INTENSITY-MODULATED WHOLE PELVIC RADIATION THERAPY IN PATIENTS WITH GYNECOLOGIC MALIGNANCIES

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Purpose: To evaluate the ability of intensity-modulated radiation therapy (IMRT) to reduce the volume of small bowel irradiated in women with gynecologic malignancies receiving whole pelvic radiotherapy (WPRT).

Methods and Materials: Ten women with cervical (5) or endometrial (5) cancer undergoing WPRT were selected for this analysis. A planning CT scan of each patient was obtained following administration of oral, i.v., and rectal contrast. The clinical target volume (CTV) was defined as the proximal vagina, parametrial tissues, uterus (if present), and regional lymph nodes. The CTV was expanded uniformly by 1 cm in all directions to produce a planning target volume (PTV). The bladder, rectum, and small bowel were also delineated in each patient. Two plans were created: a standard “4-field box” with apertures shaped to the PTV in each beam’s eye view and an IM-WPRT plan designed to conform to the PTV while minimizing the volume of normal tissues irradiated. Both plans were normalized to deliver 45 Gy to the PTV. Isodose distributions and dose–volume histograms (DVH) were compared.

Results: The IM-WPRT plan reduced the volume of small bowel irradiated in all 10 patients at doses above 30 Gy. At the prescription dose, the average volume of small bowel irradiated was reduced by a factor of two (17.4 vs. 33.8%, \( p = 0.0005 \)). In addition, the average volume of rectum and bladder irradiated at the prescription dose was reduced by 23% in both cases (\( p = 0.0002 \) and \( p = 0.0005 \), respectively). The average PTV doses delivered by the conventional and IM-WPRT plans were 47.8 Gy and 47.4 Gy, respectively. Corresponding maximum doses were 50.0 Gy and 54.8 Gy, respectively. However, on average, only 3.2% of the PTV received greater than 50.0 Gy in the IM-WPRT plans.

Conclusion: Our results suggest that IM-WPRT is an effective means of reducing the volume of small bowel irradiated in women with gynecologic malignancies receiving WPRT. This approach potentially offers a method for reducing small bowel complications in patients with gynecologic malignancies. © 2000 Elsevier Science Inc.

Gynecology, Whole pelvic radiation therapy, Inverse planning, Intensity modulation.

INTRODUCTION

Whole pelvic radiation therapy (WPRT) is commonly used in the treatment of many gynecologic malignancies, particularly cervical and endometrial carcinomas. In addition to the treatment of the primary site, WPRT is used to sterilize metastatic disease in the pelvic lymph nodes. Treatment of these nodes, however, entails irradiation of a considerable volume of small bowel. Unsurprisingly, small bowel sequelae are among the most important acute and chronic toxicities in these patients (1, 2). Sequelae include small bowel obstruction, enteritis, and diarrhea. However, more subtle problems including malabsorption of vitamin B12, bile acids and lactose have been reported following small bowel irradiation (3–6).

The incidence and severity of small bowel sequelae in women undergoing WPRT can be reduced by a variety of means. The benefits of multiple fields, high energy beams, customized blocking and low daily fraction sizes are well known (2). Various agents have also been proposed as possible radioprotectors of the small bowel (7–13). Since it is a mobile structure, mechanical means have been used to displace the small bowel from the pelvis during treatment (14–17). However, such methods are often cumbersome (on both patients and staff) and may be difficult to reproduce.

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Surgical approaches to hold the small bowel in the upper abdomen out of the treatment field include absorbable meshes (18–21), tissue expanders (22–24), and omentoplasty (25). While feasible in patients undergoing surgery, such approaches are not applicable to women undergoing definitive or preoperative RT. Moreover, such approaches have a small but finite risk of small bowel injury (23, 26).

An approach that has received little attention in these patients is intensity-modulated radiation therapy (IMRT). Unlike conventional approaches, IMRT utilizes treatment beams of varying intensity allowing the high-dose region to be conformed to the shape of the target volume. IMRT has been shown to be a promising approach in other disease sites. In prostate cancer, it has been used to minimize the volume of bladder and rectum irradiated (27). IMRT has reduced the dose to the parotid glands in head and neck cancer patients undergoing RT (28). Promising results have also been published in tumors of the lung, central nervous system, and breast (29–31). Given this background, we postulated that IMRT may prove a useful tool in the treatment of patients undergoing WPRT. The purpose of this study is to evaluate the ability of IMRT to reduce the volume of small bowel irradiated in women with gynecologic malignancies undergoing WPRT.

**METHODS AND MATERIALS**

**Patient population**

Ten consecutive women with cervical (5) or endometrial (5) carcinoma undergoing WPRT were prospectively selected. The cervical cancer patients had Stage IB–IIB disease and were receiving WPRT before intracavitary brachytherapy. The endometrial cancer patients had Stage IC–IIB disease and were treated postoperatively. The prescribed WPRT dose in all patients was 45 Gy in 1.8-Gy daily fractions.

**Simulation**

To minimize setup variability, a custom immobilization device (Alpha Cradle, Smithers Medical Product, Inc., North Canton, OH) was fabricated with each patient in the supine position. A computed tomography (CT) scan of each patient in the treatment position was then obtained using our departmental scanner (PQ5000, Marconi Medical Systems, Cleveland, OH). The scan parameters consisted of a large field-of-view pelvic protocol with a 4-mm slice thickness/table index. The CT scans were obtained from the L2 vertebral body to 5-cm below the ischial tuberosities with an average of 80 images per patient. Oral, i.v., and rectal contrast were administered to all patients before the CT scan.

**Target definition**

Following the ICRU 50 recommendations (32), a clinical target volume (CTV) was contoured on individual axial CT slices in all patients. The CTV included the upper one-half of the vagina and parametrial tissues. In women with an intact uterus, the entire uterus was included. Contrast-enhanced vessels plus a 2-cm margin were used to define the common, external, and internal iliac nodal regions to the level of the L4–5 interspace. The presacral region was included to the bottom of the S3 vertebral body to ensure coverage of the presacral lymph nodes and attachment of the uterosacral ligament. A volume-rendered image of the CTV for a typical patient is shown in Fig. 1. The CTV was expanded uniformly by 1 cm in all directions to produce a planning target volume (PTV). This margin is traditionally used in conventional WPRT and was applied to IM-WPRT for comparison purposes.

The rectum and bladder were also contoured for each patient. The rectum was defined from the level of the sacral promontory to the ischial tuberosities. The peritoneal cavity (excluding the rectum and bladder) from the level of L4–5 was used to define the small bowel region (SBR). The individual loops of small bowel were not separately contoured.

**Conventional treatment planning**

Conventional WPRT plans were generated using our three-dimensional treatment-planning system (PLanUNC) (33). The isocenter was placed at the geometric center of the PTV. A 4-field “box” plan was designed using 18-MV photons with apertures shaped to the PTV in each beam’s-eye-view. The fields consisted of anterior, posterior, right, and left lateral beam directions. Field sizes were adjusted to ensure coverage of the PTV with a 1-cm margin in all directions to account for beam penumbra. Weights of the individual fields were optimized to maximize dose uniformity in the PTV, and wedges were used as needed. All plans were normalized to cover 98% of the PTV with 45 Gy. The 2% underdose represents those voxels at the periphery. This
normalization provided conformal coverage while minimizing dose nonuniformity within the target. Dose–volume histograms (DVHs) were calculated for the PTV, SBR, rectum, and bladder.

**IMRT planning**

IMRT plans were generated using a commercial inverse treatment-planning system (CORVUS, Version 3.0, NOMOS Corporation, Sewickley, PA). Briefly, this planning system produces optimal intensity-modulation profiles using a simulated annealing algorithm. The prescription dose is defined by the user along with all dose–volume constraints of the PTV and normal tissues. To select the optimal number of fields and beam energy, plans for a test patient were generated using 4–11 equally spaced, coplanar, 6- and 18-MV photon beams. Dose constraints were set to minimize the volume of normal tissue receiving the prescription dose without compromising PTV coverage. Plans were compared in terms of isodose distributions as well as normal tissue and PTV DVHs (data not shown). This analysis demonstrated that increasing the beam number was associated with better dose conformation to the PTV. However, no significant improvement was evident with the use of more than nine beams. These results are consistent with theoretical studies showing that more than 7–9 fields does not significantly improve dose conformation (34, 35). In addition, we noted slightly better PTV dose conformation using 6-MV photons.

Based on the above analysis, a 9-field, 6-MV, coplanar, IMRT plan was generated for each patient using an identical set of dose–volume constraints. Fields were equally spaced at 40° intervals consisting of the following gantry angles: 0, 40, 80, 120, 160, 200, 240, 280, and 320°. As in conventional planning, all plans were normalized to cover 98% of the PTV with the prescription dose. DVHs were calculated for PTV, SBR, rectum, and bladder.

**Comparison**

Average and maximum doses of the PTV were calculated for the conventional and IM-WPRT plans and compared. The percent volume of the normal tissues (SBR, rectum, and bladder) was obtained at six dose levels (10, 20, 30, 40, 45, and 50 Gy) from the individual DVHs. At each level, the percent volume for both the conventional and IM-WPRT plans was averaged. These average values were then compared using Student’s t test.

**RESULTS**

**Example case**

Conventional and IM-WPRT treatment plans for an example patient are shown in Figs. 2 and 3, respectively. Highlighted on each figure are the 100%, 70%, and 50% isodose lines superimposed on an axial slice in the mid-pelvis. As seen in Fig. 2, the 100 and 70% isodose lines approximate a square providing coverage of the PTV but also irradiating the neighboring small bowel. In contrast, the IM-WPRT plan (Fig. 3) results in the 100% isodose lines conforming to the shape of the PTV reducing the volume of small bowel irradiated at the prescription dose.

Figure 4 illustrates the DVH of the PTV in this patient. Although both the conventional and IM-WPRT plans encompass the PTV with a minimum dose of 45 Gy, the average PTV doses in the conventional and IM-WPRT plans are 47.4 and 47.9 Gy, respectively. Of note, the IM-WPRT plan results in more dose inhomogeneity within the PTV. The maximum doses in the conventional and IM-WPRT plans are 49.5 and 55.2 Gy, respectively. However, only 1% of the PTV in the IM-WPRT plan receives greater than 51 Gy. The resultant “hot spots” in the IM-WPRT plans are randomly distributed throughout the PTV.

The DVH of the SBR is illustrated in Fig. 5. At low (<17 Gy) and intermediate doses (27–30 Gy), the IM-WPRT plan results in a slightly larger volume of tissue irradiated compared to the conventional plan. In contrast, the IM-WPRT results in less volume of SBR irradiated at all other dose levels. The percent volume of SBR receiving 45 Gy in the conventional and IM-WPRT plans are 25% and 13%, re-
respectively. Corresponding maximum doses are 50.0 and 52.3 Gy, respectively. The volume of SBR receiving ≥ 50 Gy in the IM-WPRT plan is 3.2 cm³ (0.33%).

DVHs of the rectum and bladder in this patient for both conventional and IM-WPRT plans are shown in Figs. 6 and 7, respectively. While comparable at low doses, significant reductions in the volume irradiated of both normal tissues are observed at doses of 25 Gy and higher. The percent volume of rectum receiving 45 Gy in the conventional and IM-WPRT plans are 77% and 52%, respectively. Corresponding maximum doses are 47.7 and 51.1 Gy, respectively. The percent volume of bladder receiving 45 Gy in the conventional and IM-WPRT plans are 99% and 54%, respectively. Corresponding maximum doses are 49.5 and 52.5 Gy, respectively. The hot spots in the bladder and rectum in the IM-WPRT plans are randomly distributed throughout these organs including their contents.

Comparison analysis
As described in the “Methods,” conventional and IM-WPRT plans are normalized to deliver 45 Gy to 98% of the PTV. The small volumes not encompassed by the prescri-
tion isodose are located at the periphery of the PTV in both plans. The average PTV doses delivered by the conventional and IM-WPRT plans are 47.8 ± 0.5 Gy and 47.4 ± 0.4 Gy, respectively. Corresponding maximum doses are 50.0 ± 1.5 Gy and 54.8 ± 1.7 Gy, respectively. However, on average, only 3.2% of the PTV receives greater than 50.0 Gy in the IM-WPRT plan.

Table 1 summarizes the comparison of conventional and IM-WPRT plans of the SBR volume irradiated in these 10 patients. At the 10-Gy level, a larger volume of the SBR is included in the IM-WPRT plan. However, the IM-WPRT plan results in significant reductions in the SBR volume irradiated at the 20, 40, and 45 Gy levels. At the 30-Gy level, there is no significant difference in the SBR volume irradiated. Moreover, the percent SBR volume irradiated at the prescription dose (45 Gy) is reduced by nearly a factor of two in the IM-WPRT plan (17.4 vs. 33.8%, \( p = 0.0005 \)). The comparison of the SBR volumes irradiated at the 45-Gy level in each of the 10 patients is illustrated graphically in Fig. 8. Of note, a reduction in the volume of SBR irradiated
is seen in all 10 women. There is no significant difference in the volume receiving greater than 50 Gy.

A comparison of rectal and bladder DVHs in these 10 patients is summarized in Tables 2 and 3, respectively. The conventional and IM-WPRT plans result in similar irradiation of the rectum and bladder at doses of 20 Gy and below. However, at doses of 30 Gy and above, the IM-WPRT plan significantly reduces the volume of both organs irradiated. The percent volume of the rectum and bladder irradiated at the prescription dose (45 Gy) is reduced by 23% in both cases (p = 0.0002 and p = 0.0005, respectively). A small volume of rectum is irradiated above 50 Gy in the IM-WPRT plans, while the bladder DVHs reveal no significant difference in the volume receiving greater than 50 Gy.

### DISCUSSION

The goal of this study was to evaluate the ability of IMRT to reduce the volume of small bowel irradiated in women with gynecologic malignancies undergoing WPRT. Our results suggest that IM-WPRT is an effective means of reducing the volume of small bowel irradiated in these women. It should be noted that the benefit of IM-WPRT is seen primarily at doses above 30 Gy. At low doses, the IM-WPRT plan results in a slightly greater volume of small bowel irradiated. The reduction seen at higher doses results from conforming the high isodose lines to the U-shaped PTV in the middle and upper pelvis. Although IM-WPRT planning results in a significant reduction in the volume of SBR irradiated, this benefit is achieved at a cost, namely a greater dose inhomogeneity in the PTV and normal tissues. However, resultant hot spots may not be of clinical significance because their magnitude and volume are small.

Although not a primary endpoint of this study, our results demonstrate that IM-WPRT limits the volume of rectum and bladder irradiated, which may reduce the risk of late sequelae (36). In conventional planning, adequate coverage of the distal external iliac lymph nodes results in irradiation of substantial portions of the bladder. Similarly, coverage of the presacral and parametrial tissues results in irradiation of a large portion of the rectum. IM-WPRT allows coverage of these regions with significant sparing of the rectum and bladder. Although IM-WPRT planning significantly reduces the volume of rectum irradiated at most dose levels, a small volume receives greater than 50 Gy. However, these hot

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### Table 1. Small bowel region comparison of conventional and IMRT plans

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Percent volume— conventional</th>
<th>Percent volume— IMRT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>91.4 ± 5.0</td>
<td>97.5 ± 1.1</td>
<td>0.004</td>
</tr>
<tr>
<td>20</td>
<td>85.3 ± 5.7</td>
<td>76.1 ± 5.4</td>
<td>0.002</td>
</tr>
<tr>
<td>30</td>
<td>49.8 ± 11.6</td>
<td>45.3 ± 7.8</td>
<td>0.32</td>
</tr>
<tr>
<td>40</td>
<td>40.7 ± 10.9</td>
<td>26.1 ± 5.9</td>
<td>0.002</td>
</tr>
<tr>
<td>45</td>
<td>33.8 ± 10.3</td>
<td>17.4 ± 4.9</td>
<td>0.0005</td>
</tr>
<tr>
<td>50</td>
<td>0.7 ± 1.2</td>
<td>0.3 ± 0.4</td>
<td>0.37</td>
</tr>
</tbody>
</table>

IMRT = intensity-modulated radiation therapy.

### Table 2. Rectum comparison of conventional and IMRT plans

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Percent volume— conventional</th>
<th>Percent volume— IMRT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
<td>1.0</td>
</tr>
<tr>
<td>20</td>
<td>100 ± 0</td>
<td>99.9 ± 0.2</td>
<td>0.34</td>
</tr>
<tr>
<td>30</td>
<td>97.9 ± 2.8</td>
<td>94.5 ± 4.2</td>
<td>0.001</td>
</tr>
<tr>
<td>40</td>
<td>91.9 ± 4.9</td>
<td>73.9 ± 9.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>45</td>
<td>80.3 ± 5.3</td>
<td>57.7 ± 13.8</td>
<td>0.0002</td>
</tr>
<tr>
<td>50</td>
<td>0 ± 0</td>
<td>1.9 ± 2.0</td>
<td>0.01</td>
</tr>
</tbody>
</table>

IMRT = intensity modulated radiation therapy.

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Fig. 8. Absolute volume of the small bowel region (SBR) irradiated in each patient to a dose of 45 Gy or greater for both conventional (Conv.) and intensity-modulated radiation therapy (IMRT) plans.
Typically, WPRT patient setup is accomplished achieving a favorable outcome in patients treated using cancer patients without evidence of endometrial extension. In women with intact uteri, we elected to include the entire uterus in the PTV. However, irradiation of the entire uterus may not be necessary in early stage cervical nodal regions. We used generous 2-cm margins around the contrast-enhanced vessels must be used to define lymph tissue irradiated was first discussed in the 1970s (37). Researchers at the Harvard Joint Center for Radiation Therapy proposed a technique known as computer-controlled radiation therapy. Briefly, this technique required a patient to be translated longitudinally during the course of treatment while the dose rate, gantry angle, and collimator jaws were varied. This resulted in a conformal dose distribution to the pelvic and para-aortic lymph node regions. However, given the available technology at that time, this approach was not clinically implemented. Today, modern computer-controlled linear accelerators equipped with dynamic multileaf collimators, along with commercial inverse planning software make the implementation and delivery of conformal nodal irradiation possible. Recently, investigators at Washington University have presented data evaluating the use of IMRT planning in the treatment of locally advanced cervical cancer with extended field RT. Similar to our results, significant reductions in the volume of small bowel, rectum and bladder irradiated at the prescription dose were achieved (38).

An important issue in the planning of IM-WPRT is proper target delineation. Target delineation is not a trivial process in these patients and requires considerable knowledge of pelvic anatomy and patterns of disease failure. Because the lymph nodes at risk are not directly visualized, contrast-enhanced vessels must be used to define lymph nodal regions. We used generous 2-cm margins around the pelvic vessels to ensure coverage of these regions. It is possible, however, that smaller margins may be adequate, which would further reduce the dose to the neighboring small bowel. In women with intact uteri, we elected to include the entire uterus in the PTV. However, irradiation of the entire uterus may not be necessary in early stage cervical cancer patients without evidence of endometrial extension.

Accurate setup and immobilization are also paramount to achieving a favorable outcome in patients treated using IMRT. Typically, WPRT patient setup is accomplished using external markers tattooed onto the skin at simulation. At the time of treatment, patients are aligned using these markers and a precision laser system. Studies have shown this method results in both systematic and random errors (39–43). Mock et al. measured patient setup errors using an electronic portal imaging device (EPID) in 25 women undergoing treatment for gynecologic malignancies. Systematic errors in setup were 1.5 mm, 2.9 mm, and 3.0 mm in the left–right (LR), anterior–posterior (AP), and superior–inferior (SI) directions, respectively. Random setup errors were observed with a standard deviation ranging from 3.5 to 4.8 mm (40). Rudat et al. observed random and systematic errors in patient setup ranging from 2.5 to 3.9 mm (39). Cruetzberg et al. examined setup errors in the LR and AP directions for patients aligned using a laser system only. Their results indicated that systematic errors ranged from 3.0 to 3.3 mm, while random errors ranged from 2.3 to 3.1 mm (43). Several authors have proposed various methods to reduce the magnitude and frequency of these errors. Luchka et al. found that use of daily online portal imaging reduced the frequency of large errors (>10 mm) from 10% to 2% (42). Rattray et al. evaluated a new pelvic stabilization device (the pelvic cradle) which appears promising in reducing setup uncertainties. The use of this device resulted in a reduction of the mean deviation from 3.8 mm to 2.0 mm in the LR direction and from 3.9 mm to 2.5 mm in the SI direction (44). Investigation and understanding of setup uncertainties can potentially lead to a smaller CTV-to-PTV margin that may, in turn, result in further reduction in the volume of normal tissues irradiated. Margin design optimization for IM-WPRT is the subject of ongoing research at our center.

Another important issue is organ motion within the pelvis. Most organ motion studies in patients with pelvic malignancies have focused on prostate cancer. Serial imaging has demonstrated significant variations in the volumes of the rectum and bladder during a course treatment (45–47). Our own work has demonstrated that the rectal and bladder volumes varied by as much as ±30% from the initial planning CT scan (45). Few studies exist regarding organ motion in the female pelvis because many of the normal tissues are almost uniformly irradiated by the large WPRT fields. Thus, until now, organ motion has not been an important issue. Gerstner et al. showed that bladder volume was correlated with the volume of small bowel in the treatment field. Patients with smaller bladder volumes tended to have a larger volume of small bowel in the field (48). Buchali et al. examined the effect of a full vs. empty bladder at the time of simulation. Their results indicated that variations in bladder filling caused significant motion of the uterus with median displacements of 7 mm and 4 mm in the SI and AP directions, respectively (49). Given the steep dose gradients present in the IM-WPRT plans, this type of motion could potentially result in underdosing portions of the CTV, or overdosing surrounding normal tissues. Thus, protocols designed to limit variations in organ motion must be developed in order for IM-WPRT to be successful.
IM-WPRT has a number of potential applications. As demonstrated here, this approach allows the delivery of conventional doses with less irradiation of normal tissues. IM-WPRT may also provide the ability to safely deliver higher than conventional doses in select patients provided that the resultant hot spots are small, not excessive in magnitude, and not located in critical structures. This is an appealing approach in node positive cervical cancer patients given their high rate of pelvic failure following surgery and adjuvant RT (50). We are currently evaluating the use of IMRT planning as a means of delivering high central doses in women with cervical cancer unable to undergo brachytherapy. A central boost delivered with IMRT in conjunction with conventional WPRT is currently being explored by Kavanagh et al. (51). Finally, IM-WPRT may also be applicable to other disease sites that routinely receive WPRT including bladder, anal, prostate and rectal cancers (52).

Several questions remain to be answered. First, it is unclear whether IM-WPRT is feasible in a busy clinic. Treatment planning and delivery are more time consuming than the conventional 4-field box approach. We are currently conducting a feasibility study of IM-WPRT in women with endometrial and cervical cancer. With experience, it is our feeling that the time required for treatment planning and delivery will be considerably shortened. We are also attempting to further optimize the treatment plan and immobilization in these patients. We are incorporating a video-assisted positioning system for our patients that has been beneficial in other treatment sites (53). Finally, the most important question is whether dosimetric improvements seen here will translate to reduced treatment sequelae. Patients are being followed closely to answer this question. Only with adequate patient numbers and follow-up can the true benefit of IM-WPRT be assessed.

REFERENCES