Title

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

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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hypothesis that intensity modulated radiation therapy (IMRT) would reduce the acute toxicity for locoregionally advanced cervical cancer. For the 83 patients enrolled, acute gastrointestinal toxicity was significantly reduced with both IMRT and positron emission tomography-guided bone marrow sparing IMRT (IG-IMRT) compared with historical controls. The incidence of neutropenia was significantly reduced in patients who underwent IG-IMRT. We conclude that IMRT reduces acute toxicity compared with standard treatment in this population and that IG-IMRT warrants testing in randomized trials.

Methods and Materials: We enrolled patients with stage IB-IVA cervical carcinoma in a single-arm phase II trial involving 8 centers internationally. All patients received weekly cisplatin concurrently with once-daily IMRT, followed by intracavitary brachytherapy, as indicated. The primary endpoint was the occurrence of either acute grade $\geq$3 neutropenia or clinically significant GI toxicity within 30 days of completing chemoradiation therapy. A preplanned subgroup analysis tested the hypothesis that positron emission tomography-based image-guided IMRT (IG-IMRT) would lower the risk of acute neutropenia. We also longitudinally assessed patients' changes in quality of life.
Results: From October 2011 to April 2015, 83 patients met the eligibility criteria and initiated protocol therapy. The median follow-up was 26.0 months. The incidence of any primary event was 26.5% (95% confidence interval [CI] 18.2%-36.9%), significantly lower than the 40% incidence hypothesized a priori from historical data ($P = .012$). The incidence of grade $\geq$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. Compared with patients treated without IG-IMRT (n = 48), those treated with IG-IMRT (n = 35) had a significantly lower incidence of grade $\geq$3 neutropenia (8.6% vs 27.1%; 2-sided χ^2 $P = .035$) and nonsignificantly lower incidence of grade $\geq$3 leukopenia (25.7% vs 41.7%; $P = .13$) and any grade $\geq$3 hematologic toxicity (31.4% vs 43.8%; $P = .25$).
Conclusions: IMRT reduces acute hematologic and GI toxicity compared with standard treatment, with promising therapeutic outcomes. Positron emission tomography IG-IMRT reduces the incidence of acute neutropenia.

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 locoregional failure, distant metastasis, and cancer mortality, especially for stage IIB-IVA disease, remain high (6). Furthermore, despite evidence that intensifying concurrent chemotherapy improves survival (7-9), high rates of gastrointestinal (GI) and hematologic toxicity have limited the adoption of such strategies. Therefore, innovations to reduce toxicity and barriers to treatment intensification are needed to improve the therapeutic ratio of CRT.

Conventional pelvic RT techniques typically use opposed anteroposterior/posteroanterior and lateral fields according to the bone anatomy, resulting in a box-shaped dose distribution that encompasses both the target (eg, tumor, parametria, pelvic lymph nodes) and normal tissues (eg, bowel, rectum, bladder, bone marrow). In contrast, intensity modulated radiation therapy (IMRT) uses multiple beam angles or arcs, along with sophisticated optimization algorithms, to generate dose distributions that conform to the target and reduce the dose to the surrounding tissues. Previous studies have found that IMRT reduces the dose to pelvic organs, maintains acceptable target coverage (10), and is associated with reduced toxicity and favorable outcomes in cervical cancer (11-15). In addition, modeling studies have indicated that optimized IMRT plans can decrease toxicity by approximately twofold (16-19). Recent evidence has also raised the possibility that positron-emission tomography (PET) could further augment the advantages of IMRT (20-22).

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/m^2), 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 (V_{45}) <200 cm^3 and pelvic bone marrow V_{10} and V_{20} <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 V_{10} and V_{20} <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 (H_0, $P=.40$). Using a 1-tailed alternative hypothesis (H_A, $P<.40$) with an α of 0.05 and β 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 χ^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 α. 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

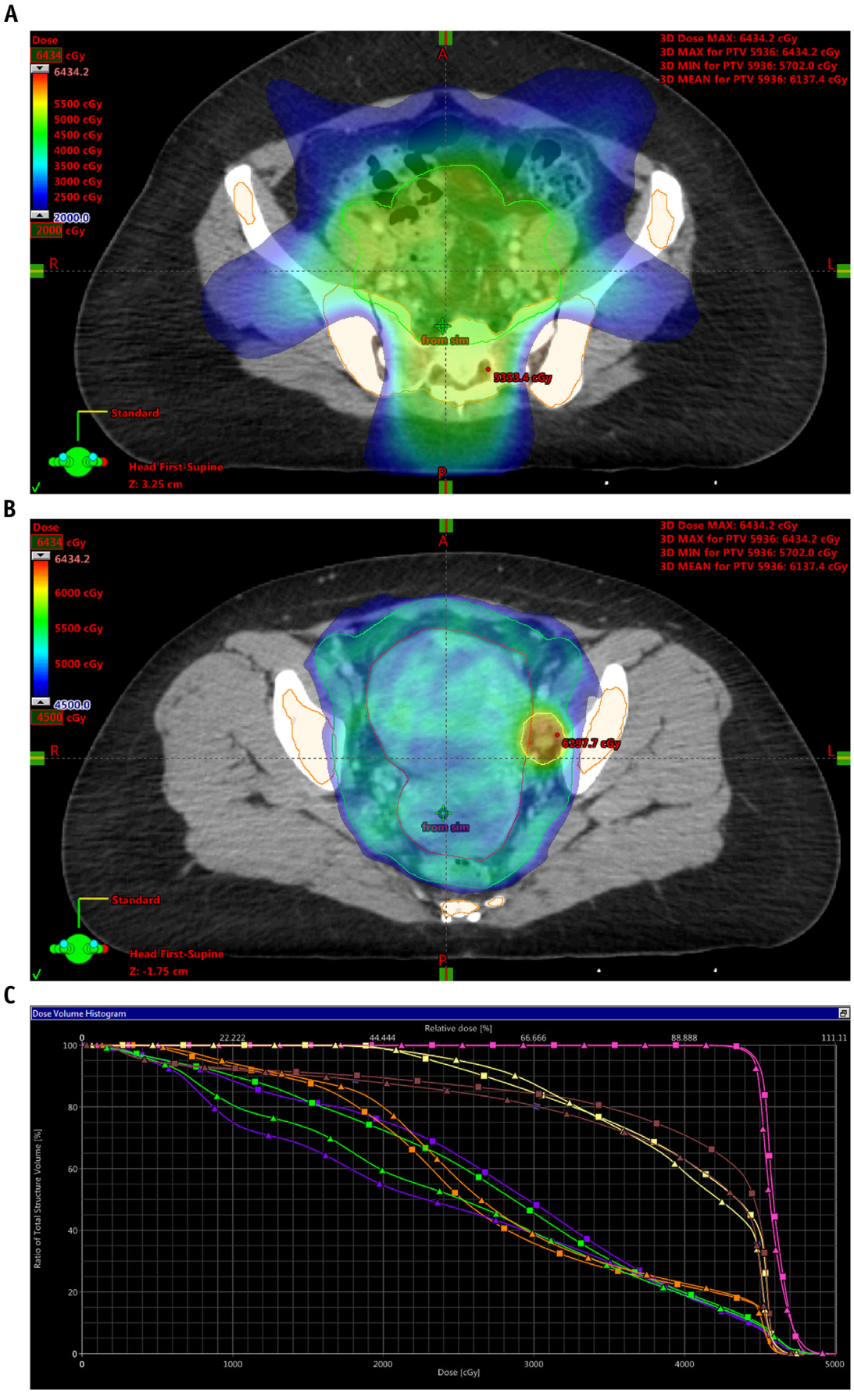
A
Dose
6434 cGy
6434.2
5500 cGy
5000 cGy
4500 cGy
4000 cGy
3500 cGy
3000 cGy
2500 cGy
2000.0
2000 cGy
3D Dose MAX: 6434.2 cGy
3D MAX for PTV 5936: 6434.2 cGy
3D MIN for PTV 5936: 5702.0 cGy
3D MEAN for PTV 5936: 6137.4 cGy
A
R
L
P
from sim
5853.4 cGy
Standard
Head First-Supine
Z: 3.25 cm
B
Dose
6434 cGy
6434.2
6000 cGy
5500 cGy
5000 cGy
4500.0
4500 cGy
3D Dose MAX: 6434.2 cGy
3D MAX for PTV 5936: 6434.2 cGy
3D MIN for PTV 5936: 5702.0 cGy
3D MEAN for PTV 5936: 6137.4 cGy
A
R
L
P
6297.7 cGy
from sim
Standard
Head First-Supine
Z: -1.75 cm
C
Dose Volume Histogram
Relative dose [%]
0
22.222
44.444
66.666
88.888
111.11
100
80
60
40
20
0
Ratio of Total Structure Volume [%]
0
1000
2000
3000
4000
5000
Dose [cGy]

Table 1 Protocol treatment received

Variable	n (%)
Subjects	83
IMRT dose (Gy)	
Mean ± SD	45.9 ± 4.4
Range	27.0-59.4
Cycles of cisplatin (n)	
0	1 (1.2)
1	0 (0)
2	2 (2.4)
3	5 (6.0)
4	7 (8.4)
5	66 (79.5)
6	2 (2.4)
Median brachytherapy dose	
After hysterectomy	
None	5 (6.0)
11 Gy in 2 fractions (vaginal surface)	6 (7.2)
Intact cervix	
None (withdrew)	1 (1.2)
30 Gy in 5 fractions (volume-directed)	37 (1.2)
30 Gy in 5 fractions (point A)	34 (1.2)

Abbreviations: IMRT = intensity modulated radiation therapy; HR-CTV = high-risk clinical target volume; SD = standard deviation.

Table 2 Patients experiencing acute toxicity, stratified by category and grade

Acute toxicity	Grade 1	2	3	4	5
Any hematologic (maximum)	9	39	27	5	0
WBC	16	33	26	3	0
ANC	16	27	14	2	0
Hemoglobin	27	32	0	0	0
Platelets	14	7	3	1	0
Genitourinary	52	17	2	0	0
Gastrointestinal	41	33	3	0	0
Diarrhea	39	16	1	0	0
Other	52	22	2	0	0

Abbreviations: ANC = absolute neutrophil count; WBC = white blood count.

Grading used the Common Terminology Criteria for Adverse Events, version 4.0.

incidence of any primary event, grade ≥3 neutropenia, and clinically significant GI toxicity was 27.3%, 22.2%, and 27.3%, respectively. The bowel V_{45} was comparable in both groups (intact cervix, 151 cm^3; postoperative, 176 cm^3).

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 χ^2 $P = .035$) 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 ($\alpha > 0.70$) at baseline, except for nausea/vomiting ($\alpha = 0.48$). 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.

Fig. 1. Axial cross-sections of a representative arc-based image-guided intensity modulated radiation therapy (IG-IMRT) dose distribution in a sample patient. (A) Colorwash, 20-Gy isodose cloud showing sparing of iliac bone marrow. (B) Colorwash, 45-Gy isodose cloud showing coverage of the uterus and cervix, plus margin, with a simultaneous integrated boost to the left pelvic lymph node. (C) Dose–volume histogram comparison of a computed tomography-based IMRT plan (squares) versus positron emission tomography-guided bone marrow-sparing IMRT plan (triangles) in a representative patient. Pink, planning target volume; purple, active bone marrow; green, pelvic bone marrow; orange, bowel; yellow, bladder; brown, rectum. (For further images visit eContour.org.) (A color version of this figure is available at www.redjournal.org.)

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

Variable	IMRT (n = 48)	IG-IMRT (n = 35)	*P* value
Mean age (y)	53.3 ± 13.1	53.7 ± 11.8	.91
Race/ethnicity			.27
Black	1 (2.1)	0 (0)	
Asian	11 (22.9)	9 (25.7)	
Latina/Hispanic	2 (4.2)	5 (14.3)	
White, non-Hispanic	34 (70.8)	20 (57.1)	
Other/unknown	0 (0)	1 (2.9)	
Mean BMI (kg/m^2)	26.8 ± 5.3	27.5 ± 6.1	.56
Karnofsky performance status			.62
80	2 (4.2)	1 (2.9)	
90	21 (43.8)	12 (34.3)	
100	25 (52.1)	22 (62.9)	
Grade			.62
1	3 (6.2)	1 (2.9)	
2	25 (52.1)	13 (37.1)	
3	15 (31.2)	11 (31.4)	
Not graded	5 (10.4)	10 (28.6)	
FIGO stage			.36
IB1	1 (2.1)	1 (2.9)	
IB2	3 (6.2)	5 (14.3)	
IIA1	1 (2.1)	1 (2.9)	
IIB	36 (75.0)	19 (54.3)	
IIIB	6 (12.5)	9 (25.7)	
IVA	1 (2.1)	0 (0)	
Histologic type			.37
Squamous cell carcinoma	43 (89.6)	29 (82.2)	
Adenocarcinoma	5 (10.4)	6 (17.1)	
Operative status			.81
After hysterectomy	6 (12.5)	5 (14.3)	
Intact cervix	42 (87.5)	30 (85.7)	
Mean EBRT dose (Gy)	46.1 ± 4.7	45.6 ± 4.1	.60
Chemotherapy cycles given			.25
0	1 (2.1)	0 (0)	
2	2 (4.2)	0 (0)	
3	4 (8.3)	1 (2.9)	
4	3 (6.2)	4 (11.4)	
5	38 (79.2)	28 (80.0)	
6	0 (0)	2 (5.7)	
PTV dose (Gy)			
Mean D_{95}	45.5 ± 2.5	44.9 ± 1.6	.18
Mean D_{97}	45.0 ± 2.5	44.6 ± 1.8	.38
Mean D_{99}	43.9 ± 2.6	43.7 ± 1.8	.72
Bowel dose (cm^3)			
Mean V_{30}	514.8 ± 227.0	545.1 ± 200.38	.52
Mean V_{45}	154.9 ± 92.4	156.5 ± 96.0	.84
Pelvic bone marrow dose (%)			
Mean V_{10}	86.9 ± 2.8	78.5 ± 6.9	<.01*
Mean V_{20}	70.8 ± 3.5	56.4 ± 9.2	<.01*
Mean V_{30}	44.8 ± 6.9	38.4 ± 7.4	<.01*
Mean V_{40}	21.9 ± 7.3	18.1 ± 6.1	.01*
Overall mean	27.6 ± 1.6	24.2 ± 2.3	<.01*
Active bone marrow dose (%)			NA
Mean V_{10}	NA	82.6 ± 7.1	
Mean V_{20}	NA	63.5 ± 6.5	
Mean V_{30}	NA	45.7 ± 8.5	
Mean V_{40}	NA	22.2 ± 8.1	
Overall mean	NA	26.4 ± 2.5	
Toxicity events			
Any primary event	17 (35.4)	5 (14.3)	.031*
Clinically significant GI toxicity†	8 (16.7)	2 (5.7)	.13
Grade ≥3 neutropenia	13 (27.1)	3 (8.6)	.035*
Grade ≥2 GI toxicity	18 (37.5)	18 (51.4)	.30
Grade ≥3 GI toxicity	1 (2.1)	2 (5.7)	.38
Grade ≥3 hematologic toxicity	21 (43.8)	11 (22.9)	.25

Abbreviations: BMI = body mass index; D_{95}, D_{97}, D_{99} = 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; V_{10}, V_{20}, V_{30}, V_{40} = 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/posteroanterior 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

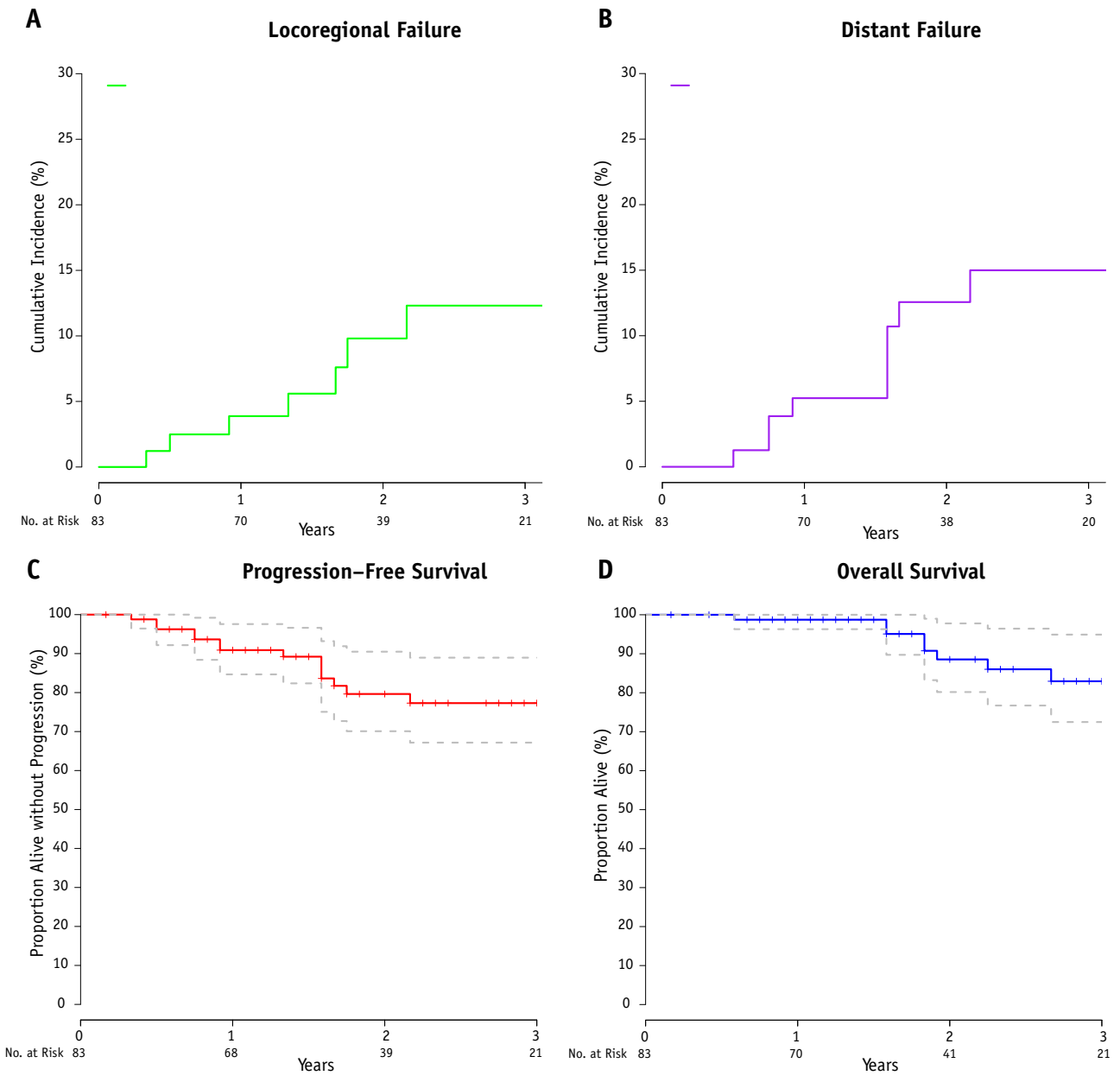

Fig. 2. Disease recurrence and survival in patients with cervical cancer treated with intensity modulated radiation therapy and concurrent cisplatin showing cumulative incidence of (A) locoregional failure, (B) distant metastasis, (C) progression-free survival, and (D) overall survival.

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 $\geq$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.

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

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

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 ($P<.05$).

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, lineage-specific 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

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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