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

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Systematic Review

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

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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 BM dose and HT in patients with LACC 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 V10 (3/14), V20 (6/14), and V40 (4/11). Recommended cut-off values were V10 > 95–75%, V20 > 80–65%, and V40 > 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 patients with LACC 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.

Bone marrow (BM) is made up of the active red marrow, comprising mostly hematopoietic tissue, and inactive yellow 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]. While 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 BM 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 among chemotherapy regimens [15–17]. Patients receiving pelvic radiotherapy with concurrent chemotherapy have a higher BM tolerance when comparing

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cisplatin-based to mitomycin-C (MMC) based chemotherapy but a lower BM tolerance when comparing cisplatin to 5-fluorouracil (5FU) [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 patients with LACC 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, the 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 Vdose (e.g. V20 and V30), 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 BM and HT in patients with LACC treated with primary cisplatin-based chemoradiation. Interpretation and discussion of the literature can give guidance on BM 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 a chemotherapeutic agent was cisplatin, another platinum-based chemotherapy was allowed in case of contraindications for cisplatin, (4) the correlation between HT 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 points of endpoint measurements, 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 is 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 Fig. 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 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

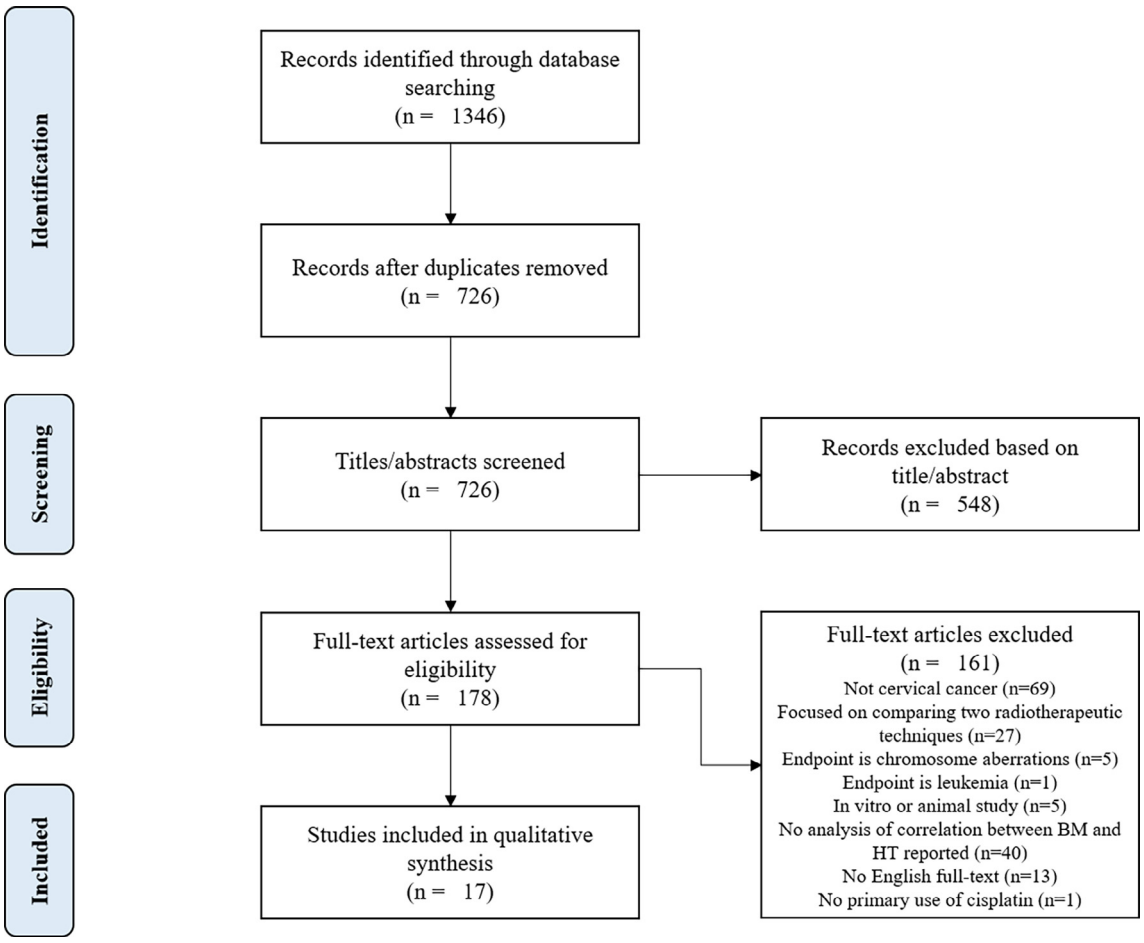

Fig. 1. PRISMA flowchart [26]. *BM = bone marrow, HT = hematologic toxicity.*

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.

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.

Whole pelvic bone

Table 2 describes that three out of fourteen articles found a significant correlation between V10 of the whole bone and grade 2 or higher HT [8,32,33]. Six out of fourteen articles demonstrated a significant relationship between V20 and HT [8,30,32,34–36]. Furthermore, four out of eleven articles showed that V40 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 Fig. 2. The recommended cut-off values for HT2+ and HT3+ for the whole pelvic bone were similar. V10 < 75–95% [8,32,33], V20 < 65–80% [30,32,35,36], and V40 < 28–37% [14,19] were recommended to reduce HT. Some other significant relationships were reported, including the V30 and V45 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 Fig. 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 keeping the D_{mean} and D_{median} below respectively 30.3 Gy and 34.1 Gy (not visualized in Fig. 2) [14,36].

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 Fig. 2. The lumbosacral spine (LSS) includes the 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 V10 [19], D_{mean} [19], and V20 [8] were each found significant by one article. D_{mean} was recommended to be < 39 Gy (not visualized in Fig. 2) and V10 < 87% [19]. Although significant LSS sparing might be difficult due to its proximity to the

Table 1
Characteristics of the included studies.

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	Time points of measurements	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] HgB[c] HT3+[f]	PB-V10[a,b,f], V20[a,b,c,f], V30[a,b], D_{mean}[a,b] PB-V10 > 95%[f] PB-V20 > 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-V40[e] PB-V40 > 28%[e] LSS-V10 > 87%[e] LSS-D_{mean} > 39Gy[e] PBM-V40[e] LSSM-$_{mean}^{e}$, V10[e], V20[e], V40[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] HgB[c] PLT[d] HT2+[e] HT3+[f]	PB-V20[a,b,f], V40[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-V40 > 37%[e] PB-D_{median} > 34.1Gy[e]
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-V5 > 95%[g] LP-PB-V20 > 45%[g] Iliac crests-PB-D_{mean} > 31 Gy[g] PB-V20 > 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] HgB[c] PLT[d] HT3+[f]	ABM-$D_{mean}^{a,b,c,d}$,V10[a], V20[a], V30[a] PB-V10[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 cm^3[f] ABM-V30 > 46.5%[f] ABM-V40 > 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] HgB[c] PLT[d]	PB-$D_{mean}^{a,b}$, V20[a,b], V30[a,b], V40[a,b] LSS-V10[a,b], V40[a,b] LOW-V20[a,b], V30[a,b]
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-V20 > 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-V20 > 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-V40[f]

(*continued on next page*)

Table 1 (*continued*)

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	Time points of measurements	Endpoint	Dosimetric predictors
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] HgB[c] PLT[d]	3m post-treatment: ABM-SUV[a], PB-D^a_{mean}, V10[a], V20[a], V30[a], V40[a], ABM-V40[a] Late follow-up: PB-D^a_{mean}, V10[a], V20[a], V30[a], V40[a], ABM-V20[a], V30[a], V40[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] HgB[c] PLT[d] HT2+[e] HT1+[g]	PB-V10[a,c,e,g], V20[c,e,g] LSS-V10[a,b,e], V20[a,c,e] LP-V10[c,e,g], V20[e,g] PB-V10 > 90%[a,e], V20 > 75%[c,e] LSS-V10 > 90%[b] LP-V10 > 90%[c]
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-V20 > 78.6%[f], V30 > 47.1%[f], V45 > 20.4%[f], D_{mean} > 30.3Gy[f] ABM-V10 > 95.5%[f], V20 > 80.5%[f], V30 > 59.6%[f], V45 > 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] HgB[c]PLT[d] HT2+[e]	Baseline HgB and PLT[c,d] PBM-V40 > 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] HgB[c] PLT[d] HT2+[e] HT3+[f]	PB-V10 > 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] HgB[c] PLT[d] HT3+[f]	Volume spared of PB: 10 Gy < 230cc[f] of ABM: V10 < 179cc[f] OR V20 < 186cc[f] OR V40 < 738cc[f]

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 (white blood cells), [b] = ANC (absolute neutrophil count), [c] = HgB (hemoglobin), [d] = PLT (platelets), [e] = HT2+, [f] = HT3+, [g] = HT1+.

Table 2
Relationship between various dosimetric parameters of the whole pelvic bone contour (PB) and hematologic toxicity (HT).

Dosimetric parameter	Number of studies showing significant correlation/number of studies employing dosimetric parameter	HT2+	HT3+	HT4+
V5	0/2 (0%)	0/1	0/1	0/1
V10	3/14 (21%)	2/8	1/7	0/1
V15	0/1 (0%)	–	–	0/1
V20	6/14 (43%)	3/8	2/7	1/1
V30	1/10 (10%)	0/7	1/4	0/1
V40	4/11 (36%)	4/7	1/5	0/1
V45	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	–

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 are provided. *HT = hematologic toxicity.*

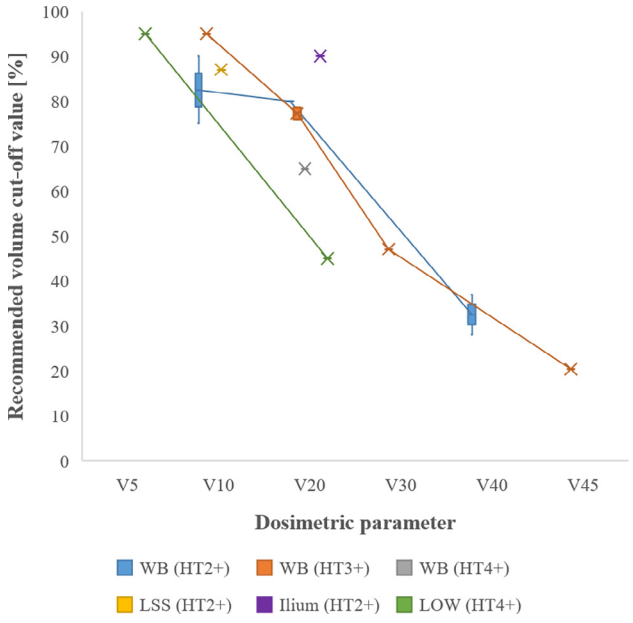

Fig. 2. Dose cut-off values for the whole pelvic bone contour (PB) and correlation to hematologic toxicity (HT) as recommended by included studies. *HT = hematologic toxicity, WB = whole bone, LSS = lumbosacral spine, LOW = lower pelvic bones.*

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 V5 [30], V10 [8], and V20 [8,30] of LOW were reported to be predictive of HT. V5 was recommended to be < 95% and V20 < 45% to decrease HT4+ [30]. Only two dosimetric parameters of the ilium, the D_{mean} [30] and V20 [29], were demonstrated to be correlated to HT and it was recommended that D_{mean} < 31 Gy [30] (not visualized in Fig. 2) and V20 < 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 V10 [8,21,32,38], V20 [21,28,32,34], V30 [21,28,32], D_{mean} [21,28,32] and WBC nadirs. Elicin et al. noted that the V10, V20, V30, and V40 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, with the exception of a lower number of studies demonstrating V10 to be a significant predictor. Only the dosimetric parameters V10 [8] and V20 [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, V20 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 V40 is determined to be associated with HT by two out of four articles [19,31]. V40 < 40% might decrease the risk of HT2+ (see Fig. 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-99 m (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.

$>SUV_{mean}$ 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 studies [37,39], or the Tc-99m sulfur colloid SPET, used by one study [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 cm^3) [39] vs. 1433 cm3 (range 901–1920 cm^3) [37]) and ABM volumes (1227 cm^3 (range 793–1671 cm^3) [39] vs. 1098 cm^3 (range 387–1671 cm^3) [37]) were reported in the articles applying 18F-FDG-PET-CT. The article focusing on Tc-99m sulfur

Table 3
Relationship between various dosimetric parameters of CT-based lower density marrow spaces (PBM) or active bone marrow (ABM) and hematologic toxicity (HT).

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)
V5	0/1 (0%)	–	–	–
V10	0/4 (0%)	0/2 (0%)	0/1 (0%)	1/1(100%)
V15	0/1 (0%)	–	–	–
V20	0/4 (0%)	0/2 (0%)	0/1 (0%)	1/1 (100%)
V30	0/3 (0%)	–	1/1 (100%)	1/1 (100%)
V40	2/4 (50%)	1/2 (50%)	1/1 (100%)	–
V45	–	–	–	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%)	–	–

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 are provided. *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.*

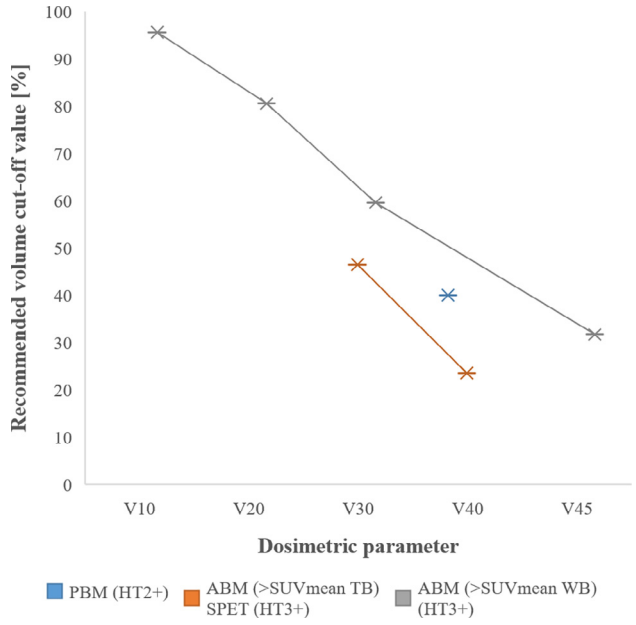

Fig. 3. Dose cut-off values for the (subsites of) the pelvic bone delineated as lower density marrow spaces (PBM) or active bone marrow (ABM) and correlation to hematologic toxicity (HT) as recommended by the included studies. *HT = hematologic toxicity, PBM = lower density marrow spaces, ABM = active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

colloid SPET showed lower volumes as the mean PB volume was 954 (156) cm^3 and the mean ABM volume was 355 (173) cm^3, which might be due to the different imaging modality 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 V30 [40] and V40 were highly predictive for HT [39,40] and V30 > 46.5% and V40 > 23.5% [40] were correlated with HT (see Fig. 3). Additionally, V40 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 (SD 224.7) cm^3 [38] and 1406.7 (SD 232.6) cm^3 [21]) and ABM (553.0 (SD 133.1) cm^3) [38] and 651.5 (SD 188.4) cm^3 [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 (SD 147.0) cm^3 [38] and 755.2 (SD 144.1) cm^3 [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 V10, V20, V30, and D_{mean} to be highly predictive for WBC nadirs [38], while the other demonstrated that V20, V30, and V40 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 (< 5 Gy). The third article compared dosimetric parameters of ABM to HT (see Table 3) [36]. It showed that for patients with para-aortic lymph node metastasis (PALN), the V20, V30, and V45 of the PB were significant predictors for HT3+ at 78.6%, 47.1%, 20.4% and V10, V20, V30, and V45 of the ABM at 95.5%, 80.5%, 59.6% and 31.7%, visualized in Fig. 3, respectively [36]. In addition, the D_{mean} to PB and ABM 30.3 and 32.4 Gy were associated with HT (not visualized in Fig. 3). Due to the large irradiation field for patients with PALN, an additional value of ABM when compared to PB 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], BM volume [34,35], comorbidity [28,32,36], PTV volume [21,31,38], pre-treatment transfusions [36], positive lymph nodes [21], inten-

sity 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 bone marrow (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 BM as the whole pelvic bone found a significant association between BM 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 V10 > 95–75%, V20 > 80–65%, and V40 > 37–28%. Except for the article by Rose et al., all included articles used a single dataset to develop an HT prediction model.

Knowledge on the effect of BM dose for patients with LACC could aid in the development of bone marrow sparing (BMS) techniques. Dose constraints are important to minimize the occurrence of HT 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 BM 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 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-V10, V20, and V40 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 ABM per se.

The effect of various dose delivery techniques on BMS has been investigated in multiple planning studies. The dose in the BM could be significantly reduced without increasing the dose in the bladder, rectum, and bowels 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 IMPT plans were designed to spare ABM, identified on 18F-fluorothymidine (FLT) PET, 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 BM 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 BM 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 BM 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. FLT-PET can identify and spare ABM in patients with pelvic cancer. FLT detects chronic suppression of BM by correlating FLT uptake to complete blood cell counts. IMRT plans sparing the FLT-identified pelvic BM significantly reduced the dose to the pelvic BM [12]. Additionally, fat fraction imaging can be utilized to measure BM composition changes during chemoradiation treatment in patients [46,47]. With water-fat imaging methods, fat fraction maps can be acquired. The fat fraction in BM 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]. The 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 BM 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 BM in patients with LACC 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 within 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 HT after treatment of LACC are lacking.

Additionally, studies reported contradicting results on dosimetric parameters correlated with HT. Some articles defining BM 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 BM and HT [14,36,39]. The inability to detect associations might be due to a lack of low-dose regions targeting the sensitive BM resulting from characteristics of the patient cohort, radiation therapy technique used, or proximity of the BM to the target volume. For instance, lumbar and pelvic BM receives high doses in the irradiation of patients with PALN [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 BM dose [30].

This systematic review is the first literature review providing an overview of articles evaluating the correlation between irradiation of the bone marrow 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 HT was observed for whole pelvic bone doses of V10 > 95–75%, V20 > 80–65%, and V40 > 37–28%. Only a limited number of studies have investigated the relationship between bone marrow dose and HT in patients with LACC 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.

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Conflicts of interest

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Appendix A. Supplementary data

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