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Reducing acute haematological toxicity in cervical cancer: a comparative study of bone marrow-sparing VMAT and 3DCRT

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Abstract

Background: Concurrent chemoradiotherapy (CCRT) is the standard of care in locally advanced cervical carcinoma, but due to irradiation of pelvic bone marrow (BM), it is associated with dose-limiting haematological toxicity (HT). Advanced radiotherapy (RT) techniques such as bone marrow-sparing volumetric modulated arc therapy (BMS-VMAT) may reduce BM dose and hence decrease treatment-related toxicities.

Aims and objectives: To compare dosimetric parameters and HTs between BMS-VMAT and three-dimensional conformal radiotherapy (3DCRT) in cervical cancer patients undergoing CCRT.

Methods: This retrospective single-institutional study included 60 patients (30 each in BMS-VMAT and 3DCRT arms), who had received external beam radiotherapy with a dose of 50 gray (Gy) in 25 fractions with concurrent weekly cisplatin 40 mg/m^2. BM was contoured anatomically and dosimetric parameters BM D_{mean}, V10, V20, V30, V40 and D_{max} were analysed. HTs were recorded weekly using CTCAE v5.0 criteria. Statistical analysis was performed using independent *t*-test, Mann–Whitney *U* test and chi-square test, *p*-value ≤0.05 was considered significant.

Results: BMS-VMAT significantly reduced BM D_{mean} (26.73 versus 36.09 Gy, $p < 0.001$); D_{max} (51.96 versus 52.72 Gy, $p = 0.004$); V30 (36.25% versus 56.69%, $p < 0.001$) and V40 (17.37% versus 44.39%, $p < 0.001$) in comparison to 3DCRT. V10 and V20 were not significantly different. Planning target volume coverage was comparable in both arms. Grade ≥2 anaemia (26% versus 53%, $p = 0.035$), leukopenia (16.7% versus 46.7%, $p = 0.025$) and neutropenia (16.7% versus 40%, $p = 0.008$) were significantly lower in the BMS-VMAT arm.

Conclusion: BMS-VMAT reduces clinically relevant dose parameters and HTs without compromising target coverage, supporting its role in cervical cancer radiotherapy.

Keywords: *bone marrow-sparing VMAT, 3DCRT, cervical cancer, haematological toxicities, VMAT, concurrent chemoradiotherapy*

Introduction

Cervical cancer is one of the leading causes of cancer-related morbidity and mortality among women worldwide. According to GLOBOCAN 2022 estimates, it accounts for over 662,301 new cases and more than 348,000 deaths annually, with major occurrences in low- and middle-income countries, especially Southeast Asia [1]. Concurrent

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chemoradiotherapy (CCRT), which is established as the standard of care, significantly improves overall survival and locoregional control in comparison to radiotherapy (RT) alone [2,3]. However, it substantially increases treatment-related toxicities, particularly acute haematological toxicity (HT), gastrointestinal and genitourinary toxicities, resulting in chemotherapy dose reductions and treatment interruptions, potentially compromising clinical outcomes [4–11]. The tumour proximity to organs at risk (OAR) contributes to this toxicity profile [12].

The pelvic bone marrow (BM) comprises approximately 40%–50% of total active haematopoietic marrow in adults and is highly radiosensitive [13, 14]. During external beam radiation, a significant proportion of active BM is exposed to low- and intermediate-dose radiation, leading to myelosuppression presenting as leukopenia, neutropenia, anaemia and thrombocytopenia. Dosimetric parameters such as V10, V20, V30 and mean BM dose correlate significantly with grade ≥2 HTs in patients receiving CCRT [15, 16].

Three-dimensional conformal radiation therapy (3DCRT) has long been utilised for pelvic irradiation in cervical cancer but has limited ability to spare surrounding normal tissues, including BM. In contrast, volumetric modulated arc therapy (VMAT) provides highly conformal dose distribution via continuous gantry rotation and intensity modulation, improving OAR sparing without compromising coverage of the planning target volume (PTV) [17, 22].

Various studies have evaluated the efficiency of bone marrow-sparing IMRT (BMS-IMRT) and bone marrow-sparing volumetric modulated arc therapy (BMS-VMAT) planning strategies in reducing radiation dose to active pelvic BM compartments. Incorporating BM dose constraints during IMRT planning is associated with reduced rates of acute grade ≥2 leukopenia and neutropenia [16, 17]. Nevertheless, the extent of dosimetric advantages of BMS-VMAT translating into clinically meaningful reductions in HT in comparison to conventional 3DCRT remains an area of ongoing research. Furthermore, the relationship between specific BM dose–volume parameters and acute haematological outcomes requires further validation in different clinical settings. In this context, this study was conducted to evaluate the dosimetric and clinical impact of BMS-VMAT compared to 3DCRT in patients with carcinoma cervix undergoing CCRT. By analysing bone marrow dose parameters alongside haematological outcomes, this study aims to assess whether dosimetric advantages result in a meaningful reduction in treatment-related toxicities, thereby improving treatment tolerability and compliance while maintaining oncologic efficacy.

Materials and methods

This is a retrospective single-centre study conducted in a tertiary care hospital in North India. It was approved by the institutional ethics committee. Requirement for informed consent was waived due to the retrospective nature of the study. The patients with biopsy-proven squamous cell carcinoma of the cervix from International Federation of Gynecology and Obstetrics stage IB to IV A, aged from 18 to 70 years and with a Karnofsky performance score >70%, were included in the study. Patients with a history of previous pelvic irradiation, surgery, metastatic disease and haematological derangement before starting treatment were excluded. In addition, patients with para-aortic lymph nodes or any contraindications to concurrent chemotherapy were excluded. The dosimetric parameters were recorded from the Eclipse treatment planning system (TPS) records and haematological parameters were obtained from the patient records treated in the Department of Radiation Oncology during the period from May 2023 to December 2025.

Intervention

The patients were planned for definitive treatment with external beam radiation therapy (EBRT) either with BMS-VMAT or 3DCRT, along with concurrent cisplatin 40 mg/m^2 for 5 weeks after assessment of renal profile, followed by high-dose rate brachytherapy. Patients were immobilised in the supine position using a four-point thermoplastic cast and knee–foot supports with arms overhead. Bladder protocol was followed as per the institutional protocol; patients were asked to urinate and then 300 mL of water was given 30 min before the scan. computed tomography (CT) simulation was performed with 3 mm slices from L1 to 5 cm below the ischial tuberosities. Intravenous contrast was administered as per the patient's body weight. This protocol was followed daily during treatment. Target volume delineation was done according to consensus guidelines. Gross tumour volume comprised the primary cervical tumour and gross nodes. Clinical target volume (CTV) involved the cervix, uterus, parametria, upper vagina and pelvic nodal basins, while the PTV was delineated by a 7 mm expansion of the CTV. OAR delineation was also done as per consensus guidelines [18]. Bladder, rectum, small bowel and femoral heads were contoured. BM was delineated as whole pelvic bones, lumbar spine and bilateral proximal femur contoured in the bone window.

Planning was done using box fields for 3DCRT patients with gantry angles of 0°, 90°, 180° and 270°, using 15 MV energy and prescription at the isocentre kept at the centre of the PTV. For the BMS-VMAT group, three arcs (i.e. 181°–179°, 179°–181°, 181°–179°) were used. All plans were generated on Eclipse TPS with 6 MV photons. The dose prescribed was 50 Gray (Gy) in 25 fractions. Dose constraints were given as per radiation therapy oncology group (RTOG) guidelines.

For bladder, V40 < 65% and for rectum, V40 < 55%; bowel V45 < 195 cc; femoral heads D_{mean} <45 Gy. For BM, dose constraints were BM: V10 < 90%, V20 < 75%, V30 < 50%, V40 < 45% and BM D_{mean} < 44 Gy [19–21]. Weekly cone beam CT scans were done in VMAT patients to ensure proper target coverage. The assessment of toxicities was done during EBRT as per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Patients were evaluated for acute HTs by performing complete blood count tests every week before concurrent chemotherapy cycles. Filgrastim (5 mcg /kg/day) was administered to patients with an absolute neutrophil count <1,000/ mm^3 until count recovery. Blood transfusions were given to patients with grade 3 anaemia.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences software (version 23.0, IBM Corp). Mean and standard deviation were estimates of quantitative data using the independent *t*-test and Mann–Whitney *U* test, as appropriate. Categorical variables were analysed using the chi-square test or Fisher's exact test. Differences in grades of HTs between the two techniques were evaluated using the Mann–Whitney *U* test. Grade ≥2 toxicities were correlated to techniques using the chi-square test. All reported *p*-values were two-sided and a *p*-value of ≤ 0.05 was considered significant.

Results

Sixty patients with histopathologically confirmed cervical cancer were included in the study, having received BMS-VMAT or 3DCRT (30 in each arm). The baseline characteristics of the patients in both arms are depicted in Table 1. All patients received EBRT with a dose of 50 Gy in 25 fractions, along with concurrent chemotherapy with Inj. cisplatin 40 mg/m^2 weekly. The median number of cycles was 5 (range 3–5) in both arms. Nineteen (63%) patients in the BMS-VMAT arm and 17 (56%) patients in the 3DCRT arm received five cycles of chemotherapy. The mean treatment duration in the BMS-VMAT arm was 53.1 days (range 48–60) and 53.4 days (range 49–62) in the 3DCRT arm.

Figure 1 shows the dose colour wash for BMS-VMAT and 3DCRT plans. The mean PTV volume was 974.22 cc (range 733–1,187.5) in the BMS-VMAT arm and 996.9 cc (733–1,187.5) in the 3DCRT arm, respectively. PTV coverage was comparable, with D_{mean} of 50.6–50.45 Gy in both arms.

BM dosimetric values showed statistically significant differences between the arms. Figure 2 shows differences in the dose volume histograms (DVH) of both techniques for the PTV and BM volumes. The D_{mean} was 26.73 Gy (22.50–30.3) for the BMS-VMAT arm and 36.09 Gy (31.9–50.8) for the 3DCRT arm (*p*-value < 0.001). Similarly, BM D_{max} was 51.96 Gy in BMS-VMAT arm and 52.72 Gy in 3DCRT arm, with statistically significant *p*-value of 0.004. BM V30 and BM V40 were 36.25% and 17.37% for the BMS-VMAT arm and 56.69% and 44.39% for the 3DCRT arm (*p*-value <0.001). BM V10 and V20 were 89.56% and 70.9% for BMS-VMAT and 91.35% and 72.97% for the 3DCRT arm (*p*-value of 0.121 and 0.251) (Table 2).

The baseline blood counts were comparable in both arms (Table 1). Higher HTs were observed in patients treated with 3DCRT compared to those with BMS-VMAT. The difference was statistically significant between the two arms concerning the highest grade of leukopenia and neutropenia (*p*-value = 0.039 and 0.001). The difference between the highest grade of anaemia between the two groups was not statistically significant (*p*-value = 0.17); however, grade 3 anaemia was seen in 6.6% of patients in the BMS-VMAT arm versus 10% in the 3DCRT arm. Grade 2 leukopenia was observed in 16.7% of patients in the BMS-VMAT arm versus 36.6% in the 3DCRT arm. Similarly, grade 2 neutropenia was present in 13.3% in the BMS-VMAT arm versus 36.6% in the 3DCRT arm. However, no significant difference was found in terms of thrombocytopenia (Table 3).

Table 1. Baseline characteristics of patients included in the study.

Characteristics	BMS-VMAT	3DCRT	*p* value
Age (years), median, (range)	54.5 (37–68)	50.5 (38–67)	0.528
Comorbidities			
Diabetes	10 (33.3%)	10 (33.3%)	0.702
Hypertension	11 (36.7%)	11 (36.7%)	
Both	3 (10%)	2 (6.7%)	
Others	1 (3.3%)	1 (3.3%)	
None	5 (16.7%)	6 (20%)	
Stage, *n* (%)			
Stage 1	0	0	0.64
Stage 2	9 (30%)	12 (40%)	
Stage 3	17 (53.7%)	13 (43.3%)	
Stage 4	4 (13.3%)	5 (16.7%)	
Addiction history, *n* (%)			
Tobacco	13 (43.3%)	11 (36.7%)	0.605
None	17 (56.7%)	19 (63.3%)	
Treatment duration (days)	53.1 (48–60)	53.4 (49–62)	0.684
Cisplatin dose (mg)	47.3	47.3	1
No. of cisplatin cycles			
3 (*n*)	2	3	0.55
4 (*n*)	9	10	
5 (*n*)	19	17	
EBRT			
Dose (Gy)	50	50	
Fractions, median	25	25	
Baseline blood counts			
Haemoglobin (g/dL)	11.4 (9.3–13.9)	11.6 (9.3–13.5)	0.716
WBC (×10^9/L)	9.1 (6.4–13.0)	8.3 (5.2–12.0)	0.10
ANC (×10^9/L)	4.5 (2.5–9.0)	4.0 (2.2–9.6)	0.403
Platelet count (×10^9/L)	1.86 (0.9–2.9)	1.76 (1.1–3.0)	0.24

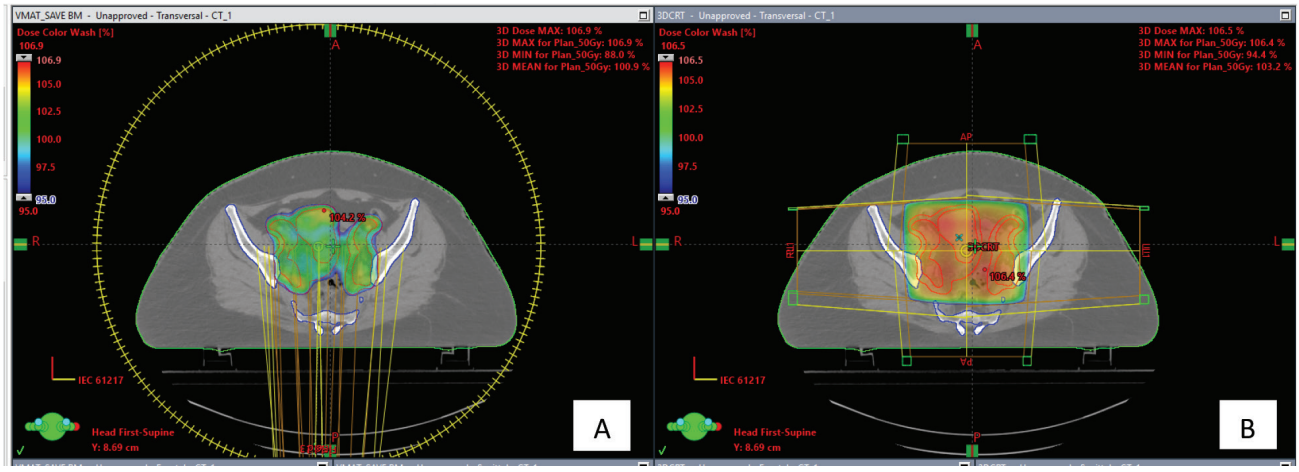

Figure 1. Colour wash for VMAT (a) and 3DCRT (b).

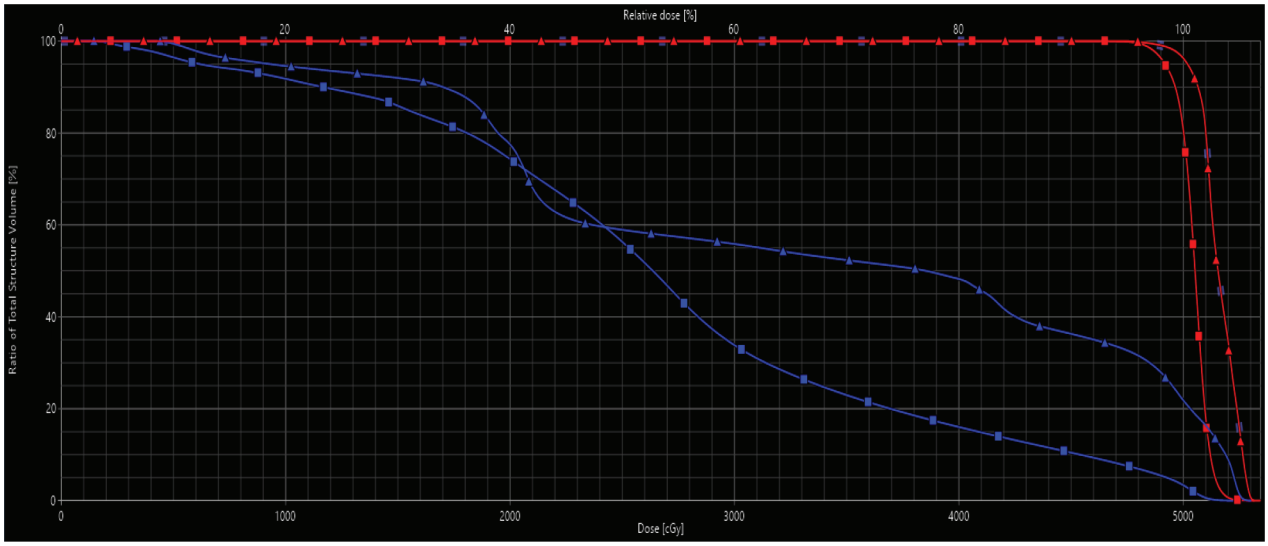

Figure 2. DVH for PTV (red) and BM (blue); triangle indicates 3DCRT, while square represents BMS-VMAT.

Table 2. Dosimetric profile (BM and target) of patients receiving BMS-VMAT versus 3DCRT.

OAR	Mean BMS-VMAT (range)	Mean 3DCRT (range)	*p* value
BM			
V10 (%)	89.56 (80.3–98.30)	91.35 (81.7–97.3)	0.121
V20 (%)	70.90 (62.80–81.50)	72.97 (62.1–93.0)	0.251
V30 (%)	36.25 (28.3–46.4)	56.69 (47.0–62.3)	**<0.001**
V 40 (%)	17.37 (10.6–26.20)	44.39 (24.7–50.3)	**<0.001**
D_{max} (Gy)	51.98 (47.8–53.06)	52.72 (52.01–54.2)	**0.004**
D_{mean} (Gy)	26.73 (22.50–30.3)	36.09 (31.9–50.8)	**<0.001**
PTV			
PTV volume (cc)	974.22 (733–1,187.5)	996.90 (733–1,187.5)	0.584
PTV D_{max} (Gy)	52.94 (51.9–53.7)	53.05 (52.7–53.7)	0.251
PTV D_{min} (Gy)	42.56 (39.10–45.3)	42.02(39.10–44.30)	0.195
PTV D_{mean} (Gy)	50.21 (50.06–50.45)	50.22 (50.06–50.45)	0.842
PTV D50 (%)	50.35 (50.2–50.5)	50.35 (50.2–50.5)	0.889

The bold values indicate significant *p* values

Grade ≥2 anaemia was observed in 26% of patients in the BMS-VMAT arm and 53% of patients in the 3DCRT arm (*p*-value = 0.035). Grade ≥ 2 leukopenia and neutropenia were both 16.7% in the BMS-VMAT arm and 46.7% & 40% in the 3DCRT arm (*p*-value = 0.025 and 0.008). However, a similar pattern was seen for thrombocytopenia, although the values were not statistically significant ($p = 0.612$) (Table 4).

Table 3. Grades of HTs in BMS-VMAT versus 3DCRT arms.

Toxicity	BMS-VMAT	3DCRT	*p* value
Anaemia			
Grade 0	5 (16.7%)	5 (16.7%)	0.176
Grade 1	17 (56.7%)	9 (30%)	
Grade 2	6 (20%)	13 (43.3%)	
Grade 3	2 (6.7%)	3 (10%)	
Leukopenia			
Grade 0	5 (16.6%)	3 (10%)	**0.039**
Grade 1	20 (66.7%)	13 (43.3%)	
Grade 2	5 (16.7%)	13 (43.3%)	
Grade 3	0	1 (3.3%)	
Neutropenia			
Grade 0	16 (53.3%)	2 (6.7%)	**0.001**
Grade 1	9 (30 %)	16 (53.3%)	
Grade 2	4 (13.3%)	11 (36.6%)	
Grade 3	1 (3.3%)	1 (3.3%)	
Thrombocytopenia			
Grade 0	19 (63.3%)	21 (70%)	1
Grade 1	10 (33.3%)	6 (20%)	
Grade 2	1 (3.33%)	3 (10%)	
Grade 3	0	0	

The bold values indicate significant *p* values

Table 4. Comparison of grade ≥2 HTs between patients receiving BMS-VMAT and 3DCRT.

HTs	BMS-VMAT	3DCRT	*p* value
Anaemia			
Grade <2	22 (73%)	14 (46%)	**0.035**
Grade ≥ 2	8 (26.6%)	16 (53%)	
Leukopenia			
Grade <2	25 (83.3%)	16 (53.3%)	**0.025**
Grade ≥ 2	5 (16.7%)	14 (46.7%)	
Neutropenia			
Grade <2	25 (83.3%)	18 (60%)	**0.008**
Grade ≥ 2	5 (16.7%)	12 (40%)	
Thrombocytopenia			
Grade <2	29 (96.7%)	27 (90%)	0.612
Grade ≥ 2	1 (3.3%)	3 (10%)	

The bold values indicate significant *p* values

Discussion

Improved tumour control is obtained by using combined therapeutic strategies, i.e. combining chemotherapy and RT; however, concomitant treatment increases toxicity. A key dose-limiting side effect is BM suppression. Adult BM incorporates red BM, which is haematopoietically active and inactive yellow marrow [17]. As revealed by magnetic resonance imaging, positron emission tomography (PET) and single photon

emission CT, red BM is concentrated in specific sub-regions of the pelvis, such as the vertebrae and ilium [12, 23, 24]. Radiation exposure depletes haematopoietic stem and progenitor cells, suppressing circulating blood components. Leukocytes and neutrophils are most affected due to rapid turnover rates. Concurrent cisplatin-based chemotherapy further increases the incidence and severity of HT. Hence, minimising radiation dose to pelvic BM is important to preserve haematopoietic function and maintain treatment continuity. Studies evaluating acute HT of pelvic RT and concomitant cisplatin in cervical cancer patients are limited [6, 7, 13, 15, 25].

This study evaluated the advantage of BMS-VMAT over 3DCRT in reducing pelvic BM dose and its clinical impact on haematological parameters in patients receiving CCRT. BMS-VMAT significantly reduced pelvic BM dose parameters, resulting in a clinically meaningful reduction in HT in comparison to 3DCRT. This dosimetric advantage was accomplished without compromising target coverage, emphasising the therapeutic benefit of advanced RT techniques.

Mell *et al* [13] demonstrated the association between BM dose and HT, showing significant reduction in V5, V10, V20, V30 and V40 in comparison to the four-field box technique. The acute HT was also reduced with decreased grade 3–4 toxicity with decreased BM dose [13]. This landmark study laid the foundation for incorporating BM constraints in RT planning. Similarly, the RTOG 0418 trial demonstrated V30, V40 and BM D_{mean} as strong predictors of grade ≥ 2 toxicity [26]. Wang *et al* [27] demonstrated that BMS-IMRT significantly reduced V10, V20, V30 and V40 without affecting PTV coverage, augmenting the dosimetric supremacy of optimised planning strategies.

In our study, significant reductions in BM D_{mean}, V30 and V40 correlated with lower HT in the BMS-VMAT group. However, V10 and V20 showed no significant difference, endorsing the view that intermediate and high volumes may be more decisive factors influencing toxicity, consistent with Konnerth *et al* [28].

Our findings align with Kapoor *et al* [29] who demonstrated significantly reduced BM V20, V30 and V40 with IMRT in comparison to 3DCRT, resulting in reduced HT with a lower incidence of grade ≥2 leukopenia and neutropenia. They concluded that BMS-IMRT improves treatment tolerance without compromising PTV coverage [29]. Similarly, Erpolat *et al* [30] compared IMRT and 3DCRT and indicated that reduced irradiation to pelvic BM resulted in lower rates of HT in the IMRT group, and the INTERTECC-2 trial demonstrated that BMS-IMRT significantly reduced acute HT and improved chemotherapy compliance, resulting in optimal clinical outcomes [31], while Gandhi *et al* [32] demonstrated a significant reduction in grade ≥2 HT with IMRT compared to conventional techniques.

We observed significantly lower rates of grade ≥2 anaemia, leukopenia and neutropenia in the BMS-VMAT arm. However, no significant difference was observed in thrombocytopenia between the two arms. This may be attributed to differences in dose-response relationships and relatively lower radiosensitivity of megakaryocytes or among various haematopoietic cell lines. Similar findings were observed by Bazan *et al* [33] where platelet counts were less affected in comparison to leukocyte and neutrophil counts. These findings support routine incorporation of BM dose constraints in RT planning. Based on available literature, recommended constraints include V10 <90%, V20 <65%–80% and V40 <35%–40% [21, 28].

Our results particularly emphasise the importance of limiting intermediate- and high-dose volumes (V30 and V40), which showed significant differences between techniques and stronger correlation with toxicity outcomes. This is instrumental in resource-limited settings and developing countries where functional imaging for active BM delineation may be challenging.

The strengths of our study include a well-balanced cohort, uniform treatment protocol with comprehensive evaluation of dosimetric as well as clinical outcomes. Inclusion of concurrent chemotherapy in all patients enhances the clinical relevance of the findings. However, there are certain limitations also, such as relatively lower sample size and the single-institutional nature of the study. Along with this, BM delineation was based on anatomical contours instead of functional imaging; hence, active haematopoietic regions may not be fully delineated.

Future directions should be focused on the analysis of BM dose constraints and inclusion of functional imaging techniques such as fluorothymidine PET for identification of active BM [34].

Conclusion

BMS-VMAT significantly reduces clinically relevant pelvic BM parameters, particularly BM D_{mean}, V40 and V30 in comparison to 3DCRT without compromising target coverage. This dosimetric advantage results in a lower incidence of grade ≥2 HTs, especially anaemia, leukopenia and neutropenia, strengthening the clinical importance of limiting intermediate and high dose BM volumes during treatment planning. These

findings support the integration of BM-sparing strategies into routine RT planning for carcinoma cervix to improve treatment tolerability and outcome.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Author contributions

Concept and design: Smriti Srivastava, Sunil Kumar, Rashmi Yadav and Vijay Kumar.

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Critical review of the manuscript for important intellectual content: Smriti Srivastava, Sunil Kumar, Rashmi Yadav and Mohammad Ali.

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