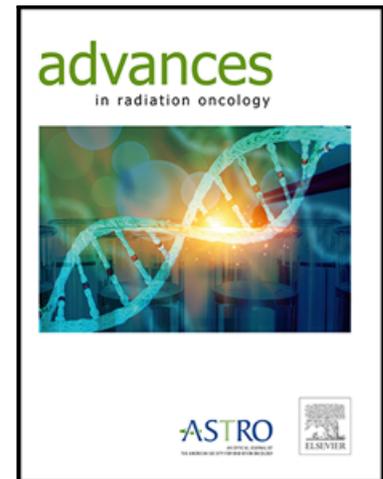# Journal Pre-proof

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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Please cite this article as: Jared H.L. Hara M.D. , Jessica M.S. Jutzy M.D., Ph.D. , Ritu Arya M.D. , Rajul Kothari M.D. , Anne R. McCall M.D. , Andrew R. Howard M.D. , Yasmin Hasan M.D. , John F. Cursio Ph.D. , Christina H. Son M.D. , Predictors of acute hematologic toxicity in women receiving extended-field chemoradiation for cervical cancer: Do known pelvic radiation bone marrow constraints apply?, *Advances in Radiation Oncology* (2022), doi: https://doi.org/10.1016/j.adro.2022.100998

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TITLE

Predictors of acute hematologic toxicity in women receiving extended-field chemoradiation for cervical cancer: Do known pelvic radiation bone marrow constraints apply?

RUNNING TITLE

Extended-Field Radiation Hematologic Toxicity

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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DATA AVAILABILITY STATEMENT FOR THIS WORK

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

ABSTRACT

Objectives

Cervical cancer patients 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 impact timely delivery of chemoradiation. Factors associated with HT in this setting have not been well-studied.

Methods

This is a retrospective analysis of women treated with EF-CRT from 2012-2018 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. BM metrics include: V5Gy, V10Gy, V15Gy, V20Gy, V25Gy, V30Gy, V35Gy, V40Gy and V45Gy. HT was defined as grade 2+ (Cooperative Group Common Toxicity Criteria) leukopenia, anemia, neutropenia, or thrombocytopenia. Univariate and multivariate analysis (UVA, MVA) were performed using chi-squared test, Fisher's 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=0.02) and grade 2+ HT (p=0.05). Most previously described radiation metrics were not reproduced in our cohort, but a similar constraint, V20Gy < 70%, was associated with reduced leukopenia 2+ on UVA (p=0.02) and MVA (p<0.05).

Conclusions

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

INTRODUCTION

Cervical cancer is the 3rd 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) are required. Patients with para-aortic lymph node (PALN) metastasis or who are at high risk for PALN involvement are frequently treated using extended-field radiotherapy with concurrent chemotherapy (EF-CRT) [2, 3]. However, these methods are associated with significant hematologic toxicity (HT). For example, over 80% of women in RTOG 0116 experienced grade 3 or higher HT [4]. Moreover, 33-50% of patients that 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 >49-56 days can negatively impact 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 NCCN 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 CCRT was associated with better 5-year OS and higher relative completion rate of scheduled chemotherapy cycles

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[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 impact on optimizing a patient's outcome. Previous studies suggest 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]. While 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 to the traditional 3-dimensional conformal RT 4-field box technique (3D-CRT) [20]. The INTERTECC-2 phase II/III trial demonstrated that BM-sparing IMRT with concurrent cisplatin for cervical cancer reduced HT as compared with historical standards [28, 29]. Similarly, a phase II trial from India demonstrated a reduction in rates of grade 2 neutropenia and HT with IMRT when comparing IMRT to 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 four-field box or IMRT techniques, mean total BM dose 30.3 Gy was correlated with grade 3 HT [23].

The purpose of this study was two-fold: 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 EFRT patient cohort to predict for toxicity.

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METHODS

Study design and patient population

We identified women with locally advanced cervical cancers treated at two 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, as IMRT has been associated with reduced HT toxicity compared to 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), chemotherapy cycles delivered, and nadirs for white blood cell (WBC) count, absolute neutrophil count (ANC), hemoglobin (Hgb) and platelet (Plt) 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 CT-based planning before the beginning of treatment with immobilization in alpha cradles with arms placed above their head. BM contours were standardized across all patients and included vertebral bodies within the radiation treatment field, sacrum, coccyx, pelvic bones, and femurs from top of the femoral head to the inferior border of the ischial tuberosities (Figure 1). The extended-field RT clinical target volume (CTV) included treatment to the uterus, cervix, primary mass, paracervical, parametrial, uterosacral region and at least upper half of the vagina. The nodal CTV treatment volumes included the external iliac, hypogastric, obturator and para-aortic lymph nodes with a 0.7-0.8 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 (Supplement, Table B). The nodal PTV was uniformly expanded by 0.7 cm to produce the planning target volume (PTV). A cervix internal target volume (ITV) was created using bladder-empty and bladder-full scans; this was expanded by 1.5-2.5 cm

to account for organ motion. Similarly, a vagina and parametrial ITV was created and expanded by 0.5-1.0 cm. In cases of urgent vaginal bleeding, radiation treatments utilized 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 (VMAT) 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 55-60 Gy using either a sequential or simultaneous integrated boost technique. Organs at risk including the rectum, bowel, and bladder were contoured for radiation planning. BM was contoured, but not utilized as avoidance structures for IMRT planning until 2017. Patients were reassessed towards the end of external beam radiation treatment and were given a parametrial boost if indicated and high-dose-rate intracavitary or interstitial brachytherapy. The boost treatment utilized iridium-192 with a dose of 28-30 Gy to the high-risk CTV or Point A in 4-5 treatments. Radiation therapy and brachytherapy were generally held if 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 cycles of chemotherapy concurrently with radiation. Cisplatin was generally held if an absolute neutrophil count was less than 1×10^9/L and/or platelet count was less than 100×10^9/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. Brachytherapy dose was not included given its

minimal contribution to bony structures; however, record of brachytherapy was notated. BM metrics collected included: Mean BM dose, V5Gy, V10Gy, V15Gy, V20Gy, V25Gy, V30Gy, V35Gy, V40Gy and V45Gy (where VxGy is defined as percentage of BM volume receiving x Gy). Specific dosimetric predictors of HT previously published in the literature for pelvic (non-extended-field) radiation were also evaluated in this patient cohort. These included V10Gy $\geq$ 90%, V20Gy $\geq$ 75%, and V40Gy > 37% [19, 27, 31]. A previously published dosimetric predictor in the extended-field setting was also evaluated in this patient cohort: mean BM dose > 30.3 Gy [23].

Toxicity Endpoints

Toxicity grading was based on the Cooperative Group Common Toxicity Criteria. HT endpoints included 1) any grade 2 or higher hematologic acute toxicity, not including lymphopenia, and 2) grade 2 or higher leukopenia. These endpoints were chosen as a measure of toxicity as these may result in modifications to systemic or radiation therapy and were previously utilized as HT endpoints in RTOG 0418 [31]. Previously published HT endpoints were utilized for examination of their respective published BM dosimetric constraints in this patient cohort, which included HT2+ [31], leukopenia 2+ [19, 31], neutropenia 2+ (grade 2-4 neutropenia) [19], HT3+ (grade 3-4 HT) [23], and leukopenia 3+ (grade 3-4 leukopenia) [27].

Statistical analysis

All statistical analyses were performed using STATA version 17.0 (StataCorp LLC, College Station, Texas). Univariate analysis (UVA) was performed using the chi-squared test and logistic regression. The chi-squared test or Fisher's exact test were used to compare rates of hematologic adverse events (AEs) for patients with a volume of BM irradiation from 5 to 45 Gy (V5Gy to V45Gy) dichotomized at the median as well as to compare rates of hematologic AEs 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 p-value < 0.1 from univariate logistic models were included in the multivariate model. Multivariate analysis (MVA) was performed using logistic regression to correlate HT2+ as well as leukopenia 2+ with patient or dosimetric characteristics. Firth's logistic regression was utilized in cases of rare events [33]. Previously published BM constraints from both the non-extended field setting (V10Gy 90%, V20Gy 75%, V40Gy 37%) [20, 27, 31] as well as the extended-field setting were evaluated (BM mean > V30.3Gy) [23] as described in each respective publication including covariates. Associations of hematologic endpoints with V5Gy 98% and V20Gy 70% were performed using Fisher's exact test.

RESULTS

Patient, cancer, treatment, and toxicity characteristics

Fifty-two locally advanced cervical cancer patients treated with EF-CRT with concurrent cisplatin were identified (Table 1). All patients were treated using an IMRT technique: 21 (40.4%) with VMAT 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) due to vaginal bleeding and converted to IMRT plans. Fifty-one (98.1%) patients were treated with brachytherapy: 17 (32.7%) were treated with interstitial and 35 (67.3%) were treated with intracavitary. One (1.9%) patient declined brachytherapy. The median mean BM dose was 28.40 Gy (IQR: 26.4-30.2). Table 1 further details radiation dosimetric characteristics.

All patients in the study received concurrent cisplatin, and 17 (33%) patients required dose reduction. The median number of cycles of cisplatin was 5 (IQR: 4-5). Forty-eight (92.31%) of the patients experienced HT2+ and 28 (53.85%) of the patients experienced HT3+ (Table 2).

Predictors of hematologic toxicity

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Supplemental Table A demonstrates univariate analysis of the association between clinical or dosimetric variables with any grade 2+ HT and grade 2+ leukopenia. African American race trended towards association with HT2+ (OR 14.84, 95% C.I.: 0.75 – 292.62, p=0.08) and leukopenia 2+ (OR 5.25, 95% C.I.: 0.79 – 57.25, p=0.06 on univariate analysis. There was no significant association between any of the HT endpoints and age, BMI or CCI (all p>0.05). Amongst the BM metrics that were analyzed, V5Gy ≥ 98% (volume of BM receiving 5 Gy) was associated with leukopenia 2+ (OR 5.89, 95% C.I.: 1.10 – 472.72, p=0.02; 96% vs 72%) and trended towards association with HT 2+ (OR 11.51, 95% C.I.: 0.59 – 225.67, p = 0.11; 100% vs 84%). V20Gy   70% was associated with increased rates of leukopenia 2+ (OR 9.21, 95% C.I.: 1.002 – 431.25, p=0.02; 96% vs 73%,).

When accounting for race on MVA, V5Gy   98% was associated with leukopenia 2+ (OR 17.73, 95% C.I.: 1.71 – 183.56, p =0.02) and HT2+ (OR 21.76, 95% C.I.: 0.99 – 473.43, p=0.05), while V20Gy 70% was associated with leukopenia 2+ (OR 9.43, 95% C.I.: 1.01 – 87.72, p<0.05) (Table 3).

While previously described radiation metrics for pelvic radiation in the literature (V10Gy   90%, V20Gy   75%, or V40Gy > 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 cervical cancer patients with para-aortic lymph node metastasis.

Our results revealed African-American race was associated with leukopenia 2+ (OR 5.25, C.I.: 0.79 – 57.25, p=0.04) and trended towards association with increased HT2+ (OR 14.84, 95% C.I.: 0.75 – 291.62, p=0.08) on UVA. Race was also associated with HT2+ (OR 26.58, C.I.: 1.21 – 578.25, p = 0.04) and leukopenia 2+ (OR 9.76, C.I.: 1.43 – 66.44, p=0.02) on MVA when including V5Gy   98% in the

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model, but trended towards significance when V20Gy 70% (HT2+: OR 13.70, C.I.: 0.70 – 268.09, p=0.08; leukopenia 2+: OR 5.39, C.I. 0.89 – 32.55, p=0.07) was included in the model (Table 4). While studies have been published on the role of pharmaco-ethnicity [34], the literature shows conflicting results with respect to differences in systemic therapy toxicity between races [35]. Toxicity results in our cohort are focused solely on hematologic toxicities and do not encompass many of the other toxicities that patients commonly experience during chemoradiation including gastrointestinal and genitourinary side effects. Moreover, as 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 cervical cancer patients treated with EF-CRT. This is in contrast to Yan et al., who found that non-obese patients (BMI < 30 kg/m^2) were more likely to experience HT during EF-CRT treatment for cervical cancer [23]. Overall, previously published studies investigating the interaction between BMI and HT demonstrate conflicting results [36-42]. These differences in our findings regarding BMI may be due to the small sample size of both of our study cohorts or the significantly lower use of 3D-CRT in our study. Overall, the cohorts included in the current study and Yan et al. are similar with the exception of: 1) a higher rate of Hispanic patients in Yan et al. compared to a higher rate of African-American patients in our cohort and 2) a greater 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 non-extended-field setting (V10Gy 90%, V20Gy 75%, V40Gy 37%), our results did not find an association with the primary endpoint studied (e.g. 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%) [31] is limited as only 4

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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 HT2+ and leukopenia 2+. Of the remaining patients with V40Gy   37%, 44/48 (92%) and 40/48 (83%) of the patients experienced HT2+ and leukopenia 2+, respectively. Unsurprisingly, the HT2+ 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 HT2+. Overall, the inability to extrapolate this particular pelvic BM dosimetric constraint may be due 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, BM mean > V30.3Gy, we similarly did not observe an association with HT [23]. This may be due to the almost exclusive use of IMRT in our study as compared the cohort from Yan et al. However, the overall rate of HT3+ was similar between our studies at ~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 [43]. Another potential explanation is that physicians may have modified the systemic therapy regimen once hematologic cell lines were noted to decrease and depending upon the timing of brachytherapy, which may differ between institutional practice. We postulate that differences in treatment planning, small patient numbers, physician behavior, and the patient population itself may lead to the differences observed between these two 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

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this study as well as 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 [44]. The general concept of the importance of low dose radiation is in line 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 as compared to the treatment of the pelvis suggest that there should be further investigation into meaningful dose constraints for patients undergoing EF-CRT.

While a validated dose constraint for EF-CRT is needed, more stringent constraints may result in increased toxicity in other organs at risk [45, 46]. However, as suggested by the INTERTECC-II trial and a phase II 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 dataset. However, our study is the largest and only IMRT-exclusive cohort to describe HT in EF-CRT. In addition, our dataset was comprised of patients from multiple treatment centers which may bias data by differences in practice patterns of oncologists or of the patient cohort. However, radiation treatment planning was performed utilizing 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 PET or other functional imaging methods to predict areas of active BM to be used as avoidance structures [47-49]. INTERTECC-2 specifically attempted to address this question in a prospective cohort and found that the use of functional image-guided radiotherapy (IG-IMRT) to guide BM sparing techniques was associated with lower rates of neutropenia compared to standard IMRT for patients treated with *non*-extended field chemoradiation [28, 29]. 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 [23]. PET-defined active BM was not included in our study due to the challenges in deformable registration of the PET to the treatment planning CT scans due 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 amongst patients and primarily appears to be in the sacrum and thoracolumbar spine [50], 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 age, BMI, or CCI. Limiting low-dose BM V5Gy to < 98% and V20Gy<70-75% may reduce rates of HT2+ 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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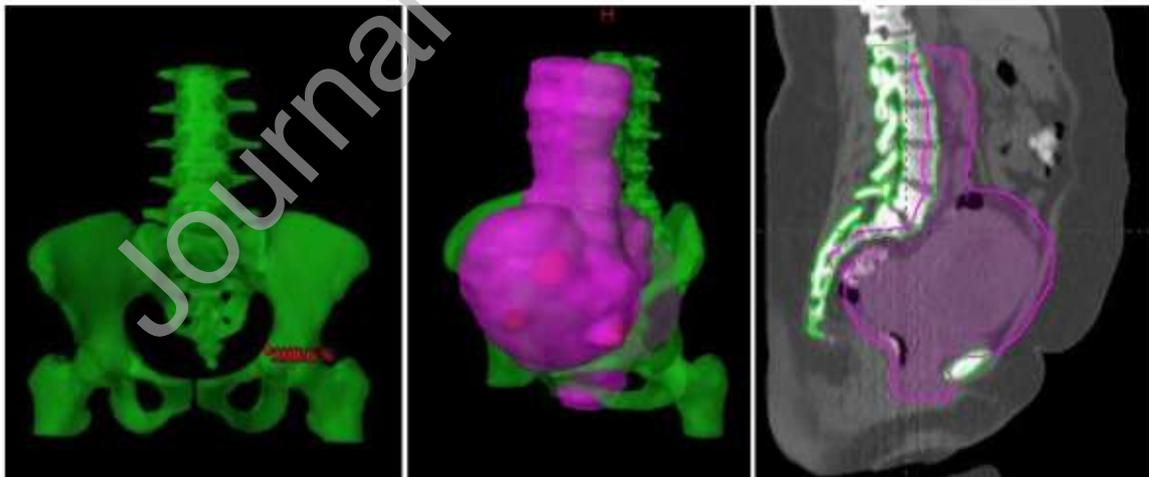
Figure 1. Representative contours. Green: bone marrow, Purple: PTV45, Red: PTV55 lymph node boost.

Table 1. Patient and treatment characteristics

Patient characteristics	N=52
Age, median (years)	44.5 (IQR: 39.3-58.8)
BMI, median (kg/m^2)	25.1 (IQR:22.7-31.2)
Race, No. (%)	
White	13 (25%)
African American	30 (58%)
Other	9 (17%)
FIGO 2009 Clinical Stage, No. (%)	
I	12 (23%)
II	18 (35%)
IIIA	19 (36%)
IV	3 (6%)
Treatment characteristics	N=52
Radiation technique, No. (%)	
Intensity-modulated radiation therapy	52 (100%)
3D-conformal radiation therapy	2 (3.9%)
Brachytherapy	51 (98%)
Intracavitary brachytherapy	35 (67.3%)
Interstitial brachytherapy	17 (32.7%)
Declined	1 (1.9%)
Dosimetric characteristics, median (IQR)	
V5Gy	98 (IQR: 94-100)
V10Gy	89 (IQR: 85-93)
V15Gy	79 (IQR: 73-87)

V20Gy	70 (IQR: 65-76)
V25Gy	59 (IQR: 54-64)
V30Gy	49 (IQR: 44-53)
V35Gy	37 (IQR: 32-42)
V40Gy	26 (IQR: 21-32)
V45Gy	12 (IQR: 9-17)
Mean Dose	26.4 (28.4-30.2)
Chemotherapy	
Cisplatin, No. (%)	52 (100%)
Cycles of cisplatin, median (IQR)	5 (IQR: 4-5)
Chemotherapy dose-reduction, No. (%)	
Yes	17 (33%)
No	34 (67%)

VxGy – percentage of bone marrow volume receiving x Gy.

Table 2. Distribution of hematologic toxicities

	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.

Table 3. Multivariate analysis of hematologic toxicity with models including A) race and V5Gy and B) race and V20 Gy using logistic regression.

Model A	V5Gy < vs. ≥ 98%			Race (African-American vs others)		
	OR	95% C.I		p-value	OR	95% C.I		p-value
Grade 2+ Hematologic Toxicity	21.76	0.99	473.43	0.05*	26.58	1.21	578.25	0.04*
Grade 2+ Leukopenia	17.73	1.71	183.56	0.02	9.76	1.43	66.44	0.02
Model B	V20Gy < vs. ≥ 70%			Race (African-American vs others)		
	OR	95% C.I		p-value	OR	95% C.I		p-value
Grade 2+ Hematologic Toxicity	2.31	0.28	18.75	0.43*	13.70	0.70	268.09	0.08*
Grade 2+ Leukopenia	9.43	1.01	87.72	0.049	5.39	0.89	32.55	0.07

*denotes that Firth's logistic regression was utilized to account for rare events

VxGy – percentage of bone marrow volume receiving x Gy. OR – odds ratio. C.I. – confidence interval.

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

Author	Sample size	Dates	Radiation Field	Technique (IMRT vs 3DCRT)	Identified Dosimetric Constraint	Toxicity Endpoint
Mell et al. [19]	44	2000-2004	Pelvis	IMRT	bone marrow V10Gy ≥ 90%	grade 2 or worse leukopenia
						grade 2 or worse neutropenia
					bone marrow V20Gy ≥ 75%	grade 2 or worse leukopenia
						grade 2 or worse neutropenia
Rose et al. [27]	81	2000-2008	Pelvis	94% IMRT	bone marrow V10Gy ≥ 95%	grade 3 or worse leukopenia
					bone marrow V20Gy ≥ 76%	grade 3 or worse leukopenia
Klopp et al. [31]	40	2006-2008	Pelvis	IMRT	bone marrow V40Gy > 37%	grade 2 or worse hematologic toxicity
						grade 2 or worse leukopenia
Yan et al. [23]	38	2008-2015	Extended-Field	71% IMRT	mean dose to total bone marrow >30.3 Gy	grade 3 or worse hematologic toxicity
					mean dose to total bone marrow	grade 3 or worse hematologic toxicity

*Each hematologic endpoint and dosimetric constraint were analyzed via the statistical methodology in each respective publication including covariates.

**V20Gy ≥ 70% was associated with grade 2+ leukopenia in this study (p=0.05)

IMRT – intensity-modulated radiation therapy. 3DCRT – three-dimensional conformal radiation therapy. VxGy – percentage of bone marrow volume receiving x Gy.