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Hematologic Toxicity on RTOG 0418: A Phase II Study of Postoperative IMRT for Gynecologic Cancer

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Abstract

Purpose—Intensity modulated radiation therapy (IMRT), compared with conventional 4-field treatment, can reduce the volume of bone marrow irradiated. Pelvic bone marrow sparing has produced a clinically significant reduction in hematologic toxicity (HT). This analysis investigated HT in RTOG 0418, a prospective study to test the feasibility of delivering postoperative IMRT for cervical and endometrial cancer in a multi-institutional setting.

Methods and Materials—Patients in the RTOG 0418 study were treated with postoperative IMRT to 50.4 Gy to the pelvic lymphatics and vagina. Endometrial cancer patients received IMRT alone, whereas patients with cervical cancer received IMRT and weekly cisplatin (40 mg/m^2). Pelvic bone marrow was defined within the treatment field by using a computed tomography–density–based auto-contouring algorithm. The volume of bone marrow receiving 10, 20, 30, and 40 Gy and the median dose to bone marrow were correlated with HT, graded by CTCAE v 3.0 criteria.

Results—Eighty-three patients were eligible for analysis (43 with endometrial cancer and 40 with cervical cancer). Patients with cervical cancer treated with weekly cisplatin and pelvic IMRT

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had grades 1-5 HT (23%, 33%, 25%, 0%, and 0% of patients, respectively). Among patients with cervical cancer, 83% received 5 or more cycles of cisplatin, and 90% received at least 4 cycles of cisplatin. The median percentage volume of bone marrow receiving 10, 20, 30, and 40 Gy in all 83 patients, respectively, was 96%, 84%, 61%, and 37%. Among cervical patients with a median percentage volume of > 37% who received 40 Gy (V40 > 37%), 75% had grade ≥ 2 HT compared with 40% of patients with a V40 ≤ 37% who had this grade ($p = 0.025$). Cervical patients with a median bone marrow dose of >34.2 Gy also had higher rates of grade ≥ 2 HT than did those with a dose of ≤ 34.2 Gy (74% vs. 43%, $p = 0.049$).

Conclusions—Pelvic IMRT with weekly cisplatin is associated with low rates of HT and high rates of weekly cisplatin use. The volume of bone marrow receiving 40 Gy and the median dose to bone marrow correlated with higher rates of grade ≥ 2 toxicity among patients receiving weekly cisplatin (cervical patients). Evaluation and limitation of the volume of bone marrow treated with pelvic IMRT is warranted in patients receiving concurrent chemotherapy.

Introduction

Pelvic bone marrow is a primary site of hematopoiesis. Standard pelvic irradiation typically treats a substantial amount of bone marrow, resulting in the depletion of hematopoietic stem cells, which are needed to repopulate erythrocytes, leukocytes, and platelets (1). As a result, pelvic irradiation has the potential to increase hematologic toxicity (HT), which can limit tolerance for chemotherapy.

For women with high-risk features after hysterectomy for cervical or endometrial cancer, pelvic irradiation is required to treat the lymphatics as well as the vagina. Concurrent chemotherapy, most commonly weekly cisplatin, is indicated for women with cervical cancer with positive nodes, margins, or parametria and may also benefit women with endometrial cancer who have high-risk features (2).

Pelvic intensity modulated radiation therapy (IMRT) can reduce the volume of normal tissue irradiated, including bone marrow, which has the potential to reduce HT and improve chemotherapy tolerance (3-6). To investigate this, other authors have identified dosimetric parameters that predict HT after pelvic irradiation and found that the volume of bone marrow irradiated predicts the occurence of HT. In a retrospective analysis, Rose *et al*. (4) found that patients in whom ≥95% of the bone marrow received 10 Gy had higher rates of grade 3 leucopenia than did those in whom <95% of the bone marrow received this dose (68.8% vs. 24.6%; $p < 0.001$) In an independent study, Albuquerque *et al*. (7) found that a volume of bone marrow receiving 20 Gy was most strongly predictive of grade ≥ 2 HT. When > 80% of the pelvic bone received 20 Gy, the risk of grade ≥ 2 HT was increased by a factor of 4.5 (7).

The goal of this study was to determine whether these dosimetric parameters could predict HT in a cohort of patients treated with IMRT in a prospective multi-institutional study.

Methods and Materials

Patients

RTOG 0418 eligibility criteria for patients with endometrial cancer included FIGO 1988 stage IB, grade 3 disease; stage IC, grade 1-3 disease; stage IIA, IIB, or IIIC (positive pelvic nodes only) disease or patients with FIGO stage IB, grade 2 disease who had no lymph node dissection. Patients with papillary serous, clear cell, or neuroendocrine carcinoma, endometrial stromal sarcoma, leiomyosarcoma, or malignant mixed Mullerian tumor were excluded. Concurrent chemotherapy was not allowed for patients with endometrial cancer. Patients with cervical cancer were enrolled if they had high-risk features, which included positive pelvic nodes with negative para-aortic nodes; microscopically positive parametria or two of the following three features: 1/3 or more stromal invasion, lymph-vascular space invasion, and large clinical tumor diameter (>4 cm). Concurrent chemotherapy with weekly cisplatin was given to all patients with cervical cancer. Patients with cervical or endometrial cancer were ineligible for the study if they had a Zubrod performance status of 3 or higher, previous pelvic irradiation, or a weight or lateral body diameter exceeding the limits of the treatment table or computed tomography (CT) scanner.

IMRT treatment planning

RTOG 0418 specified that the pelvic lymphatics were contoured according to RTOG guidelines(8). The vaginal internal target volume was created with use of a full and empty bladder scan. The protocol specified a 7-mm expansion on these volumes to generate a planning target volume (PTV), and 50.4 Gy was prescribed to the PTV. The protocol specified that the volume of small bowel receiving >40 Gy was limited to <30%; <60% of the rectum was to receive >30 Gy, and <35% of the bladder was to receive >45 Gy. No bone marrow constraints were recommended. One patient was excluded because of technical issues with CT images, which prevented the bone marrow from being successfully contoured.

Bone marrow contouring and dose-volume histogram analysis

For all analyzed patients, the entire pelvic bone was contoured for the full extent of the PTV. Initial autocontouring was performed by including tissue with density of 600-3000 on each slice through the PTV. This threshold was adjusted slightly for each patient to produce the most accurate contour. The pelvic bone from the superior aspect to the inferior aspect of the PTV was auto-contoured as a surrogate for the pelvic bone marrow, accomplished with use of a CT-density–based auto-contouring algorithm and MIM software (Cleveland, OH). Contours were then reviewed and edited as necessary in ensure that lower density marrow spaces were included by two dosimetrists (E.H. and J.N.). In addition, the contour was edited to include the femoral head but not the rest of the femur. Image files were then transferred to the Advanced Technology Consortium website (http://atc.wustl.edu/), where dose-volume histogram data were exported according to the treatment IMRT plan. A selected group of plans was reviewed by a physicist (M.S.) to ensure that the plans transferred into the Advanced Technology Consortium were identical to those in the treatment plan. Bone marrow contour data were available for 82 of the 83 study patients. The entire bone was used as a surrogate for the bone marrow. The volume of bone marrow

irradiated to at least 10, 20, 30, and 40 Gy and the median dose to the bone marrow were then exported for each patient to correlate with HT.

Statistics

RTOG 0418 adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 criteria. *Acute toxicity* in this analysis was defined as AEs occurring ≤ 90 days from the start of radiation therapy. The chi-square test was used to compare rates of hematologic AEs for patients with a volume of bone marrow irradiation from 10 to 40 Gy (V10 to V40) dichotomized at the median.

Univariate logistic regression models were used to determine if there is any correlation between volume of bone marrow irradiation, number of cisplatin cycles, cancer site, age, BMI, and hematologic AEs. Two-variable logistic models were also built using these variables.

Results

Patient characteristics

RTOG 0418 enrolled 83 eligible patients (40 with cervical cancer and 43 with endometrial cancer) who were treated with pelvic IMRT between March 20, 2006, and October 6, 2008. Concurrent chemotherapy with weekly cisplatin was given to patients with cervical cancer, and patients with endometrial cancer received radiation therapy alone. Clinical and tumor characteristics of all patients enrolled in the RTOG 0418 study are shown in Table 1.

Delivery of protocol treatment

Radiation therapy was prescribed to 50.4 Gy in 28 fractions, and the full dose was delivered to all but one patient whose treatment was stopped at 12 fractions (with grade 2 hematologic and GI toxicity and grade 3 fatigue). Of the 40 patients with cervical cancer, 83% received at least 5 cycles of cisplatin, and 90% received at least 4 cycles (Fig. 1C). Three of the 40 patients received <4 cycles due to non-HT. One patient who was included in analysis of the cervical cancer group was treated without cisplatin due to a decision by the treating physician before starting treatment,

HT in the RTOG 0418 study

Of the 40 patients with cervical cancer, 9 (23%) developed grade 1 HT, 13 (33%) developed grade 2 HT, and 10 (25%) developed grade 3 HT. Of the 43 patients with endometrial cancer, 6 (14%) developed grade 1 HT, 3 (7%) developed grade 2 HT, and 7 (16%) developed grade 3 HT. There were no grade 4 or 5 HTs. All grade 3 HTs in the patients with endometrial cancer and all but one HT in the patients with cervical cancer were lymphopenias, which are of minimal clinical impact. Rates of grade 1-5 HT and leukopenia for patients treated with endometrial or cervical cancer are shown in Fig. 1A and 1B.

Bone marrow irradiation

No specifications were given in the protocol about the volume of bone marrow to be irradiated. The impact of the volume of bone marrow irradiated was evaluated by contouring

the pelvic bone for all patients in the study. The total pelvic bone from the superior to inferior extent of the PTV was used as a surrogate of bone marrow (Fig. 2A). Examples of treatment plans and bone marrow dose-volume histograms of patients with a larger (Fig. 2B, upper panel) or smaller (Fig. 2B, lower panel) volume of bone marrow irradiated are shown. The range and median percentage volume of bone marrow irradiated to 10, 20, 30, and 40 Gy are shown in the boxplots in Fig. 2C. The median percentage volume of bone marrow receiving 10, 20, 30, and 40 Gy for all patients was 96%, 84%, 60%, and 37% (Fig. 2C) (Table 2).

Correlation of volume of bone marrow irradiated and HT

The median percentage volumes of marrow treated to 10, 20, 30, and 40 Gy were used as cutoff points for statistical analysis (Table 2). Among patients with cervical cancer with V40 > 37% (median), 75% had grade ≥ 2 HT compared with 40% of patients with V40 ≤ 37% (Fig. 3, $p = 0.025$). Patients with cervical cancer who had a mean bone marrow dose of > 34.1 Gy (dichotomized at the median) also had higher rates of grade ≥ 2 HTs than did those with a dose of ≤ 34.2 Gy (74% vs. 43%; $p = 0.049$). There was no statistically significant correlation with V10, V20, or V30 with HT. For the cervical patients, the percentage volume of bone marrow receiving 40 Gy (> 37% vs. ≤ 37%) did not correlate with the number of cycles of cisplatin (<5 vs. ≥ 5) received.

In a univariate regression analysis of all patients, the disease site (cervical) correlated with a higher risk of grade ≥ 2 HT, as would be expected given that the cervical cancer patients received chemotherapy while the endometrial cancer patients did not. For all patients, V40 > 37% showed a trend toward correlation with increased risk of grade ≥ 2 HT (OR=2.1, 95% C.I. = [0.8, 5.0], $p = 0.12$). For patients with cervical cancer, however, V40 > 37% was correlated with an increased risk of grade ≥ 2 HT (OR=4.5, 95% C.I. = [1.2, 17.4], $p = 0.029$). In the univariate regression analysis, age and body mass index were not associated with grade ≥ 2 HT among patients with cervical cancer. In a multivariate regression analysis of patients with cervical cancer, the association of V40 > 37% ($p = 0.032$) with grade ≥ 2 HT remained statistically significant after adjusting for body mass index. No statistically significant correlations of dose volume parameters was detected for patients with endometrial cancer who did not receive chemotherapy, as would be expected based on the low rate of hematologic toxicity in patients receiving pelvic radiation without chemotherapy.

Discussion

Previous studies have reported that the volume of bone marrow treated to low doses can predict HT in patients undergoing pelvic irradiation for cervical and anal cancers(3, 6). Our findings are consistent with those from other reports in that patients with higher volumes of irradiated bone marrow exhibited higher rates of HT. However, in this study we identified the V40, rather than V10 or V20, as the best predictor of hematologic toxicity in patients receiving pelvic IMRT and chemotherapy.

Weekly cisplatin was administered successfully in the study, with 90% of patients receiving at least 4 cycles of weekly cisplatin. This compares favorably with results from other series that administered concurrent cisplatin, although differences in approach limited the ability to

make any direct comparisons (9-11). A prospective randomized trial comparing standard pelvic irradiation and bone marrow sparing IMRT is underway (RTOG 1203) and will be able to determine if IMRT results in a clinically meaningful reduction in hematologic toxicity.

Minimizing bone marrow toxicity is particularly important with the introduction of more intensive concurrent and adjuvant chemotherapy regimens for cervical and endometrial cancer. Duenas-Gonzales *et al.* (12) recently reported on the incorporation of gemcitabine in addition to cisplatin for the treatment of intact cervix. This regimen improved progression-free survival and overall survival but was associated with significantly higher rates of grade 3 and 4 toxicities, highlighting the importance of minimizing radiation therapy toxicity with multi-agent chemotherapy regimens. The degree to which bone marrow sparing influences tolerance of adjuvant therapy is unknown but is of increasing relevance, with the investigation of adjuvant chemotherapy in addition to concurrent chemotherapy for cervical and endometrial cancer.

The major difference between the findings of this study and those of previous studies investigating bone marrow irradiation and HT is that this analysis found that the volume of bone marrow receiving higher doses correlated with HT. In contrast, studies by Mell *et al*. and Albuquerque *et al* found that the volume of marrow receiving 10 and 20 Gy more accurately predicted HT than did the volume receiving 30 or 40 Gy (5-7). This difference may be accounted for by the fact that a very small number of patients (n = 12) had a V10 ≤ 90% in our study. This may reflect a lack of awareness of bone marrow sparing among the diverse institutions and physicians who enrolled patients in the RTOG 0418 study, in contrast to the single institutions which have been conducted where bone marrow sparing has been emphasized. IMRT, in contrast to standard 4-field or anteroposterior/posteroanterior (AP/PA) treatment, is particularly effective at reducing the volume of bone marrow receiving higher doses while the V10 may be lower with three-dimensional treatment planning, in particular with an AP/PA approach (3). However, AP/PA treatment delivers much higher doses to the small bowel than IMRT.

Bone marrow sparing may have particular utility in the treatment of intact cervical cancer. HT can often limit the ability to deliver a full course of concurrent chemotherapy and is a major limitation to the introduction of additional cytotoxic agents (13). IMRT treatment planning for intact cervical cancer requires large margins on the cervix, perhaps on the order of several centimeters, to allow for uterine motion (14). These large margins reduce the potential for IMRT to spare the small bowel. However, the sacral bone limits posterior excursion of the uterus, so portions of the pelvic bone may be safely spared with IMRT when setup accuracy is high. As a result, bone marrow sparing may have more clinical benefit than bowel sparing in intact cervical cancer.

In conclusion, limiting the volume of bone marrow irradiated is associated with reduced rates of HT and may improve chemotherapy tolerance. For patients receiving chemotherapy and pelvic IMRT, the bone marrow can be contoured, and the median dose and V40 can be evaluated in addition to the volume of bone marrow receiving lower doses with the goal of reducing HT. Future studies should define the clinical benefit of IMRT in reducing

hematologic toxicity as well as validate the most critical dosimetric predictors of hematologic toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Pelvic bone marrow sparing reduced hematologic toxicity in patients receiving chemotherapy and pelvic IMRT on RTOG 0418. The volume of bone marrow receiving 40 Gy predicted the development of hematologic toxicity.

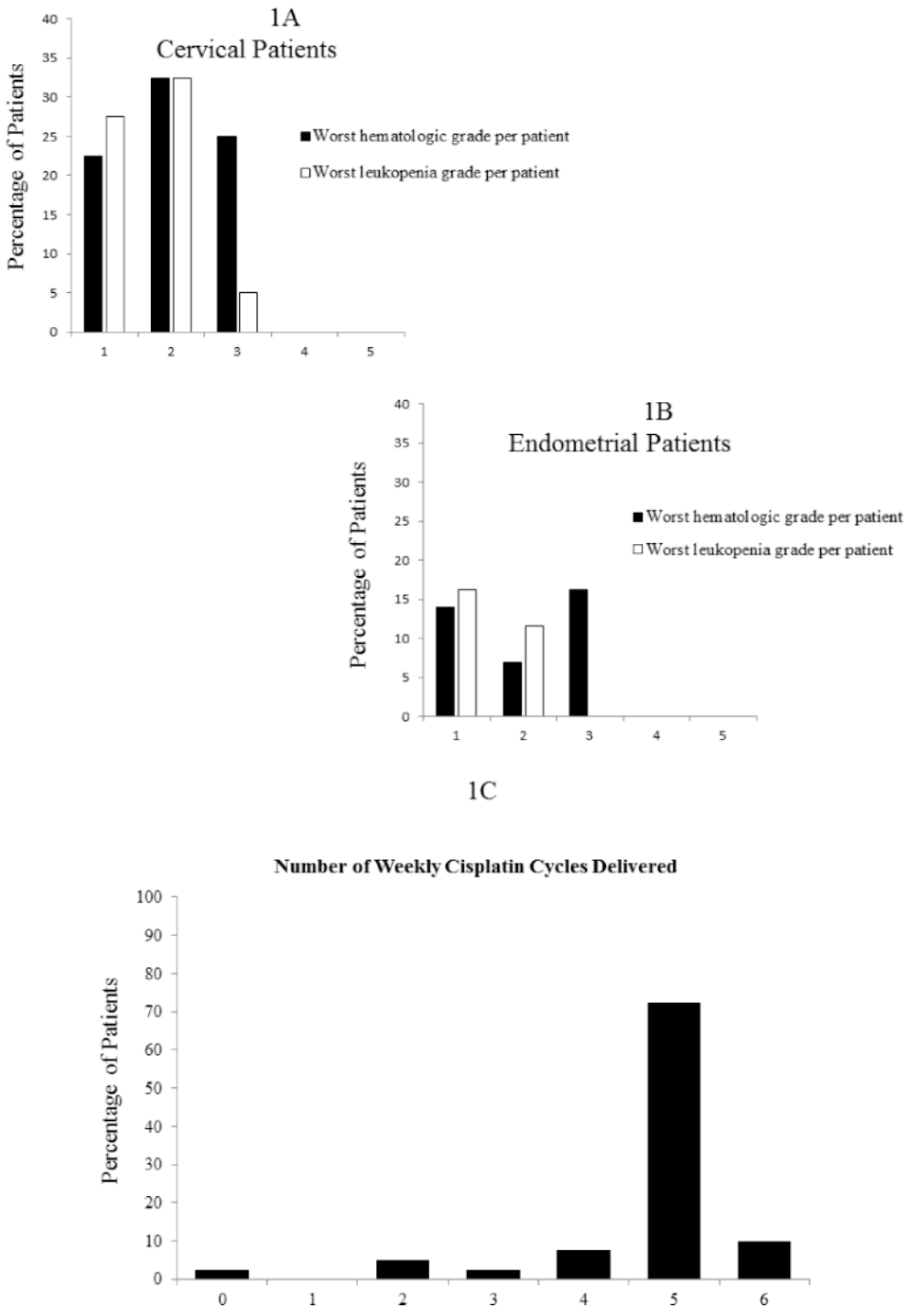
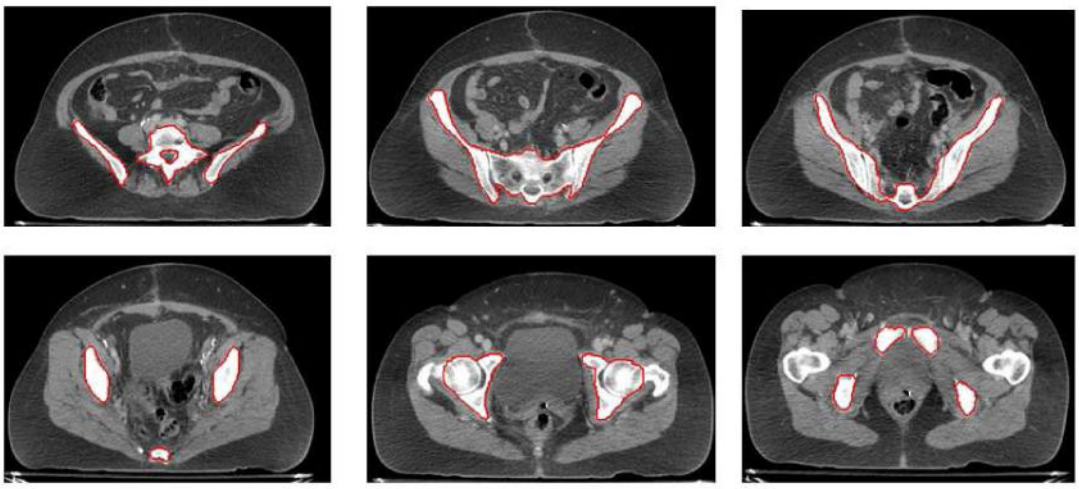


Fig. 1.

Hematologic toxicity in the RTOG 0418 study among patients with (A) cervical cancer treated with weekly cisplatin and (B) endometrial cancer treated with radiation therapy without weekly cisplatin. All hematologic toxicity included anemia, thrombocytopenia, neutropenia, leukopenia, and lymphopenia. Leukopenia included both total white blood cell

and absolute neutrophil counts. (C) Number of weekly cisplatin cycles given to patients with cervical cancer.

2A.



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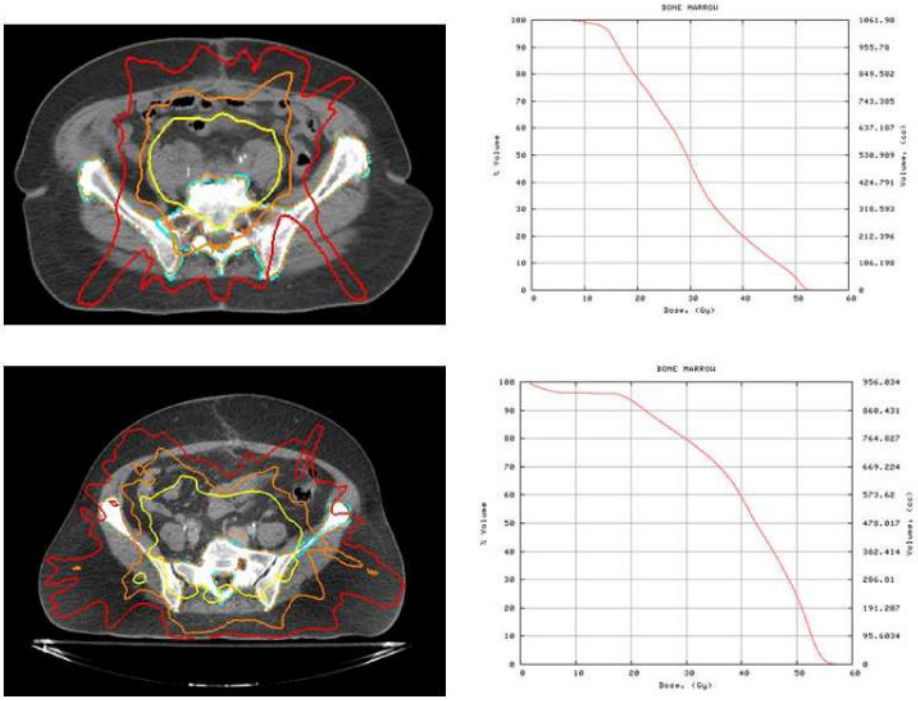

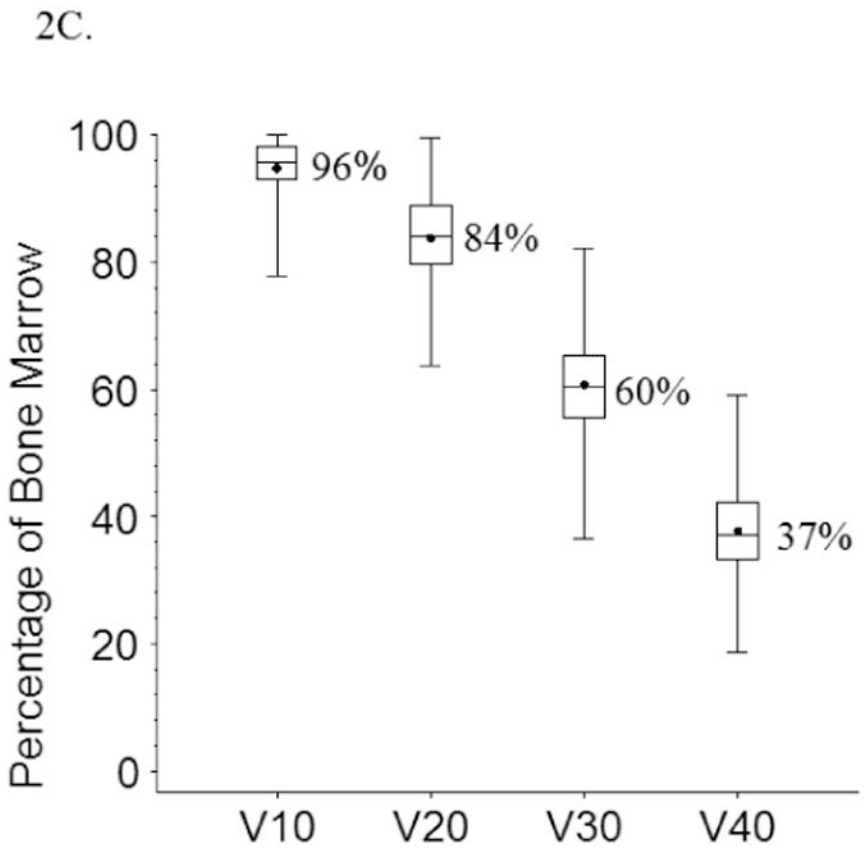

Fig. 2.

(A) Pelvic bone marrow (BM) was defined within the treatment field by using a computed tomography (CT)-density–based auto-contouring algorithm. (B) Examples of patients with a V40 = 19% (upper panel) and V40 = 59% (lower panel). (C) Distribution of dose-volume histogram parameters for all patients in the study.

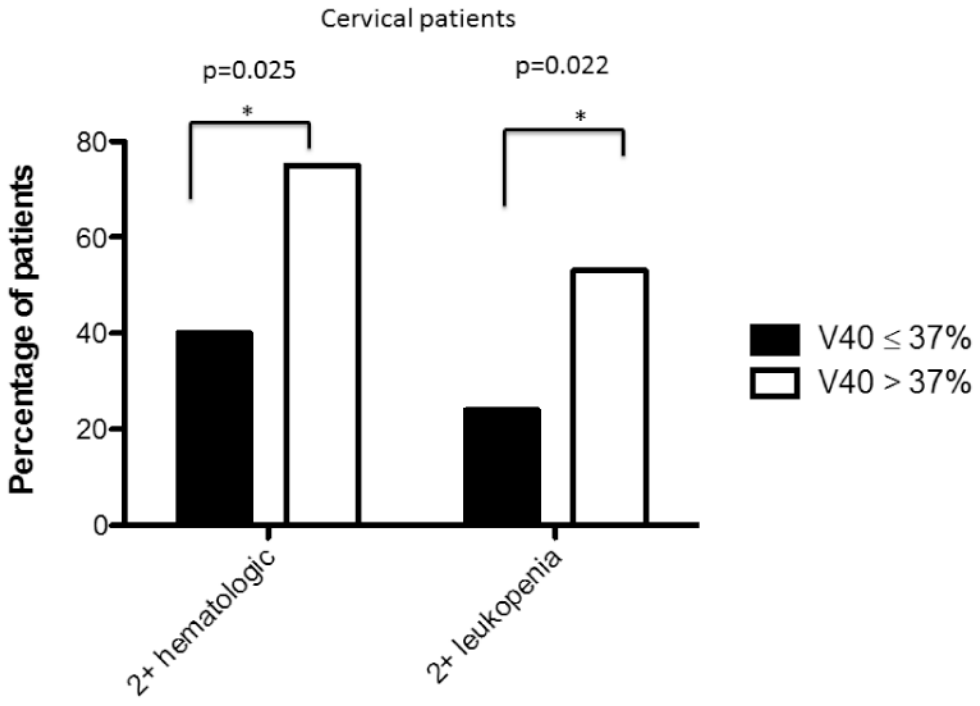

Fig. 3.

Rates of hematologic toxicity and leukopenia in patients with cervical cancer who have a V40 greater than or less than the median value (37%). $p < 0.05$ χ^2 test.

Table 1
Clinical and tumor characteristics of patients on RTOG 0418

	Endometrial (n=43)		Cervical (n=40)	
Age				
Median	57		43	
Min-max	36-73		22-71	
	n	**%**	**n**	**%**
Zubrod Performance Status				
0	38	88.4	31	77.5
1	5	11.6	9	22.5
Surgical Procedure				
TAH	32	74.4	3	7.5
Vaginal hysterectomy	0	0.0	3	7.5
Radical hysterectomy	5	11.6	28	70.0
Laparoscopic assisted vaginal hysterectomy	6	14.0	6	15.0
Endometrial - Tumor Staging				
Stage IB grade 3	1	2.3	-	-
IC grade 1-3	19	44.2	-	-
IIA	5	11.6	-	-
IIB	14	32.6	-	-
Unstaged Stage IB grade 2	1	2.3	-	-
Stage IIIC with pelvic lymph nodes	3	7.0	-	-
Cervical - FIGO				
IA	-	-	2	5.0
IB	-	-	31	77.5
IIA	-	-	4	10.0
IIB	-	-	3	7.5
Cervical - T-stage				
T1a	-	-	2	5.0
T1b	-	-	31	77.5
T2a	-	-	4	10.0
T2b	-	-	3	7.5
Cervical - N-stage				
N0	-	-	25	62.5
N1	-	-	15	37.5

Table 2

Distribution of Dosimetric Parameters

	Endometrial (n=42/43*)	Cervical (n=40)	Total (n=82)
Volume of bone marrow			
Median	1135.7	1039.5	1085.9
Q1-Q3	974.1 - 1250.3	908.0 - 1130.2	956.0 - 1173.2
Min-Max	747.0 - 1462.4	723.2 - 1391.0	723.2 - 1462.4
Mean	1119.5	1036.0	1078.8
Standard Error	25.9	23.6	18.0
V10 (%)			
Median	95.7	95.6	95.6
Q1-Q3	93.3 - 98.2	92.5 - 98.0	92.9 - 98.2
Min-Max	77.7 - 100.0	82.6 - 99.9	77.7 - 100.0
Mean	94.8	94.8	94.8
Standard Error	0.7	0.6	0.5
Volume of bone marrow getting 10 Gy			
Median	1077.4	985.3	1017.7
Q1-Q3	940.6 - 1162.6	857.7 - 1087.2	892.4 - 1130.3
Min-Max	732.7 - 1396.3	694.5 - 1339.0	694.5 - 1396.3
Mean	1060.5	983.0	1022.7
Standard Error	25.5	24.1	18.0
V20 (%)			
Median	85.0	83.2	84.0
Q1-Q3	79.9 - 88.7	78.7 - 89.0	79.6 - 88.9
Min-Max	66.8 - 99.6	63.6 - 97.0	63.6 - 99.6
Mean	84.5	83.3	83.9
Standard Error	1.1	1.1	0.8
Volume of bone marrow getting 20 Gy			
Median	942.8	865.8	908.8
Q1-Q3	825.5 - 1043.0	756.1 - 942.2	777.0 - 1005.7
Min-Max	645.7 - 1317.2	586.0 - 1246.9	586.0 - 1317.2

	Endometrial (n=42/43*)	Cervical (n=40)	Total (n=82)
Mean	945.5	863.4	905.4
Standard Error	25.2	23.3	17.7
V30 (%)			
Median	61.4	59.9	60.5
Q1-Q3	56.4 - 66.1	55.4 - 64.3	55.5 - 65.3
Min-Max	37.0 - 82.1	36.4 - 77.9	36.4 - 82.1
Mean	61.4	59.9	60.7
Standard Error	1.4	1.2	0.9
Volume of bone marrow getting 30 Gy			
Median	688.9	602.1	649.1
Q1-Q3	582.4 - 761.5	528.0 - 703.9	554.7 - 763.5
Min-Max	357.5 - 1086.3	372.4 - 1039.1	357.5 - 1086.3
Mean	686.0	622.2	654.9
Standard Error	21.4	20.8	15.3
V40 (%)			
Median	37.1	37.0	37.0
Q1-Q3	33.3 - 42.3	31.3 - 42.4	33.2 - 42.3
Min-Max	18.8 - 59.1	21.3 - 53.3	18.8 - 59.1
Mean	38.2	37.2	37.7
Standard Error	1.5	1.2	1.00
Volume of bone marrow getting 40 Gy			
Median	407.0	360.8	383.6
Q1-Q3	335.8 - 527.0	312.4 - 458.2	320.5 - 476.2
Min-Max	181.2 - 734.2	217.7 - 740.7	181.2 - 740.7
Mean	427.0	387.1	407.5
Standard Error	19.1	16.9	12.9
Median Dose to Bone Marrow, Gy			
Median	34.4	34.2	34.2
Q1-Q3	33.1 - 36.5	32.2 - 36.4	32.3 - 36.4
Min-Max	25.4 - 43.6	25.4 - 41.3	25.4 - 43.6
Mean	34.9	34.4	34.7

	Endometrial (n=42/43*)	Cervical (n=40)	Total (n=82)
Standard Error	0.6	0.5	0.4
Mean Dose to Bone Marrow, Gy			
Median	34.1	34.1	34.1
Q1-Q3	32.3 - 36.2	31.9 - 35.1	31.9 - 35.3
Min-Max	23.1 - 40.3	26.0 - 39.3	23.1 - 40.3
Mean	34.0	33.8	33.9
Standard Error	0.6	0.4	0.3

* One endometrial patient did not have bone marrow contour data.

Q1: 25th percentile, Q3: 75th percentile

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