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A COMPARATIVE STUDY OF PELVIC BONE MARROW SPARING IMRT AND STANDARD IMRT IN PATIENTS WITH CARCINOMA CERVIX WITH CONCURRENT CHEMOTHERAPY- AN INSTITUTIONAL OBSERVATIONAL STUDY

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ABSTRACT

Aims: The aim of the study was to evaluate feasibility and benefits of Bone Marrow Sparing IMRT over Standard IMRT.

Materials and methods: It is a prospective, randomized study evaluating bone marrow sparing IMRT compared to standard IMRT. One hundred ninety two patients met the eligibility criteria, gave informed consent and were accrued as part of the study and randomized into two arms. They were treated with concurrent chemo radiation therapy and brachytherapy and evaluated for hematological toxicity at weekly intervals.

Results: Our results show a significant difference in hemoglobin nadir, grade 2 and above hemoglobin toxicity in favour of bone marrow sparing arm. This may be more relevant in Indian scenario due to more prevalent anemia and low baseline hemoglobin. There was a difference observed in TLC nadir and grade 2 and above leukopenia in favour of bone marrow sparing but did not reach statistical significance. Our sample size was based on results from a retrospective analysis and our sample size might not have been sufficient for a prospective analysis. Our study was not powered enough to detect a difference in neutropenia between both arms, and as expected no significant difference was observed. There was no significant difference in need of growth factor support and PRBC transfusions between both arms, nor was there difference in number of chemotherapy cycles or treatment duration.

Conclusions: Our results show that bone marrow sparing is feasible without compromising on target coverage or normal tissue sparing.

Keywords: Intensity modulated radiotherapy(IMRT), Pelvic Bone Marrow Sparing(PBMS), Image guided radiotherapy(IGRT), Standard Intensity Modulated Radiation Therapy (SIMRT)

INTRODUCTION

Carcinoma cervix is the third most commonly diagnosed cancer in India and the second leading cause of cancer mortality in women, with about 123,907 new cases and 77,348 death in India in last 5 years. It is major cause in mortality in women after breast carcinoma in India and majority of cases arise in low socio economic groups. Carcinoma cervix is 90% caused due to Huma papilloma virus(HPV). Other known causes are sexually transmitted disease, smoking , multiparity. Majority of present in late or advanced stages. Squamous cell carcinoma is the most common histological type of carcinoma cervix. Persistent high risk HPV infection lead to dysplastic changes progressing to high grade squamous intraepithelial lesion (HSIL), a precursor for carcinoma cervix.[1]

The two major forms of treatment are surgery and radiotherapy. Furthermore, radiation therapy also has a role in the adjuvant setting post-surgery. Addition of chemotherapy concurrently with radiation has shown to improve outcome but this comes at a cost of increased gastrointestinal, genitourinary and hematological toxicity . This leads to decreased blood counts, poor compliance to chemotherapy, treatment breaks and increase in overall treatment time. Anemia , lack of compliance with concurrent chemotherapy and prolonged treatment time lead to poor response and sub-optimal outcomes.[2]

Various factors play a role in post radiation therapy bone marrow functioning. The dose and duration of radiation, age of patients and usage of concurrent chemotherapy all affect the recovery of bone marrow. Combining chemotherapy and radiation compounds the bone marrow suppression leading to hematological toxicity. Pelvic radiation used in cervical carcinoma , leads to high doses of radiating to the pelvic bones which contain more than half of functioning bone marrow. Increase in volume of bone marrow receiving low dose radiation leads to increases hematological toxicity . Reduction of this may lead to reduced hematological toxicity and better chemotherapy compliance. The role of adjuvant chemotherapy in locally advanced cases is also being evaluated. Reducing the damage to bone marrow during concurrent chemo radiation will enable patients to receive further chemotherapy.

Radiation therapy has been an effective form of treatment for cervical cancer for many decades. The conventional AP/PA and Four Field box have been used for many years and led to good coverage primary and lymph nodal targets. The high dose received by normal tissues and the ensuing complications were unavoidable in the cobalt era. With the development of the linear accelerator and techniques like intensity modulated radiation therapy (IMRT) it is now possible to reduce some of these complications without compromising on tumour control.

The use of Intensity Modulated Radiation Therapy has led to better dose conformality which in turn enabled us to reduce doses to normal structures. Doses to bowel, bladder and rectum have been significantly reduced, leading to decreased gastrointestinal and genitourinary toxicities and better compliance to treatment. Clinical studies have shown upto 50% reduction in acute gastrointestinal and upto 30% reduction in acute genitourinary toxicity using IMRT(1). Errors in patient setup, variations in bladder and rectum filling all lead to an increase in chances of a geographical miss and adequate margins must be given to account for them but increase in margins leads to reduction in the amount of sparing achieved diminishing its benefit. Alternately, bladder and rectal filling protocols, on board imaging and proper immobilization can reduce some of these uncertainties enabling us to derive maximum benefit from IMRT.

Delivery of extended field radiation to para aortic nodes or boost radiation to gross nodes is also possible with manageable gastrointestinal and genitourinary toxicity. Similarly, reduced dose to the

Bone Marrow can also be achieved. Bone marrow can be identified using various imaging techniques like MRI, FDG PET and FLT PET. Bone marrow sparing had been attempted for many years even with conventional radiation. Shielding of femoral heads, pelvic wings and use of AP/PA can lead to reduced bone marrow dose but there are limitations to the amount of bone marrow that can be spared. IMRT can be used to spare bone marrow more effectively and various techniques have been developed. It has been shown that increased low dose radiation of 10Gy and 20Gy is responsible for majority of bone marrow suppression. [3]Constraints have been developed on the basis of retrospective data but the exact extent of benefit derived from these over standard IMRT techniques in terms of hematological toxicity, chemotherapy compliance and treatment duration has also not been established. Dosimetric studies evaluating their feasibility exist, but very few clinical studies have prospectively evaluated these techniques. The effect of bone marrow sparing on dose to bowel and bladder is also not established. The present study is a feasibility study for Bone Marrow sparing IMRT in a community hospital in the Indian setting.

MATERIALS AND METHODS

A Double Arm, Open label Feasibility Study for Bone Marrow Sparing IMRT in all eligible patients at Basavatarakam Indo American Cancer Hospital , Hyderabad were enrolled in the study. The patient accrual was done over a period of 1.8 years starting from February 2021 to June 2022.

Inclusion Criteria: Patients over 18 years of age with pathologically confirmed Primary Tumour (squamous cell and adenocarcinoma), ECOG Performance Status 0-2, adequate Bone Marrow and Renal Function Tests, haemoglobin >10 g/dl, total Leukocyte Count > 4000 cells/cu mm, absolute Neutrophil Count > 1800 cells/cu mm, total Platelet Count > 100,000 cells/cu mm and Serum. Creatinine < 2 mg/dl

Exclusion Criteria: Para aortic nodal disease needing extended field radiation prior radiation Therapy to pelvis, prior chemotherapy, sarcoma or Neuroendocrine histology, metastatic disease outside the pelvis and prior Hematological disorder.

Sample Size:

The incidence of Hematologic toxicities in the PPBMS group was (P_1 =50%) significantly lower than the Standard IMRT group (P_2 =69.5%) has been observed from the previous study[]. Considering the $Z_{\alpha/2} = 1.96$ is critical value of normal distribution at 95% confidence interval, $Z_\beta = 0.842$ is the critical value of the Normal distribution at β with the power of 80%.

$$n = \frac{(Z_{\alpha/2} + Z_\beta)^2 \times (p_1(1-p_1) + p_2(1-p_2))}{(p_1 - p_2)^2}$$

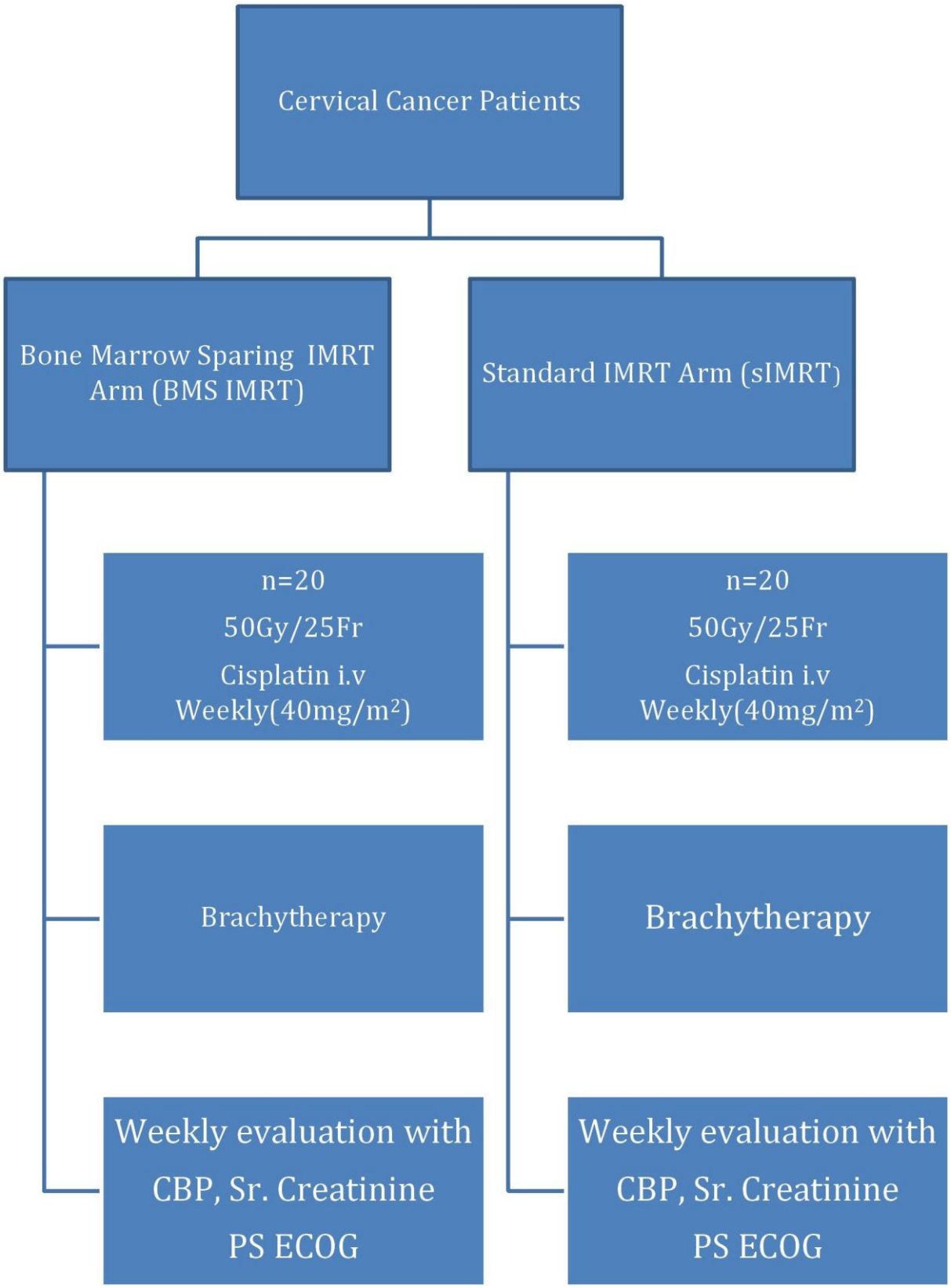
$$n = \frac{(1.96 + 0.842)^2 \times (0.50(1-0.50) + 0.695(1-0.695))}{(0.50 - 0.695)^2}$$

n= 95.38 ≅ 95.

∴The minimum required sample per group is 95.

Article considered for the sample size calculation: "Pelvic bone marrow sparing intensity modulated radiotherapy reduces the incidence of the hematologic toxicity of patients with cervical cancer

receiving concurrent chemoradiotherapy: a single center prospective randomized controlled trial" by Jin Huang[4]



Baseline Evaluation for Complete Blood Picture, Renal Function Tests, Liver Function Tests and ECOG Performance Status and Haematological toxicity

All toxicities were evaluated using the RTOG Acute Radiation Haematological Scoring. All Patients of cervical cancer planned for concurrent chemo radiation therapy were screened as per the above inclusion and exclusion criteria. Patients eligible for the study were counselled in detail and after taking informed consent, randomised to two arms by random number tables which was generated using an

Statistical Analysis:

All the qualitative parameters like Sex, Treatment method, ECOG, etc., will be represented with frequencies and percentages. Quantitative parameters like Age, Height, Weight, BMI, WBC, ANC, HGB, PLT, etc., will be presented with mean and standard deviation. To find the association between qualitative parameters we will use Chi- Square test for measure of association. The data will be entered using M.S. Office and the analysis will be performed by using SPSS 19.0v. P value less than 0.05 will be considered as significant. All the information derived from the data will be represented with relevant graphs. All the study data obtained through the study Performa was entered into an electronic spread sheet and analysed using a statistical package with bio-statistical assistance.

ANOVA Test was used for statistical analysis of variables compared between two arms over the course of treatment and Student's T Test was used to analyse other variables which did not have a time factor. Chi-square test was used to calculate difference in haematological toxicity between both arms.

RESULTS

Table-1: Age of patients per ARM

Age (Years)	**No. of Subjects**	**Percentage**
<= 45	58	30.2%
46 - 60	89	46.4%
61 & Above	45	23.4%
Total	192	100%

A total number of 192 patients of age 70 or less were enrolled in the study. The mean age was 57.25 years and median age was 59.5 years. The mean age of presentation in PPBMS IMRT was 55 years (range 37-79) and that of sIMRT was 59 years (38-73).

Table-2: Distribution by constraints achieved status

V10<=10Gy	**No. of Subjects**	**Percentage**
Achieved	62	64.6%
Not Achieved	34	35.4%
Total	96	
V20<=20Gy		
Achieved	54	56.3%
Not Achieved	42	43.8%
Total	96	

Dose constraints were more achieved in both the constraints but more in the V10 < 10 Gy arm of 64.58% and in the V20<20 Gy arm it was 53.3 % so more of V10< 10 Gy was achieved and PBMS

constraints were achieved without compromising tumor dose.

Table-3: Total Chemo cycles received by both groups

Chemo Cycles	No. of Subjects	Percentage
1	1	0.5%
2	2	1.0%
3	31	16.1%
4	39	20.3%
5	119	62.0%
Total	192	

Most of the patients received 5 cycles of chemotherapy in both the arms but more patients were there in with less chemotherapy cycles in the sIMRT arm.

Table-4: Hemoglobin distribution by both arms

Hemoglobin	Group		P Value
	PBMS	Standard	
Week 1	12.02 ± 0.996	12.24 ± 1.181	0.171
Week 2	11.58 ± 0.823	11.8 ± 0.933	0.093
Week 3	11.13 ± 0.809	11.31 ± 0.833	0.123
Week 4	10.93 ± 1.025	11.23 ± 1.063	0.049
Week 5	10.58 ± 0.498	10.77 ± 0.48	0.005
Hemoglobin Grade			
Week 1	0.06 ± 0.243	0.11 ± 0.32	0.206
Week 2	0.42 ± 0.496	0.33 ± 0.474	0.235
Week 3	0.64 ± 0.484	0.48 ± 0.502	0.029
Week 4	0.64 ± 0.484	0.48 ± 0.502	0.029
Week 5	0.93 ± 0.261	0.77 ± 0.423	0.002

Mostly in both the arms there was no difference in Haemoglobin and its grade from week 1 to week 5 .But till week 5 it was slightly better in the PBMS arm.

Table-5: WBC difference in both arms

WBC	Group		P Value
	PBMS	Standard	
Week 1	7.62 ± 1.711	8.11 ± 1.729	0.052
Week 2	6.49 ± 1.627	6.74 ± 1.512	0.26

Week 3	5.27 ± 1.428	5.42 ± 1.311	0.435
Week 4	4.84 ± 1.049	4.79 ± 1.019	0.767
Week 5	4.27 ± 0.747	4.21 ± 0.879	0.615
WBC Grade			
Week 1	0 ± 0	0 ± 0	NA
Week 2	0 ± 0	0.02 ± 0.204	0.319
Week 3	0.01 ± 0.102	0.03 ± 0.227	0.414
Week 4	0.14 ± 0.373	0.24 ± 0.453	0.084
Week 5	0.36 ± 0.545	0.46 ± 0.579	0.249

There was no difference in WBC count in general but according to the grade toxicity PBMS was having grade 3 and less toxicity and in was statistically significant.

Table-6: Platelet distribution in both arms

Platelet	**Group**		**P Value**
	PBMS	**Standard**	
Week 1	3.88 ± 0.575	4.02 ± 0.615	0.122
Week 2	3.82 ± 0.395	3.91 ± 0.443	0.119
Week 3	3.24 ± 0.575	3.17 ± 0.684	0.483
Week 4	3.46 ± 0.831	3.24 ± 1.034	0.109
Week 5	3.44 ± 0.518	3.23 ± 0.75	0.025

There was not much difference in Platelet count in both the arms.

DISCUSSION

Carcinoma cervix continues to be a global health problem despite advances in screening, diagnosis and treatment techniques. The advent of HPV vaccination is an important step towards reducing the burden of cervical cancer. Though the basic principles of cervical cancer treatment have not changed over the years, our understanding of the disease has improved due to the research that has been done on cervical cancer over the past few decades. This, coupled with technical advances enable us to deliver optimal treatment with minimal toxicity. Addition of Concurrent chemotherapy to radiation has led to an increase in gastrointestinal, genitourinary and haematological toxicity. The use of IMRT has enabled us to reduce dose received by bowel, bladder and rectum leading to lower gastrointestinal and genitourinary toxicity. The higher conformal planning led to reduction in haematological toxicity due to inadvertent sparing of bone marrow. This had led to studies evaluating the role of bone marrow sparing techniques. Several studies have looked at techniques of identifying active bone marrow using FDG PET, FLT PET and MRI. To ensure reproducibility, several studies

have used the outer contour of the bone as a surrogate for bone marrow and constraints have been devised.

The present study is a prospective, observational study undertaken to evaluate the role of pelvic bone marrow sparing in patients of carcinoma cervix treated with IMRT technique. Though several dosimetric studies have shown the feasibility of bone marrow sparing using IMRT, no clinical studies exist. Furthermore, its impact in terms of treatment duration, number of cycles of chemotherapy and impact on PRBC and WBC is unknown. The present study was undertaken to answer the above questions. In India the peak age for cervical cancer incidence is 55-59 years(3). In our study the mean age was 51.91 yrs and median age was 51 yrs. The mean age of patients in PBMS IMRT arm was 52.49 yrs (33-69) and in sIMRT arm was 51.33 yrs (30-76). All of patients had squamous cell histology.

Contouring of target structures and OAR's was done as per internationally accepted guidelines.[5] The Target dose reporting was done as per ICRU-83. There was no statistically significant difference in terms of D mean, D98% and D2% between both the arms. Bone marrow sparing did not result in compromised coverage of target. Dose received by bowel, bladder and rectum was also analysed. OAR dose constraints as per QUANTEC were satisfied. There was no statistically significant difference in OAR doses in both arms. It was possible to achieve bone marrow sparing without increasing the dose to OAR's.

Several studies have demonstrated that the volume of pelvic bone marrow receiving low-dose radiation is associated with HT and chemotherapy delivery in cervical cancer patients undergoing concurrent chemo radiotherapy.[6] ***Jin Huang et al***[4] analysed 37 cervical cancer patients receiving concurrent chemo radiation therapy. Multivariate regression models were used to test associations between dosimetric parameters and HT and chemotherapy delivery. Increased pelvic BM V10 was associated with an increased Grade 2 or worse leukopenia and neutropenia. Patients with BM-V10>90% had higher rates of Grade 2 or worse leukopenia and neutropenia than did patients with BM-V10<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; $p = 0.02$) analysis. Albuquerque et al[7] analysed the medical records of 40 women receiving concurrent chemo radiation for cervical cancer. Multiple logistic regression analysis of potential predictors showed that only the volume of bone receiving 20 Gy (V20) for whole pelvic bone tended toward significance for predicting HT2+. A strong correlation was noted between HT2+ and V20 ($r = 0.8$, $p < 0.0001$). A partitioning analysis to predict HT2+ showed a cut- off value of 79.42% (approximately 80%) for V20 of whole pelvic bone. Based on the above two studies a bone marrow dose cut-off of V10<90% and V20<75% was thought to be appropriate in our study. The above two studies used the external contour of the bone as a surrogate for the marrow and our study used the same. Bone marrow constraints were achieved in most of our patients in PBMS IMRT Arm. The mean BM V10 values in PBMS IMRT arm were 64.58% respectively . The mean BM V20 values in PBMS IMRT arm were 56.3% respectively . Jin Huang et al[8] also demonstrated PBMS using IMRT compared to 3DCRT using AP/PA techniques and 4 Field Box technique. Overall, PBMS-IMRT was superior to the four-field technique in reducing the dose to the PBM. The PBM volume receiving 10Gy was lower with PBMS-IMRT than with Four-field box (76.5% vs. 97.3 %; $p < 0.05$). The PBM volume receiving 20Gy was lower with PBMS-IMRT than with Four-field box and AP/PA technique (57.5% vs. 92.7% vs. 62.9%; $p<0.05$ PBMS IMRT vs. AP/PA; $p<0.05$ PBMS
IMRT vs. Four-field box). The PBM volume receiving 30Gy was lower with PBMS-IMRT than with

Four-field box and AP/PA technique (46.1% vs. 59.9% vs. 59.1%; p<0.05 PBMS IMRT vs. AP/PA; p<0.05 PBMS IMRT vs. Four-field box). The BM V10 and V20 values achieved in the above study are higher than those achieved in our present study, probably due to the higher dose prescription of 45Gy used compared to 50Gy used in our study.

Haematological toxicity was analysed by recording weekly complete blood counts for all patients until the end of the last brachytherapy application. RTOG Acute Haematological Scoring was used to analyse the grade of toxicity for each of the parameters namely haemoglobin, WBC, TLC, ANC and TPC. Grade 2 or worse toxicity during the course of treatment was calculated by arm.

There is a fall in haemoglobin with each week of treatment in both arms which is statistically significant (p<0.001). The fall appears to be steeper in sIMRT arm when compared to PBMS IMRT arm. The recovery of Hb after completion of External Beam Radiation appears to be better in PBMS IMRT arm when compared to sIMRT arm. The grade of haemoglobin toxicity also increases as treatment progresses and is statistically significant (p<0.001). When analysed at end of treatment, the mean grade of toxicity in PBMS IMRT and sIMRT arms are 1 and 1.6 respectively, and the difference is statistically significant (p=.04). The number of patients with Grade 2 and above toxicity in PBMS IMRT arm and sIMRT arm are 6 and 13 respectively (p=0.02). There were no Grade 3 toxicities encountered in PBMS IMRT arm and 6 Grade 3 toxicities in sIMRT arm. Anaemia prior to radiation therapy is a poor prognostic factor leading to poor outcomes at the end of chemo radiation. Studies have highlighted the importance of correcting anaemia prior to start of radiation.[9] Given the rationale that low haemoglobin levels blunt radiosensitivity, it would be justifiable to maintain haemoglobin to at-least 10g/dL before the initiation of treatment. Due impetus must also be placed on the value of haemoglobin across the course of CCRT. Repeated blood transfusions come with their own set of side effects and erythropoietin has been shown to have unacceptable toxicity. Bone Marrow sparing appears to reduce the fall in haemoglobin and mean Hb level at end of EBRT is 10.2g/dL in PBMS IMRT arm. Jin Huang et al[4] found on univariate analysis that a BM-V10 of >90% and BM-V20 of >75% correlated with Hb nadir. The Hb nadirs encountered were 11.4 g/dL vs. 10.6 g/dL using BM-V10 as cut-off (p=0.06) and 11.6 g/dL and 10.4 g/dL using BM-V20 as cut-off (p<0.01). The Hb nadirs encountered in our study are lower probably due to a lower baseline Hb observed in an Indian population compared to a Western one.

There is a fall in TLC with each week of treatment in both arms which is statistically significant (p<0.001). The fall appears to be steeper in sIMRT arm when compared to PBMS IMRT arm. The recovery of TLC after completion of External Beam Radiation appears to be better in PBMS IMRT arm when compared to sIMRT arm. At the end of treatment (week 8), the mean TLC in PBMS IMRT and sIMRT arm are 3743/cu mm and 3322/cu mm respectively, which appears to favour PBMS IMRT arm, but the difference is not statistically significant (p=0.25). The grade of TLC toxicity also increases as treatment progresses and is statistically significant (p<0.001). When analysed at end of treatment, the mean grade of toxicity in PBMS IMRT and sIMRT arms are 0.85 and 1.16 respectively, which appears to favour PBMS IMRT arm, but the difference is not statistically significant (p=0.26).

The number of patients with Grade 2 and above toxicity in PBMS IMRT arm and sIMRT arm are 7 and 10 respectively (p=0.2). There were no Grade 3 toxicities encountered in either arm. The leukopenia described by ***Jin Huang et al***[4] in their study differ from those encountered in our present study. They encountered Grade 2 and above leukopenia in 43% of their patients, Grade 3 leukopenia was seen in 11%. In our present study 42% of patients had Grade 2 leukopenia but no patient developed

Grade 3 leukopenia. Using BM V10 of 90% as a cut-off Jin Huang et al[4] observed that Grade 2-3 leukopenia was 11.1% vs. 73.7%, whereas in our present study the observed Grade 2-3 leukopenia was 35% vs. 50% in PBMS IMRT and sIMRT arm respectively. Our present study was powered to detect a difference in leukopenia. Sample size was calculated on the basis of the above study by Jin Huang et al[4], which was a retrospective study. To the best of our knowledge ours is the first prospective study evaluating bone marrow sparing and we had no other studies to compare our results to.[10] It is possible that the calculation we based our sample size on was exaggerated and our present sample size was too small to detect a statistically significant difference.

There is a fall in TPC with each week of treatment in both arms which is statistically significant ($p<0.001$). The fall appears to be steeper in sIMRT arm when compared to PBMS IMRT arm. The recovery of TPC after completion of External Beam Radiation appears to be better in PBMS IMRT arm when compared to sIMRT arm. There is no statistically significant difference in TPC at end of treatment in both arms. We did not encounter any Grade 1, 2 or 3 thrombocytopenia in our study.

Concurrent chemotherapy with Weekly Inj. Cisplatin (40mg/m^2, max dose of 70 mg) was administered. 62% of the patients (119/192) received all 5 doses as scheduled (64 in PBMS arm and 55 in sIMRT arm). All patients received at least 3 doses of chemotherapy. None of the patients had omission of chemotherapy due to haematological toxicity. There was no significant difference in number of cycles of chemotherapy between both arms (Mean number of cycles: 4.5 in PBMS IMRT vs. 4.0 in sIMRT; $p=0.6$).

In the study by Jin Huang et al[8] 64% of patients had at least 1 cycle of chemotherapy held, 16.7% vs 47.4% using BM-V10 as cut-off ($p=0.08$). There was no such difference observed in our study. The mean treatment duration in our study was 59 days, there was no statistically significant difference in treatment duration in both arms (58.5 in PBMS IMRT vs. 60.7 in sIMRT; $p=0.3$). There were no delays in treatment due to haematological toxicity and bone marrow sparing did not have any impact on treatment duration.

CONCLUSIONS

There was no significant difference in need of growth factor support and PRBC transfusions between both arms, nor was there difference in number of chemotherapy cycles or treatment duration. We conclude that bone marrow sparing using IMRT is safe and feasible in patients of carcinoma cervix treated with concurrent chemo radiation therapy. Given the small percentage of haematological toxicity encountered in concurrent chemo radiation therapy using IMRT the maximum benefit of Bone Marrow Sparing might be seen in patients with intensified treatment regimens. Thus bone marrow sparing may be evaluated in patients treated with extended field radiation, nodal boost radiation, neo adjuvant or adjuvant chemotherapy.

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