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CLINICAL INVESTIGATION **Uterus**

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

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Purpose: To develop an atlas of the clinical target volume (CTV) definitions for postoperative radiotherapy of endometrial and cervical cancer to be used for planning pelvic intensity-modulated radiotherapy.

Methods and Materials: The Radiation Therapy Oncology Group led an international collaberation of cooperative groups in the development of the atlas. The groups included the Radiation Therapy Oncology Group, Gynecologic Oncology Group, National Cancer Institute of Canada, European Society of Therapeutic Radiology and Oncology, and American College of Radiology Imaging Network. The members of the group were asked by questionnaire to define the areas that were to be included in the CTV and to outline theses areas on individual computed tomography images. The initial formulation of the group began in late 2004 and culminated with a formal consensus conference in June 2005.

Results: The committee achieved a consensus CTV definition for postoperative therapy for endometrial and cervical cancer. The CTV should include the common, external, and internal iliac lymph node regions. The upper 3.0 cm of the 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.

Conclusion: This report serves as an international template for the definition of the CTV for postoperative intensity-modulated radiotherapy for endometrial and cervical cancer.

Intensity-modulated radiotherapy, Adjuvant therapy, Pelvic radiotherapy, Endometrial cancer, Cervical cancer.

INTRODUCTION

Intensity-modulated radiotherapy (IMRT) enables the delivery of complex RT plans that previously could not be accomplished with conventional techniques, including the most sophisticated three-dimensional (3D) conformal RT (3D-CRT). Conventional 3D-CRT is accomplished with a set of fixed radiation beams that 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 3D-CRT is also the greatest challenge facing the radiation oncology community—that is,

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defining the targets that need to be irradiated to accomplish the goals of therapy. This is particularly challenging in whole pelvic RT for gynecologic malignancies. Traditional conformal postoperative RT has delivered RT in a ''four-field box'' technique. The anteroposterior–posteroanterior portions of the field's lateral extents tend to be defined by the bony pelvis. The lateral fields often include the presacral 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 bony landmarks as surrogates for the clinical target volume (CTV), do not lend themselves to customized treatment planning using an individual patient's CTV and results in substantial irradiation of normal organs such as the small bowel, rectum, and bone marrow.

The use of IMRT provides the ability to confine the high-dose portions of the radiation fields to nontraditional shapes. It is generally considered that the CTV to be irradiated postoperatively for endometrial cancer and cervical cancer includes the draining lymphatics, parametrium, and upper vagina. The middle of the pelvis, in the postoperative situation, is often occupied by relatively radiosensitive small intestine. In addition, the rectum and bone marrow are not thought to be at risk of recurrence and hence are unnecessary to irradiate. 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 with conventional 3D-CRT.

Critical to the use of IMRT as a standard option for postoperative therapy for endometrial and cervical cancer is a clear understanding of the CTV definitions. In preparation for a prospective clinical trial (Radiation Therapy Oncology Group [RTOG] trial 0418), the RTOG led an international collaboration to define an atlas of target definitions for postoperative pelvic RT for endometrial and cervical cancer. This report provides the conclusions of this collaboration.

METHODS AND MATERIALS

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

The groups included in the atlas development were the RTOG (W.S., L.M., J.D., D.G., K.W., and A.M.), Gynecologic Oncology Group (P.A., M.V.), National Cancer Institute of Canada (L.P.), European Society of Therapeutic Radiology and Oncology (C.C.), and the American College of Radiology Imaging Network (R.I.). The representatives of the groups were asked to obtain formal endorsement of the final atlas before publication.

The initial formulation of the group began in late 2004. The final representatives were formalized early in 2005. During the ensuing months, multiple informal discussions were held by both electronic mail and telephone. Ultimately, a sample set of computed tomography (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 postoperative therapy, and the members of the group were asked to contour the CTV for postoperative therapy for endometrial and cervical cancer on each individual CT image. A formal consensus conference was sponsored by the RTOG and held in Philadelphia June 23, 2005. The 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 (21–28), and experience were used for this purpose. At this meeting, a general consensus regarding the CTVs was obtained. During the ensuing months, the chairs of the guideline (W.S., A.M.) worked out the remaining inconsistencies and presented the group with a final product. This CTV guideline atlas was approved and formally placed on the RTOG Website February 17, 2006 (29). The RTOG 0418 trial was activated March 20, 2006.

To allow for feedback and address any problems during the initiation of the RTOG 0418 protocol, formal publication of this atlas awaited the first amendment to the protocol in case of changes needed in the atlas. Amendment 1 occurred on September 20, 2006 without the need for any changes 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 the 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 was also recommended that the CTV include the presacral lymph node region. Specific recommendations have been given for a bladder integrated target volume (ITV) to take into account bladder filling variations on a day-to-day basis [see ''Inferior CTV (below and including vaginal cuff)'' below]. No consensus opinion was reached regarding the variation in rectal filling other than if excessive rectal distension was observed on the planning CT scan, repeat treatment planning should be considered. The superior border of the CTV should begin 7 mm below the L4–L5 interspace. A uniform, 3D planning target volume expansion (typically 7 mm) will mimic a block edge at the L4–L5 interspace, such as would customarily be used in a conventional four-field box. The inferior border should extend to 3.0 cm below the upper extent of the vagina (as 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 (see also Figs. 1–8).

Superior CTV (above bifurcation of 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 (Fig. 1). The CTV should be

Table 1. Consensus clinical target volume for adjuvant (postoperative) radiotherapy for cervical and endometrial cancer

Target site	Definition
Common iliac lymph nodes	From 7 mm below L4–L5 interspace to level of bifurcation of common iliac arteries into external and internal iliac arteries
External iliac lymph nodes	From level of bifurcation of common iliac artery into external artery to level of superior aspect of femoral head where it becomes femoral artery
Internal iliac lymph nodes	From level of bifurcation of common iliac artery into internal artery, along its branches (obturator, hypogastric) terminating in paravaginal tissues at level of vaginal cuff
Upper vagina	Vaginal cuff and 3 cm of vagina inferior to cuff
Parametrial/paravaginal tissue	From vaginal cuff to medial edge of internal obturator muscle/ischial ramus on each side
Presacral lymph nodes*	Lymph node region anterior to S1and S2 region

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

extended to include any 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 to follow the path of the common iliac vessels, starting 1.5–2.0 cm below the aortic bifurcation (Fig. 2). If the presacral lymph nodes will be treated, 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 (Fig. 3).

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

As the CTV progresses inferiorly, a 7-mm margin around the internal and external iliac vessels should be maintained, excluding bone, bowel, and/or muscle. Suspicious lymph nodes, lymphoceles, and pertinent surgical clips should continue to be included in the CTV. In patients in whom the presacral nodal region is not part of the CTV, the CTV will be disjointed at this level (Fig. 4). In patients requiring presacral lymph node RT, the presacral lymph node coverage should discontinue when the piriformis muscle is clearly visualized (approximately at 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 (Fig. 5).

Inferior CTV (below and including vaginal cuff)

The inferior extent of the vaginal cuff can be identified by a vaginal marker. However, the vaginal cuff tissue frequently extends superior to the vaginal marker, and this tissue should be included in the CTV. The tissue volume to be included above the vaginal marker will depend on the location of any adjacent small bowel (that will not be considered a part of the CTV) and the amount of soft tissue present. Generally, the tissue to be included above the vaginal marker is 0.5–2 cm. The rectum, bladder, bone, and muscle should be excluded from the CTV. When the vaginal cuff becomes visible, this volume can be conjoined with the two converging perivascular (''nodal'') volumes to make a single CTV (Fig. 6). At this level, the internal iliac vessels might become poorly visualized. In this case, the CTV should be bounded posteriorly by the piriformis muscle, even if the CTV extends

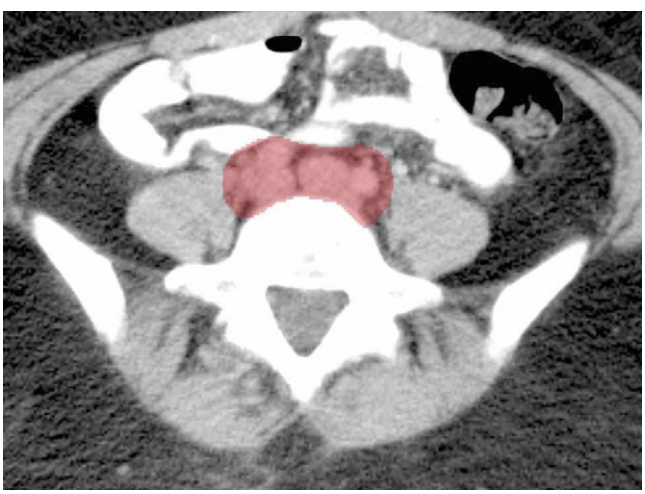

Fig. 1. Upper common iliac clinical target volume.

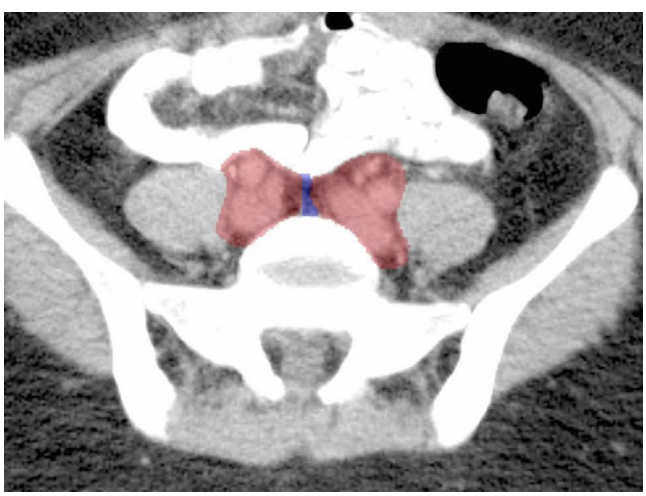

Fig. 2. Mid-common iliac (red) and presacral clinical target volume (blue).

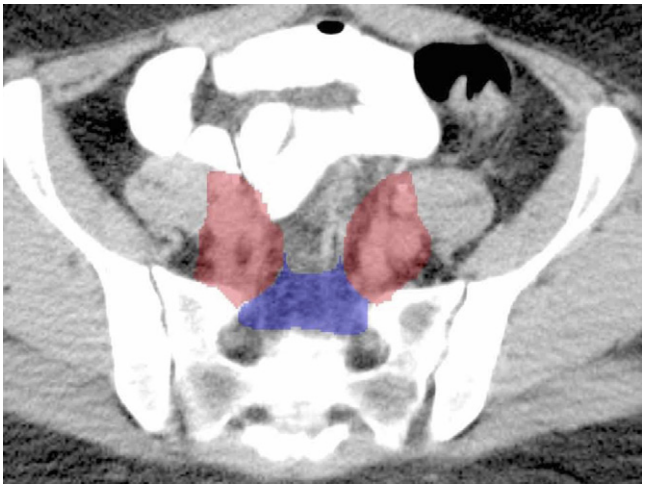

Fig. 3. Lower common iliac (red) and presacral clinical target volume (blue).

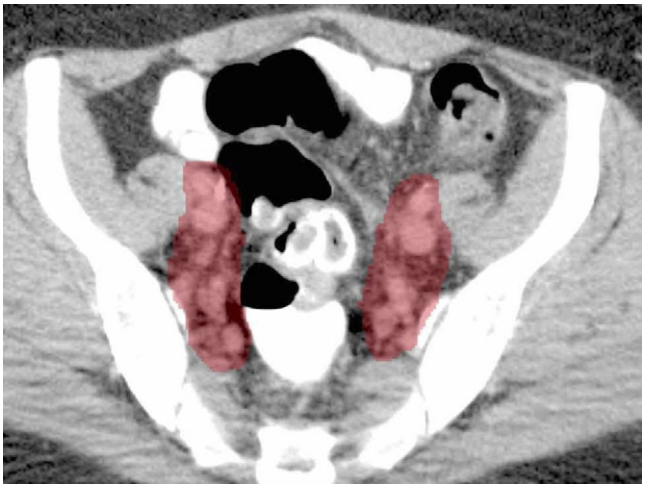

Fig. 5. External and internal iliac clinical target volume.

more than 7 mm beyond visible vasculature. The vaginal/parametrial CTV should be outlined on a CT scan that was obtained with a full and empty bladder. These volumes should then be merged to form an ITV that accounts 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 in relation to the variations in 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 that can extend into the perivesicular or perirectal fat (Fig. 7). The bladder and rectum should be excluded from the CTV; however, the CTV can 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 (Fig. 8).

DISCUSSION

The use of IMRT for gynecologic malignancies has increased significantly in recent years (29). Interest in the application of IMRT for gynecologic cancer has been increasingly supported by retrospective analyses reporting favorable toxicity rates (7–9, 16–18) compared with conventional techniques. Moreover, the use of IMRT has not apparently compromised target coverage or the therapeutic results, because outcome data from several institutional series have been favorable (7, 9, 16–20). These studies have indicated 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 and conventional techniques in gynecologic cancers have been performed.

The standardization of the target volume definition provides an important basis for both the prospective study of IMRT for gynecologic cancer in the multi-institutional setting and the formation of treatment guidelines for the

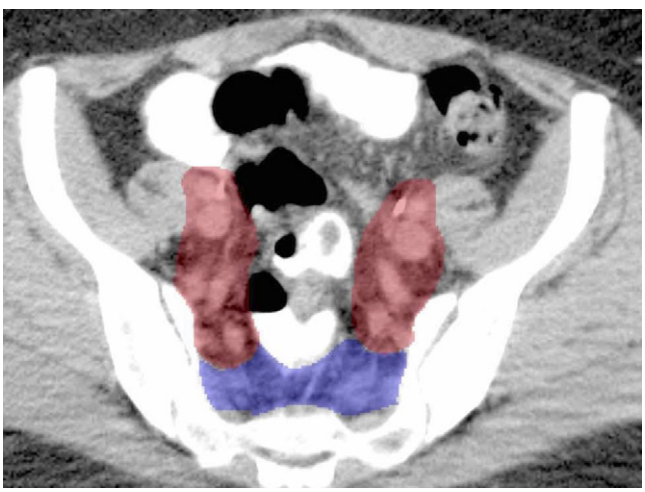

Fig. 4. Upper external and internal iliac (red) and presacral clinical target volume (blue).

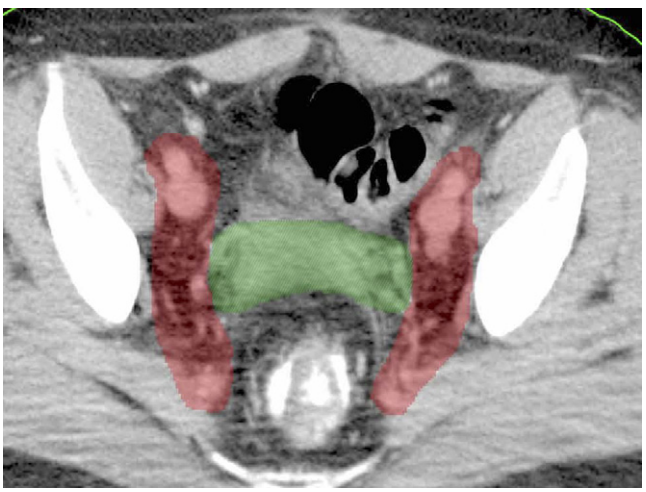

Fig. 6. External and internal iliac (red) and parametrial/vaginal (green) clinical target volume.

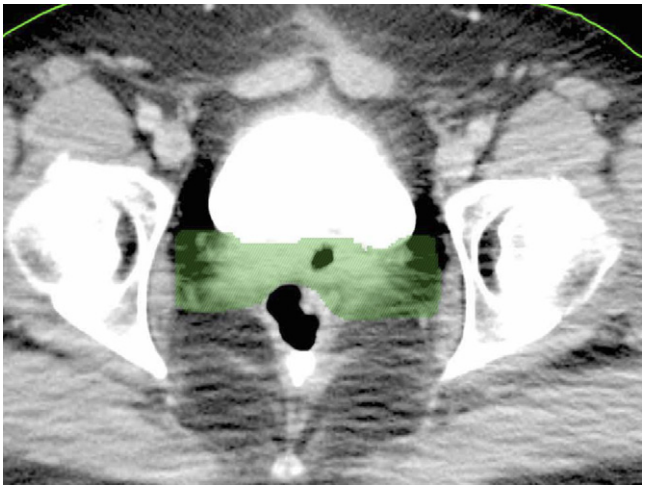

Fig. 7. Parametrial/vaginal clinical target volume.

radiation oncology community. The guidelines established in this report apply only to the postoperative setting for cervical and endometrial cancer and represent the consensus of a panel with expertise and interest in gynecologic IMRT. The target recommendations were determined from both a knowledge of the patterns of disease spread and recurrence and the findings from imaging studies identifying typical anatomic distributions of areas at risk of harboring subclinical disease (21–27). These recommendations are intended to be guidelines, and the treating physician should be cognizant of the anatomic variations and is responsible for taking into consideration the clinicopathologic, imaging, and surgical information for individualized treatment planning.

Taylor *et al*. (23) used magnetic resonance imaging with intravenous injection of iron oxide particles to identify the location of pelvic lymph nodes in 20 patients with gynecologic tumors. A 7-mm margin around the vessels encompassed >95% of the common iliac, internal iliac, medial and anterior external iliac, and obturator lymph node contours. The presacral and lateral external iliac lymph node regions, however, were not adequately covered by the 7-mm uniform margin. The investigators advocated a modified 7-mm margin as a surrogate target for lymph nodes in pelvic IMRT planning. Chao and Lin (21) advocated larger margins of approximately 15–20 mm, with certain modifications, as determined from the findings from CT lymphangiography in 16 patients with cervical cancer. Larger margins were required in their study to encompass 100% of the lymph nodes identified by lymphangiography; however, magnetic resonance imaging is better able to identify small lymph nodes, and lymphangiography might overestimate the lymph node size (23); thus, smaller margins more consistent with the findings from Taylor *et al*. (23) were advocated in the present study.

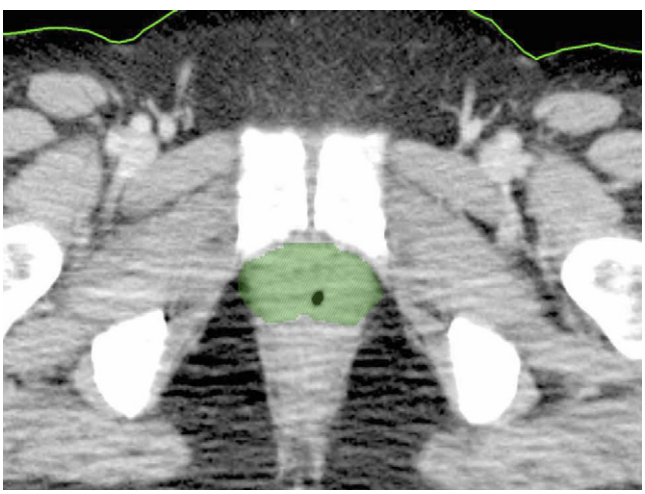

Fig. 8. Vaginal clinical target volume.

Three retrospective studies compared the toxicity of IMRT and that of conventional techniques in gynecologic cancer patients (7–9). Mundt *et al*. (7, 9) reported reductions in both acute and chronic gastrointestinal toxicity with IMRT compared with a four-field box technique. The benefits of IMRT were seen primarily in the reduction of low-grade (Grade 1-2) toxicity. Genitourinary toxicity was not significantly lower with IMRT. Brixey *et al*. (8) reported lower rates of acute leukopenia and neutropenia, and improved chemotherapy delivery, in gynecologic cancer patients treated with IMRT compared with those treated with a four-field box technique. These results and those from multiple dosimetric planning studies have indicated the 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). Because of 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 and conventional techniques also makes the clinical significance and cost-efficacy of IMRT uncertain. Finally, an approximate doubling of the risk of second malignancies with IMRT compared with conventional techniques, due to an increased total body dose from radiation leakage and the increased volume of tissue exposed to low-dose radiation, has been hypothesized (31).

Organ motion and patient setup uncertainty are important considerations with conformal planning in gynecologic cancer patients. Although no consensus planning margins for 3D-CRT and IMRT have been created, a 1.0–1.5 cm (or institution-specific) uniform CTV expansion has been commonly advocated. Image-guided RT is receiving attention as a method to reduce setup uncertainty and account for interfraction organ motion (32). Image-guided RT could reduce the required planning target volume 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) RT (17, 18) or pelvic-inguinal RT (33). IMRT has also been investigated for bone

marrow-sparing approaches (2, 34, 35). Intensity-modulated proton therapy is another potentially valuable conformal treatment technique and is an area for future investigation.

CONCLUSION

Intensity-modulated RT is a promising development in RT, with a significant body of published data supporting its utility for gynecologic and other cancers. Additional careful study of this technique is warranted. The consensus guidelines presented in this report have standardized an important aspect of IMRT planning for 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 ensure that these CTV guidelines are appropriate.

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