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ORIGINAL RESEARCH

Pelvic Bone Marrow Sparing Using Different Radiotherapy Techniques in Patients with Cervical Cancer Receiving Concurrent Chemoradiotherapy: A Retrospective Study

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Abstract

Purpose: To evaluate the association between pelvic bone marrow irradiation and hematological toxicity in patients with cervical cancer treated with concurrent chemoradiotherapy and to assess whether bone marrow-sparing conformal radiotherapy may reduce treatment-related toxicity. **Materials and Methods:** This retrospective study included 44 patients with cervical cancer treated with pelvic external-beam radiotherapy and weekly cisplatin (40 mg/m²) between July and September 2011. Hematological toxicity was assessed according to Common Terminology Criteria. Clinical and dosimetric factors, including age, body mass index, pelvic bone marrow volume, transfusion requirements, and irradiated bone marrow volume, were analyzed. Multivariable regression was used to evaluate the association between bone marrow dose-volume parameters and hematological toxicity. **Results:** Hematological toxicity occurred in 24 of 44 patients (54.5%). A pelvic bone marrow volume receiving ≥20 Gy (V20) was significantly associated with hematological toxicity. Patients with V20 >70% had a higher risk of hematological toxicity than those with V20 ≤70% (p=0.008). Five-field conformal radiotherapy was also associated with a lower incidence of hematological toxicity. **Conclusion:** Pelvic bone marrow irradiation is associated with hematological toxicity during concurrent chemoradiotherapy for cervical cancer. A pelvic bone marrow V20 of 70% may serve as a useful dosimetric threshold for predicting toxicity. Five-field conformal radiotherapy may provide a practical bone marrow-sparing approach, particularly in resource-limited settings.

Keywords: Cervical cancer; concurrent chemoradiotherapy; hematological toxicity; pelvic bone marrow

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Introduction

Radiotherapy has been a cornerstone of cervical cancer treatment for more than a century, with the introduction of intracavitary radium therapy in the early 1900s representing an important milestone in the development of radiation-based treatment [1]. Advances in external-beam radiotherapy, chemotherapy, imaging, and brachytherapy have subsequently improved disease control and survival. Currently, concurrent chemoradiotherapy (CCRT) with cisplatin followed by intracavitary brachytherapy is a standard treatment approach for patients with locally advanced cervical cancer.

The addition of chemotherapy to radiotherapy has significantly improved treatment outcomes in locally advanced cervical cancer. Earlier attempts to enhance the effectiveness of radiotherapy using agents such as hydroxyurea and hypoxic-cell radiosensitizers did not demonstrate sufficient clinical benefit [2, 3]. Subsequent randomized clinical trials conducted in the 1990s demonstrated improved outcomes with concurrent cisplatin-based chemoradiotherapy, leading to the adoption of cisplatin-based CCRT as a standard treatment approach [3].

Despite its therapeutic benefits, CCRT is associated with acute and late toxicities that may compromise

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treatment completion and overall clinical outcomes. Hematological toxicity is particularly relevant because pelvic irradiation exposes substantial volumes of active bone marrow to radiation. This risk may be further increased by concurrent cisplatin chemotherapy. Treatment-related myelosuppression can result in treatment interruptions, dose reductions, transfusion requirements, and, in severe cases, compromised treatment intensity.

The pelvic bones contain a substantial proportion of the body's active hematopoietic marrow. Consequently, the volume of pelvic bone marrow receiving clinically relevant radiation doses has been investigated as a potential predictor of hematological toxicity during pelvic chemoradiotherapy. Modern conformal radiotherapy techniques may reduce unnecessary irradiation of bone marrow while maintaining adequate target coverage. However, access to advanced techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) may be limited in resource-constrained settings because of equipment, planning, and treatment costs.

Therefore, identifying practical and cost-effective approaches to pelvic bone marrow sparing remains clinically relevant, particularly in developing countries. This study evaluated the relationship between pelvic bone marrow dose-volume parameters and hematological toxicity in patients with cervical cancer treated with concurrent cisplatin-based chemoradiotherapy. We also assessed whether five-field conformal radiotherapy was associated with reduced hematological toxicity and explored a potential pelvic bone marrow V20 threshold for predicting treatment-related toxicity.

Toxicity of Concurrent Chemoradiotherapy

Treatment-related toxicity during concurrent chemoradiotherapy (CCRT) for cervical cancer results from the combined effects of chemotherapy, pelvic irradiation, and potential interactions between these treatment modalities. The severity of toxicity depends on treatment intensity, patient characteristics, irradiated tissue volume, and the dose delivered to normal organs.

Cisplatin-Related Toxicity

Cisplatin is the most commonly used concurrent chemotherapy agent in cervical cancer. Its major toxicities include nephrotoxicity, nausea and vomiting, neurotoxicity, ototoxicity, and myelosuppression. The administration of cisplatin concurrently with pelvic radiotherapy may further increase hematological toxicity and contribute to treatment interruptions or delays.

Pelvic Radiation-Related Toxicity

Pelvic radiotherapy can cause acute and late gastrointestinal and genitourinary toxicities. Acute gastrointestinal effects may include diarrhea, rectal discomfort, tenesmus, and bleeding, whereas late complications may include radiation proctitis, bowel obstruction, strictures, and, rarely, perforation [4]. Genitourinary toxicity may present as urinary frequency and dysuria during treatment, while late complications can include bladder dysfunction, strictures, and radiation-induced hemorrhagic cystitis.

Other recognized late effects of pelvic radiotherapy include pelvic insufficiency fractures and lower-extremity lymphedema, particularly in patients receiving combined surgery and radiotherapy [5]. However, the clinical significance of these toxicities varies considerably among patients.

Pelvic Bone Marrow and Hematological Toxicity

The pelvic bones contain a substantial proportion of the body's active hematopoietic marrow and are therefore particularly vulnerable to radiation exposure during pelvic radiotherapy. The extent of hematological toxicity depends on the radiation dose, irradiated bone marrow volume, fractionation, and the extent of marrow reserve.

When a limited volume of bone marrow is irradiated, unexposed marrow can compensate by increasing hematopoietic activity. However, irradiation of larger marrow volumes can impair hematopoietic recovery and increase the risk of leukopenia, neutropenia, anemia, and thrombocytopenia. These effects may become clinically more significant when pelvic radiotherapy is combined with myelosuppressive chemotherapy.

Consequently, minimizing unnecessary irradiation of pelvic bone marrow has become an important consideration in the planning of pelvic radiotherapy. Dose-volume parameters describing the proportion of pelvic bone marrow receiving specific radiation doses have been investigated as potential predictors of hematological toxicity. Identifying clinically relevant dose thresholds may allow treatment plans to be optimized to reduce toxicity while maintaining adequate tumor coverage.

Enhanced Toxicity During Concurrent Chemoradiotherapy

The combination of chemotherapy and radiotherapy improves tumor control but may also increase treatment-related toxicity. In the GOG 123 trial, Keys et al. reported comparable rates of grade 3–4 genitourinary, cutaneous, and neurological toxicities between patients treated with radiotherapy alone and those receiving concurrent cisplatin-based chemoradiotherapy. However, hematological toxicity was substantially more frequent in the chemoradiotherapy group (21.0% vs. 1.6%), as was gastrointestinal toxicity (14.2% vs. 4.8%) [6- 8]. These findings highlight the additional hematological burden associated with concurrent cisplatin and pelvic irradiation.

Hematological toxicity is clinically important because it may result in treatment interruptions, hospitalization, transfusion requirements, use of growth factors or antibiotics, and reduced chemotherapy delivery. Both pelvic irradiation and chemotherapy contribute to myelosuppression. Radiation can damage hematopoietic stem and progenitor cells and the bone marrow microenvironment, while chemotherapy may impair hematopoietic recovery in both irradiated and non-irradiated marrow. The combined effects can therefore result in greater hematological toxicity than either treatment modality alone.

The extent of radiation-induced marrow toxicity

is influenced by the volume of active bone marrow exposed and the radiation dose delivered. Consequently, identification of pelvic bone marrow dose-volume parameters associated with hematological toxicity may help optimize radiotherapy planning and reduce treatment-related complications.

Bone Marrow Imaging

Several imaging techniques have been investigated for the assessment of bone marrow distribution and activity, including bone marrow scintigraphy, magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET). Early studies used radionuclide imaging to characterize functional marrow distribution, whereas MRI and PET can provide information related to marrow composition and metabolic activity.

Bone marrow scintigraphy can demonstrate the distribution of hematopoietically active marrow using various radiotracers, but its clinical application may be limited by cost, availability, and technical considerations. MRI provides detailed information regarding marrow composition and can distinguish active from fatty marrow, although it is not routinely incorporated into radiotherapy treatment planning.

CT remains the most practical imaging modality for radiotherapy planning because it is routinely acquired for treatment simulation and provides the anatomical information required for treatment planning. Although conventional CT does not directly measure marrow hematopoietic activity, pelvic bone structures can be delineated on planning CT and used to estimate the volume of marrow exposed to radiation. Accordingly, CT-based pelvic bone marrow dose-volume parameters have become useful tools for investigating the relationship between radiation exposure and hematological toxicity.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is highly sensitive for evaluating bone marrow composition and pathology. Conventional T1-weighted and fluid-sensitive sequences, including short tau inversion recovery (STIR) and fat-suppressed T2-weighted sequences, can distinguish fatty from hematopoietically active marrow based on differences in signal intensity [9]. MRI can therefore provide detailed information regarding marrow cellularity and distribution. However, its routine use for pelvic bone marrow assessment during radiotherapy planning is limited by availability, cost, and the need for integration with treatment-planning workflows.

Positron Emission Tomography

Positron emission tomography (PET) provides functional information regarding tissue metabolism and cellular activity. Tracers such as 18F-fluorothymidine (18F-FLT), a marker of cellular proliferation, have been investigated for assessing hematopoietically active bone marrow and treatment-related changes. PET may provide quantitative information about marrow activity and can potentially be used to evaluate tumor response and marrow toxicity simultaneously. However, its cost, limited availability, and lack of routine integration into radiotherapy planning restrict its clinical use for this purpose.

Aim of the Study

The aim of this study was to evaluate the relationship between pelvic bone marrow irradiation and hematological toxicity in patients with cervical cancer treated with concurrent cisplatin-based chemoradiotherapy and to identify a practical and potentially cost-effective radiotherapy approach for reducing treatment-related myelosuppression.

Specific Objectives

The specific objectives were:

1. To determine the incidence and severity of hematological toxicity, particularly neutropenia, in patients with cervical cancer treated with concurrent chemoradiotherapy.
2. To evaluate the association between pelvic bone marrow dose-volume parameters and the occurrence of hematological toxicity.
3. To identify clinical and dosimetric factors associated with an increased risk of hematological toxicity.
4. To compare pelvic radiotherapy techniques with respect to their potential for reducing pelvic bone marrow irradiation and hematological toxicity.
5. To assess whether a clinically relevant pelvic bone marrow dose-volume threshold can be identified for predicting hematological toxicity.

Materials and Methods

This retrospective study included patients with histologically confirmed cervical cancer who were treated at [Institution name] between July 2011 and September 2011. Eligible patients had International Federation of Gynecology and Obstetrics (FIGO) stage II–III disease and were treated with pelvic external-beam radiotherapy (EBRT) with concurrent cisplatin-based chemotherapy. Patients who were considered unsuitable for concurrent cisplatin chemotherapy were excluded.

Baseline clinical assessment included renal, hepatic, and cardiac evaluation. Patients with a hemoglobin level <10 g/dL received packed red blood cell transfusion before or during treatment, according to clinical requirements.

All patients received weekly cisplatin at a dose of 40 mg/m² for 4–5 cycles concurrently with pelvic EBRT. EBRT was followed by high-dose-rate brachytherapy, consisting of 2–3 fractions, with parametrial boost when clinically indicated. All patients were counseled regarding the treatment plan and potential adverse effects.

A total of 44 patients met the eligibility criteria and were included in the analysis.

A non-contrast computed tomography (CT) scan was acquired with patients in the treatment position. CT images were obtained from the level of the 12th thoracic vertebra (T12) to approximately 5 cm below the ischial tuberosities. Slice thickness was 5 mm for three-dimensional conformal

radiotherapy (3D-CRT) and 3 mm for volumetric-modulated arc therapy (VMAT).

The clinical target volume and planning target volume (PTV) were delineated according to institutional treatment-planning protocols. The bladder, rectum, and pelvic bones were contoured as organs at risk and normal tissues as depicted in Figure 1.

For the purposes of this study, the pelvic bone marrow volume was defined anatomically by contouring the lower lumbar vertebrae, sacrum, ilium, ischium, pubis, and the proximal portions of both femora. The external contours of these bony structures were delineated on the planning CT images and collectively defined as the pelvic bone volume as shown in Figure 2.

Dose-volume histograms (DVHs) were generated for the contoured pelvic bone volume. The maximum and mean doses and the percentage of pelvic bone volume receiving ≥5, ≥10, ≥15, ≥20, ≥30, ≥40, and ≥50 Gy (V5, V10, V15, V20, V30, V40, and V50, respectively) were recorded.

Patients were treated using either 3D-CRT or VMAT. Among the 44 patients, 25 were treated using a four-field conformal technique, 16 using a five-field conformal technique, and 3 using VMAT.

For four-field 3D-CRT (Figure 3), anterior, posterior, and two lateral open fields were used. For five-field 3D-CRT (Figure 4), one anterior field and two pairs of lateral oblique fields were used, with appropriate wedges when required. A 5-mm margin between the field edge and the PTV was used to account for beam penumbra.

VMAT plans were generated using dual complementary arcs with the aim of achieving adequate PTV coverage while minimizing exposure of organs at risk and surrounding normal tissues. All treatment plans were generated using Eclipse version 8.6 (Varian Medical Systems, Palo Alto, CA, USA) with the Anisotropic Analytical Algorithm.

All patients received EBRT at 1.8 Gy per fraction to a total dose of 50.4 Gy in 28 fractions.

Patients were positioned using skin marks. For VMAT, treatment position was verified daily using orthogonal kilovoltage (kV) imaging with the Varian On-Board Imager. For patients receiving conformal radiotherapy, image verification was performed weekly.

All patients underwent clinical pelvic examination during treatment, including at approximately 30 Gy and at completion of EBRT, to assist in determining the timing of brachytherapy. Chemotherapy was completed before brachytherapy.

Complete blood counts were monitored during treatment. Hematological parameters were assessed before each chemotherapy cycle. Chemotherapy was deferred when the total white blood cell count was <2,000 cells/mm^3. Patients with prolonged neutropenia or febrile neutropenia received appropriate supportive treatment, including growth-factor support and antibiotics.

Baseline clinical variables included age, FIGO stage, hemoglobin level, height, weight, and body mass index (BMI). The occurrence and severity of neutropenia and other hematological toxicities were recorded during treatment.

Hematological toxicity was graded from Grade 0 to Grade 3 according to the Radiation Therapy Oncology Group (RTOG) acute morbidity scoring criteria.

Statistical Analysis

Clinical, treatment, hematological, and dosimetric data were entered into SPSS [version]. Continuous variables were summarized using appropriate descriptive statistics, and categorical variables were presented as frequencies and percentages. Associations between clinical or dosimetric variables and hematological toxicity were assessed using appropriate statistical tests. Dose-volume parameters were evaluated to identify potential predictors of hematological toxicity, with particular attention to pelvic bone V20.

A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 44 patients were included in the analysis. Eight patients (18.2%) were aged 30–40 years, 17 (38.6%) were aged 40–50 years, 18 (40.9%) were aged 50–60 years, and 1 (2.3%) was older than 60 years.

Regarding FIGO stage, 7 patients (15.9%) had stage IIA1 disease, 17 (38.6%) had stage IIA2 disease, 13 (29.5%) had stage IIB disease, and 7 (15.9%) had stage III disease.

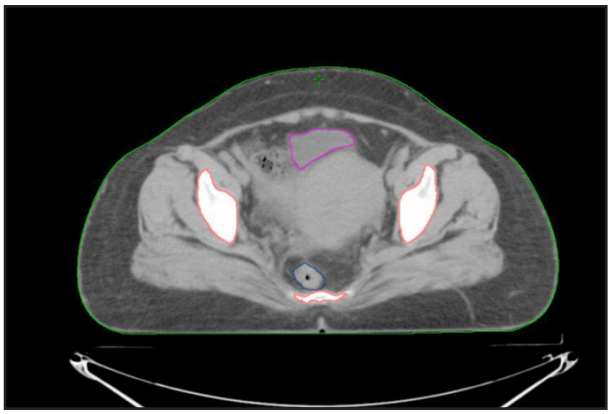


Figure 1. Normal Structure Segmentation (Blue-rectum, Magenta-bladder, Peach-pelvic bone).

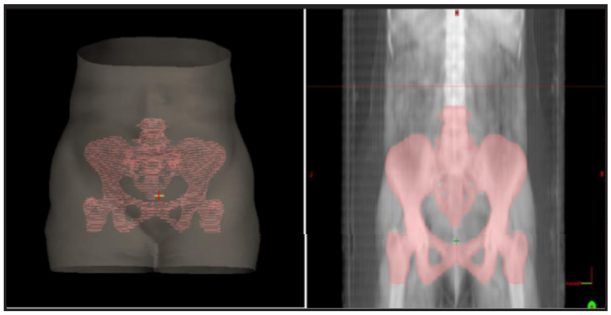


Figure 2. Pelvic Bone Segmentation.

Table 1. Distribution of Hematological Toxicity According to Radiotherapy Technique.

Radiotherapy technique	Grade 0, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Total, n (%)
VMAT	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
4-field 3D-CRT	8 (32.0)	10 (40.0)	4 (16.0)	3 (12.0)	25 (100.0)
5-field 3D-CRT	9 (56.3)	4 (25.0)	3 (18.8)	0 (0.0)	16 (100.0)
Total	20 (45.5)	14 (31.8)	7 (15.9)	3 (6.8)	44 (100.0)

Abbreviations: 3D-CRT, three-dimensional conformal radiotherapy; VMAT, volumetric-modulated arc therapy. Note: Hematological toxicity was graded according to the Radiation Therapy Oncology Group (RTOG) acute morbidity scoring criteria.

Incidence and Severity of Neutropenia

Of the 44 patients, 20 (45.5%) did not develop neutropenia during treatment. Grade 1 neutropenia occurred in 14 patients (31.8%), Grade 2 in 7 (15.9%), and Grade 3 in 3 (6.8%).

Chemotherapy was deferred in patients who developed Grade 2 or Grade 3 neutropenia, according to the institutional treatment protocol.

Overall, 24 patients (54.5%) developed at least Grade 1 neutropenia, whereas 10 patients (22.7%) developed Grade 2–3 neutropenia.

Three patients were treated with VMAT, 25 with four-field conformal radiotherapy, and 16 with five-field conformal radiotherapy. The distribution of neutropenia grades according to treatment technique is presented in Table 1.

Because of the small number of patients treated with VMAT, comparisons involving this technique should be interpreted cautiously.

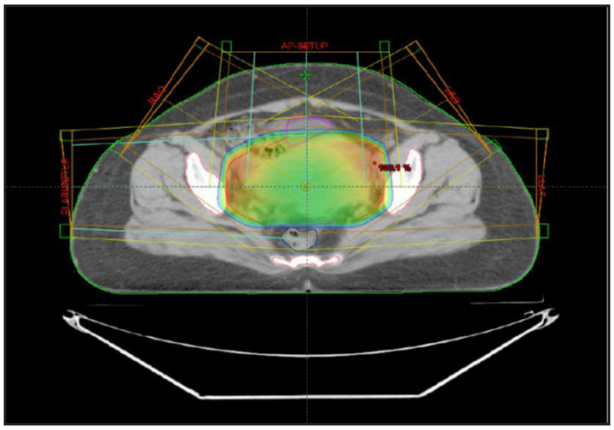


Figure 3. 5 Field Conformal Technique Portals.

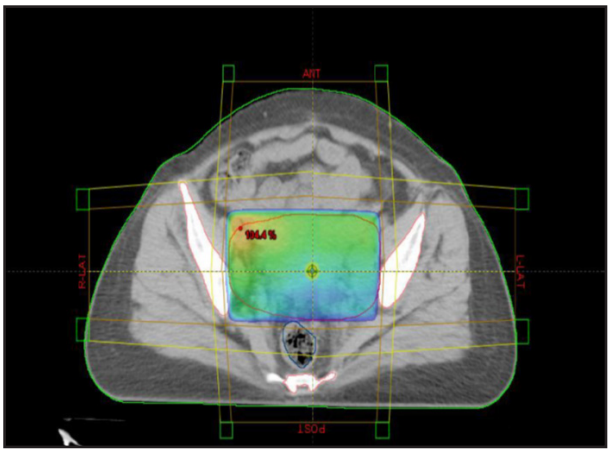


Figure 4. 4 Field Conformal Technique Portals.

Dose-volume histogram (DVH) parameters for the contoured pelvic bone volume were evaluated in relation to hematological toxicity. The DVH is generated as in Figure 5. The analyzed parameters included pelvic bone volume, mean dose, and the percentage of pelvic bone volume receiving ≥10, ≥15, ≥20, ≥30, ≥40, and ≥50 Gy (V10, V15, V20, V30, V40, and V50, respectively).

Multivariable analysis was performed to evaluate the relationship between pelvic bone dose-volume parameters and hematological toxicity. A pelvic bone V20 >70% was significantly associated with greater hematological toxicity compared with a V20 ≤70% (p=0.008).

The dosimetric characteristics of four-field conformal radiotherapy, five-field conformal radiotherapy, and VMAT were compared using DVH analysis (Figure 6). Four-field conformal plans showed a relatively greater low-dose exposure of the pelvic bone volume, whereas five-field conformal and VMAT plans demonstrated lower V20 values.

A pelvic bone V20 ≤70% was achieved in 28% of four-field conformal plans, 56% of five-field conformal plans, and 100% of VMAT plans (Table 2). These findings indicate that five-field conformal radiotherapy may reduce pelvic bone V20 compared with the four-field technique, while VMAT achieved the lowest V20 in this small treatment group.

Given the limited number of patients treated with VMAT, these findings should be considered primarily descriptive and hypothesis-generating.

Discussion

Hematological toxicity is an important adverse effect of concurrent chemoradiotherapy for cervical cancer and may lead to chemotherapy delays, treatment interruptions, and reduced treatment intensity. Because a substantial proportion of active hematopoietic marrow is located within the pelvis, minimizing unnecessary pelvic bone marrow irradiation has become an important consideration in radiotherapy planning. The present study evaluated clinical and dosimetric factors associated with hematological toxicity and explored whether commonly available conformal radiotherapy techniques could reduce pelvic bone marrow exposure.

In our cohort of 44 patients (Table 3), 54.5% developed at least Grade 1 neutropenia, while 22.7% developed Grade 2–3 neutropenia. The most important dosimetric finding was the association between pelvic bone V20 and hematological toxicity. Patients with a V20

Table 2. Comparison of Pelvic Bone V20 According to Radiotherapy Technique.

Radiotherapy technique	Patients/plans, n	V20 ≤70%, n (%)	V20 >70%, n (%)
4-field 3D-CRT	25	7 (28.0)	18 (72.0)
5-field 3D-CRT	16	9 (56.3)	7 (43.8)
VMAT	3	3 (100.0)	0 (0.0)
Total	44	19 (43.2)	25 (56.8)

Note: Because only three patients received VMAT, comparisons involving VMAT should be interpreted cautiously.

Table 3. Distribution of Hematological Toxicity According to Pelvic Bone Dose-Volume Parameters.

DVH parameter	Grade 0, n	Grade 1, n	Grade 2, n	Grade 3, n	Total, n
Mean pelvic bone dose					
<2500 cGy	7	1	0	1	9
2500–3000 cGy	13	11	6	2	32
>3000 cGy	0	2	1	0	3
Pelvic bone volume					
<700 cm³	2	2	2	1	7
700–800 cm³	8	6	1	1	16
800–900 cm³	5	4	2	0	11
>900 cm³	5	2	2	1	10
V10					
<90%	19	11	5	2	37
≥90%	1	3	2	1	7
V15					
<80%	20	9	4	2	35
≥80%	0	5	3	1	9
V20					
≤70%	16	0	2	0	18
>70%	3	13	4	3	23
V30					
<50%	19	10	6	0	35
≥50%	1	4	1	3	9
V40					
<30%	20	11	7	3	41
≥30%	0	3	0	0	3
V50					
<5%	14	6	1	1	22
≥5%	6	8	6	2	22

Abbreviations: DVH, dose-volume histogram; V10, V15, V20, V30, V40, and V50, percentage of pelvic bone volume receiving ≥10, ≥15, ≥20, ≥30, ≥40, and ≥50 Gy, respectively.

>70% had significantly greater hematological toxicity than those with a V20 ≤70% (p=0.008). This finding supports the concept that the volume of pelvic marrow receiving moderate radiation doses may be clinically relevant in patients receiving concurrent cisplatin-based chemoradiotherapy.

Previous studies have similarly demonstrated an association between pelvic bone marrow irradiation and hematological toxicity. Brixey et al. reported reduced hematological toxicity with intensity-modulated radiotherapy (IMRT), even without the use of specific bone marrow dose constraints [10]. Lujan et al. subsequently investigated iliac bone marrow sparing and demonstrated a reduction in hematological toxicity with marrow-sparing IMRT [11]. These findings suggest that reduction of unnecessary pelvic bone marrow exposure may improve hematological tolerance during concurrent chemoradiotherapy.

The identification of the most clinically relevant marrow volume for sparing remains an area of investigation. Early approaches focused primarily on the iliac bones and femoral heads, whereas subsequent studies emphasized the importance of broader pelvic marrow volumes. Roeske et al. used sulfur colloid SPECT to identify areas of active bone marrow and incorporated this information into IMRT planning [12]. Although functional imaging can provide

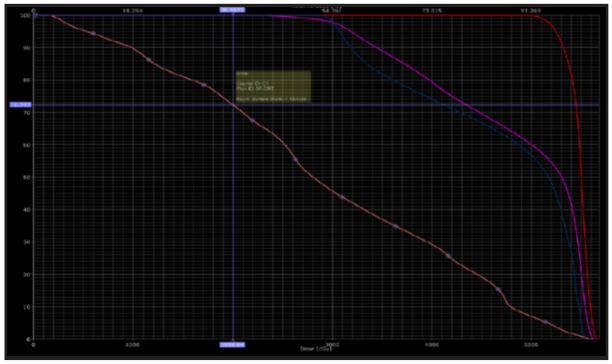


Figure 5. Dose Volume Histogram for Bony Pelvis.

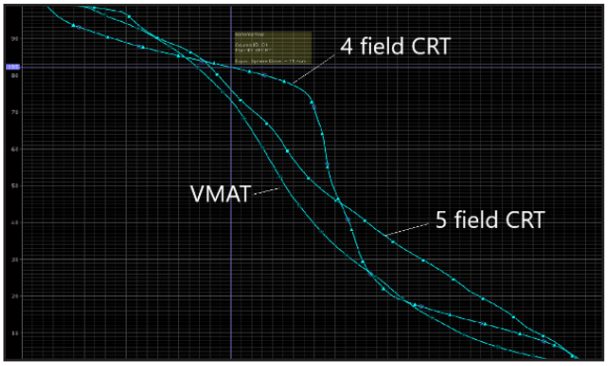


Figure 6. Comparison of V20 of Different Techniques.

information regarding marrow activity, its routine use may be limited by cost, availability, and technical complexity.

More recently, ^18F-fluorothymidine (FLT) PET/CT has been investigated for functional delineation of proliferating bone marrow. McGuire et al. demonstrated the feasibility of incorporating FLT-PET-based marrow information into IMRT planning without compromising target coverage or organ-at-risk constraints [13, 14]. However, the cost and limited availability of functional imaging techniques restrict their widespread use, particularly in resource-limited settings.

An important contribution of the present study is therefore the evaluation of a readily available CT-based approach. Rather than relying on sophisticated functional imaging, we assessed the dose delivered to the anatomically defined pelvic bone volume using routine treatment-planning CT and DVH analysis. This approach is relatively simple and can be incorporated into conventional radiotherapy planning workflows.

Our findings are broadly consistent with the dose-volume relationship reported by Rose et al., who developed a normal tissue complication probability model for hematological toxicity in cervical cancer patients receiving chemoradiotherapy [15]. Their analysis suggested that limiting pelvic bone marrow V10 and V20 could reduce hematological toxicity, with proposed constraints of V10 <95% and V20 <76%. In the present study, a V20 threshold of 70% was associated with a significantly higher risk of hematological toxicity. Although the threshold observed in our cohort is similar to previously reported values, it should be regarded as a potential threshold rather than a definitive clinical constraint because of the small sample size and retrospective design.

The comparison of radiotherapy techniques also provides clinically relevant findings. Five-field conformal radiotherapy achieved a lower pelvic bone V20 than the four-field technique in a greater proportion of treatment plans. This suggests that modification of beam arrangement may reduce unnecessary pelvic bone marrow irradiation without requiring highly sophisticated treatment-planning techniques. Such an approach may be particularly useful in centers where access to advanced radiotherapy technologies is limited.

However, the results regarding VMAT require careful interpretation. Only three patients in our cohort were treated with VMAT. Although all three patients had V20 values below 70% and did not develop clinically significant leukopenia, this small sample does not permit reliable comparison between VMAT and conformal techniques. Similarly, the present study cannot establish that five-field conformal radiotherapy is equivalent to IMRT or VMAT in terms of hematological toxicity. Larger comparative studies are required to determine whether the observed dosimetric advantage translates into a clinically meaningful reduction in toxicity.

The findings also raise an important practical question regarding the need for sophisticated active bone marrow imaging. Functional imaging with SPECT or FLT-PET may allow more precise identification of hematopoietically active marrow, but these techniques are not routinely available in many radiotherapy centers. Our results suggest that a simpler CT-based pelvic bone contour and DVH assessment may provide clinically useful information for identifying patients at increased risk of hematological toxicity. This possibility is particularly relevant in resource-limited settings, although formal cost-effectiveness analyses would be required before any economic conclusions can be made.

This study has several limitations. First, its retrospective, single-center design limits the generalizability of the findings. Second, the sample size was small, particularly for the VMAT subgroup. Third, treatment techniques were not randomly assigned, introducing the possibility of selection bias and confounding. Fourth, the study focused on anatomically defined pelvic bone rather than functionally active marrow. Finally, the proposed V20 threshold requires validation in larger prospective cohorts and should not be considered an established dose constraint.

Despite these limitations, the study demonstrates a significant association between pelvic bone marrow irradiation and hematological toxicity during concurrent chemoradiotherapy for cervical cancer. The findings support further investigation of pelvic bone V20 as a practical dosimetric parameter and suggest that five-field conformal radiotherapy may offer a simple approach to reducing marrow exposure when more advanced techniques are unavailable.

In conclusion, pelvic bone marrow irradiation was associated with hematological toxicity in patients with cervical cancer treated with concurrent cisplatin-based

chemoradiotherapy. In particular, a pelvic bone marrow V20 >70% was associated with a higher frequency of hematological toxicity (p=0.008). Five-field conformal radiotherapy demonstrated the potential to reduce pelvic bone marrow exposure compared with the four-field technique.

These findings suggest that pelvic bone marrow dose-volume parameters, particularly V20, may be useful for identifying patients at increased risk of treatment-related hematological toxicity. However, the proposed V20 threshold of 70% should be considered a potential dosimetric threshold rather than a definitive clinical constraint. Given the retrospective design, small sample size, and limited number of patients treated with VMAT, larger prospective studies are needed to validate these findings and determine whether five-field conformal radiotherapy provides a clinically meaningful advantage over more advanced techniques.

Acknowledgments

Statement of Transparency and Principles

•The authors declare no conflict of interest.

•The study was approved by the Research Ethics Committee of the authors' affiliated institution.

•The study data are available upon reasonable request.

•All authors contributed to the implementation of this research.

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