CONSENSUS GUIDELINES FOR THE DELINEATION OF THE CLINICAL TARGET VOLUME FOR INTENSITY MODULATED PELVIC RADIOThERAPY IN THE POSTOPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER

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Abstract

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PURPOSE—To develop an atlas of the clinical target volumes (CTV) definitions for the post-operative radiotherapy of endometrial and cervical cancer to be utilized for planning pelvic Intensity Modulated Radiation Therapy (IMRT).

METHODS AND MATERIALS—The Radiation Therapy Oncology Group (RTOG) led an international collaboration of cooperative groups in development of the atlas. The groups included RTOG the Gynecologic Oncology Group (GOG), the National Cancer Institute of Canada (NCIC), the European Society of Therapeutic Radiology and Oncology (ESTRO), and the American College of Radiology Imaging Network (ACRIN). Members of the group were asked by questionnaire to define areas that were to be included in the CTV and were asked to outline these areas on individual Computed Tomography (CT) images. The initial formulation of the group began in late 2004 and culminated with a formal consensus conference in June of 2005.

RESULTS—The committee achieved a consensus CTV definition for the post-operative therapy of endometrial and cervical cancer. The CTV should include the common, external, and internal iliac lymph node regions. The upper 3.0 cm of vagina and paravaginal soft tissue lateral to the vagina should also be included. For patients with cervical cancer, or endometrial cancer with cervical stromal invasion, it is also recommended that the CTV include the presacral lymph node region.

CONCLUSIONS—This manuscript serves as an international template for the definition of the CTV for the post-operative IMRT of endometrial and cervical cancer.

Keywords
IMRT; Adjuvant Therapy; Pelvic Radiotherapy; Endometrial Cancer; Cervical Cancer

INTRODUCTION

Intensity modulated radiation therapy (IMRT) enables the delivery of complex radiotherapy treatment plans that previously could not be accomplished with conventional techniques, including the most sophisticated 3-D conformal radiation therapy (3-D CRT). Conventional 3D-CRT is accomplished with a set of fixed radiation beams, which are shaped using the projection of the target volume and normally have a uniform intensity across the field. When appropriate, conventional fields can be modified by simple devices such as compensating filters or wedges. IMRT delivers optimized nonuniform radiation beam intensities to deliver highly conformal therapies, especially to targets that have complex shapes and/or concave regions.

The advantage IMRT has over 3-D CRT is also the greatest challenge facing the radiation oncology community – that is – defining the targets that need to be irradiated to accomplish the goals of therapy. This is particularly challenging in whole pelvic radiotherapy for gynecological malignancies. Traditional conformal post-operative radiotherapy has delivered radiotherapy in a “four-field box” technique. The AP/PA portions of the field’s lateral extents tend to be defined by the boney pelvis. The lateral fields often include the pre-sacral space posteriorly, especially in cervical cancer; anteriorly the field is defined by the external iliac lymph nodes. This traditional treatment volume has provided excellent tumor control with what is traditionally considered acceptable toxicity. However, these techniques based on generic boney landmarks as surrogates for clinical target volume (CTV) do not lend themselves to customized treatment planning based on individual patient’s CTV resulting in substantial irradiation of normal organs such as small bowel, rectum and bone marrow.

IMRT provides the ability to confine the high-dose portions of the radiotherapy fields to non-traditional shapes. It is generally considered that the CTV to be irradiated post-operatively for endometrial cancer and cervical cancer include the draining lymphatics, parametrium and upper vagina. The middle of the pelvis, in the postoperative situation, is often occupied by
relatively radio-sensitive small intestine. In addition, rectum and bone marrow are not felt to be at risk for recurrence and hence unnecessary to irradiate. Utilizing IMRT has been shown to reduce normal tissue irradiation (1–6) and has been associated with reduced acute (7–8) and chronic (9) toxicity compared to conventional 3-D CRT.

Critical to IMRT being a standard treatment option for the post-operative therapy for endometrial and cervical cancer is a clear understanding of the clinical target volume (CTV) definitions. In preparation for a prospective clinical trial (RTOG 0418), the Radiation Therapy Oncology Group (RTOG) led an international collaboration to define an atlas of target definitions for post-operative pelvic radiotherapy for endometrial and cervical cancers. This manuscript provides the conclusions of this collaboration.

**METHODS AND MATERIALS**

RTOG elected to proceed with a prospective trial evaluating the role of IMRT in the post-operative radiotherapy of endometrial and cervical cancer (RTOG 0418). The primary objective of the trial is to determine the transportability of IMRT to a multi-institutional setting. Secondary objectives include toxicity and disease control endpoints. In preparation for the activation of the trial, it was felt an atlas would improve the ability to obtain the trial’s primary objective. The RTOG gynecologic working group felt that to be successful the atlas would need to be a consensus document with inclusion of multiple national and international cooperative groups.

The groups that were included in the atlas development included RTOG (WS, LM, JD, DG, KW, AM), the Gynecologic Oncology Group (PA, MV), the National Cancer Institute of Canada (LP), the European Society of Therapeutic Radiology and Oncology (CC), and the American College of Radiology Imaging Network (RI). The representatives of the groups were asked to obtain formal endorsement of the final atlas prior to publication.

The initial formulation of the group began in late 2004. The final representatives were formalized early in 2005. Over the ensuing months multiple informal discussions were held both by e-mail and phone. Ultimately a sample set of CT images were distributed to the members of the group along with a questionnaire. The questionnaire asked which sites should be considered target volumes for post-operative therapy and members of the group were asked to contour the CTV for postoperative therapy of endometrial and cervical cancer on each individual CT image. A formal consensus conference was sponsored by RTOG and held in Philadelphia on June 23rd, 2005. Members reviewed the sites and the contoured CTV data. Atlases of pelvic anatomy (10), pelvic surgery textbooks (11), surgical atlases (12), pelvic imaging textbooks (13–15), published pelvic IMRT experience (1–9,16–20), imaging studies (21–27) and experience were utilized for this purpose. At this meeting a general consensus regarding volumes was obtained. Over the ensuing months the chairs of the guideline (WS, AM) worked out the remaining inconsistencies and presented the group with a final product. This CTV guidelines atlas was approved and formally placed on the RTOG website on 2/17/06 (29). RTOG 0418 was activated on 3/20/06.

In order to allow for feedback and address any problems during the initiation of the RTOG 0418 protocol, formal publication of this atlas would await the first amendment to the protocol in case of changes needed in the atlas. Amendment one occurred on 9/20/06 without a need for change in the current atlas.

**RESULTS**

The committee achieved a consensus CTV definition. The CTV should include the common, external, and internal iliac lymph node regions (Table 1). The upper 3.0 cm of vagina and
paravaginal soft tissue lateral to the vagina should also be included. For patients with cervical cancer, or endometrial cancer with cervical stromal invasion, it is also recommended that the CTV include the presacral lymph node-region. There are specific recommendations noted below for a bladder integrated target volume (ITV) to take into account bladder filling variations on a day to day basis. There was no consensus opinion regarding the variation in rectal filling other than if the planning CT scan notes excessive rectal distention there should be a consideration for repeat treatment planning.

The superior border of the CTV should begin 7 mm below the L4–L5 interspace. A uniform, 3-dimensional PTV expansion (typically 7 mm) will mimic a block edge at the L4–L5 interspace, as would customarily be used in a conventional 4-field box. The inferior border should extend to 3.0 cm below the upper extent of the vagina (defined by the vaginal marker), or to 1.0 cm above the inferior extent of the obturator foramen, whichever is lower, to mimic a lower block edge. A more detailed description of the CTV design follows and is depicted in Figures 1–8.

Superior CTV (above the bifurcation of the common iliac vessels)

The superior portion of the CTV should be defined initially by adding a 7 mm margin around the common iliac vessels seen on the axial CT slice (Figure 1). The CTV should be extended to include adjacent visible or suspicious lymph nodes, lymphoceles, and pertinent surgical clips. The CTV should also include a minimum of 1.5 cm of soft tissue anterior to the vertebral body at the midline. The CTV should be modified to exclude the vertebral body, psoas muscle, and bowel.

If the presacral lymph nodes will not be treated, the CTV should be split, following the path of the common iliac vessels, starting 1.5 to 2.0 cm below the aortic bifurcation (Figure 2). If the presacral lymph nodes are included, the CTV should not be split, and at the midline a 1.5 cm margin between the anterior border of the CTV and the anterior border of the vertebral body or sacrum should be maintained. The CTV should not be extended into the sacral foramina (Figure 3).

Middle CTV (from the bifurcation of the common iliac vessels to the vaginal cuff)

As the CTV progresses inferiorly, a 7 mm margin around the internal and external iliac vessels should be maintained, excluding bone, bowel, or muscle. Suspicious lymph nodes, lymphoceles, and pertinent surgical clips should continue to be included in the CTV. In patients where the presacral nodal region is not part of the CTV, the CTV will be disjoint at this level (Figure 4). In patients requiring presacral lymph node irradiation, the presacral lymph node coverage should discontinue when the piriformis muscle is clearly visualized (approximately the inferior border of S2). The CTV should be disconnected into two volumes at this level, and the CTV should include a 7 mm margin around the internal and external iliac vessels, with exclusion of the piriformis muscle (Figure 5).

Inferior CTV (below and including the vaginal cuff)

The inferior extent of the vaginal cuff may be identified by a vaginal marker. Vaginal cuff tissue frequently extends superior to the vaginal marker, however, and this tissue should be included in the CTV. The volume of tissue to be included above the vaginal marker will depend on the location of adjacent small bowel (that will not be considered CTV) and the amount of soft tissue present. Generally, the tissue to be included above the vaginal marker ranges from 0.5 – 2 cm. The rectum, bladder, bone, and muscle should be excluded from the CTV. When the vaginal cuff becomes visible, this volume may be conjoined with the two converging perivascular (“nodal”) volumes to make a single CTV volume (Figure 6). At this level the internal iliac vessels may become poorly visualized. In this case, the CTV should be bounded...
posteriorly by the piriformis muscle, even if the CTV extends more than 7 mm beyond visible vasculature. The vaginal/parametrial CTV should be outlined on a CT scan that is obtained with a full and empty bladder. These volumes should then be merged to form an integrated target volume (ITV) accounting for the movement of the vagina. The ITV will be used for treatment planning to account for the daily variation in the location of the vaginal cuff related to variation in the daily bladder filling.

At the superior border of the femoral heads, the nodal volume should be discontinued, and the CTV should include the vagina and parametrial tissue with a generous (approximately 0.5 cm) margin, which may extend into the perivesicular or perirectal fat (Figure 7). The bladder and rectum should be excluded from the CTV, however, the CTV may overlap these structures to maintain a 1.5 cm distance between the anterior and posterior borders of the CTV at the midline. The CTV should end 3.0 cm below the vaginal marker, or 1.0 cm above the bottom of the obturator foramen, whichever is most inferior (Figure 8).

**DISCUSSION**

The use of IMRT in the treatment of gynecologic malignancies has increased significantly in recent years (29). Interest in the application of IMRT to gynecologic cancer is increasingly supported by retrospective analyses reporting favorable rates of toxicity (7–9,16–18) compared to conventional techniques. Moreover, the use of IMRT has not apparently compromised target coverage or therapeutic results, as outcome data from several institutional series have been favorable (7,9,16–20). These studies indicate significant potential for IMRT to alter the therapeutic ratio of RT in gynecologic cancer. However, prospective multi-institutional studies of IMRT are only now underway, and, to date, no randomized comparisons of IMRT to conventional techniques in gynecological cancers have been performed.

Standardization of target volume definition provides an important basis for both the prospective study of IMRT in gynecologic cancer in the multi-institutional setting and the formation of treatment guidelines for the radiation oncology community. The guidelines established in this report apply only to the post-operative setting for cervical and endometrial cancer and represent the consensus of a panel with expertise and interest in gynecologic IMRT. Target recommendations have been based on both knowledge of patterns of disease spread and recurrence, and imaging studies identifying typical anatomic distributions of areas at risk for harboring subclinical disease [21–27]. These recommendations are intended to be guidelines and the treating physician should be cognizant of anatomic variations and is responsible for taking into consideration the clinico-pathologic, imaging and surgical information for individualized treatment planning.

Taylor et al. used magnetic resonance imaging (MRI) with intravenous injection of iron oxide particles to identify the location of pelvic lymph nodes in 20 patients with gynecologic tumors [23]. A margin of 7 mm around the vessels encompassed greater than 95% of common iliac, internal iliac, medial and anterior external iliac, and obturator lymph node contours. Presacral and lateral external iliac lymph node regions, however, were not adequately covered with a 7 mm uniform margin. The authors advocated a modified 7 mm margin as a surrogate target for lymph nodes in pelvic IMRT planning. Chao et al. advocated larger margins of approximately 15–20 mm, with certain modifications, based on findings from CT lymphangiograms (LAG) in 16 patients with cervical cancer [21]. Larger margins were required in this study to encompass 100% of the lymph nodes identified by LAG; however, MRI is better able to identify small lymph nodes, and LAG may overestimate lymph node size [23], thus smaller margins more consistent with findings from Taylor et al. have been advocated in the current study.
Three retrospective studies have compared toxicity of IMRT versus conventional techniques in gynecologic patients [7–9]. Mundt et al. reported reductions in both acute [7] and chronic [9] GI toxicity with IMRT compared to a 4-field box technique. Benefits of IMRT were seen primarily in reduction of low grade (1–2) toxicity. GU toxicity was not significantly lower with IMRT. Brixey et al. reported lower rates of acute leukopenia and neutropenia, and improved chemotherapy delivery, in gynecologic patients treated with IMRT compared to 4-field box [8]. These results and multiple dosimetric planning studies indicate significant potential advantages to IMRT, but studies reporting long-term outcomes remain limited.

Some concerns have been raised about the widespread application of IMRT [30]. Due to the presence of steep dose gradients and longer treatment times with IMRT, concerns remain about possible inferior tumor control. The absence of prospective comparisons of IMRT to conventional techniques also makes the clinical significance and cost-efficiency of IMRT uncertain. Finally, an approximate doubling of the risk of second malignancies with IMRT compared to conventional techniques has been hypothesized [31], due to increased total body dose from leakage radiation and the increased volume of tissue exposed to low dose radiation.

Organ motion and patient setup uncertainty are important considerations with conformal planning in gynecologic patients. Although no consensus planning margins for 3-D and IMRT treatment have been created, a 1.0–1.5 cm (or institution-specific) uniform CTV expansion is commonly advocated. Image guided radiation therapy (IGRT) is receiving attention as a means to reduce setup uncertainty and account for inter-fraction organ motion [32]. IGRT could reduce the required PTV margins, permitting more normal tissue sparing, and obviate the need for an ITV, by allowing daily imaging of bladder and rectal filling.

Future advancements in IMRT include extending its application to the definitive setting (i.e., patients with an intact uterus) and to extended field (para-aortic) [17,18] or pelvic-inguinal RT [33]. IMRT has also been investigated for bone marrow sparing approaches treatment technique and is an area for future investigation.

CONCLUSIONS

IMRT is a promising development in radiotherapy with a significant body of literature supporting its utility in gynecologic and other cancers. Further careful study of this technique is warranted. These consensus guidelines standardize an important aspect of IMRT planning for the postoperative treatment of cervical and endometrial cancer. It is imperative that new technology be investigated as carefully as any new therapy in oncology. The results of the currently active RTOG trial are eagerly awaited. Particular attention will need to be given to patterns of recurrence to assure these CTV guidelines are appropriate.

References


Figure 1.
Upper Common Iliac CTV
Figure 2.
Mid Common Iliac (red) and Pre-sacral CTV (blue)
Figure 3.
Lower Common Iliac (red) and Pre-sacral CTV (blue)
Figure 4.
Upper External and Internal Iliac (red) and Pre-Sacral CTV (blue)
Figure 5.
External and Internal Iliac CTV
Figure 6.
External and Internal Iliac (red) and Parametrial/Vaginal (green) CTV
Figure 7.
Parametrial/Vaginal CTV
Figure 8.
Vaginal CTV
TABLE 1
Consensus Clinical Target Volume (CTV) for Adjuvant (Post-operative) Radiotherapy for Cervical and Endometrial Cancer

<table>
<thead>
<tr>
<th>Target Site</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common iliac lymph nodes</td>
<td>From 7mm below the L4/L5 interspace to the level of the bifurcation of the common iliac arteries into the external and internal iliac arteries.</td>
</tr>
<tr>
<td>External iliac lymph nodes</td>
<td>From the level of the bifurcation of the common iliac artery into the external artery to the level of the superior aspect of the femoral head where it becomes the femoral artery.</td>
</tr>
<tr>
<td>Internal iliac lymph nodes</td>
<td>From the level of the bifurcation of the common iliac artery into the internal artery, along its branches (obturator, hypogastric) terminating in the paravaginal tissues at the level of the vaginal cuff.</td>
</tr>
<tr>
<td>Upper vagina</td>
<td>Vaginal cuff and 3 cm of vagina inferior to the cuff.</td>
</tr>
<tr>
<td>Parametrial/Paravaginal tissue</td>
<td>From the vaginal cuff to the medial edge of the internal obturator muscle/ischial ramus on each side.</td>
</tr>
<tr>
<td>Presacral lymph nodes *</td>
<td>Lymph node region anterior to S1 and S2 region.</td>
</tr>
</tbody>
</table>

* If patient has cervical cancer or endometrial cancer with cervical stromal invasion