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Longitudinal Changes in Active Bone Marrow for Cervical Cancer Patients Treated With Concurrent Chemoradiation Therapy

Longitudinal Changes in Active Bone Marrow for Cervical Cancer Patients Treated With Concurrent Chemoradiation Therapy

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Summary

Hematologic toxicity (HT) is a common adverse effect in patients with cervical cancer treated with concurrent chemoradiation therapy. In this study, we used ^{18}F-fluorodeoxyglucose positron emission tomography to quantify changes in functional bone marrow (BM) in unirradiated (extrapelvic) and irradiated (pelvic) BM in cervical cancer patients treated with concurrent chemotherapy of varying intensities. We found that patients have varying

Purpose: To quantify longitudinal changes in active bone marrow (ABM) distributions within unirradiated (extrapelvic) and irradiated (pelvic) bone marrow (BM) in cervical cancer patients treated with concurrent chemoradiation therapy (CRT).

Methods and Materials: We sampled 39 cervical cancer patients treated with CRT, of whom 25 were treated with concurrent cisplatin (40 mg/m^2) and 14 were treated with cisplatin (40 mg/m^2) plus gemcitabine (50-125 mg/m^2) (C/G). Patients underwent ^{18}F-fluorodeoxyglucose positron emission tomographic/computed tomographic imaging at baseline and 1.5 to 6.0 months after treatment. ABM was defined as the subvolume of bone with standardized uptake value (SUV) above the mean SUV of the total bone. The primary aim was to measure the compensatory response, defined as the change in the log of the ratio of extrapelvic versus pelvic ABM percentage from baseline to after treatment. We also quantified the change in the proportion of ABM and mean SUV in pelvic and extrapelvic BM using a 2-sided paired t test.

Results: We observed a significant increase in the overall extrapelvic compensatory response after CRT (0.381; 95% confidence interval [CI]: 0.312, 0.449) and separately in patients treated with cisplatin (0.429; 95% CI: 0.340, 0.517) and C/G (0.294; 95% CI: 0.186, 0.402). We observed a trend toward higher compensatory response in patients treated with cisplatin compared with C/G ($P = .057$). Pelvic ABM percentage

compensatory response, and intensive chemotherapy regimens appear to decrease the compensatory response, which may increase the risk of HT.

was reduced after CRT both in patients receiving cisplatin ($P<.001$) and in those receiving C/G ($P<.001$), whereas extrapelvic ABM percentage was increased in patients receiving cisplatin ($P<.001$) and C/G ($P<.001$). The mean SUV in pelvic structures was lower after CRT with both cisplatin ($P<.001$) and C/G ($P<.001$). The mean SUV appeared lower in extrapelvic structures after CRT in patients treated with C/G ($P=.076$) but not with cisplatin ($P=.942$). We also observed that older age and more intense chemotherapy regimens were correlated with a decreased compensatory response on multivariable analysis. In patients treated with C/G, mean pelvic bone marrow dose was found to be negatively correlated with the compensatory response. **Conclusion:** Patients have differing subacute compensatory responses after CRT, owing to variable recovery in unirradiated marrow. Intensive chemotherapy regimens appear to decrease the extrapelvic compensatory response, which may lead to increased hematologic toxicity.

Introduction

Concurrent chemoradiation therapy (CRT) is standard treatment for locoregionally advanced cervical cancer. However, hematologic toxicity (HT) is a common adverse effect [1-3] that can lead to delayed or missed chemotherapy cycles and treatment breaks [2, 4-6], which may ultimately jeopardize disease control [7]. Previous studies have found that chemotherapy intensification can improve pathologic response, progression-free survival, and overall survival [1, 4, 8, 9]. However, HT can compromise chemotherapy delivery, making its prevention an important objective.

Both radiation and chemotherapy are myelosuppressive, but the extent to which bone marrow (BM) irradiation contributes to low peripheral blood cell counts in the setting of CRT is unclear. Hematopoietically active BM (ABM) stem cells are sensitive to ionizing radiation [10]. In cervical cancer patients, the pelvic BM and much of the lumbar BM may be included in the radiation field, encompassing up to 50% of the total ABM [11, 12]. HT is rare in patients who receive solely pelvic radiation therapy (RT) [13], largely as a result of compensatory hematopoiesis in unirradiated BM [12]. However, chemotherapy can suppress compensatory hematopoiesis, making the volume of pelvic and lumbar BM exposed to radiation a significant factor.

Previous normal tissue complication probability modeling studies have found that acute HT is associated with increased radiation dose to the pelvic BM in patients undergoing CRT [14, 15]. Furthermore, sparing ABM using intensity modulated RT (IMRT) may be an effective strategy to reduce HT [16, 17]. Various functional imaging modalities have been used to identify ABM, such as 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG) and 3′-deoxy-3′-[18F]fluorothymidine (^{18}F-FLT) positron emission tomography (PET) [18-21]. These studies suggest that BM-sparing IMRT may improve tolerance to chemotherapy in the concurrent and potentially the adjuvant and salvage settings. However, significant variability in the incidence of HT remains even in patients treated with BM-sparing IMRT, and the effects of

CRT on compensatory hematopoiesis, particularly in the subacute setting, are largely unknown.

A leading hypothesis is that variation in the BM compensatory response is a determinate of patients' tolerance to chemotherapy. The aim of the present study was to quantify changes in ABM distributions in unirradiated and irradiated BM in a sample of cervical cancer patients treated with concurrent chemotherapy of varying intensities. We hypothesized that there would be variation in the compensatory response to CRT and that ABM in unirradiated extrapelvic structures would increase after CRT, in a manner dependent on chemotherapy intensity.

Methods and Materials

Patient selection

We studied 39 patients with stage IB to IVA cervical cancer treated with concurrent CRT between July 2009 and December 2015 at The University of California San Diego (UCSD). The study was approved by our institutional review board. Eligible patients had biopsy-proven clinical stage IB to IVA cervical carcinoma and underwent postoperative or definitive RT with concurrent weekly chemotherapy. All patients underwent ^{18}F-FDG-PET at baseline and within 1.5 to 6 months of completing treatment. We identified 146 patients with stage IB to IVA cervical cancer treated at our institution (July 2009 to December 2015). We excluded patients who were treated with extended field RT (n=13), had external beam RT (EBRT) at outside facilities (n=24), did not receive cisplatin or cisplatin plus gemcitabine (C/G) (n=22), lacked a baseline ^{18}F-FDG-PET (n=26), lacked a follow-up ^{18}F-FDG-PET within window (i.e. >6 weeks and < 6 months following RT (n=21)), or who received granulocyte-monocyte colony stimulating factor (n=1). In the end, we were left with 39 patients. Of the 39 patients, 25 were treated with cisplatin and 14 were treated with C/G.

Chemotherapy delivery, transfusions, and growth factors

Of the 39 patients, 25 patients were treated with concurrent cisplatin (40 mg/m^2 weekly) and 14 patients were treated with concurrent cisplatin (40 mg/m^2 weekly) and gemcitabine (50-125 mg/m^2 weekly) (C/G). Ten patients treated with cisplatin were on a phase 2 clinical trial (clinicaltrials .gov identifier: NCT01554397). Patients treated with gemcitabine were on a phase 1 clinical trial (clinicaltrials.gov identifier: NCT01554410). No patients were treated with adjuvant chemotherapy. Chemotherapy was held for white blood cell count <2.0 × 10^9/L, absolute neutrophil count <1.0 × 10^9/L, platelet count <50 × 10^9/L, or creatinine clearance <50 mL/min. No patients received platelet transfusions. All patients underwent collection of blood for complete blood counts at baseline (before treatment) and weekly during CRT, including for 2 weeks after EBRT.

Radiation simulation, planning, and delivery

Patients were simulated with customized immobilization in the supine position with computed tomography (CT) scans extending from T12 to midfemur at 2.5- to 3.0-mm slice thickness. The clinical target volume (CTV) consisted of the cervical tumor, cervix and uterus (if present), superior vagina, paracervical and parametrial tissue, and regional lymph nodes (common, internal iliac, external iliac, obturator, and presacral). Lymph node areas were identified by a 5- to 7-mm margin around visualized blood vessels. The planning target volume (PTV) consisted of a 5- to 7-mm margin around the nodal CTV, a 10-mm margin around the parametria and upper vagina, and a 15-mm margin around the cervix and uterus or vaginal cuff. The small bowel, rectum, bladder, bilateral femoral heads, and total pelvic BM were delineated as avoidance structures.

All patients underwent pelvic IMRT, 45.0 to 59.4 Gy in 25 to 28 fractions, 5 fractions per week. The IMRT plans were generated using 6 or 15 MV photons using the Eclipse treatment planning system. Image-guided ABM sparing was performed in 15 patients, of whom 8 were treated with cisplatin and 7 were treated with gemcitabine according to a protocol we developed (16). For image guided ABM sparing, the ABM was defined as a subvolume of pelvic BM with standardized uptake values corrected for body weight (SUV) greater than or equal to the individuals' mean SUV over the entire pelvic BM volume. For patients requiring simultaneous integrated boost to gross nodal disease, the primary PTV was treated to 47.6 Gy in 1.7-Gy fractions (28 fractions), and the integrated boost PTV was treated to 59.4 Gy in 2.12-Gy fractions (28 fractions). Patients with parametrial disease received a boost of 2 to 10 Gy in 1 to 5 fractions. Patients with nodal disease received a boost of 2 to 12 Gy in 1 to 6 fractions.

For definitive treatment, patients received high-dose-rate (HDR) intracavitary brachytherapy insertions twice weekly after receiving EBRT. The prescribed dose for HDR brachytherapy was 5.5 to 6.0 Gy per fraction in 5 fractions or 7.0 Gy in 4 fractions to the high-risk CTV.

^{18}F-FDG-PET imaging and bone marrow delineation

The patients imaged with ^{18}F-FDG-PET/CT had intravenous administration of 200 to 400 MBq of ^{18}F-FDG 60 minutes before being scanned. The patients in this study received a total body ^{18}F-FDG-PET/CT scan before starting CRT and within 1.5 to 6 months of completing CRT. All patients had baseline and follow-up ^{18}F-FDG-PET/CT imaging performed at The University of California San Diego (UCSD).

We used the MIM platform (MIM Software, Inc, Cleveland, OH) to contour both pelvic and extrapelvic bone marrow structures on each patient's baseline and follow-up ^{18}F-FDG-PET/CT scans. The following pelvic structures were contoured: L5/sacrum, ilium, and ischium/pubes/proximal femorae. The following extrapelvic structures were contoured: cervical vertebrae, thoracic vertebrae, scapula/proximal humerus, clavicle/sternum, and ribs. The lumbar vertebrae (L1-L4) were also contoured and were not treated as pelvic or extrapelvic structures, given that the lumbar vertebrae received varying doses of radiation. The external contours of all vertebrae and bones were outlined on the CT scan to define the total BM volume.

Identification of ABM volumes using ^{18}F-FDG-PET/CT imaging

For each pre-RT and post-RT imaging scan, the mean SUV (corrected for body weight) of the total BM served as a threshold. ABM was identified as regions with SUV greater than the threshold SUV. We calculated ABM volumes and determined the proportion of ABM within each structure using this equation:

$$\mathrm{ABM_{structure}\%} = \mathrm{Volume\ of\ ABM_{structure}} / \mathrm{Volume\ of\ BM_{structure}}$$

$$(1)$$

Statistical analyses

We used an independent-sample t test to analyze baseline differences in age, body mass index (BMI), and mean time to follow-up PET scan between the 2 treatment groups. The Fisher exact test was used to compare categoric variables.

The primary endpoint was the compensatory response, defined as the change in the log of the ratio of the ABM% in extrapelvic versus pelvic bone marrow from baseline to after treatment, ie,:

$$\log\left(\mathrm{ABM\%_{extra-pelvic}} / \mathrm{ABM\%_{pelvic}}\right)_{\mathrm{Post-RT}}$$
$$- \log\left(\mathrm{ABM\%_{extra-pelvic}} / \mathrm{ABM\%_{pelvic}}\right)_{\mathrm{Pre-RT}} \quad (2)$$

We tested the null hypothesis that there is no compensatory response (ie, the quantity in equation 2 is 0), versus the

2-tailed alternative hypothesis, using a paired t test. In a pilot study, we estimated this quantity in 7 patients and found a statistically significant increase in compensatory response (t statistic $= 3.636$; $P = .011$), indicating increased hematopoiesis in unirradiated BM. We sought to confirm this finding in 2 cohorts stratified by chemotherapy intensity (cisplatin vs C/G). We used a Bonferroni correction to adjust for multiple hypothesis testing of the 2 groups. We also assessed the difference in compensatory response in patients treated with cisplatin versus C/G using an independent-sample t test.

In secondary analyses, we tested the hypothesis that the proportion of ABM (ABM volume/total BM volume) in the extrapelvic structures is increased after CRT, using a 2-sided paired t test. We also compared the difference in mean SUV before and after CRT in each of the bone marrow structures using a 2-sided paired t test. An independent-sample t test was used to compare blood counts between cisplatin- and gemcitabine-treated patients. A Spearman rank coefficient was used to correlate compensatory response with mean pelvic bone marrow dose. Univariable and multivariable analysis was used to correlate compensatory response to predictors such as chemotherapy regimen, age, BMI, mean pelvic bone marrow dose, and mean lumbar vertebrae dose. All statistical tests had statistical significance defined as $P < .05$. Data analysis was performed in IBM SPSS Version 23 (IBM SPSS Inc, Chicago, IL).

Results

Sample characteristics and blood count nadirs

Sample characteristics are shown in Table E1 (available online at www.redjournal.org). The mean age was 48.0 years for the whole cohort. There were no significant differences in mean age, BMI, comorbidity status, and mean time to follow-up ^{18}F-FDG-PET after completion of RT between the 2 treatment groups. Also, there was no significant difference in histology, tumor stage, and number of chemotherapy cycles given between the 2 subgroups. For both treatment groups, the majority of patients had squamous cell carcinoma and had stage $\geq$IIB disease. In both treatment groups, the plurality of patients received 4 or more cycles of chemotherapy. Nadirs of white blood cells, neutrophil, hemoglobin, and platelets were lower in patients treated with C/G than in those treated with cisplatin alone, but this was not statistically significant (Table E2; available online at www.redjournal.org).

Change in mean SUV

Mean changes in SUV before and after completion of RT are shown in Table 1 and Figure 1. In the pretreatment ^{18}F-FDG-PET scans for the whole sample, mean SUV was found to be higher in the vertebrae and pelvis and lower in the scapula/proximal humerus, clavicle/sternum, and ribs, suggesting regional heterogeneity of the bone marrow.

For all patients, patients treated with cisplatin, and patients treated with C/G, mean SUV was significantly decreased after completion of RT in the lumbar vertebrae ($P < .001$ for all patients and patients treated with C/G; $P = .005$ for cisplatin), L5/sacrum ($P < .001$), ilium ($P < .001$ for all patients and patients treated with cisplatin; $P = .001$ for C/G), and ischium/pubes/proximal femorae ($P < .001$ for all patients and patients treated with cisplatin; $P = .008$ for C/G). Overall, the pelvis (L5/sacrum, ilium, and ischium/pubes/proximal femorae) had a significant decrease in SUV ($P < .001$) in all patients and the individual subgroups. However, the extrapelvic structures as a whole (cervical

Table 1 Change in mean SUV_{bw}, overall and by treatment group

Structures	All			Cisplatin			Cisplatin + gemcitabine		
	Change in mean SUV_{bw}	95% CI	P value*	Change in mean SUV_{bw}	95% CI	P value*	Change in mean SUV_{bw}	95% CI	P value*
Scapula/proximal humerus	−0.002	−0.041-0.044	.942	0.007	−0.046-0.060	.781	−0.009	−0.090-0.072	.823
Clavicle/sternum	−0.019	−0.063-0.025	.394	−0.007	−0.066-0.053	.815	−0.040	−0.110-0.030	.239
Ribs	−0.010	−0.044-0.024	.555	0.010	−0.036-0.056	.661	−0.046	−0.093-0.001	.056
Cervical vertebrae	−0.044	−0.120-0.032	.246	−0.020	−0.128-0.087	.699	−0.086	−0.188-0.015	.090
Thoracic vertebrae	−0.060	−0.144-0.024	.155	−0.028	−0.144-0.089	.629	−0.119	−0.240-0.003	.055
Lumbar vertebrae (L1-L4)	−0.216	−0.300 to −0.134	<.001	−0.184	−0.306 to −0.062	.005	−0.274	−0.359 to −0.190	<.001
L5/sacrum	−0.377	−0.475 to −0.279	<.001	−0.379	−0.517 to −0.241	<.001	−0.374	−0.514 to −0.234	<.001
Ilium	−0.278	−0.369 to −0.187	<.001	−0.287	−0.415 to −0.158	<.001	−0.262	−0.392 to −0.132	.001
Ischium/pubes/ proximal femorae	−0.147	−0.204 to −0.089	<.001	−0.155	−0.234 to −0.076	<.001	−0.132	−0.223 to −0.041	.008
Extrapelvis	−0.025	−0.075-0.024	.307	−0.002	−0.070-0.065	.942	−0.066	−0.141-0.008	.076
Pelvis	−0.252	−0.330 to −0.175	<.001	−0.258	−0.368 to −0.149	<.001	−0.241	−0.351 to −0.131	<.001

Abbreviations: CI = confidence interval; SUV_{bw} = standard uptake value corrected for body weight.

* P values from paired t test comparing mean SUV_{bw} at baseline and after completing radiation treatment.
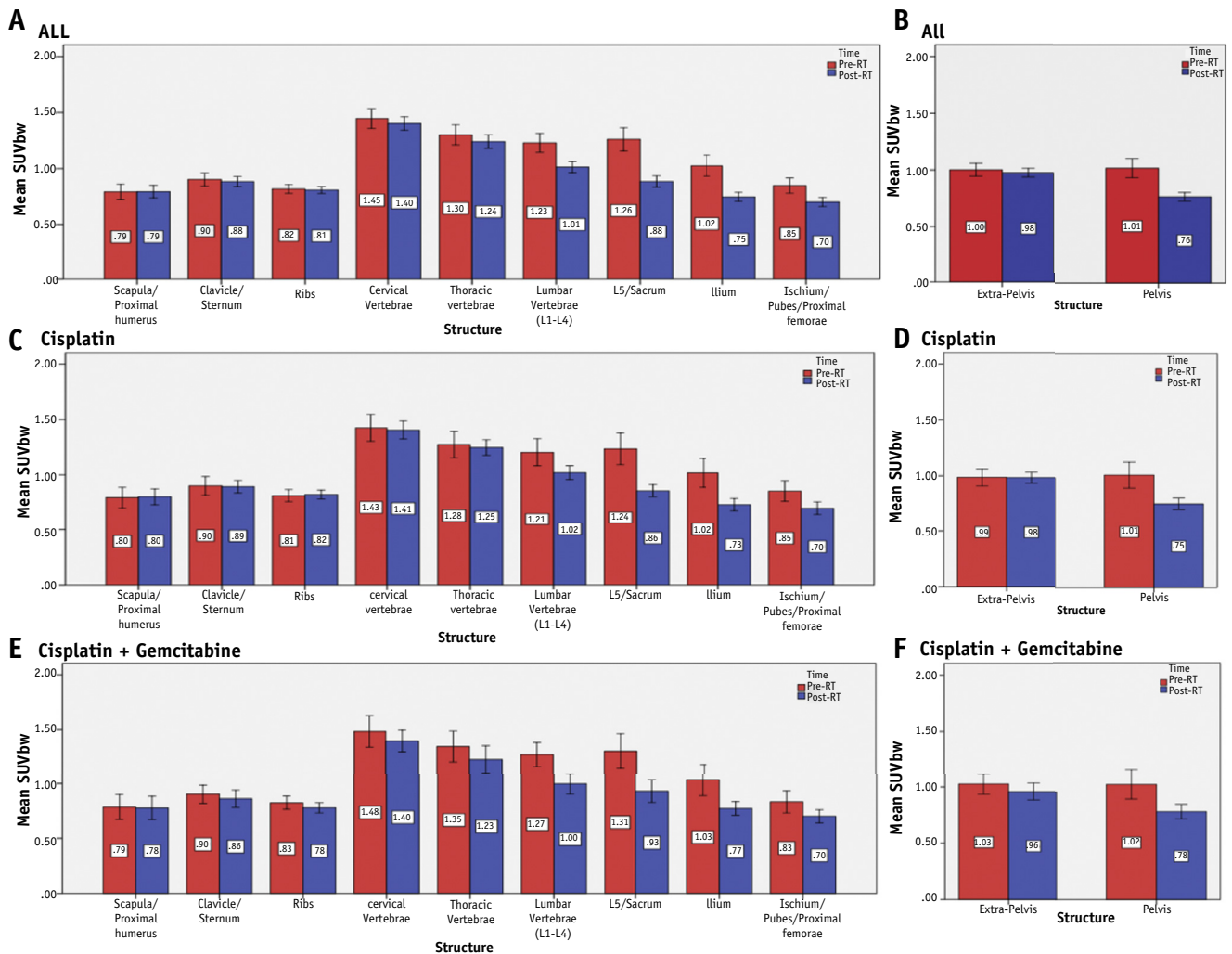
Fig. 1. Bar plots of mean standard uptake value corrected for body weight (SUVbw) (95% confidence interval) of pelvic and extrapelvic structures before (red) and after (blue) radiation therapy (RT) for all (A and B), cisplatin (C and D), and cisplatin + gemcitabine (E and F)−treated patients. (A color version of this figure is available at www.redjournal.org.)

vertebrae, thoracic vertebrae, scapula/proximal humerus, clavicle/sternum, and ribs) did not show significant reductions in mean SUV after completion of RT ($P = .307$ in all patients; $P = .942$ in cisplatin-treated patients). The thoracic vertebrae ($P = .055$), ribs ($P = .056$), and extrapelvic bone marrow as a whole ($P = .076$) of patients treated with C/G tended to have a decrease in mean SUV after RT, but this was not statistically significant.

Change in ABM percentage

The mean changes in ABM before and after the completion of RT are shown in Table 2 and Figure 2. Similarly to mean SUV, the mean proportion of ABM was found to be higher in the vertebrae and pelvis and lower in the scapula/proximal humerus, clavicle/sternum, and ribs, suggesting regional heterogeneity of the bone marrow in the baseline FDG-PET scans for all patients.

For all patients, the cisplatin subgroup, and the C/G subgroup, the mean ABM percentage was significantly

decreased after the completion of RT in the L5/sacrum ($P < .001$) and ilium ($P < .001$ for all patients and cisplatin; $P = .001$ in C/G), and the ischium/pubes/proximal femorae ($P < .001$ for all patients and $P = .001$ for cisplatin). However, the individual extrapelvic structures (cervical vertebrae, thoracic vertebrae, scapula/proximal humerus, clavicle/sternum, and ribs) showed a significant increase in mean ABM percentage after the completion of RT ($P < .001$). Overall, the mean ABM after the completion of RT was reduced in the pelvic ($P < .001$) and increased in the extrapelvic ($P < .001$) bone marrow. Figure 3 shows an increase in the volume of ABM within the extrapelvic bones and a concomitant decrease in the volume of ABM within the pelvic bones after treatment.

Compensatory response

Compensatory response is shown in Figure 4. The compensatory response was defined as the change in the log of the ratio of the ABM percentage in the extrapelvic versus

Table 2   Mean change in percentage of active bone marrow (%), overall and by treatment group

Structures	All			Cisplatin			Cisplatin + gemcitabine		
	Change in ABM %	95% CI	P value*	Change in ABM %	95% CI	P value*	Change in ABM %	95% CI	P value*
Scapula/proximal humerus	13.91	10.95-16.87	<.001	13.71	10.62-16.81	<.001	14.26	7.45-21.07	.001
Clavicle/sternum	14.92	11.38-18.45	<.001	14.44	10.01-18.88	<.001	15.76	9.09-22.42	<.001
Ribs	12.49	9.45-15.53	<.001	14.58	10.30-18.86	<.001	8.76	5.34-12.19	<.001
Cervical vertebrae	6.41	4.06-8.76	<.001	6.93	3.64-10.22	<.001	5.48	2.06-8.91	.004
Thoracic vertebrae	11.76	8.94-14.58	<.001	12.35	8.96-15.74	<.001	10.70	5.07-16.34	.001
Lumbar vertebrae (L1-L4)	−0.91	−4.76-2.94	.635	−0.27	−4.67-4.14	.902	−2.06	−10.22-6.10	.594
L5/sacrum	−27.59	−33.95 to −21.23	<.001	−30.07	−38.46 to −21.68	<.001	−23.17	−33.66 to −12.68	<.001
Ilium	−24.47	−29.24 to −19.69	<.001	−26.89	−32.40 to −21.38	<.001	−20.15	−29.71 to −10.59	.001
Ischium/pubes/ proximal femorae	−5.83	−8.91 to −2.75	<.001	−7.51	−11.64 to −3.38	.001	−2.84	−7.42 to 1.75	.205
Extrapelvis	12.20	10.09-14.31	<.001	13.28	10.75-15.81	<.001	10.26	6.27-14.26	<.001
Pelvis	−18.01	−21.36 to −14.65	<.001	−20.00	−24.30 to −15.71	<.001	−14.44	−19.98 to −8.89	<.001

Abbreviations: ABM = active bone marrow; CI = confidence interval.

* *P* values generated from paired *t* test comparing mean ABM % at baseline and after completion of radiation treatment.

the pelvic BM from baseline to after treatment. The whole cohort had a significantly increased compensatory response of 0.381 (95% confidence interval [CI]: 0.312, 0.449; $P<.001$). Subgroup analysis showed that the compensatory response was 0.429 (95% CI: 0.340, 0.517; $P<.001$) in patients treated with cisplatin and 0.294 (95% CI: 0.186, 0.402; $P<.001$) in patients treated with C/G. The compensatory response trended toward being higher in patients treated with cisplatin than in those treated with C/G ($P=.057$).

Univariable and multivariable analysis

We sought to identify predictors of compensatory response, including chemotherapy intensity, age, BMI, mean pelvic BM dose, and mean lumbar BM dose. The results from univariable and multivariable analyses are shown in Table E3 (available online at www.redjournal.org). On univariable analysis, the patients receiving C/G trended toward having a lower compensatory response than did patients treated with cisplatin alone ($P=.057$). Older patients tended to have a lower compensatory response on univariable analysis ($P=.005$). On multivariable analysis, the chemotherapy regimen and age were significant predictors of compensatory response. However, BMI, mean pelvic bone marrow dose, and mean lumbar dose were not predictors of compensatory response on univariable and multivariable analyses. Interestingly, mean pelvic bone marrow dose was negatively correlated to the compensatory response in patients treated with C/G, with a Spearman rank correlation of −0.75 ($P=.002$), but not in patients treated with cisplatin alone. Thus, there was a decreased compensatory response in patients receiving higher mean pelvic bone marrow doses in patients treated with C/G.

Discussion

There is known to be a substantial variability in the rates of HT in patients undergoing CRT. One hypothesis is that variation in compensatory hematopoiesis among patients may explain the observed variation in chemotherapy tolerance. In this study, we used ^{18}F-FDG-PET to quantify longitudinal changes in hematopoietically ABM distributions in unirradiated and irradiated BM in a sample of cervical cancer patients treated with concurrent chemotherapy of varying intensities. At baseline, the mean SUV and mean ABM percentage were higher in the vertebrae and pelvis and lower in the scapula/proximal humerus, clavicle/sternum, and ribs, suggesting regional heterogeneity of the distribution of ABM. We observed reduced SUV of the extrapelvic structures in patients treated with C/G; this could have been caused by the addition of gemcitabine, which augments the insult to the extrapelvic BM, likely affecting compensatory hematopoiesis. We also saw evidence of a compensatory response in all patients, regardless of chemotherapy regimen. The compensatory response appeared reduced in patients receiving more intensive chemotherapy (C/G). On the whole, our findings indicate that variation in compensatory response after CRT could explain the increased HT seen with more intensive chemotherapy, resulting from impaired recovery of hematopoiesis in unirradiated structures.

Many imaging modalities have been used to identify regions of functional (active) BM, including ^{18}F-FDG-PET, ^{18}F-FLT-PET, and magnetic resonance imaging (MRI) (16, 19-25). In 1 study, Elicin et al (19) used ^{18}F-FDG-PET imaging of pelvic BM to identify hematopoietically ABM and found that relatively low doses of radiation were associated with a reduction in SUV, which was correlated
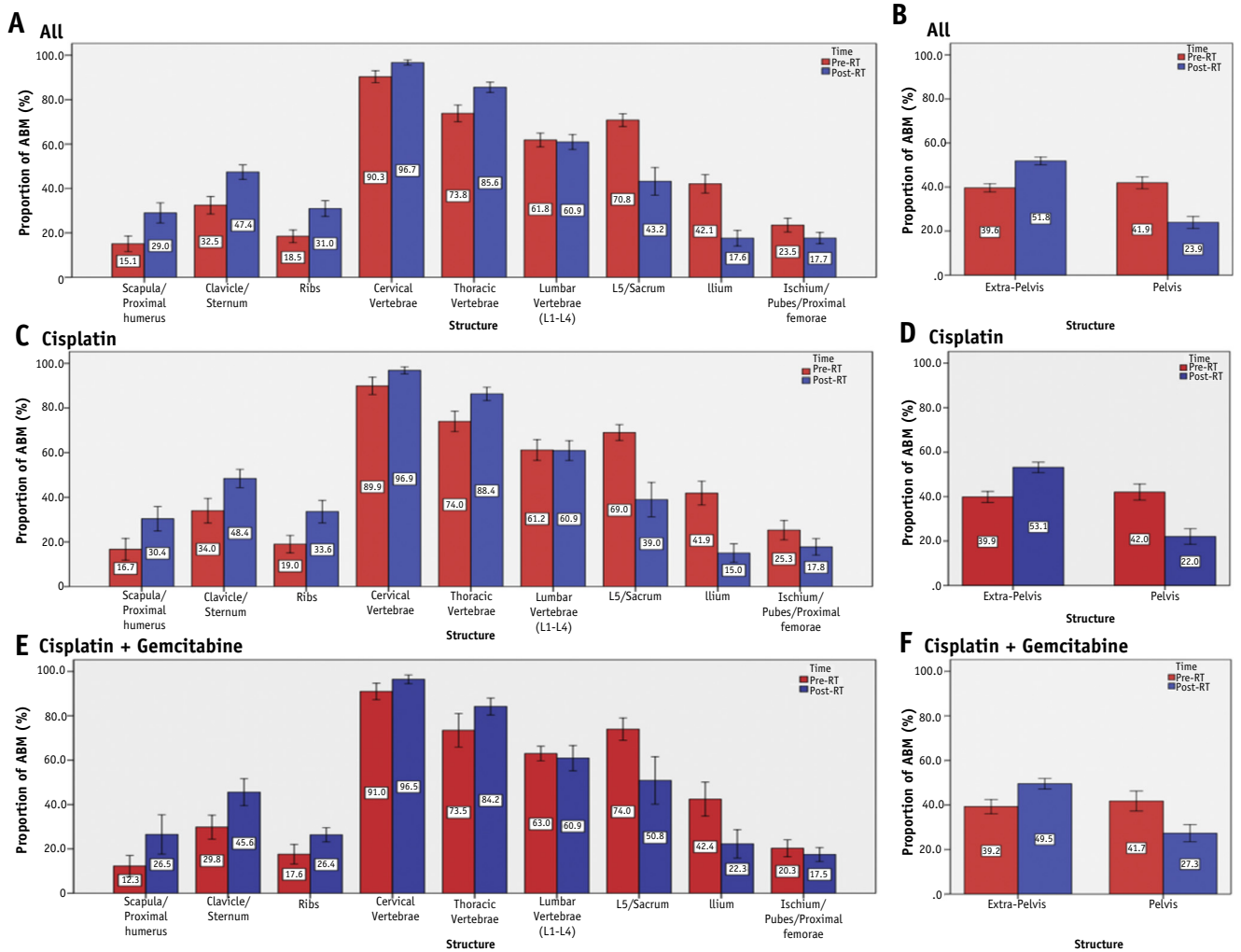
Fig. 2. Bar plots of mean proportion of active bone marrow (ABM) (95% confidence interval) of pelvic and extrapelvic structures before (red) and after (blue) radiation therapy (RT) for all (A and B), cisplatin (C and D), and cisplatin + gemcitabine (E and F)−treated patients. (A color version of this figure is available at www.redjournal.org.)

with decreased white blood cell nadir counts after CRT. In another study, Yagi et al (20) showed regional functional heterogeneity of BM site-dependent response to treatment using longitudinal ^{18}F-FDG-PET imaging data. Thus, ^{18}F-FDG-PET imaging appears to be a valid imaging method for localizing functional BM, although recent studies suggest that ^{18}F-FLT-PET could be better for this purpose (21).

In pelvic malignancies, intensive chemotherapy regimens have been associated with increased rates of acute HT. Using normal tissue complication probability models, Bazan et al (26) found that the incidence of acute grade >3 HT was higher in patients receiving IMRT plus cisplatin or IMRT plus mitomycin (MMC) compared with IMRT plus 5-fluorouracil in patients treated for pelvic malignancies. Furthermore, patients treated with MMC had greater rates of HT than did patients treated with cisplatin. Another study compared the acute effects of chemotherapy (cisplatin/etoposide [C/E] vs carboplatin/paclitaxel [C/P])

on cellular proliferation and BM recovery in the acute setting using ^{18}F-FLT-PET imaging in patients with non-small cell lung cancer (23). Patients treated with C/E had reductions in ^{18}F-FLT uptake from baseline to week 2 but BM recovery at week 4, reflecting the absence of chemotherapy between weeks 2 and 4, whereas patients treated with C/P had nonsignificant decreases in ^{18}F-FLT uptake. Newman et al (27) found that rectal cancer patients treated with preoperative CRT (capecitabine or 5-FU) have lasting BM suppression in the form of increased rates of HT when treated with postoperative chemotherapy, suggesting that sparing functional BM in the preoperative setting can improve tolerance to adjuvant chemotherapy. Collectively, these studies begin to elucidate the importance of chemotherapy intensity in the context of concurrent RT, and they highlight the potential of BM-sparing techniques to reduce rates of HT.

We also observed that older age and more intense chemotherapy regimens are correlated with a decreased
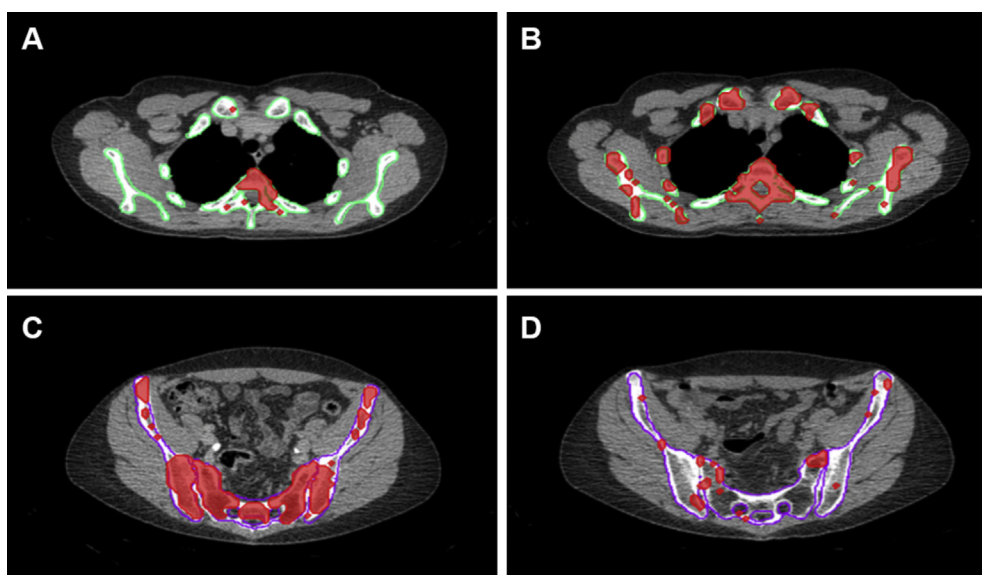
Fig. 3. Representative axial computed tomography images in a patient showing changes in active bone marrow (ABM) before and after chemoradiation. An increasing volume of ABM (red) within the extrapelvic bones (green) is shown before (A) and after (B) treatment. A decreasing volume of ABM (red) within the pelvic bones (purple) is shown before (C) and after (D) treatment. (A color version of this figure is available at www.redjournal.org.)

compensatory response on multivariable analysis. This suggests that more intense chemotherapy regimens blunt the compensatory response. Also, older patients are more likely to see an even more decreased compensatory
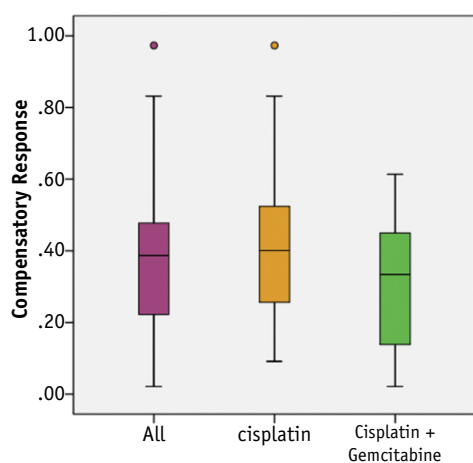
Treatment	Compensatory Response		
	Mean	95% CI	*P*-value
ALL	0.381	0.312, 0.449	**<.001**
Cisplatin	0.429	0.340, 0.517	**<.001**
Cisplatin + Gemcitabine	0.294	0.186, 0.402	**<.001**

Fig. 4. Box plot of compensatory response in all, cisplatin-, and cisplatin + gemcitabine−treated patients. Mean based on log $(ABM\%_{extra\text{-}pelvic}/ABM\%_{pelvic})_{Post\text{-}RT}$ − log $(ABM\%_{extra\text{-}pelvic}/ABM\%_{pelvic})_{Pre\text{-}RT}$. *P* values generated from paired *t* test comparing log $(ABM\%_{extra\text{-}pelvic}/ABM\%_{pelvic})$ before and after completion of RT. *Abbreviation:* CI = confidence interval.

response, given that older patients have lower reserves of hematopoietically ABM in the extrapelvic structures. Furthermore, in patients treated with C/G, mean pelvic bone marrow dose was negatively correlated with the compensatory response. However, this was not the case for patients treated with cisplatin only. This suggests that the compensatory response is sensitive to the radiation dose in patients receiving an intense chemotherapy regimen. Thus, BM-sparing techniques may be beneficial in improving tolerance to chemotherapy in the concurrent and potentially the adjuvant and salvage settings. McGuire et al [28] postulate that reducing the bone marrow volume receiving 10 or 20 Gy in total dose may delay the time to the occurrence of a hematologic toxicity event, which could result in the delivery of more chemotherapy. Also, we found that specific patient-related and treatment-related characteristics appear to play a role in the hematopoietic compensatory response.

This study has several limitations. The small sample size, the heterogeneity in chemotherapy doses, and the timing of PET scans prevents us from making definitive statements about the impact of intensifying chemotherapy, especially in the concurrent or acute phase of treatment. Another limitation is that because chemotherapy is typically held in the setting of low blood counts, the proportion of ABM after treatment could reflect the subsequent effects of dose modification. However, mitigating this limitation to some degree is the presumption that once severe hematologic dysfunction is discovered, there has generally been a lag in the exposure to the bone marrow injury, based on the dynamics of hematopoiesis. Future longitudinal studies using alternative functional imaging modalities (eg, ^{18}F-FLT-PET) would be desirable to evaluate the

compensatory response in the acute setting and examine how its variation relates to peripheral blood counts.

In conclusion, we found ^{18}F-FDG-PET was useful for measuring the functional heterogeneity of bone marrow and the associated subacute compensatory response in patients treated with varying intensities of CRT. Further investigation is warranted to determine whether intensifying chemotherapy alters the acute compensatory response and how this correlates with low peripheral blood counts.

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