Predictors of Acute Hematologic Toxicity in Women Receiving Extended-Field Chemoradiation for Cervical Cancer: Do Known Pelvic Radiation Bone Marrow Constraints Apply?

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Abstract

Purpose: Patients with cervical cancer who are at high risk for para-aortic lymphatic involvement may receive extended-field chemoradiation (EF-CRT), with inclusion of the para-aortic region. Increased radiation to bone marrow (BM) may heighten hematologic toxicity (HT) and affect timely delivery of chemoradiation. Factors associated with HT in this setting have not been well studied.

Methods and Materials: This study was a retrospective analysis of women treated with EF-CRT from 2012 to 2018 with platinum-based chemotherapy. Factors including age, body mass index (BMI), race, Charlson Comorbidity Index (CCI), and nadirs for white blood cell count, absolute neutrophil count, hemoglobin, and platelet count were collected. The BM metrics included V5Gy, V10Gy, V15Gy, V20Gy, V25Gy, V30Gy, V35Gy, V40Gy and V45Gy (VxGy was defined as the percentage of BM volume receiving x Gy). Hematologic toxicity was defined as grade ≥2 (Cooperative Group Common Toxicity Criteria) leukopenia, anemia, neutropenia, or thrombocytopenia. Univariate analysis (UVA) and multivariate analysis (MVA) were performed using the χ² test, the Fisher exact test, and logistic regression. Previously published dosimetric BM constraints were examined as detailed in each respective study.

Results: Fifty-two women underwent EF-CRT with cisplatin. UVA showed no association between HT and age, BMI, or CCI. When accounting for race, V5Gy ≥98% was associated with grade ≥2 leukopenia (P = .02) and grade ≥2 HT (P = .05). Most previously described radiation metrics were not reproduced in our cohort, but a similar constraint, V20Gy <70%, was associated with reduced leukopenia of grade ≥2 on UVA (P = .02) and MVA (P < .05).

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: Acute HT in patients receiving EF-CRT was associated with large volumes of low-dose radiation to the BM and was also associated with race. Restricting the BM V20Gy to less than 70% to 75% may be beneficial in reducing HT, but other pelvic radiation BM constraints may not be applicable to this population.

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Introduction

Cervical cancer is the third most common cancer in women worldwide.1 Many of these patients present with advanced-stage disease, for which either postoperative or primary (definitive) chemoradiation (CRT) is required. Patients with para-aortic lymph node metastasis or who are at high risk for para-aortic lymph node involvement are frequently treated using extended-field radiation therapy (RT) with concurrent chemotherapy (EF-CRT).2,3 However, these methods are associated with significant hematologic toxicity (HT). For example, more than 80% of women in RTOG 0116 experienced grade 3 or higher HT.4 Moreover, 33% to 50% of patients who undergo EF-CRT treatment require cisplatin dose reductions or discontinuation, which leads to treatment interruptions or delays.5,6 Furthermore, studies suggest that a radiation treatment course delay of more than 49 to 56 days can negatively affect survival.7,8

From a systemic therapy perspective, concurrent cisplatin is associated with improved overall survival and is considered the standard-of-care regimen per the National Comprehensive Cancer Network guidelines.9-15 In the neoadjuvant setting, dose reductions and fewer cycles of chemotherapy have been associated with lower complete response rates.16 In the concurrent setting, the importance of cisplatin dosing and treatment completion is less established. Ryu et al previously demonstrated that triweekly cisplatin concurrent chemoradiation was associated with better 5-year overall survival and a higher relative completion rate of scheduled chemotherapy cycles.17 Similarly, recent meta-analyses demonstrated that triweekly cisplatin with concurrent RT was superior to weekly cisplatin with respect to local recurrence, treatment compliance, and anemia.18 These data suggest that completion of concurrent, full-dose chemotherapy may be important for optimal treatment outcomes. Therefore, efforts to reduce treatment delay and interruptions should be investigated.

Identifying factors that reduce HT may therefore have a significant effect on optimizing a patient’s outcome. Previous studies suggested that several clinical factors are associated with HT in the setting of concurrent chemoradiation to the pelvis, including decreased body mass index (BMI), female sex, and lymph node positivity.19,20 Although valuable for risk assessment, these clinical factors are not modifiable. Dosimetric constraints to the bone marrow (BM) may provide an actionable means to guide treatment and reduce HT, given that approximately 60% of hematopoietic stem cells in adults are within the lumbar spine and pelvis and are particularly radiosensitive.21 Multiple studies have evaluated the role of BM radiation dose on acute HT and provided dosimetric constraints to decrease HT.19,22-27 Mell et al demonstrated that intensity modulated RT (IMRT) can be used to decrease BM radiation dose compared with the traditional 3-dimensional conformal RT (3D-CRT) 4-field box technique.20 The INTOPECC-2 phase 2/3 trial demonstrated that BM-sparing IMRT with concurrent cisplatin for cervical cancer reduced HT compared with historical standards.28,29 Similarly, a phase 2 trial from India demonstrated a reduction in rates of grade 2 neutropenia and HT with IMRT when comparing IMRT with 3D-CRT.30 However, these studies excluded patients receiving EF-CRT, which is associated with significantly greater HT.31,32 Recently, Yan et al found that in 38 patients treated with EFRT using conventional 4-field box or IMRT techniques, a mean total BM dose ≥30.3 Gy was correlated with grade 3 HT.23

The purpose of this study was twofold: to identify clinical and dosimetric factors associated with acute HT for patients treated with EF-CRT with an IMRT technique and concurrent cisplatin and to determine whether existing pelvic BM dosimetric constraints could successfully be extrapolated to the patient cohort treated with EFRT to predict for toxicity.

Methods

Study design and patient population

We identified women with locally advanced cervical cancers treated at 2 urban, academic institutions from 2012 to 2018. This study was approved by the institutional review boards of both institutions. Only patients treated with extended-field chemoradiation using IMRT with platinum-based chemotherapy were included in this study, because IMRT has been associated with reduced HT toxicity compared with a 3D-CRT technique.28 Patient demographics and clinical characteristics are summarized in Table 1. BMI, race (as self-reported in the medical record), Charlson Comorbidity Index (CCI) score, chemotherapy cycles delivered, and nadirs for white blood cell count, absolute neutrophil count, hemoglobin, and platelet count were obtained. Stage was defined using the International Federation of Gynecology and Obstetrics (FIGO) 2009 cervical cancer staging system.
Radiation therapy

Patients underwent individualized computed tomography–based planning before the beginning of treatment with immobilization in alpha cradles with their arms placed above their head. The BM contours were standardized across all patients and included vertebral bodies within the radiation treatment field, sacrum, coccyx, pelvic bones, and femurs from the top of the femoral head to the inferior border of the ischial tuberosities (Fig. 1). The extended-field RT clinical target volume (CTV) included treatment to the uterus, cervix, and primary mass; the paracervical, parametrial, and uterosacral regions; and at least the upper half of the vagina. The nodal CTV treatment volumes included the external iliac, hypogastric, obturator, and para-aortic lymph nodes with a 0.7- to 0.8-cm margin around the vessels minus anatomic subtraction as clinically indicated. The superior extent of the para-aortic field was defined by the renal vessels in all patients, with the exception of 1 patient who had high para-aortic nodal disease (Table B in the Supplement). The nodal planning target volume was uniformly expanded by 0.7 cm to produce the planning target volume. A cervix internal target volume was created using bladder-empty and bladder-full scans; this was expanded by 1.5 to 2.5 cm to account for organ motion. Similarly, a vaginal and parametrial internal target volume was created and expanded by 0.5 to 1.0 cm. In cases of urgent vaginal bleeding, radiation treatments used 3D-CRT for the first fractions to expedite treatment. These plans were subsequently incorporated into the composite dose calculations for IMRT treatment planning. Volumetric-modulated arc therapy or static-field IMRT were used to treat the volume to a total dose of 45 Gy in 1.8-Gy daily fractions, which was followed by a boost to gross nodal disease to a total dose of 55 to 60 Gy using either a sequential or simultaneous integrated boost technique. Organs at risk, including the rectum, bowel, and bladder, were contoured for radiation planning. The BM was contoured but was not used as an avoidance structure for IMRT planning until 2017. Patients were reassessed toward the end of external beam radiation treatment; they were given a parametrial boost if indicated and high-dose-rate intracavitary or interstitial brachytherapy. The boost treatment used iridium-192 with a dose of 28 to 30 Gy to the high-risk CTV, or point A, in 4 to 5 treatments. RT and brachytherapy were generally held if the absolute neutrophil count was less than 0.5 £ 10^9/L or if the platelet count was less than 50 £ 10^9/L.

Chemotherapy

Patients received concurrent weekly chemotherapy with cisplatin (40 mg/m^2). Doses were based on patient weight and surface area. Patients were planned to receive 5 to 6

Table 1 Patient and treatment characteristics

| Characteristic                      | Patients, No. (%) (N = 52)* |
|-------------------------------------|-----------------------------|
| **Patients**                        |                             |
| Age, median (IQR), y                | 44.5 (39.3-58.8)            |
| BMI, median (IQR), kg/m^2           | 25.1 (22.7-31.2)            |
| **Race**                            |                             |
| White                               | 13 (25)                     |
| African American                    | 30 (58)                     |
| Other                               | 9 (17)                      |
| **FIGO 2009 clinical stage**        |                             |
| I                                   | 12 (23)                     |
| II                                  | 18 (35)                     |
| IIIA                                | 19 (36)                     |
| IV                                  | 3 (6)                       |
| **Treatment**                       |                             |
| Radiation technique                 |                             |
| Intensity modulated radiation therapy | 52 (100)                  |
| 3D conformal radiation therapy      | 2 (3.9)                     |
| Brachytherapy                       | 51 (98)                     |
| Intracavitary brachytherapy         | 35 (67.3)                   |
| Intersitial brachytherapy           | 17 (32.7)                   |
| Declined                            | 1 (1.9)                     |
| **Dosimetric characteristics, median (IQR)** |         |
| V5Gy                                | 98 (94-100)                 |
| V10Gy                               | 89 (85-93)                  |
| V15Gy                               | 79 (73-87)                  |
| V20Gy                               | 70 (65-76)                  |
| V25Gy                               | 59 (54-64)                  |
| V30Gy                               | 49 (44-53)                  |
| V35Gy                               | 37 (32-42)                  |
| V40Gy                               | 26 (21-32)                  |
| V45Gy                               | 12 (9-17)                   |
| Mean dose                           | 28.4 (26.4-30.2)            |
| **Chemotherapy**                    |                             |
| Cisplatin                           | 52 (100)                    |
| Cycles of cisplatin, median (IQR), No. | 5 (4-5)                    |
| Chemotherapy dose reduction         |                             |
| Yes                                 | 17 (33)                     |
| No                                  | 34 (67)                     |

*Data are presented as the number (percentage) of patients unless otherwise indicated.
cycles of chemotherapy concurrently with radiation. Cisplatin was generally held if an absolute neutrophil count was less than $1 \times 10^9/L$ and/or a platelet count was less than $100 \times 10^9/L$, although this was at the discretion of the treating gynecologic oncologist. Any cisplatin dose reduction was also at the discretion of the treating physician.

**Dosimetry**

Contours and dose summation were completed on the Eclipse treatment planning system, version 15.5, and the Pinnacle treatment planning system, version 9.8. A cumulative plan was created from all external beam portions of the patient’s treatment (if applicable), and a dose-volume histogram was generated for each contoured BM region for each patient. The brachytherapy dose was not included, given its minimal contribution to bony structures; however, a record of brachytherapy was noted. The BM metrics collection included the mean BM dose, V5Gy, V10Gy, V15Gy, V20Gy, V25Gy, V30Gy, V35Gy, V40Gy and V45Gy (VxGy was defined as the percentage of BM volume receiving x Gy). Specific dosimetric predictors of HT previously published in the literature for pelvic (nonextended-field) radiation were also evaluated in this patient cohort. These included V10Gy $\geq 90\%$, V20Gy $\geq 75\%$, and V40Gy $>37\%$. A previously published dosimetric predictor in the extended-field setting (mean BM dose $>30.3$ Gy) was also evaluated in this patient cohort.

**Toxicity endpoints**

Toxicity grading was based on the Cooperative Group Common Toxicity Criteria. The HT endpoints included (1) any grade 2 or higher hematologic acute toxic effect, not including lymphopenia, and (2) grade 2 or higher leukopenia. These endpoints were chosen as a measure of toxicity because these may result in modifications to systemic or RT and were previously used as HT endpoints in RTOG 0418. Previously published HT endpoints were used for examination of their respective published BM dosimetric constraints in this patient cohort, which included HT $\geq 2$, leukopenia $\geq 2$, neutropenia $\geq 2$ (grade 2-4 neutropenia), HT $\geq 3$ (grade 3-4 HT), and leukopenia $\geq 3$ (grade 3-4 leukopenia).

**Statistical analysis**

All statistical analyses were performed using STATA, version 17.0 (StataCorp LLC, College Station). Univariate analysis was performed using the $\chi^2$ test and logistic regression. The $\chi^2$ test or Fisher exact test was used to compare rates of hematologic adverse events for patients with a volume of BM irradiation from 5 to 45 Gy (V5Gy to V45Gy), dichotomized at the median, and to compare rates of hematologic adverse events for patients according to dichotomized patient characteristics (African American race vs other; CCI), as appropriate. Tests for normality were performed for age and BMI with the Shapiro-Wilk statistic, and these variables were transformed using the natural logarithm to eliminate skew. Logistic regression was used to test for associations between natural log-transformed age or natural log-transformed BMI and hematologic endpoints. Variables with a $P$ value $<.1$ from univariate logistic models were included in the multivariate model. Multivariate analysis (MVA) was performed using logistic regression to correlate HT $\geq 2$ and leukopenia $\geq 2$ with patient or dosimetric characteristics. Firth’s logistic regression was used in cases of rare events. Previously published BM constraints from both the nonextended-field setting (V10Gy $\geq 90\%$, V20Gy $\geq 75\%$, and V40Gy $\geq 37\%$) and the extended-field setting were evaluated (BM mean $>30.3$ Gy) as described in each respective publication, including covariates. Associations
of hematologic endpoints with $V_{5Gy} \geq 98\%$ and $V_{20Gy} \geq 70\%$ were performed using the Fisher exact test.

**Results**

**Patient, cancer, treatment, and toxicity characteristics**

Fifty-two patients with locally advanced cervical cancer treated with EF-CRT with concurrent cisplatin were identified (Table 1). All patients were treated using an IMRT technique: 21 (40.4%) with volumetric-modulated arc therapy and 31 (59.6%) with static-field IMRT. Two patients (3.9%) started treatment urgently with 3D-CRT (9 Gy in 5 fractions and 18 Gy in 10 fractions) owing to vaginal bleeding and were converted to IMRT plans. Fifty-one patients (98.1%) were treated with brachytherapy: 17 (32.7%) interstitial and 35 (67.3%) intracavitary. One patient (1.9%) declined brachytherapy. The median mean BM dose was 28.40 Gy (interquartile range [IQR], 26.4-30.2). Table 1 further details radiation dosimetric characteristics.

All patients in the study received concurrent cisplatin, and 17 patients (33%) required dose reduction. The median number of cycles of cisplatin was 5 (IQR, 4-5). Forty-eight of the patients (92.31%) experienced HT $\geq 2$ and 28 (53.85%) experienced HT $\geq 3$ (Table 2).

**Predictors of hematologic toxicity**

Supplemental Table A demonstrates univariate analysis of the association between clinical or dosimetric variables with any grade $\geq 2$ HT and grade $\geq 2$ leukopenia. African American race trended toward association with HT $\geq 2$ (odds ratio [OR], 14.84; 95% CI, 0.75-292.62; $P = .08$) and leukopenia $\geq 2$ (OR, 5.25; 95% CI, 0.79-57.25; $P = .06$) on univariate analysis. There was no significant association between any of the HT endpoints and age, BMI, or CCI (all $P > .05$). Among the BM metrics that were analyzed, $V_{5Gy} \geq 98\%$ (volume of BM receiving 5 Gy) was associated with leukopenia $\geq 2$ (OR, 5.89; 95% CI, 1.10-472.72; $P = .02$; 96% vs 72%) and trended toward association with HT $\geq 2$ (OR, 11.51; 95% CI, 0.59-225.67; $P = .11$; 100% vs 84%). $V_{20Gy} \geq 70\%$ was associated with increased rates of leukopenia $\geq 2$ (OR, 9.21; 95% CI, 1.002-431.25; $P = .02$; 96% vs 73%).

When accounting for race on MVA, $V_{5Gy} \geq 98\%$ was associated with leukopenia $\geq 2$ (OR, 17.73; 95% CI, 1.71-

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**Table 1** Radiation dosimetric characteristics.

| Toxicity                  | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---------------------------|---------|---------|---------|---------|---------|
| Any hematologic toxicity  | 1 (1.92)| 3 (5.77)| 20 (38.46)| 19 (36.54)| 9 (17.31)|
| Leukopenia                | 3 (5.77)| 5 (9.62)| 21 (40.38)| 16 (30.77)| 7 (13.46)|
| Neutropenia               | 12 (24.00)| 8 (16.00)| 12 (26.00)| 13 (26.00)| 5 (10.00)|
| Anemia                    | 6 (11.54)| 11 (21.15)| 25 (48.08)| 9 (17.31)| 1 (1.92)|
| Thrombocytopenia          | 27 (51.92)| 12 (23.08)| 8 (15.38)| 3 (5.77)| 2 (3.85)|

* Toxicity grading was based on the Cooperative Group Common Toxicity Criteria.

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**Table 2** Distribution of hematologic toxicity.

| Patient, No. (%)         | Patients, No. (%) | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|--------------------------|------------------|---------|---------|---------|---------|
| Any hematologic toxicity | 1 (1.92)         | 3 (5.77)| 20 (38.46)| 19 (36.54)| 9 (17.31)|
| Leukopenia               | 3 (5.77)         | 5 (9.62)| 21 (40.38)| 16 (30.77)| 7 (13.46)|
| Neutropenia              | 12 (24.00)       | 8 (16.00)| 12 (26.00)| 13 (26.00)| 5 (10.00)|
| Anemia                   | 6 (11.54)        | 11 (21.15)| 25 (48.08)| 9 (17.31)| 1 (1.92)|
| Thrombocytopenia         | 27 (51.92)       | 12 (23.08)| 8 (15.38)| 3 (5.77)| 2 (3.85)|

* Denotes that Firth’s logistic regression was used to account for rare events.

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**Table 3** Multivariate analysis of hematologic toxicity with models including (A) race and $V_{5Gy}$ and (B) race and $V_{20Gy}$ using logistic regression.

| Model A                |                          | $V_{5Gy} <98\%$ vs $\geq 98\%$ |                          | Race (African American vs others) |                          |
|------------------------|--------------------------|---------------------------------|--------------------------|----------------------------------|--------------------------|
|                        | OR (95% CI)              | $P$ value                       | OR (95% CI)              | $P$ value                        |                          |
| Grade $\geq 2$ hematologic toxicity | 21.76 (0.99-473.43) | .05*                           | 26.58 (1.21-578.25) | .04*                            |                          |
| Grade $\geq 2$ leukopenia         | 17.73 (1.71-183.56) | .02                            | 9.76 (1.43-66.44)       | .02                             |                          |

| Model B                |                          | $V_{20Gy} <70\%$ vs $\geq 70\%$ |                          | Race (African American vs others) |                          |
|------------------------|--------------------------|---------------------------------|--------------------------|----------------------------------|--------------------------|
|                        | OR (95% CI)              | $P$ value                       | OR (95% CI)              | $P$ value                        |                          |
| Grade $\geq 2$ hematologic toxicity | 2.31 (0.28-18.75) | .43*                           | 13.70 (0.70-268.09)      | .08*                            |                          |
| Grade $\geq 2$ leukopenia         | 9.43 (1.01-87.72) | .049                           | 5.39 (0.89-32.55)        | .07                             |                          |

*Abbreviations: CI = confidence interval; OR = odds ratio; $V_{xGy}$ = percentage of bone marrow volume receiving $x$ Gy.

*Denotes that Firth’s logistic regression was used to account for rare events.
18.356; \( P = .02 \) and HT \( \geq 2 \) (OR, 21.76; 95% CI, 0.99-473.43; \( P = .05 \)), whereas V20Gy \( \geq 70\% \) was associated with leukopenia \( \geq 2 \) (OR, 9.43; 95% CI, 1.01-87.72; \( P < .05 \)) (Table 3).

Although previously described radiation metrics for pelvic radiation in the literature (V10Gy \( \geq 90\% \), V20Gy \( \geq 75\% \), or V40Gy \( \geq 37\% \)) and their respective HT endpoints were not exactly found to be associated in our extended-field patient cohort, the V20Gy metric was very similar to our findings \(^{19,27,31}\) (Table 4). 

**Discussion**

To our knowledge, this is the largest study to evaluate the dosimetric patterns specifically of extended-field IMRT with concurrent chemoradiation to predict HT in patients with cervical cancer with para-aortic lymph node metastasis.

Our results showed that African American race was associated with leukopenia \( \geq 2 \) (OR, 5.25; CI, 0.79-57.25; \( P = .04 \)) and trended toward association with increased HT \( \geq 2 \) (OR, 14.84; 95% CI, 0.75-291.62; \( P = .08 \)) on univariate analysis. Race was also associated with HT \( \geq 2 \) (OR, 26.58; 95% CI, 1.21-578.25; \( P = .04 \)) and leukopenia \( \geq 2 \) (OR, 9.76; 95% CI, 1.43-66.44; \( P = .02 \)) on MVA when including V5Gy \( \geq 98\% \) in the model but trended toward significance when V20Gy \( \geq 70\% \) (HT \( \geq 2 \); OR, 13.70; 95% CI, 0.70-268.09; \( P = .08 \)); leukopenia \( \geq 2 \); OR, 5.39; 95% CI, 0.89-32.55; \( P = .07 \)) was included in the model (Table 4). Although studies have been published on the role of pharmac-ethnicity, the literature shows conflicting results with respect to differences in toxicity of systemic therapy among races. Toxicity results in our cohort were focused solely on hematologic toxicity and did not encompass many of the other toxic effects that patients commonly experience during chemoradiation, including gastrointestinal and genitourinary adverse effects. Moreover, because socioeconomic information for this cohort was not available, the clinical implications of these results are limited.

Our results do not demonstrate an association between BMI and HT for patients with cervical cancer treated with EF-CRT. This is in contrast to Yan et al, who found that nonobese patients (BMI <30 kg/m\(^2\)) were more likely to experience HT during EF-CRT treatment for cervical cancer. Overall, previously published studies investigating the interaction between BMI and HT showed conflicting results. The differences in our findings regarding BMI may be owed to the small sample size of both of our study cohorts or to the significantly lower use of 3D-CRT in our study. Overall, the cohorts included in the current study and that by Yan et al are similar, with the exception of (1) a greater proportion of Hispanic patients in the study by Yan et al compared with a greater proportion of African American patients in our cohort and (2) a greater proportion of African American patients in our cohort and (2) a greater proportion of Hispanic patients in the study by Yan et al compared with a greater proportion of African American patients in our cohort.

### Table 4 Summary of existing published dosimetric bone marrow constraints for cervical cancer concurrent chemoradiation

| Authors          | Sample size | Dates Radiation field | Technique (IMRT vs 3D-CRT) | Identified dosimetric constraint | Toxicity endpoint | Validated | P-value |
|------------------|-------------|-----------------------|---------------------------|---------------------------------|-------------------|----------|---------|
| Mell et al \(^{19}\) | 44          | 2000-2004 Pelvis IMRT | Bone marrow V10Gy \( \geq 20\% \), Bone marrow V20Gy \( \geq 27\% \) | Grade 2 or worse hematologic toxicity | No | No | (.96) |
| Rose et al \(^{27}\) | 81          | 2000-2008 Pelvis 94% IMRT | Bone marrow V10Gy \( \geq 25\% \), Bone marrow V20Gy \( \geq 26\% \) | Grade 2 or worse hematologic toxicity | No | No | (.26) |
| Klopp et al \(^{31}\) | 40          | 2006-2008 Pelvis IMRT | Bone marrow V20Gy \( \geq 42\% \), Bone marrow V40Gy \( \geq 37\% \) | Grade 2 or worse hematologic toxicity | No | No | (.85) |
| Yan et al \(^{23}\) | 38          | 2008-2015 Extended field IMRT | Mean dose to total bone marrow \( >30.3 \) Gy | Mean dose to total bone marrow \( >30.3 \) Gy | No | No | (.96) |

**Abbreviations:** 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; V\( _{x} \)Gy = percentage of bone marrow volume receiving \( x \) Gy. 
*Each hematologic endpoint and dosimetric constraint were analyzed via the statistical methodology in each respective publication including covariates.

**Table 4**
proportion of patients with stage 3B disease or higher in our cohort (43.9% vs 26.3%).

In terms of dosimetric predictors, our study suggests that V5Gy and V20Gy are associated with acute HT in patients with locally advanced cervical cancer undergoing EF-CRT. When we assessed previously described radiation metrics specified for the nonextended-field setting (V10Gy ≥90%, V20Gy ≥75%, and V40Gy ≥37%), our results did not show an association with the primary end-point studied (eg, grade 2 or higher leukopenia, grade 3 or higher leukopenia, etc) (Table 4).19,27,31 However, we found that a similar V20Gy metric that was previously found to be associated with leukopenia ≥2 in pelvic RT patients (V20Gy ≥75%) also applied to our patient population (V20Gy ≥70%).19,27 Additionally, validation of the RTOG-identified BM constraint (V40Gy >37%) is limited, because only 4 patients in the 52-patient cohort had a BM V40Gy >37%. All 4 of the patients in our cohort with V40 GY >37% experienced both HT ≥2 and leukopenia ≥2. Of the 48 remaining patients with V40Gy ≤37%, 44 (92%) and 40 (83%) experienced HT ≥2 and leukopenia ≥2, respectively. Unsurprisingly, the HT ≥2 rates in our study of EF-CRT are much higher than the findings of Klopp et al, who reported that 40% of patients with V40Gy ≤37% experienced HT ≥2.11 Overall, the inability to extrapolate this particular pelvic BM dosimetric constraint may be owed to the much larger radiation field used in EFRT, which extends up the spine, generally to T12 or L1. To that end, our results suggest that some previously published pelvic BM constraints may not be applicable to the extended-field radiation setting.

When we evaluated the only other described radiation metric in the extended-field setting, mean BM >V30.3Gy, we similarly did not observe an association with HT.23 This may be owed to the almost exclusive use of IMRT in our study as compared with the cohort from Yan et al.23 However, the overall rate of HT ≥3 was similar between our study and that by Yan et al, at approximately 50%. This may be explained by the higher stage of disease of patients in our cohort (43% vs 26% were FIGO ≥III), with the caveat that the staging was based on FIGO 2009 staging. In our practice, most patients who receive IMRT receive a simultaneous integrated boost for any gross nodal involvement, which may further lead to variation in dosimetric patterns between 3D-CRT and IMRT planning.42 Another potential explanation is that physicians may have modified the systemic therapy regimen once hematologic cell lines were noted to decrease and depending on the timing of brachytherapy, which may differ between institutional practices. We postulate that differences in treatment planning, small patient numbers, physician behavior, and the patient population itself may have led to the differences observed between these 2 studies.

Comparison with other published dosimetric pelvic BM constraints is unsurprisingly difficult given the small sample size (N <100) of each of the published cohorts.19,23,27,31 Given the high volume receiving 5 Gy that was noted in this study (V5Gy ≥98%), it is unclear whether the dosimetric constraint is clinically meaningful. Additionally, the V20Gy constraint was found to be important in both this study and a prior pelvic RT study.19,27 Taken together, these findings suggest that heightened attention to volumetric low-dose spill to the BM may be beneficial to reduce rates of HT. From a radiobiological perspective, the exquisite radiation sensitivity of hematopoietic cells is well established and supports this low-dose importance conceptually.43 The general concept of the importance of low-dose radiation is consistent with other published series,19,27 but the optimal cutoff from an inverse planning perspective has not been robustly identified in the extended-field radiation setting. Despite these limitations, the overall higher rates of HT in the extended-field setting compared with the treatment of the pelvis suggest that there should be further investigation into meaningful dose constraints for patients undergoing EF-CRT.

Although a validated dose constraint for EF-CRT is needed, more stringent constraints may result in increased toxicity in other organs at risk.44,45 However, as suggested by the INTERTECC-II trial and a phase 2 study out of India, IMRT has the potential benefit to reduce both gastrointestinal and HT.28–30 Other methods of decreasing HT may include further investigation optimizing chemotherapy delivery and dosing. For instance, there is some suggestion that cisplatin administered every 3 weeks is associated with lower rates of HT.17 Advances in imaging, radiation techniques, and improved patient selection of those who would benefit most from prophylactic para-aortic nodal radiation may assist in reducing the high rates of HT associated with EF-CRT.

Limitations and future directions

Aside from the retrospective nature of our study, we were principally limited by a small data set. However, to our knowledge, our study is the largest and only IMRT-exclusive cohort to describe HT in EF-CRT. In addition, our data set comprised patients from multiple treatment centers, which may have biased data by differences in practice patterns of oncologists or of the patient cohort. However, radiation treatment planning was performed using consistent extended-field radiation treatment fields and dosing schemes. Moreover, the multi-institutional nature of this study may improve generalizability. It is also unclear whether varying dose metrics would apply to different anatomic bone marrow regions. Perhaps the biggest limitation of the study was the lack of positron emission tomography (PET) or other functional imaging methods to predict areas of active BM to be used as avoidance structures.46–48 INTERTECC-2 specifically attempted to address this question in a prospective cohort and found that the use of
functional image—guided RT to guide BM sparing techniques was associated with lower rates of neutropenia compared with standard IMRT for patients treated with nonextended-field chemoradiation. On the contrary, Yan et al did not find an added benefit to the use of functional imaging in identifying dosimetric predictors of HT in the extended-field setting. Active BM defined by PET was not included in our study because of the challenges in deformable registration of the PET scans to the treatment-planning computed tomography scans owing to the large fields involved. These technical factors may have contributed to the lack of benefit of functional imaging as observed by Yan et al. Moreover, areas of active BM are common among patients and primarily appear to be in the sacrum and thoracolumbar spine, which may be difficult to meaningfully avoid with low-dose isodose lines when treating para-aortic disease burden. Overall, more work must be done to further explore methods to decrease HT for extended-field radiation therapy, including exploring the potential utility and feasibility of integrating functional imaging for BM sparing techniques, such as development of a standardized atlas that is inclusive of the para-aortic region.

Conclusions

In conclusion, our results demonstrate that there may be a role in dosimetric constraints to limit HT for patients undergoing EF-CRT. Acute HT in patients receiving EF-CRT was associated with BM radiation dose and race but not with age, BMI, or CCI. Limiting low-dose BM V5Gy to <98% and V20Gy to <70% to 75% may reduce rates of HT ≥2 and the subsequent need for chemotherapy reduction or treatment interruption. Given the limitation of sample size as well as the retrospective nature of the data, these findings are hypothesis generating, and future studies are needed to further validate these results. Overall, these data support the role of BM-sparing techniques to reduce HT for patients receiving EF-CRT.

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