

Haematological toxicity in cancer cervix patients treated with concurrent chemoradiation by conventional technique- correlation with bone marrow radiation dose

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Introduction: The standard of care for treatment of cancer cervix is concurrent chemoradiation followed by brachytherapy in the majority of cases. Conventional radiotherapy with chemotherapy causes haematological toxicities which may be related to radiation to pelvic bone marrow. **Material and Methods:** Retrospective data of cancer patients treated in the institute in the year 2019 was retrieved. Haematological toxicities were analyzed in terms of CTCAE criteria. Mean dose to bone marrow was calculated after the delineation in the CT scan. **Results:** The data of 20 patients were retrieved. Anaemia Grade, I and Grade II-IV was seen in 65% and 35% respectively. Leukopenia Grade I and Grade II-IV were seen in 85% and 15% respectively and Lymphopenia Grade I and Grade II-IV were seen in 55% and 45% respectively. **Conclusion:** Conventional radiotherapy can safely be practice for patients with cancer cervix with acceptable haematological toxicities.

Keywords: Cancer cervix, Haematological toxicities, Mean dose bone marrow

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Introduction

Concurrent chemoradiation followed by brachytherapy is the standard of care for cervical cancer [1,2]. The role of this combined therapy is to maximise tumour cell death with the radiosensitizing effects of chemotherapy. Traditionally conventional radiotherapy fields (4 field box technique) were based on bony anatomy, which has resulted in good loco-regional controls, but the geographic miss of the clinical target volume may often result in an increased risk of failures and the large volumes treated resulted in an increase in gastrointestinal (GI), genitourinary (GU) and haematological toxicity (HT) [3]. The patients are planned radiotherapy by conventional technique to the whole pelvis which includes the tumour, pelvic lymph nodes along with organs at risk like the rectum, urinary bladder, bone marrow (BM) and small intestine. Bone marrow is a radiosensitive tissue and there is a strong link between the dose and the volume irradiated and the risk of haematological toxicity. The decline in bone marrow hematopoietic cells is associated with an increased level of adipocytes and a chronic inhibition of hematopoiesis [4], as confirmed by experimental studies [5]. In adults' pelvic bone is the primary site of haematopoiesis. It is estimated that >50% of proliferating BM is located in the pelvic region, including lumbar spine [6]. The irradiation to the whole pelvis may lead to suppression of bone marrow resulting in the decrease of haematological parameters. This may lead to anaemia, neutropenia and thrombocytopenia. The toxicity may further be enhanced by the chemotherapy drugs commonly used for the treatment of cancer cervix during radiotherapy. The newer radiotherapy techniques like intensity-modulated radiotherapy (IMRT) are emerging to decrease the dose to the BM. However, the ability of IMRT to reduce the PBM dose, particularly low-dose radiation, compared with conventional forward planning techniques have not been fully investigated [7-9]. This decrease in dose to the bone marrow, theoretically seems may decrease the haematological toxicities, but the clinical advantage is still controversial. IMRT is a costly radiotherapy technique and not available in most of the centres of the country. The present study aims to study the haematological toxicities caused due to chemoradiation in patients of cancer cervix treated with conventional radiotherapy technique and try to find out if there is any correlation between radiotherapy dose to the pelvic

Bone marrow and haematological toxicities.

Material and Methods

Study Setting: Department of Radiation Oncology, Shri Ram Murti Institute of Medical Sciences

Duration of study: January 2019 to December 2019

Type of Study: Observational study.

Sampling methods: Retrospective data of all the patients of cancer cervix treated in the year 2019 were selected

Study tool: Correlation between the mean dose of bone marrow and haematological toxicity was evaluated.

Inclusion criteria: Biopsy proven cervical carcinoma, 18-65 years age and KPS \geq 70

Exclusion criteria: Previous history radiation or chemotherapy, synchronous malignancy or metastatic disease

Data collection procedure: Retrospective data of all the patients of cancer cervix treated with conventional radiotherapy technique along with concurrent chemotherapy in the year 2019 were selected who had received 50 Gy in 25 fractions at 2 Gy per fractions over 5 weeks followed by 3 fractions of ICRT of 7 Gy each along with weekly Cisplatin (35mg/m²) concurrently.

Radiation Planning: All the patients had similar radiotherapy planning technique. They were immobilized with the thermoplastic cast and a planning computed tomography of the pelvis (CT RTP) with 3mm slice thickness was taken. The radiotherapy was planned by four-field box technique (anterior-posterior, posterior-anterior and two laterals) using standard bony landmarks.

Bone Marrow Contouring: Bone marrow was contoured in all these patients as described by Mell et al[10]. The external contour of all bones within pelvis was contoured on planning CT scan depicting BM. The external contour was chosen, rather than the low-density regions within bones, to ensure reproducibility and to minimize dependence of the contours on CT windowing and levelling. Whole pelvis bone marrow included the following bones-

- Ilium-including the iliac crests extending to the superior border of the femoral head
- Lower pelvis- consisting of the pubis, ischia,

Acetabula, and proximal femora extending from the superior border of the femoral head to the inferior of the ischial tuberosities

- Lumbosacral spine-extending superiorly from the appearance of the iliac bone and inferiorly to include the entire sacrum

Retrospective data were retrieved which included details of various haematological parameters-haemoglobin (Hb), total leukocyte count (TLC), lymphocyte count (LC), neutrophil count (NC) and platelets.

Any scoring procedure: Mean dose (Dmean) of BM was calculated. Hematologic toxicity was graded according to CTCAE v4.03.

Surgical procedure: None

Ethical consideration and permission: Not required

Statistical analysis: Correlation between Dmean of BM and haematological toxicity was seen using paired t-test and p-value less than 0.05 was considered significant.

Results

Twenty patients of cancer cervix were treated with concurrent chemoradiation in the year 2019. The haematological parameters and mean doses of BM are shown in Table 1.

Table-1: Haematological parameters and mean bone marrow dose of each patient (n=20).

S.No.	Haematological parameters					Mean Bone Marrow dose (Gy)
	Hb (g/dL)	TLC (cells/mm3)	LC (%)	NC (%)	Platelets (lacs/mm3)	
1	8.6	3300	6	83	1.78	34.79
2	11.1	3600	13	71	2.2	27.51
3	10.9	4200	9	56	1.9	35.75
4	8	2900	7	81	1.45	40.75
5	11.5	5000	10	72	1.4	34.42
6	9.3	6800	6	70	1.4	34.70
7	10	6500	6	59	1.56	38.44
8	10.9	4200	9	76	1.9	38.50
9	10	4400	7	72	2.6	36.81
10	7.7	2600	11	60	2.65	33.57
11	9.9	3700	8	76	1.22	34.16
12	9	4900	7	65	2.82	36.55
13	6.6	5800	7	75	3	38.25
14	8	8700	5	86	4.6	33.30
15	9.7	3900	10	63	2.98	33.80
16	10.8	3300	8	74	1.9	41.70
17	9.1	2600	7	82	1.2	34.52
18	8.1	8000	10	71	2.2	38.89
19	10.4	3700	9	81	1.1	34.56
20	10.1	6800	11	85	2.1	33.49

Haematological toxicity was stratified into mild grading (Grade I) and moderate to severe grading (Grade II to IV) and correlated with mean dose to bone marrow (Table 2).

Table-2: Correlation of haematological toxicities with the mean dose of bone marrow.

Haematological Toxicity	Grading	n (%)	Dmean (Gy)	P-value
Anaemia	Grade I	13 (65)	35.41	0.5
	Grade II-IV	7 (35)	36.3	

Leukopenia	Grade I	17 (85)	35.62	0.8
	Grade II-IV	3 (15)	36.28	
Lymphopenia	Grade I	11 (55)	35.53	0.38
	Grade II-IV	9 (45)	35.95	

There was no Grade II-IV toxicity of neutropenia and thrombocytopenia.

Discussion

Bone marrow is a radiosensitive tissue and the irradiation may cause its suppression leading to

Various haematological toxicities like anaemia, leukopenia and thrombocytopenia. Albuquerque et al [2] treated patients with conventional radiotherapy and all patients had some grade of hematologic toxicity. Moderate to severe toxicity (Grade 2 or more) was observed in 67.5% of patients. In the present study also, all patients developed some grade of anaemia, leukopenia and lymphopenia. Around 30% of patients showed haematological toxicity in terms of neutropenia and thrombocytopenia. On the contrary, the majority of patients in the present study had grade 1 toxicity and only a few patients had toxicity more than grade 2. The RTOG 0418 [11] phase II clinical trial showed that the volume of bone marrow receiving 40Gy or more had higher rates of grade 2 toxicity. In the present study, the mean dose of bone marrow was less than 40Gy and this may be the possible reason why our majority of patients had grade 1 haematological toxicity. In the RTOG 0418 phase II clinical radiotherapy technique IMRT was used whereas the present study utilized conventional radiotherapy. It clearly shows that complex and advanced techniques though may show the theoretical advantage, may not always give better clinical outcomes. In a study by Gandhi AK et al [12] the haematological toxicity was compared between whole pelvis conventional radiotherapy (WP-CRT) and IMRT (WP-IMRT). In WP-CRT arm 54.5% patients had more than grade 2 and 18.2% had more than grade 3 haematological toxicity, whereas 72.7% had more than grade 2 and more than 13.6% had more than grade 3 toxicity in WP-IMRT arm. The difference in haematological toxicities was statistically non-significant. It is important to note that most of the centres in our country do not have higher modalities of radiotherapy treatment and routinely practice conventional radiotherapy. In this scenario, the study by Gandhi AK et al concluding that both WP-CRT and WP-IMRT had comparable clinical outcomes supports the practice of standard conventional radiotherapy techniques and eliminates the feeling of the patient being devoid of advanced techniques. Ashitha EA et al [13] in their study found that IMRT reduces the volume of bone marrow getting irradiated to higher doses and decreasing the severity of acute haematological toxicities. Patients with IMRT had fewer more than grade 2 toxicities 28% vs 72% compared to 3DCRT ($p = .03$). The results of this study are contrary to haematological toxicity by the conventional technique in the present study. The present study would like to suggest that if the clinical outcomes in terms of tumour control

Are comparable in both conventional and advanced techniques, there is no reason why the standard practice of conventional radiotherapy cannot be continued. The newer techniques like IMRT may cause an unnecessary financial burden on the patient and may not be always a good choice for patients who belong to a developing country. Recently, there have been several reports on the applications of BM-sparing IMRT, which was thought to effectively reduce the irradiated volume of BM compared with conventional techniques. In patients with cancer cervix, Brixey et al [7] showed that IMRT was associated with both lower HT and lower BM dose compared with patients treated with conventional 4-field box techniques, indicating that IMRT could be used to reduce HT. Iliac, lumbar, and sacral BM irradiation was reduced with IMRT, even though the plans were not optimized to spare the BM. Subsequent studies demonstrated that IMRT and intensity-modulated arc therapy plans could be optimized to improve IBM sparing [9,14]. In postoperative cervical cancer patients, Chen et al. [15] have previously shown that, without entering PBM as a planning constraint, IMRT reduced PBM irradiation compared with four-field box techniques. Others have shown that IMRT plans can be optimized to reduce BM irradiation compared with conventional techniques with extended-field and whole abdomen RT [16,17]. The addition of concurrent chemotherapy in the treatment of cervical cancer has led to improved tumour control and survival [18-21], generally at the expense of increased toxicity, particularly HT. A legitimate concern is whether HT is enough of a problem in cervical cancer to warrant the application of the highly technical treatment, particularly when the predicted advantages compared with a simple AP-PA plan are not clear. The reported acute HT with whole pelvic RT and concurrent chemotherapy in cervical cancer trials has been variable, with acute Grade 3 or greater HT about 35% in some studies [22] but much lower in others [23]. In our experience, and others [10,15,24], acute Grade 3 or greater HT has been relatively low with concurrent weekly cisplatin and RT, although Grade 2 or greater HT has approached to about 45%. Therefore, the potential benefits of BMS-IMRT might be better realized by combining it with more aggressive chemotherapy. This study may support the use of high-end technology, but at the same time, it also incorporates the higher cost of treatment. Our present study has acceptable mild grades of haematological toxicities in the majority of patients. The treatment by conventional radiotherapy is

Cheaper, affordable and available in most of the centres across the country. IMRT may be offered to a selected class of patients where cost is not a barrier.

Limitations

Small sample size and using the entire bone as a proxy for BM constitutes another limitation of the study.

Conclusion

Conventional radiotherapy can be safely practised for the patients of cancer cervix with acceptable haematological toxicities. The newer techniques like IMRT which are costly and not available in most of the parts of the country may not show a clinical advantage in terms of decreasing the haematological toxicities.

What does the study add to the existing knowledge

In the era of advancement in radiotherapy technology, but the limitation of availability of such techniques develops a feeling of compromising the treatment in the minds of treating physician and the patient. This study suggests that the conventional technique of radiotherapy in patients of cancer cervix is no way inferior in terms of treatment-related haematological toxicities when compared to advanced techniques.

Author's Contribution

Dr. Prachi Upadhyay: Collection data and manuscript review

Dr. Pavan Kumar: Drafting methodology, verification of data and review of the manuscript

Dr. Piyush Kumar: Drafting the methodology, drafting and review of the manuscript

Dr. Ayush Garg: Collection data and manuscript review

Dr. Arvind Kumar Chauhan: Manuscript review

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