Predicting and evaluating side effects of radiotherapy in cervical cancer

Corbeau, A.

Chapter 2

Correlations between bone marrow radiation dose and hematologic toxicity in locally advanced cervical cancer patients receiving chemoradiation with cisplatin: a systematic review

Anouk Corbeau, Sander C. Kuipers, Stephanie M. de Boer, Nanda Horeweg, Mischa S. Hoogeman, Jeremy Godart, Remi A. Nout

Radiotherapy and Oncology, 2021, 164:128-137.

ABSTRACT

Patients with locally advanced cervical cancer (LACC) treated with chemoradiation often experience hematologic toxicity (HT), as chemoradiation can induce bone marrow (BM) suppression. Studies on the relationship between BM dosimetric parameters and clinically significant HT might provide relevant indices for developing BM-sparing (BMS) radiotherapy techniques. This systematic review studied the relationship between bone marrow dose and HT in LACC-patients treated with primary cisplatin-based chemoradiation. A systematic search was conducted in Embase, Medline, and Web of Science. Eligibility criteria were treatment of LACC-patients with cisplatin-based chemoradiation and report of HT or complete blood cell count (CBC). The search identified 1346 papers, which were screened on title and abstract before two reviewers independently evaluated the full text. 17 articles were included and scored according to a selection of the TRIPOD-criteria. The mean TRIPOD-score was 12.1 out of 29. Fourteen studies defining BM as the whole pelvic bone contour (PB) detected significant associations with V_{10Gy} (3/14), V_{20Gy} (6/14), and V_{40Gy} (4/11). Recommended cut-off values were V_{10Gy}>95-75%, V_{20Gy}>80-65%, and V_{40Gy}>37-28%. The studies using lower density marrow spaces (PBM) or active bone marrow (ABM) as a proxy for BM only found limited associations with HT. Our study was the first literature review providing an overview of articles evaluating the correlation between BM and HT for LACC-patients undergoing cisplatin-based chemoradiation. There is a scarcity of studies independently validating developed prediction models between BM dose and HT. Future studies may use PB contouring to develop normal tissue complication probability models.

INTRODUCTION

Bone marrow (BM) is made up of the active red marrow, comprising mostly hematopoietic tissue, and inactive yellow bone marrow, containing mostly fatty tissue [1]. Most of the red marrow can be found within the axial skeleton and upper half of the limbs [2]. Within the BM, hematopoietic stem cells are important for hematopoiesis, which is the process of generation of all the cell types present in the blood [3]. Whereas circulating blood cells have no self-renewal ability, stem cells can undergo a self-renewing proliferation [4]. However, if the stem cells are injured, the hematopoietic system suffers long-term or permanent damage and BM-failure may occur, resulting in immunosuppression. Chemoradiation for cancer patients can damage stem cells and therefore induce hematologic toxicities (HT), including lymphopenia, neutropenia, and anemia [5-9]. Such decrease in bone marrow and blood cells may lead to infection, bleeding, or transfusions, and can be graded following the toxicity criteria of the Common Terminology Criteria for Adverse Events (CTCAE) or the Radiation Therapy Oncology Group (RTOG) [10, 11]. McGuire et al. reported a dose threshold for BM-suppression of 4 Gy, with no benefit from fractionation, for pelvic cancer patients undergoing chemoradiation [12]. During external beam radiotherapy (EBRT) both BM and circulating blood cells are exposed to possibly toxic radiation doses leading to an increased risk of lymphopenia [13]. An increase in BM-toxicity was demonstrated when adding chemotherapy to the treatment in comparison to radiotherapy (RT) alone [6, 14]. The extrapelvic compensatory response was decreased with intensive chemotherapy regimens, which may lead to increased HT. The BM-tolerance to chemotherapy differs between chemotherapy regimens [15-17]. Patients receiving pelvic radiotherapy with concurrent chemotherapy have a higher BM-tolerance when comparing cisplatin-based to mitomycin-C (MMC) based chemotherapy but a lower BM-tolerance when comparing cisplatin to 5-fluorouracil (5-FU) [17].

The standard chemoradiation treatment for patients with locally advanced cervical cancer (LACC) combines EBRT with concurrent platinum-based chemotherapy followed by brachytherapy [18]. Huang et al. showed HT grade 2 or higher in 69.5% of cervical cancer patients undergoing chemoradiation [19]. High-grade HT might lead to postponing or stopping chemotherapy and hospitalizations or blood transfusions for cancer patients [5, 20]. It was demonstrated that LACC-patients can have HT during chemoradiation until at least three months post-treatment [21]. The slow recovery of the immune suppression underlines the importance to decrease the incidence of HT in this patient group [9, 21].

Currently, development of effective pelvic bone marrow sparing (BMS) RT-techniques is limited. The introduction of proton therapy raises interest in the correlation between RT-dose and HT. The beneficial physical characteristics of proton therapy and its ability to achieve satisfactory target dose distributions using only a few beams enable BMS [22, 23]. Gort et al. and Dinges et al. showed significantly better BMS for proton therapy when compared to photon therapy [22, 24]. However, knowledge on the spatial location of bone marrow sparing and the required degree of sparing is essential for the development of BMS-radiotherapy techniques [25]. Assessing the relationship between BM dose-volume histogram (DVH) parameters and clinically relevant HT can provide indices for BMS, such as the V_{dose} (e.g. V_{20Gy} and V_{30Gy}), defined as the percentage of organ volume receiving a dose greater than a threshold (20 and 30 Gy, respectively). The occurrence of HT might depend on multiple factors in addition to dosimetric parameters, such as chemotherapy regimen [17].

The aim of this systematic review is to provide an overview of the medical literature evaluating the relationship between the dose to (subsites of) pelvic bone marrow and HT in LACC-patients treated with primary cisplatin-based chemoradiation. Interpretation and discussion of the literature can give guidance on bone marrow contouring methods and the clinical utilization of detected relationships.

METHODS

Search strategy

We conducted a systematic search based on Embase, Medline, and Web of Science for the period from the earliest data to February 24th, 2021. The search term consisted of three parts focusing on pelvic cancer, radiotherapy, and BM. The search term can be found in Supplementary Material A. Firstly, two reviewers screened the studies on eligibility by title and abstract. The results were reviewed within the authors group. Then, a full-text evaluation was independently performed by two reviewers. Disagreements on the inclusion of articles were resolved by consensus-based discussion. The following inclusion criteria were used: 1) patients had cervical cancer, 2) received chemoradiation as primary or postoperative treatment, 3) the first choice of chemotherapeutic agent was cisplatin, another platinum-based chemotherapy was allowed in case of contraindications for cisplatin, 4) the correlation between hematologic toxicity or complete blood count (CBC) and dose-volume parameters of the BM was analyzed, 5) the study was published in English.

Data extraction and analysis

Clinical and methodological data were extracted using prespecified data collection forms covering the reference, study design, number of patients, number of patients treated postoperatively, the chemotherapeutic agent used, radiation technique, delineation method for BM, whether BMS was applied, method for HT-scoring (following the toxicity criteria of the CTCAE or the RTOG), time of follow-up and measuring HT, definition of endpoints (grade of HT or blood counts nadirs), and the (dosimetric) predictors for the risk of the endpoints. For each dosimetric parameter that was identified, both the number of studies investigating that particular dosimetric parameter and the percentage of those studies showing a significant correlation of that parameter with HT were determined. Corresponding dose cut-off values, which are values of specific dose-volume parameters for predicting HT, were described and visualized in graphs. The data points in the graphs were connected with a mean line.

Quality Assessment

The included papers were evaluated using a checklist depicting whether key items from the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) consensus statement on model development and validation were addressed [26]. The selected key items were based on the selection as performed by Brodin et al. and highlight the variation in statistical methodology in the various models [27]. The number of items to be checked are listed in Supplementary Material B and summed to a total score of 29. Additionally, the studies were classified according to the type of prediction model depending on whether the investigators developed or validated a model, using the classification from Collins et al. [26]:

- Type Ia defines the development of a model where the predictive performance is directly evaluated using the same data.
- Type Ib defines the development of a model where performance is evaluated on the development dataset using resampling techniques.
- Type IIa defines a model where a dataset is randomly split into two groups, one used to develop a model and the other to evaluate its predictive performance.
- Type IIb applies a more robust technique by non-random splitting of data (by location, time, etc.).
- Type III defines a model developed and evaluated on separate datasets by the model developers.
- Type IV defines an external validation of an existing prediction model.

RESULTS

Eligible studies

Seventeen studies were included in this systematic review. A study flowchart diagram is visualized in Figure 1. During the full-text evaluation, the selection of three studies showed discrepancy from the two independent reviewers, which was discussed and resolved during a consensus meeting. Table 1 provides an overview of the characteristics and outcomes of the included studies. The included articles had a mean TRIPOD-adherence score of 12.1 (sd 3.3) out of 29. A detailed overview of the TRIPOD-scoring per item and study is provided in Supplementary Table C.1. The paper by Rose et al. had the highest TRIPOD-adherence score (22 out of 29) and was the only type IV prediction model included. The majority of the included articles used all data from a single data set to develop a prediction model without validation and were therefore type IA prediction models. In total, three delineation methods for BM were identified. Seven articles only delineated the whole pelvic bone (PB), four articles used the lower density marrow spaces (PBM) as a proxy for BM and compared this with PB, and six articles contoured both the active bone marrow (ABM) and the PB for comparison. The ABM was visualized using fluorodeoxyglucose positron emission tomography (FDG-PET) or technetium-99m (99mTc) sulfur colloid single-photon emission tomography (SPET). Six articles not only recorded dosimetric parameters for the whole pelvic bone but also divided the pelvic bone into subregions and analyzed dosimetric parameters per subsite [8, 19, 28-31]. In this systematic review, the correlation between BM and HT will be described per delineation method.

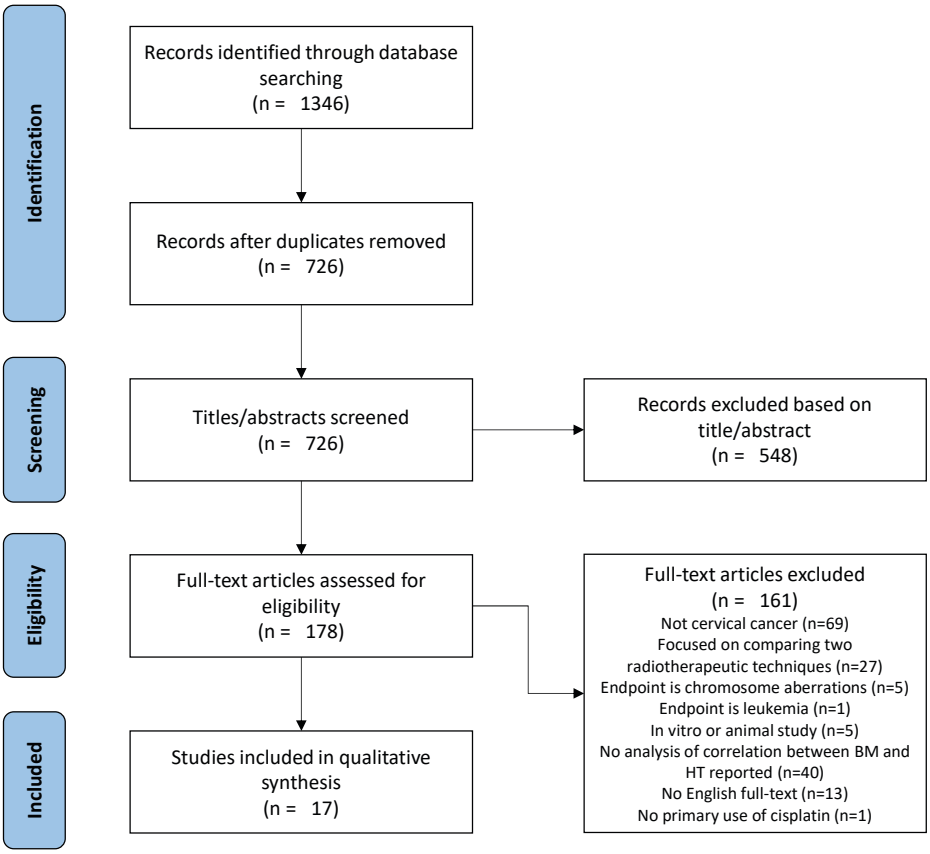

Figure 1: *PRISMA flowchart [26]. BM = bone marrow, HT = hematologic toxicity.*

Whole pelvic bone contour (PB)

Delineation method specified

In total, sixteen out of the seventeen included articles reported correlations between BM, approximated by the CT-based whole bone contour (PB), and the development of HT. The majority of these articles, including the studies by Rose et al., Zhu et al., Lewis et al., Kumar et al., Chang et al., and Albuquerque et al., based their contouring method on the strategy as proposed by Mell et al. [8]. Mell et al. delineated the external contour of all bones within the pelvis, extending from L5 to the inferior border of the ischial tuberosities, as a proxy for the BM in order to ensure reproducibility. Other methods applied specified CT-window settings or anatomical landmarks of the vertebrae, ischium, and/or femora.

Table 1: *Characteristics of included studies. HT = hematologic toxicity. 3DCRT = 3D conformal radiation therapy, IMRT = intensity modulated radiation therapy, IMPT = intensity modulated proton therapy, CT = computed tomography, FDG-PET = fluorodeoxyglucose positron emission tomography, SPET = single-photon emission tomography, SUV = standardized uptake value, TB = total body, WB = whole bone, RTOG = Radiation Therapy Oncology Group, CTCAE = Common Terminology Criteria for Adverse Events. CRT = chemoradiotherapy, RT = radiation therapy, BM = bone marrow, PB = whole pelvic bone, LSS = lumbosacral spine, LOW = lower pelvic bones, PBM = pelvic bone marrow (lower density marrow spaces), LSSM = lumbosacral spine marrow (lower density marrow spaces), ABM = active bone marrow, IBM = inactive bone marrow (PB minus ABM), CBC = complete blood cell counts.* [a] *= WBC,* [b] *= ANC,* [c] *= HB,* [d] *= PLT (platelets),* [e] *= HT2+,* [f] *= HT3+,* [g] *= HT1+*

TRIPOD-score	Author	Year	Study design	No of patients	No of patients treated postoperatively	Chemotherapeutic regimen	RT-technique	BM definition	BM optimization	HT-scoring scale	Timing of measuring endpoints	Endpoint	Dosimetric predictors
22	Rose, B.S. et al	2011	Validate NTCP on retrospective data	81	0 (0%)	Cisplatin 40 mg/m^2 (81, 100%)	IMRT	CT-based PB contour [Mell]	No	RTOG	Weekly during CRT	WBC[a] ANC[b] HB[c] HT3+[f]	PB-V_{10Gy} [a,b,f], V_{20Gy} [a,b,c,f], V_{30Gy} [a,b], D_{mean} [a,b] PB-V_{10Gy}>95%[f] PB-V_{20Gy}>76%[f]
17	Huang J. et al	2020	Prospective RCT	164	0 (0%)	Cisplatin 40 mg/m^2 (164, 100%)	IMRT	CT-based PB contour and low-density marrow spaces (PBM)	Yes, using PB and LSS	RTOG	Weekly to end of CRT	HT2+[e]	PB-V_{40Gy} [e] PB-V_{40Gy}>28%[e] LSS-V_{10Gy}>87%[e] LSS-D_{mean} >39Gy[e] PBM-V_{40Gy} [e] LSSM-mean[e], V_{10Gy} [e], V_{20Gy} [e], V_{40Gy} [e]
15	Chang, Y. et al	2016	Retrospective case series, officially cohort	100	0 (0%)	Cisplatin 25 mg/m^2 (100, 100%)	3DCRT, IMRT, RapidARC	CT-based PB contour [Mell]	No	Unknown	Weekly during treatment	WBC[a] ANC[b] HB[c] PLT[d] HT2+[e] HT3+[f]	PB-V_{20Gy} [a,b,f], V_{40Gy} [e,f]
13	Klopp, A.H.	2013	Retrospective case series	43	43 (100%)	Cisplatin 40 mg/m^2 (43, 100%)	IMRT	CT-based PB contour	No	CTCAEv3	<90 days from start RT	HT2+[e]	PB-V_{40Gy}>37%[e] PB-D_{median}>34.1Gy[e]

TRIPOD-score	Author	Year	Study design	No of patients	No of patients treated postoperatively	Chemotherapeutic regimen	RT-technique	BM definition	BM optimization	HT-scoring scale	Timing of measuring endpoints	Endpoint	Dosimetric predictors
12	Kumar, T. et al	2019	Retrospective case series	114	0 (0%)	Cisplatin 40 mg/m^2 (102, 89.5%) or carboplatin (12, 10.5%)	3DCRT, IMRT	CT-based PB contour [Mell] and low-density marrow spaces (PBM)	No	CTCAEv4	Weekly during CRT prior to brachytherapy implantation	HT4+[g]	LP-PB-V_{5Gy}>95%[g] LP-PB-V_{20Gy}>45%[g] Iliac crests-PB-D_{mean}>31 Gy[g] PB-V_{20Gy}>65%[g]
12	Rose, B.S. et al.	2012	Retrospective case series	26	5 (19%)	Cisplatin 40 mg/m^2 (26, 100%)	IMRT	CT-based PB contour FDG-PET (> SUVmean WB) based ABM inactive BM (IBM) = PB - ABM	No	RTOG	Weekly during CRT	WBC[a] ANC[b] HB[c] PLT[d] HT3+[f]	ABM-D_{mean}[a,b,c,d], V_{10Gy}[a], V_{20Gy}[a], V_{30Gy}[a] PB-V_{10Gy}[a] ABM-D_{mean} <26.8Gy[f] No correlation with IBM
12	Wang, S.B. et al	2019	Prospective clinical trial	39	0 (0%)	Cisplatin 30-40 mg/m^2 (39, 100%)	VMAT	CT-based PB contour Tc-99m SPET (> SUVmean TB) based ABM	No	CTCAEv3	Weekly to two weeks after CRT	HT3+[f]	ABM-volume > 387.5 cm3[f] ABM-V_{30Gy}>46.5%[f] ABM-V_{40Gy}>23.5%[f]
12	Zhu, H. et al	2015	Retrospective multicenter cohort	102	Unknown	Cisplatin 40 mg/m^2 (102, 100%)	IMRT, 3DCRT	CT-based PB contour [Mell]	According to the discretion of the treating oncologist	/	Weekly during CRT	WBC[a] ANC[b] HB[c] PLT[d]	PB-D_{mean}[a,b], V_{20Gy}[a,b], V_{30Gy}[a,b], V_{40Gy}[a,b] LSS-V_{10Gy}[a,b], V_{40Gy}[a,b] LOW-V_{20Gy}[a,b], V_{30Gy}[a,b]

TRIPOD-score	Author	Year	Study design	No of patients	No of patients treated postoperatively	Chemotherapeutic regimen	RT-technique	BM definition	BM optimization	HT-scoring scale	Timing of measuring endpoints	Endpoint	Dosimetric predictors
11	Lewis, S. et al	2018	Retrospective case series	75	75 (100%)	Cisplatin 40 mg/m^2 (75, 98.5%) and carboplatin (1, 1.5%)	IMRT, 3DCRT	CT-based PB contour [Mell] and low-density marrow spaces (PBM)	No	CTCAEv3	Weekly during CRT	HT2+[e]	Ilium PB-V_{20Gy}>90%[e]
11	Albuquerque, K. et al	2011	Retrospective case series	40	0 (0%)	Cisplatin 40 mg/m^2 (40, 100%)	3DCRT	CT-based PB contour [Mell]	No	CTCAEv3	During RT	HT2+[e]	PB-V_{20Gy}>80%[e]
11	Khullar K. et al	2017	Retrospective case series	21	0 (0%)	Cisplatin (21, 100%)	3DCRT, IMRT	FDG-PET (> SUVmean TB) based ABM	No	CTCAEv4	Weekly to 6 weeks after end of CRT	HT3+[f]	ABM-volume <1201 ml[f] ABM-V_{40Gy}[f]
10	Elicin, O. et al.	2014	Retrospective case series	17	0 (0%)	Cisplatin 40 mg/m^2 (17, 100%)	IMRT	CT-based PB contour FDG-PET (> SUVmean WB) based ABM	No	RTOG	FDG-PET: Pre- and 3 months post-treatment CBC: 1 week before, weekly during, 3 months after, and at last follow-up after treatment	WBC[a] ANC[b] HB[c] PLT[d]	3m post-treatment: ABM-SUV[a], PB-D_{mean}[a], V_{10Gy}[a], V_{20Gy}[a], V_{30Gy}[a], V_{40Gy}[a], ABM-V_{40Gy}[a] Late follow-up: PB-D_{mean}[a], V_{10Gy}[a], V_{20Gy}[a], V_{30Gy}[a], V_{40Gy}[a], ABM-V_{20Gy}[a], V_{30Gy}[a], V_{40Gy}[a]
10	Mell, L.K. et al	2006	Retrospective case series	37	3 (8.1%)	Cisplatin 40 mg/m^2 (37, 100%)	IMRT	CT-based PB contour	No	RTOG	Weekly during CRT	WBC[a] ANC[b] HB[c] PLT[d] HT2+[e] HT1+[g]	PB-V_{10Gy}[a,c,e,g], V_{20Gy}[c,e,g] LSS-V_{10Gy}[a,b,e], V_{20Gy}[a,c,e] LP-V_{10Gy}[c,e,g], V_{20Gy}[e,g] PB-V_{10Gy}>90%[a,e], V_{20Gy}>75%[c,e] LSS-V_{10Gy}>90%[b] LP-V_{10Gy}>90%[c]

TRIPOD-score	Author	Year	Study design	No of patients	No of patients treated postoperatively	Chemotherapeutic regimen	RT-technique	BM definition	BM optimization	HT-scoring scale	Timing of measuring endpoints	Endpoint	Dosimetric predictors
10	Yan, K. et al	2018	Retrospective case series	38	0	Cisplatin 40 mg/m^2 (38, 100%)	3DCRT, IMRT	CT-based PB contour FDG-PET (> SUV_{mean} WB) based ABM	No	CTCAEv4	Weekly to end treatment	HT3+[f]	PB-V_{20Gy}>78.6%[f], V_{30Gy}>47.1%[f], V_{45Gy}>20.4%[f], D_{mean}>30.3Gy[f] ABM-V_{10Gy}>95.5%[f], V_{20Gy}>80.5%[f], V_{30Gy}>59.6%[f], V_{45Gy}>31.7%[f], D_{mean}>32.4Gy[f]
9	Mahantshetty, U. et al	2012	Retrospective case series	47	0	Cisplatin 40 mg/m^2 (47, 100%)	IMRT	CT-based PB contour and low-density marrow spaces (PBM)	No	RTOG	Weekly during CRT	WBC[a] ANC[b] HB[c] PLT[d] HT2+[e]	Baseline HB and PLT[c,d] PBM-V_{40Gy}>40%[e]
9	Gupta, N. et al	2019	Retrospective case series	43 (16 excluded for this review (neo-adjuvant chemotherapy)	4 out of 43 (8%)	Cisplatin 40 mg/m^2 (37, 97%)	IMRT	CT-based PB contour	No	CTCAEv4	Weekly during CRT and 6 weeks after treatment	WBC[a] ANC[b] HB[c] PLT[d] HT2+[e] HT3+[f]	PB-V_{10Gy}>75%[e]
9	Zhou, Y.M. et al	2018	Retrospective case series	31	0	Cisplatin 40 mg/m^2 (31, 100%)	IMRT, 3DCRT	CT-based PB contour FDG-PET (> SUV_{mean} TB) based ABM	No	CTCAEv4	Weekly and one week after treatment	WBC[a] ANC[b] HB[c] PLT[d] HT3+[f]	Volume spared of PB: 10 Gy <230cc[f] of ABM: V_{10Gy}<179cc[f] OR V_{20Gy}<186cc[f] OR V_{40Gy}<738cc[f]

Whole pelvic bone

Table 2 describes that three out of fourteen articles found a significant correlation between V_{10Gy} of the whole bone and grade 2 or higher HT [8, 32, 33]. Six out of fourteen articles demonstrated a significant relationship between V_{20Gy} and HT [8, 30, 32, 34-36]. Furthermore, four out of eleven articles showed that V_{40Gy} is a significant predictor for HT2+ or HT3+ [14, 19, 31, 34]. An overview of the cut-off values for dosimetric parameters as recommended by the included studies is provided in Figure 2. The recommended cut-off values for HT2+ and HT3+ for the whole pelvic bone were similar. V_{10Gy}<75-95% [8, 32, 33], V_{20Gy}<65-80% [30, 32, 35, 36], and V_{40Gy}<28-37% [14, 19] were recommended to reduce HT. Some other significant relationships were reported, including the V_{30Gy} and V_{45Gy} of the whole pelvic bone. Additionally, one article investigated the volume of the whole pelvic bone spared 10, 20, and 40 Gy and found the volume of whole pelvic bone spared 10 Gy <230 cc to be associated with HT2+ (not visualized in Figure 2) [37]. Lastly, the mean or median dose to the whole pelvic bone was found to be associated with HT by two out of eight articles [14, 36]. These studies recommended to keep the D_{mean} and D_{median} below respectively 30.3 Gy and 34.1 Gy (not visualized in Figure 2) [14, 36].

Table 2: *Relationship between various dosimetric parameters of the whole pelvic bone contour (PB) and hematologic toxicity (HT). For each dosimetric parameter that was identified, both the number of studies investigating that particular dosimetric parameter and the percentage of those studies showing a significant correlation of that parameter with HT. HT = hematologic toxicity.*

Dosimetric parameter	Number of studies showing significant correlation / number of studies employing dosimetric parameter	HT2+	HT3+	HT4+
V_{5Gy}	0/2 (0%)	0/1	0/1	0/1
V_{10Gy}	3/14 (21%)	2/8	1/7	0/1
V_{15Gy}	0/1 (0%)	-	-	0/1
V_{20Gy}	6/14 (43%)	3/8	2/7	1/1
V_{30Gy}	1/10 (10%)	0/7	1/4	0/1
V_{40Gy}	4/11 (36%)	4/7	1/5	0/1
V_{45Gy}	1/2 (50%)	0/1	1/1	-
D_{mean}/D_{median}	2/8 (25%)	1/4	1/3	0/1
Spared 10 Gy	1/1 (100%)	-	1/1	-
Spared 20 Gy	0/1 (0%)	-	0/1	-
Spared 40 Gy	0/1 (0%)	-	0/1	-

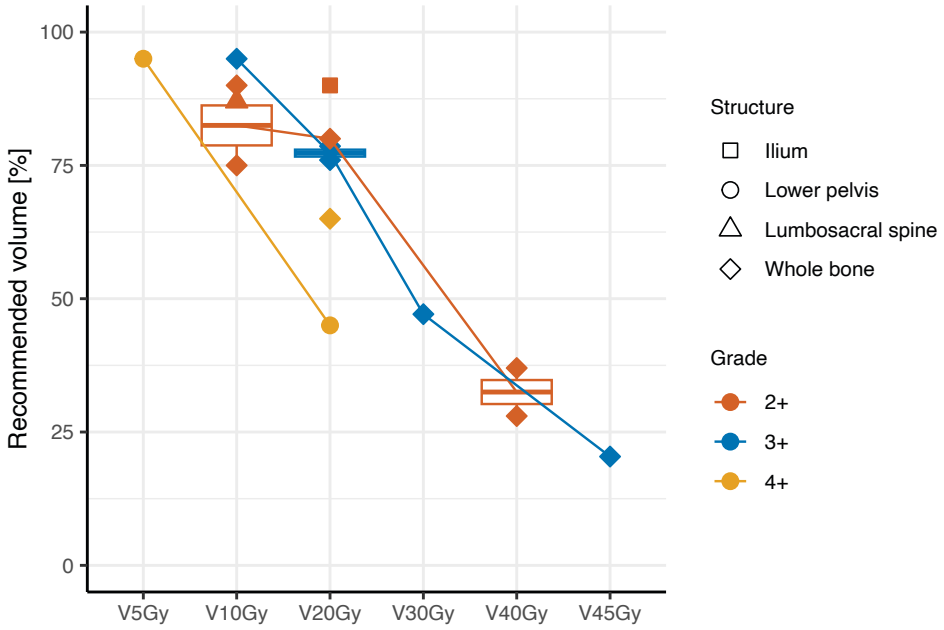

***Figure 2**: Dose cut-off values for the whole pelvic bone contour (PB) and correlation to hematologic toxicity (HT) as recommended by included studies.*

Subsites of the pelvic bone

Six articles analyzed the correlation between three subsites of the pelvic bone and HT but the studies detected different relationships, as can be concluded from Supplementary Table D.2 [8, 19, 29-31, 35]. An overview of the corresponding cut-off values can be found in Figure 2. The lumbosacral spine (LSS) includes lumbar vertebrae and the entire sacrum, the lower pelvis (LOW) consists of the pubes, ischia, acetabula, and femoral heads, and the ilium extends from the iliac crests to the superior border of the femoral heads. For LSS, the V_{10Gy} [19], D_{mean} [19], and V_{20Gy} [8] were each found significant by one article. D_{mean} was recommended to be <39 Gy (not visualized in Figure 2) and V_{10Gy}<87% [19]. Although significant LSS-sparing might be difficult due to its proximity to the target volume, efforts to constrict the dose of the LSS and whole pelvic bone simultaneously were expected to result in a more homogeneous dose distribution of the pelvic region [8, 19]. The V_{5Gy} [30], V_{10Gy} [8], and V_{20Gy} [8, 30] of LOW were reported to be predictive of HT. V_{5Gy}<95% and V_{20Gy}<45% would decrease HT4+ [30]. Only two dosimetric parameters of the ilium, the D_{mean} [30] and V_{20Gy} [29], were demonstrated to be correlated to HT and it was recommended that D_{mean}<31 Gy [30] (not visualized in Figure 2) and V_{20Gy}<90% [29].

One study additionally analyzed the hip bone (HIP), which was defined as the total area of LOW and ilium, but did not find any dosimetric parameters that were associated with HT (results not visualized in Supplementary Table D.2) [19].

Relationship with blood cell nadirs

Lastly, some articles demonstrated a significant relationship between the dose received by PB and nadirs of blood cells, including white blood cells (WBC), absolute neutrophil count (ANC), hemoglobin (HgB), and platelets (PLT) as visualized in Supplementary Table E.3. However, the reported dose cut-offs for HT vary widely. Several studies detected a correlation between V_{10Gy} [8, 21, 32, 38], V_{20Gy} [21, 28, 32, 34], V_{30Gy} [21, 28, 32], D_{mean} [21, 28, 32] and WBC nadirs. Elicin et al. noted that the V_{10Gy}, V_{20Gy}, V_{30Gy}, and V_{40Gy} even have an effect on the WBC-count three months after treatment and during late follow-up [21]. Similar dosimetric findings were reported for ANC nadirs, besides that a lower number of studies demonstrated V_{10Gy} to be a significant predictor. Only the dosimetric parameters V_{10Gy} [8] and V_{20Gy} [8, 32] were significantly correlated with HgB nadirs. None of the dosimetric parameters analyzed had any statistically significant association with PLT nadirs. Only three articles evaluated the dosimetric parameters of pelvic bone subsites and the consequences for nadirs of blood cells (results not visualized in this article) [8, 28, 31]. Dosimetric parameters of the LOW and LSS were found to be significantly related to nadirs in ANC, WBC, and HgB [8, 28]. For the ilium, V_{20Gy} was predictive for HgB [8]. None of the dose-volume parameters influenced the PLT-count.

Lower density marrow spaces (PBM)

Four articles included the marrow cavity (PBM) as a surrogate for BM in their analyses [19, 29-31]. Table 3 shows that only the V_{40Gy} is found to be associated with HT by two out of four articles [19, 31]. A V_{40Gy}<40% might decrease the risk of HT2+ (see Figure 3) [31]. Two other studies did not demonstrate any associations of the PBM with HT [29, 30]. All authors noted that other contouring methods might be more suitable for BM-definition.

Active bone marrow (ABM)

Delineation method specified

Six of the included studies examined the correlation between radiation dose to the active bone marrow (ABM) and the development of HT [21, 36-40]. 18F-FDG-PET-CT was used by five studies and the technetium-99m (Tc-99m) sulfur colloid SPET was used by one study to quantify standardized uptake values (SUVs). Two methods for identifying ABM were applied: defining ABM as >SUV_{mean} of the total body or as >SUV_{mean} of the whole bone.

Table 3: *Relationship between various dosimetric parameters of CT-based lower density marrow spaces (PBM) or active bone marrow (ABM) and hematologic toxicity (HT). For each dosimetric parameter that was identified, both the number of studies investigating that particular dosimetric parameter and the percentage of those studies showing a significant correlation of that parameter with HT. HT = hematologic toxicity, CT = computed tomography, SUV = standardized uptake value, TB = total body, FDG-PET = fluorodeoxyglucose positron emission tomography, SPET = single-photon emission tomography, WB = whole bone.*

Dosimetric parameter	**Number of studies showing significant correlation / number of studies employing dosimetric parameter**			
	CT-based PBM	**ABM (>SUV_{mean} TB FDG-PET)**	**ABM (>SUV_{mean} TB SPET)**	**ABM (>SUV_{mean} WB FDG-PET)**
V_{5Gy}	0/1 (0%)	-	-	-
V_{10Gy}	0/4 (0%)	0/2 (0%)	0/1 (0%)	1/1(100%)
V_{15Gy}	0/1 (0%)	-	-	-
V_{20Gy}	0/4 (0%)	0/2 (0%)	0/1 (0%)	1/1 (100%)
V_{30Gy}	0/3 (0%)	-	1/1 (100%)	1/1 (100%)
V_{40Gy}	2/4 (50%)	1/2 (50%)	1/1 (100%)	-
V_{45Gy}	-	-	-	1/1 (100%)
D_{mean}	0/2 (0%)	0/2 (0%)	0/1 (0%)	1/1(100%)
Spared 10 Gy	-	1/1 (100%)	-	-
Spared 20 Gy	-	1/1 (100%)	-	-
Spared 40 Gy	-	1/1 (100%)	-	-

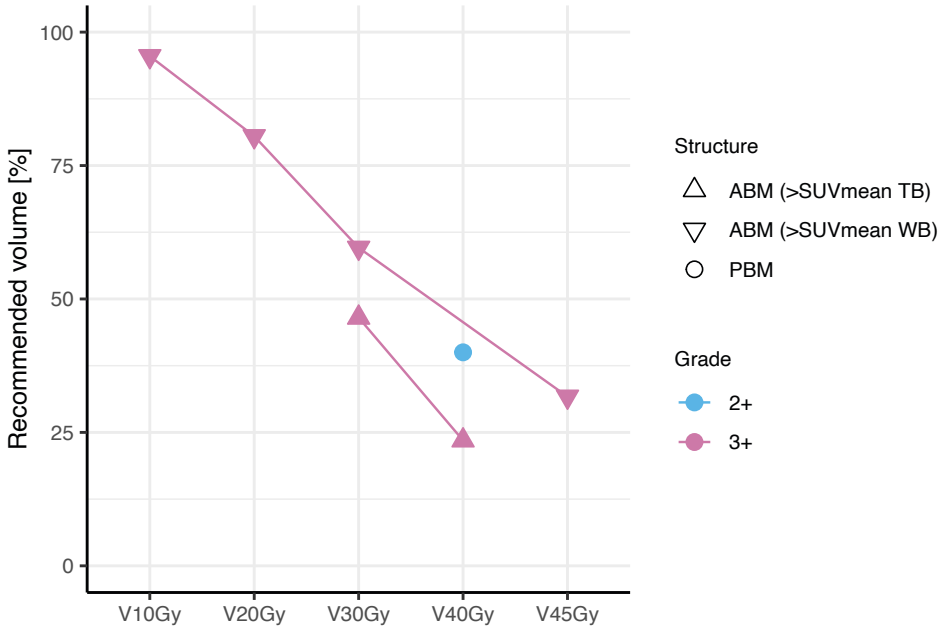

Figure 3: *Dose cut-off values for the (subsites of) the pelvic bone delineated as lower density marrow spaces (PBM) or active bone marrow (ABM) and correlation to hematologic toxicity (HT) as recommended by included studies. HT = hematologic toxicity, PBM = lower density marrow spaces, ABM = active bone marrow, SUV = standardized uptake value, TB = total body, WB = whole bone.*

>SUV_{mean} of the total body

ABM was defined as the region within the pelvic bone with an SUV greater than the SUV_{mean} of the total body using the 18F-FDG-PET-CT, applied by two authors [37, 39], or the Tc-99m sulfur colloid SPET, used by one author [40]. A volume consisting of SUVs higher than the SUV_{mean} and the total pelvic bone was defined as the ABM. Similar mean PB-volumes (1553 cm^3 (range 1117-1920) [39] vs 1433 cm^3 (range 901-1920) [37]) and ABM-volumes (1227 cm^3 (range 793-1671) [39] vs 1098 cm^3 (range 387-1671) [37]) were reported in the articles applying 18F-FDG-PET-CT. The article focusing on Tc-99m sulfur colloid SPET showed lower volumes as the mean PB-volume was 954 cm^3 (sd 156) and the mean ABM-volume was 355 cm^3 (sd 173), which might be due to the different imaging modalities used [40]. All three authors agreed that patients with a low pretreatment ABM-volume were more likely to develop HT3+ than patients with a larger ABM-volume before irradiation. Cut-off values of <1201 mL [39] and 387.5 cm^3 [40] were suggested. The V_{30Gy} [40] and V_{40Gy} were highly predictive for HT [39, 40] and V_{30Gy}>46.5% and V_{40Gy}>23.5% [40] were correlated with HT (see Figure 3). Additionally,

V_{40Gy} was also identified as a predictor of lymphocytes nadir [39]. Lastly, the volume of ABM spared was compared against HT and correlations were found for the volume spared 10, 20, and 40 Gy when <179 cc, <186 cc, and <738 cc, respectively [37].

>SUV_{mean} of the whole bone

A different method for determining ABM defines the SUV_{mean} of the pelvic bones to be the threshold instead of the SUV_{mean} of the total body. Three articles applied this method and studied the correlation between ABM and HT or nadirs of blood cells [21, 36, 38]. All three articles defined the ABM following the method as described by Rose et al. [38]. ABM was contoured by selecting the subset of the pelvic bones that had an SUV greater than or equal to the individual's SUV_{mean} in the pelvic bones. Two authors reported similar mean values for the whole pelvic bone contour (1278.0 cm^3 (sd 224.7) [38] and 1406.7 cm^3 (sd 232.6) [21]) and ABM (553.0 cm^3 (sd 133.1) [38] and 651.5 cm^3 (sd 188.4) [21]). The researchers also evaluated inactive bone marrow (IBM), defined as the whole pelvic bone contour minus the ABM, and reported similar volumes (respectively 695.5 cm^3 (sd 147.0) [38] and 755.2 cm^3 (sd 144.1) [21]). These two articles analyzed the correlation between dosimetric parameters and complete blood cell counts (results not visualized in a table). Most associations were identified for WBC. One article found the V_{10Gy}, V_{20Gy}, V_{30Gy}, and D_{mean} to be highly predictive for WBC nadirs [38], while the other demonstrated that V_{20Gy}, V_{30Gy}, and V_{40Gy} were predictors [21]. For ANC, HgB, and PLT-count, only D_{mean} was associated [38]. Lastly, Rose et al. found no correlation between the D_{mean} of IBM and blood cell nadirs [38]. A mean relative SUV-reduction in the whole pelvic bone and ABM of respectively 27% and 38% in comparison to the SUVs at pre-treatment was described [21]. This even occurred in parts of the ABM receiving relatively small doses (<5Gy). The third article compared dosimetric parameters of ABM to HT (see Table 3) [36]. It showed that for para-aortic lymph node metastasis (PALN) patients, the V_{20Gy}, V_{30Gy}, and V_{45Gy} of the whole pelvic bone were significant predictors for HT3+ at 78.6%, 47.1%, 20.4% and V_{10Gy}, V_{20Gy}, V_{30Gy}, and V_{45Gy} of the ABM at 95.5%, 80.5%, 59.6% and 31.7%, visualized in Figure 3, respectively [36]. In addition, a PB and ABM D_{mean} of 30.3 and 32.4 Gy, respectively, were associated with HT (not visualized in Figure 3). Due to the large irradiation field for PALN-patients, an additional value of ABM when compared to the whole pelvic bone could not be detected [36].

Other predictors

All studies evaluated other predictors, besides dose volume characteristics, for HT except for four studies [29, 33, 37, 40]. The baseline WBC, ANC, HgB, and PLT were demonstrated to be predictive for their nadir values [31, 34]. The use of para-aortic irradiation was also associated with HT3+ [21], in contrast to other findings [30]. Lastly, articles did report different outcomes for the association between body mass index (BMI) and HT. While some articles found BMI to be highly predictive for WBC nadir [32] or HT3+ [31], other articles did not show this correlation [14, 21, 28, 30, 34, 35, 38]. No associations were found between HT and race [14, 21, 28, 32, 35, 38], age [14, 21, 28, 30-32, 34-36, 38, 39], stage [21, 32, 35, 36, 38, 39], bone marrow volume [34, 35], comorbidity [28, 32, 36], PTV-volume [21, 31, 38], pre-treatment transfusions [36], positive lymph nodes [21], intensity or number of cycles of chemotherapy [21, 30, 31, 39], performance status [30], chemotherapy regimen (cisplatin vs. carboplatin) [30], and smoking history [39].

DISCUSSION

To our knowledge, this systematic review is the first literature review providing an overview of articles evaluating the correlation between irradiation of the BM in patients with locally advanced cervical cancer and the development of hematologic toxicity (HT). Seventeen articles were included. Three BM-delineation methods were identified: contouring of the whole pelvic bone (PB), lower density marrow spaces (PBM), and nuclear imaging-based active bone marrow (ABM). Dosimetric parameters of (subsites of) the pelvic bone associated with HT or nadirs of blood cells were identified for each delineation method. The majority of the studies defining bone marrow as the whole pelvic bone found a significant association between bone marrow and HT, in contrast to studies evaluating lower density marrow spaces or active bone marrow. A significant increase in hematologic toxicity was observed for whole pelvic bone doses of V_{10Gy}>95-75%, V_{20Gy}>80-65%, and V_{40Gy}>37-28%. Except for the article by Rose et al., all included articles used a single dataset to develop a HT-prediction model.

Knowledge on the effect of bone marrow dose for LACC-patients could aid in the development of bone marrow sparing (BMS)-techniques. Dose constraints are important to minimize the occurrence of hematologic toxicity and can be applied during treatment planning. Studies by Platta et al. and Mell et al. were excluded in this systematic review, since their articles did not analyze the correlation between bone marrow dosimetric

parameters and HT, but showed a significant decrease in dosimetric parameters with the use of BMS-techniques [41, 42]. Platta et al. applied the method proposed by Mell et al. to contour the whole pelvic bone (PB) for cervical or endometrial cancer patients and created a standard and BMS IMRT-plan [41]. For the standard IMRT-plan and BMS IMRT-plan, the resulting PB-V_{10Gy}, V_{20Gy}, and V_{40Gy} were respectively 94%, 74%, and 37% and 83%, 65%, and 35%. Secondly, Mell et al. demonstrated that PET-CT-based BMS-IMRT, sparing the ABM, showed significantly lower rates of HT3+ (neutropenia) when compared to CT-based BMS-IMRT, sparing the PB [42]. The authors suggested that this difference could be related to an overall reduced pelvic bone marrow dose in patients undergoing PET-CT-based BMS-IMRT, rather than sparing active bone marrow per se.

The effect of various dose delivery techniques on BMS has been investigated in multiple planning studies. The dose in the bone marrow could be significantly reduced without increasing the dose in the bladder, rectum, and bowel with both IMRT and VMAT compared to 3D conventional RT [43]. The developments in intensity-modulated proton therapy (IMPT) technique are promising for BMS. A study wherein ABM, identified on 18F-fluorthymidine (FLT) PET, was used to delineate bone marrow in cervical cancer patients showed a significant reduction in median volume with IMPT compared to IMRT for all dose levels, with reductions from 23% to 41% [22]. IMPT could not only reduce the dose directly received by the BM but also reduce the field size and the volume of the body exposed to radiation [13, 44]. A large field size bears a higher risk of bone marrow suppression, as more circulating cells receive irradiation dose. This effect is more profound on lymphocytes, which are highly sensitive to radiation [13, 44]. However, a readily available method to measure and control radiation effects on circulating blood cells is lacking [13, 44, 45]. The impact of such dose reductions on the risk of HT should be further evaluated and compared among radiation techniques before certain techniques can be recommended.

In general, volume-based metrics might be a better predictor for HT when compared to dose-volume metrics. Included studies emphasized the importance of sparing a threshold volume and believed that bone marrow acts as a parallel organ, similar to the liver [37, 39, 40]. As long as there are enough active functional cells left, HT will not occur. The detected correlation between a low baseline bone marrow volume and HT supports the idea of sparing threshold volumes. However, further evaluation of a volume-based model is warranted.

Studies have evaluated delineation methods different from those included in this systematic review for other pelvic cancers than LACC. 18F-fluorthymidine (FLT) PET can identify and spare ABM in patients with pelvic cancer. FLT detects chronic suppression of bone marrow by correlating FLT-uptake to complete blood cell counts. IMRT-plans sparing the FLT-identified pelvic bone marrow significantly reduced the dose to the pelvic bone marrow [12]. Additionally, fat-fraction imaging can be utilized to measure bone marrow composition changes during chemoradiation treatment in patients [46, 47]. With water-fat imaging methods, fat fraction maps can be acquired. The fat fraction in bone marrow can significantly increase during the treatment, especially in areas close to the target radiation field, and is associated with declining peripheral blood cell counts [47]. An increase in the fat fraction is the highest in regions close to the target volume, whereas chemotherapy gives more uniform changes [46]. Continued efforts should be made to identify functional pelvic bone marrow using PET-tracers, MR-imaging, or other imaging modalities. Since functional imaging is expensive and not commonly available, earlier studies proposed an atlas-based method for delineating the ABM in patients with cervical cancer [48, 49]. Atlas-based BMS-IMRT can reduce the dose to the ABM. Future studies on delineation and sparing methods for bone marrow in LACC-patients are required to establish the most optimal sparing strategy.

It should be noted that the majority of the included studies in this systematic review had a retrospective design and a limited sample size. We utilized the TRIPOD-system as a way to quantitatively analyze the prediction strength of models. Only one of the articles was dedicated to model validation. The majority of the included articles, however, did not develop a complete dose-response model but evaluated selected dosimetric parameters. For these articles, the overall adherence to the TRIPOD-statement was low. Our review demonstrated therefore scarcity of studies independently validating developed prediction models. Ideally, studies should include both the development and external validation of a complete dose-response model before implementing it as a normal tissue complication probability (NTCP) tool in the clinic to support decision-making during treatment planning. External validation studies are important to improve a model's generalizability, validity, and clinical usefulness.

Recommended cut-off values for the whole pelvic bone were similar for HT2+ and HT3+. A possible explanation could be that in some studies, for instance by Albuquerque et al. and Huang et al., chemotherapy was held when leukopenia or neutropenia grade 3 or higher was observed in order to prevent high-grade HT [19, 35]. Limiting chemotherapy

dose could impact the correlation between BM-dose and high-grade HT and therefore eliminate differences in recommended cut-off values between HT2+ and HT3+. However, studies evaluating the effect of chemotherapy intensity or the number of chemotherapy cycles on HT found no significant correlation [21, 30, 31, 39]. In future studies, the impact of the chemotherapy scheme delivered on HT should be considered.

Furthermore, the majority of the articles measured endpoints only during treatment and focused on acute toxicity. Nonetheless, Elicin et al. reported that BM-dose affected WBC hematological counts even at three months post-treatment and at last follow-up [21]. A study by Terrones-Campos et al. evaluated the kinetics of circulating blood cells in patients who received curative radiotherapy for solid tumor diagnoses [44]. It was demonstrated that the lymphocyte count remains low up to one year after radiotherapy. Radiation-induced lymphopenia might be associated with poor response to adjuvant therapies, including immunotherapy, and decreased survival [50, 51]. However, studies evaluating the occurrence, effect on the patient, and therapeutic approaches to reduce the incidence and severity of long-term hematologic toxicity after treatment of LACC are lacking.

Additionally, studies reported contradicting results on dosimetric parameters correlated with HT. Some articles defining bone marrow as the whole bone contour (PB) detected a correlation between low dose-volume parameters and HT [8, 32, 33], while other articles only reported high dose parameters to be associated [14, 19]. A reason for this could be multicollinearity. It is highly likely that dose-volume parameters are correlated. Entry of multiple dose parameters in one model could lead to incorrect estimates. Likewise, multiple studies investigating ABM reported difficulties in finding a correlation between dose-volume parameters of the bone marrow and HT [14, 36, 39]. The inability to detect associations might be due to a lack of low-dose regions targeting the sensitive bone marrow resulting from characteristics of the patient cohort, radiation therapy technique used, or proximity of the bone marrow to the target volume. For instance, lumbar and pelvic bone marrow receives high doses in the irradiation of PALN-patients [36]. 3DCRT leads to a sharper gradient between moderate and low isodose levels when compared to IMRT and may therefore limit dose-volume associations [35, 39]. Lastly, the proximity of pelvic bone subsites, including the lumbosacral spine, to the target volume leads to high bone marrow dose [30].

This systematic review is the first literature review providing an overview of articles evaluating the correlation between irradiation of the BM in patients with locally advanced cervical cancer and the development of hematologic toxicity (HT). The majority of the studies defining bone marrow as the whole pelvic bone found a significant association between bone marrow and HT, in contrast to studies evaluating lower density marrow spaces or active bone marrow. A significant increase in hematologic toxicity was observed for whole pelvic bone doses of V_{10Gy}>95-75%, V_{20Gy}>80-65%, and V_{40Gy}>37-28%. Only a limited number of studies have investigated the relationship between bone marrow dose and HT in LACC-patients treated with primary cisplatin-based chemoradiation and clinically useful predictions models are currently not available. Future studies may use whole pelvic bone contouring to develop normal tissue complication probability models.

ACKNOWLEDGEMENTS

The authors wish to thank the Erasmus MC Medical Library for developing and updating the search strategy.

SUPPLEMENTARY MATERIAL

Supplementary material is available on

REFERENCES

1. Moore SG, Dawson KL. Red and yellow marrow in the femur: age-related changes in appearance at MR imaging. Radiology. 1990;175(1):219-23.
2. Cristy M. Active bone marrow distribution as a function of age in humans. Phys Med Biol. 1981;26(3):389.
3. Boron WF, Boulpaep EL. Medical physiology E-book: Elsevier Health Sciences; 2016.
4. Shao L, Luo Y, Zhou D. Hematopoietic stem cell injury induced by ionizing radiation. Antioxidants & redox signaling. 2014;20(9):1447-62.
5. Abu-Rustum NR, Lee S, Correa A, Massad LS. Compliance with and acute hematologic toxic effects of chemoradiation in indigent women with cervical cancer. Gynecol Oncol. 2001;81(1):88-91.
6. Kirwan JM, Symonds P, Green JA, Tierney J, Collingwood M, Williams CJ. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. Radiother Oncol. 2003;68(3):217-26.
7. Lei C, Ma S, Huang M, An J, Liang B, Dai J, et al. Long-term survival and late toxicity associated with pelvic intensity modulated radiation therapy (IMRT) for cervical cancer involving CT-based positive lymph nodes. Front Oncol. 2019;9:520.
8. Mell LK, Kochanski JD, Roeske JC, Haslam JJ, Mehta N, Yamada SD, et al. Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy. International Journal of Radiation Oncology* Biology* Physics. 2006;66(5):1356-65.
9. van Meir H, Nout R, Welters M, Loof N, De Kam M, Van Ham J, et al. Impact of (chemo) radiotherapy on immune cell composition and function in cervical cancer patients. Oncoimmunology. 2017;6(2):e1267095.
10. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). International Journal of Radiation Oncology*Biology*Physics. 1995;31(5):1341-6.
11. Common Terminology Criteria for Adverse Events (CTCAE): U.S. Department of Health and Human Services; 2017 [updated November 27, 2017. v5:[Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
12. McGuire SM, Bhatia SK, Sun W, Jacobson GM, Menda Y, Ponto LL, et al. Using [18F] fluorothymidine imaged with positron emission tomography to quantify and reduce hematologic toxicity due to chemoradiation therapy for pelvic cancer patients. International Journal of Radiation Oncology* Biology* Physics. 2016;96(1):228-39.
13. Ellsworth SG. Field size effects on the risk and severity of treatment-induced lymphopenia in patients undergoing radiation therapy for solid tumors. Advances in radiation oncology. 2018;3(4):512-9.
14. Klopp AH, Moughan J, Portelance L, Miller BE, Salehpour MR, Hildebrandt E, et al. Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer. International Journal of Radiation Oncology* Biology* Physics. 2013;86(1):83-90.

15. Cheng Y, Ma Y, Zheng J, Deng H, Wang X, Li Y, et al. Impact of Chemotherapy Regimens on Normal Tissue Complication Probability Models of Acute Hematologic Toxicity in Rectal Cancer Patients Receiving Intensity Modulated Radiation Therapy With Concurrent Chemotherapy From a Prospective Phase III Clinical Trial. Front Oncol. 2019;9:244.
16. Noticewala SS, Li N, Williamson CW, Hoh CK, Shen H, McHale MT, et al. Longitudinal changes in active bone marrow for cervical cancer patients treated with concurrent chemoradiation therapy. International Journal of Radiation Oncology* Biology* Physics. 2017;97(4):797-805.
17. Bazan JG, Luxton G, Kozak MM, Anderson EM, Hancock SL, Kapp DS, et al. Impact of chemotherapy on normal tissue complication probability models of acute hematologic toxicity in patients receiving pelvic intensity modulated radiation therapy. International Journal of Radiation Oncology* Biology* Physics. 2013;87(5):983-91.
18. Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie-Meder C, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. Virchows Arch. 2018;472(6):919-36.
19. Huang J, Gu F, Ji T, Zhao J, Li G. Pelvic bone marrow sparing intensity modulated radiotherapy reduces the incidence of the hematologic toxicity of patients with cervical cancer receiving concurrent chemoradiotherapy: a single-center prospective randomized controlled trial. Radiation Oncology. 2020;15(1):1-9.
20. Dueñas-González A, Cetina-Perez L, Lopez-Graniel C, Gonzalez-Enciso A, Gómez-Gonzalez E, Rivera-Rubi L, et al. Pathologic response and toxicity assessment of chemoradiotherapy with cisplatin versus cisplatin plus gemcitabine in cervical cancer: a randomized phase II study. International Journal of Radiation Oncology* Biology* Physics. 2005;61(3):817-23.
21. Elicin O, Callaway S, Prior JO, Bourhis J, Ozsahin M, Herrera FG. [18F] FDG-PET standard uptake value as a metabolic predictor of bone marrow response to radiation: impact on acute and late hematological toxicity in cervical cancer patients treated with chemoradiation therapy. International Journal of Radiation Oncology* Biology* Physics. 2014;90(5):1099-107.
22. Dinges E, Felderman N, McGuire S, Gross B, Bhatia S, Mott S, et al. Bone marrow sparing in intensity modulated proton therapy for cervical cancer: Efficacy and robustness under range and setup uncertainties. Radiother Oncol. 2015;115(3):373-8.
23. Song WY, Huh SN, Liang Y, White G, Nichols RC, Watkins WT, et al. Dosimetric comparison study between intensity modulated radiation therapy and three-dimensional conformal proton therapy for pelvic bone marrow sparing in the treatment of cervical cancer. J Appl Clin Med Phys. 2010;11(4):83-92.
24. Gort EM, Beukema JC, Matysiak W, Sijtsema NM, Aluwini S, Langendijk JA, et al. Inter-fraction motion robustness and organ sparing potential of proton therapy for cervical cancer. Radiotherapy and Oncology. 2021;154:194-200.
25. Liang Y, Messer K, Rose BS, Lewis JH, Jiang SB, Yashar CM, et al. Impact of bone marrow radiation dose on acute hematologic toxicity in cervical cancer: principal component analysis on high dimensional data. International Journal of Radiation Oncology* Biology* Physics. 2010;78(3):912-9.
26. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement.

Journal of British Surgery. 2015;102(3):148-58.

27. Brodin NP, Kabarriti R, Garg MK, Guha C, Tomé WA. Systematic review of normal tissue complication models relevant to standard fractionation radiation therapy of the head and neck region published after the QUANTEC reports. International Journal of Radiation Oncology* Biology* Physics. 2018;100(2):391-407.
28. Zhu H, Zakeri K, Vaida F, Carmona R, Dadachanji KK, Bair R, et al. Longitudinal study of acute haematologic toxicity in cervical cancer patients treated with chemoradiotherapy. J Med Imaging Radiat Oncol. 2015;59(3):386-93.
29. Lewis S, Chopra S, Naga P, Pant S, Dandpani E, Bharadwaj N, et al. Acute hematological toxicity during post-operative bowel sparing image-guided intensity modulated radiation with concurrent cisplatin. The British journal of radiology. 2018;91(1092):20180005.
30. Kumar T, Schernberg A, Busato F, Laurans M, Fumagalli I, Dumas I, et al. Correlation between pelvic bone marrow radiation dose and acute hematological toxicity in cervical cancer patients treated with concurrent chemoradiation. Cancer Manag Res. 2019;11:6285.
31. Mahantshetty U, Krishnatry R, Chaudhari S, Kanaujia A, Engineer R, Chopra S, et al. Comparison of 2 contouring methods of bone marrow on CT and correlation with hematological toxicities in non–bone marrow–sparing pelvic intensity-modulated radiotherapy with concurrent cisplatin for cervical cancer. International Journal of Gynecologic Cancer. 2012;22(8).
32. Rose BS, Aydogan B, Liang Y, Yeginer M, Hasselle MD, Dandekar V, et al. Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. International Journal of Radiation Oncology* Biology* Physics. 2011;79(3):800-7.
33. Gupta N, Prakash C, Patel A, Chakrabarty K, Giri U, Choudhary S. Potential Advantages of Bone Marrow Sparing IMRT in Cancer Cervix: A Dosimetric Evaluation. Journal of Clinical & Diagnostic Research. 2019;13(4).
34. Chang Y, Yang Z-Y, Li G-L, Li Q, Yang Q, Fan J-Q, et al. Correlations between radiation dose in bone marrow and hematological toxicity in patients with cervical cancer: a comparison of 3DCRT, IMRT, and RapidARC. International Journal of Gynecologic Cancer. 2016;26(4).
35. Albuquerque K, Giangreco D, Morrison C, Siddiqui M, Sinacore J, Potkul R, et al. Radiation-related predictors of hematologic toxicity after concurrent chemoradiation for cervical cancer and implications for bone marrow–sparing pelvic IMRT. International Journal of Radiation Oncology* Biology* Physics. 2011;79(4):1043-7.
36. Yan K, Ramirez E, Xie X-J, Gu X, Xi Y, Albuquerque K. Predicting severe hematologic toxicity from extended-field chemoradiation of para-aortic nodal metastases from cervical cancer. Pract Radiat Oncol. 2018;8(1):13-9.
37. Zhou Y, Freese C, Meier T, Go D, Khullar K, Sudhoff M, et al. The absolute volume of PET-defined, active bone marrow spared predicts for high grade hematologic toxicity in cervical cancer patients undergoing chemoradiation. Clinical and Translational Oncology. 2018;20(6):713-8.
38. Rose BS, Liang Y, Lau SK, Jensen LG, Yashar CM, Hoh CK, et al. Correlation between radiation dose to 18F-FDG-PET defined active bone marrow subregions and acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. International Journal of Radiation Oncology* Biology* Physics. 2012;83(4):1185-91.

39. Khullar K, Sudhoff M, Elson J, Herzog T, Jackson A, Billingsley C, et al. A comparison of dosimetric parameters in PET-based active bone marrow volume and total bone volume in prediction of hematologic toxicity in cervical cancer patients treated with chemoradiation. Journal of Radiation Oncology. 2017;6(2):161-5.

40. Wang SB, Liu JP, Lei KJ, Jia YM, Xu Y, Rong JF, et al. The volume of 99mTc sulfur colloid SPET-defined active bone marrow can predict grade 3 or higher acute hematologic toxicity in locally advanced cervical cancer patients who receive chemoradiotherapy. Cancer medicine. 2019;8(17):7219-26.

41. Platta CS, Bayliss A, McHaffie D, Tomé WA, Straub MR, Bradley KA. A dosimetric analysis of tomotherapy based intensity modulated radiation therapy with and without bone marrow sparing in gynecologic malignancies. Technol Cancer Res Treat. 2013;12(1):19-29.

42. Mell LK, Sirák I, Wei L, Tarnawski R, Mahantshetty U, Yashar CM, et al. Bone marrow-sparing intensity modulated radiation therapy with concurrent cisplatin for stage IB-IVA cervical cancer: an international multicenter phase II clinical trial (INTERTECC-2). International Journal of Radiation Oncology* Biology* Physics. 2017;97(3):536-45.

43. Jodda A, Urbański B, Piotrowski T, Malicki J. Relations between doses cumulated in bone marrow and dose delivery techniques during radiation therapy of cervical and endometrial cancer. Phys Med. 2017;36:54-9.

44. Terrones-Campos C, Ledergerber B, Vogelius IR, Helleberg M, Specht L, Lundgren J. Hematological toxicity in patients with solid malignant tumors treated with radiation – Temporal analysis, dose response and impact on survival. Radiotherapy and Oncology. 2021;158:175-83.

45. Vitzthum LK, Heide ES, Park H, Williamson CW, Sheridan P, Huynh-Le M-P, et al. Comparison of Hematologic Toxicity and Bone Marrow Compensatory Response in Head and Neck vs. Cervical Cancer Patients Undergoing Chemoradiotherapy. Front Oncol. 2020;10:1179-.

46. Bolan PJ, Arentsen L, Sueblinvong T, Zhang Y, Moeller S, Carter JS, et al. Water–fat MRI for assessing changes in bone marrow composition due to radiation and chemotherapy in gynecologic cancer patients. J Magn Reson Imaging. 2013;38(6):1578-84.

47. Carmona R, Pritz J, Bydder M, Gulaya S, Zhu H, Williamson CW, et al. Fat composition changes in bone marrow during chemotherapy and radiation therapy. International Journal of Radiation Oncology* Biology* Physics. 2014;90(1):155-63.

48. Li N, Noticewala SS, Williamson CW, Shen H, Sirak I, Tarnawski R, et al. Feasibility of atlas-based active bone marrow sparing intensity modulated radiation therapy for cervical cancer. Radiother Oncol. 2017;123(2):325-30.

49. Yusufaly T, Miller A, Medina-Palomo A, Williamson CW, Nguyen H, Lowenstein J, et al. A Multi-atlas Approach for Active Bone Marrow Sparing Radiation Therapy: Implementation in the NRG-GY006 Trial. International Journal of Radiation Oncology* Biology* Physics. 2020;108(5):1240-7.

50. Wang Y, Deng W, Li N, Neri S, Sharma A, Jiang W, et al. Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions. Front Pharmacol. 2018;9:185-.

51. Venkatesulu BP, Mallick S, Lin SH, Krishnan S. A systematic review of the influence of radiation-induced lymphopenia on survival outcomes in solid tumors. Critical Reviews in Oncology/Hematology. 2018;123:42-51.