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Anal cancer

Modeling early haematologic adverse events in conformal and intensity-modulated pelvic radiotherapy in anal cancer

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ABSTRACT

Background and purpose: To determine if there are differences between dose to pelvic bone marrow (PBM) using intensity modulated radiotherapy (IMRT) under UK guidance versus conformal radiotherapy (CRT) per ACT II protocol and if differences translate to rates of early haematological adverse events grade 3 or greater (HT3+).

Methods and materials: Two groups of 20+ patients, treated under IMRT and CRT regimes respectively, were identified. All patients underwent weekly blood cell count: haemoglobin (HgB), white cell count (WCC), absolute neutrophil count (ANC) and platelets (plats).

Percent volume of PBM and sub structures receiving 5–25 Gy were tested for statistical significance. Regression models were used to test for correlation to blood counts. NTCP modeling was also performed.

Results: PMB dose metrics showed a significant increase in the IMRT group. Regression analysis showed iliac and lumbosacral PBM dose metrics to associate with reduced nadir ANC and WCC. NTCP at HT3+ was 0.13 using IMRT relative to 0.07 using CRT ($p < 0.05$).

Conclusion: Whilst this is a relatively small retrospective study and lacks information on the distribution of active PBM, IMRT treatment has been shown to significantly increase PMB irradiation. PBM dose metrics have been shown to be predictive of WCC and ANC suppression. NTCP modeling predicts much high risk of HT3+. Paradoxically, actual rates of HT3+ were comparable suggesting that differences in the distributions of dose metrics maybe a significant factor and/or that there are insufficiency in the NTCP modeling.

Radical chemoradiation is the standard treatment in loco-regional anal cancer, achieving a 3 year disease free survival of 73% with organ preservation [1–3]. Recently, there has been an increasing move from conformal to intensity-modulated radiotherapy (IMRT). IMRT can deliver varying dose levels to multiple targets while decreasing low to intermediate dose (V30 Gy, V40 Gy etc.) to organs at risk, reducing adverse events (early gastrointestinal and dermatological, grade 3+) [4]. However, the impact of IMRT in delivering a 'low dose bath' to normal tissue needs to be considered in this tumour type, particularly in the context of concurrent chemotherapy. This impact is most pronounced in highly chemo-radiation sensitive tissue such as bone marrow (BM). Increased irradiation of BM has been shown to increase likelihood of early haematologic adverse events (HT) [5,6]. Approximately one third of proliferating bone marrow is located in the pelvic bones [7]; therefore differences in delivery system in anal irradiation may result in significant changes in rates of early adverse events. Irradiation of BM in IMRT can be reduced by applying appropriate dose objectives in the optimisation, i.e. through sparing [8], but this is not routinely done during the planning process.

UK ACT II trial delivering a 2 phase conformal radiotherapy (CRT) technique reported early haematologic adverse events grade 3 or 4 (HT3+) in the mitomycin arm as 26% [2]. The US Radiation Therapy Oncology Group (RTOG) 98–11 trial reported maximum grade 3 of 35% and max grade 4 in 26% of patients recruited in the mitomycin arm [3]. The RTOG 0529 trial looking at IMRT for anal cancer reported 58% HT3+ (4). Other US IMRT studies which have reported HT3+ at 24 and 53% [9,10].

This study aims to determine differences in pelvic bone marrow (PBM) dose associated with IMRT per UK guidelines (IMRT group), relative to CRT per ACT II (CRT group), and implications on acute haematological toxicity.

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Methods and materials

Patient selection

Twenty-five and twenty-one anal cancer patients treated with CRT and IMRT chemoradiotherapy respectively were identified in this retrospective study. Patients were treated in two sequential blocks in 2009 and 2014 respectively. Patients had a diagnosis of anal carcinoma with squamous carcinoma (one adenocarcinoma, IMRT group), disease localised to the pelvis, were radiotherapy naïve and considered fit enough with adequate baseline bloods by the treating clinician for radiotherapy alone or chemoradiotherapy. Patient gender, age, tumour staging and nodal status were collected.

Treatment

Radiotherapy

Twenty-five patients were treated as per ACT II protocol [2], using a two phase CRT technique. Phase one was a two field (anterior-posterior parallel opposing) technique to 30.6 Gy in 17 fractions which covered primary tumour, anal canal and elective nodes, field borders were placed superiorly 2 cm above the bottom of the sacroiliac joints, inferiorly 3 cm below anal margin or 3 cm below the most inferior extent of tumour, laterally to femoral heads. Phase two was a standard three field CRT technique to 19.8 Gy in 11 fractions covering gross tumour. The gross tumour was delineated by the treating oncologist with a margin of 3 cm added to create the PTV. No constraint was placed on pelvic bone dose including dose to femoral heads.

21 patients were treated using 7–9 field IMRT in 28 fractions using simultaneous integrated boost. Delineation was as per UK guidance [11]. In summary, gross anal tumour plus a 2.5 cm margin received either 53.2 Gy (if T3 and T4) or 50.4 Gy (if <T3); the involved nodes plus a 2 cm margin received 50.4 Gy and the prophylactic nodes received 39.2 (12 patients) or 40 Gy (9 patients) due to the protocol being updated during the audit period. A constraint was placed on femoral head dose (dose to 50% less than 30 Gy, dose to 35% less than 40 Gy and dose to 5% less than 44 Gy) but dose to other pelvic bone structures was unconstrained.

Chemotherapy

Patients fit enough for concurrent chemotherapy were planned to receive either Mitomycin 12 mg/m^2 Day 1 monotherapy if 5-fluorouracil was contraindicated, Mitomycin 12 mg/m^2 and 5FU 1000 mg/m 2 Days 1–5 and 29–33. 1 patient had Mitomycin 12 mg/m^2 Day 1 with Capecitabine 825 mg/m^2 twice daily on all days of radiotherapy. The second course of 5-fluorouracil was reduced by 25 or 50% following any episodes of any Grade 3 non-haematological related toxicity such as diarrhoea or Grade 3–4 haematological toxicity. 5-Fluorouracil was withheld at Grade 4 non-haematological toxicity and Capecitabine was withheld with thrombocytopenia Grade 2 or neutropenia G3 or any Grade 3 non-haematological toxicity related to Capecitabine; until it resolved to G1 then restarted at the same dose or at a reduced dose.

Bone marrow delineation

Pelvic bone marrow (PBM) was delineated using the external surface of bone and sub divided into three components; iliac BM, extending from the iliac crest to the superior edge of femoral head, lower pelvis BM, extending from the superior edge of femoral heads and including all pelvic bone as well as proximal femoral bone down to the level of and including the inferior ischial tuberosities, and lumbosacral BM, extending from the level of the superior border of L5 to the superior edge of femoral heads. Sub division of BM was based on previously published work by Mell et al. [5,6]. The method of delineating BM using the external surface of bone is consistent with the Radiation Therapy Oncology Group (RTOG) 0418 clinical trial as well as the aforementioned previous published work [5,6].

Dose metrics

The percent volume of pelvic, iliac, lower pelvis and lumbosacral BM receiving 5, 10, 15, 20 and 25 Gy (V5–25) was extracted. IMRT and CRT group dose metrics were compared using a two tailed Mann–Whitney *U* test.

Blood parameter analysis

Haemoglobin (HgB), white cell count (WCC) including absolute neutrophil count (ANC) and platelets (Plats) were determined from blood samples collected at baseline and weekly during radiotherapy. In addition to absolute counts, blood count ratios were calculated by dividing counts at each week by baseline count. Toxicity was graded using Common Terminology Criteria for Adverse Events, version 4.0. Maximum toxicity grading during radiotherapy was noted for each patient. Analysis endpoints were blood count nadirs, blood count ratio nadirs and whether a patient had experienced acute HT3+. IMRT and CRT group blood count nadirs were tested using a two tailed unpaired Student *t*-test assuming unequal variance.

Dose metrics were compared with analysis endpoints using univariate and multivariate linear and logistic regression models to determine if statistically significant correlation to decreasing nadir blood counts, both absolute and count ratio, and increasing HT3+ probability could be established. Covariants of female gender, age, T3/4 and node positive status were also compared using regression models. Additionally, weekly blood counts and count ratios were compared between groups using a two tailed unpaired Student *t*-test assuming unequal variance.

Significance testing using the Holm–Bonferroni method of correction for multiple testing was applied. False discovery rate was controlled at 5%. In regression analysis false discovery rate was controlled at 5% for analysis of whole PBM and each PBM sub structures dose metrics against each individual blood count for IMRT and CRT groups separately.

NTCP modeling

Lyman–Kutcher–Burman (LKB) NTCP [12] modeling on PBM was performed using parameter value estimates and 95% CI taken from previously published work by Bazan et al. [13] which estimated HT3+ parameter values based on anal cancer patients receiving mitomycin plus fluorouracil (mitomycin 10 mg/m^2 on day 1 and 29 with fluorouracil 1000 mg/m^2 on days 1–3 and days 29–32). Constraining n to one (i.e. treating bone marrow as an entirely parallel organ), m was reported as 0.09 (95% CI, 0.4–0.3) and TD50 as 30 Gy (95% CI, 28–32 Gy). NTCP was calculated using Eqs. (1–4) [14] where v_i is the volume within dose bin D_i at 0.1 Gy intervals and e is the number of fractions. The alpha beta ratio $\left(\frac{\alpha}{\beta}\right)$ of PBM was taken as 10 Gy n.b. In the case of CRT plan D_{eff} was the sum of D_{eff} calculated for each phase.

$$\mathrm{NTCP} = (2pi)^{-0.5}\int_{-\infty}^{x}\exp\left(-\frac{t^2}{2}\right)dt \tag{1}$$

$$x = \frac{D_{eff} - \mathrm{TD50}}{m \times \mathrm{TD50}} \tag{2}$$