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Original Research Article

Integrating dosimetric and clinical insights: correlating acute bone marrow toxicity with irradiated marrow volume in rectal cancer patients undergoing concurrent chemoradiation

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ABSTRACT

Background: Concurrent chemoradiation is one of the major treatments for locally advanced rectal cancer. As radiation therapy suppresses the bone marrow, it is essential to quantify the dose received by the pelvic bone marrow (PBM), which constitutes about 50% of the hematopoietic bone marrow.
Methods: A prospective study conducted in 50 patients with locally advanced rectal cancer treated with long course concurrent chemoradiation. All the patients were followed up with weekly complete blood count for assessing hematological toxicities and were graded. PBM was contoured and subdivided into ilium bone marrow (IBM), lower pelvis bone marrow (LPBM) and lumbosacral bone marrow (LSBM). Volumes of bone marrow receiving different doses were quantified.
Results: Among the 50 patients, 40 (80%) developed acute bone marrow toxicity, during the course of treatment. Highest grade of bone marrow toxicity developed in 20 (40%) patients which was grade 2. Compared to grade 1, grade 2 neutropenia patients exhibited significantly higher levels of V10 to V40 ($p<0.05$) in PBM and significantly higher levels of V20 in IBM and LSBM. In LPBM, compared to grade 1 leukopenia and neutropenia, grade 2 leukopenia and neutropenia exhibited significantly higher levels of V10 and V20 ($p<0.05$).
Conclusions: Increased PBM V10 to V40, IBM V20, LSBM V20, LPBM V10 and V20 were significantly related to the higher grades of neutropenia in locally advanced rectal cancer patients undergoing long course concurrent chemoradiation. Increased LPBM V10 and V20 were also significantly related with higher grades of leukopenia

Keywords: Rectal cancer, Bonemarrow toxicity, Dosimetric parameters, Concurrent chemoradiation

INTRODUCTION

Colorectal cancer (CRC) remains a major worldwide health problem. In 2020, nearly 2 million cases of colorectal cancer were diagnosed, making it the third most prevalent cancer form globally. It causes about 1 million cancer deaths annually and is the second most prevalent cancer death cause.[1] More than half of all cases and deaths from colorectal cancer are reported from Asia, where the disease is most prevalent. According to the international agency for research on cancer (IARC), there will be more than 3 million new cases of colorectal cancer per year by 2040, a 56% rise in the worldwide burden of the disease. Even more significantly, an anticipated 69% rise in disease-related deaths, or over 1.6 million deaths globally in 2040, is estimated. The majority of the increase is anticipated to take place in nations with high human development indexes.[1] In India, the annual incidence rates (AARs) for rectal cancer in men is 4.1 per 100000. Rectal cancer ranks ninth among men.[2] Management of rectal cancer will depend on stage of disease. The results of surgical treatment of rectal tumors have been limited by the development of local-

regional recurrence following "curative operations". This is expected to occur in about one fourth of patients.[3]

Advances in pelvic radiation techniques, new adjuvant systemic therapies and experimentation of different neoadjuvant (preoperative) regimens and adjuvant (postoperative) therapies have contributed to reduce the high rates of local recurrence in patients with rectal cancer.[4] This multimodality intervention associated with refinement of surgical techniques, particularly the standardization of sharp total mesorectal excision and improvements in perioperative care, has contributed to improve both management and overall survival of these patients during the last three decades.[5] As a result of this integrated effort, the management of rectal cancer has evolved tremendously. It is widely accepted that decisions regarding therapeutic options need to be individualized and should preferably be based on a multidisciplinary discussion.

Currently, concurrent chemoradiotherapy is one of the main treatments for both pre-op and post-op locally advanced carcinoma rectum, this suppresses tumor local recurrence as well as improves overall survival. Both radiotherapy and chemotherapy cause damages to bone marrow in different degree and loss of blood cells.[6]

Hematological toxicity is a major factor in treatment interruptions, which can prolong the course of treatment overall and have negative side effects. Hematopoietic stem cells (HSCs), multipotent progenitors (MPPs), hematopoietic progenitor cells (HPCs), and numerous fully formed blood cells are all found in bone marrow (BM), the major hematopoietic tissue in humans.[7] HSCs are kept in a quiescent state under normal physiological conditions, which is advantageous for lifelong hematopoiesis. Leukopenia is the first symptom of BM suppression since granulocytes only live for 6-8 hours (neutropenia).[7] Apoptosis and reduced proliferative capacity of HSCs and progenitor cells are results of irradiation to the BM cavity. Inducing the cells to enter the cell cycle and disrupting the HSC niche also disturbs the resting state of HSC.[8] Radiation not only suppresses the BM but also kills granulocytes directly or cause chromosomal alterations. BM and lymphoid tissues are highly radiosensitive due to their excessive proliferation and low-grade differentiation. Healthy adults hematopoietic bone marrow is mostly found in flat, irregular bones. Radiation therapy for rectal cancer can cause acute and chronic hematologic toxicity because more than 50% of the hematopoietic bone marrow is in the hip, sacrum, proximal epiphysis of the femur, and lumbosacral spine.[9,10]

Since the rates of grade 2 and 3 leukopenia are 19.7% and 3.3%, respectively, Jin et al found that leukopenia is the most severe side effect brought on by capecitabine chemotherapy combined with radiotherapy in rectal cancer patients.[11] Additionally, 69% of rectal patients getting concurrent chemoradiotherapy and capecitabine experience leukopenia, with grade 3 leukopenia developing in 4% of the patients, according to research.[12] In colon cancer patients receiving capecitabine chemotherapy only 4% develop bone marrow suppression, showing minimal side effects to bone marrow.[13] As a result, assumption has been made that radiation therapy may be main reason for hematologic toxicity when chemotherapy and radiation therapy are being used concurrently to treat rectal cancer.

This study is to analyse acute bone marrow suppression in rectal cancer patients receiving concurrent chemoradiation and to provide potential predictors for bone marrow suppression.

METHODS

Study method

A prospective observational study was conducted in the department of radiation oncology, government medical college, Kozhikode, Kerala, among 50 rectal cancer patients receiving long course concurrent chemoradiation, from February 2021 to August 2022. Patients in the age group 18-80 years and Eastern cooperative oncology group performance status <2 were selected after attaining informed written consent. Patients with pre-existing bone marrow suppression, bone metastasis or prior pelvic radiotherapy were excluded.

Most of the patients were treated with a dose of 45 Gy in 25 fractions (1.8 Gy/Fr) followed by a boost of 5.4 Gy in 3 fractions over 5-6 weeks. Three patients were treated with different doses, 46 Gy in 23Fr, 45 Gy in 25 Fr and 51.4 Gy in 26 Fr. All the patients received concurrent chemotherapy with Tab. Capecitabine 825 mg/m^2 twice daily for 5 days a week.

All the patients were planned by CT simulation. Patients were asked to void bladder and drink 500 ml of water half an hour before the CT simulation, to obtain a full bladder. Similar bladder voiding and fluid intake instructions were given while treating patients. After preparation, patients were made to lie supine on couch in CT simulator. CT scan obtained from mid lumbar spine to middle femur, with 2.5 mm thickness. These images were transferred to treatment planning system (TPS) and contouring was done.

The primary tumor and the metastatic lymph nodes included in gross tumor volume (GTV). Clinical target volume (CTV) should include the GTV plus areas at risk for microscopic spread from the primary tumor and at-risk nodal areas, which were obtained by contouring vessels from common iliac bifurgation and giving 7 mm margin.[14] At-risk nodal regions include mesorectal, presacral, internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures. Superiorly CTV includes entire rectum and mesorectum, usually up to L5/S1 and at least 2 cm

margin superior to gross disease, whichever is most cephalad. Inferiorly CTV extends to pelvic floor or at least 2 cm below the gross disease, whichever is caudal. The planning target volume (PTV) was obtained by expanding CTV with a 0.5-1.0 cm margin to account for set up uncertainty and organ motion.[15]

OAR delineated according to the guidelines for delineation by radiation therapy oncology group (RTOG), including bladder, the intestine within the irradiation range, femoral head.

Delineation of PBM

PBM was delineated to replace hematopoietic bone marrow as first described by Mell et al.[9] PBM was contoured after treatment planning (Figure 1), not as an OAR. The external contours of pelvic bones were contoured in bone window. The entire PBM includes bilateral IBM including the iliac crest extending to the upper border of femoral head; LPBM including region extending from the superior border of femoral head to the inferior border of ischial tuberosities, including pubes, ischia, acetabula and proximal femora; lumbosacral spine bone marrow (LSBM) including the region extending from the superior border of L5 to coccyx (Figure 2).

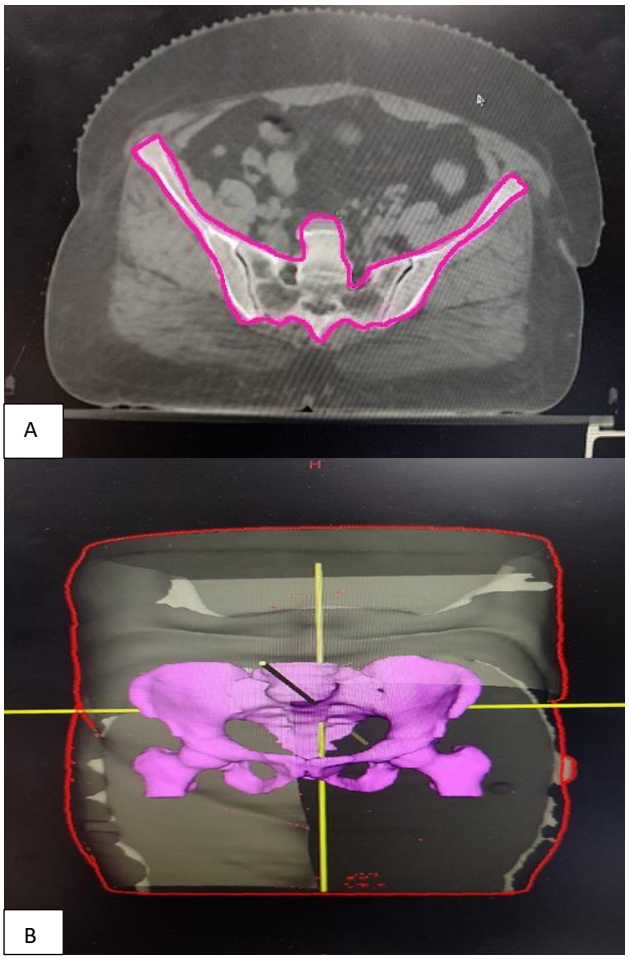

Figure 1 (A and B): PBM contouring.

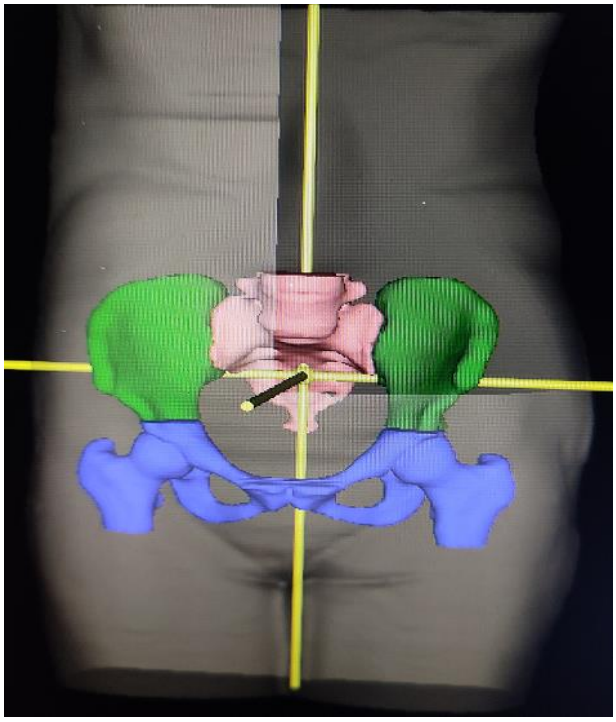

Figure 2: PBM subdomains: IBM (green), LPBM (blue), LSBM (pink).

The volumes of PBM receiving 10, 20, 30 and 40 Gy (V10, V20, V30 and V40) were quantified using dose volume histogram. The volumes of IBM, LPBM and LSBM receiving 10, 20 Gy (V10, V20) were also quantified.[7]

Grading of acute bone marrow suppression

The initiation and completion of radiotherapy were the starting point and end point of this study. Blood routine examinations were carried out before initiation of treatment to rule out pre-existing bone marrow suppression. Weekly complete blood count (CBC) was collected during concurrent chemoradiation. Acute bone marrow toxicities were graded according to the CTCAE version 5 grading for hematological adverse events. Acute bone marrow toxicity was defined as any grade of haematological toxicity development.

Ethical considerations

Institutional ethics committee (IEC) clearance was obtained. Data collection was started only after getting ethics committee approval for study. Confidentiality have been ensured and maintained.

Statistical analysis

Data was coded, entered in Microsoft excel and analysed using SPSS software version 18. Qualitative variables were expressed in frequency and percentages and quantitative variables were expressed as mean and standard deviation. The association between acute bone

marrow toxicity and irradiated bone marrow volume was statistically tested using Pearson chi square test and t test, strength of association was expressed as odds ratio and 95% confidence interval. The level of significance of association was set at $p<0.05$. Receiver operating characteristic curve (ROC) analysis was performed to determine the bone marrow dosimetric thresholds of acute bone marrow suppression.

RESULTS

A total of 50 patients with locally advanced rectal cancer treated with concurrent chemoradiation in the age group 18-80 years were included in the study, the mean age was 59±11.3 years.

Table 1: Clinical factors, disease and treatment details.

Variables	N
Gender	
Male	30
Female	20
Age (in years)	
<60	22
≥60	28
TNM stage	
I-II	11
III-IV	39
Surgery	
Yes	5
No	45
Dose received	
50.4 Gy/28 Fr	47
46 Gy/23 Fr	1
45 Gy/25 Fr	1
51.4 Gy/26 Fr	1
Radiotherapy plan	
3DCRT	49
Rapid arc	1

Majority of the patients were males (60%), with a male to female ratio of 3:2. Majority of the patients were stage IIIB (50%), followed by stage IIIC (24%). The 45 patients (90%) were treated with neoadjuvant chemoradiation, while only 5 patients (10%) were treated with adjuvant chemoradiation.

Majority of the patients (94%) were treated with 50.4Gy/28Fr. Only 3 patients were treated with different doses like 46Gy/23Fr, 45Gy/25Fr and 51.4Gy/26Fr.49 out of 50 patients (98%) were treated with 3DCRT technique. Only one patient treated with rapid arc technique.

The mean volume of PBM receiving 10 Gy, 20 Gy, 30 Gy, 40 Gy in the study are 94.7±4.26%, 90±10.6%, 54.8±10% and 37.5±9% respectively. Mean dose received by PBM is 34±2.8Gy (Table 2).

Among the patients who developed bonemarrow toxicity, leukopenia and neutropenia was most common (64%) followed by anemia (54%). Only 2 patients (4%) developed thrombocytopenia. Only grade 1 and grade 2 toxicities were developed in the patients. In total, 20 patients developed grade 1 toxicity and 20 patients developed grade 2 toxicity (Including anemia, leukopenia, neutropenia and the thrombocytopenia together).

There is no significant difference in the development of bone marrow toxicity among males and the females ($p>0.05$).

There is no significant difference in the development of bone marrow toxicity among different composite stages ($p>0.05$).

Bone marrow toxicity at different levels of exposure

Only grade 1 and grade 2 toxicities were developed in the study population.

There is a statistically significant difference in the mean percentage of irradiated bone marrow volume and development of Grade 1 and Grade 2 neutropenia from volume receiving 10 Gy to volume receiving 40 Gy ($p=<0.05$)) (Table 2).

There is a statistically significant difference in the mean dose received by PBM and development of grade 1 and grade 2 neutropenia ($p\leq0.05$). The development of grade 2 anemia require more mean dose compared to grade 1 anemia, but it is statistically not significant ($p>0.05$) (Table 3).

There is a statistically significant difference in the mean percentage of irradiated bone marrow volume in IBM V20, LPBM V10, LPBM V20, LSBM V20 and development of grade 1 and grade 2 neutropenia ($p\leq0.05$) (Table 4).

Bone marrow dose volume constraints

The Receiver operating characteristic curve (ROC) analysis was performed to determine the bone marrow dosimetric thresholds of acute bone marrow suppression. The ROC analysis done for V10, V20 and mean dose as predictors of anemia, leukopenia and neutropenia (Figure 3).

To prevent anemia, leukopenia and neutropenia, PBM volume receiving 10Gy (V10) should be <98.9%, 94.5% and 92% respectively (Table 5). To prevent anemia and neutropenia, PBM volume receiving 20 Gy (V10) should be <96.2% and 83.5% respectively (Table 5). To prevent anemia, leukopenia and neutropenia, the mean PBM dose should be 32.8Gy, 34.1Gy and 37.3 Gy respectively (Table 5).

Table 2: Volumes of PBM receiving different doses and grades of BM toxicity.

Dose (Gy)	Bone marrow toxicity	Volume of bone marrow (%)		P value
		Grade 1 toxicity	Grade 2 toxicity	
10	Anemia	95.6±3	97.8±3.3	0.26
	Leukopenia	96.5±2.3	97.4±3.5	0.42
	Neutropenia	94.6±2.5	98.7±0.9	0.00
	Thrombocytopenia	94	87	
20	Anemia	90.6±4.2	95±5.2	0.16
	Leukopenia	91.9±4.2	94±8.1	0.35
	Neutropenia	88.7±5.6	96.7±1.3	0.00
	Thrombocytopenia	89	69	
30	Anemia	55.4±8.9	65.6±18.3	0.10
	Leukopenia	55.9±9.9	55±11.3	0.82
	Neutropenia	53.4±8.6	60.4±10.7	0.04
	Thrombocytopenia	37	39	
40	Anemia	39.3±9.7	44.6±15.6	0.41
	Leukopenia	37.8±8.6	40.7±13.3	0.46
	Neutropenia	34±8.3	43.9±9.7	0.004
	Thrombocytopenia	26	15	

Table 3: PBM mean dose and grades of BM toxicity.

BM toxicity	Mean dose received by PBM (Gy)		P value
	Grade 1 toxicity	Grade 2 toxicity	
Anemia	34.3±2.2	36.6±4.4	0.13
Leukopenia	34.6±2.3	34.5±3.6	0.92
Neutropenia	33.3±2.4	35.9±2.6	0.008
Thrombocytopenia	30.6	36.1	

Table 4 : Volumes of subdomains of PBM and BM toxicity.

Subdomain of PBM	Dose (Gy)	Bone marrow toxicity	Volumes of bone marrow (%)		P value
			Grade 1	Grade 2	
IBM	10	Anemia	95.7±3.6	97±5.3	0.56
		Leukopenia	96.3±3.5	95.8±4	0.69
		Neutropenia	95±3.7	97.2±2.7	0.06
	20	Anemia	89.4±6.1	92±8.1	0.47
		Leukopenia	89.9±6.3	91.2±6	0.57
		Neutropenia	87.5±6.1	92.9±4.3	0.00
LPBM	10	Anemia	93.8±5.4	96.8±4.7	0.30
		Leukopenia	95.2±3.9	98.1±3.8	0.04
		Neutropenia	92.6±3.6	99.3±1.3	0.00
	20	Anemia	88.1±9.8	87.7±16.2	0.95
		Leukopenia	89.3±9.4	97±5.5	0.01
		Neutropenia	87.2±6	98.5±2.1	0.00
LSBM	10	Anemia	98.7±3.2	100±0.1	0.08
		Leukopenia	99.5±2.1	99.5±1.7	0.96
		Neutropenia	98.4±3.2	100±0.01	0.06
	20	Anemia	97.2±5.3	99±2	0.52
		Leukopenia	98.1±3.7	98.6±3.4	0.70
		Neutropenia	96±5.8	99.7±0.6	0.01

Table 5 : Threshold volume or dose to develop BM toxicity.

Acute BM toxicity	Sensitivity (%)	Specificity (%)	AUC	Threshold value (%)
V10 (Anemia)	66.7	83	0.75	<98.9
V10 (Leukopenia)	66.7	42.6	0.31	<94.5

Continued.

Acute BM toxicity	Sensitivity (%)	Specificity (%)	AUC	Threshold value (%)
V10 (Neutropenia)	83.3	22.7	0.39	<92
V20 (Anemia)	66.7	83	0.76	<96.2
V20 (Leukopenia)	66.7	87.5	0.89	-
V20 (Neutropenia)	83.3	18.2	0.38	<83.5
Mean dose (Anemia)	83.3	34.1	0.5	32.8 Gy
Mean dose (Leukopenia)	66.7	51.2	0.46	34.1 Gy
Mean dose (Neutropenia)	66.7	91.5	0.70	37.3 Gy

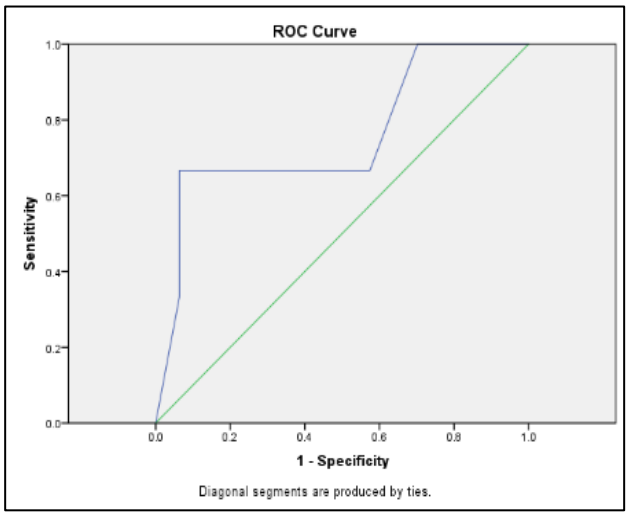

Figure 3: ROC characteristic of PBM V10 as predictor of anemia.

DISCUSSION

The treatment protocol for locally advanced rectal cancer consists of neoadjuvant chemoradiation followed by surgery and adjuvant chemotherapy. Bone marrow is highly sensitive to radiation. As more than 50% of hematopoietic bone marrow is found in hip, sacrum, proximal epiphysis of femur, and lumbosacral spine, all of which are within irradiation range of radiotherapy for rectal cancer, pelvic radiotherapy can lead to acute bone marrow toxicity. Thus, it is important to analyse the dose received by PBM and its relation with bone marrow toxicity. This study was conducted among 50 patients with locally advanced rectal cancer who underwent long course chemoradiation, either before or after surgery.

The mean age of the study population was 59±11.3 years and majority of the patients were males (60%). In our study, grade 1 and grade 2 anemia developed in 48% (24 patients) and 6% (3 patients) respectively, grade 1 and grade 2 leukopenia developed in 40% (20 patients) and 24% (12 patients) respectively and grade 1 and grade 2 neutropenia developed in 30% (15 patients) and 34% (17 patients) respectively. Grade 1 and grade 2 thrombocytopenia was found in one patient (2%) each. No patients developed ≥grade 3 bone marrow toxicity. Considering all bone marrow toxicities together, total 40 patients (80%) developed bone marrow toxicity in which 20 (40%) had grade 2 bone marrow toxicity. In a study conducted by Li et al 74% patients developed acute bone marrow suppression and incidence of ≥grade 2 bone marrow suppression was 28%.[7] An increase in development of bone marrow toxicity in our study is due to the fact that all the patients except one were treated with three-dimensional conformal radiotherapy while in the study by Li et al patients were treated by intensity modulated radiation therapy (IMRT) technique, which reduces the irradiated bone marrow volume and also related to the patient characteristics.[7] A study by Yang et al on clinical and dosimetric predictors of acute hematologic toxicity in rectal cancer patients undergoing chemoradiotherapy also demonstrated that patients who were treated with 3DCRT experienced lower cell count ratio trend which is consistent with our study.[16]

Different studies by Yang et al and Li et al demonstrated that age is not a significant predictor of acute bone marrow toxicity.[7,17] In our study, since most of the patients were in the similar age group (50-60 years) with mean age 59±11.3 years, the relationship between age and acute bone marrow toxicity development were not compared.

The study has demonstrated that there is no significant difference in the development of acute bone marrow toxicity among males and females and also with composite stage, which is comparable with the results of different studies by Li et al and Yang et al.[7,17]

Only two patients in our study experienced thrombocytopenia. Therefore, dosimetric factors associated with decrease in total count, absolute neutrophil count and hemoglobin during pelvic RT were only examined. In our study, there was statistically significant difference in the mean percentage of irradiated bone marrow volume receiving 10 Gy, 15 Gy, 20 Gy, 25 Gy, 30 Gy, 35 Gy, 40 Gy and development of grade 1 and grade 2 neutropenia. There is also statistically significant difference in the mean dose received by PBM and development of grade 1 and grade 2 neutropenia in our study. Study by Li et al stated that the PBM volume receiving 20 Gy (V20) of ≥grade 2 neutropenia patients were significantly higher than that of grade 0-1 neutropenia patients. But they only analysed V15 and V20 of PBM.

Patients who developed grade 2 anemia and leukopenia received higher V10 to V40 compared to grade 1 toxicity,

but it is not statistically significant (p>0.05). In this, the data related to anemia is similar to the study by Li et al but development of grade 2 leukopenia was significantly related with irradiated bone marrow volume.[7] In our study, among 50 patients only 12 patients develop grade 2 leukopenia and 20 patients develop grade 1 leukopenia.

The volumes of subdomains of PBM, including the bilateral IBM, LPBM and LSBM were also quantified. There is statistically significant difference in the mean percentage of irradiated volume of IBM and LSBM, receiving 20 Gy (V20) and development of grade 1 and grade 2 neutropenia (p<0.05). In case of LPBM, volume receiving 10 Gy (V10) and 20 Gy (V20) has statistically significant difference in the mean percentage of irradiated volume and development of grade 1 and grade 2 leukopenia and neutropenia (p<0.05). Several other studies show similar results especially in LSBM and LPBM receiving 10 Gy and 20 Gy.

The ROC analysis performed for V10, V20 and PBM mean dose. Since the statistically significant relation in entire PBM was only between mean percentage of irradiated bone marrow and development of grade 1 and grade 2 neutropenia, ROC as predictor of neutropenia can be used for deciding bone marrow dose volume constraints. Our study has demonstrated that to avoid neutropenia, PBM volume receiving 10 Gy (V10) should be <92%, PBM volume receiving 20 Gy (V20) should be <83.5% and mean PBM dose should be <37.3Gy. A study conducted by Kumar et al assessing the correlation between PBM radiation dose and acute hematological toxicity in cervical cancer patients proposed the constraint of V20≤65%.[18] The 114 patients were included in their study while we included only 50 patients and the study was done for cervical cancer patients receiving concurrent chemoradiation.

The limitations of the study include small sample size and most of the patients were in the older age group which can lead to increased levels of bone marrow toxicity. All the patients are receiving concurrent chemotherapy along with radiotherapy, which produce additive bone marrow toxicity, which forms another limitation of study. Another limitation is that external contours of pelvic bones were contoured as a surrogate for PBM which makes over estimation of volume.

CONCLUSION

This study highlights the importance of contouring PBM as organ at risk in locally advanced rectal cancer patients receiving concurrent chemoradiation for reducing bone marrow toxicity. Higher PBM volumes receiving 10 Gy, 20 Gy, 30 Gy and 40 Gy were significantly related to the higher grades of neutropenia in locally advanced rectal cancer patients undergoing long course concurrent chemoradiation. Subgroup analysis demonstrated that higher IBM volume receiving 20 Gy (V20), LSBM volume receiving 20 Gy (V20), LPBM volume receiving 10 Gy and 20 Gy (V10 and V20) were also significantly related to the higher grades of neutropenia. Higher LPBM volume receiving 10 Gy and 20 Gy (V10 and V20) were also significantly related with higher grades of leukopenia. Thus, bone marrow delineation should be advised and particularly recommended to avoid acute bone marrow toxicity.

The significant dose constraints obtained in our study: PBM V10<92%, V20<83.5%, mean <37.3 Gy, which can be used to reduce acute hematological toxicity during whole pelvic radiation for rectal cancer.

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