RESEARCH ARTICLE

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Comparative Analysis of VMAT and IMRT Techniques: Evaluation of Dose Constraints and Bone Marrow Sparing in Cervical Cancer Patients Undergoing Chemoradiotherapy

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Abstract

Background: Carcinoma of the cervix is a globally significant cause of morbidity and mortality among women. Concurrent chemoradiotherapy, a standard approach for locally advanced cervical cancer, invariably involves pelvic irradiation. Although this strategy is effective, it inevitably affects the pelvic bone marrow, a crucial hematopoietic site, and leads to hematological toxicity The potential of IMRT to spare bone marrow in pelvic irradiation settings has been an area of significant interest, with the aim to mitigate the hematological toxicity associated with pelvic radiotherapy. Radiotherapy techniques have evolved in terms of conformity and normal tissue sparing. Our study intends to explore the use of BM sparing techniques among patients of carcinoma cervix. **Patients and Methods:** Twenty patients of carcinoma cervix FIGO Stage IIIB treated with concurrent chemoradiotherapy were selected for this study. The external contour of bones was delineated on planning CT as a surrogate for BM. We generated three plans on a single patient:1. without BM as the dose constraint, namely N-IMRT plan; 2. with BM constraint, namely BMS-IMRT plan; 3. VMAT plan in which BM constraint was given. The dose volume histogram (DVH) for planning target volume (PTV) and organs at risk (OAR) were analyzed. BM parameters: V10, V20, V30, V40, mean, maximum and minimum dose were compared. **Results:** PTV coverage was comparable in all techniques. VMAT plans resulted in superior BM sparing compared with N-IMRT plan (P-<0.001) and BMS-IMRT plan (P-<0.001, 0.021 and 0.001 respectively for V20, V30 and V40). VMAT plans had better CI compared with BMS-IMRT (P-0.002) and N-IMRT (P-0.001) plans. **Conclusion:** Our study adds to the growing evidence that VMAT might be the preferred technique for patients with carcinoma of the cervix undergoing concurrent chemoradiotherapy, as it provides comparable target coverage and better sparing of bone marrow compared to IMRT.

Keywords: Carcinoma cervix, bone marrow sparing-intensity modulated radiation therapy (IMRT)

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Introduction

Carcinoma of the cervix, a primary malignancy of the female reproductive tract, is a globally significant cause of morbidity and mortality among women. Despite advancements in screening and vaccination strategies, a substantial number of cases are diagnosed at advanced stages, necessitating complex treatment modalities. Concurrent chemoradiotherapy, a standard approach for locally advanced cervical cancer, invariably involves pelvic irradiation [1, 2]. Although this strategy is effective, it inevitably affects the pelvic bone marrow, a crucial hematopoietic site, and often leads to hematological toxicity (HT) [3- 5]. Hematological toxicity can result in treatment interruption, dose reduction, and substantial impact on patients' quality of life and potentially treatment outcome.

With the advent of sophisticated radiotherapy techniques, Intensity-Modulated Radiation Therapy (IMRT) has emerged as a promising treatment strategy that allows for enhanced target coverage and sparing of adjacent organs at risk. The potential of IMRT to spare bone marrow in pelvic irradiation settings has been an area of significant interest, with the aim to mitigate the hematological toxicity associated with pelvic radiotherapy [6, 7].

In this study, we present our approach to bone marrow sparing with modern radiotherapy techniques such as IMRT and volumetric modulated arc therapy (VMAT) in cervical carcinoma, highlighting the clinical relevance,

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feasibility, and potential advantages of these techniques. The present study's objective is to study the dosimetric parameters of standard IMRT (one without bone marrow (BM) as the dose-volume constraint, namely N-IMRT plan); bone marrow sparing IMRT (BMS-IMRT) (one in which plans are optimized to limit BM irradiation, namely BMS-IMRT plan); and volumetric modulated arc therapy (VMAT), namely VMAT plan.

Materials and Methods

Patients and methods

Patient data

A total of twenty, biopsy proven, patients of squamous cell carcinoma cervix, with FIGO Stage III B and treated with concurrent chemoradiotherapy at our hospital were selected for the present study. Post-operative patients were excluded from this study.

Patients were treated with external beam radiotherapy (EBRT) with concurrent cisplatin based chemotherapy followed by brachytherapy. Before EBRT, all the baseline investigations including MRI of the abdomen and pelvis were done.

CT Simulation

CT simulation was done using Siemens Somatom Definition AS Open 20-slice CT Simulator with 3 mm slice thickness. Before the computed tomography (CT) simulation, we followed a thorough and standard bowel and bladder protocol for each patient. On the day of the CT simulation, an enema was used to prepare the bowels. For bladder protocol, the patients were first instructed to void urine and then drink 500ml of water. After 30 minutes, CT simulation was done. Patients were positioned supine with their arms over the chest, and immobilized with a rigid thermoplastic mask. Consistent education and clear communication with patients were done to ensure reproducibility during the treatment. The Monaco 5.11.03 (Elekta AB, Stockholm, Sweden) planning system was used for contouring and planning.

Target and OAR Delineation

Target volume and OARs were delineated by the same radiation oncologist in accordance with the recommendations of the Radiation Therapy Oncology Group (RTOG) [8] and the International Commission on Radiation Units and Measurements (ICRU) Report 62.

Bladder, small intestine, rectum, spinal cord, femoral heads, and bone marrow were identified as avoidance structures.

BM delineation

The exterior contour of all bones in the pelvis were defined on the planning CT scan to identify bone marrow rather than the low-density areas inside the bones. This was done to ensure reproducibility during treatment. The entire sacrum, bilateral ilium, ischium, acetabulum, femoral heads up to the ischial tuberosity, and the vertebral body were all contoured as part of the planning treatment volume. Bone marrow constraints were not included in the N-IMRT plan, but they were in the BMS-IMRT and VMAT plans together with all the other OARs. The OARs' constraints are shown in Table 1 [9, 10, 7, 11].

Treatment planning

We generated three different IMRT plans for each patient which are as follows: first one without BM as the dose-volume constraint, namely N-IMRT plan; second one with BM constraint, namely BMS-IMRT plan; third one VMAT plan in which BM constraint was given. Monaco 5.11.03 planning system was used. The inverse plans were generated with 6 MV photon beam with placement of 9 coplanar fields in IMRT plans and 2 arcs in VMAT plans using Monte Carlo algorithm. The plans were normalized to cover 95% of the PTV with at least 95% of the prescription dose.

Plan Evaluation

The dose-volume histogram (DVH) parameters for PTV and OARs were analyzed. For PTV, dosimetric parameters, including D_{98}% (the dose received by 98% volume of the PTV), D_{50}%, D_{2}%, the mean dose (Dmean), conformity index (CI), and homogeneity index (HI), were quantified while for bone marrow parameters like V_{10}, V_{20}, V_{40}, mean, maximum and minimum dose were noted. CI was calculated with the formula as follows [12]:

$CI = TV_{PIV}^{2}/(TV*PIV)$

Here, TVPIV is the volume of target volume covered by prescription isodose, TV is target volume and PIV is prescription isodose volume. The CI ranges from 0 to 1. A value of CI close to 1 indicates improved PTV conformity.

The HI was calculated according to ICRU report no. 83 [13]: $HI = (D_{2}\% - D_{98}\%)/D_{50}\%$

EBRT dose prescription and delivery

The external beam radiotherapy dose to the PTV was prescribed as 50 Gy/25 fractions, 2 Gy/fraction, five fractions/week over five weeks in all the patients. Consistent bowel and bladder protocol was followed before every fraction, as was done during the process of CT simulation. Moreover, the use of anti-gas medications and mild laxatives was recommended during treatment to further reduce bowel content and maintain consistency. Treatment setup verification was done using image guidance with daily cone-beam CT (CBCT).

Statistical analysis

The data was analyzed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA). A student's paired t-test was used to interpret the results. A p-value of less than 0.05 was considered statistically significant.

Results

The median age of patients at the time presentation was 50 years. OAR dose constraints for rectum, bladder, head of the femur, and bowel bag were achieved in all the three arms. The Table 1 mentions the dose-volume constraints of normal tissues. The mean PTV volume was 1601.63±157.12cc. Figure 1 shows the PTV in blue colour, and the whole pelvic bone as representative of the

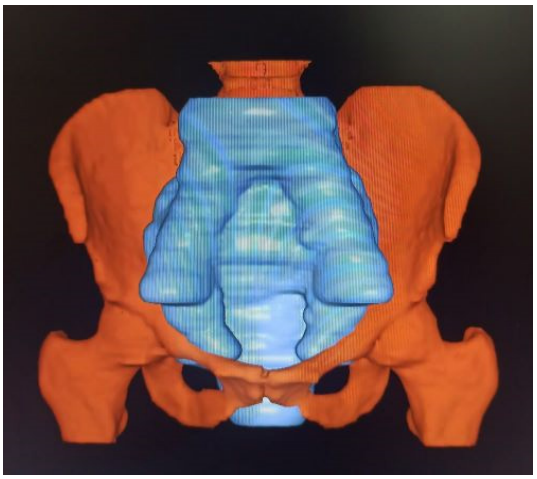

Figure 1. Blue Colour Depicts Planning Target Volume (PTV), and Orange Colour Depicts the whole Pelvic Bone as a Representative of the Bone Marrow (BM)

bone marrow in orange colour. The PTV coverage was comparable in all the treatment plans. The mean value of PTV receiving 95% of the prescribed dose was 99.56% in VMAT plan, 99.85% in BMS-IMRT plan and 99.88% in the N-IMRT plan. (Table 2).

The mean value of CI and HI are 0.818±0.032 and 0.061±0.062 respectively in VMAT plan, 0.791± 0.045 and 0.047±0.004 respectively in BMS-IMRT plan, 0.760±0.063 and 0.044±0.003 respectively in N-IMRT plan (Table 2). In terms of CI, VMAT plan showed better conformity than N-IMRT plan (P=0.020) and BMS-IMRT plan (P<0.001) while N-IMRT plan and BMS-IMRT plan showed better HI than VMAT plan (P<0.001).

Table 1. The Dose-Volume Constraints of Normal Tissues

OAR	Dose constraints
Small Bowel	V_{45}<195cc
Rectum	V_{50}<50%
Bladder	V_{50}<50%
Femoral Head	V_{50}<5%, D_{max}<50 Gy
Bone Marrow	V_{10}<90%, V_{20}<75%, V_{30}<65%, V_{40}<45%

OAR, Organ at risk

On comparing the GI, VMAT plan were better than BMS-IMRT plan (P=0.001) and comparable with N-IMRT plan (P=0.227) (Table 2).

The mean bone marrow volume was 1105.96± 147.75 cc. In N-IMRT plan, the mean V_{10}, V_{20}, V_{30}, and V_{40} of pelvic bone marrow were 95.6%, 82.4%, 64.5%, 42.3%, respectively, with overall mean dose 34.6 Gy. For patients undergoing BMS-IMRT, the mean V_{10}, V_{20}, V_{30}, and V_{40} of bone marrow were 83.2%, 73.4%, 58.8%, and 39.19%, respectively, with overall mean dose of 31.6 Gy. In VMAT, the mean V10, V20, V30, and V40 of bone marrow were 83.2%, 70.1%, 56.9% and 36.4% respectively, with overall mean dose of 30.7 Gy (Table 3).

Among all the three radiotherapy techniques, the bone marrow mean dose was significantly lower in VMAT plans [(VMAT vs BMS-IMRT (P=0.002) and VMAT vs N-IMRT (P<0.001)]. VMAT plans significantly resulted in superior BM sparing taking into account V_{10}, V_{20}, V_{30} and V_{40} parameters as compared with N-IMRT plan (P<0.001). However, comparing VMAT with BMS-IMRT plan, VMAT plans were significantly better than BMS-IMRT plans considering V_{20}, V_{30} and V_{40} parameters (P-value

Table 2. DVH Comparisons for PTV

PTV parameters	N-IMRT	BMS-IMRT	VMAT	P-value		
				N-IMRT vs BMS-IMRT	VMAT vs. BMS-IMRT	N-IMRT vs VMAT
D_{mean}	50.30±0.276	50.19±0.337	50.09±0.343	0.135	0.442	0.043
CI	0.76±0.063	0.79±0.045	0.81±0.032	0.087	0.02	<0.001
HI	0.04±0.003	0.04±0.004	0.06±0.006	0.063	<0.001	<0.001
V95	99.88±0.133	99.85±0.213	99.56±0.334	0.597	0.006	0.001

DVH, Dose Volume Histogram; PTV, Planning target volume; D_{mean}, Mean dose, CI, Conformity index; HI, Homogeneity index; V_{95}, Volume of PTV receiving 95% of the prescription dose

Table 3. DVH Comparison for Bone Marrow (BM)

BM parameters	N-IMRT	BMS-IMRT	VMAT	P-value		
				N-IMRT vs BMS-IMRT	VMAT vs BMS-IMRT	N-IMRT vs VMAT
D_{mean} (Gy)	34.67±1.18	31.66±1.62	30.79±1.25	<0.001	0.002	<0.001
D_{min} (Gy)	2.68±1.09	1.60±0.373	1.91±0.537	<0.001	0.002	<0.001
D_{max} (Gy)	53.30±0.455	53.17±0.513	53.23±0.581	0.399	0.712	0.758
V_{10}	95.63±2.13	84.16±2.36	83.25±2.96	<0.001	0.229	<0.001
V_{20}	82.48±2.67	73.40±3.11	70.16±2.88	<0.001	<0.001	<0.001
V_{30}	64.58±3.91	58.88±4.40	56.94±3.06	<0.001	0.021	<0.001
V_{40}	42.35±4.03	39.19±5.08	36.46±3.28	0.001	<0.001	<0.001

BM, Bone marrow; D_{mean}, mean dose; D_{min}, minimum dose; D_{max}, maximum dose; V_{10}, Volume of BM receiving 10 Gy; V_{20}, Volume of BM receiving 20 Gy; V_{30}, Volume of BM receiving 30 Gy; V_{40}, Volume of BM receiving 40 Gy

<0.001, 0.021 and 0.001 respectively) (Table 3).

Discussion

The objective of this study was to compare the dosimetric parameters different radiotherapy planning methods for bone marrow sparing in patients with cervical carcinoma undergoing chemoradiation, which included IMRT and VMAT plan. In this dosimetric study, our principal aim was to examine and quantify the dose distribution and conformity of these two techniques, alongside assessing the impact on bone marrow.

It is well recognized that both VMAT and IMRT techniques are designed to deliver precise radiation doses to malignant tumorous tissues, while minimizing the irradiation of surrounding healthy tissues. In this context, our study centers on bone marrow sparing, which is critical due to its role in generating new blood cells and maintaining immune function, which is important for patients undergoing cancer treatments. Radiation-induced damage to the bone marrow can lead to hematological toxicity, which can cause treatment interruptions, negatively affect patients' quality of life, and potentially impact treatment outcomes. They observed that individuals undergoing concurrent chemoradiation with a lesser pelvic BM volume (V_{10}, V_{20}) are less likely to have acute HT. Rose (2011) [10] and Albuquerque (2011) [14] discovered that patients with higher BM V_{20} levels were more likely to develop leukopenia. Doses greater than 50 Gy can result in complete hypoplasia with no regeneration [9]. These findings revealed the bone marrow stem cells' remarkable susceptibility to radiation at low doses. As a result, lowering V_{10} may help to reduce haematological toxicities.

On the contrary, other studies found a strong correlation between the volume of pelvic BM receiving high-dose radiation (V_{30}, V_{40}) and HT [4]. Furthermore, increasing bone marrow V_{40} is linked to greater BM toxicity. The probability of any grade of neutropenia rose in patients who received bone marrow V40Gy and V50Gy greater than 40% and 15%, respectively [5].

As has been mentioned aforesaid, the volume of pelvic BM receiving a certain radiation dose could be a significant contributor of acute hematological toxicities, therefore, employing bone marrow sparing radiotherapy techniques to reduce BM irradiation is necessary. Highly conformal radiation techniques such as IMRT and VMAT have dramatically improved bone marrow sparing in pelvic tumors. The main findings from this study indicate that VMAT may offer a more effective approach to spare the bone marrow without compromising on the target coverage. The PTV coverage in all treatment plans was comparable, and the mean value of PTV receiving 95% of the prescribed dose was highest in the N-IMRT plan followed closely by the BMS-IMRT and VMAT plans. However, when we consider the conformity index (CI), VMAT outperformed both N-IMRT and BMS-IMRT. While the N-IMRT and BMS-IMRT plans showed better homogeneity index (HI) than VMAT. These results suggest a more concentrated dose distribution in the target and less radiation to surrounding healthy tissues with the VMAT plan.

Bao (2019) [15] studied dosimetric parameters of different bone marrow sparing strategies in cervical cancer patients undergoing postoperative intensity-modulated radiotherapy (IMRT). The three BMS-IMRT plans used the BM, os coxae (OC), OC and lumbosacral spine (LS) respectively, as the BM OAR. The study recommended adding the os coxae and lumbosacral spine as the dose-volume constraint for BM sparing as the plans with OC and LS as BM OAR exhibited the best sparing of the bone marrow without compromising the dose to surrounding normal structures in such plans. Corbeau (2021) [16] reported that significant correlation were seen between bone marrow V_{10}, V_{20} and V_{40} and hematologic toxicity in locally advanced cervical cancer patients receiving chemoradiation with cisplatin. They observed a significant increase in hematological toxicity for whole pelvic bone doses of V_{10} > 95–75%, V_{20} > 80–65%, and V_{40} > 37–28%. In our study, regarding bone marrow dose parameters, VMAT demonstrated a clear advantage. VMAT significantly reduced the mean bone marrow dose compared to both N-IMRT and BMS-IMRT plans. In addition, VMAT provided superior bone marrow sparing for V_{10}, V_{20}, V_{30}, and V_{40} parameters compared to the N-IMRT plan and for V_{20}, V_{30}, and V_{40} parameters compared to the BMS-IMRT plan. These findings highlight the potential for VMAT to minimize the bone marrow toxicity that often accompanies radiotherapy, a significant advantage considering the critical role of bone marrow in overall patient health and treatment tolerance.

Mell (2006) [9] reported higher rates of Grade 2 or worse leukopenia and neutropenia in patients with BM V_{10} >10% than patients with BM-V_{10} <90%. No associations between HT and V_{30} and V_{40} were observed. The dosimetric parameters for PTV were comparable in all the treatment arms. The dose constraints were achieved in other OARs such as the rectum, bladder, bilateral femoral head, and small bowel. We observed that the dosimetric evaluation of these approaches in BM sparing showed better results with VMAT plans as they matched our clinical requirement since they demonstrated the highest CI with superior bone marrow sparing. In their study. Yu (2020) [17] proposed VMAT as a better bone marrow sparing IMRT option for cervical cancer patients, particularly in developing countries, due to greater dose conformity and OAR sparing.

In a study [18], (18)(F) fluorothymidine (FLT)-positron emission tomography (PET) images were used to delineate the active bone marrow volume to spare pelvic bone marrow using intensity modulated radiation therapy. The patients with more FLT-identified bone marrow who were treated to 4 Gy after one week developed grade 2 leukopenia earlier than those with less marrow who were exposed to 4 Gy. Functional imaging techniques, such as magnetic resonance imaging (MRI), single photon emission CT (SPECT), and positron emission tomography (PET), are potential modalities for identifying the active BM. But functional imaging is expensive and not universally available. We contoured the whole bone to ensure reproducibility as it is difficult to delineate bone marrow on CT images.

Our study is fraught with some limitations. Firstly, the study was carried out in a single centre with a small sample size, making it impossible to draw firm conclusions. As a result, a multi-center study with a bigger sample size and a longer follow-up period is required to obtain an appropriate comparison. Secondly, our study was purely dosimetric. The significant advantages of VMAT in sparing bone marrow need to be further corroborated with clinical studies. Moreover, the impact on acute and chronic hematological toxicity and quality of life needs to be assessed. Lastly, we did not include functional, imaging such as PET to delineate bone marrow.

Our study adds to the growing evidence that VMAT might be the preferred technique for patients with carcinoma of the cervix undergoing concurrent chemoradiotherapy, as it provides comparable target coverage and better sparing of bone marrow compared to IMRT. VMAT can be considered as a promising option to reduce hematological toxicity in such patients. However, further clinical trials are warranted to confirm these findings and to investigate the potential impact on patient outcomes. We hope that our findings stimulate further discussion and research towards the optimal integration of bone marrow sparing radiotherapy techniques into the standard treatment paradigm for carcinoma cervix, and ultimately enhance patient outcomes in this prevalent and impactful disease.

Author Contribution Statement

All authors contributed equally in this study.

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Ethics Committee

The research is hereby approved by the Institutional Ethics Committee. Sri Guru Ram Das University of Health Sciences Institutional Ethics Committee issued approval.

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