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ORIGINAL ARTICLE

Predictors of acute toxicities during definitive chemoradiation using intensity-modulated radiotherapy for anal squamous cell carcinoma

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ABSTRACT

Purpose. To identify clinical and dosimetric factors associated with acute hematologic and gastrointestinal (GI) toxicities during definitive therapy using intensity-modulated radiotherapy (IMRT) for anal squamous cell carcinoma (ASCC).

Materials and methods. We retrospectively analyzed 108 ASCC patients treated with IMRT. Clinical information included age, gender, stage, concurrent chemotherapy, mitomycin (MMC) chemotherapy and weekly hematologic and GI toxicity during IMRT. From contours of the bony pelvis and bowel, dose-volume parameters were extracted. Logistic regression models were used to test associations between toxicities and clinical or dosimetric predictors.

Results. The median age was 59 years, 81 patients were women and 84 patients received concurrent MMC and 5-fluorouracil (5FU). On multivariate analysis (MVA), the model most predictive of Grade 2 + anemia included the maximum bony pelvis dose (Dmax), female gender, and T stage [$p = 0.035$, cross validation area under the curve (cvAUC) = 0.66]. The strongest model of Grade 2 + leukopenia included V10 (percentage of pelvic bone volume receiving ≥ 10 Gy) and number of MMC cycles ($p = 0.276$, cvAUC = 0.57). The model including MMC cycle number and T stage correlated best with Grade 2 + neutropenia ($p = 0.306$, cvAUC = 0.57). The model predictive of combined Grade 2 + hematologic toxicity (HT) included V10 and T stage ($p = 0.016$, cvAUC = 0.66). A model including VA45 (absolute bowel volume receiving ≥ 45 Gy) and MOH5 (mean dose to hottest 5% of bowel volume) best predicted diarrhea ($p = 0.517$, cvAUC = 0.56).

Conclusion. Dosimetric constraints to the pelvic bones should be integrated into IMRT planning to reduce toxicity, potentially reducing treatment interruptions and improving disease outcomes in ASCC. Specifically, our results indicate that Dmax should be confined to ≤ 57 Gy to minimize anemia and that V10 should be restricted to $\leq 87\%$ to reduce incidence of all HT.

Definitive pelvic radiotherapy (RT), along with concurrent 5-fluorouracil (5FU) and mitomycin (MMC) chemotherapy, is the standard treatment for anal squamous cell carcinoma (ASCC) patients, and has achieved five-year overall survival (OS) rates of approximately 75% [1]. Historically, with the use of three-dimensional conformal radiotherapy (3DCRT), adverse effects, including skin desquamation, gastrointestinal (GI) and hematologic toxicities, often necessitated treatment breaks. More recently, intensity-modulated radiotherapy (IMRT) has been increasingly used in the treatment of ASCC, with the goal of reducing toxicity and minimizing treatment breaks, while maintaining high rates of local control [2]. Multiple studies have demonstrated that the use of IMRT over 3DCRT significantly reduces the incidence of clinically significant acute GI and dermatologic toxicities [3–6]. As well, early evidence indicates favorable outcomes with IMRT, with a two-year OS rate of 94% in a phase II RTOG trial [6]. Despite these improvements with IMRT, hematologic toxicities (HT) remain a significant concern and cause of treatment interruption. However, our understanding of the tolerance of pelvic bone marrow to RT during definitive combined modality therapy for ASCC remains limited [2,7]. There is also limited information

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concerning the correlation between clinical and dosimetric parameters and acute hematologic or GI toxicities. Identifying predictors of radiation-related hematologic and GI side effects is key for optimal IMRT treatment planning, in order to reduce complications, avoid treatment delays and improve disease control [2,7]. Therefore, in this study we assessed clinical and dosimetric variables to identify predictors of significant acute hematologic and GI toxicities in a large cohort of ASCC patients treated with definitive chemoradiation (CRT) using IMRT planning.

Material and methods

Patients

After obtaining a waiver of authorization from the Institutional Review Board, we retrospectively analyzed all 108 consecutive ASCC patients treated with definitive IMRT at our institution between 2005 and 2012. Biopsy tissue was confirmed as squamous cell carcinoma by the Memorial Sloan-Kettering Cancer Center Department of Pathology. To establish clinical stage, patients underwent pretreatment imaging consisting of computed tomography (CT) chest, abdomen, pelvis or positron-emission tomography (PET) CT, examination by a colorectal surgeon (including proctoscopy and/or endorectal ultrasound), clinical examination and routine laboratory testing. Clinical information collected included age, gender, stage, concurrent chemotherapy and MMC chemotherapy. Weekly toxicity grading, including HT [white blood cell (WBC) count, absolute neutrophil count (ANC) and hemoglobin (HGB) level], diarrhea and proctitis, was obtained through chart review. All toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0.

Radiation planning and delivery

Patients underwent CT simulation, primarily on a PET-CT simulator (GE Discovery ST, GE Healthcare, Waukesha, WI, USA) to obtain fused PET images with the treatment planning CT scan. A majority of patients were simulated with a full bladder and intravenous contrast. For most patients, oral contrast (MD-Gastroview, Covidien Pharmaceuticals, USA) was also administered to delineate the small bowel. All patients were simulated in the prone position and immobilized in a thermoplastic body mold. Information from the pretreatment imaging, sigmoidoscopy and clinical examination was utilized to delineate the gross tumor volume (GTV), which was expanded by 1.0–1.5 cm to generate the clinical target volume (CTV) for the primary tumor (CTV_primary). If inguinal or pelvic nodes were clinically or radiographically involved, these were identified as separate GTVs and expanded by 1.0 cm to generate the CTV_involved nodes. The CTVA consisted of the CTV primary and mesorectal and internal iliac nodes; the CTVB included the external iliac nodes; and the CTVC encompassed the inguinal nodal basin, based on the Radiation Therapy Oncology Group Anorectal Atlas [8]. A PTV margin of 5 mm was created around the CTVA, CTVB, and CTVC to create a PTV_elective nodes field. The CTV_primary and CTV_involved nodes were expanded by 5 mm to create a PTV_boost [9]. These PTV margins are not universally adopted, but are those used at our institution.

Normal tissue structures relevant to IMRT planning were contoured on each CT slice and included the bladder, bowel, anal canal (anal verge to anorectal ring), rectum (anorectal ring to rectosigmoid flexure), external genitalia, vagina in female patients and the bony structures of the pelvis (femoral head, ilium, ischium and sacrum). Although the anal canal is included in the GTV and CTV, we delineate it as a normal structure, as the GTV does not always encompass the full cranio-caudal extent of the anal canal. The bowel contour included small bowel and sigmoid colon as individual loops, excluding the rectum and anal canal, extending to 1.0 cm above the PTV. IMRT treatment planning was completed using custom in-house software. Radiation dose depended upon disease stage. Clinically uninvolved pelvic and inguinal nodes (PTV_elective nodes) were treated to 45 Gy at 1.8 Gy per fraction. For T1 tumors, the primary tumor and involved lymph node (PTV_boost) dose was brought to 50 Gy in 2 Gy fractions using an integrated boost. For primary tumors ≥ 2.0 cm, an additional 6 Gy in 3 fractions was added as a sequential boost to bring the primary tumor and involved nodes to 56 Gy. In patients with T1 primary tumors and involved inguinal nodes, these nodes were treated using an integrated boost at 2.12 Gy over 25 fractions to 53 Gy, while the primary site received 50 Gy in 2 Gy fractions. Treatment was delivered using mixed 6 and 15 MV energies and a median of seven coplanar beams. The following institutional dose constraints were used for normal tissue doses: 95% of the small bowel to receive <45 Gy; mean bladder dose 30–33 Gy; maximum dose to the femoral head 50 Gy; maximum dose to the cauda equina <50 Gy [9].

Chemotherapy

Chemotherapy regimens are shown in Table I. Most patients received concurrent chemotherapy (97%),

Table I. Patient characteristics.

Patients (n)		108
Age at RT initiation (years)	Median (range)	59 (36–86)
Gender (n)	Female	81
	Male	27
cT Stage (n)	T1	19
	T2	44
	T3	21
	T4	17
cN Stage (n)	N0	37
	N1	34
	N2	15
	N3	12
Chemotherapy agent used (n)	MMC + 5-FU	84
	MMC + Capecitabine	10
	5-FU alone	6
	Capecitabine alone	5
	None	3
Mitomycin cycles	0–1	47
	2	61
Radiation therapy dose (cGy)	Median (range)	5400 (5000–5600)
Median follow-up for survivors (months)		29.42

with the majority (78%) receiving 5FU venous infusion (1000 mg/m^2 over 96 hours) and MMC (10 mg/m^2) during weeks 1 and 5. Of the remaining patients undergoing concurrent chemotherapy, 10 (9%) received MMC and capecitabine (825mg/m^2), six (6%) received 5FU alone and five (5%) received capecitabine alone.

Follow-up

Following completion of IMRT, patients underwent rectal examination and anoscopy every six weeks until they obtained a clinical complete response, then every three months for two years, every six months for five years and finally, yearly. Annual CT scans were also performed for patients with clinical T3/T4 or node-positive disease [9]. Based upon recent data in ASCC concerning the prognostic significance of pre- and post-chemoradiation fluorodeoxyglucose (FDG)-PET-CT scans, most patients received a follow-up PET-CT at three months following completion of IMRT [10]. If the FDG uptake resolved to the background level, patients were followed with an annual CT of the chest/abdomen/pelvis [9].

Statistical analysis

For hematologic and GI toxicity during IMRT, logistic regression analysis was conducted to identify significant clinical and dosimetric variables and to build predictive models. For this analysis, clinical variables considered included dichotomized age (≤ 59 and > 59 years), gender, concurrent chemotherapy regimen, cycles of MMC (0/1 vs. 2) and the American Joint Committee on Cancer T stage and N stage, as continuous variables. Dose-volume parameters for pelvic bones and bowel were extracted for modeling using our in-house software tools: CERR (Computational Environment for Radiotherapy Research) and DREES (Dose Response Explorer System) [11,12]. The risk of toxicity was given by:

$$\mathrm{NTCP} = \frac{1}{1+\exp(-y)}$$

where NTCP denotes normal tissue complication probability and Y represents linear regression with selected variables.

In order to obtain an unbiased estimate of the generalized performance of each model, we performed a 10-fold cross validation (CV). At each iteration of the 10-fold CV, a nested leave-one-out CV was performed for model selection, and the models most frequently observed were chosen as NTCP models for hematologic and GI toxicities. The 10-fold CV was repeated 50 times, and the model performance was averaged. To evaluate the predictive models generated, the area under the receiver operating characteristic (ROC) curve (AUC) and Spearman's rank correlation coefficient (Rs) metrics were employed. For those toxicities where predictive models were sufficiently strong, we suggest radiation dose or volume constraints. To find the best cut-offs of dosimetric variables, the ROC curve was used such that the summation of sensitivity and specificity was maximized. In addition, the goodness-of-fit of these models was evaluated by using R-squared (R^2) between the predicted incidence of hematologic and GI toxicity, calculated from the

predictive models, and the actuarial incidence in the cohort. Fisher's exact test was used for comparison of categorical variables. A generalized estimating equation (GEE) approach was used for modeling the change of toxicity over time.

Results

Patient characteristics

The median age was 59 years and 81 patients (75%) were female. 19 (17%) patients had T stage 1 disease and 37 (34%) had N stage 0 tumors. In total 84 (78%) patients were treated with concurrent MMC and 5FU chemotherapy, with 47 (44%) patients receiving zero or one cycle of MMC, and the remainder receiving two cycles. Table I provides an overview of patients' clinical characteristics.

Treatment compliance

The average duration of RT in our cohort was 39 days, and 41 (38%) patients required breaks during RT. 78% of delays in RT occurred due to HT, most commonly leukopenia, neutropenia, or both concurrently. Infrequent non-hematologic causes of delays in RT included transportation problems, diarrhea, dermatitis, occurrence of an incarcerated inguinal hernia and need for a colostomy.

In cases where chemotherapy was withheld entirely, this was most often due to advanced age or HIV positive status. The majority of patients (56%) received two cycles of MMC, with 31 (29%) patients receiving one cycle and 16 (15%) receiving no MMC. Among patients who received MMC-based chemotherapy, the most common reason for withholding of the second cycle of MMC was HT. Sixty-one percent of instances in which the second cycle of MMC was held were due to HT, most frequently leukopenia and neutropenia, or both. Non-hematologic reasons for receiving only one MMC cycle included HIV, advanced age, or development of allergic reaction, mouth sores or rash following administration of the first cycle.

Outcomes

With a median follow-up time of 29.4 months, the three-year OS rate was 91.5%. Only 11 patients developed a local recurrence (LR) and 16 were diagnosed with distant metastases (DM); of these patients, five experienced both LR and DM.

Hematologic toxicity

During the course of IMRT, 28 (26%) patients developed Grade 2 + anemia. Rates of clinically significant anemia increased during the first several weeks of RT, and remained elevated throughout the remainder of treatment, as detailed in Figure 1A. On multivariate analysis (MVA) combining dosimetric and clinical variables, the logistic regression model most predictive of Grade 2 + anemia was statistically significant, and included the maximum radiation dose (Dmax) to the bony pelvis, female gender and higher tumor T stage, with cvAUC = 0.66 and Rs = 0.25 (p = 0.035):

$$Y = 0.139 \times \text{Dmax} + 1.51 \times \text{gender} + 0.746 \times \text{T stage} - 11.6$$

A comparison of the predicted incidence of Grade 2 + anemia using the above NTCP model and actual incidence in our study population is shown in Figure 2. This analysis revealed a very good correlation between the NCTP model and the actual toxicity, with $R^2 = 0.96$ and p = 0.001. In this cohort, increasing incidence of Grade 2 + anemia correlates with higher T stage and Dmax, and females experienced more clinically significant anemia, as demonstrated

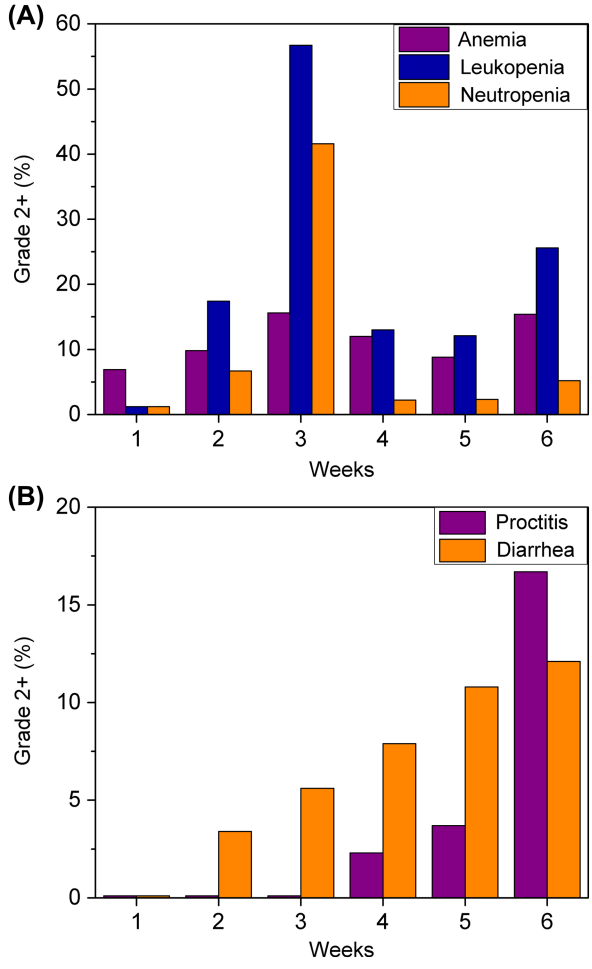

Figure 1. Weekly percentage of patients with Grade 2 + CTCAE scores (A) for GI toxicities and (B) for HT.

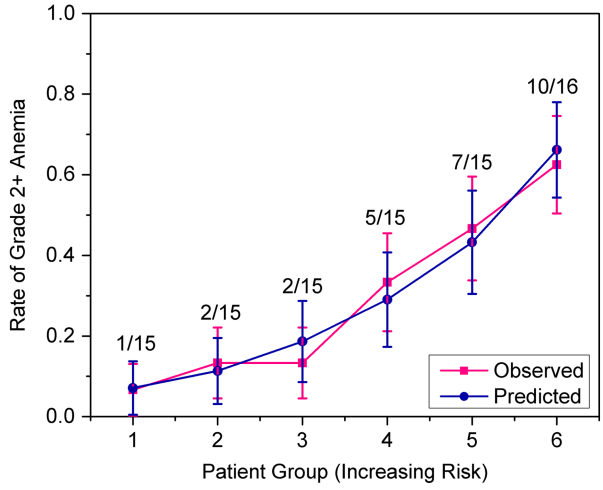

Figure 2. Comparison between the incidence of predicted Grade 2 + toxicity by applying the NTCP model and the actuarial incidence experienced by the study population for anemia. Patients were binned into six categories based on the predicted and actual toxicity, with 1 being the lowest toxicity group and 6 the highest.

in Figure 3. Our analysis also suggests a dosimetric constraint for the pelvic bones in order to minimize anemia, specifically limiting Dmax to ≤ 57 Gy (sensitivity 0.67, specificity 0.69).

During the course of IMRT, 67 (62%) patients developed Grade 2 + leukopenia, with the highest rate of clinically significant leukopenia observed during week 3 of RT, as demonstrated in Figure 1A. The logistic regression model most predictive of Grade 2 + leukopenia included V10 (percentage of the bony pelvis volume receiving ≥ 10 Gy) and the number of MMC cycles, categorized as 2 versus 0/1, with cvAUC = 0.57 and Rs = 0.12 (p = 0.276):

$$Y = 5.15 \times V10 + 0.469 \times \text{MMC cycles} - 4.41$$

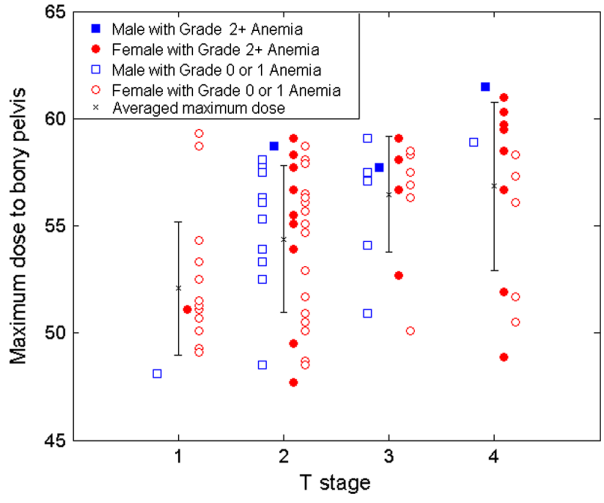

Figure 3. Scatter plot of the maximum dose to the bony pelvis by T stage, for male and female patients, with or without clinically significant anemia.

During the course of IMRT treatment, 42 (39%) patients developed Grade 2 + neutropenia, with the highest rate of Grade 2 + neutropenia observed during week 3 of RT, as shown in Figure 1A. The logistic regression model most predictive of Grade 2 + neutropenia included higher number of MMC cycles (2 vs. 0/1) and tumor T stage, but no dosimetric variables, with cvAUC = 0.57 and Rs = 0.12 (p = 0.306):

$$Y = 0.411 \times \text{MMC cycles} + 0.373 \times \text{T stage} - 1.64$$

During the course of IMRT treatment, 21 (19%) patients developed Grade 2 + thrombocytopenia. There were no clinical or dosimetric characteristics that were predictive of clinically significant thrombocytopenia, and no good logistic regression model for this toxicity was identified.

For all HT combined, during the course of IMRT, 75 (69%) patients developed Grade 2 + HT. The logistic regression model most predictive of Grade 2 + HT was statistically significant and included V10 and T stage, with cvAUC = 0.66 and Rs = 0.227 (p = 0.016):

$$Y = 5.23 \times V10 + 0.445 \times \text{T stage} - 4.08$$

Our analysis also suggests a dosimetric constraint for the pelvic bones in order to minimize combined HT, specifically limiting V10 to ≤ 87% (sensitivity 0.60, specificity 0.63).

GI toxicity

During the course of IMRT, Grade 2 + diarrhea was experienced by 13 (12%) patients with, rates of clinically significant diarrhea increasing as RT progressed, as detailed in Figure 1B. Using GEE for longitudinal analysis of weekly diarrhea over time, no statistically significant difference was seen between men and women (p = 0.114), or between patients ≤ 59 and > 59 years of age (p = 0.197). With dose-volume analysis, women generally demonstrated significantly larger volume of bowel receiving irradiation (15–45 Gy) compared to men, as shown in Supplementary Table I (to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1043396). However, gender was not significantly predictive of weekly diarrhea.

On MVA combining dosimetric and clinical variables, the logistic regression model including VA45 (absolute bowel volume receiving 45 Gy) and MOH5 (mean dose to hottest 5% of bowel volume) was most predictive of Grade 2 + diarrhea, with cvAUC = 0.56 and Rs = 0.07 (p = 0.517):

$$Y = 0.0004 \times VA45 + 0.249 \times MOH5 - 13.5$$

During the course of IMRT, Grade 2 + proctitis was experienced by 14 (13%) patients, with rates of clinically significant proctitis increasing over the course of treatment, as seen in Figure 1B. For weekly proctitis, over time no statistically significant difference was seen between men and women ($p = 0.830$), or between patients ≤ 59 and > 59 years of age ($p = 0.267$).

Discussion

Despite the use of IMRT to deliver more conformal RT fields, concurrent chemotherapy and pelvic RT causes clinically significant acute hematologic and GI toxicities that frequently lead to treatment delays. In fact, in this cohort, 78% of RT treatment breaks and 61% of cases in which MMC cycles were withheld could be attributed to HT, highlighting the prevalence of such toxicities and the clinical importance of reducing their incidence. Therefore, there is a need to identify clinical and dosimetric characteristics correlated with acute hematologic and GI adverse events during definitive CRT for ASCC. In this study, we investigated clinical and dosimetric variables, utilizing NTCP modeling to determine the most predictive variables for hematologic and GI toxicities. Further, based on this modeling, where appropriate, we suggest pelvic bone dose and volume constraints to minimize toxicity.

Hematologic toxicity

Clinically significant anemia was documented in 28 (26%) patients and was correlated with Dmax to the bony pelvis, female gender and higher tumor T stage. Our analysis suggests that the maximum dose to the pelvic bones should be constrained such that Dmax ≤ 57 Gy in order to reduce the incidence of Grade 2 + anemia. As outlined, the maximum planned dose to macroscopic tumor was 56 Gy (for tumors ≥ 2.0 cm and enlarged lymph nodes). However, hotspots of up to 110% of the target dose were accepted within the PTV, as dose coverage of the primary tumor took precedence over constraining Dmax within the PTV or the pelvic bones. This accounts for the occurrence of radiation doses above 56 Gy within the pelvic bones. An analysis of radiation doses to the pelvic bones revealed a range of 48–61 Gy for Dmax. Therefore, a suggested Dmax constraint of ≤ 57 Gy is clinically meaningful, even in the setting of a target PTV dose of 56 Gy.

In addition to maximum dose, T stage was also included in the best predictive model for anemia, although it is unlikely that the tumor size was directly related to HT, but was a surrogate for the volume of the region boosted to the higher dose. Moreover, as described, patients with higher T stage disease were treated with higher maximum radiation doses. Thus, higher T stage tumors may have had a larger volume of pelvic bone marrow irradiated to higher dose, contributing to greater observed rates of anemia. In support of these explanations linking T stage to radiation dose and volume, we tested the association between T stage and dosimetric variables, and indeed found that small high dose regions were statistically significantly correlated with T stage.

The way in which anemia is measured varies in the literature, with studies reporting reductions in hemoglobin, hematocrit or red blood cell count, but reported rates of clinically significant anemia are comparable to those seen among our patients. Reported rates of Grade 2 + anemia range from 39% to 49% among ASCC patients [3,13]. Unfortunately, none of these studies considered clinical or dosimetric predictors of anemia and, to our knowledge, this is the first study suggesting dosimetric predictors of anemia in ASCC.

Almost two-thirds (62%) of our patients developed Grade 2 + leukopenia, and clinically significant leukopenia correlated best with the percentage of the pelvic bone volume receiving ≥ 10 Gy and the number of MMC cycles. Recent studies of ASCC patients treated with concurrent IMRT and 5FU/MMC chemotherapy have found similarly high incidence of leukopenia. Rates of Grade 2 + leukopenia ranging from 75% to 85% have been reported in the literature [3,7,13,14]. Of the studies referenced, only Mell and colleagues have evaluated clinical or dosimetric variables correlated with leukopenia, and, similarly to our study, found that lower doses of radiation to larger volumes of the bony pelvis predict leukopenia. Specifically, the authors reported that V5, V10, V15 and V20 radiation to the bony pelvis and V10, V15 and V20 radiation to the sacrum were all significantly associated with leukopenia. Among clinical variables, female gender, lower BMI and lymph node positivity correlated with leukopenia [14].

Approximately 40% of our patients developed Grade 2 + neutropenia and, although none of the dosimetric variables assessed correlated with neutropenia, clinically significant neutropenia was most strongly predicted by the number of MMC cycles and higher T stage. Studies of ASCC patients receiving concurrent IMRT and 5FU/MMC chemotherapy at different institutions have reported widely variable rates of significant neutropenia, with incidence ranging from 25% to 73% of patients [3,7,13,14]. Again, only Mell et al. investigated clinical or dosimetric predictors of neutropenia, and, in contrast to our study, found that dosimetric variables did correlate with neutropenia. As with leukopenia, they reported that lower doses of radiation to larger

volumes (V5, V10, V15 and V20 to the pelvic and lumbosacral bone marrow) were predictive of neutropenia. Additionally, female gender and lower BMI were significant non-dosimetric predictors [14].

It is interesting to note that, as for anemia, T stage is included in the best predictive model for neutropenia. Although patients with higher T stage disease may have been treated with higher radiation doses, no dosimetric variables were predictive of neutropenia. As for anemia, a possible explanation for this finding is that higher T stage tumors may have had larger cone-down high dose radiation areas, such that the volume of the high dose area was larger. This could increase the volume of pelvic bone marrow that was irradiated, though the overall dose was not necessarily higher. As mentioned, our analysis revealed that small high dose regions were statistically significantly correlated with T stage, supporting this conclusion. It is also important to emphasize the distinction that, while the model including T stage and MMC was most predictive of neutropenia, T stage alone was not significantly associated with neutropenia.

It is noteworthy that in our cohort, while leukopenia correlated with low dose radiation to the pelvic bones, neutropenia was not significantly predicted by any dosimetric variables. Leukocytes encompass all WBCs, including lymphocytes, and lymphopenia is a known side effect of radiation of pelvic bone marrow. Significant leukopenia and neutropenia are side effects of MMC, as established by numerous trials of anal cancer patients [15,16]. Our data further corroborate the impact of MMC on the WBC count, as the number of MMC cycles was a predictor of both Grade 2 + leukopenia and neutropenia. Thus, the drop in the total WBC count may have been more closely associated with pelvic bone marrow radiation dose than the neutropenia, where the effect of the concurrent MMC may be more significant than any dosimetric variables.

Clinically significant HT was very prevalent in this cohort of ASCC patients, highlighting the importance of understanding predictors of this adverse effect and minimizing its incidence. Overall, almost 70% of our patients developed Grade 2 + HT, and clinically significant HT was predicted by V10 and higher T stage. Our analysis suggests that radiation to the pelvic bones should be constrained such that V10 $\leq$ 87% in order to reduce the incidence of HT. Several studies have investigated the effect of clinical and dosimetric variables on all combined HT. Two studies lend support to the notion that low dose radiation to larger volumes of bony pelvis predict clinically significant HT, as suggested by our results. Specifically, Bazan et al. reported a significant correlation between above median bony pelvic V10, V15 and V20 and risk of HT, while Cheng et al. found that V5, V10, V15 and V20 to the bony pelvis and lumbosacral spine predicted HT [2,17]. An additional study by Bazan et al. lends further support to the notion that radiation dose to the bony pelvis correlates with clinically significant HT. The authors reported that mean dose to the bony pelvis, volume of bony pelvis receiving 5–40 Gy, mean dose to the sacrum, volume of sacrum receiving 5–40 Gy, mean dose to the lower pelvis (ischium, pubis and femoral heads) and volume of the lower pelvis receiving 5–40 Gy all correlated significantly with HT [7]. In contrast to all of the other studies referenced, Milano et al. found no correlation between overall Grade 2 + HT and the total pelvic radiation dose [13].

Taken together, these results suggest that radiation to the bony pelvis has important implications in terms of acute HT during definitive CRT for ASCC, even when using more conformal techniques of RT, such as IMRT. Our data suggest that minimizing the maximum dose to the bony pelvis and the volume of pelvic bone irradiated, both of which are feasible with IMRT planning, should be considered to reduce the incidence of HT. Furthermore, our findings support the use of IMRT in the treatment of ASCC, with the goal of reducing radiation dose to the bony pelvis, thus reducing acute HT. As demonstrated in our cohort, HT was overwhelmingly the most frequent cause of RT delays and chemotherapy dose reductions. Decreasing the incidence of acute HT in the treatment of ASCC may reduce the need for such dose reductions or treatment delays, which may increase the likelihood of local control and improve outcomes.

GI toxicity

Thirteen (12%) of our patients experienced Grade 2 + diarrhea, and this correlated best with a predictive model consisting of the absolute bowel volume receiving 45 Gy (VA45) and the mean dose to hottest 5% (MOH5) of the bowel volume. Recent studies of ASCC patients treated with concurrent IMRT and chemotherapy, commonly 5FU/MMC, have demonstrated a wide range of GI toxicity rates, with generally higher incidence than that seen in our cohort. Grade 2 + diarrhea was reported among 66% of ASCC patients in a representative study, while in publications assessing all combined Grade 2 + GI toxicities, reported rates range from 49% to 72% [3,6,13,18]. Two of these studies assessed the correlation between clinical and dosimetric variables and GI toxicities, and generally support our results, concluding that clinical variables do not correlate with GI toxicities, but that only high doses of radia-

tion are predictive. Kachnic et al. found only GTV dose to be predictive of Grade 2 + GI toxicity, while DeVisetty and colleagues found that V30 to the bowel was the only factor correlating with clinically significant GI toxicity [6,18].

Limitations

This study has several limitations. Our dataset was generated from a retrospective, single-institution study and, therefore, can be utilized only for hypothesis generation. Our results will need to be corroborated by prospective, multi-institution studies. In this study, we contoured the entire bone, rather than the bone marrow specifically. However, contouring the entire bone has some advantages, including reduced variability regardless of windowing, compared with contouring the bone marrow. As well, there was some variation in chemotherapy regimen (Table I). While 78% of patients received 5FU/MMC, the remainder received some combination of 5FU, MMC and capecitabine, and three patients received no concurrent chemotherapy.

Conclusion

In this large cohort of ASCC patients treated with IMRT and concurrent chemotherapy, anemia correlated significantly with maximum dose to the bony pelvis, female gender and T stage. Our results suggest that in order to minimize anemia, Dmax should be confined to ≤ 57 Gy. Leukopenia was associated most strongly with low dose to larger volumes of the pelvic bones and neutropenia was best predicted by number of MMC cycles administered and T stage. All combined HT correlated with low dose to larger pelvic bone volumes and to T stage. In order to minimize incidence of HT, V10 should be restricted to $\leq 87\%$. Dosimetric variables most associated with diarrhea were related to total bowel volume irradiated and maximum radiation doses. Dosimetric constraints to the pelvic bony structures should be integrated into IMRT planning for pelvic malignancies to reduce HT and allow for completion of planned chemotherapy, potentially improving outcomes.

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Supplementary material available online

Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1043396.