LETTER TO THE EDITOR

The volume of PET-defined, active bone marrow spared predicts acute hematologic toxicities in anal cancer patients receiving concurrent chemoradiotherapy

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Introduction

In 2016, anal cancer (AC) incidence was estimated to be 8080 which represented 0.5% of all cancer cases [1]. Despite advancing technology, the overall treatment paradigm has not changed since Nigro et al. [2] first published their results of chemoradiotherapy in the early 1970s. This regimen is very efficacious but is not without side effects. Bone marrow (BM) suppression is a significant risk with rates of acute Grade 3–4 hematologic toxicity (G3 + HT) ranging from 26% to 61% [3–5]. This toxicity is thought in large part to be secondary to the volume of pelvic bone marrow receiving radiation. These treatment related cytopenias can lead to unplanned treatment breaks, chemotherapy dose reductions, transfusions, and infections.

To help lower this risk, dosimetric parameters to reduce hematologic toxicity (HT) have been investigated. Mell et al. first reported on V10 and V20 of pelvic bone marrow (PBM) being associated with acute leukopenia and neutropenia in patients with AC and subsequent studies have shown similar results [6–12]. Recent studies suggest that BM, much like the liver, is a parallel organ and the volume spared a threshold dose may better predict acute HT [10,13]. In this report, we hypothesize that the PET-defined active pelvic bone marrow (APBM) volume spared a pre-specified dose will better predict the rate of G3 + HT compared to conventional dosimetric parameters. We defined the APBM as the PBM volume with an SUV greater than or equal to the total body mean SUV.

Material and methods

We retrospectively reviewed 18 patients with the diagnosis of AC who received definitive radiotherapy with concurrent mitomycin (MMC)/fluoropyrimidine based chemotherapy at a single institution between 2010 and 2015 under guidance from the institutional review board. PET CT imaging was obtained prior to therapy and was fused in MIMvista (Mimvista, Cleveland, OH, USA) to the simulation CT for target delineation. Radiotherapy was delivered using IMRT, volumetric arc therapy (VMAT), or helical tomotherapy. Target volumes, dosing, and dose constraints were defined by RTOG 0529 [14].

The PBM was contoured similarly to Mell et al. [12] using bone windows on the simulation CT. As previously stated, the APBM was defined as the region of PBM with an SUV greater than or equal to the total body mean SUV consistent with previous works (Figure 1) [7]. The total body mean SUV was derived in MIMvista using the pretreatment PET CT fused with the simulation CT.

For each patient, we evaluated conventional and volume based dosimetry metrics. HT was defined using the common terminology criteria for adverse events (CTCAE), version 4.03 [15]. G3 + HT was defined as any G3 + toxicity for hemoglobin (Hb), absolute neutrophil count (ANC), platelets (Plt), or white blood cell (WBC) based on weekly labs concurrent with and one month post treatment. Receiver operator characteristic (ROC) curves were performed comparing the predefined dosimetric continuous variables against the binary variable of G3 + HT. Fisher's exact test was then used to evaluate significant variables using a two-sided p value. Statistical analysis was performed using MedCalc® version 15.11.4.

Results

Patient characteristics are described in Table 1. The median total dose of radiation to the primary PTV was 54.0 Gy (39.6–60). The mean volumes for PBM and APBM were 1532 cc (1189–2028) and 941 cc (291–1486), respectively. The mean doses to the PBM and APBM were 30 Gy (20–37) and 29 Gy (17–38), respectively. The primary toxicity endpoint was G3 + HT which occurred in 44% (8/18) of the cohort.

The results of the ROC curve analysis are displayed in Table 2. The V10, V20, V40, and mean dose did not significantly predict for G3 + HT for APBM or PBM. The baseline APBM volume of 954 cc (AUC 0.788, $p = .017$) was shown to be a significant predictor of G3 + HT; however, the volume of PBM were nonsignificant. An APBM volumetric sparing goal of 216 cc was significant at a threshold dose of 20 Gy (AUC 0.788, $p = .015$). APBM volume of 564 cc spared at a threshold dose of 40 Gy was also significant (AUC 0.788, $p = .016$). The volume of PBM spared at threshold doses of 10 Gy, 20 Gy,

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40 Gy and APBM spared at 10 Gy were nonsignificant. In patients with ≤64 cc of APBM spared 40 Gy, 86% (6/7) developed G3 + HT compared to 18% (2/11) of patients with >564 cc spared 40 Gy ($p = .0128$). In patients with ≤216 cc of APBM spared 20 Gy, 70% (7/10) developed G3 + HT compared to 13% (1/8) of patients with >216 cc spared 20 Gy ($p = .0248$).

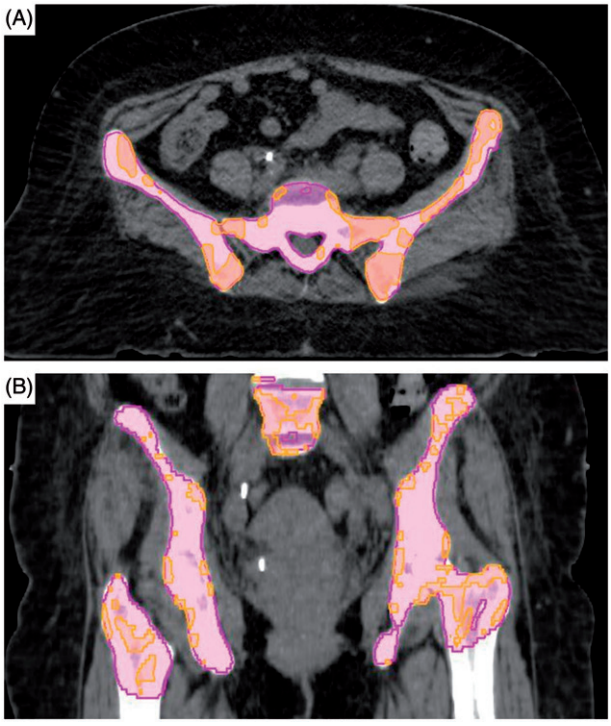

Figure 1. Representative volumes for pelvic bone marrow (pink) and active pelvic bone marrow (orange) contoured on axial (A) as well as coronal (B) CT slices.

Discussion

This study is the first to report that the volume of PET-defined APBM spared a threshold dose can predict acute G3 + HT in patients treated with definitive chemoradiation for AC confirming our initial hypothesis. The rate of acute G3 + HT in our cohort appears to be similar to those presented previously in the literature.

Mell et al. [12] was first to publish an analysis correlating WBC/ANC nadirs with radiation dose to PBM in AC. The authors were also able to confirm the hypothesis that a large volume of low-dose radiation to the PBM is associated with acute HT. IMRT has been attempted to reduce this low-dose radiation volume using the PBM as a surrogate for BM but this can be challenging due to competing goals of reducing bowel

Table 2. ROC analysis for grade 3 + hematologic toxicity.

Parameter	Criterion	AUC[d]	*p* Value
PBM[a] V10		0.512	.934
PBM V20		0.519	.904
PBM V40		0.519	.900
PBM mean		0.512	.934
APBM[b] V10		0.617	.394
APBM V20		0.656	.275
APBM V40		0.581	.580
APBM mean		0.613	.455
APBM volume	≤954 cc	0.788	.017
PBM volume		0.588	.547
PBM (cc[c]) spared 10 Gy		0.512	.936
PBM (cc) spared 20 Gy		0.512	.935
PBM (cc) spared 40 Gy		0.637	.329
APBM (cc) spared 10 Gy		0.738	.067
APBM (cc) spared 20 Gy	≤216 cc	0.788	.015
APBM (cc) spared 40 Gy	≤564 cc	0.788	.016

[a]Pelvic bone marrow.
[b]Active pelvic bone marrow.
[c]Cubic centimeters.
[d]Area under the curve.

Table 1. Characteristics ($n = 18$).

Characteristic		Value	Range
Median age (year)		60	(48–77)
Median dose (Gy)		54.0	(39.6–60.0)
Duration of therapy (days)		42	(37–51)
Chemotherapy (n)			
	Mitomycin +5FU	16	
	Mitomycin + Capecitabine	1	
	Mitomycin + unknown	1	
Gender			
	Female	12	
	Male	6	
Stage			
	Stage I	11% (2)	
	Stage II	39% (7)	
	Stage IIIA	16% (3)	
	Stage IIIB	22% (4)	
	Stage IV	11% (2)	
Rate of grade 3+ hematologic toxicity			
	Any	44% (8)	
	Leukopenia	39% (7)	
	Neutropenia	39% (7)	
	Anemia	11% (2)	
	Thrombocytopenia	22% (4)	
Mean PBM[a] volume (cc[b])		1532	(1189–2028)
Mean APBM[c] volume (cc)		941	(291–1486)
Mean PBM dose (Gy)		30	(20–37)
Mean APBM dose (Gy)		29	(17–38)

[a]Pelvic bone marrow.
[b]Cubic centimeters.
[c]Active pelvic bone marrow.

dose and maintaining target coverage. Therefore, identifying smaller volumes of active BM within the bony compartment is of interest. Using FDG-PET, several investigators have evaluated whether metabolically active regions of BM may better represent the BM compartment at risk. Rose et al. first evaluated using the APBM as a predictor for HT which was validated by Franco et al. [7,9]. These studies showed a significant correlation using linear modeling at various APBM values for ANC and WBC nadirs but not Plt or Hb.

Active pelvic bone marrow use has been validated in cervical cancer in the recently published INTERTECC-2 trial [16]. This study tested the hypothesis that BM sparing IMRT with concurrent cisplatin could reduce rates of G3 + neutropenia or significant gastrointestinal toxicity. A preplanned subgroup analysis evaluating PET CT image-guided IMRT to spare functional BM showed significantly lower rates of G3 + neutropenia (8.6% vs 27.1%, $p = .035$) in patients who received APBM sparing IMRT. The current NRG-GY006 phase II study in cervical or vaginal cancer evaluating definitive chemoradiation with or without triapine is also currently using similar dose constraints to the INTERTECC-2 (NCT02466971).

Although constraints have varied in regard to predicting HT, there appears to be a consistent trend that a large volume of low dose radiation to the PBM is strongly correlated with the development of G3 + HT. This property coincides with the PBM being a parallel organ where its functional capacity depends on the number of functional subunits (FSU) [13]. In synthetic parallel structures, such as the liver and BM, a threshold volume spared a specific dose is important in predicting toxicity. Schefter et al. [17] demonstrated this in the liver describing low rates of hepatotoxicity with $\geq$700 cc of normal liver receiving $<$15 Gy. A recent study by Lee et al. [10] tested this hypothesis in AC patients receiving concurrent chemoradiation and showed a threshold volume of 750 cc of PBM spared 30 Gy was able to predict G3 + leukopenia and neutropenia. Patients with $\geq$750 cc spared 30 Gy had 5% rates of G3 + leukopenia and neutropenia vs 54% for those not meeting this constraint ($p < .01$). Our study did not replicate this threshold volume but we did support the conclusion that the volume of active bone marrow spared may be an important constraint for future studies. Potential reasons for our lack of significance in looking at the volume of PBM spared may be related to our small cohort size and our larger PBM volume (L4 was included which is more commonly performed in cervical cancer). However, since previous studies have shown the APBM to be the most sensitive region of the bone marrow compartment, the absolute volume of APBM volume spared is rationale constraint.

Conclusions

Despite the use of IMRT, there has been minimal reduction in the rate of G3 + HT. With improved radiation techniques and understanding of the relationship APBM has with the development of hematologic toxicity, the morbidity associated with AC treatment may be further reduced. In this report, we demonstrate a practical method of measuring APBM spared as well as its ability to predict G3 + HT. Patients with low baseline APBM appear to be at a higher risk of HT and this suggests that these patients may have insufficient baseline hematologic reserves. The use of APBM as a volume sparing constraint shows promise and warrants further evaluation in additional cohorts.

Disclosure statement

No potential conflict of interest was reported by the authors.

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LETTER TO THE EDITOR

Successful treatment of high-grade pancreatic neuroendocrine neoplasms with everolimus

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Current systemic anti-tumor therapies for the treatment of neuroendocrine neoplasms (NEN) include somatostatin analogs (SSAs), cytotoxic chemotherapeutics, peptide receptor radionuclide therapy (PRRT) and molecular-targeted therapy. Following the European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines, treatment choices are mainly based on tumor grade, primary tumor site and progression on treatment lines, requiring experience and knowledge in selecting the appropriate therapy [1]. Tumor grade is defined by the proliferation activity, determined as mitotic count or Ki67 protein staining. Tumors with Ki67 exceeding 20% are mostly poorly differentiated (G3) and are generally called neuroendocrine carcinomas (NEC) [2]. These high-grade malignancies are aggressive and usually require early onset of platinum-based chemotherapy [3]. However, more recently cases of NEC have been reported with more favorable disease course and Ki67 in the range of 20–50%. It is questioned if, within this patient population, platinum-based chemotherapy is required as first-line therapy. The mTOR inhibitor everolimus is a valid therapeutic option for low or intermediate grade (G1/G2) neuroendocrine tumors (NET), but data outside of regulatory trials are sparse and not available for high-grade neoplasms [4].

Acceleration of tumor grade by dedifferentiation have been described for several tumor types [5]. For NET however, very few cases have been published so far. Here, we describe two patients treated at an academic hospital in Germany, with advanced pancreatic NET who showed dedifferentiation from intermediate to high-grade. Due to general good condition and lack of further treatment options, both patients were treated with everolimus as last resource and showed radiological and clinical benefit.

Two patients were treated at an academic hospital in Germany. Despite several lines of systemic treatment, clinical and radiological progression was seen together with dedifferentiation of the tumor metastases, after six and five lines of prior therapy. Due to general good condition and lack of further treatment options, both patients were treated with everolimus as last resource.

Figure 1 summarizes the treatment over time in relation to the tumor burden for both patients. Measurements of the tumor and metastases were taken of radiological scans performed during the course of disease. Tumor burden was defined as the sum of the largest liver metastases, primary tumor and the largest pathological lymph nodes. Response to treatment was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) [6].

The first patient, a 35-year-old Caucasian male, presented with a primary pancreatic tail mass, not suitable for resection, together with liver metastasis. Histopathology showed an intermediate grade NET (Ki67 5–10%) and palliative chemotherapy with fluorouracil (5-FU) and streptozocin was given for 12 months. The resulting partial remission made radical resection of the primary tumor possible, which revealed a proliferation rate of 2%. Over the course of the following 5 years, disease progression was treated with repeated regimen of streptozocin/5FU (6 months response), two times transarterial chemoembolization (TACE) (insufficient response), vatalanib (PTK787/ZK) within a clinical trial (progressive disease), 5FU/oxaliplatin (FOLFOX) (6 months response) and temozolomide/capecitabine (CAPTEM) (15 months response). In the presence of liver disease only, and lack of other established therapies, a partial liver resection was performed without any complications. Histopathology revealed an increase in Ki67 proliferation index to 25%, dedifferentiating the tumor to a NEC. A fifth-line systemic treatment with 5-FU, irinotecan and becavizumab was given to treat multifocal recurrence in the liver,

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