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Scientific Article

NTCP Modeling and Dose-Volume Correlations of Significant Hematocrit Drop 3 Months After Prostate Radiation Therapy

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Purpose: Our purpose was to determine and model the dose-response relations of different parts of the pelvis regarding the endpoint of hematocrit level drop after pelvic radiation therapy (RT).

Methods and Materials: Two hundred and twenty-one patients treated with RT for prostate adenocarcinoma between 2014 and 2016 were included. All patients had complete blood counts collected at baseline and 3 months post-RT. The net difference of hematocrit level post-RT versus baseline was calculated, and the level of the 15th percentiles defined the thresholds of response in each case. The doses to 8 different pelvic structures were derived and fitted to the hematocrit levels using the relative seriality normal tissue complication probability model and the biologically equivalent uniform dose ($\bar{\bar{D}}$).

Results: Pelvic structures that correlated with significant decreases in hematocrit were the os coxae bilaterally superior to the acetabulum (OCUB), the total os coxae bilaterally, and the bone volume of the whole pelvis. The structure showing the highest correlation was OCUB with a maximum area under the curve (AUC) of 0.74. For V20 Gy < 30% the odds ratio was 9.8 with 95% CI of 2.9 to 32.9. For mean dose (D_{mean}) to OCUB, an AUC of 0.73 was observed where the dose threshold was 23 Gy and the odds ratio was 2.7 and 95% CI 1.3 to 5.6. The values for the D50, γ, and s parameters of the relative seriality model were 26.9 Gy (25.9-27.9), 1.3 (1.2-2.2), and 0.12 (0.10-0.83), respectively. The AUC of $\bar{\bar{D}}$ was 0.73 and patients with $\bar{\bar{D}}$ to OCUB $\geq$ 27 Gy had 8.2 times higher rate of significant hematocrit drop versus <27 Gy.

Conclusions: These findings confirm the association of radiation-induced damage to pelvic bone marrow with a drop in hematocrit. A threshold of V20 Gy < 30%, D_{mean} < 23 Gy, or $\bar{\bar{D}}$ < 27 Gy to OCUB may significantly reduce the risk for this endpoint.

Introduction

Anemia is commonly present in patients with cancer, with etiologies related to the cancer itself (anemia of chronic disease, marrow infiltration, hemolysis) as well as treatments—namely chemotherapy and radiation therapy (RT).[1] The effects of cytotoxic chemotherapy have been well studied, with 1 large retrospective cohort study finding an 89.5% rate of anemia of any grade in patients receiving chemotherapy alone for a variety of solid tumors.[2] The effect of radiation is thought to be less dramatic, but detailed information on the dose/volume effects of RT are not well defined. The mechanism of

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hematologic toxicity is due to radiation-induced damage of hematopoietic stem cells in the bone marrow, which is considered a radiosensitive organ.[3,4] Most published studies with data concerning RT-associated anemia are in patients with gynecologic cancers receiving pelvic RT; however, they are usually treated with chemotherapy also.[5,6] The availability of data in this population is expected to show some correlation with dose, as the pelvis contains approximately 40% of the total body bone marrow reserve, increasing the likelihood of significant bone marrow suppression.[7] Given the profound hematologic toxicity of chemotherapy itself, the effect of radiation alone in these patients receiving concurrent chemotherapy is unclear. In our study, we have attempted to clarify the effects of radiation alone on red blood cells (RBCs) as measured by hematocrit in a population of patients with prostate cancer.

Methods and Materials

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study analyzed 221 patients who received RT for prostate cancer between 2014 and 2016 at a single institution. Patients received either 78 Gy to the prostate primary or 70 Gy post-prostatectomy, with many patients receiving 54 Gy to the pelvic lymph nodes. All patients had complete blood counts (CBCs) collected at baseline (pre-RT) and 3 months post-RT, which were analyzed in conjunction with dose-volume histograms (DVHs) corresponding to 8 different volumes in the pelvis. These 8 volumes were contoured by the radiation oncologist during the treatment planning process and included the bone volume of the whole pelvis (BVWP), the bilateral os coxae superior to the acetabulum (OCUB), the total bilateral os coxae (OCTB), the sacrum, L4/L5 spinal levels, the superior aspect of the bilateral femurs, the soft tissue volume with bone, and vascular volume. The net differences of patients' CBC values 3 months post-RT versus baseline were calculated, and the level of the 15th percentiles defined the thresholds of response in each case. Illustrations of the bony structures that were used to correlate the dose delivered to them with significant drops in the CBC post-RT are shown in Fig. 1.

The relative seriality normal tissue complication probability model

The dose-response relation that was used in this study for uniform organ irradiation is described by the Poisson model based on the following mathematical expression[8,9]:

$$P(D) = exp\left(e^{e\gamma-\left(D_{2\ Gy}/D_{50}\right)(e\gamma-\ln\ln 2)}\right) \quad (1)$$

where $P(D)$ is the probability of response for a voxel, which is irradiated with a dose D. $D_{2\ Gy}$ is the 2 Gy equivalent dose and it is calculated by the following equation[8]:

$$D_{2\ Gy} = D \cdot \left(\frac{1+\frac{d}{\alpha/\beta}}{1+\frac{2}{\alpha/\beta}}\right) \quad (2)$$

where D is the total voxel dose, d is the corresponding dose per fraction, and α/β is a parameter that expresses the fractionation characteristics of that organ.

The probability of normal tissue injury (complications), P_I, is expressed by the relative seriality model[10-13]:

$$P_I = \left[1-\prod_{i=1}^{M}\left[1-P(D_i)^s\right]^{\Delta v_i}\right]^{1/s} \quad (3)$$

where M is the total number of voxels or subvolumes of the organ at risk. Δv_i is the fractional subvolume of the organ being irradiated. To express the radiobiological effectiveness of a given dose distribution in dosimetric terms, the concept of biologically effective uniform dose, $\bar{\bar{D}}$, is used.[12]

$$P(D) \equiv P\left(\bar{\bar{D}}\right) \Rightarrow \bar{\bar{D}} = \frac{e\gamma - \ln(-\ln(P(D)))}{e\gamma - \ln(\ln 2)} \quad (4)$$

The dose-response parameters of those models are the $D50$, which is the dose for having 50% response, and γ, which is the maximum normalized dose-response gradient. In the relative seriality model, the relative seriality parameter, s, characterizes the volume effect of the tissue. The value of α/β was assumed to be 3 Gy, which is typical for normal tissues.

Statistical methods

The values of the parameters of the relative seriality model and their 95% CIs were determined using the maximum likelihood method.[14-16] The CIs of the model parameters were determined using the profile likelihood method. The ability of the normal tissue complication probability (NTCP) models to distinguish patients with and without the examined symptoms was evaluated using the area under the curve (AUC) measure, which is used as a summary of the receiver operating characteristic curve.[16,17] Additionally, the odds ratio (OR) method was applied to identify NTCP thresholds beyond which the risk of toxicity increases significantly.[15,16] Those thresholds were identified in 3 steps. First, we identified the thresholds for which the OR values were larger than 1 and sorted them by OR value (largest to smallest); second, we identified the thresholds for which the low limit of the 95% CI was larger than 1; and third, we identified the threshold with the smallest 95% CI.

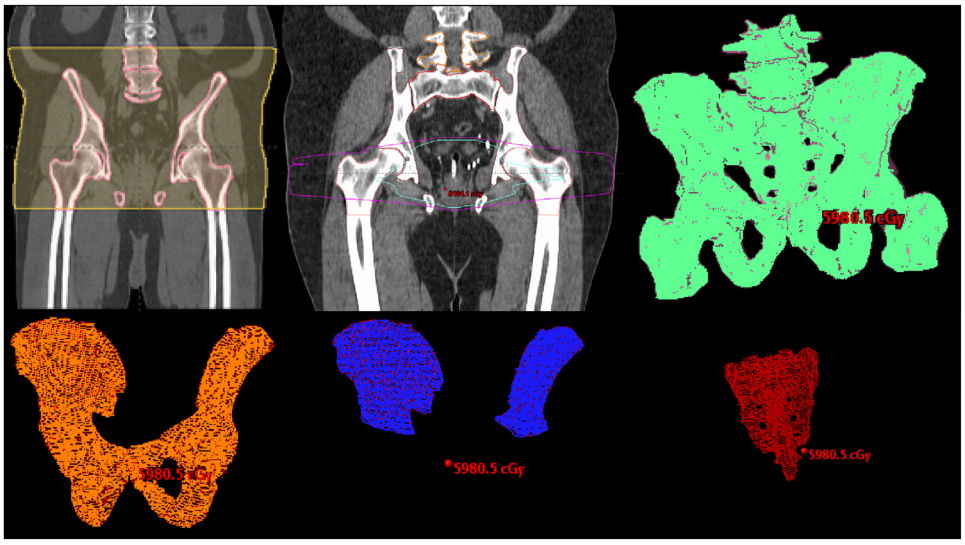

Figure 1 Illustration of the bony structures, the dose to which showed correlation with significant drop in hematocrit post-RT. In the upper left and middle images, the pelvis bones are outlined. The shaded area is the "whole volume" whereas the pink and blue isodose lines correspond to 10 and 20 Gy, respectively. In the upper right image, the bone volume of the whole pelvis is shown. In the lower images, the 2 os coxae, the 2 upper os coxae, and the sacrum are also shown.

Results

The clinical endpoint for this study was a significant net difference of patients' blood count test levels 3 months post-RT versus baseline. The 15th percentiles defined the thresholds of response in each case. Figure 2 shows the variation of AUC against a range of dose volume metrics (VD) for all the combinations of pelvic bone structures and CBC metrics. The volumes that correlated with significant decreases in hematocrit upon irradiation were OCUB, OCTB, and the BVWP. For hematocrit, the 15th percentile threshold was a 5.3% drop from baseline, which indicates 34 patients as responders. Based on the literature, the normal range of hematocrit is 40.7% to 50.3% for males.[18] Generally, a hematocrit level of less than 41% is considered anemic. In our patient cohort, 70 (32%) patients had a hematocrit value of <41% at baseline and 135 (62%) at 3 months post-RT. The patients who were considered responders in this study had an average hematocrit value of 36.5%.

The structure showing the highest correlation was OCUB with a maximum AUC of 0.74. For V20 Gy < 30% the OR was 9.8 with 95% CI of 2.9 to 32.9. For D_{mean} to OCUB, an AUC of 0.73 was observed for a dose threshold of 23 Gy, and the OR was 2.7 (95% CI, 1.3-5.6). For OCTB, AUC was 0.69 with a V20 Gy < 50% showing an OR of 9.3 (95% CI, 2.7-31.8). For BVWP, AUC was 0.71 with a V20 Gy < 40% associated with an OR of 7.5 (95% CI, 2.2-25.4). Further, for this structure, D_{mean} < 24 Gy had an OR of 2.6 (95% CI, 1.1-6.1) showing an AUC of 0.72. Table 1 shows analytically the results of the dose correlations to the different pelvic volumes. Figure 3 demonstrates the DVHs of the OCUB indicating the patients with and without significant hematocrit drop at 3-months post-RT. Although a significant overlap between the 2 groups of patients is observed, it is clear

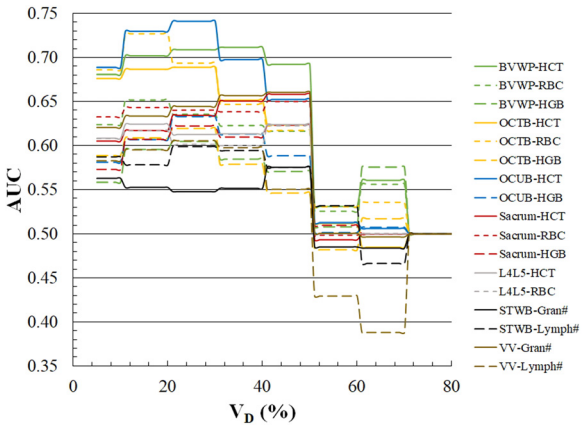

Figure 2 Area under the curves of dose-volume metrics (VD) to different pelvic structures and different blood tests. Only the most pronounced correlations are shown in the plot. The x-axis refers to the dose (D) of the dose volume metric (VD) and has units of Gy. *Abbreviations:* BFU = superior aspect of the bilateral femurs; BVWP = bone volume of the whole pelvis; Gran# = granulocytes (counts); HCT = hematocrit; HGB = hemoglobin; Lymph# = lymphocytes (counts); OCTB = total bilateral os coxae; OCUB = bilateral os coxae superior to the acetabulum; RBC = red blood cell; STWB = soft tissue volume with bone; VV = vascular volume.

Table 1 Summary of the results from the fit of the dose to the different pelvic volumes

Pelvic volume	Dose metric	AUC	Volume threshold (%)	Odds ratio	95% CI	Practical meaning
BVWP	V20 Gy	0.71	40	7.5	2.2-25.4	V20 Gy < 40% has 7.5 times less chance to have a significant HCT value drop 3 months post-RT.
OCTB	V20 Gy	0.69	50	9.3	2.7-31.8	V20 Gy < 50% has 9.3 times less chance to have a significant HCT value drop 3 months post-RT.
OCUB	V20 Gy	0.74	30	9.8	2.9-32.9	V20 Gy < 30% has 9.8 times less chance to have a significant HCT value drop 3 months post-RT.
BVWP	D_{mean}	0.72	24	2.6	1.1-6.1	Mean dose to BVWP < 24 Gy has 2.6 times less chance to have a significant HCT value drop 3 months post-RT.
OCUB	D_{mean}	0.73	23	2.7	1.3-5.6	Mean dose to OCUB < 23 Gy has 2.7 times less chance to have a significant HCT value drop 3 months post-RT.

Abbreviations: AUC = area under the curve; BVWP = bone volume whole pelvis; HCT = hematocrit; OCTB = os coxae total bilateral; OCUB = os coxae upper (above acetabulum) bilateral; ROC = receiver operating characteristic; RT = radiation therapy.
The area under the ROC curve and odds ratio methods were used to evaluate the correlations.

that the group with the signifcant drop dominates the domain of the higher doses (solid lines).

Table 2 provides a summary of the best estimates of the parameter values for the relative seriality model together with their 95% CIs for the structures with the highest correlations of dose and significant hematocrit drop. Regarding OCUB, the values for the $D50$, γ, and s parameters of the relative seriality model were 26.9 Gy (25.9-27.9), 1.3 (1.2-2.2), and 0.12 (0.10-0.83), respectively. The AUC of $\bar{\bar{D}}$ was 0.73, and patients with $\bar{\bar{D}}$ to OCUB $\geq$ 27 Gy had 8.2 times higher rate of significant hematocrit drop versus < 27 Gy. Volumes BVWP and OCTB also showed significant correlations for the same endpoint (AUC values of 0.72 and 0.69, respectively). In those cases, similar $\bar{\bar{D}}$ thresholds were found (27 and 28 Gy, respectively) but with lower ORs (2.8 and 2.9, respectively). A summary of the results from the fit of the dose to the different structures with the different blood tests is shown in Table 3. Figure 4 illustrates the dose-response curves for the OCUB, OCTB, and BVWP structures for significant hematocrit drop at 3-months post-RT as they were determined using the relative seriality model.

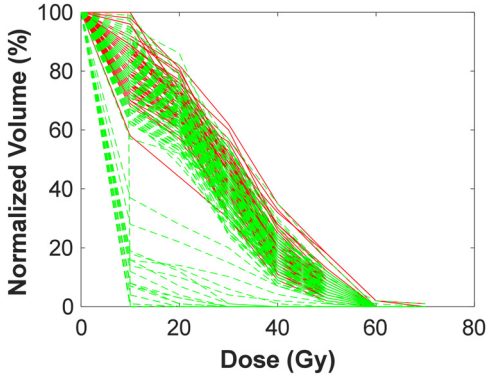

Figure 3 The dose-volume histograms of the os coxae upper (above acetabulum) bilateral are shown. The red lines indicate the patients who experienced a drop in hematocrit at 3-months posttreatment above the specified threshold, whereas the green dashed lines indicate the patients who experienced a smaller drop in hematocrit.

Discussion

Mature RBCs are considered radioresistant. In blood banking, doses of up to 200 Gy are delivered with minimal effect on RBC viability beyond the decline seen with cell aging.[19] The pluripotent hematopoietic stem cells, including the common myeloid (precursor to erythrocytes) and lymphoid progenitors, are considered radiosensitive to modest doses. For whole body exposure, a single dose of as little as 4 Gy results in 50% mortality (LD_{50}) because of loss of hematopoietic cells, whereas doses greater than 8 Gy result in total loss of bone marrow progenitor cells.[20] For bone marrow transplant patients with fractionated whole-body radiation, doses of 12 to 15 Gy combined with chemotherapy are most typically used to ablate the marrow components. For radiation alone, doses of 18 to 20 Gy are more effective, but with limitations due to toxicity.[21] Previous studies have associated doses of around 20 Gy to the pelvic bones with increased incidence of hematologic toxicity, which could be explained by the large volume of active bone marrow falling within the radiation field.[6]

Most studies evaluating the effects of RT on blood parameters include patients who are also receiving chemotherapy. This is especially true currently, where combined modality treatment is the standard for the cancers studied. In addition, most studies focus on white blood cells (WBCs) and RBC results are rarely

Table 2 Summary of the best estimates of the parameter values for the relative seriality model together with their 95% CIs

NTCP model Parameters	Relative seriality model		
	D50 (Gy)	γ	s
OCUB	26.9 (25.9-27.9)	1.3 (1.2-2.2)	0.12 (0.10-0.83)
OCTB	36.9 (35.5-38.3)	1.3 (1.2-2.2)	0.11 (0.10-0.79)
BVWP	32.9 (31.7-34.2)	1.4 (1.3-2.9)	0.11 (0.09-0.77)

Abbreviations: BVWP = bone volume whole pelvis; NTCP = normal tissue complication probability; OCTB = os coxae total bilateral; OCUB = os coxae upper (above acetabulum) bilateral.

Table 3 Summary of the results from the fit of the dose to the different structures with the endpoint of significant HCT value drop from baseline at 3-months post-RT

Pelvic volume	AUC	$\bar{D}$ threshold	Odds ratio	95% CI
OCUB	0.73	27	8.2	1.5-43.5
OCTB	0.69	28	2.9	1.2-5.9
BVWP	0.72	27	2.8	1.2-6.4

Abbreviations: AUC = area under the curve; BVWP = bone volume whole pelvis; HCT = hematocrit; OCTB = os coxae total bilateral; OCUB = os coxae upper (above acetabulum) bilateral; ROC = receiver operating characteristic; RT = radiation therapy.
The area under the ROC curve and odds ratio methods were used to evaluate the correlations.

reported. A study of patients with gynecologic cancers by Brixey et al[22] evaluated the differences between classic whole pelvis radiation versus intensity modulated RT to the whole pelvis, ostensibly sparing more pelvic bone marrow. Forty-four percent of patients received radiation without chemotherapy (most likely in the earlier whole pelvis patients). Overall, grade 2 hemoglobin toxicity (<10.0 g/dL) occurred in 6.8% with radiation alone and in 19.4% with chemoradiation. In both radiation alone and the combination of radiation and chemotherapy, the utilization of intensity modulated RT made no difference for any parameter (WBC, absolute neutrophile count, hemoglobin) compared with conventional whole pelvis.

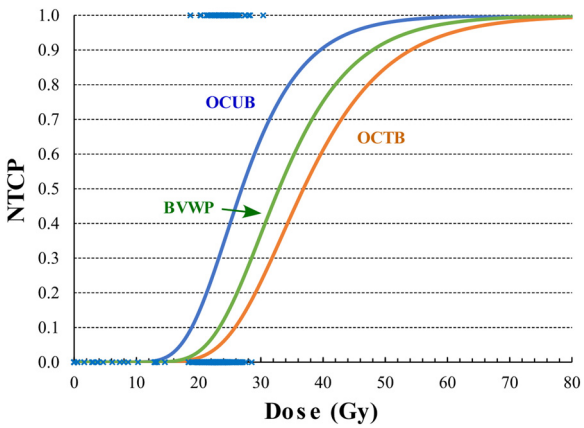

Figure 4 The dose response curves for the OCUB, OCTB, and BVWP structures for the examined endpoint based on the data fit using the relative seriality model are shown. Toxicity was defined as a significant hematocrit value drop from baseline at 3-months post-RT. *Abbreviations:* BVWP = bone volume whole pelvis; NTCP = normal tissue complication probability; OCTB = os coxae total bilateral; OCUB = os coxae upper (above acetabulum) bilateral; RT = radiation therapy.

With the risk of a significant drop in hemoglobin with radiation alone being low, there has been no interest in doing a prospective study. With chemoradiation, there have been numerous retrospective studies and dosimetric evaluations suggesting that for the other hematologic parameters, namely WBC, the dose/volume does make a difference. For example, an early study with chemoradiation in cervical cancer showed that when V20 Gy of the pelvis exceeded 80%, the risk of grade 2 or higher hematologic toxicity increased by 4.5 times.[6]

In patients with prostate cancer treated with radiation, effects on hemoglobin levels are rarely reported and in small patient numbers. In one example, in a group of 19 patients with prostate cancer, 5% were already anemic (hemoglobin < 12 g/dL) at presentation (baseline), increasing to 32% by the end of treatment; however, in this study, no dosimetry information was given.[23] We evaluated the actual RBC count with concomitant hemoglobin and hematocrit levels in our population of patients receiving RT without the confounding effects of chemotherapy. The decline with radiation was <10%, with hematocrit being the most sensitive measure. Based on AUC and OR, the most sensitive dose level was for 20 Gy to various parts of the pelvis. This would support data from prior studies that 20 Gy is a valid threshold for the ablation of hematopoietic stem cells. Unique aspects of our study include our large number of patients with prostate cancer, the absence of the confounding effects of concurrent chemotherapy, and the measured effects on the RBC count as measured by hematocrit.

Conclusion

These findings confirm the association of radiation-induced damage to pelvic bone marrow with a significant drop in hematocrit at 3 months post-RT. Specifically, the doses to OCUB, OCTB, and BVWP were found to correlate with a significant drop of hematocrit. A threshold of V20 Gy < 30% or D_{mean} < 23 Gy to OCUB may reduce almost 10-fold the risk for this endpoint. The dose-response curve of os coxae upper bilateral for a significant hematocrit drop could be determined by fitting the clinical data with the relative seriality NTCP model. A threshold of $\bar{\bar{D}}$ < 27 Gy was found to significantly reduce the risk for this endpoint.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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