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Comparative dosimetric and clinical evaluation of bone marrow sparing IMRT (BM-IMRT) versus without bone marrow sparing IMRT (WBM-IMRT) in pelvic radiotherapy for cervical cancer

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Abstract

Background: Acute hematologic toxicity (HT) during concurrent chemoradiotherapy (CCRT) for cervical cancer is strongly associated with pelvic bone marrow (PBM) irradiation. While prior randomised and multicenter studies have evaluated PBM sparing, limited prospective data exist in homogeneous cohorts assessing dosimetric, clinical and treatment compliance outcomes.

Methods: In this prospective study conducted at a single tertiary center, 50 women with International Federation of Gynecology and Obstetrics stage IB2–IVA cervical cancer (locally advanced: *n* =33, 66%; early stage: *n* =17, 34%) undergoing definitive pelvic CCRT were assigned to bone marrow–sparing intensity-modulated radiation therapy (BM-IMRT, *n* = 25) or without bone marrow-sparing IMRT (*n* = 25). All patients received 50 Gy in 25 fractions with weekly cisplatin, followed by brachytherapy. PBM was delineated as the pelvic bones and proximal femur. Primary endpoints included PBM dose-volume parameters (V_{10}–V_{50}, mean dose), and secondary endpoints included acute HT (Common Terminology Criteria for Adverse Events v5.0), Gastrointestinal (GI)/Genitourinary (GU) toxicity, chemotherapy delivery and target coverage.

Results: BM-IMRT achieved significant reductions in PBM dose, including V_{20} (77.2% versus 83.4%, p = 0.03) and mean dose (31.2 versus 35.9 Gy, p = 0.01), with comparable target coverage and organ at risk doses. Clinically, BM-IMRT was associated with significantly fewer ≥grade 2 HTs (**0**% versus **20**%, p < **0.05**), driven by reductions in leukopenia and anemia (0% versus 20% each) and fewer chemotherapy interruptions. No significant differences were observed in GI or GU toxicity (p > 0.05).

Conclusion: Incorporation of explicit PBM constraints in pelvic IMRT for cervical cancer reduces marrow dose and acute HT without compromising target coverage or increasing GI/GU toxicity. These findings suggest that PBM-based planning objectives may improve treatment adherence; however, further validation in larger studies is required before routine clinical implementation.

Keywords: *cervical cancer, bone marrow sparing, IMRT, hematologic toxicity, chemoradiotherapy, dosimetry*

Research

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Introduction

Cervical cancer remains a leading cause of cancer morbidity and mortality globally, with chemoradiotherapy (CRT) the standard of care for locally advanced disease due to a survival advantage over radiotherapy (RT) alone [1–3]. However, CRT increases acute hematologic toxicity (HT), leading to treatment delays, chemotherapy dose omissions and potential compromise of outcomes. More than half of adult active bone marrow resides within the pelvis and lower lumbar vertebrae volumes commonly encompassed by pelvic fields, making pelvic bone marrow (PBM) a critical organ at risk (OAR) [4–7].

Intensity-modulated radiation therapy (IMRT) reduces dose to normal tissues compared with 3D-CRT and enables dedicated PBM-sparing optimisation [8–12]. Both earlier and more recent prospective and multicenter studies have consistently linked intermediate PBM dose-volume metrics (e.g., V_{10}, V_{20}, V_{30} and V_{40}) with acute HT and demonstrated clinically meaningful benefit from PBM-sparing strategies [9–12]. Recent prospective, dosimetric and clinical studies further support that reduction in PBM dose–volume parameters is associated with decreased HT and improved treatment tolerance [13, 14]. In addition, advances in modern planning techniques, including volumetric modulated arc therapy (VMAT)/RapidArc-based approaches, have further improved dose conformity and OAR sparing while maintaining target coverage [15].

However, randomised and institutional experiences remain somewhat heterogeneous partly due to differences in PBM delineation (whole-bone versus functional FLT-PET), variation in planning objectives and differences in patient populations (definitive versus adjuvant) [16, 17]. Despite growing interest in bone marrow–sparing RT, clinical outcomes across studies continue to show variability. While earlier reports highlighted these inconsistencies, recent systematic reviews and meta-analyses demonstrate that PBM-sparing approaches significantly reduce HT and chemotherapy interruptions, yet heterogeneity in methodology and clinical outcomes persists. This variability is largely driven by differences in bone marrow delineation (total bone marrow versus functionally active marrow), contouring techniques and optimisation strategies, with no clear consensus on optimal dose constraints or delineation methods [18].

Furthermore, comparative and planning-based studies have demonstrated consistent reductions in PBM dose with bone marrow–sparing IMRT (BM-IMRT) compared with conventional techniques, supporting its dosimetric advantage but also highlighting variability in clinical translation. This variability is largely driven by differences in bone marrow delineation (total bone marrow versus functionally active marrow) and optimisation strategies.

This study provides a prospective, randomised comparison of BM-IMRT versus without bone marrow sparing IMRT (WBM-IMRT) in pelvic CRT for cervical cancer, evaluating comprehensive dosimetric endpoints and acute clinical outcomes with explicit reporting of sample size assumptions and methodology to facilitate reproducibility and planning standardisation. The primary endpoints included PBM dose volume parameters (V_{10}–V_{50} and mean dose). Secondary endpoints included acute HT Common Terminology Criteria for Adverse Events (CTCAE v5.0), gastrointestinal (GI) and genitourinary (GU) toxicity, chemotherapy delivery and target coverage metrics.

Methods

Study design and setting

This was a prospective, single-center, randomised controlled study conducted at a tertiary cancer care center in women undergoing pelvic CRT for cervical cancer (2018–2021). The protocol adhered to the Declaration of Helsinki and received institutional ethics approval; written informed consent was obtained.

Eligibility

Inclusion criteria: histologically confirmed cervical carcinoma (squamous, adeno or adenosquamous), International Federation of Gynecology and Obstetrics 2018 stage IB2–IVA planned for definitive pelvic CRT, age ≥18 years, ECOG 0–2, adequate organ function and no prior pelvic RT or systemic therapy. Exclusion criteria: para-aortic field indication, distant metastasis, pregnancy, uncontrolled comorbidities (e.g.,

uncontrolled hypertension, diabetes mellitus, active cardiac disease or ongoing infection requiring treatment), prior malignancies (except non-melanoma skin cancer), collagen vascular diseases or contraindications to cisplatin.

Randomisation and masking

Eligible patients were randomised in a 1:1 ratio to BM-IMRT (experimental) or WBM-IMRT (control) using a computer-generated permuted block randomisation sequence with concealed allocation. A fixed block size of four was used to maintain balanced treatment allocation between study arms. No stratification factors were applied during randomisation because of the single-center design and relatively homogeneous study population. Medical physicists involved in treatment planning were not blinded because of the PBM sparing objectives; however, radiation oncologists involved in patient management and toxicity assessors were blinded to treatment assignment.

Simulation and contouring

The patients were standardised bladder filling (approximately 400–500 ml) and rectal emptying protocols were used at simulation and treatment. The computed tomography (CT) simulation was done in supine position, with immobilisation, intravenous contrast as per institutional protocol and 3–5 mm slice thickness from L3 to 5 cm below the ischial tuberosities. The target volumes viz. clinical target volumes and planning target volume (PTVs) were defined per consensus guidelines for definitive cervix RT, including gross disease, uterus (if present), parametria, upper vagina and pelvic nodal basins (common, external, internal iliac, obturator and presacral) with appropriate margins; PTV created with 5–7 mm anisotropic expansions considering setup and motion. OARs like small bowel (bowel bag), bladder, rectum, femoral heads and spinal canal delineated per consensus atlases. For Bone marrow, PBM contoured using the whole-bone technique encompassing ilium, ischium, pubis, sacrum, coccyx, L5 body (± L4 if included) and proximal femora to lesser trochanters, as a validated surrogate for active marrow when functional imaging is unavailable (Figure 1). To minimise interobserver variability, contouring was performed according to consensus guidelines and independently reviewed by an experienced radiation oncologist.

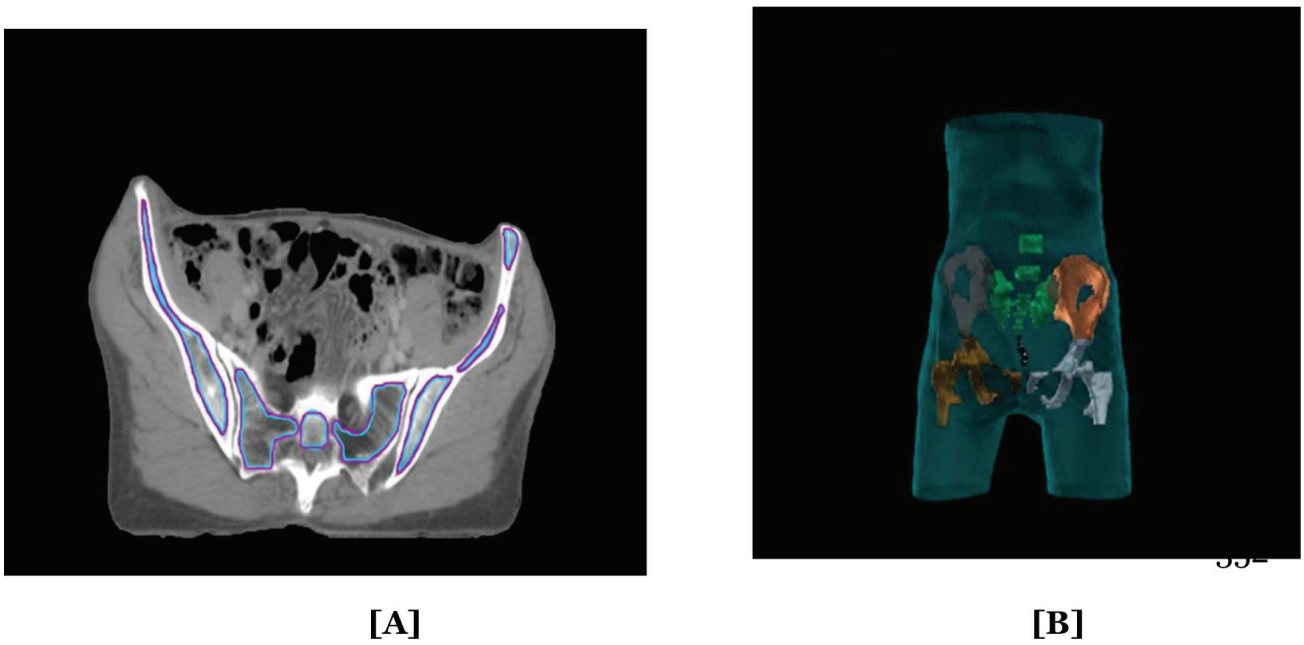

Figure 1. Representative images demonstrating PBM contouring. (a): CT slice showing PBM delineation. (b): Three-dimensional volumetric rendering.

Treatment planning

The prescription dose was 50 Gy in 25 fractions (2 Gy/fraction, 5 fractions/week) to the pelvis using 6 MV photons with seven beams coplanar IMRT/VMAT per institutional practice, followed by high-dose-rate brachytherapy per disease extent. The PTV coverage prioritised in both arms with goal: $V_{95\%} \geq 95\%$ and $D_{max} \leq 107\%$. OAR constraints (BM and WBM): small bowel $V_{45} < 195$ cc; rectum $V_{50} < 50\%$; bladder $V_{50} < 50\%$; femoral heads $D_{max} \leq 50$ Gy, with effort to reduce spinal canal per tolerance. PBM constraints (BM-IMRT only): planning objectives targeted PBM $V_{10} \leq 90\%–95\%$, $V_{20} \leq 75\%–90\%$, $V_{30} \leq \sim 60\%$, $V_{40} \leq 35\%–45\%$ and minimised mean PBM dose, reflecting dose–toxicity modeling and prospective trials, while preserving target/OAR priorities [9–11, 13, 19–21]. WBM-IMRT: no explicit PBM objectives were used; PBM dose recorded for analysis. The plan evaluation was done with the help of dose-volume histograms and assessed PTV metrics (V_{95}, D_{98}, D_2, homogeneity index [HI = D_2-D_{98}/D_{50}] as per ICRU-83, conformity index [CI = V_{95}/PTV]), OAR constraints and PBM endpoints (V_{10}, V_{20}, V_{30}, V_{40}, V_{50} and mean dose).

Chemotherapy and image guidance

Concurrent cisplatin 35–40 mg/m^2 weekly was administered on days 1, 8, 15, 22, 29 and 36 as tolerated [1–3, 14]. Daily Image Guided Radiation therapy with kV imaging and weekly cone-beam CT verified setup and organ filling.

Toxicity assessment

Acute toxicities were graded according to the CTCAE, v5.0. Hematologic parameters (hemoglobin, total leukocyte count, absolute neutrophil count and platelet count) were assessed at baseline and monitored weekly during concurrent chemoradiation. The highest grade of toxicity observed during treatment was recorded for analysis. GI and GU toxicities were similarly assessed weekly and graded as per CTCAE criteria. The sample size was calculated based on an expected ~6%–8% difference in PBM V_{20} (or a 20% difference in grade ≥2 HT) between groups, with a two-sided $\alpha = 0.05$ and 80% power.

Statistical analysis

The statistical study was carried out using the R project statistical programme. Given the parallel-group study design, independent-samples *t*-tests were used to compare differences between groups and the Mann–Whitney *U* test was used for toxicity data; if the *p*-value was <0.05, the difference was considered statistically significant.

Results

Planning target volume

All treatment plans achieved excellent target coverage. The mean PTV V_{95} exceeded 95% in both groups, i.e., BM and WBM plans, with no significant differences in dosimetric indices between BM-IMRT and WBM-IMRT (Table 1). For example, PTV D_{max} was 54.14 ± 0.77 Gy versus 53.61 ± 1.47 Gy ($p = 0.30$) and PTV D_{min} was 40.89 ± 3.17 Gy versus 41.26 ± 4.28 Gy ($p = 0.82$). Mean PTV dose (≈50.3 Gy in both arms) and homogeneity index (HI ≈0.07–0.08) were also statistically equivalent ($p = 0.87$ and $p = 0.70$, respectively). Likewise, conformity index (CI ≈0.72 versus 0.77) showed no significant difference ($p = 0.78$). In summary, explicit bone-marrow constraints did not compromise PTV coverage or dose homogeneity; all plans met standard coverage goals ($V_{95}\% \geq 95\%$, $D_{max} \leq 107\%$) and institutional limits. OAR constraints for small bowel, bladder, rectum and femoral heads were satisfied in both arms.

Table 1. Dosimetric indices for BM-IMRT and WBM-IMRT.

Parameters		BM	WBM	*p*-value
		Mean ± SD		
PTV	D_{max}	54.14 ±0.77	53.61± 1.47	0.301
	D_{min}	40.89 ± 3.17	41.26 ± 4.28	0.820
	D_{mean}	50.34 ± 0.36	50.25± 1.69	0.868
	Homogeneity Index (HI)	0.07 ± 0.02	0.08 ± 0.01	0.701
	Conformity Index (CI)	0.72 ± 0.12	0.77 ± 0.08	0.784
LS	D_{mean}	31.22 ± 3.75	35.89 ± 4.05	**0.010**
	V_{10}	87.54 ± 16.38	92.93 ± 6.98	0.326
	V_{20}	77.22 ± 9.71	83.40 ± 15.22	**0.030**
	V_{30}	60.61 ± 11.55	68.26 ± 17.98	0.248
Pelvic	D_{mean}	29.46 ± 2.66	30.61 ± 2.22	0.283
	V_{10}	97.41 ± 2.30	97.85 ± 2.60	0.675
	V_{20}	80.12 ± 9.46	85.54 ± 6.78	0.137
	V_{30}	45.24 ± 10.11	46.36 ± 8.59	0.782
Bladder	D_{max}	53.27 ± 0.65	53.91 ± 2.40	0.402
	V_{50}	25.05 ± 11.81	25.73 ± 13.76	0.903
	V_{45}	47.48 ± 14.35	40.26 ± 16.63	0.287
Rectum	D_{max}	52.89 ± 0.72	49.98± 8.23	0.254
	V_{50}	24.24 ± 14.10	24.87 ± 15.67	0.922
	V_{45}	62.41 ± 23.51	54.93 ± 24.28	0.471
Femoral head(left)	D_{max}	45.00 ±6.77	45.25 ± 6.39	0.910
	V_{50}	0.04 ± 0.07	1.45 ± 4.69	0.330
	V_{40}	3.79 ± 6.03	3.55 ± 4.96	0.917
Femoral head(right)	D_{max}	46.25 ± 5.75	45.90 ± 5.69	0.887
	V_{50}	0.03 ± 0.06	1.47 ± 4.77	0.327
	V_{40}	4.08 ± 6.31	3.90 ± 5.50	0.944

SD: Standard deviation; BM-IMRT: Bone Marrow Sparing IMRT; WBM-IMRT: Without Bone Marrow Sparing IMRT; D_{max}: Maximum dose; D_{min}: Minimum dose; D_{mean}: Mean dose; V_x is the volume receiving x% of the prescribed dose; D_x% is dose received by x% of volume; LS: Lumbosacral

Bone marrow dose-volume parameters

Bone marrow dose was substantially reduced with BM-IMRT. The mean dose to the lumbosacral (LS) spine (part of PBM) was significantly lower in the BM-IMRT arm (31.22 ± 3.75 Gy) than in the WBM-IMRT arm (35.89 ± 4.05 Gy, $p = 0.01$). Correspondingly, the percentage of LS marrow receiving ≥20 Gy (V_{20}) was reduced (77.2% versus 83.4%, $p = 0.03$). Lower-dose volumes showed similar trends: LS V_{10} was 87.5% versus 92.9% ($p = 0.33$) and V_{30} was 60.6% versus 68.3% ($p = 0.25$). Figure 2 that dose differences between without bone marrow sparing (WB) and BM are more pronounced in the LS region. In the pelvic bones (ilium/acetabulum), mean dose differences were not statistically

significant (29.46 ± 2.66 Gy versus 30.61 ± 2.22 Gy, $p = 0.28$). Pelvic bone V_{10} (97.41% versus 97.85%, $p = 0.67$) and V_{20} (80.12% versus 85.54%, $p = 0.14$) also trended lower with BM-IMRT, though these did not reach formal significance. Overall, all assessed PBM dose–volume metrics (mean dose and V_{10}–V_{40}) were lower in the BM-IMRT group, with the largest absolute reduction in V_{20} (~6%–8% absolute difference) as anticipated. Figure 3 shows that the PBM (B), dose–volume parameters between WB and BM were largely comparable, with no statistically significant differences, although WB tended to show slightly higher values at lower dose levels (e.g., V_{20}, $p = 0.137$).

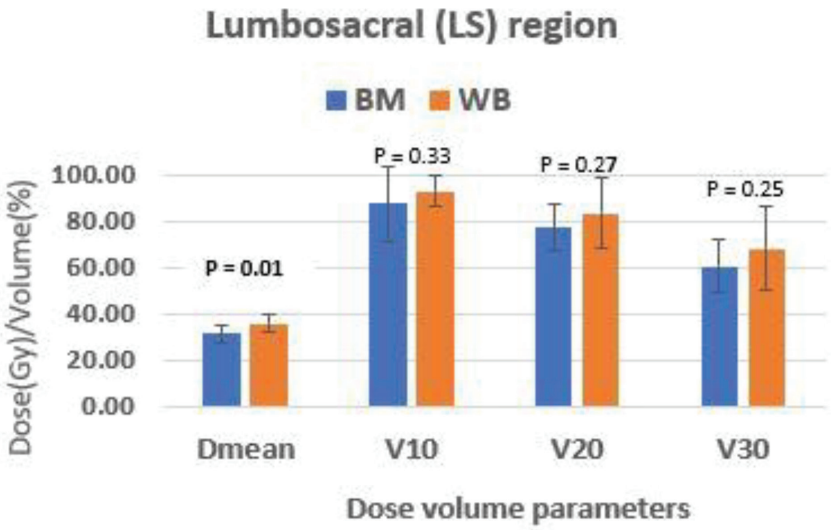

Figure 2. Comparison of dose–volume parameters for LS region.

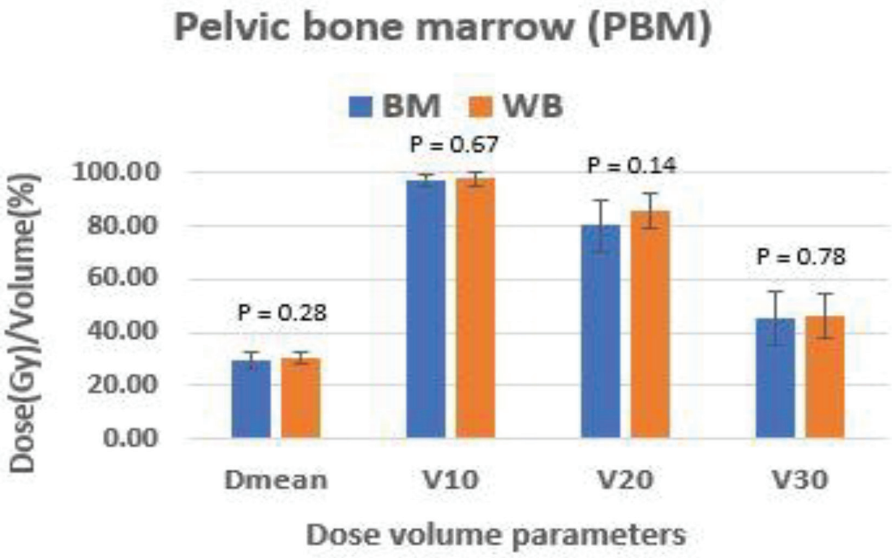

Figure 3. Comparison of dose–volume parameters for PBM.

OAR doses

Doses to pelvic OARs were comparable between arms. For the bladder, D_{max} was 53.27 ± 0.65 Gy versus 53.91 ± 2.40 Gy (p = 0.40) and bladder V_{50} was similar (25.05% versus 25.73%, p = 0.90). Rectal D_{max} (52.89 ± 0.72 versus 49.98 ± 8.23 Gy, p = 0.25) and rectal V_{45} (62.4% versus 54.9%, p = 0.47) showed no significant differences. Both femoral heads met constraints without disparity: left femur D_{max} ~45.0 Gy (p = 0.91) and right femur D_{max} ~46.3 versus 45.9 Gy (p = 0.89). The volumes of femoral heads receiving ≥40–50 Gy were minimal in both arms (all p > 0.3). Thus, integration of PBM objectives did not lead to unintended OAR dose increases; all other OAR metrics remained clinically equivalent.

Clinical toxicity outcomes

HT: Incorporation of PBM constraints significantly reduced acute HT. Grade ≥2 toxicity occurred in 5/25 patients (20%) in the WBM-IMRT group versus 0/25 (0%) in the BM-IMRT group (absolute reduction 20%, p < 0.05) (Table 2). This reduction was driven by leukopenia and anemia, each observed in 5/25 patients (20%) in the WBM-IMRT arm and none in the BM-IMRT arm, with no grade ≥2 thrombocytopenia in either group. Lower-grade toxicities were also reduced, with more patients maintaining grade 0 counts (leukopenia: 84% versus 44%) and fewer requiring chemotherapy interruptions. Patients treated with WBM-IMRT experienced a higher incidence of grade ≥2 HT compared with those treated with BM-IMRT.

GI and GU toxicity: Acute lower GI (e.g., diarrhea) and GU (e.g., cystitis) toxicities were similar between groups. There were no significant differences in the incidence of grade ≥2 GI or GU events (p > 0.05), consistent with preserved small bowel and bladder dosimetry.

Chemotherapy delivery: Patients in the BM-IMRT arm completed a higher proportion of planned chemotherapy. A greater fraction of BM-IMRT patients received all planned weekly cisplatin cycles without delays, and RT was completed on schedule (≤56 days) more often than in the WBM-IMRT group. These treatment-delivery improvements align with the reduced hematologic burden.

Table 2. Acute HT at 6 weeks (CTCAE-based, *n* = 25 per arm).

Toxicity	Grade	WBM-IMRT (*n* = 25, *n*%)	BM-IMRT (*n* = 25, *n*%)
Anaemia	0	9 (36%)	11 (44%)
	1	11 (44%)	14 (56%)
	≥2	5 (20%)	0 (0%)
Leukopenia	0	11 (44%)	21 (84%)
	1	9 (36%)	4 (16%)
	≥2	5 (20%)	0 (0%)
Thrombocytopenia	0	19 (76%)	24 (96%)
	1	6 (24%)	1 (4%)
	≥2	0 (0%)	0 (0%)

Abbreviations: IMRT = intensity-modulated radiotherapy; PBM = pelvic bone marrow

Discussion

This study demonstrates that incorporating explicit PBM constraints into IMRT planning is associated with reduced marrow irradiation (particularly V_{10}–V_{40}, most notably V_{20}) and a lower incidence of acute HT, without compromising target coverage or other OAR doses. Patients treated with BM-IMRT were also more likely to complete planned chemotherapy on schedule, suggesting a clinically meaningful benefit.

These findings are consistent with and extend prior evidence linking pelvic marrow dose to blood count nadirs. Several prospective studies (e.g., Mell *et al* [9] INTERTECC-2) have reported that IMRT with marrow avoidance lowers high-grade HT [9]. In a large single-center randomized controlled trial Huang *et al* [21] found that PBM-sparing IMRT reduced grade ≥2 HT from 69.5% to 50.0% (p = 0.02), which is comparable in magnitude to the benefit observed in our cohort. Importantly, we did not observe an increase in GI or GU toxicities, supporting prior observations that PBM sparing does not compromise other OAR constraints when appropriately planned.

From a dose-response perspective, our results align with established threshold-based analyses. Multiple studies have identified dose thresholds predictive of HT (e.g., pelvic V_{10}–V_{20} and V_{30}–V_{40}). The systematic review by Konnerth *et al* [22] summarised that pelvic marrow V_{10} <90%–95% and V_{20} <65%–86% are desirable to mitigate toxicity. In our study, BM-IMRT plans roughly met these targets (e.g., pelvic V_{20} ≈80%), whereas WBM-IMRT plans often exceeded them. Consistent with the literature, we found that patients whose PBM V_{20}–V_{40} exceeded about 75%–80% had higher odds of grade ≥2 HT, reinforcing dose constraints in this range. Our whole-bone PBM contouring aligns with practical recommendations: although functional imaging (FLT-PET) can further focus sparing to active marrow regions, whole-bone contours have been shown to correlate well with HT risk and are widely used in clinical trials.

These observations are further supported by modeling studies. Albuquerque *et al* [10] demonstrated that each 10% increase in pelvic V_{20} significantly raised the risk of grade ≥3 HT. Similarly, Rose *et al* [13] and others proposed normal tissue complication probability models incorporating mean PBM dose and Vx thresholds to predict HT. The reduction in mean PBM dose (~4–5 Gy) and V_{20} (~6%) in our BM-IMRT cohort likely corresponds to a clinically relevant shift along these dose–response curves, providing a plausible explanation for the observed reduction in toxicity.

In contrast to some smaller studies reporting modest or negligible benefits, our study demonstrated a more pronounced dosimetric and clinical effect. This may be attributable to the prospective application of explicit and quantifiable PBM constraints, ensuring consistent marrow sparing across patients. Such an approach may be particularly important in patients with limited marrow reserve (e.g., lower BMI or baseline cytopenias), where HT is more likely to be dose-limiting [23, 24].

This was a single-center trial with a modest sample size, which may limit the statistical power and generalisability of the findings. We focused on acute toxicities; longer-term marrow recovery, late hematopoietic effects and survival outcomes remain to be evaluated. We also did not use functional marrow imaging, so our contouring may include some inactive bone; PET-based sparing might further improve outcomes but is not yet routine. Finally, while our planning objectives were derived from prior data, the optimal PBM constraints (exact Vx cutoffs) require refinement in larger studies.

Our findings support incorporating PBM objectives (e.g., aim for PBM $V_{20}\lesssim$75%–80%, $V_{40}\lesssim$35%–40%) into routine cervical cancer IMRT planning. Future research should test adaptive strategies (replanning if weekly counts fall) and directly compare whole-bone versus functional marrow sparing. International efforts to harmonise marrow contouring and dose constraints (akin to consensus OAR atlases) would facilitate wider adoption. Ultimately, prospective trials with clinical endpoints (progression-free survival, quality of life) are needed to confirm that reducing HT via IMRT translates into long-term benefit.

Conclusion

In pelvic chemoradiation for cervical cancer, BM-IMRT with explicit PBM constraints was associated with reduced marrow dose–volume parameters and lower acute HT, without compromising PTV coverage or increasing GI/GU toxicity. These findings may support improved

adherence to chemotherapy schedules. The present results support the potential utility of PBM-based planning objectives; however, further validation in larger studies is required before routine clinical implementation.

Conflicts of interest

The authors state that they have no conflicting interests in this manuscript.

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