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Abstract

Introduction: Hematologic toxicity is an important side effect occurring in patients affected with anal cancer, undergoing combined radio-chemotherapy, with consistent clinical meaningfulness.

Areas covered: Since more than a half of bone marrow is comprised within the pelvic region, the radiation dose received by this functional compartment is crucial. Modern imaging modalities may provide a useful tool to identify bone marrow and new delivery technology may enhance the radiation oncologist's possibility to selectively spare these structures, potentially decreasing acute hematologic toxicity profile in this setting.

Expert commentary: Correlation between dose to pelvic structures and acute hematologic toxicity has been studied in several oncological settings, mainly on a retrospective frame. Different dose metrics were found to be correlated including mean doses and different points within the dose–volume histogram ranging from low to medium-high doses. Several imaging modalities were used to identify bone marrow both morphological and functional. Several clinical endpoints were used. In general, accounting for bone marrow during the treatment planning process may be important to decrease the acute hematologic toxicity profile during concurrent chemo-radiation in anal cancer patients. The most appropriate

strategy to address this issue need further investigation and deserve validation in a prospective clinical framework.

KEYWORDS: Anal cancer, hematologic toxicity, radiotherapy, IMRT, bone-marrow dose

1. Introduction

Concurrent chemo-radiotherapy (CT-RT) is presently considered as a standard of care in squamous cell carcinoma of the anal canal (1). In this combined modality approach, radiotherapy (RT) is combined with 5-fluorouracil (5-FU) and mytomicin C (MMC) following the seminal report by Nigro et al. (2). Clinical results in terms of both local control and survival are favorable as the rate of sphincter preservation (3, 4). Nevertheless, the acute toxicity profile is not negligible and major reactions can occur in the genitalia, skin, or gastrointestinal tract, particularly if nonconformal techniques are used (5). Hematologic toxicity (HT) can be a critical issue in this setting of patients leading to unplanned treatment breaks with a consequent increase in overall treatment time and a potential detrimental effect on treatment intensity or increasing the likelihood to develop bleeding, infections, or asthenia that may impact on patient's compliance to therapy (6). Hence, minimization of HT is cogent in anal cancer (AC) patients submitted to combination therapy. Chemotherapy (CHT) is considered the most important trigger for HT because of its direct induction of myelosuppression (7). Nevertheless, given the exquisite radiosensitivity of circulating blood cells and precursors within bone marrow (BM), RT has a consistent influence in the occurrence of HT (8). This is particularly evident during combination therapy for pelvic malignancies, including anal cancer (9,10). Interestingly, in the average adult population, pelvis and lumbar vertebrae comprise about half of the total hematopoietically active BM (11). Hence, selective sparing of pelvic bone structures may be a viable option to decrease HT during concomitant CT-RT in patients affected with pelvic malignancies (12,13). The aim of this review is to provide a glimpse into the role of RT dose delivered to pelvic BM (PBM) during concomitant CT-RT for cancer of the anal canal and to highlight current perspective in the prevention and management of HT from a radiation oncology perspective.

2. BM characteristics

The vast majority of the medullary cavity of osseous segments is made up of BM. In general, up to 50% of BM is active from a hematopoietic point of view (red marrow) and it is primarily located within the axial skeleton and proximal aspect of the limbs, while the remaining 50% is made up of inactive BM (yellow marrow) and can be mainly found in the appendicular skeleton (14). Pathological studies showed that yellow BM is composed of approximately 95% of fat cells and 5% of nonfat cells (15). Conversely, red BM comprises 60% of hematopoietic cells and up to 40% fat cells (15). The relative proportion of this two compartments is a strong influence on the magnetic resonance signal intensity during dedicated imaging procedures. Within red BM, three major components can be identified, namely progenitors of blood cells responsible for hematopoiesis, reticuloendothelial cells, and cells involved in the trabecular cellular pattern which act as a support tissue (15). BM weight depends on gender and varies between 2600 and 3000 g (16). Since one half of red marrow by weight is made of adipose tissue, up to 75% of total BM weight is made of adipose tissue in the adult population (16). Inside active BM, hematopoietic stem cells are able to replicate and differentiate mature cells of myeloid, lymphoid, and erythroid lineages, driven by a complex network of growth factors and cellular ‘cross talk’ (7). BM microenvironment, consisting of adipocytes, fibroblast, endothelial and adventitial cells, and macrophages, also contributes in maintaining the hematopoietic function (7). In children, the appendicular skeleton (humerus, femur) has hematopoietic activity. With age, active BM progressively retracts from peripheral to axial skeleton and from diaphyseal to metaphyseal long bones (7). Moreover, red marrow itself develops age-related changes with respect to distribution and composition, with an increase in the proportion of fat cells in the axial skeleton, and a progressive conversion from red to yellow BM in the peripheral skeleton (15).

In the average adult population, almost 60% of total BM is comprised within pelvic bones and lumbar spine (7). This observation provides a causal relation between the dose received by these regions during CT-RT and the occurrence of HT.

3. BM and radiation

BM has a high intrinsic radiosensitivity which leads to some degree of damage for any dose received (7, 17) The sequence of histologic alterations has been clearly described by Sykes et al. in humans (18). Using fractionated RT, a moderate decrease in precursors of red blood cells and granulocyte can be observed after 4 Gy (18). Dilatation of sinusoids

with associated hemorrhage and vanishing of young hematopoietic precursors occurs after 10 Gy (18). At 20 Gy radiation, cellularity of nucleated cells has decreased to 20%, while above 50 Gy a consistent hypoplasia can be seen with consequent fat accumulation (18). Medium- to long-term effects may include partial recovery but also irreversible BM depression depending on several intrinsic and extrinsic factors (7). Hence, a clear dose–response relationship can be pointed out. However, another parameter that should be taken into account is irradiated volume of BM, as clearly shown by data on acute response of the marrow organ after single total body exposure (7). One week after total body RT up to 1.5–7.5 Gy, a rapid depletion of vital stem cells can be seen with a consequent prominent granulocytopenia and thrombocytopenia (19). At those doses, the microvasculature survives allowing for eventual implantation and proliferation of infused stem cells, but the entity of BM damage is strictly correlated to the volume receiving RT (7). Interestingly, when small field radiation is employed, exposing limited BM volumes (10–15%) to RT, unexposed BM is able to compensate for the hematopoietic demand increasing the progenitor cell population (7, 20). Whenever larger field radiations are used, such as in the case of radiation treatments for anal cancer or other pelvic malignancies, HT may become an issue (7. 20. 21).

4. BM distribution in the body

The seminal work by Ellis derived an average active BM distribution in adult man using fractional regional estimates of BM weight compared to total bone weight as a surrogate for BM identification. Pelvic bone and sacrum accounted for 40% of the total BM amount, lumbar spine for 10%, and thoracic vertebrae for 14% in that study (11) Ellis RE. The distribution of active bone marrow in the adult. Phys Med Biol. 1961;5:255–258. Using the entire bone as a surrogate for BM is an option, but this method does not differentiate between active and inactive BM and does not provide any information on the correct localization of red marrow (9). Functional imaging is a useful tool to selectively identify BM and potentially characterize red and yellow marrow (15). Tc-99m sulfur colloid single-photon-emission computed tomography has been investigated in this setting, as Tc-99m sulfur colloids may be internalized and sequestrated by macrophages associated to the reticuloendothelial compartment of BM, consequently providing a three-dimensional (3D) map of BM distribution (22). With this method, Roeske et al. were able to characterize BM mainly within lumbar vertebrae, sacrum, and medial aspect of the iliac crests. However,

the poor quantitative ability of this imaging modality should be taken into account (22). Another option for BM functional imaging is 3′-deoxy-3′-^{18}F-fluorothymidine-labeled positron-emission tomography (^{18}F-FLT-PET), as a mean to identify cells with DNA synthesis (23). ^{18}F-fluorothymidine (FLT) is a thymidine analogue able to be retained inside the cell through a thymidine kinase-mediated phosphorylation process which takes place mainly during the S-phase of the cell cycle (24). Even if FLT cannot be incorporated into DNA, its uptake is a marker of DNA replication and active cellular proliferation. A reduction in FLT uptake within bone regions is a sign for the loss of precursor cells in the proliferative compartment of BM (25). Hayman et al. investigated the relative distribution of active BM through the body, using ^{18}F-FLT-PET, in 13 patients affected with different types of cancer (24). Interestingly, significant individual variations were observed among cases. The mean percentage of proliferating BM was 25.3% at the pelvis, 19.9% and 16.6% at the thoracic and lumbar spine, respectively, 9.2% at the sacrum, and 8.8% at the ribs and clavicles. Less than 5% of active BM was found at the skull, proximal humeri, sternum, scapulas, cervical spine, and proximal femurs (25). Interestingly, a recent study by McGuire et al. reported that, within the pelvis, regions located in the central part, such as the upper sacrum, the inner halves of iliac crests, and the fifth lumbar vertebral body, have the ^{18}F-FLT highest uptake (26). A larger cohort of 51 lung cancer patients was analyzed by Campbell et al. with respect to BM distribution according to ^{18}F-FLT-PET (27). The pelvic bones had the highest proportion of proliferating BM regardless of gender and age (27). Interestingly, women had a higher proportion of functional BM in the pelvis, proximal femurs, and skull, while men in the sternum and ribs, clavicles, and scapulae (27). Elderly patients (>75 years) had a higher relative proportion of active BM in the ribs, clavicles, and scapulae. The proximal long bones (femurs and humeri) had the largest variations in the mean proportion of functional BM with respect to age with a 20–30% increase according to gender and osseous segment taken into account (27). Another potentially useful examination is ^{18}F-fluorodeoxyglucose-labeled positron-emission tomography (^{18}FDG-PET), which has been demonstrated to be able to detect the volume of active BM with an uptake pattern corresponding to histologic distribution (15). Franco et al. described the relative distribution of active BM within the pelvic region using ^{18}FDG-PET (28). Active BM was observed in 44% of the volume of pelvic bones with lumbar–sacral vertebrae (67%) and iliac bones (57%) having the highest percentages (28). However, the ability of ^{18}FDG-PET to correctly discriminate between active and inactive BM is still a matter of debate (15 28)

5. HT in randomized phase III trial

HT is a clinically meaningful occurrence in anal cancer patients, potentially affecting patient compliance and treatment outcomes. This finding has been observed since the first randomized phase III trials exploring the role of concurrent CT-RT employing 5-FU and MMC in AC, namely the ACT I and EORTC 22861 trials (see Table 1) (29,30). For example in the ACT I trial, patients were randomized to receive either exclusive RT (45 Gy in 20 or 25 fractions) over 4–5 weeks or the same regimen concomitant to 5-FU and MMC. Treatment response was assessed at 6 weeks and good responders were boosted with RT while poor responders were submitted to salvage surgery. RT was delivered employing two-dimensional (2D) approaches with supposedly large BM volumes within treatment fields (Table 1). These findings prompted clinicians to explore the withdrawal of MMC, as in the RTOG 8704/ECOG 1289 trial, where randomization consisted of treatment with either RT (45–50.4 Gy to the pelvic region) concurrent to 5-FU or 5-FU/MMC (30). Removing MMC from treatment schedule lowered the rate of G4-G5 acute HT from 18% to 3%, but also the colostomy-free and disease free-survival rates, with an excess in definitive colostomies (15% vs. 8%) (31). More recent trials, such as RTOG 98-11 investigating the role of cisplatin (DDP) added to 5-FU and RT in decreasing the toxicity profile compared to standard RT + 5-FU/MMC continued showing high rates of HT. Patients in the standard arm (5-FU/MMC) experienced a 61% rate of G3-G4 acute HT, while those in the experimental arm (5-FU/DDP) a 42% rate (5). The use of DDP lowered the acute HT rate, which nevertheless remained consistent. Even better results were described in most the recent trials such as the ACT II and the ACCORD 3 trials, where, in the arms employing DDP, the rates of G3-G4 acute HT were 16% and 19%, respectively (32,33). In these trials, DDP was also used as neoadjuvant or maintainance therapy combined to 5FU. All the aforementioned studies used standard RT techniques, such as 2D RT including anterior–posterior/posterior–anterior (AP/PA) parallel-opposed fields or AP/PA fields added to paired laterals fields or a four-field box techniques or a 3D conformal RT approach based on a four-field class solution (Table 1). The boost dose to the macroscopic disease within the anal canal was delivered sequentially to the whole-pelvis phase either with photons, electrons, or ^{192}Ir implants. Pelvic bony segments containing BM were not taken into account to be selectively spared and thus, medium to high doses were received by these structures in all these studies.

Table 1. Acute hematologic toxicity in phase III randomized trials of anal cancer patients.

6. HT in IMRT series

Intensity-modulated radiotherapy (IMRT) is a RT approach able to deliver external beam radiation with robust conformality and modulation, abrupt dose falloff, and reliable accuracy (34,35). This technique has been implemented in several clinical context and is presently considered standard of care to deliver RT in anal cancer patients (1,36). A large number of clinical series have been published in recent years (see Table 2) (21,37–47). Compared to 2D or 3D approaches, IMRT is able to decrease medium to high dose to critical structures, conversely increasing volumes of normal tissues receiving low dose bath (48). The contribution of this peculiar dose distribution to the occurrence, duration, and characteristics of HT has yet to be determined. In this sense, the report by Robinson et al. rises up some concerns on the significant increase in the dose received by PBM during IMRT treatments compared to 3D-conformal approaches, with normal tissue complication probability (NTCP) modeling suggesting an approximately doubling in the risk of occurrence of major HT (49). Early IMRT reports employed static techniques (either step and shoot or sliding window IMRT) and a sequential approach to deliver a boost dose to the primary tumor within the anal canal (37–40). During the treatment planning process, optimization on BM as a critical structure was sporadically performed and, when present, was addressed only to iliac crests. For example, Salama et al. reported on 53 patients treated with IMRT for anal cancer at three tertiary-care academic centers. RT was delivered with a static approach mainly using nine equally spaced fields with a planning priority set primarily to target coverage and secondarily to small bowel, bladder, and genitalia avoidance. No specific dose constraints were applied to bony structures to decrease HT. Patient were given 45 Gy to the pelvic region and inguinal groins and a sequential boost dose to the macroscopic disease up to 50–54 Gy concurrent to 5-FU and MMC. A total of 39.6% of patients experienced G4 HT. The most common major events were acute G3-G4 leukopenia (53%), thrombocytopenia (28%), and anemia (9%) (38). Most recent series used volumetric approaches such as volumetric-modulated arc therapy (VMAT) and tomotherapy, with a simultaneous integrated boost strategy to boost the macroscopic disease and a plan optimization accounting for PBM (21,46,47). Nevertheless, the acute HT profile remains not negligible. In the multicentric series by Call

et al., reporting on 152 anal cancer patients treated with IMRT and different combinations of concurrent drugs, the overall acute HT rate was 41% (47). Franco et al. observed in their cohort of patients treated with VMAT and concurrent 5-FU/MMC rates of leukopenia up to 36%, neutropenia 31%, and thrombocytopenia 13% (21). Similar findings come from the RTOG 0529 trial that investigated whether dose-painted IMRT could reduce by at least 15% the ≥G2 gastrointestinal and genitourinary toxicity rates compared to conventional treatments as delivered in the RTOG 98-11 trial. The primary end point of the study was not reached. However, a significant reduction in acute G2 HT (73% vs. 85 % for RTOG 98-11) was observed (44). A better HT toxicity profile was seen with IMRT, but still with substantially high toxicity rates and substantial room for clinical improvement in this setting.

Table 2. Acute hematologic toxicity in IMRT series of anal cancer patients.

7. Correlation between dose to pelvic bones and HT

7.1. Definition of PBM

Contouring strategy for PBM has been set in the pivotal study by Mell et al. in cervical cancer patients (48). The external surface of bone is used for delineation as a surrogate for BM, according to the RTOG 0418 trial (50). The pelvic region is generally divided into three different subsites: (a) the iliac BM (IBM), extending from the iliac crests to the upper border of femoral head; (b) lower pelvis BM (LPBM), accounting for bilateral pube, ischia, acetabula, and proximal femura, from the upper limit of the femoral heads to the lower limit of the ischial tuberosities; and (c) lumbosacral BM (LSBM), extending from the superior border of L5 somatic body to the superior edges of the femoral heads (48). Since the trabecular bone is the subregion containing active BM, Cheng et al. outlined the marrow cavity, corresponding to the lower Hounsfield Unit part of an osseous segment as seen on computed tomography imaging (51). They compared the NTCP models for HT prediction between whole bone- and marrow cavity-based contouring strategies finding out a better fitting for the whole-bone delineation approach (51). Functional imaging may be a useful tool in defining active BM within a osseous segment, potentially providing a better spatial definition of BM as avoidance structure and eventually limiting the absolute volume to be spared during RT treatments (15). Several studies investigated this field in the setting of

both anal and cervical cancer radiation therapy (28,52,53). From a methodological point of view, ^{18}FDG-PET images were co-registered with planning computed tomography and RT structures. Standardized uptake values (SUVs) were calculated for pelvic structures after correcting for body weight and standardization with normalization to liver SUVs. Active BM was defined as the volume having higher SUV values than the SUV_{mean} for each patient to better account for individual variations (28,52,53).

7.2. Clinical and dosimetric data in anal cancer patients

Correlation between dose to pelvic bones and HT has been explored in several studies in the context of anal cancer (6,10,28,49,51,53–55) . Detailed description of the available reports may be found in Table 3. The first report is by Mell et al. who observed on multiple regression analysis that an increased volume of PBM receiving doses between 5 and 20 Gy was significantly associated to decreased white blood cells (WBC) and absolute neutrophil count (ANC) nadirs as was the volume of LSBM receiving a dose range between 10 and 20 Gy. On the contrary, the same authors could not find any association between dosimetric parameters and G3-G4 leukopenia or neutropenia, even if the volume of LSBM receiving 10 Gy (V_{10}-LSBM) had a non-statistically significant trend in increasing the likelihood of experiencing G4 leukopenia (odds ratio [OR]: 1.06; 95% confidence interval: 0.99–1.12; $p = 0.051$) (10) This finding shows the high sensitivity of BM stem cells toward radiation. Their early destruction is thought to be responsible for acute myelosuppression together with effects on peripheral blood stem cells and stromal tissue 7. These data are supported by Franco et al. who described PBM-V_{20} as a significant predictor of WBC nadir (β-coefficient: −0.035; standard error [SE]: 0.017; $p = 0.048$) (55). In that cohort of anal cancer patients, mean PBM-V_{20} was 75% (standard deviation: ±9%), consistently with threshold values found to be predictive for HT in other clinical contexts, such as the data reported by Rose et al. in cervical cancer patients (56). Hence, PBM dose metrics have been shown to be predictive of blood cell nadirs, even at low doses, especially in terms of leukopenia, neutropenia, and thrombocytopenia. In a small retrospective study of anal cancer patients treated within the UK ACT II trial, Robinson et al. performed a tailored analysis of patients treated with 3D-conformal radiation vs. patients submitted to IMRT (49). In general, an IMRT treatment strategy significantly increased irradiation of PBM, with a potential suppressive effect on WBC and neutrophilic cells corresponding to a higher risk of developing major HT (49). Surprisingly, the

observed rates of major HT were similar between the two groups, highlighting the fact that the correlation between PBM dose and blood cells nadirs found in linear regressions analyses not always corresponds to a correlation with a major grade toxicity event in logistic regression analyses. Even more difficult is to demonstrate the clinical meaningfulness of toxic events based on a dedicated scoring scale. Nevertheless, some informative studies reporting on graded HT toxicity are present. Cheng et al. recently observed that several low-dose dosimetric parameters of either PBM and LSBM were associated with a higher chance to develop ≥G3 HT. Of notice, volumes of LSBM receiving doses ranging from 5 to 20 Gy were found to be the most consistent predictors 51. That points out the hypothesis that dose to specific osseous segments may have a strong correlation to HT, depending on the relative percentage of active BM that they may comprise. In this sense, LSBM has a consistent relative proportion of active BM (28). In the study by Franco et al., authors showed a significant correlation between LSBM-V_{40} and a higher likelihood to develop ≥G3 HT (OR: 1.328; SE: 0.160; $p = 0.019$) (55). The optimal cutoff point for LSBM-V_{40} was found to be 41%. Patients with LSBM-$V_{40} \geq 41\%$ were more likely to develop ≥G3 HT (60.9% vs. 39.1%; $p = 0.041$) (55). This findings seems to be confirmed also when BM is defined according to ^{18}FDG-PET imaging to delineate its active portion. Franco et al. showed that volume of LSBM receiving doses in the range of 10–30 Gy were significantly correlated to WBC and ANC nadirs (28). Other subsites within pelvic bones, such as IBM and LPBM, do have a role in the occurrence of HT (28). However, it has to be noted that the role of ^{18}FDG-PET in the precise identification of active BM has been recently debated. Rose et al. investigated the ability of ^{18}FDG-PET-defined active BM to predict ANC nadir during or within 2 weeks of completion of treatment in anal cancer patients (52). The model performance of equivalent uniform dose (EUD) to active BM was equivalent to that of inactive and total BM, suggesting that ^{18}FDG may not be the ideal tracer to provide accurate discrimination between hematopoietic elements and background non-hematologic cells (52).

Table 3. Dosimetric parameters with a correlation to hematologic toxicity in anal cancer series.

7.3. Clinical and dosimetric data in patients with other type of cancer

Several authors investigated the correlation between dose to pelvic osseous structures and HT in oncological scenarios other than anal cancer (48,52,56–64). Detailed descriptions of the studies may be seen in Table 4. In cervical cancer, with patients treated with concurrent RT and weekly DDP 40 mg/m^2, Mell et al. observed that PBM-$V_{10} \geq 90\%$ and PBM-$V_{20} \geq 75\%$ were associated with a lower WBC nadir. Moreover, an increased PBM-V_{10} and -V_{20} predicted for a higher likelihood to develop ≥G2 leukopenia as the LSBM-V20, LPBM-V_{10}, and -V_{20}. A higher PBM-V_{10} was also found to be a predictor of ≥G2 neutropenia (10). In line with this findings are the reports by Rose et al. and Albuquerque et al., again in cervical cancer patients (56,57) . Rose et al. observed that PBM-V_{10} > 95% and PBM-V_{20} > 76% increased the likelihood to experience ≥G3 leukopenia, while Albuquerque et al. showed that PBM-V_{20} > 80% increased the risk to develop ≥G2 overall HT. These studies stress the importance of volumes of PBM receiving low doses in the occurrence of HT, when myelosuppressive CT regimens (such as DDP) are used. A recent longitudinal study by Zhu et al., in a similar setting of patients, demonstrated that increased PBM-V_{20}, -V_{30}, and -V_{40} were significantly associated with a higher weekly reduction of WBC and ANC, estimating that every 1 Gy increase in mean PBM dose could lead to a 9.6/μl per week reduction in the natural logarithm of ANC (64). The regimen of CHT employed strongly affects the correlation between dose to pelvic bony structures and the occurrence of HT. This has been elegantly shown by Bazan et al., in patients submitted to different combination of RT and CHT for different malignancies (65). Patients undergoing whole-pelvic RT and 5-FU had a higher BM tolerance toward radiation compared to those receiving DDP or MMC. Patients incorporating MMC in their combined modality treatment program had a lower maximum tolerated dose-50% and a steeper NTCP curve. Overall, the dose tolerance of PBM and LSBM resulted to be lower for patients receiving MMC compared to dose treated with DDP (65). Interesting data come from Sini et al. in the context of prostate cancer patients undergoing post-prostatectomy whole-pelvic RT (62). Data on these patients are very intriguing, given their ‘chemo-naïve’ profile. The absence of any confounding effect due to CHT may provide the chance to explore a ‘pure’ dose–volume effect for irradiated BM. Authors observed that higher PBM-V_{40} were significantly associated to a higher likelihood to develop acute G3 (OR: 1.018) and late G2 (OR: 1.005) lymphopenia. Moreover, IBM-V_{40} was found to be correlated to the probability risk for 1-year G2 lymphopenia, with a dichotomizing cutoff point at 94.6 cc absolute IBM volume (62). The finding of the role of higher doses to the whole PBM, such as PBM-$V_{40,}$ and to specific subregions, such as LSBM-$V_{40,}$ is in line with

data coming from rectal and anal cancer (55,58,59). For example, Wan et al. showed, in rectal cancer patients undergoing preoperative CT-RT with concomitant capecitabine, a significant correlation between LSBM-V_{40} and ≥G2 HT with patients having LSBM-$V_{40} \geq 60\%$ more likely to develop HT(59). As previously described, the same dose–volume parameter (LSBM-V_{40}) was found by Franco et al., but with a more restrictive cutoff point at 41%, which seems reasonable taking into account the different CHT regimens used (capecitabine vs. 5FU-MMC).

Table 4. Dosimetric parameters with a correlation to hematologic toxicity in clinical series with tumors other than anal cancer.

8. Expert commentary

HT may be a consistent issue in anal cancer patients undergoing concurrent CT-RT, with potentially detrimental effects on clinical outcomes and patient's compliance to treatment. RT is an important factor in determining HT and hence attention should be paid to BM during the treatment planning process. Nevertheless, several aspects still need to be clarified. The most appropriate BM dose–volume parameters still need to be investigated. Some data stress the role of low doses to the whole-pelvic osseous structures, some other medium to high doses. In general, Lyman–Kutcher–Burman model confirm that BM act like a parallel organ and thus mean dose is a useful tool to predict for the occurrence of acute HT (54). The most important irradiated regions within the pelvis to enhance HT have yet to be determined. Those containing a large amount of active BM are for sure crucial, such as the sacrum and iliac subsites (28). However, the dose to the whole PBM plays a role (10). Probably both of them are important and an interaction between low doses to PBM and medium to high doses to specific subsites is a potential trigger for the development of HT (66). Modern morphological and functional imaging modalities may enhance our ability to carefully define and delineate BM regions within treatment volume areas. Computed tomography-based delineation of the external aspect of bones prevents missing BM but may lead to extended normal tissue volumes to be spared, with challenging treatment plans in terms of both target coverage and organs at risk sparing. The incorporation of ^{18}FDG-PET in the diagnosis and staging of anal cancer is widespread and thus it is easy to implement its use for BM identification. Nevertheless, its sensitivity and specificity in correctly identifying BM have been questioned (53). In this sense, ^{18}F-FLT-PET may be a

more adequate tool but its use in the clinical practice is still anecdotal. Adjunctively, the influence of CT on the relative distribution of active BM within osseous structures should also be taken into account, with potential differences compared to baseline status (67,68). The most proper clinical endpoints to be used in this setting are still uncertain. Blood cell nadirs, acute HT as determined by a codified scoring scale or modification in the clinical management (CT dose reduction, treatment breaks, overall treatment time increase), have been used in the available studies, leading to different correlation with dosimetric parameters. Radiation oncologists have a crucial role in the prevention and management of HT in anal cancer patients. The systematic inclusion of BM volumes in the planning algorithm as avoidance structures should be strongly advised in patients undergoing RT for pelvic malignancies. However, the most appropriate imaging modalities for BM identification as the most proper dose–volume parameters to be used and clinical endpoints to be addressed, still deserve investigation. Prospective clinical validation of BM-sparing treatment strategies is mandatory (69) .

9. Five-year view

In the next 5 years, clinical research in the field of anal cancer should focus to find out the most reliable imaging modality to define and delineate BM within pelvic osseous structures to help its selective avoidance during RT treatments. Prospective trials addressing the issue of acute HT would be helpful to define robust endpoints with clinical meaningfulness and to better identify significant dosimetric parameters correlating with the toxicity profile to be incorporated within the treatment planning process to decrease this important side effect. Selection and definition of BM as an organ at risk should be advised on a routine basis to tailor sparing strategies and to increase the therapeutic index in this subset of patients.

10. Key issues

- Acute hematologic toxicity is an important side effects in anal cancer patients undergoing concurrent chemoradiation
- Radiation is a consistent trigger for hematologic toxicity and pelvic bone marrow is a crucial organ at risk

- A dose-response relationship is evident but dose-volume parameters and robust clinical endpoints have yet to be determined
- The systematic inclusion of bone marrow in the planning algorithm as avoidance structures should be strongly advised, but prospective clinical validation is needed

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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