Original Article

Indian Journal of Cancer Education and Research
Volume 6 Number 1, January - June 2018
DOI: http://dx.doi.org/10.21088/ijcer.2321.9815.6118.2

Prospective Analysis of Dosimetric Parameters and Toxicity Outcomes in Cervical Cancer Patients undergoing Concurrent Chemoradiation with Bonemarrow Sparing IMRT Using Spect Correlation

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Received on 19.02.2018, **Accepted on** 02.04.2018

Abstract

Aim: Study was to evaluate feasibility and benefits of Bone Marrow Sparing IMRT over Standard IMRT. *Materials and Methods:* Cervical cancer patients undergoing Concurrent Chemo Radiation and brachytherapy and evaluated for haematological, gastrointestinal and genitourinary toxicity at weekly intervals were included in study. *Results*: Dose constraints to bone marrow of V10<90% and V20<75% were achieved in all patients. Significant reduction in bone marrow V10 and V20 is possible using bone marrow sparing as compared to standard IMRT (V10 87.15% vs. 93.7% and V20 73.55% vs. 83.15%). Bone marrow sparing can be achieved without compromise to target coverage and without increased dose to OAR's which include bowel, rectum and bladder.

Bone marrow sparing appears to show significant reduction in haematological toxicity in terms of fall in haemoglobin, haemoglobin nadir and grade 2 and worse anaemia. Bone marrow sparing appears to show a trend towards reduced haematological toxicity in terms of fall in WBC count, leukocyte nadir and grade 2 and worse leukopenia. *Conclusions:* SPECT-BM imaging may be added to the ever growing list of functional imaging techniques that may play a role in IMRT planning. Bone marrow sparing approach may also benefit patient s with anal and rectal cancers.

Keywords: Intensity Modulated Radiation Therapy (IMRT); Single-Photon Emission Computed Tomography (*SPECT*) bone Marrow (*BM*) *Imaging*; Cervical Cancer.

Introduction

Cervical cancer is the fourth most common cancer in women worldwide with 528,000 new cases worldwide. The majority of cases arise in the developing world and in low socio-economic groups. It is the fourth most common cause of cancer related death in women worldwide. 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 outcomes but this comes at a cost of increased gastrointestinal, genitourinary and haematological toxicity. This leads to decreased blood counts, poor compliance to chemotherapy, treatment breaks and increase in overall treatment time. Anaemia,lack of compliance with concurrent chemotherapy and prolonged treatment time lead to poor response and sub-optimal outcomes.

Pelvic Radiation used in cervical carcinoma, leads to high doses of radiation 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 increasedhaematological toxicity. The use of Intensity Modulated Radiation Therapy has led to better dose conformity which in turn enabled us to reduce doses to normal structures. Bladder and rectal filling protocols, on board imaging and proper immobilisation can reduce some of these un-certainities enabling us to derive maximum benefit from IMRT. Reduced dose to the Bone Marrow can also be achieved. Bone Marrow is present in the interior of bones. Haematopoiesis in the bone marrow begins in the intrauterine period. With advancing age

there is a slow conversion of red active marrow to yellow inactive form. Beyond the age of 20 most of the active marrow is restricted to the axial skeleton, and a small part of the appendicular skeleton. In adults, more than 50% of the functioning bone marrow is present in the sacrum, pelvic bone and femoral head [1,2].

Bone marrow can be identified using various imaging techniques like MRI, FDG PET and FLT PET and by SPECT. Bone marrow sparing had been attempted for many years even with conventional radiation. 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. 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 withprospective analysis in a community hospital in the Indian setting.

Materials and Methods

It is a Prospective inCervical cancer patients undergoing Concurrent Chemo Radiation at MNJIO and RCC, Red Hills, Hyderabad were enrolled in the study.

Study was done over a period of 2 years starting from September 2015 to July 2017.

Patients were selected on eligibility criteria

Inclusion Criteria

- Patients between 20-60 years of age
- Pathologically confirmed Primary Tumour (Squamous cell carcinoma)
- ECOG Performance Status 0-2
- Adequate Bone Marrow and Renal Function Tests
  - Haemoglobin> 10 g/dl
  - Total Leukocyte Count> 4000 cells/cumm
  - Absolute Neutrophil Count> 1800 cells/cumm
  - Total Platelet Count > 100,000 cells/cumm
  - Sr. Creatinine < 2 mg/dl

Exclusion Criteria

- Para aortic nodal disease needing extended field radiation
- Prior RadiationTherapy to pelvis
- Prior Chemotherapy
- Sarcoma or Neuro-endocrine histology
- Metastatic disease outside the pelvis
- Prior Haematological disorder

Sample size for power of 80% and two sided difference of 0.05 significance was calculated by Altman's Nomogram. Standardised difference used was calculated based on study by Mell et al. [3] using the difference in TLC grade observed. Sample size obtained from the above calculation was 20 patients in each arm.

Total of 40 patients were properly identified as per the eligibility criterion mentioned above and who underwent concurrent chemoradiation was studied over a period of 2 years .

Study Methods and Procedure

Patients satisfying the criteria were eligible to participate in the study. Benefits and risks of the procedure were explained in detail and informed consent was obtained after explaining the procedure in detail. The study was an open label study where both the participants and investigators were aware of the intervention planned.

Simulation

PGI guidelines for delineation of CTV was followed.

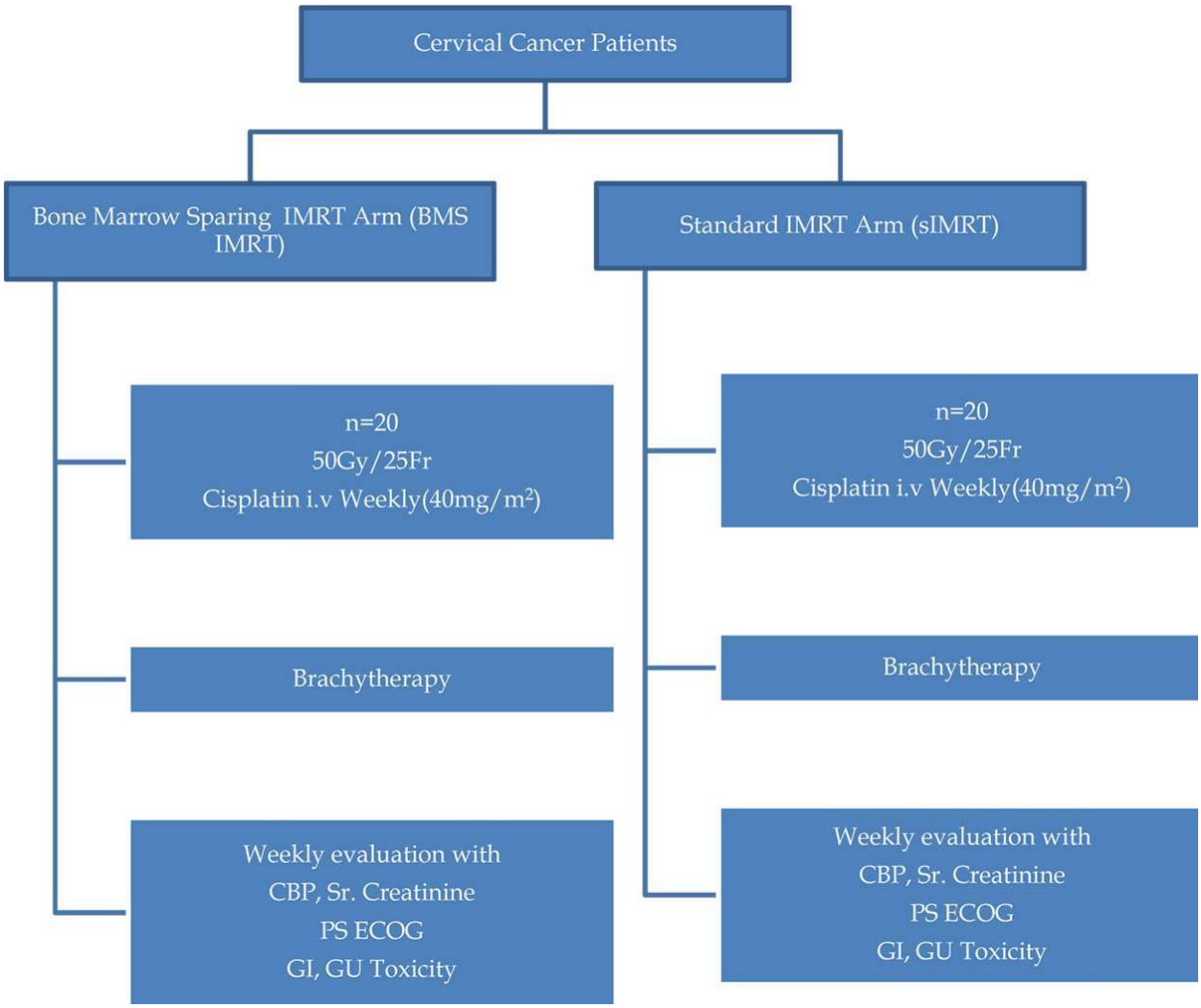
SPECT Scanning

One hour prior to imaging the patient was administered a 12.2 mCi dose of Tc-99m sulphur colloid. The patient was placed on the table and a SPECT scan of the pelvis was obtained from above the top of the iliac crest to below the ischial tuberosities using a low-energy, high resolution collimator. The SPECT-BM images were taken on to a Compact Disk, compared and used to delineate Bone marrow while contouring OAR from L4-L5 vertebral body till ischial tuberosities.

Patients eligible for the study were counselled in detail and after taking informed consent and ethical clearance.

BMS IMRT

- Bone Marrow Sparing IMRT
- 20 patients.

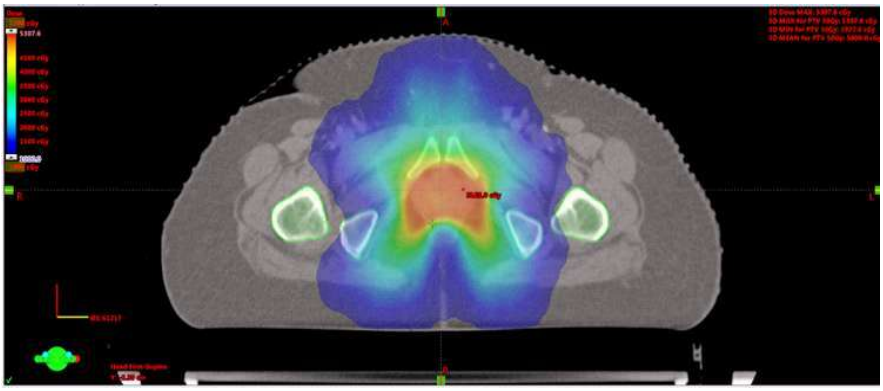


Standard IMRT

- 20 patients

Strict Institutional protocols are followed for delivery of IMRT

- For each patient, the external contour of all bones within thepelvis is delineated on the planning CT scan, as a proxy for theBM
- IMRT plans were generated on Eclipse planning system version 8.3
- Dose volume Histograms corresponding to the IMRT plans are generated and following constraints applied.
- PTV 50 Gy95%
- Bladder Max <60 Gy



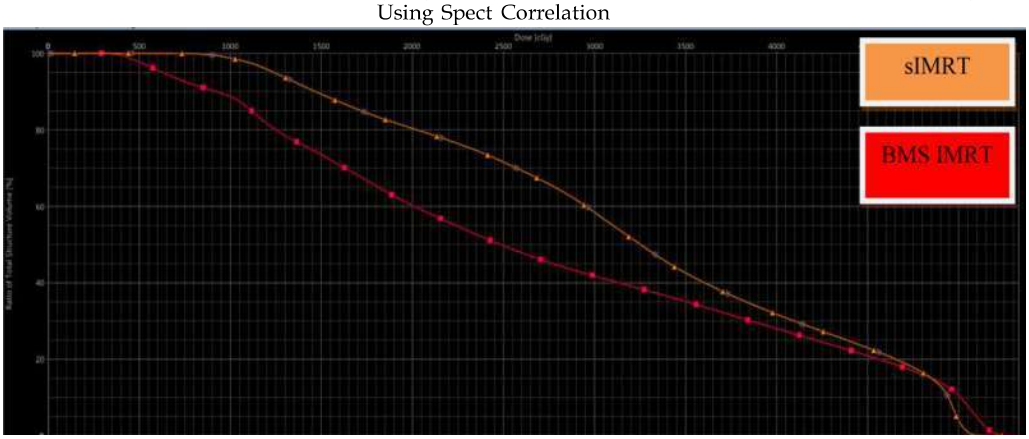


Fig. 3:

- Rectum V50 <50%
- Bowel V45<195 cc
- Femoral Head V52 <100%
- Bone Marrow D40 <30 Gy

Target and nodal volume delineation was done as per institutional protocols as per internationally accepted guidelines

Treatment Delivery

Treatment planning was done on Varian treatment planning system version 8.3. Treatment was delivered on DHX Linear Accelerator with Intensity Modulated Radiation Therapy Technique.

Chemotherapy Protocol

- Concurrent chemotherapy was administered weekly and the drug used was Cisplatin
- Cisplatin dosage at 40mg/m2 weekly (max dose of 70 mg) for 4 weeks
- Chemotherapy for the week is deferred or delayed if any of the following criteria are met
  - Serum Creatinine > 1.5 mg/dl
  - Absolute Neutrophil Count < 1500/cu mm
  - Total Platelet Count < 1,00,000/ cu mm

Brachytherapy Protocol

- Brachytherapy was administered as per institution protocols 1 week after completion of concurrent chemo radiotherapy

Post Treatment Evaluation

- Complete Blood Picture was repeated before each Brachytherapy applications
- Analysis of haematological toxicity, bowel and bladder toxicity was repeated prior to each brachytherapy session
- Quality of life analysis was repeated on the last day of treatment and first follow up visit post treatment
- Number of cycles of chemotherapy received documented
- Total duration of treatment documented

Results

Of the 40 patients accrued for the study, 20 patients were present in each arm. Patients who refused concurrent chemotherapy were excluded from the study. All patients were followed up to a period of 6 weeks following Intracavitary radiation.

A total number of 20 patients of age 60 or less were enrolled in the study. The mean age was 47.25 years

Table 1: Distribution by FIGO stage

	IB (%)	IIA (%)	IIB (%)	IIIA (%)	IIIB (%)	Grand Total
BMS IMRT	6(30)	1 (5)	9 (45)	1(5)	3 (15)	20
SIMRT	2 (10)	2 (10)	12 (60)	1 (5)	3(15)	20
Grand Total	8(20)	3(7.5)	21 (52.5)	2 (5)	6 (15)	40

Most of the patients presented in Stage IIB. More number of Stage IB patients in BMS IMRT compared tosIMRT.

Table 2: Dose reporting and received by Organs at Risk

	BMS IMRT (Gy)	SIMRT (Gy)	p Value
Dose reporting as per ICRU-83			
D 98%	48.25 (±0.47)	48.5 (±0.42)	p=0.16
D 2%	52.6 (±1.0)	52.1 (±0.6)	p=0.05
D mean	51.37 (±0.53)	51.04 (±0.61)	p=0.2
Dose received by organs at risk			
Bladder Mean	46.8 Gy (±2.8)	45 Gy (±4.5)	p=0.12
Bladder V50	37.7% (±15.9)	32.7% (±13.3)	p=0.28
Bowel Mean	29.4 Gy (±5.6)	28.3 Gy (±10.3)	p=0.6
Rectum Mean	47.8 Gy (±2.6)	47.7 Gy (±2.7)	p=0.9
Rectum V50	42.2% (±19.1)	40.7% (±22.5)	p=0.8
Bone Marrow dose			
BM V10	87.25% (±2.3)	93.7% (±2.0)	p<0.0001
BM V20	73.55% (±3.4)	83.15% (±5.1)	p<0.0001
BM V30	61.35% (±8.0)	67.6% (±6.4)	p=0.01

and median age was 49.5 years. The mean age of presentation in BMS IMRT was 45 years (range 37-49) and that of sIMRT was 49 years (38-53). Most common histology was squamous cell carcinoma. There was no case of adenocarcinoma, from S IMRT. (Table 1).

Dose reporting was done as per ICRU-83. No significant difference was seen with regards to target coverage between both the arms.

Dose received by Organs at Risk (OAR) i.e. bladder, bowel and rectum was recorded. QUANTEC dose constraints were achieved in all patients. No significant difference in doses to OAR's between both the arms was noted.

Bone Marrow dose constraints were applied to BMS IMRT. Dosimetric difference in Bone Marrow V10, V20 and V30 was observed between both the arms with significant p value. (Table 2).

Haemoglobin values fall with time in both BMS IMRT and sIMRT. Recovery of haemoglobin values to pre-treatment levels is observed at 6 weeks follow up. The difference of haemoglobin with each week of treatment received is statistically significant (p<0.001). (Figure 1).

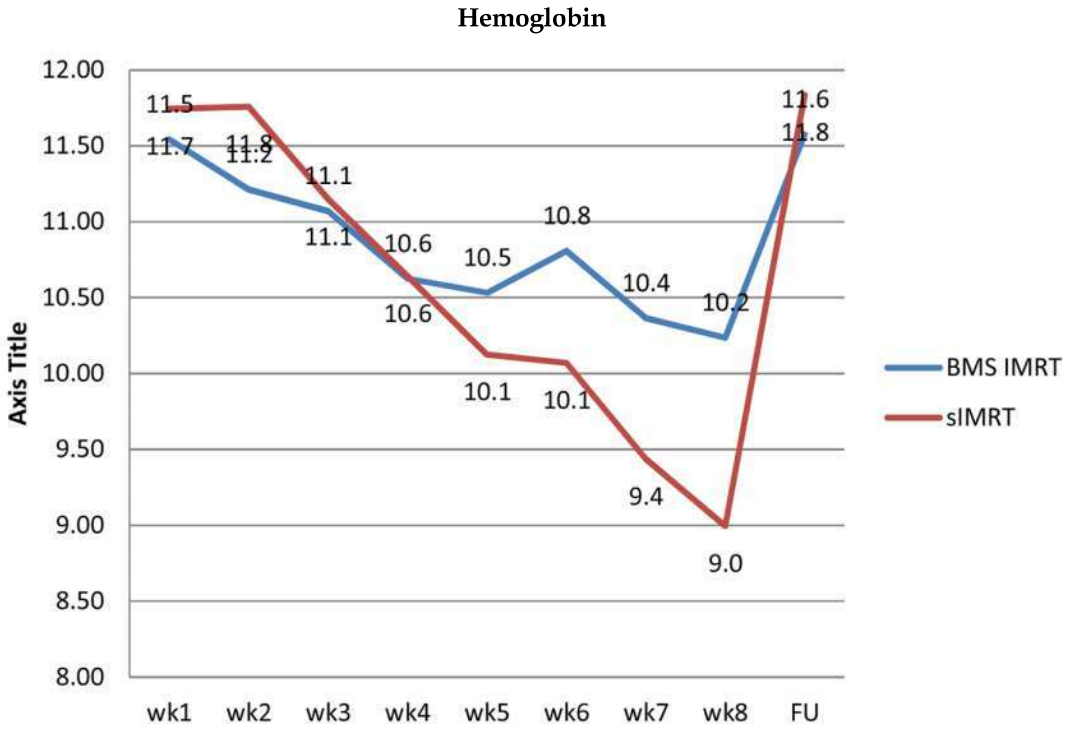


Fig. 1: Trend of mean hemoglobin during treatment

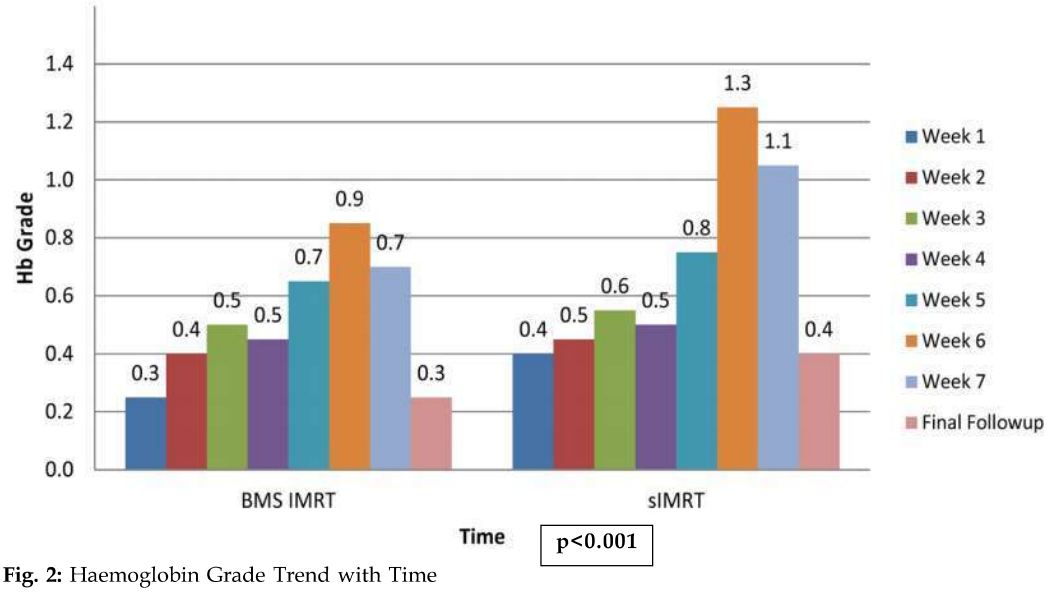


Fig. 2: Haemoglobin Grade Trend with Time

Haemoglobin fall seen in both arms. Steeper fall in sIMRT after Week 5 of treatment compared to BMS IMRT.

Statistically significant difference in haemoglobin at end of treatment between both arms (p=0.01). Better haemoglobin values in BMS IMRT.

Grade of haemoglobin toxicity increases with time and is worst in week 6 in both arms and is statistically significant (p<0.001). Worse toxicity scores are seen in sIMRT as compared to BMS IMRT in the final weeks of treatment. Recovery to pre-treatment values is seen in both arms by 6 week follow up.

Higher Grade 2 and above toxicity seen in sIMRT compared to BMS IMRT. No Grade 3 toxicity observed in sIMRT. The difference in Grade 2 and above toxicity is statistically significant (p=0.02). (Figure 2).

TLC fall is seen in both BMS IMRT and sIMRT with each week of treatment. Values of TLC at 6 weeks follow up approach those of pre-treatment values but do not recover completely in both arms. The fall in

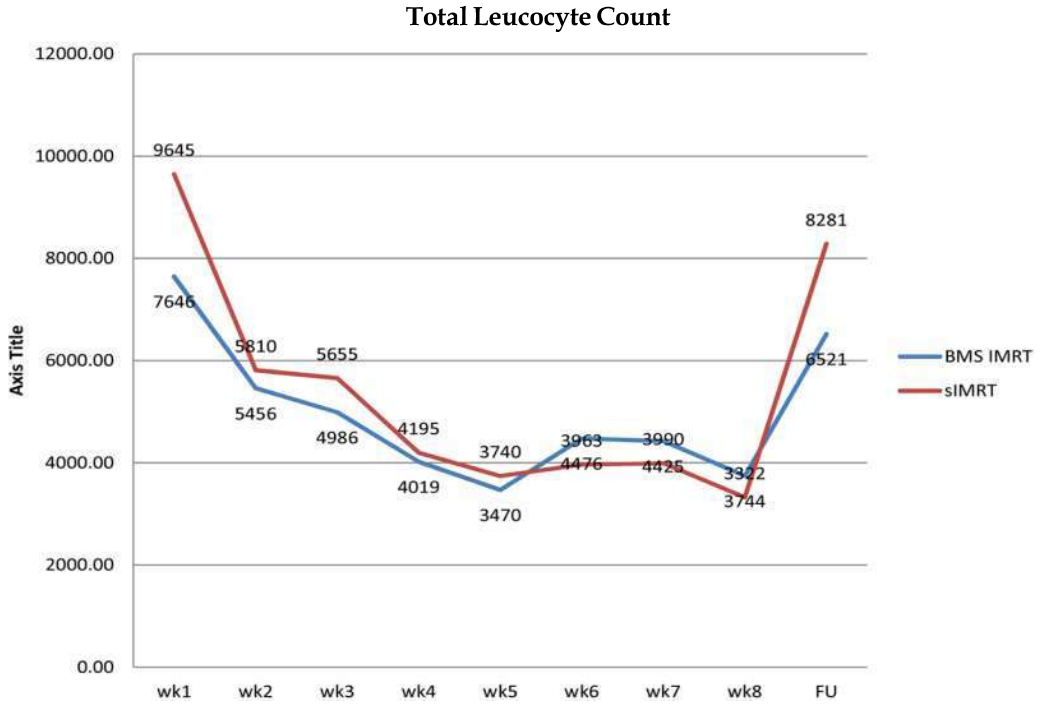


Fig. 3: Trend of mean TLC during treatment

TLC with respect to time is statistically significant (p<0.001).

TLC fall is seen in both arms during treatment. Steeper fall is seen in sIMRT compared to BMS IMRT. Recovery of TLC count is seen in BMS IMRT from week 5 to week 8 which is not seen in sIMRT.

TLC at the end of treatment appears to be better in BMS IMRT compared to sIMRT, but not statistically significant (p=0.2). (Figure 3).

Grade of TLC toxicity increases with time and is worst in Week 5 in both arms and is statistically significant (p<0.001). Worse toxicity scores are seen in sIMRT compared to BMS IMRT in the final weeks of treatment. Recovery to pre-treatment levels seen at 6 weeks follow up in both arms.

Higher Grade of toxicity seen in sIMRT compared to BMS IMRT, but not statistically significant (p=0.2). Higher Grade 2 and above toxicity in sIMRT compared to BMS IMRT, but not statistically significant (p=0.2). No Grade 3 toxicity observed in either arm. (Figure 4).

ANC fall is seen in both BMS IMRT and sIMRT with each week of treatment and this fall is statistically significant (p<0.001). At 6 weeks follow up ANC counts seem to recover to almost match the pre-treatment values in both arms. Fall in ANC is seen in both arms during treatment. Steeper fall is seen insIMRT compared to BMS IMRT. ANC at the end of treatment appears to be better in BMS IMRT compared to sIMRT but is not statistically significant (p=0.3).

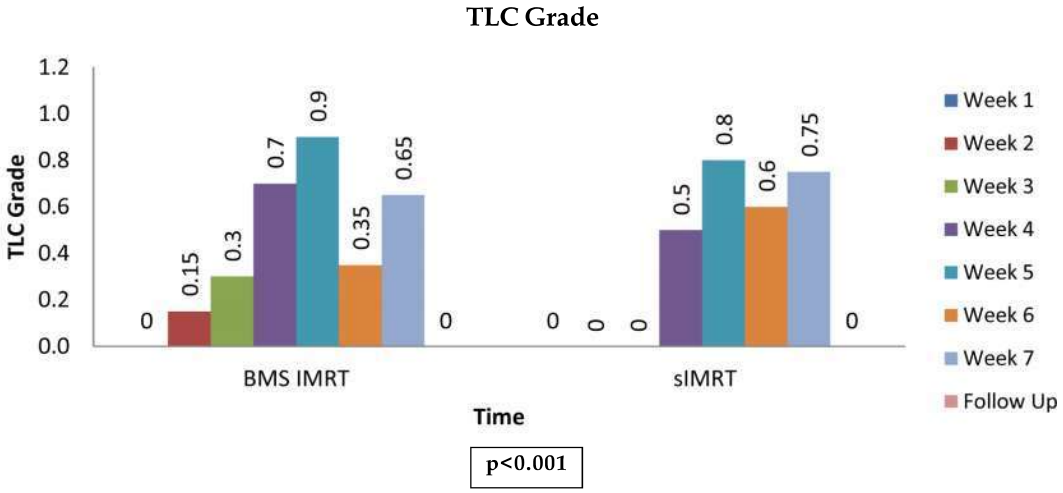


Fig. 4: TLC Grade Trend with Time

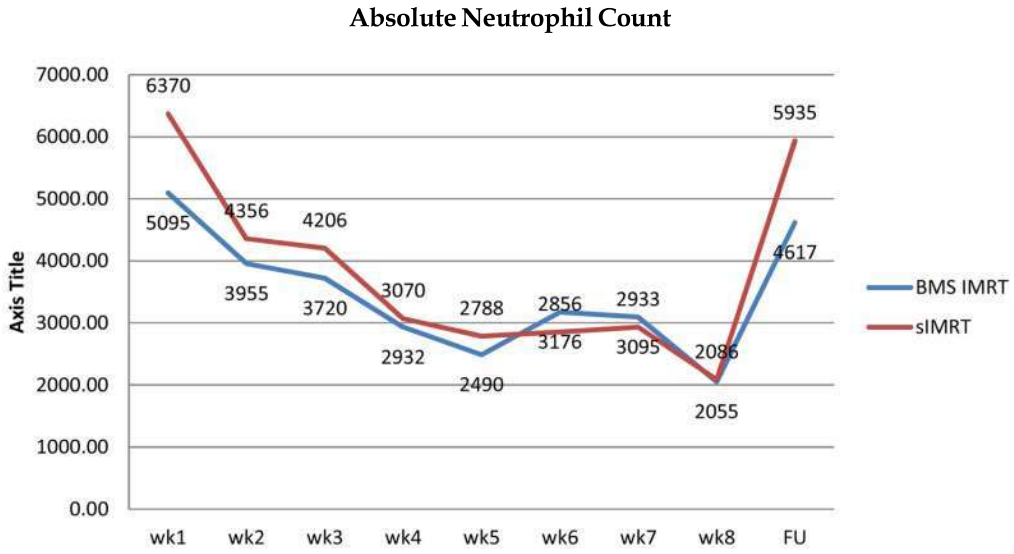


Fig. 5: Trend of mean ANC during treatment

ANC Grade 2 toxicity was observes in a total of 3 patients, 2 in BMS IMRT and 1 in sIMRT. No grade 3 toxicities were observed in either arm. The difference between both arms was not statistically significant (p=0.5). (Figure 5).

TPC fall is seen in both BMS IMRT and sIMRT with each week of treatment and this fall is statistically significant (p<0.001). Recovery to pre-treatment levels is seen in both arms by 6 weeks follow up. Fall in ANC values seen in both arms. Steeper fall during Week 1 to Week 5 and slower recovery during Week 5 to Week 8 seen in sIMRT when compared to BMS IMRT.

TPC at the end of treatment appears to be better in BMS IMRT compared tosIMRT but is not statistically significant (p=0.1) (Figure 6)

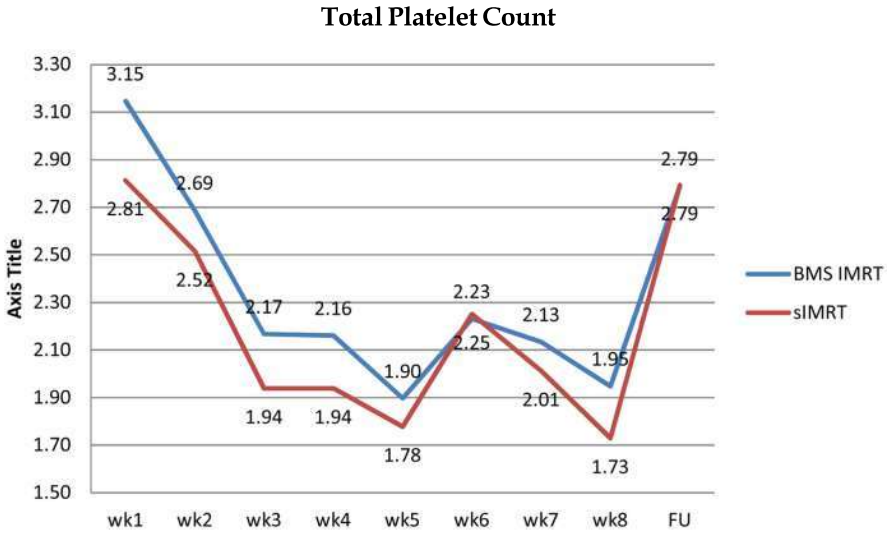


Fig. 6: Trend of mean TPC during treatment

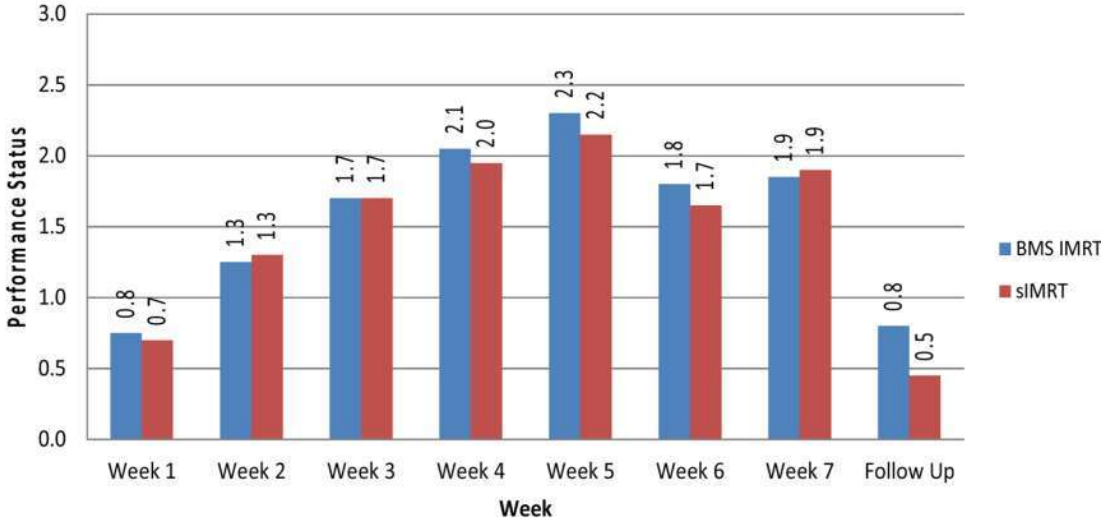


Fig. 7: ECOG Performance Status

p=0.08

Chemotherapy

No statistically significant difference (p=0.6) in number of cycles chemotherapy received in both arms. No statistically significant difference in treatment duration between both arms (p=0.3).

Performance status worsens with each week of treatment and nadir is seen at Week 5. There is no statistically significant difference between both the arms (p=0.08). (Figure 7).

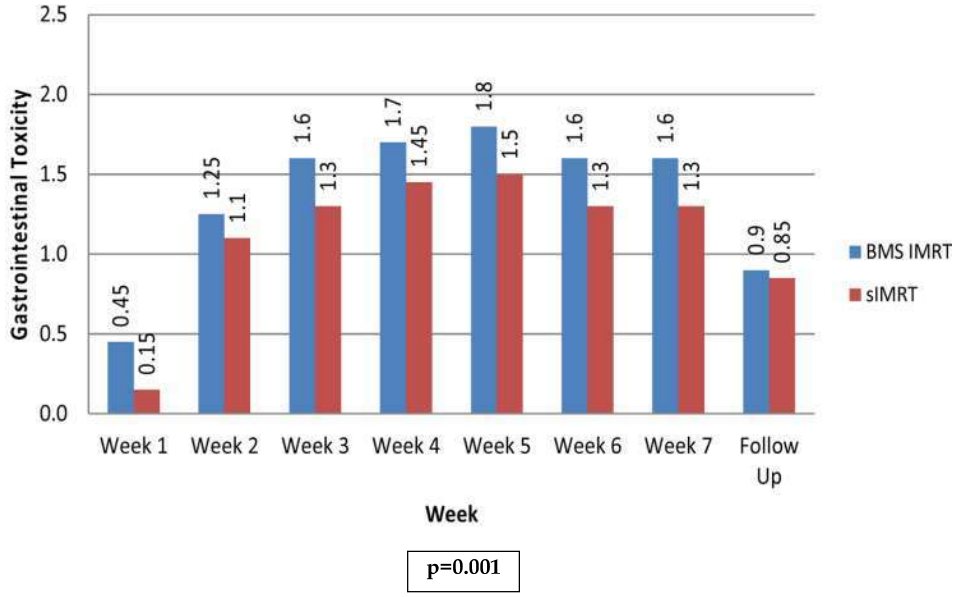


Fig. 8: Gastrointestinal Toxicity as per RTOG Toxicity Scoring

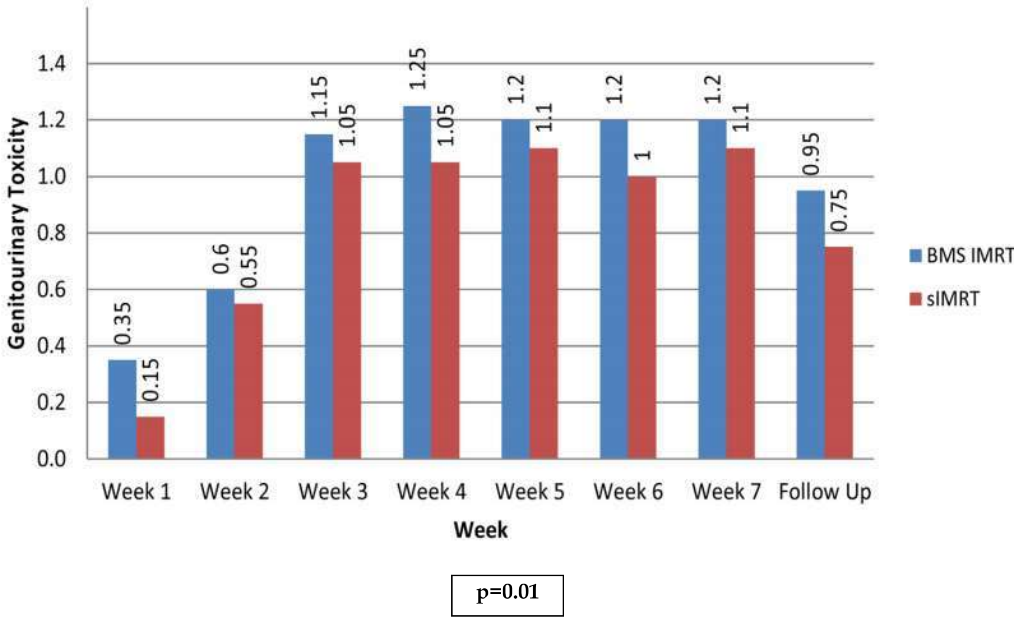


Fig. 9: Genitourinary toxicity

Gastrointestinal toxicity worsens with every week of treatment and the nadir is seen at Week 5. There appears to be a small but statistically significant difference in GI toxicity in favour of sIMRT. (Figure 8).

Genitourinary toxicity worsens with every week of treatment and the nadir is seen at Week 5. There appears to be a small but statistically significant difference in GI toxicity in favour of sIMRT. (Figure 9).

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. The present study is a prospective, observational study undertaken to evaluate the role of 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. The impact of bone marrow sparing on haematological toxicity, gastrointestinal, genitourinary toxicity and quality of life has not been evaluated prospectively. Furthermore, its impact in terms of treatment duration, number of cycles of chemotherapy and impact on PRBC and Growth Factor requirement 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 57 yrs and median age was 59 yrs. The mean age of patients in BMS IMRT arm was 55yrs (37-79) and in sIMRT arm was 59yrs (38-73). The patients presented in stage I were 20%,stage II were 60%,and in state III were 20% among all the fourty patients studied. Majority of patients had squamous cell histology. Only 3 patients had adeno-carcinoma histology (7.5%), all of them in BMS IMRT arm.

Mell et al. [3] showed 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. [4] found 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 all our patients in BMS IMRT Arm. The mean BM V10 values in BMS IMRT and sIMRT arm were 87.15% vs. 93.7% respectively (p<.0001). The mean BM V20 values in BMS IMRT and sIMRT arm were 73.55% and 83.15% respectively (p<.0001). The mean BM V30 values in BMS IMRT and sIMRT arm were 61.35% and 67.6% respectively (p=.01).

Mell et al. [3] also demonstrated BMS using IMRT compared to 3DCRT using AP/PA techniques and 4 Field Box technique. Overall, BMS-IMRT was superior to the four-field technique in reducing the dose to the PBM. Th e PBM volume receiving 10 Gywaslower with BMS-IMRT than with Four-field box (76.5% vs. 97.3%; p<0.05). ThePBM volume receiving 20 Gywaslower with BMS-IMRT than with Four-field box and AP/PA technique (57.5% vs. 92.7% vs. 62.9%; p<0.05 BMS IMRT vs. AP/PA; p<0.05 BMS IMRT vs. Four-field box). ThePBM volume receiving 30 Gywaslower with BMS-IMRT than with Four-field box and AP/PA technique (46.1% vs. 59.9% vs. 59.1%; p<0.05 BMS IMRT vs. AP/PA; p<0.05 BMS IMRT vs. Four-field box). The BM V10 and V20 values achieved in the above study are lower than those achieved in our present study, probably due to the lower dose prescription of 45Gy used compared to 50Gy used in our study.

Haematological Toxicity

Haematological toxicity was analysed by recording weekly complete blood counts for all patients until the end of the last brachytherapy application. RTOG Acute Morbidity 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.

Haemoglobin

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 BMS IMRT arm. The recovery of Hb after completion of External Beam Radiation appears to be better in BMS IMRT arm when compared to sIMRTarm.At the end of treatment (week 8), the mean haemoglobin in BMS IMRT and sIMRT arm are 10.2 and 8.9 respectively and the difference is statistically significant (p=0.01).

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 BMS 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 BMS IMRT arm and sIMRT arm are 6 and 13 respectively (p=0.02). There were no Grade 3 toxicities encountered in BMS 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 [5,6]. 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 ofhaemoglobin 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 BMS IMRT arm.

Mell et al. [3] found on univariate analysis that a BM-V10 of >90% and BM-V20 of >75% correlated with Hb nadir. The Hb nadirs encountered were 11.4g/dL vs. 10.6g/dL using BM-V10 as cut-off (p=0.06) and 11.6g/dL and 10.4g/dL using BM-V20 as cut-off (p<0.01). The Hbnadirs encountered in our study are lower probably due to a lower baseline Hb observed in an Indian population compared to a Western one.

TLC

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 BMS IMRT arm. The recovery of TLC after completion of External Beam Radiation appears to be better in BMS IMRT arm when compared to sIMRTarm.At the end of treatment (week 8), the mean TLC in BMS IMRT and sIMRT arm are 3743/cu mm and 3322/cu mm respectively, which appears to favour BMS 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 BMS IMRT and sIMRT arms are 0.85 and 1.16 respectively, which appears to favour BMS IMRT arm, but the difference is not statistically significant (p=0.26).The number of patients with Grade 2 and above toxicity in BMS 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 *Mell et al. [3]* 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 Mell et al 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 BMS 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 Mell et al., 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. 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.

ANC:There is a fall in ANC 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 BMS IMRT arm. The recovery of ANC after completion of External Beam Radiation appears to be better in BMS IMRT arm when compared to sIMRTarm. At the end of treatment (week 8), the mean ANC in BMS IMRT and sIMRT arm are 2568/cu mm and 2317/cu mm respectively, which appears to favour BMS IMRT arm, but the difference is not statistically significant (p=0.3).

The grade of ANC toxicity also increases as treatment. When analysed at end of treatment, the mean grade of toxicity in BMS IMRT and sIMRT arms are 0.1 and 0.3 respectively, which is not statistically significant (p=0.2). Only 3 patients (7.5%) in our present study had Grade 2 neutropenia and Grade 3 neutropenia was not encountered. Grade 2 and above toxicity was encountered in 19% of patients in the study by Mell et al which is double of what we observed.Our study was not powered to detect a difference in ANC as the required sample size was 50.

TPC: 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 BMS IMRT arm. The recovery of TPC after completion of External Beam Radiation appears to be better in BMS IMRT arm when compared to sIMRTarm.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.

Cycles of Chemotherapy

Concurrent chemotherapy with Weekly Inj. Cisplatin (40mg/m^2, max dose of 70 mg) was administered. 60% of the patients (24/40) received all 5 doses as scheduled (12 in each 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 BMS IMRT vs. 4.5 in sIMRT; p=0.6).In the study by Mell et al 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.

Treatment Duration: 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 BMS 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.

Blood Transfusions and Growth Factor Support: No patient in our study required growth factor support. 8 patients had low Hb to warrant blood transfusions, 2 in BMS IMRT arm and 6 in sIMRTarm. Due to less Grade 3 Hb toxicity in BMS IMRT arm the transfusion requirement was less than sIMRT arm.

Performance Status: The performance status as per ECOG Scale of each patient was recorded at weekly intervals from the start of treatment till the last brachytherapy application. The performance status worsens as treatment progresses in all patients and nadir is seen at week 5, i.e. at the end of external beam radiation. There is no statistically significant difference in performance status between both the treatment arms (p=0.08).

Gastrointestinal Toxicity: The gastrointestinal toxicity as per RTOG Acute Morbidity Scale was recorded at weekly intervals from the start of treatment till the last brachytherapy application in all patients. As expected, the grade of toxicity worsens as treatment progresses and is statistically significant (p=0.001). There appears to be slightly more gastrointestinal toxicity in BMS IMRT arm when compared to sIMRT arm (1.3 vs. 1.1; p=0.001). As there was no significant difference in dose to bowel and rectum between both the arms this difference observed is probably due to more number of post-op patients in BMS IMRT arm compared to sIMRT arm (17.5% vs. 5%). Acute Grade 2 toxicity was encountered in 52.5% of all our patients and Acute Grade 3 toxicity was seen in 7.5% of patients.

Gandhi et al. [7] evaluated GI and GU toxicities in 44 patients of locally advanced cervical cancer treated with CTRT at AIIMS. Patients in the WP-IMRT arm 31.8% experienced Grade ≥ 2 acute gastrointestinal toxicities and 4.5% experienced grade ≥ 3 gastrointestinal toxicities. They studied patients treated with only Radical CTRT. The higher GI toxicities encountered in our study could be due to more number of post-op patients (22.5%).

Genitourinary Toxicity

The genitourinary toxicity as per RTOG Acute Morbidity Scale was recorded at weekly intervals from the start of treatment till the last brachytherapy application in all patients. As expected, the grade of toxicity worsens as treatment progresses and is statistically significant (p=0.001). There appears to be slightly more genitourinary toxicity in BMS IMRT arm when compared to sIMRT arm (0.9 vs. 0.8; p=0.01). As there was no significant difference in dose to bladder between both the arms this difference observed is probably due to more number of post-op patients in BMS IMRT arm compared to sIMRT arm (17.5% vs. 5%). Acute Grade 2 toxicity was encountered in 15% of all our patients and Acute Grade 3 toxicity was seen in 2.5% of patients.

Gandhi et al. [7] evaluated GI and GU toxicities in 44 patients of locally advanced cervical cancer treated with CTRT at AIIMS. Patients in the WP-IMRT arm 23.8% experienced Grade ≥ 2 acute genitourinary toxicities and 0% experienced grade ≥ 3 gastrointestinal toxicities. The toxicity observed in our study is comparable to the study by Gandhi et al. In our study only one patient treated with post-op adjuvant CTRT had Grade 3 GU toxicity.

There are also few studies done by others also [8,9,10]. Our study is a randomised study prospectively evaluating bone marrow sparing IMRT in comparison to standard IMRT. It is a single institution study, with a small sample size of 20 in each arm. Though our sample size was adequately powered to detect a statistically significant difference, we based it on retrospective data which might have underestimated the number of patients needed in each arm. We also had no other prospective data to compare our results with. Our patients were not stratified prior to start of randomisation and so there appear to be more post-op cases in our bone marrow sparing arm which might explain the increased toxicity encountered in them. Inspite of the above limitations we conclude that bone marrow sparing using IMRT using SPECT is safe and feasible. Further randomised, prospective studies are required to validate our results.

Conclusions

The present one is a randomised study evaluating bone marrow sparing IMRT compared to standard IMRT. Our results show that bone marrow sparing is feasible without compromising on target coverage or normal tissue sparing. Our results show a significant difference in haemoglobin nadir, grade 2 and above haemoglobin toxicity in favour of bone marrow sparing arm. This may be more relevant in Indian scenario due to more prevalent anaemia and low baseline haemoglobin.

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.The above results suggest that SPECT-BM imaging may be added to the ever growing list of functional imaging techniques that may play a role in IMRT planning. Bone marrow sparing approach may also benefit patient s with anal and rectal cancers. The patients with anal cancers may particularly benefit as often they receive highly myelotoxic regimens in conjunction with pelvic RT.

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