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Rectal cancer

Clinical and dosimetric predictors of acute hematologic toxicity in rectal cancer patients undergoing chemoradiotherapy

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ABSTRACT

Background and purpose: To identify clinical and dosimetric factors associated with hematologic toxicity (HT) during chemoradiotherapy for rectal cancer.

Materials and methods: We analyzed 120 rectal cancer patients treated with neoadjuvant pelvic radiotherapy (PRT) with concurrent 5-fluorouracil-based chemotherapy. The coxal (ilium, ischium, and pubis) bone marrow (BM), sacral BM, and femoral BM were contoured and dose-volume parameters were extracted. Associations between cell count trend and clinical predictors were tested using repeated-measures analysis of variance (ANOVA) test. Associations between clinical variables, Vx (percentage volume receiving x Gy), and cell count ratio at nadir were tested using linear regression models.

Results: Nadirs for white blood cell count (WBC), absolute neutrophil count (ANC), and platelets (PLT) occurred in the second week of PRT and the fifth week for hemoglobin and absolute lymphocyte count (ALC). Using cell count ratio, patients treated with 3DCRT had a lower WBC ratio trend during PRT compared to patients treated with IMRT ($p = 0.04$), and patients $\geqslant 59$ years of age had a lower hemoglobin ratio trend during PRT ($p = 0.02$). Using absolute cell count, patients treated with 3DCRT had lower ANC cell count trend ($p = 0.03$), and women had lower hemoglobin cell count trend compared to men ($p = 0.03$). On univariate analysis, use of 3DCRT was associated with a lower WBC ratio at nadir ($p = 0.02$). On multiple regression analysis using dosimetric variables, coxal BM V45 ($p = 0.03$) and sacral BM V45 ($p = 0.03$) were associated with a lower WBC and ANC ratio at nadir, respectively.

Conclusions: HT trends during PRT revealed distinct patterns: WBC, ANC, and PLT cell counts reach nadirs early and recover, while hemoglobin and ALC decline steadily. Patients who were treated with 3DCRT and older patients experienced lower cell count ratio trend during PRT. Dosimetric constraints using coxal BM V45 and sacral BM V45 can be considered.

Pelvic radiotherapy (RT) is an integral part of the multidisciplinary care for patients with locally advanced rectal cancer. The use of pre-operative RT with 5-fluorouracil (FU)-based chemotherapy has been shown to improve locoregional control in several randomized trials [1–5]. Despite the established therapeutic advantage of RT in rectal cancer management, there is paucity of data on the impact of pelvic RT on bone marrow (BM) suppression and incidence of acute hematologic toxicity (HT). Given that pelvic BM is routinely included in a pelvic field, and approximately 40% of the total-body BM reserves are located within the pelvic bones [6], the destruction of the radiosensitive marrow stem cells by RT can lead to acute myelosuppression [7]. Studies in patients with cervical and anal cancer have demonstrated associations between concurrent chemoradiotherapy (CRT) and an increased risk of Grade 2–4 anemia, neutropenia, and thrombocytopenia during treatment [8–11]. However, the timing of the development of acute HT during CRT remains unclear.

Isolating clinical and dosimetric factors associated with pelvic radiotherapy-related hematologic toxicity is important as investigational agents are being combined with standard 5-FU-based chemoradiation for rectal cancer. Predictors of HT may help stratify patients who can tolerate intensification of therapy or guide dosimetric constraints that can reduce the risk of HT from the pelvic radiotherapy. In this study, we assessed HT in locally advanced rectal cancer patients receiving pelvic RT with concurrent FU-based chemotherapy. Given that infusional 5-FU or capecitabine chemotherapy functioned mainly as a radiosensitizer in patients undergoing neoadjuvant CRT for rectal cancer and had been reported to be associated with a low rate of myelosuppression [12,13–16], we felt that analyzing HT in this population would help us

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determine the myelosuppressive effect predominantly caused by pelvic RT. Our study aimed to establish the impact of standard long-course pelvic RT on BM suppression and to identify clinical and dosimetric predictors of HT. We tested the hypothesis that different hematologic cell types reach nadir at different time points during pelvic RT due to their distinct radiosensitivities, and that unique predictors for HT are associated with each cell type. Finally, we report potential dosimetric constraints for pelvic bony structures that can be used for pelvic RT planning, in particular IMRT planning, which has become more common in the treatment of rectal cancer.

Methods and materials

Patients and radiation planning and delivery

After obtaining approval of the Institutional Review Board, we retrospectively analyzed 120 consecutive rectal cancer patients treated with neoadjuvant pelvic RT with concurrent chemotherapy at our institution between 2007 and 2010. Patients who received induction chemotherapy prior to CRT or received CRT in the adjuvant setting were excluded. Concurrent chemotherapy was primarily continuous infusion 5-FU (225 mg/m^2/day) (95%). Only 5% received concurrent capecitabine (875 mg/m^2 twice daily). Patient's clinical information and weekly hematologic cell counts during pelvic RT were obtained through chart review.

All patients underwent computed tomography (CT) simulation in the prone position with marker placed at the anal verge. The gross tumor volume (GTV) consisted of the primary tumor and enlarged regional lymph nodes. For the standard pelvic fields, the clinical target volume (CTV) consisted of the GTV, rectum, and lymph node regions including mesorectum, pre-sacral nodes, internal iliac nodes, and the inferior rectal nodes. The initial planning target volume (PTV) is a 0.5 cm three-dimensional (3D) expansion of CTV. For the boost fields, CTV-boost consisted of the GTV, adjacent mesorectum, and presacral space, and PTV-boost is a 1.5 cm expansion and the CTV-boost. Normal tissues contoured at the time of RT planning included the bladder, rectum, small bowel, femoral heads, external genitalia, and vagina in female patients.

Patients underwent either 3DCRT or IMRT treatment planning with the in-house planning software, according to the treating physician's preference. 3DCRT was the RT delivery method for the majority (56%) of patients (Fig. 1). The median RT dose of the study cohort was 50 Gy in 25 fractions, and coverage of the PTV by at least 95% of the prescribed dose was required for all plans. 3DCRT plans consisted of three or four orthogonal beams for the pelvic fields and two lateral beams and one posterior–anterior beam for the boost fields. PTV was treated with 45 Gy in 1.8 Gy fractions followed by a 5.4 Gy boost to PTV-boost. IMRT plans consisted of seven to nine equally spaced coplanar fields. Dose homogeneity was assessed to minimize volume receiving more than 5% of the prescribed dose. The majority of patients treated with IMRT received 45 Gy in 1.8 Gy fractions to PTV and 50 Gy in 2 Gy fractions to the PTV-boost as an integrated boost.

Bone marrow delineation and dose calculation

Pelvic bone structures were contoured on the planning CT using bone windows. Pelvic BM was divided into three anatomic sites (Fig. 1): (1) sacral BM, extending from the L5-S1 junction to coccyx, (2) coxal BM, consisting of bilateral ilium, ischium, and pubis, and (3) proximal femoral BM, consisting of bilateral femoral heads and proximal femur. Doses to bony structures were calculated using the original treatment plan and dose-volume parameters were extracted for modeling using our in-house CERR (Computational Environment for Radiotherapy Research) [17] and DREES (Dose Response Explorer System) [18] software tools.

Toxicity and grading

All patients were monitored weekly during RT for acute toxicity including fatigue, dermatitis, mucositis, nausea, vomiting, diarrhea, proctitis, and cystitis. Weekly complete blood work with differentials was performed and documented: hemoglobin (g/dL), platelet count (K/mcL, PLT), white blood cell count (K/mcL, WBC), absolute neutrophil count (K/mcL, ANC), and absolute lymphocyte count (K/mcL, ALC). No patient required granulocyte–monocyte colony stimulating factor, or received packed red blood cell or platelet transfusion during CRT. HT was scored according to the

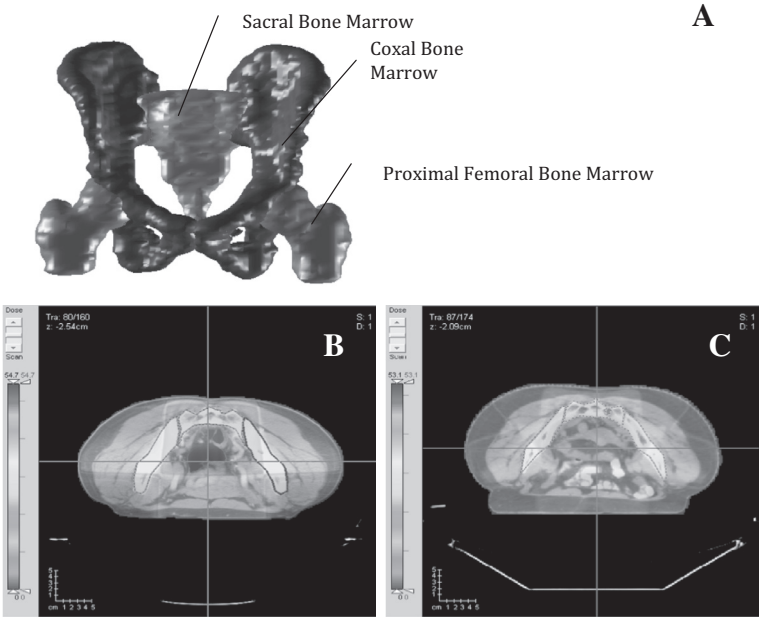

Fig. 1. Pelvic bone marrow subsites (A), and a comparison of dose distribution of intensity modulated radiation therapy rectal cancer treatment (B) versus three-dimensional conformal radiation therapy rectal cancer treatment (C). These snapshots were captured using our in-house software (Computational Environment for Radiotherapy Research).