity to spare critical normal tissue, which is of significant importance for cancers that are managed with concurrent chemoradiation. For patients receiving pelvic radiation for anal or rectal cancer, normal tissue can often be better protected with IMRT than other conformal techniques as demonstrated by dosimetric investigations (1–8). Use of IMRT has also been associated with reduced acute toxicity for anal cancer (6, 9, 10).

Critical to the use of IMRT, is a clear understanding of the elective CTV targets. Treatment with IMRT demands much more detailed knowledge of target structures than the conventionally planned two- to four-field technique. The ''four-field box'' technique is based on bony landmarks and does not lend itself to customized conformal treatment

Reprint requests to: Robert J. Myerson, M.D., Department of Radiation Oncology, 4921 Parkview Place, Box 8224, St., Louis, MO 63110. Tel: (314) 747-7236; Fax: (314) 454-5276; E-mail: myerson@radonc.wustl.edu

Conflict of interest: none.

*Acknowledgments*—L. A. K. and R. J. M. co-wrote the manuscript. This work was supported by RTOG U10 CA21661, CCOP U10 CA37422, Stat U10 CA32115 NCI grants. The contents are the sole responsibility of the authors and do not necessarily represent official views of the National Cancer Institute. Advanced Technology QA Consortium supported by National Institutes of Health/National Cancer Institute U24 Grant CA81647.

Received July 22, 2008, and in revised form Aug 26, 2008. Accepted for publication Aug 29, 2008.

planning based on an individual's anatomy. Target volumes for anal and rectal cancer also differ substantially from those appropriate for gynecologic (GYN) or genitourinary cancer (GU). The most striking differences arise from the need for proper coverage of the perirectal and presacral regions. Although the rectum and its associated mesentery are avoidance structures for GYN or GU malignancies, they represent first-echelon drainage for both the anus and rectum.

The elective CTV atlas that follows was produced by a consensus panel of nine radiation oncologists (R.A., P.D., M.G., L.G., T.H., L.K., J.K., R.M., and C.W.) who were assigned by the Gastrointestinal Committee of the Radiation Therapy Oncology Group (RTOG). Co-chairs were M.G., L.K., and R.M.. The formation of this panel was motivated, in part, by what was believed to be inadequate contouring in a large number of cases enrolled on RTOG 0529 (a Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal) (11). Because of a rapid submission and review process, patient care was not compromised, but an educational need was identified. This report provides the recommendations of this consensus panel, and serves as a template for the definition of the elective CTVs to be used in IMRT planning for anal and rectal cancers.

## METHODS AND MATERIALS

After the development of the RTOG anorectal contouring consensus panel, multiple informal discussions were held by both electronic mail and telephone conference to develop three elective CTVs for the purpose of this atlas. *CTVA*, defined as the internal iliac, presacral and perirectal nodal groups; *CTVB*: the external iliac nodal region, and *CTVC*: the inguinal nodal region.

For anal cancers, the elective regional target volume would include all three CTVs. For rectal cancers, in most cases, *CTVA* would be the only volume to receive elective radiation. However, for certain presentations, discussed below, one could consider adding *CTVB* and even *CTVC*.

Ultimately, a sample set of computed tomography (CT) images were distributed to the members of the panel, along with a questionnaire to answer further detailed questions concerning the three elective CTVs. The case used for this atlas was a clinical T3 N2 rectal cancer located 7 cm above the anal verge. The case was selected because of the presence of multiple perirectal lymph nodes, without major distortion of the mesorectum. For reasons unrelated to the rectal cancer, this case also had multiple small inguinal and external iliac lymph nodes, which inform the process of outlining *CTVB* and *CTVC*. The patient was simulated in the prone position (with a styrofoam bowel displacement device (12, 13) incorporated into the alpha cradle), with a flexible endorectal tube placed at the distal edge of palpable disease and a skin marker placed 4 cm below the distal edge of palpable disease.

It should be noted that the use of the prone position is not mandatory in the RTOG anal cancer protocols. Nonetheless, it should be considered in cases where diagnostic imaging in the supine position demonstrates a substantial volume of small bowel near the target volumes. Similarly the use of small bowel contrast and the placement of markers for the distal edge of disease, although not mandatory, can be very helpful. The identification of the iliac vessels is also important. Unlike this patient, who had arterial calcifications and a clear fat plane between the ileopsoas muscles and the iliac vessels, many patients could also benefit from intravenous contrast at the time of simulation.

The consensus generating process consisted of answering the questionnaire as well as contouring the three elective target structures. The imaging files were shared via the Advanced Technology Consortium, with each participant using his/her own treatment planning system to contour. A software program developed by one of the co-authors (I.E.N.) used the binomial distribution to generate a 95% confidence level group consensus contour. The computer-estimated consensus contours and questionnaire responses were then reviewed by the group at a formal consensus conference sponsored by the RTOG and held in San Diego on January 17, 2008. At this meeting, a general consensus regarding the three CTVs was obtained, and one of the chairs (R.M.) has presented the panel with final modified contouring images.

### *Statistical analysis*

We have developed a MATLAB (Mathworks Inc., Natick, MA) software program for estimating consensus contours from given individual experts contours. The software is an imputation method using expected maximum (EM) algorithms for simultaneous truth and performance level estimation (STAPLE) (14). In this approach, the true contouring decisions at each voxel are formulated as maximum-likelihood estimates from the observed contours by optimizing sensitivity and specificity parameters of each expert's performance using the EM algorithm, assuming a binomial distribution. Estimated sensitivities/specificities for the different CTVs are listed in Table 1. We estimated overall agreement using generalized $\kappa$ statistics (15). The goodness of agreement was evaluated according to Landis and Koch criteria (16). According to these criteria, the agreement on CTVA was considered substantial and on CTVB and CTVC was considered moderate (Table 1 and Results section below).

## RESULTS

In Fig. 1, the individual panel submissions are superimposed and displayed on four representative slices. In general, there is good agreement on the location of the core portions of the mesorectum, as well as the iliac and femoral vessels. For *CTVA*, differences between individual contourers were primarily a matter of margin. Therefore, for this target volume, the group agreed to accept the computer-generated consensus contours. For *CTVB* and *C*, the panel believed that small lymph nodes, if present, should be incorporated into the elective target volume, even if it was deemed that they were probably uninvolved reactive nodes. Including nodes that were not covered by some of the members led to modifications of the computer-generated contours. The agreed-upon extensions was primarily into the lateral inguinal regions. The resulting consensus CTV contours are displayed in Fig. 2. Specific CTV definition details, as decided through this consensus process and other planning recommendations are described.

### *CTVA (perirectal, presacral, internal iliac regions)*

*Lower pelvis.* The caudad extent of this elective clinical target volume should be a minimum of 2 cm caudad to gross disease. In addition there should be coverage of the entire mesorectum to the pelvic floor (located approximately at slice −41.08 in the sample case) even for upper rectal cancers. It should be understood that, after accounting for PTV margin

Table 1. Preconsensus statistical analysis of agreement level

| | STAPLE estimates | | |
|---|---|---|---|
| CTV | Sensitivity | Specificity | $\kappa$ Statistics agreement |
| CTVA | 0.83 ± 0.18 | 0.96 ± 0.04 | 0.68 ($p < 0.0001$) "Substantial" |
| CTVB | 0.61 ± 0.18 | 0.99 ± 0.02 | 0.49 ($p < 0$ .0001) "Moderate" |
| CTVC | 0.66 ± 0.21 | 0.98 ± 0.04 | 0.49 ($p < 0.0001$) "Moderate" |

*Abbreviations:* CTV = clinical target volume; STAPLE = simultaneous truth and performance level estimation.

and beam penumbra, a 2 cm CTV margin is equivalent to a block edge margin of ~ 4 cm. For anal canal cancers, the 2-cm CTV margin should extend at least 2 cm around the anal verge into apparently normal perianal skin (in RTOG 0529, the requirement is 2.5 cm). For cancers with perianal skin involvement, the CTV margin should extend at least 2 cm beyond areas of involvement.

For this sample case of a mid-rectal cancer, the caudad extent of *CTVA* is at slice −42.58, because that slice is 2 cm caudad to the distal extent of palpable disease (demarcated by the tube placed at simulation). If this had been an upper rectal cancer, the caudad extent of *CTVA* would be at the pelvic floor (*i.e.,* CTVA would extend down to slice −41.08).

The group believed that unless there is radiographic evidence of extension into the ischiorectal fossa, extension of *CTVA* does not need to go more than a few millimeters beyond the levator muscles. For very advanced anal or rectal cancers extending through the mesorectum or the levators, the panel's recommendation is to add a ~1- to 2-cm margin up to bone, wherever the cancer extends beyond the usual compartments. Similarly, if the tumor is invading a neighboring organ (T4 disease), the CTVA should include a 1- to 2-cm margin around the identified areas of invasion. Magnetic resonance imaging and/or a positron emission tomograpy/CT scan is strongly recommended in such cases.

*Mid-pelvis.* In the mid-pelvis, *CTVA* includes the rectum and its mesentery, the internal iliac region, and a margin for bladder variability. The posterior and lateral margins of *CTVA* should extend to pelvic sidewall musculature or, where absent, bone. Anteriorly, the consensus group recommended extending *CTVA* ~1 cm into the posterior bladder, to account for day-to-day variation in bladder position (17).

The panel also recommended including at least the posterior portion of the internal obturator vessels (which lie between the external and internal iliacs in the mid pelvis) with *CTVA*.

*Upper pelvis.* The recommended superior extent of the perirectal component of *CTVA* was whichever is more cephalad: the rectosigmoid junction or at least 2 cm proximal to the superior extent of macroscopic disease in the rectum/perirectal nodes. The full length of the rectum should always be in *CTVA*, but more of the large bowel should be incorporated, if the 2-cm proximal margin requires that.

The most cephalad extent of *CTVA* will be higher than the rectum, to properly cover the internal iliac and presacral

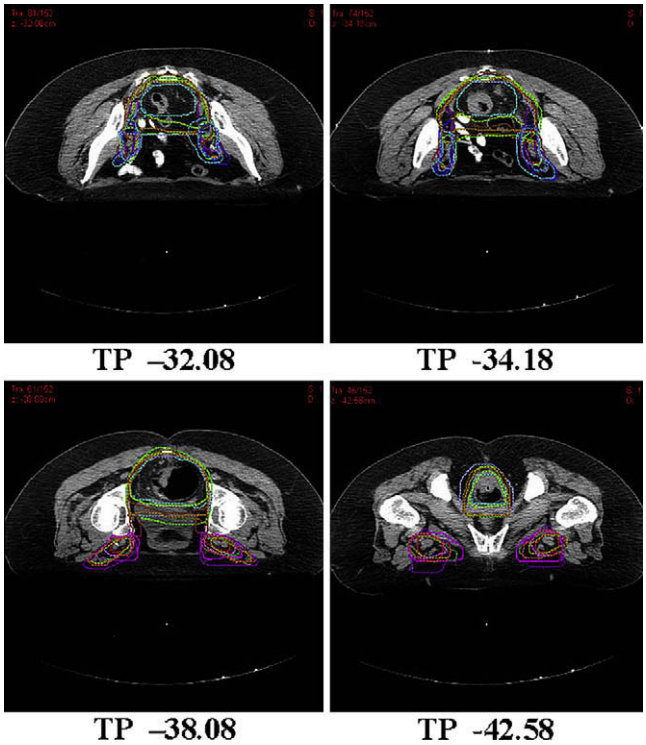


Fig. 1. Superposition of individual investigator's contours of elective clinical target volumes for anorectal cancer. Each panel member is assigned a different color. Table position (TP) is given in centimeters.

regions. The most cephalad aspect of *CTVA* should be where the common iliac vessels bifurcate into external/internal iliacs (approximate boney landmark: sacral promontory). At midline, CTVA should extend at least 1 cm anterior to the sacrum, to provide proper coverage of the presacral region.

For all areas of *CTVA*, care should be taken to avoid contouring into uninvolved bone. In general the CTVA contour does not extend into uninvolved pelvic sidewall muscles but does include the levators. It should be noted that when small bowel fell into the region normally taken by rectal mesentery (see slices −30.88 to −34.18 of this sample case), the panel opted to keep it in the elective target volume CTVA, inasmuch as the location of small bowel could vary from day to day.

In principle, the day-to-day variation of adjacent organs like the bladder and bowel should be incorporated in the PTV margin. It is more practical, however, to assign a uniform PTV margin and to account for physiologic variability by adjusting the CTV. The panel opted for this approach.

*CTVB (external iliac region) and CTVC (inguinal region)*

*Indications for elective irradiation.* The consensus group believed that elective coverage of the inguinal and external iliac regions should be routine for anal carcinomas. There was some disagreement as to the indications for covering these regions for rectal carcinomas. For rectal carcinomas extending into GYN or GU structures (the most common manifestation of T4 disease), the panel agreed that the external iliac region should be added (elective nodal

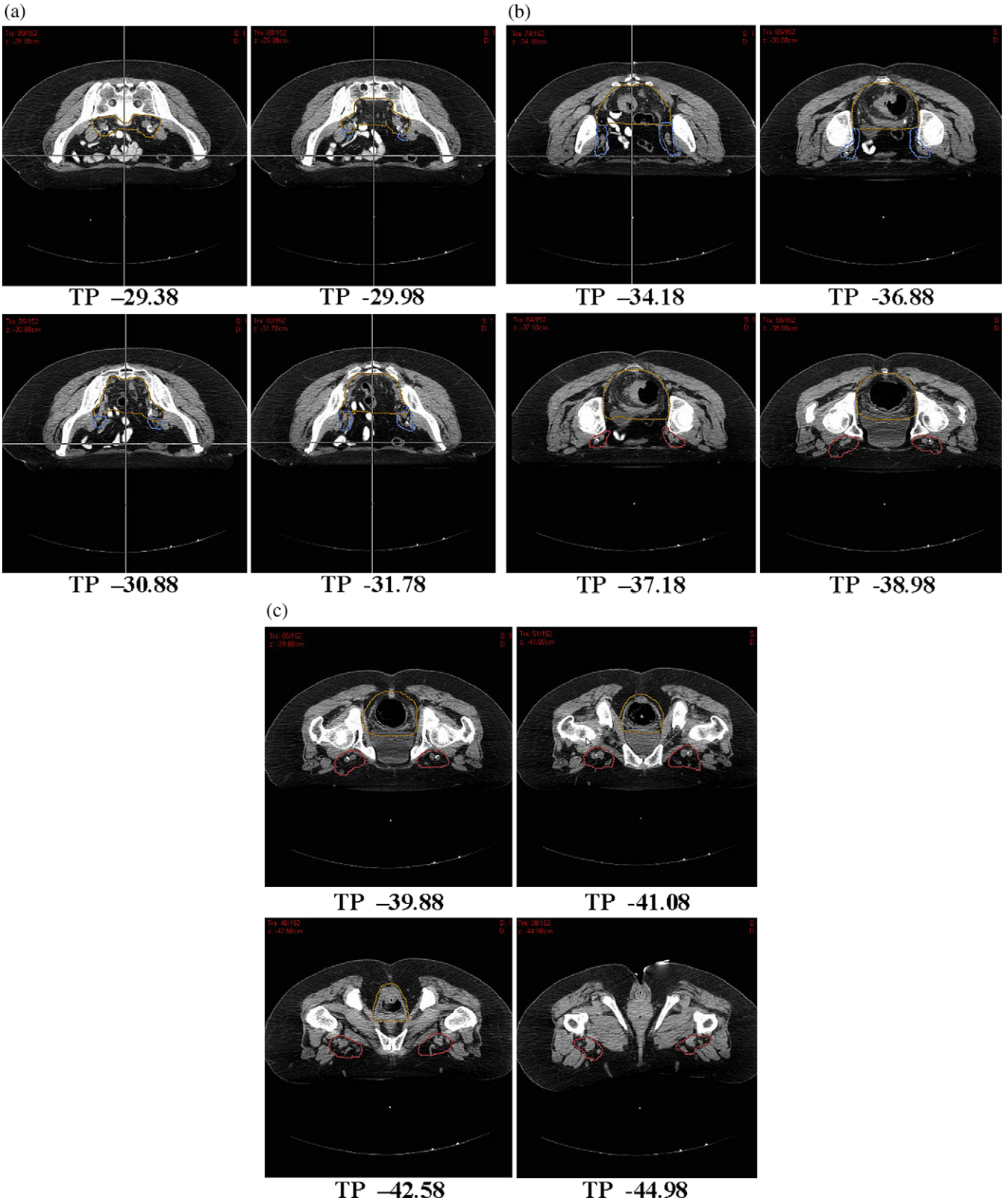


Fig. 2. Group consensus contours for elective clinical target coverage for anorectal cancer. Brown = *CTVA* (perirectal, presacral, internal iliac), blue = *CTVB* (external iliac), red = *CTVC* (inguinal). Table position (TP) is given in centimeters. (a) Upper pelvis; (b) mid- pelvis; (c) lower pelvis.

coverage = *CTVA* + *CTVB* for these cases). Some, but not all, of the panel would also include the external iliacs for rectal cancers that extend into the anal canal. Similarly, the group was divided on whether to electively irradiate the inguinal nodal region for rectal adenocarcinomas that extend to the anal verge, perianal skin, or lower third of the vagina.

Caudad extent of elective target volumes: The consensus panel recommended that the caudad extent of the inguinal region (*CTVC*) should be 2 cm caudad to the saphenous/femoral junction. The transition between inguinal and external iliac regions (*CTVC* to *CTVB*) is somewhat arbitrary, but the group recommended that this be at the level of the caudad extent of the internal obturator vessels (approximate boney landmark: upper edge of the superior pubic rami).

*Margin around blood vessels.* The group recommended at least a 7- to 8-mm margin in soft tissue around the iliac vessels, but one should consider a larger, ≥10-mm, margin anterolaterally, especially if small vessels or nodes are identified in this area. The inguinal/femoral region should be contoured as a compartment with any identified nodes (especially in the lateral inguinal region) included. If automated expansions, are used the CTVs should be trimmed off uninvolved bone and muscle.

*Boost volumes and planning target volumes*

The consensus panel opted not to include boost target volumes in this atlas. It was believed that boosts might be defined differently in different protocols, might be affected by evolving imaging capabilities, and might vary sharply among patients. The group did recommend that any boost CTV extend to the entire mesorectum and presacral region at involved levels, including ~1 to 2 cm cephalad and caudad in the mesorectum and ~2 cm on gross tumor within the anorectum.

Similarly, this atlas does not present planning target volumes (PTVs). It was generally agreed that the PTV margin should be ~0.7 to 1.0 cm, except at skin, where planning system requirements mandate it be trimmed to ~2-5 mm within the skin surface.

*Normal tissues*

Although normal tissues were not contoured in this atlas, there were several general recommendations by the consensus panel. The femoral head and neck should be avoidance structures. The small bowel and large bowel are important structures to consider when planning treatment. To avoid unnecessary contouring effort, they need be contoured only to ~1 cm above the PTV. This, in turn, implies that absolute volume of bowel (in cubic centimeters) is more important than relative volume (in percent). Otherwise, cases with good exclusion of small bowel from the pelvis (*e.g.,* with a bowel displacement device) would be unfairly penalized.

The group believed that it is important that dose–volume histograms (DVH) be consistent from one contourer to the next. Therefore, we recommended that bowel be contoured tightly, rather than with a broad, ill-defined margin. It is recognized that the location of bowel could vary from one day to the next, but the dose–volume histogram (DVH) from the simulation should remain representative. It was suggested that a broader avoidance structure could be used for IMRT planning purposes (*e.g.,* anterior pelvic contents above the bladder and ~1 cm outside the PTVs), whereas the tightly contoured bowel would remain the structure evaluated in DVHs.

With regard to large bowel, it is very important to recognize that all of the rectum and much of the rectosigmoid will be part of *CTVA* and therefore should *not* be treated as an avoidance structure. Therefore, it is recommended that ''uninvolved colon,'' defined to be that part of the large bowel outside the CTVs, be contoured separately from rectum.

On the other hand, if small bowel happens to lie within a CTV, the CTV is *not* modified and the portion of small bowel that fell within the target volume is *not* extracted from the DVHs, as discussed above.

The panel opted not to set specific DVH recommendations for normal tissue, because this is still under active investigation. There are differing DVH constraints in the two recent RTOG IMRT protocols: 0529 (anal carcinoma) and 0822 (rectal carcinoma) (www.rtog.org). In RTOG 0822, major deviations are generated if criteria for bladder, small bowel, and femoral heads are exceeded. In RTOG 0529, the bladder is not a deviation generating structure, but criteria for femoral heads and small bowel are stricter.

## DISCUSSION

Research into the potential benefits of IMRT in the treatment of anal and rectal cancer has only recently been undertaken. In terms of definitive chemoradiation for anal canal cancer, several recent studies, including RTOG 98-11, support the administration of higher radiation doses in the treatment of anal cancer in attempts to improve local–regional disease control (18–21). The current standard dose recommendations with conventional external beam RT range from 45 Gy for early lesions to 59.4 Gy for T2 to T4 disease. The combination of these increased radiation doses with 5-fluorouracil (5FU) and mitomycin-C therapy have resulted in encouraging local control rates, but have been tempered by significant acute morbidity, most notably Grade 2+ hematologic, dermatologic and gastrointestinal, as well as late toxicity including femoral head and neck fractures (18, 19, 22). Use of IMRT in the treatment of anal canal cancer has tremendous potential for reducing these toxicities, while allowing for these higher radiation doses to the gross tumor volume. With IMRT, radiation dose to the normal structures (particularly small bowel, skin, femoral heads, bladder, and external genitalia) is reduced compared with conventional 2D and more sophisticated 3D treatment planning (1, 5, 6). Small pilot series show IMRT in this population to be well tolerated, with most patients experiencing only mild to moderate acute symptoms, and few patients experiencing treatment breaks (6, 9, 10). Moreover, the use of IMRT has not compromised elective target coverage, as locoregional control in these reports appears favorable, albeit with limited follow-up.

Concerning preoperative chemoradiation for clinically staged muscle invasive or node positive rectal cancer, 5FU-based chemoradiotherapy has been associated with moderate rates of acute gastrointestinal toxicity (23–25). More recently,

the addition of irinotecan to 5FU and radiation has yielded impressive pathologic complete response rates, but at the expense of marked small bowel morbidity (26). The risk of Grade 3 or greater GI toxicity has been shown to increase with both radiation dose and volume of irradiated bowel, for rectal cancer patients undergoing radiation in combination with 5FU or 5FU and oxaliplatin (27, 28). Therefore, IMRT could potentially reduce the radiation dose to the small bowel and, consequently, could reduce gastrointestinal side effects for rectal cancers. Dosimetric analyses comparing 3D-CRT and IMRT planning have shown that IMRT improved small-bowel sparing without compromising target volume coverage (2–4, 7, 8). Moreover, IMRT in the prone position with a bowel displacement device was more effective than IMRT in the supine position at minimizing the radiation dose to small bowel (4). To date, there is only one clinical report concerning the clinical use of IMRT for rectal cancer (29). This Phase I effort examined the mean tolerated dose of preoperative radiotherapy using IMRT and an integrated boost (2 Gy to the gross tumor volume daily) with concurrent capecitabine in patients with locally advanced rectal cancer. Eight patients completed radiation at the initial dose level of 55 Gy, but the study was discontinued because six Grade 3 toxicities occurred among the 8 patients, with no patient achieving a pathologically complete response. Details of IMRT target volumes and planning directives were not described.

One of the significant hurdles facing implementation of IMRT for pelvic malignancies has been the complexity of target and elective lymphatic definition. The standardization of the CTV target volume definition will not only provide an important basis for the prospective study of IMRT for anorectal malignancies in the multi-institutional setting, but will also establish contouring guidelines for the radiation oncology community, if IMRT proves efficacious in reducing normal tissue toxicities while not compromising outcome. Herein, the RTOG anorectal contouring consensus panel demonstrated good concordance in their CTV definitions. This is understandable, considering that the panel members are physicians who specialize in the delivery of radiation for these malignancies. However, this was not the case in RTOG 0529 (A Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal), despite the availability of perhaps a less robust anal contouring atlas (11). As part of this effort, real-time quality assurance of all IMRT treatments was successfully performed by the principal investigators before the start of treatment. Many cases required revisions because of incomplete coverage of the perirectal and presacral regions (mesorectum).

Although this report serves as the first contouring guideline consensus for anal cancer, there has been one previous publication providing target volume directives for rectal carcinoma (30). The RTOG panel recommendations are quite consistent with the CTV definitions of target structures for rectal cancer provided by Roels *et al.* (30). However, there is some disagreement on the anterior border for the mesorectum. The RTOG anorectal group was more generous on this border to account for day-to-day variability in the location of structures immediately anterior to the rectum (including bladder, gynecologic structures, and low-lying loops of small bowel and sigmoid colon) (17). In addition, the group believed that failure in the ischiorectal fat in the absence of frank invasion on presentation was very infrequent and opted for more conformal coverage of the low anorectum.

## CONCLUSION

This is the first report of the Radiation Therapy Oncology Group anorectal consensus panel. The guidelines and images should serve as a template for the definition of the elective clinical target volumes to be used in conformal planning for anal and rectal cancers. As there is no long-term outcome data demonstrating the efficacy of IMRT in this setting, this atlas will be used as a contouring guideline for two prospective IMRT trials, RTOG 0822, a Phase II evaluation of preoperative chemoradiotherapy using IMRT in combination with capecitabine and oxaliplatin for patients with locally advanced rectal cancer, and a developing Phase II follow-up study to RTOG 0529, incorporating cetuximab with standard 5FU and mitomycin-C for anal canal cancer. In these studies, particular attention will be warranted to the patterns of recurrence, to ensure that these CTV consensus panel recommendations, as well as the use of IMRT for the management of anorectal cancers, are appropriate.

## REFERENCES

1. Chen YJ, Liu A, Tsai PT, *et al*. Organ sparing by conformal avoidance intensity-modulated radiation therapy for anal cancer: Dosimetric evaluation of coverage of pelvis and inguinal/femoral nodes. *Int J Radiat Oncol Biol Phys* 2005;63:274–281.
2. Duthoy W, De Gersem W, Vergote K, *et al*. Clinical implementation of intensity-modulated arc therapy (IMAT) for rectal cancer. *Int J Radiat Oncol Biol Phys* 2004;60:794–806.
3. Guerrero Urbano MT, Henrys AJ, Adams EJ, *et al*. Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. *Int J Radiat Oncol Biol Phys* 2006;65:907–916.
4. Kim JY, Kim DY, Kim TH, *et al*. Intensity-modulated radiotherapy with a belly board for rectal cancer. *Int J Colorectal Dis* 2007;22:373–379.
5. Menkarios C, Azria D, Laliberte B, *et al*. Optimal organ-sparing intensity-modulated radiation therapy (IMRT) regimen for the treatment of locally advanced anal canal carcinoma: A comparison of conventional and IMRT plans. *Radiat Oncol* 2007;2:41.
6. Milano MT, Jani AB, Farrey KJ, *et al*. Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: Toxicity and clinical outcome. *Int J Radiat Oncol Biol Phys* 2005;63:354–361.
7. Nuyttens JJ, Robertson JM, Yan D, *et al*. The influence of small bowel motion on both a conventional three-field and intensity modulated radiation therapy (IMRT) for rectal cancer. *Cancer Radiother* 2004;8:297–304.
8. Tho LM, Glegg M, Paterson J, *et al*. Acute small bowel toxicity and preoperative chemoradiotherapy for rectal cancer:

Investigating dose-volume relationships and role for inverse planning. *Int J Radiat Oncol Biol Phys* 2006;66:505–513.
9. Salama JK, Mell LK, Schomas DA, *et al*. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: A multicenter experience. *J Clin Oncol* 2007; 25:4581–4586.
10. Tsai HK, Hong TS, Willins J, *et al*. Early clinical outcome in patients treated for anal canal cancer using dose-painted intensity modulated radiation therapy. American Society of Clinical Oncology Gastrointestinal Cancer Symposium, Orlando, FL, January 2008.
11. RTOG 0529: A Phase II evaluation of dose-painted IMRT in combination with 5-fluorouracil and mitomycin-C for reduction of acute morbidity in carcinoma of the anal canal. http://rtog.org/members/protocols/0529/0529.pdf.
12. Gallagher MJ, Brereton HD, Rostock RA, *et al*. A prospective study of treatment techniques to minimize the volume of pelvic small bowel with reduction of acute and late effects associated with pelvic irradiation. *Int J Radiat Oncol Biol Phys* 1986;12: 1565–1573.
13. Myerson R, Drzymala R. Technical aspects of image-based treatment planning of rectal carcinoma. *Semin Radiat Oncol* 2003;13:433–440.
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; 23:903–921.
15. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: Wiley, J.; 1981.
16. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–174.
17. Nuyttens JJ, Robertson JM, Yan D, *et al*. The variability of the clinical target volume for rectal cancer due to internal organ motion during adjuvant treatment. *Int J Radiat Oncol Biol Phys* 2002;53:497–503.
18. Flam M, John M, Pajak TF, *et al*. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: Results of a phase III randomized intergroup study. *J Clin Oncol* 1996;14: 2527–2539.
19. Ajani JA, Winter KA, Gunderson LL, *et al*. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: A randomized controlled trial. *JAMA* 2008 23;299:1914–1921.
20. John M, Pajak T, Flam M, *et al*. Dose escalation in chemoradiation for anal cancer: Preliminary results of RTOG 92-08. *Cancer J Sci Am* 1996;2:205–211.
21. Martenson JA, Lipsitz SR, Wagner H Jr., *et al*. Initial results of a phase II trial of high dose radiation therapy, 5-fluorouracil, and cisplatin for patients with anal cancer (E4292): An Eastern Cooperative Oncology Group study. *Int J Radiat Oncol Biol Phys* 1996;35:745–749.
22. Baxter NN, Habermann EB, Tepper JE, *et al*. Risk of pelvic fractures in older women following pelvic irradiation. *J Am Med Assoc* 2005;294:2587–2593.
23. Bosset JF, Collette L, Calais G, *et al*. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; 355:1114–1123.
24. Gerard JP, Conroy T, Bonnetain F, *et al*. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3–4 rectal cancers: Results of FFCD 9203. *J Clin Oncol* 2006;24:4620–4625.
25. Sauer R, Becker H, Hohenberger W, *et al*. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731–1740.
26. Mitchell E, Winter K, Mohiuddin M, *et al*. Randomized Phase II Trial of preoperative combined modality chemoradiation for distal rectal cancer. Proceedings of The American Society of Clinical Oncology. Vol 23. New Orleans, LA; 2004. p. 254.
27. Baglan KL, Frazier RC, Yan D, *et al*. The dose-volume relationship of acute small bowel toxicity from concurrent 5-FU-based chemotherapy and radiation therapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2002;52:176–183.
28. Gunnlaugsson A, Kjellen E, Nilsson P, *et al*. Dose-volume relationships between enteritis and irradiated bowel volumes during 5-fluorouracil and oxaliplatin based chemoradiotherapy in locally advanced rectal cancer. *Acta Oncol* 2007;46:937–944.
29. Freedman GM, Meropol NJ, Sigurdson ER, *et al*. Phase I trial of preoperative hypofractionated intensity-modulated radiotherapy with incorporated boost and oral capecitabine in locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2007;67: 1389–1393.
30. Roels S, Duthoy W, Haustermans K, *et al*. Definition and delineation of the clinical target volume for rectal cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1129–1142.