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ORIGINAL RESEARCH ARTICLE

Comparative Analysis of Dose Volume Histograms of Pelvic Bone Marrow and their Clinical Correlation in Patients of Cancer Cervix Treated with Conventional and 3-Dimensional Conformal Radiotherapy

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ABSTRACT

Introduction: Radiotherapy (RT) is the treatment of choice for cancer cervix in FIGO stage IIB and beyond and also in selected cases in initial stages. Conventional RT is planned on the basis of bony landmarks. Three-dimensional conformal RT (3D CRT) is planned on computed tomography (CT) which includes three-dimensional (3D) identification of visible tumor and organs at risk (OAR) that need to be included or avoided. Dose-volume histograms (DVH) are excellent tools for evaluating and compare isodose distribution in the concerned volumes. Hematological toxicity in cancer cervix is due to bone marrow radiation and concurrent chemotherapy given. The present study focuses on the delineation of bone marrow and comparing the DVH in conventional and 3D CRT to find clinical correlation in both groups.

Materials and Methods: A total of 50 patients were randomized into two groups - Group A treated by conventional radiotherapy and group B treated with 3D CRT. All patients received 50 Gy in 25 fractions at 2 Gy per day along with concurrent cisplatin followed by three fractions of intracavitary brachytherapy of 7 Gy each. Conventional planning was based on bony landmarks. 3D planning included the delineation of gross, clinical and planning target volumes along with different Organs at risk (OAR) s, including the bone marrow. Dosimetry parameters evaluated were D-max, D-mean and PTV-95 for planning target volumes (PTV) and V10, V20, V30, V40 and V50 for all subsites of bone marrow and as a whole bone marrow. Clinical correlation of hematological toxicity with dosimetric parameters of bone marrow were evaluated and statistical significance was seen using paired student t-test.

Results: Mean age of the patients was 48.22 years (range 28–70 years). The commonest symptom was yellowish/whitish discharge per vagina 44 (88%), and most patients had FIGO stage II(60%). Field sizes used in the 3D-CRT arms were significantly larger than those used for the conventional plans (p = 0.000). The difference in dosimetric parameters for PTV in both groups were not statistically significant. After 6 months, the complete response was 88% in group A and 92% in group B. No grade III and IV hematological toxicity was found except two patients who had grade III haemoglobin toxicity. In group A the whole bone marrow and ilium showed a significant correlation with the incidence of haematological toxicity for V-10, LSS forV-10, V-20, V-30 and lower pelvisbonefor V-10, V- 20, when compared to the other volumes. In group B, the whole bone marrow and ilium showed a significant correlation with the incidence of hematological toxicity for V-10, LSS and lower pelvis for V-10 and V-20 when compared to other volumes.

Conclusion: Bone marrow sparing should be done as much as possible to reduce hematological toxicity. Newer radiotherapy techniques like intensity-modulated RT may help achieve bone marrow's dose constraints.

Keywords: Bone marrow sparing, Conventional radiotherapy, three-dimensional conformal radiotherapy, hematological toxicity

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INTRODUCTION

Radiotherapy (RT) is the cornerstone and the treatment of choice for FIGO stage IIB, IIIA, IIIB or IVA carcinoma of the cervix and is an excellent alternative tosurgery in selected patients with stage IA, IB, or IIA diseases.[1,2] It usually consists of a combination of external beam radiotherapy (EBRT) and brachytherapy (BT), except in the stage IA disease where BT alone may be used.[2]

Historically, RT planning was guided by fluoroscopic or x-ray imaging that provided 2D data to determine areas to be treated by using bony landmarks. Limited soft tissue delineation was sometimes possible, for example, by instilling contrast in to the bowel and bladder.

With the introduction of advanced planning software and more powerful computers, the process of planning and delivering radiation changed. Information obtained from magnetic resonance imaging (MRI) and CT scanning could be incorporated into the planning.

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This includes three-dimensional (3D) identification of visible tumors and organ at risk (OAR) that needed to be included or avoided. Therefore, a better quantitative assessment of what tissues and/ or structures were being radiated was obtained. 3-dimensional conformal radiation therapy (3DCRT) has been shown to give better and more precise target coverage (20% reduction in the risk of a geographical miss) and has significantly reduced the volume of radiation-exposed bladder and bowel.[3,4]

Dose-volume histograms (DVH) are the mathematical tool of the 3D treatment planning system, which summarizes the entire treatment plan into 2D graph. It is an excellent tool to evaluate and compare different optimal isodose distribution of treatment plans using dose-volume parameters, isodose curves, colored display of isodose distributions in treatment volume, dose homogeneity index and dose conformity index.

With the increasing use of concomitant chemotherapy (CTX), particularly in cervical cancer patients, HT is now one of the most common acute sequelae in Gynaecology patients undergoing RT. The bone marrow (BM) is the most radiosensitive pelvic organ. Moreover, approximately 40% of the total body BM reserve lies within the pelvic bones. Because most patients undergo whole pelvic RT (WPRT), much of the total body BM reserve is within the treatment fields and thus exposed to the toxic effects of radiation. Moreover, most CTX agents used in these women are myelotoxic.[5-8]

Most studies have confirmed that the myelosuppression observed in the patients receiving concurrent chemotherapy and pelvic radiation therapy is related to the volume of BM receiving 10 or 20 Gy. Therefore, reducing the incidence of acute hematologic toxicity is possible by reducing the volume to low-dose irradiation. So, the present study focuses on comparing and evaluating the dose volume histograms of pelvic bone marrow in cervical cancer patients treated with conventional and 3D conformal radiotherapy to find the clinical correlation of both groups.

MATERIALS AND METHODS

The study was conducted at Department of Radiation Oncology at R.R. Cancer Institute and Research Centre, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly.

Pre-treatment assessment was done by complete medical and physical examination including bimanual pelvic and rectal examination, cervical biopsy, baseline haematological test (hemogram, renal function test, liver function test), chest radiography, ultrasound abdomen or CECT abdomen and pelvis and cystoscopy and proctosigmoidoscopy (only if clinically indicated).

Inclusive criteria included patients having cancer proven biopsy, age >18 years, Karnofsky performance scale above 70, stage IB1 to IV A, no history of previous malignancy and normal haematological, hepatic, renal and cardiopulmonary functions.

Exclusion criteria include patients having carcinoma of the cervix FIGO stage IV B, metastatic disease and any previous pelvic malignancy.

Patients were randomized to either the conventional radiotherapy technique (Group A)or the 3-dimensional radiotherapy technique (Group B).

Radiotherapy Planning

Conventional Radiotherapy technique was planned by four field box techniques-anteroposterior (AP) and posterior-anterior (PA) and two opposing laterals (90 and 270°) using standard bony landmarks. In AP/PA field: Superior: L4/L5 junction; Inferior: 3 cm distal to vaginal marker placed in vagina; Lateral: 1.5 to 2.0 cm beyond pelvic brim. In lateral field: Superior and inferior: As in AP field; Lateral: Anterior- Anterior border of pubic symphysis; Posterior- S2/S3 junction.

In 3D radiotherapy first the delineation of gross tumor volume (GTV), clinical target volume1 (Tumor CTV1), including GTV, uterus, vagina, bilateral parametrium and CTV2 (Nodal CTV) including pelvic lymph nodes – common iliac, external iliac, internal iliac, obturator and presacral. The PTV was taken 1 cm beyond CTV (CTV1 +CTV2). The radiotherapy dose delivered was 50 Gy in 25 fractions in 5 weeks at 200 cGy/day by linear accelerator.

This was followed by 3 applications of intracavitary brachytherapy of 7 Gy/ fraction each to point A.

Chemotherapy Administration

Patients received concurrent cisplatin 35 mg/m^2 on weekly basis during radiotherapy. They were adequately hydrated with 2–2.5 L of fluids and supplemented with injectable KCL, MgSO4 and MVI. Radiotherapy was delivered within 30 minutes of administration of cisplatin and proper antiemetic therapy with 5-HT3 antagonist, dexamethasone, and ranitidine was given prior to chemotherapy administration.

Complete blood counts, kidney function tests and liver function tests were repeated in all patients every week before each chemotherapy cycle.

Clinical response was assessed during radiotherapy and every month after radiotherapy for at least 6 months. The patients were assessed for objective tumor response according to WHO criterion complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Radiation toxicity was assessed by RTOG acute and late morbidity scoring criteria. Hematological toxicities were graded according to common toxicity criteria version 4.03.

Delineation of Bone Marrow

For each patient, in both the groups the external contour of all bones within the pelvis was delineated on the planning CT scan, as a proxy for the BM. The external contour was chosen, rather than the low-density regions within the bones, to ensure reproducibility and to minimized ependence of the contours on CT window in and levelling.

The Entire Bony Contour was Divided into Four Subsites:

- Ilium—including the iliac crests extending to the superior border of the femoral heads;
- Lowerpelvis (LP)—consisting of the pubis, ischia, acetabula, and proximal femora extending from the superior border of the femoral heads to the inferior border of the ischial tubero sities;
- Lumbo sacralspine (LSS)—extending superiorly from the appearance of the iliac bone and inferiorly to include the entire sacrum; and
- Whole pelvic bone marrow (WBM) — which includes all the above three subsites.

Dosimetric Parameters

Conformal plans were generated for optimal PTV coverage, ensuring that 95% of the PTV received 95% of the prescribed dose. Dose was normalized at isocentre. Subsequently, the field sizes were recorded. Dosimetric parameters of PTV that were evaluated were -

- **Dmax(%):** Maximum percentage of dose received by PTV.
- **Dmean(%):** Minimum percentage of dose received by PTV.
- **PTV-95(%):** Dose received by 95% of the PTV

DVHs corresponding to the delivered conventional 2-D plan and 3-D CRT plan were generated for each contoured BM region. The volume of each region receiving 10, 20, 30, 40, and 50 Gy (V10, V20, V30, and V40, V50, respectively) were quantified.

These Dosimetric parameters were designated as follows:

- Whole Pelvic BM: - WBM-V10, WBM-V20, WBM-V30, WBM-V40 and WBM-V50;
- liumBM:- I-V10, I-V20, I-V30, and I-V40;
- LowerPelvis:- LP-V10, LP-V20, LP-V30, LP-V40 and LP-V50; and
- LSSBM:- LSS-V10, LSS-V20, LSS-V30, LSS-V40 and LSS-V50.

The total volume (mL) and the mean dose (cGy) of each bone marrow subsite were also generated.

Statistical Analysis

Collected data were analyzed using standard statistical methods and software's (SPSS Version. 21.) to calculate significance levels using"p" value either by chi square test, or Z score. Paired student-t test has been used to find the significance of study parameters like correlation between haematological toxicity and dosimetric values on a continuous scale in each group. Statistical significance was considered with *p-value* of < 0.05.

RESULTS

A total of 50 patients were enrolled in this study. In this study, the mean age of the patients was 48. 22 years, the median age of thepatient were 49.5 years and the patient range between 28 years to 70 years. Less than half of the patients belonged to 4^{th} decade, with 48% patients in both group A and 40% patients in group B.

Among all patients 62% (31 patients) are post-menopausal, 34% (17 patients) are pre-menopausal, and 4% (2 patients) are peri-menopausal. It has been seen that a significantly higher incidence of cancer cervix is seen in post-menopausal women.

During initial presentation, the commonest symptom was yellowish/whitish discharge per vagina 44 (88%) followed by post-menopausal bleeding P/V (74%) and pain in lower abdomen (60%). Therewerenosymptomsof rectal bleeding or hematuria seen in any of the patients.

Most of the patients were of stage IIB (48%) followed by stage IIIB (20%) and stage IIA (12%

Field Size

Fieldsizesused in the 3D-CRTarmswere significantly largely than those used for the conventional plans (p = 0.000). Field sizes in the AP field ranged from 15.8*16.6 –21.3*22.4 cm^2 in the conventional arm, whereas it was between 15.3*21–22.7*24.4 cm^2 in the 3D-CRT arm. Field sizes in the Lateral field ranged from 10*18 cm^2 to 20*20 cm^2 in the conventional arm, whereas it was between 11.5*20 to 16.8*24.4 cm^2 in the 3D-CRT arm.

Dosimetric parameters for PTV

- ThePTVD-max was similar in both the groups (p=0.12)
- The D-mean was not statistically different in both the arms (p = 0.47),
- There was no significant difference in PTV-95 in both groups(p = 0.82).

Response Evaluation

Following EBRT, 72% of patients in group A and 64% of patients in group Bhad complete the response. At 6^{th} month follow-up, 88% of the patients in group A and 92% of patients in group B had complete responses. Two patients in group A had progressive disease.

Hematological Toxicities

No grade III and IV hematological toxicity was found except two patients who had grade III haemoglobin toxicity in both groups (Table 1).

Table 1: Arrangement of the table so that Group A and Group B can be identified seperately. A line in between or something. Present arrangement is confusing

Hematological parameters	No.of patients(%)								p-value
	Group A				Group B				
	Grades				Grades				
	0	1	2	3	0	1	2	3	
Hemoglobin	06	10	08	01	15	04	05	01	0.29
TLC	19	04	02	00	21	02	02	00	0.33
DLC (Neutrophils)	20	04	01	00	22	03	00	00	0.15
Platelet	24	01	00	00	25	00	00	00	-
Serum urea	25	00	00	00	25	00	00	00	-
Serum creatinine	18	06	01	00	22	02	01	00	0.23
Serumbilirubin	20	03	02	00	21	04	00	00	0.45

Table 2: Clinical correlation between hematological toxicity and dosimetric parameters in patients of Group A (n)

Parameter	Group A	Hematological	
DVH	Mean ± (SD)	Toxicity (WBC)	p-value
Whole BM			
V-10	101.13 ± 2.04	8	0.03
V-20	99.24 ± 3.46	6	0.08
V-30	94.83 ± 8.50	2	0.12
V-40	87.01 ± 14.06	3	0.37
V-50	75.17 ± 16.94	2	0.29
LSS			
V-10	101.33 ± 2.55	6	0.04
V-20	96.24 ± 20.21	6	0.03
V-30	97.69 ± 7.10	4	0.04
V-40	94.36 ± 11.36	3	0.26
V-50	88.87 ± 17.53	3	0.36
Ilium			
V-10	99.56 ± 3.29	9	0.04
V-20	95.46 ± 6.07	6	0.07
V-30	85.04 ± 18.70	7	0.24
V-40	75.02 ± 15.54	5	0.39
V-50	62.25 ± 18.26	4	0.42
Lower pelvis			
V-10	100.42 ± 2.29	9	0.03
V-20	94.6 ± 6.88	8	0.04
V-30	78.08 ± 17.28	4	0.18
V-40	58.22 ± 25.05	6	0.23
V-50	45.37 ± 25.86	3	0.45

Clinical correlation between hematological toxicity and Dosimetric parameters of bone marrow

- In group A the whole bone marrow and ilium showed a significant correlation with the incidence of hematological toxicity for V-10, LSS for V-10, V-20, V-30 and lower pelvisbonefor V-10, V- 20, when compared to the other volumes (Table 2).
- In group B, the whole bone marrow and ilium showed a significant correlation with the incidence of hematological toxicity for V-10, LSS and lower pelvis for V-10 and V-20 when compared to other volumes (Table 3).

P-value of the means of all dosimetric parameters of bone marrow in both groups (Table 4)

- In group A, the Lumbosacral spine showed a much higher dose distribution, especially in the V10, V20 and V30 volumes and in group B the lumbo sacral spine showed higher dose distributions in V10 and V20 volumes.The pvaluewassignificantintheV50volume.(p = 0.04)
- In group A, Lower Pelvis showed least dose distribution especially in the V40 and V50 volumes and in group B the Lower Pelvis showed least dose distribution in all the volumes. The p-value was significant in the V50volume.(p = 0.04)
- In group A, Ilium showed moderate dose distribution, especially in theV30, V40 and V50 volumes and in group B the Lower Pelvis showed leastdose distribution in all the volumes. The p-value was significant in theV40 and V50volumes.(p=0.04 and p=0.03)
- In group A, Whole bone marrow showed a much higher dose distribution in all the volumes and in group B the Whole bone marrow showed lower dose distributions in V40 and V50 volumes, the p-value for all the sites were not significant except for V50 volume when compared in both the groups.(p = 0.02)

DISCUSSION

Sectional CT scan enables the visualization and delineation of the cervix, uterus, vagina, iliac vessels, and organs at risk such as bladder, rectum,and intestine, 3D-CRT has become a preferred treatment for gynecologic malignancies. It gives better, more precise target coverage while reducing the risk of a geographical miss by 20%.[3] Studies have shown that 3D-CRT improves patient tolerance to curative treatment and allows for dose escalation.[9]

Table 3: Clinical correlation between hematological toxicity and dosimetric parameters in patients of Group B (n)

Parameter	*Group B*	*Hematological*	
DVH	Mean ± (SD)	*Toxicity (WBC)*	*p-value*
Whole BM			
V-10	93.77 ± 9.88	5	0.04
V-20	89.28 ± 10.4	3	0.07
V-30	59.36 ± 6.47	2	0.18
V-40	41.39 ± 8.65	2	0.64
V-50	22.58 ± 16.61	2	0.38
LSS			
V-10	99.16 ± 2.17	5	0.04
V-20	98.16 ± 3.53	6	0.03
V-30	78.74 ± 21.46	3	0.61
V-40	64.92 ± 20.94	2	0.49
V-50	29.05 ± 23.34	1	0.83
Ilium			
V-10	88.71 ± 21.06	6	0.04
V-20	83.27 ± 20.33	4	0.09
V-30	56.36 ± 15.07	4	0.49
V-40	36.82 ± 8.66	3	0.67
V-50	20.15 ± 10.13	1	0.35
Lower pelvis			
V-10	84.22 ± 27.74	6	0.03
V-20	74.13 ± 30.97	4	0.04
V-30	44.31 ± 8.84	3	0.61
V-40	29.88 ± 9.58	2	0.89
V-50	15.94 ± 8.2	3	0.26

Table 4: *p-value* of the mean so fall dosimetric parameters in both the groups

DVH	*Conventional (mean)*	*3D-CRT (mean)*	*p-value*
Whole BM			
V-10	101.13	93.77	0.79
V-20	99.24	89.28	0.60
V-30	94.83	59.36	0.93
V-40	87.01	41.39	0.95
V-50	75.17	22.58	0.02
Total volume	1019.14	965.8	0.59
Total dose	34.57	35.63	0.08
Ilium			
V-10	99.56	88.71	0.26
V-20	95.46	83.27	0.67
V-30	85.04	56.36	0.79
V-40	75.70	36.82	0.04
V-50	62.25	20.15	0.03
Total volume	908.27	299.22	0.14
Total dose	31.5	34.36	0.21
Lower pelvis			
V-10	100.42	84.22	0.20
V-20	94.60	74.13	0.75
V-30	78.08	44.31	0.60
V-40	58.22	29.88	0.74
V-50	45.37	15.94	0.04
Total volume	403.33	375.62	0.84
Total dose	28.49	32.71	0.20
LSS			
V-10	101.33	99.16	0.31
V-20	96.24	98.16	0.52
V-30	97.69	78.74	0.33
V-40	94.36	64.92	0.22
V-50	88.87	29.05	0.04
Total volume	390.49	262.06	0.70
Total dose	43.12	42.03	0.66

Hence this study was done to assess the compliance, hematological toxicities, dosimetric parameters and clinical correlation in patients with cancer cervix treated with external beam radiotherapy by either conventional or three-dimensional conformal radiotherapy along with concurrent chemotherapy followed by HDRB rachy therapy applications.

Field Sizes

Pendlebury *et al.*,[10] also found that 62% of patients required alteration of the conventional pelvic portals based on lymph angiographic findings, with most requiring enlargement of one/more portals while in 20% of patients, portals could actually be reduced. They found that the lateral border of the AP/PA portals and the anterior border of the lateral portals were most often inadequate and recommended 2.5 cm margin from the pelvic brim for the former and 0.5 cm margin anterior to the symphysis pubis for the latter so as to cover 90% of the pelvic nodes.

A study by Finlay *et al.*,[11] found that had conventional portals alone been used for radiotherapy planning, the majority (95.4%) of subjects would have had atleast one inadequate margin, the majority located superiorly though in around half the subjects, at least one margin would have been generous (>2 cm beyond the blood vessel), usually the lateral borders of the AP/PA portal.

Ina study by Beadle *et al.*,[12] it was found that the majority (66%) of pelvic nodal failures were marginal; 71 out of 119 patients recurred above the treatment field, 2 had inguinal nodal failures while 2 other patients had recurrences both above the treatment field and in the inguinal lymph nodes. This was one of the first studies to correlate the site of regional recurrence with respect to the treatment portals.

In our study the field sizes used in the 3D-CRT arms were significantly larger than those used for the conventional plans (p = 0.00001 for both anteroposterior

fields and lateral fields are significant), which was in accordance to the study done by Finlay *et al.*.[11]

Hematological Toxicities During Treatment

Hematologic toxicity can lead to delayed or missed chemotherapy cycles and treatment breaks,which potentially may compromise disease control. Hematologic toxicity predisposes patients to infection, hospitalization,and requirements for transfusions and growth factors. The hematopoietic stem cells of the bone marrow are very sensitive to radiation.[13] It is shown that increased dose to the bone marrow and increased volume of the marrow in the field of radiation can proportionately increase the risk of acute hematological toxicities.[14] Pelvic bones, proximal femur and lumbar vertebra contain 34.5, 4.5, and 16.6% of the functional bone marrow in an adult.[13]

Nearly, 50% of body bone marrow is in pelvic and neighboring bones, which come in the field of radiation in the treatment of carcinoma cervix.

In a study by Rose *et al.*[5] sparing functiona lBM subregions instead of the entire BM is one investigational approach to limiting hematologic toxicity. Functional imaging with positron emission tomography (PET), single positron emission CT (SPECT), and/or specialized MRI sequences has been proposed asa means to identify active BM subregions. Irradiation of BM subregions with higher fluoro deoxyglucose(18F-FDG)-PET activity was associated with hematologic toxicity, whereas irradiation of subregions with lower FDG activity was not.

In the study by Che SM *et al.*, the rate of bone marrow depression between the 3-DCRT and conventional RT groups were respectively 71% and 63% with nosignificant difference ($p > 0.05$).[16]

In our study, we found that 21 (42%) patients had normal hemoglobin level, 14 (28%) patients had grade I toxicity and 13(26%) patients had grade II toxicity, 2(4%) patients had grade III toxicity. Grade 2 anemia was seen in 8 (32%) patients in group A and 5(20%) patients in group B, but the difference was not statically significant ($p = 0.29$) which was similar to the study done by Che S M *et al.*,[16]

Higher doses of radiation may lead to chronic myelo suppressive effects and poor tolerance to subsequent chemotherapy by damaging the bone marrow (BM) microenvironment. Large prospective studies have demonstrated that the rate of grade 3 hematologic toxicity with cisplatin-based pelvic chemoradiotherapy is approximately 20–25%. Extended-field RT leads to the irradiation of a larger proportion of the total BM and a correspondingly higher rate of hematologic toxicity. Especially grade neutropenia and grade thrombocytopenia.[17]

In our study 40 (80%) patients, the TLC was normal, while 06(12%) and 04(08%)patients showed grade I and grade II toxicity, respectively. There was grade 1 thrombocytopenia in 1 (4%) patients in group A, which was similar to the study done by Mauch Petal.[17]

Response Evaluation

Our results are in conjunction with the results of various studies in which concurrent chemotherapy was used with conventional radiotherapy. Sorbe B *et al.*[18] conducted a study in which carcinoma cervix patients were treated with concurrent chemoradiotherapy (conventional radiotherapy) and intracavitary brachytherapy. It was observed in this study that patients with squamous cell carcinoma had a complete response rate of 96%. In a retrospective study by Tharavichitkul E *et al.*, it was observed that local control rates in patients who received conventional radiotherapy with concurrent chemotherapy (cisplatin) was between 84 to 96% depending on the number of cycles received.[19]

In the study by Che SM *et al.*, in which the clinical treatment effect of 3D-CRT in cervical carcinoma was compared with conventional radiotherapy, it was observed that the local control rates in the treatment group and the control group were respectively 96 and 97%, with no significant difference ($p > 0.05$).[16]

In our study, the local control rates were 84 and 88%, respectively in groups A and B (*p-value* = 0.078) and were similar to the results of Che SM *et al.*, study. The follow-up time is too short to assess definitively the local control as the response was assessed at 6 months only, further follow-up is needed to ascess the local control and treatment response.

Hematological Toxicity and Bone Marrow Dosimetry

The results of our study have provided quantitative evidence of an association between the volume of pelvic BM receiving low-dose radiation (V10, V20) and acute HT in patients who are treated in the conventional arm. In addition, better delivery of chemotherapy was noted in the patients with decreased BM RT. The association with low dose dosimetric parameters were consistent with the known radio sensitivity of bone marrow.[20-25] Previous studies have shown that prolonged BM suppression and irreversible morphologic BM changes can occur at doses 30–50 Gy.

In our study, we did not find significant associations between HT and BM volumes receiving greater doses (V30,V40); however, the small sample size may preclude dourability to detect such correlations. Alternatively,it may be the case that greater doses are not as relevant as low doses for acute HT,but have a significant effect on chronic toxicity.

Mundt *et al.*[26] in his study stated that BM-V10 < 90% had reduced grade 2 orworse leukopenia and neutropenia (11.1 and 5.6%, respectively) compared with patients with a BM-V10 of > 90% (73.7 and 31.6%, respectively).

Brent S. Rose[27] *et al.* in his study of normal tissue complication probability modelling of Acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy observed that in the validation cohort, significant negative correlations were observed between white blood cell count (WBC) nadir and V10 (regression coefficient ($\beta = -0.060$, $p = 0.009$) and V20 ($\beta = -0.044$, $p = 0.010$). In the combined cohort, the (adjusted) β estimates for log (WBC) vs.V10 and V20 were 0.022 ($p = 0.025$) and −0.021 ($p = 0.002$), respectively. Patients with V10 ≥ 95% were more likely to experience grade ≥ 3 leukopenia (68.8 vs. 24.6%, $p < 0.001$) as were patients with V20 > 76% (57.7 vs. 21.8%, $p = 0.001$). Finally, he stated that his findings support the hypothesis that HT increases with increasing pelvic BM volume irradiated. Effortstomaintain V10 < 95 and V20 < 76% may reduce hematologicaltoxicity.

In our study, we found out that the BM- V 10 and V 20 <90 % had less incidence of grade 2 anemia and leucopenia, which was in accordance with the study donebyMundtetal[26]

Loren K *et al.*[28] in his study observed that Increased pelvic BM V10 (BM-V10)was associated with an increased grade 2 or worse leukopenia and neutropenia (odds ratio [OR], 2. 0995% confidence interval [CI], 1.24–3.53; p-0.006; and OR 1.41; 95% CI 1.02–1.94; p-0.037, respectively). Patients with BM-V10 > 90% had higher rates of grade 2 or worse leukopenia and neutropenia than did patients with BM-V 10 < 90% (11.1 vs.73.7%, p<0.01; and 5.6 vs.31.6%, p=0.09) and were more likely to have chemotherapy held on univariate (16.7 vs. 47.4%,p = 0.08) and multivariate (OR, 32.2; 95% CI, 1.67– 622; p-v0.02) analysis. No associations between HT and V30 and V40 were observed. Dosimetric parameters involving the lumbosacral spine and lower pelvis had stronger associations with HT than did those involving the ilium.

Beina Hui *et al.*,[29]in his study, stated that the bone marrows V30, V40, and V50 were lower in the IMRT group than in the 3D-CRT group (62.93 vs 76.91%, 31.36 vs 39.60%, and 9.79 vs 15.44%, respectively). No statistical difference was observed for both V10 and V20.

As compared to the study done by Beina Hui *et al.*[29] in our study we observed that there was no clinical correlation of hematological toxicity in V-40 and V-50 in all the sites of bone marrow

CONCLUSION

Bone marrow sparing is important to reduce hematological toxicity. In our study strongest associations with HT were with the lumbosacral spine and lower pelvis rather than the ilium. Although the intentional use of iliac-sparing in some patients may have minimized the association between iliac BM RT and hematological toxicity, sparing of all BM subsites is clinically important. Newer radiotherapy techniques like intensity-modulated RT may help obtain bone marrow dose constraints.

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