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Phase 2 Multicenter Clinical Trial of Bone Marrow-Sparing Intensity Modulated Radiation Therapy With Concurrent Cisplatin for Stage IB-IVA Cervical Cancer.

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Clinical Investigation

Bone Marrow-sparing Intensity Modulated Radiation Therapy With Concurrent Cisplatin For Stage IB-IVA Cervical Cancer: An International Multicenter Phase II Clinical Trial (INTERTECC-2)

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Summary

We performed an international phase II trial to test the hypothesis that intensity modulated radiation therapy (IMRT) reduces acute hematologic and gastrointestinal (GI) toxicity for patients with locoregionally advanced cervical cancer.

Purpose: To test the hypothesis that intensity modulated radiation therapy (IMRT) reduces acute hematologic and gastrointestinal (GI) toxicity for patients with locoregionally advanced cervical cancer.

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Conflict of interest: none.

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Introduction

Cervical cancer is a leading cause of morbidity and mortality in women worldwide (1), typically presenting in advanced stages, for which either postoperative or primary (definitive) chemoradiation therapy (CRT) is required. Multiple clinical trials have established that cisplatin-based CRT is the standard treatment approach for locoregionally advanced cervical cancer (2-5). However, acute and late toxicity are significant problems, and the incidence of advanced cervical cancer (2-5). Nonetheless, the routine use of IMRT for cervical cancer remains controversial, in particular, for patients with unresected disease. Concerns about the cost and complexity of IMRT, along with questions about the magnitude of its benefits, have slowed adoption of the technology, in contrast to its adoption for other diseases, such as prostate and head and neck cancer, for which IMRT is widely considered standard. Large and frequent changes in target positioning due to organ motion, uncertainties in target position, and wide variation in methods have also resulted in a lack of consensus regarding the best IMRT approach. Consequently, large multicenter trials testing IMRT for unresected cervical cancer have been lacking. Therefore, we initiated a multicenter phase II trial to test the efficacy and feasibility of IMRT in the international cervical cancer population, with special attention to the potential for testing PET image-guided IMRT (IG-IMRT) in a future phase III trial.

Methods and Materials

Study design, population, and sampling methods

The present study was a single-arm multicenter phase II clinical trial conducted at 8 centers internationally. Patients were recruited for participation at their treating institutions...
at the time of consultation. Eligible patients had International Federation of Gynecology and Obstetrics stage IB-IVA, biopsy-proven invasive carcinoma of the cervix. Patients with para-aortic, inguinal, or distant metastasis or with clear cell or small cell neuroendocrine carcinoma or who had undergone previous RT to the abdomen or pelvis or previous systemic therapy within the previous 3 years were excluded. Posthysterectomy patients were allowed only if positive lymph nodes, positive surgical margins, parametrial invasion, or cervical cancer was discovered after nonradical surgery (ie, simple hysterectomy).

The pretreatment assessment consisted of a medical history, physical examination, demographic and health information questionnaire, quality of life (QOL) assessment, and screening laboratory studies. Staging with computed tomography (CT) or magnetic resonance imaging (MRI) of the pelvis or PET/CT was required, along with chest and abdominal imaging. In general, MRI and PET/CT were optional but encouraged, if feasible. Patients at 3 institutions were offered participation in an optional substudy to investigate the effect of PET IG-IMRT to spare functional bone marrow. The study was supported by the US National Cancer Institute and was approved by each participating center’s institutional review board. All patients provided written informed consent. The trial is registered with ClinicalTrials.gov (NCT01554397).

Therapeutic intervention and quality assurance

All patients underwent IMRT to 45.0 to 50.4 Gy in 25 to 28 daily fractions to the planning target volume (PTV) with 5 to 6 cycles of concurrent weekly cisplatin (40 mg/m²), followed by an intracavitary brachytherapy boost with a high-dose-rate technique. Patients with gross lymphadenopathy were treated with a simultaneous integrated boost regimen of 47.6 Gy in 1.7-Gy fractions to the gross tumor and elective nodal regions and 54.0 to 59.4 Gy in 1.93- to 2.12-Gy fractions to the grossly abnormal lymph nodes. For postoperative patients, CRT was initiated within 8 weeks after surgery. Chemotherapy was withheld for grade 4 neutropenia or thrombocytopenia, febrile neutropenia, renal failure, grade 2 neurotoxicity, or persistent (>24 hours) grade 3 or 4 nausea/emesis.

Patients underwent CT or PET/CT simulation with a 2.5- to 3.0-mm slice thickness in the supine position with custom immobilization. Pelvic MRI and/or PET/CT images were fused whenever available to facilitate treatment planning. The clinical target volume was defined as the gross tumor plus areas containing potential microscopic disease, including the cervix and uterus (if present), the superior third of the vagina (or superior half of the vagina, if clinically involved), the parametria, and the regional lymph nodes. The planning margins consisted of 15 mm around the cervix and uterus, 10 mm around the vagina and parametria, and a 5- to 7-mm margin around the nodal regions, according to the protocol recommended by Khan et al (23). The IMRT plans consisted of 7 to 9 coplanar fields or 2 to 3 coplanar arcs and were designed to optimize bowel and pelvic bone marrow sparing and maintain PTV coverage. The key organ dosimetric constraints were the bowel volume receiving ≥45 Gy (V45) <200 cm³ and pelvic bone marrow V10 and V20 <90% and <75%, respectively, according to validated normal tissue complication probability models (16, 18). The “bowel” was contoured beginning from the axial slice situated 1 cm superior to the superior-most slice containing the PTV and continuing to its most inferior extent in the pelvis, with the outermost extent of the small and large bowel loops outlined on each axial CT slice, as described previously (16). Individual loops of bowel were not contoured separately. The rectum was contoured separately from the bowel. For patients participating in the study to spare functional bone marrow (defined as the subvolume of pelvic bone marrow with a standardized uptake value greater than the mean), the constraints were also V10 and V20 <90% and <75%, respectively. A consistent bladder filling state (eg, always full or always empty) was used for simulation and treatment. The use of daily online imaging for setup verification and the use of an internal target volume were optional; however, weekly online imaging for setup verification was required; 86% of patients underwent daily online image-guided RT.

Patients with an intact cervix received high-dose-rate brachytherapy with either standard (point-directed) or volume-directed techniques with 4 to 5 fractions of 6 to 7 Gy per fraction to point A or the high-risk clinical target volume, respectively. Postoperative patients received 2 to 3 fractions of 5 to 6 Gy to the vaginal surface after IMRT, according to their institutional standard. Brachytherapy was initiated no sooner than the fourth week of treatment and was not started before the delivery of ≥39.6 Gy of external beam RT. Insertions were separated by a minimum of 48 hours, and no more than 2 insertions were performed per week.

All institutions underwent central credentialing for IMRT through the Advanced Technology Consortium (ATC; Houston, TX and St. Louis, MO). All IMRT plans were centrally reviewed by a committee of study investigators (LKM, CMY, RC, CWW, AJM). All centers underwent an on-site audit by ≥2 members of the data monitoring committee.

Assessments

All patients underwent history taking, physical examination, complete blood count, comprehensive metabolic panel, and diagnostic imaging of the chest, abdomen, and pelvis at baseline. Baseline questionnaires gathered information on patients’ demographic and health and disease characteristics, treatment planning, toxicity, and QOL. QOL was measured using the European Organization for the Research and Treatment of Cancer QOL general cancer and cervical cancer forms. The physical examination, blood tests, and toxicity evaluations were repeated weekly during treatment ≤2 weeks after completion of IMRT. These
assessments were repeated at 1 month after treatment and at 6-month intervals thereafter for ≤3 years. The QOL measurements were recorded at 1, 4, and 12 months after treatment. Patients underwent diagnostic imaging at 4 to 6 months after treatment and biannually thereafter to evaluate for disease recurrence.

Statistical analysis

The primary endpoint was acute hematologic or GI toxicity. A primary event was defined as either (1) acute grade ≥3 neutropenia or (2) clinically significant grade ≥2 diarrhea or any grade ≥3 GI toxicity, using the Common Terminology Criteria for Adverse Events, version 4.0, grading system. Clinically significant diarrhea was defined as requiring intravenous fluids and/or combination opiate/anticholinergic antidiarrheal medication (eg, diphenoxylate/atropine or equivalent). Acute was defined as occurring between the beginning of treatment and 1 month after treatment. Note that diarrhea treated only with loperamide was not considered a primary event.

Using data from previous published studies (2-6, 10, 24), we estimated the probability of a primary event with treatment with the standard of care to be ≥40%. The aim of the present study was to test the null hypothesis (H0, \( P = 0.40 \)). Using a 1-tailed alternative hypothesis (\( H_A, P < 0.40 \)) with an \( \alpha \) of 0.05 and \( \beta \) of 0.10, a required sample size of 91 was estimated (allowing for loss of 10% of patients for follow-up evaluations), based on an expected probability of a primary event of 25% with experimental therapy and using a 1-sample binomial test.

The incidence rates were tested and compared using the test of binomial proportions with a normal approximation; 95% confidence intervals (CIs) for the rates were computed using the Wilson method. Differences in characteristics between groups were assessed using \( \chi^2 \) tests, \( t \) tests, and Fisher’s exact tests. Progression-free and overall survival were computed using the Kaplan-Meier estimator. The cumulative incidence of locoregional failure, distant metastasis, and grade ≥3 late toxicity was estimated by treating death as a competing risk. The 95% CIs for survival and cumulative incidence were computed using the log negative log approximation. Raw QOL scores were scaled according to the European Organization for the Research and Treatment of Cancer instructions. We assessed internal consistency with Cronbach’s \( \alpha \). Changes from baseline were assessed using linear mixed-effects models, including a random intercept for each patient, with the time point treated as a categorical variable. The effect of missing data was tested using Little’s test of missing completely at random (25).

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (L.K.M.) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From October 2011 to April 2015, 91 patients agreed to the study, of whom, 83 met the eligibility criteria and initiated protocol therapy. Of the 91 patients, 7 were ineligible, 1 was not assigned to the protocol therapy owing to an emergency, and 2 withdrew before completing treatment; 81 patients completed protocol therapy (Fig. E1; available online at www.redjournal.org). The initial version of the protocol excluded gross pelvic nodal metastases, which resulted in the exclusion of 2 patients. However, the protocol was subsequently amended to allow for gross nodal disease. The data for all patients who initiated protocol therapy were analyzed using an intention-to-treat approach, leaving 83 patients for analysis. The data set was frozen for analysis on April 5, 2016. The baseline sample characteristics are listed in Table E1 (available online at www.redjournal.org). Figure 1 depicts a representative IG-IMRT plan.

Protocol compliance was high, with 98% completing all planned RT, and 82% completing ≥5 cycles of cisplatin (Table 1). The median duration of treatment for patients receiving definitive CRT was 50 days. The mean dose to 95%, 97%, and 99% of the PTV (ie, \( D_{95\%}, D_{97\%}, \) and \( D_{99\%} \)) was 45.3 Gy, 44.9 Gy, and 43.9 Gy, respectively. The mean volume of bowel receiving an excess of 30 Gy (\( V_{30} \)) and 45 Gy (\( V_{45} \)) was 522 cm\(^3\) and 154 cm\(^3\), respectively. The mean \( V_{10}, V_{20}, V_{30}, \) and \( V_{40} \) of the pelvic bone marrow was 83.7%, 65.2%, 42.4%, and 20.3%, respectively, with an overall mean dose 26.3 Gy. For patients undergoing IG-IMRT, the mean \( V_{10}, V_{20}, V_{30}, \) and \( V_{40} \) of active bone marrow was 82.6%, 63.5%, 45.7%, and 22.2%, respectively, with an overall mean dose of 26.4 Gy.

The median follow-up period was 26.0 months. The incidence of any primary event was 26.5% (95% CI, 18.2%-36.9%), significantly lower than the 40% incidence hypothesized a priori from historical data (1-sided \( P = .006 \); 2-sided \( P = .012 \)). The incidence of grade ≥3 neutropenia and clinically significant GI toxicity was 19.3% (95% CI 12.2%-29.0%) and 12.0% (95% CI 6.7%-20.8%), respectively. The incidence of any grade ≥3 hematologic and grade ≥2 GI toxicity was 38.6% (95% CI 28.8%-49.3%) and 43.4% (95% CI 33.2%-54.1%), respectively (Table 2). Most grade ≥2 GI toxicity events not classified as clinically significant were either diarrhea managed with loperamide or nausea.

For patients with intact cervical cancer (n = 72), the incidence of any primary event, grade ≥3 neutropenia, and clinically significant GI toxicity was 26.4%, 19.4%, and 9.7%, respectively. For postoperative patients (n = 11), the...
incidence of any primary event, grade ≥3 neutropenia, and clinically significant GI toxicity was 27.3%, 22.2%, and 27.3%, respectively. The bowel V45 was comparable in both groups (intact cervix, 151 cm³; postoperative, 176 cm³).

The demographic data and key radiation dose–volume metrics for patients receiving IG-IMRT versus IMRT are listed in Table 3. The subgroups were demographically well-balanced. The patients who did not undergo IG-IMRT received a mean external beam dose of 46.1 Gy, with 79.2% of patients receiving ≥5 cycles of chemotherapy. In contrast, patients undergoing IG-IMRT received a mean external beam dose of 45.6 Gy, with 85.7% of patients receiving ≥5 cycles of chemotherapy. Compared with patients not undergoing IG-IMRT (n = 48), those undergoing IG-IMRT (n = 35) had significantly lower grade ≥3 neutropenia (8.6% vs 27.1%; 2-sided χ² P = .035) and nonsignificantly lower grade ≥3 leukopenia (25.7% vs 41.7%; P = .13) and any grade ≥3 hematologic toxicity (31.4% vs 43.8%; P = .25).

The 2-year progression-free survival and overall survival for all patients was 78.6% (95% CI 69.0%-89.5%) and 90.8% (95% CI 83.2%-99.0%), respectively (Fig. 2). The 2-year cumulative incidence of locoregional failure, distant metastasis, and grade ≥3 late toxicity for all patients was 9.5% (95% CI 3.7%-18.6%), 12.4% (95% CI 5.7%-22.0%), and 7.6% (95% CI 2.7%-15.9%), respectively.

For the longitudinal QOL assessment, the questionnaire response rates at baseline and 1, 4, and 12 months after treatment were 100%, 89%, 80%, and 65%, respectively. The null hypothesis of data missing completely at random was not rejected at the .05 significance level for any QOL domain. Internal consistency was high for all assessed multi-item domains (α > 0.70) at baseline, except for nausea/vomiting (α = 0.48). At 1 month, the global QOL, constipation, and pain were significantly improved, and nausea/vomiting was significantly worse compared with baseline (Table 4; Fig. E2; available online at www.redjournal.org). At 4 months after treatment, the global QOL, constipation, pain, and overall symptom experience were significantly improved, and nausea/vomiting had returned to baseline; however, diarrhea was worsened. At 12 months, global QOL, constipation, and symptom experience remained improved, and diarrhea had returned to baseline. Global QOL was similar among the treatment sites. No significant differences were found in physical function, fatigue, or appetite loss.

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Table 3 Characteristics of patients who received image-guided bone marrow-sparing intensity modulated radiation therapy compared with patients who received computed tomography-based bone marrow-sparing intensity modulated radiation therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>IMRT (n=48)</th>
<th>IG-IMRT (n=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>53.3 ± 13.1</td>
<td>53.7 ± 11.8</td>
<td>.91</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td>.27</td>
</tr>
<tr>
<td>Black</td>
<td>1 (2.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>11 (22.9)</td>
<td>9 (25.7)</td>
<td></td>
</tr>
<tr>
<td>Latina/Hispanic</td>
<td>2 (4.2)</td>
<td>5 (14.3)</td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>34 (70.8)</td>
<td>20 (57.1)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>0 (0)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>26.8 ± 5.3</td>
<td>27.5 ± 6.1</td>
<td>.56</td>
</tr>
<tr>
<td>Karnofsky performance status</td>
<td></td>
<td></td>
<td>.62</td>
</tr>
<tr>
<td>80</td>
<td>2 (4.2)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>21 (43.8)</td>
<td>12 (34.3)</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>25 (52.1)</td>
<td>22 (62.9)</td>
<td></td>
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<tr>
<td>Grade</td>
<td></td>
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<td>.62</td>
</tr>
<tr>
<td>1</td>
<td>3 (6.2)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>25 (52.1)</td>
<td>13 (37.1)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15 (31.2)</td>
<td>11 (31.4)</td>
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<tr>
<td>Not graded</td>
<td>5 (10.4)</td>
<td>10 (28.6)</td>
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<td>FIGO stage</td>
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<td>.36</td>
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<tr>
<td>IB1</td>
<td>1 (2.1)</td>
<td>1 (2.9)</td>
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<tr>
<td>IB2</td>
<td>3 (6.2)</td>
<td>5 (14.3)</td>
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<tr>
<td>IB3</td>
<td>1 (2.1)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>36 (75.0)</td>
<td>19 (54.3)</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>6 (12.5)</td>
<td>9 (25.7)</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>1 (2.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td>.37</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>43 (89.6)</td>
<td>29 (82.2)</td>
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<tr>
<td>Adenocarcinoma</td>
<td>5 (10.4)</td>
<td>6 (17.1)</td>
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<tr>
<td>Operative status</td>
<td></td>
<td></td>
<td>.81</td>
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<tr>
<td>After hysterectomy</td>
<td>6 (12.5)</td>
<td>5 (14.3)</td>
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<tr>
<td>Intact cervix</td>
<td>42 (87.5)</td>
<td>30 (85.7)</td>
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</tr>
<tr>
<td>Mean EBRT dose (Gy)</td>
<td>46.1 ± 4.7</td>
<td>45.6 ± 4.1</td>
<td>.60</td>
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<tr>
<td>Chemotherapy cycles</td>
<td></td>
<td></td>
<td>.25</td>
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<tr>
<td>given</td>
<td>1 (2.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (4.2)</td>
<td>0 (0)</td>
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</tr>
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<td>3</td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td>3 (6.2)</td>
<td>4 (11.4)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>38 (79.2)</td>
<td>28 (80.0)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0 (0)</td>
<td>2 (5.7)</td>
<td></td>
</tr>
<tr>
<td>PTV dose (Gy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean D95</td>
<td>45.5 ± 2.5</td>
<td>44.9 ± 1.6</td>
<td>.18</td>
</tr>
<tr>
<td>Mean D97</td>
<td>45.0 ± 2.5</td>
<td>44.6 ± 1.8</td>
<td>.38</td>
</tr>
<tr>
<td>Mean D99</td>
<td>43.9 ± 2.6</td>
<td>43.7 ± 1.8</td>
<td>.72</td>
</tr>
<tr>
<td>Bowel dose (cm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean V30</td>
<td>514.8 ± 227.0</td>
<td>545.1 ± 200.38</td>
<td>.52</td>
</tr>
<tr>
<td>Mean V45</td>
<td>154.9 ± 92.4</td>
<td>156.5 ± 96.0</td>
<td>.84</td>
</tr>
</tbody>
</table>

Table 3 (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>IMRT (n=48)</th>
<th>IG-IMRT (n=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic bone marrow dose (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean V10</td>
<td>86.9 ± 2.8</td>
<td>78.5 ± 6.9</td>
<td>&lt;.01 *</td>
</tr>
<tr>
<td>Mean V20</td>
<td>70.8 ± 3.5</td>
<td>56.4 ± 9.2</td>
<td>&lt;.01 *</td>
</tr>
<tr>
<td>Mean V30</td>
<td>44.8 ± 6.9</td>
<td>38.4 ± 7.4</td>
<td>&lt;.01 *</td>
</tr>
<tr>
<td>Mean V40</td>
<td>21.9 ± 7.3</td>
<td>18.1 ± 6.1</td>
<td>.01 *</td>
</tr>
<tr>
<td>Overall mean</td>
<td>27.6 ± 1.6</td>
<td>24.2 ± 2.3</td>
<td>&lt;.01 *</td>
</tr>
<tr>
<td>Active bone marrow dose (%)</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Mean V10</td>
<td>NA</td>
<td>82.6 ± 7.1</td>
<td></td>
</tr>
<tr>
<td>Mean V20</td>
<td>NA</td>
<td>63.5 ± 6.5</td>
<td></td>
</tr>
<tr>
<td>Mean V30</td>
<td>NA</td>
<td>45.7 ± 8.5</td>
<td></td>
</tr>
<tr>
<td>Mean V40</td>
<td>NA</td>
<td>22.2 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Overall mean</td>
<td>NA</td>
<td>26.4 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>Toxicity events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any primary event</td>
<td>17 (35.4)</td>
<td>5 (14.3)</td>
<td>.031 *</td>
</tr>
<tr>
<td>Clinically significant GI toxicity</td>
<td>8 (16.7)</td>
<td>2 (5.7)</td>
<td>.13</td>
</tr>
<tr>
<td>Grade ≥3 neutropenia</td>
<td>13 (27.1)</td>
<td>3 (8.6)</td>
<td>.035 *</td>
</tr>
<tr>
<td>Grade ≥2GI toxicity</td>
<td>18 (37.5)</td>
<td>18 (51.4)</td>
<td>.30</td>
</tr>
<tr>
<td>Grade ≥3 GI toxicity</td>
<td>1 (2.1)</td>
<td>2 (5.7)</td>
<td>.38</td>
</tr>
<tr>
<td>Grade ≥3 hematologic toxicity</td>
<td>21 (43.8)</td>
<td>11 (22.9)</td>
<td>.25</td>
</tr>
</tbody>
</table>

Abbreviations: BMI = body mass index; D95, D97, D99 = radiation dose delivered to 95%, 97%, and 99% of the PTV, respectively; EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; GI = gastrointestinal; IG-IMRT = image-guided intensity modulated radiation therapy; NA = not applicable; PTV = planning target volume; V10, V20, V30, V40 = volume receiving ≥10, ≥20, ≥30, ≥40 Gy, respectively. Data presented as n (%) or mean ± standard deviation.

Differences between characteristics were compared using the Kruskal-Wallis tests for continuous variables and Fisher’s exact tests for categorical variables.

* Variable was unbalanced (P<.05) between groups.
† Defined as any grade ≥3 GI toxicity or grade ≥2 GI toxicity requiring intravenous fluids or diphenoxylate/atropine (or equivalent).

Discussion

Multiple previous retrospective and prospective studies have found that the use of IMRT is associated with reduced normal tissue dose and toxicity compared with conventional radiation techniques (ie, either anteroposterior/posterio-anterior or 4-field box methods) (10-21, 26-29). However, IMRT has not been widely tested in multicenter trials of cervical cancer, in particular, for the large international population of patients undergoing definitive CRT. Our study is unique in that regard, and our findings suggest that reducing the radiation dose to both the bowel and the pelvic bone marrow, specifically the functional bone marrow, can...
reduce acute GI and hematologic toxicity, respectively, in this population. Furthermore, we found that high-quality IMRT plans can be successfully delivered in the international community, with a potential favorable effect on QOL, while providing high rates of disease control.

Our findings add to a large body of evidence supporting the hypothesis that IMRT reduces acute GI toxicity in gynecologic cancer patients receiving pelvic RT. In postoperative patients, both the Radiation Therapy Oncology Group 0418 (27) and the RTCMIENDOMETRE (28) phase II trials found low rates of GI toxicity with IMRT. In patients with an intact uterus, the Uterus-11 (29) and All-India Institute of Medical Sciences (AIIMS) (15) trial results similarly support the hypothesis that IMRT reduces GI toxicity. The rate of acute grade ≥3 GI toxicity in our trial (3.6%) was considerably lower than that observed in trials with conventional RT (7%-14%), despite the inclusion of postoperative patients, which would tend, if anything, to increase our observed toxicity. Ongoing phase III trials are randomizing IMRT versus conventional techniques in the postoperative setting and will give further indications of the clinical effect of reducing bowel irradiation. Future trials should assess the effect of IMRT on QOL in patients treated with definitive CRT.

Fig. 2. Disease recurrence and survival in patients with cervical cancer treated with intensity modulated radiation therapy and concurrent cisplatin showing cumulative incidence of (A) locoregional failure, (B) distant metastasis, (C) progression-free survival, and (D) overall survival.
A key unanswered question is whether reducing the pelvic bone marrow radiation dose can reduce hematologic toxicity and permit better chemotherapy delivery in patients undergoing CRT. This hypothesis was posited in early studies investigating IMRT and techniques to image the bone marrow (13, 21, 30). Retrospective studies subsequently correlated lower rates of hematologic toxicity with a reduced radiation dose to the pelvic bone marrow and metabolically active bone marrow, lending support to this hypothesis (17-19, 26). To the best of our knowledge, INTERTECC-2 is the first prospective controlled study to test the hypothesis that reducing the radiation dose to functional bone marrow can reduce hematologic toxicity. We found that, compared with patients who underwent CT-based bone marrow-sparing IMRT, those who underwent PET IG-IMRT had lower rates of neutropenia, consistent with previous modeling studies.

Our use of contemporaneous cohorts comparing varying bone marrow doses and the hypothesis-driven, lineagespecific nature of our investigation mitigates the potential effect of both temporal and confirmation bias, lending considerable strength to the conclusion that bone marrow-sparing reduces neutropenia. However, it is possible that institutional or patient selection factors could explain the observed differences. The quantitative nature of the endpoint also tends to diminish any role of selection bias in explaining the differences in hematologic toxicity. The present trial was also unusual in being primarily designed to measure toxicity, which might otherwise be underreported in studies primarily designed to measure efficacy. Other strengths of our study included that it was a multicenter trial addressing a diverse population conducted by an international team with considerable expertise in IMRT and clinical trials, including centralized quality assurance. These findings with respect to bone marrow-sparing IMRT technology have potential applicability to a variety of gynecologic, gastrointestinal, and genitourinary malignancies treated with CRT.

The mechanism of the observed benefit of IG-IMRT, although ostensibly related to the specific reduction in dose to the functional bone marrow, is not fully understood. Overall, the pelvic bone marrow dose was reduced in patients undergoing IG-IMRT (Table 3; Fig. 1C), which could be the primary factor, leading to lower rates of neutropenia, rather than sparing functional bone marrow per se. Defining metabolically active subregions could simply serve as an internal “tuning structure” in IMRT planning, facilitating better sparing of the overall organ. Regardless, we did not find lower rates of hematologic toxicity with CT-based bone marrow-sparing IMRT than that reported in studies using conventional RT. Although the toxicity in the present trial could have been greater than that in trials not designed to monitor toxicity as a primary endpoint, it appears that IG-IMRT, despite its relatively increased complexity, is the experimental method to test in future trials, at least wherever PET is available. Atlas-based IG-IMRT approaches are also emerging as a promising method to facilitate bone marrow sparing where access to PET is limited.

### Conclusions

Although intensive chemotherapy can improve the outcomes in cervical cancer, toxicity has inhibited the widespread adoption of this approach. Ongoing trials of adjuvant carboplatin/paclitaxel will lend further insight into whether chemotherapy intensification is advantageous. Irrespective of the treatment approach, the greatest effect of IG-IMRT is likely to be found in the definitive setting with intensified chemotherapy. The INTERTECC-3 trial is randomizing patients to IG-IMRT versus non–bone

### Table 4

Mean baseline quality of life scores and changes from baseline* at 1, 4, and 12 months post-treatment

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Mean baseline (95% CI)</th>
<th>Mean change at 1 mo vs baseline (95% CI)</th>
<th>P value (1 mo vs baseline)</th>
<th>Mean change at 4 mo vs baseline (95% CI)</th>
<th>P value (4 mo vs baseline)</th>
<th>Mean change at 12 mo vs baseline (95% CI)</th>
<th>P value (12 mo vs baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global QOL</td>
<td>64.0 (59.3, 68.7)</td>
<td>9.6 (4.0, 15.1)</td>
<td>&lt;.001</td>
<td>10.7 (4.9, 16.5)</td>
<td>&lt;.001</td>
<td>11.6 (5.3, 17.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Symptom experience</td>
<td>15.6 (12.9, 18.3)</td>
<td>-3.9 (-6.8, -1.1)</td>
<td>.006</td>
<td>-4.8 (-7.7, -1.8)</td>
<td>.002</td>
<td>-5.1 (-8.2, -2.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>85.8 (82.3, 89.3)</td>
<td>-1.6 (-4.6, 1.4)</td>
<td>.285</td>
<td>0.1 (-3.0, 3.3)</td>
<td>.946</td>
<td>1.1 (-2.2, 4.5)</td>
<td>.505</td>
</tr>
<tr>
<td>Pain</td>
<td>19.6 (14.3, 24.8)</td>
<td>-5.9 (-11.4, -0.4)</td>
<td>.036</td>
<td>-4.4 (-10.1, 1.4)</td>
<td>.139</td>
<td>-1.6 (-7.8, 4.6)</td>
<td>.613</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26.8 (21.8, 31.8)</td>
<td>1.7 (-3.3, 6.7)</td>
<td>.508</td>
<td>-0.6 (-5.8, 4.7)</td>
<td>.836</td>
<td>-3.0 (-8.7, 2.8)</td>
<td>.31</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>13.4 (8.3, 18.4)</td>
<td>1.1 (-4.8, 7.1)</td>
<td>.714</td>
<td>-4.5 (-10.6, 1.7)</td>
<td>.156</td>
<td>-4.6 (-11.3, 2.0)</td>
<td>.169</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3.9 (1.5, 6.2)</td>
<td>4.2 (1.1, 7.2)</td>
<td>.008</td>
<td>1.1 (-2.0, 4.3)</td>
<td>.485</td>
<td>-0.5 (-3.9, 3.0)</td>
<td>.789</td>
</tr>
<tr>
<td>Constipation</td>
<td>16.4 (11.7, 21.0)</td>
<td>-8.1 (-13.6, -2.7)</td>
<td>.004</td>
<td>-7.3 (-12.9, -1.6)</td>
<td>.012</td>
<td>-10.7 (-16.8, -4.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.0 (3.7, 12.3)</td>
<td>-0.5 (-6.0, 5.0)</td>
<td>.861</td>
<td>5.8 (0.0, 11.6)</td>
<td>.050</td>
<td>3.3 (-2.9, 9.6)</td>
<td>.292</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; QOL = quality of life.
* Estimates are based on linear mixed-effects model with a random intercept for patients, treating time as categorical.
† Statistically significant changes (P<.05).

Nausea/vomiting 3.9 (1.5, 6.2) 4.2 (1.1, 7.2) .008
Appetite loss 13.4 (8.3, 18.4) 1.1 (4.4, 7.3) .002
Constipation 16.4 (11.7, 21.0) 1.1 (4.4, 7.3) .002
Diarrhea 8.0 (3.7, 12.3) -0.5 (-6.0, 5.0) .861
marrow-sparing RT with concurrent cisplatin. The NRG
GY-006 trial is testing the addition of concurrent Triapine
to standard CRT, with IG-IMRT allowed as a treatment
option. These trials will help further determine the value of
IG-IMRT relative to non–bone marrow-sparing RT
approaches.

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