RESEARCH ARTICLE

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Analysis of Rapid arc-based Radiation Therapy on Dosimetric Parameters in Cervical Cancer Patients with and without Bone Marrow Sparing

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Abstract

Background: The standard treatment for cervical cancer is chemoradiation therapy. Pelvic radiation is associated with higher dose to bone marrow (BM) causing interrupted treatment due to haematologic toxicity with inferior outcomes. This study aims to evaluate rapid arc technique in sparing pelvic BM and dosimetric parameters for pelvis V5GY, V10GY, V20GY, V30GY, and V40GY dose. **Method:** Twenty one cervical cancer patients were selected for the analysis. Planning target volume (PTV) contours, total pelvic BM and surrounding structures contours were standardised. Two rapid arc based procedures were designed for individual patient. One was done using bone marrow sparing (BMS) constraints while other was performed without BMS constraints. Data for both plans was calculated with regard to PTV, normal structures and pelvic BM. Difference in dose distribution in both groups was analysed using Wilcoxon and Friedman ANOVA test. **Results:** In the presence of BM constraint a significant changes in pelvic BM dose for values of V10GY (p=0.002), V20GY (p=0.002) and V40GY (p=0.025) was observed. The coverage of PTV was found to be unaffected by adding BM constraint. **Conclusion:** The BM is radiosensitive structure so dosage is linked with haemtological toxicity. Increased dose is associated with higher grade of haematological toxicity in pelvic radiotherapy. The study suggests that adding BM constraint in plans reduced the pelvic BM dose while not affecting PTV coverage and dose to bowel, bladder and rectum. Bone marrow constraint in pelvic radiotherapy can be considered for better treatment toleration and to determine its role in decreasing haematological toxicity.

Keywords: Bone marrow sparing- Cervical Cancer- Rapid arc

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Introduction

In patients diagnosed as case of cervical cancer, the current standard of treatment is pelvic radiotherapy with a simultaneous application of chemotherapy following which brachytherapy is performed (Rose et al., 1999; Whitney et al., 1999). Concurrent chemoradiation improves tumor control but it has also demonstrated increase in acute haematologic toxicity in up to 67% patients (John et al., 1996). This can impact the treatment delivery and outcome. Bone marrow (BM) is radiosensitive structure and the BM volume irradiated due to the dosage applied has been seen to be linked with haemtological toxicity in patients. Approximately 50% of haematopoeisis occurs in pelvic bones including Lumbar spine and irradiating these regions results in apoptosis of stem cells and stromal damage (Hayman et al., 2011; Hui et al., 2014). This leads to anaemia, neutropenia and thrombocytopenia. Radiation causes suppression of the stem cells of bone marrow causing apoptosis as well as radiation induced injury to BM (González et al.,2011). Concurrent chemotherapy further enhances this toxicity (Mauch et al., 1995). Clinical studies have shown that the extent of radiation induced BM injury depends on both the dose and the volume of BM irradiated (Mell et al., 2008). In cases treated with conventional techniques large volume of active BM in pelvis and lumbar spine gets irradiated (Bucci et al., 2005). Multiple studies showed that intensity modulated radiotherapy (IMRT) can decrease dose to normal surrounding structures including BM as compared to conventional techniques (Chino et al., 2020; Mundt et al., 2002).

Consequently, application of BMS IMRT was determined based on greater degree of Conformality and dosimetric analyses (Lujan et al., 2003). A problem with standard IMRT technique is large volume of bone marrow to be spared without changing optimisation. Dosimetric analysis has shown that V20>80% to pelvic bone

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marrow increases the severity of haematological toxicity (Albuquerque et al., 2011). Many newer techniques of radiotherapy have shown that BM doses are reduced with using plans with the newer techniques as compared to conventional techniques (Lujan et al., 2003; Brixey et al., 2002). Rapid Arc (Varian Medical Systems, USA) is a unique IMRT where multi leaf collimator (MLC) leaf position, gantry speed, as well as rate of dosage can alter at the time of delivery (Bedford et al., 2009). This technique decreases treatment delivery time, improves dose to organs at risk and produces better or similar dose distribution as compared to IMRT (Cozzi et al., 2008; Teoh et al., 2011; Renard-Oldrini et al., 2012). The phase II clinical trial, RTOG 0418, indicated that the mean dose more than 40 Gy received by bone marrow is related to the haematological toxicity in concurrent chemo radiotherapy for cervical cancer (Klopp et al., 2013).

Our primary aim is to study the hypothesis that use of rapid arc-based BM sparing may help in reducing the dosage to pelvic BM among cervical cancer patients undergoing chemoradiation therapy. The Pelvic BM dose analysis was done with different dose volume objectives as no exact sparing level has been recommended. The bone marrow constraints of V5GY, V10GY, V20GY, V30GY and mean dose were analysed.

With more conformity of dose distribution offered by Rapid ARC® technique, we try to determine the feasibility to decrease BM dose devoid of any increase in the dose to adjacent critical organs or compromising coverage of our target structures.

Materials and Methods

We analysed 21 cervical cancer patients with median age 58 years and range (33-72years) treated by concurrent chemoradiation therapy at our institution DMCH cancer care centre, Ludhiana, Punjab between April, 2020-January, 2021. Inclusion criteria were histopathological proven cervical cancer patients planned for chemoradiation therapy. The disease was staged according to FIGO (Federation of Gyanecology and Obstetrics). All the patients were treated on True Beam® Linear Accelerator with RapidARC® plans. All the plans were generated using grid size of 0.25cm with 2 arcs as required dose constrains. Arc angles, collimator angles keep the same along with optimization constrains to keep the uniformity for all plans. Varian CBCT used for image guidance for all the cases with pelvic mode selection, half fan type - full trajectory, 125 KV and 1080 mAs as per Varian protocol.

Radiation Planning

The procedure was planned for all patients using contrast CT scan dependent simulation having slice thickness of 2.5mm. Immobilisation for each patient was done using Vaclocs for precision in repositioning for daily treatments. Full bladder and empty rectum protocol was followed in all the patients. Images were scanned from L1 vertebrae till upper thigh. Contouring in all patients for primary and nodal regions was done as per standards defined by RTOG-0418 (Klopp et al., 2013). Normal structures included bladder, rectum, bowel and femoral heads were contoured in both sets of contours. The BM constraint included iliac BM, lumbosacral BM, and Lower Pelvic BM structures (Mell et al., 2008). Lumbosacral BM included lumbar vertebra 1 cm above PTV to inferiorly including sacrum to the coccyx. The iliac BM extended from iliac crest to superior aspect of femoral heads. The lower pelvic bone marrow extended from femoral head to ischio pubic ramii. The total pelvic (TP) BM included all the three mentioned structures. The BM constraints of V5GY, V10GY, V20GY, V30GY and mean dose were given.

Two rapid arc procedures were designed for individual patient. One was performed using BMS constraints while in the other it was not included. Data for both the plans was calculated with regard to PTV, normal structures and TP-bone marrow.

Dosimetric Parameters

The PTV prescription was in 46-50.4 Gy in 25-28 fractions in 1.8-2 Gy per fraction. All patients were taken up for brachytherapy after external beam radiotherapy (EBRT). The constraints given as per RTOG 0418 Bladder was V45Gy<35%, Rectum V30Gy<60%, Bowel V45Gy<195cc, Femoral Heads max<45Gy and V50Gy<5%. In all patients RapidARC® planning for pelvic irradiation was performed without prescribing constraint dose to BM and the second plan was performed with the constraint dose to BM was prescribed as V5Gy <90%, V10<80%, V20<80%, V30<55%, Dmean <31Gy. Dose distribution data was collected from dose volume histogram (DVH) of each patient for all the structures contoured. In addition, 2D gamma pass results of 3%, 3mm and Normal tissue integral dose were compared (Mohandass et al., 2019).

Statistical Analysis

For individual data points the mean dosage was determined. Any statistical difference between both sets of plans was determined using Wilcoxon and Friedman ANOVA test. SPSS software (version 19.0, SPSS Inc., USA) was used for performing the statistical analysis for the study. A p value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

Twenty-one women were included in the study having a mean age of 58 years (range, 33-72 years). It has been observed that only 1 patient was from the age group of <35 while 11 and 9 patients were from the age group of 35-60 years and >60 years respectively. All the patients were found to belong to FIGO Stage IIB and IIIB among which 12 and 9 patients were in the stage IIB and IIIB respectively. Among the patients 12 patients had adenocarcinoma and 9 patients had squamous cell carcinoma. All individual patients were administered chemotherapy following which brachytherapy was performed (Table 1).

It was also observed from the study that there was

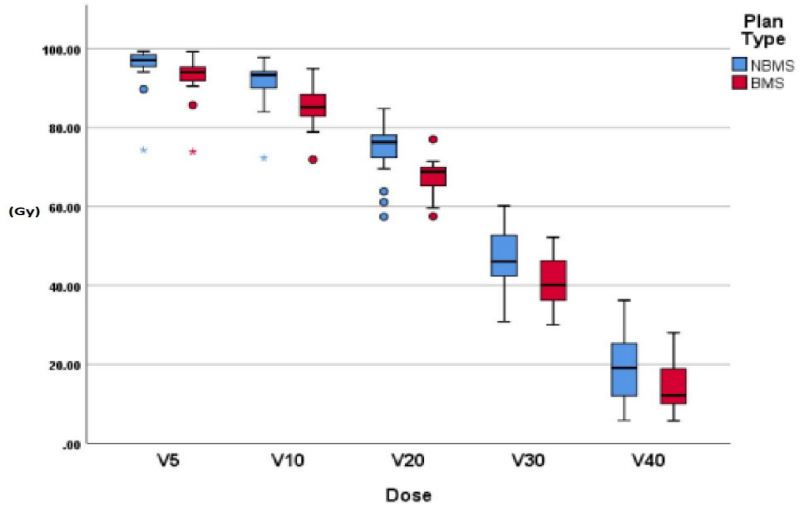

Figure 1. Dosimetric Analysis of BM Sparing

a significant decrease in the dose to left femoral head (p=0.018) and right femoral head (p=0.002) among patients with BMS in comparison to those without BMS. In other surrounding normal structures there was minimal difference noted in average dose distribution. There were no data points which showed increased dose to bladder and rectum. The means dose received by all these two structures was same in both the sets of plans indicating that on application of BMS the dosage to adjacent normal tissues of the body did not alter other than left and right femoral heads (Figure 2) (Table 3).

Table 1. Table Representing Characteristics of the Patients

Variable	Number of patients (%) / Mean (Median)
Age group	
<35	1 (33)
35-60	11 (53)
>60	9 (67)
Stage	
IIB	12 (57.14%)
IIIB	9 (42.86%)
Type of Carcinoma	
Adenocarcinoma	12 (57.14%)
Squamous Cell Carcinoma	9 (42.86%)

Table 2. Table Comparing the Dose to TP in Presence and Absence of BMS Constraint

TP doses	NBMS (Mean±SD) (%)	BMS (Mean±SD) (%)	P value
TP V5	95.69±5.51	92.89±5.38	0.022*
TP V10	91.29±5.67	85.38±5.13	0.003*
TP V20	74.18±7.05	67.56±4.34	0.003*
TP V30	46.00±8.31	40.63±6.80	0.044*
TP V40	19.46±8.34	14.33±5.62	0.000*

Total Pelvic, NBMS, Non bone marrow sparing; BMS, Bone marrow sparing; SD, Standard deviation; *, Significant at p<0.05

On comparing the mean and max bowel amount with and without BMS it has been observed that there was no significant difference in the amount of mean and max bowel observed for patients with BMS and those without BMS indicating that the BMS did not affect the bowel among the patients (Figure 3) (Table 4). On comparing the PTV coverage in presence and absence of BMS constraint no significant difference has been observed among the

Table 3. Table Comparing the Dose to Bladder, Rectum and Femoral Heads in Presence and Absence of BMS Constraint

Variable		NBMS (Mean±SD)	BMS (Mean±SD)	P value
Bladder (Gy)		48.01±2.87	46.23±4.11	0.192
Rectum (Gy)		36.17±6.91	38.89±7.81	0.237
Femoral Heads (Gy)	Left	49.68±1.69	48.17±1.39	0.018*
	Right	49.60±1.39	48.03±1.39	0.002*

NBMS, Non bone marrow sparing; BMS, Bone marrow sparing; SD, Standard deviation; *, Significant at p<0.05

Table 4. Table Comparing the amount of Mean and Max Bowel in Presence and Absence of BMS Constraint

Variable (Gy)	NBMS (Mean±SD)	BMS (Mean±SD)	P value
Bowel (Mean)	19.07±3.55	19.09±2.00	0.728
Bowel (Max)	50.11±2.59	50.05±2.78	0.823

NBMS, Non bone marrow sparing; BMS, Bone marrow sparing; SD, Standard deviation; *Significant at p<0.05

Table 5. Table Comparing the PTV Coverage in Presence and Absence of BMS Constraint

Variable	NBMS (Mean±SD) (%)	BMS (Mean±SD) (%)	P value
PTV 95	98.00±1.90	98.75±2.26	0.187
PTV 107	0.10±0.12	-	-

NBMS, Non bone marrow sparing; BMS, Bone marrow sparing; SD, Standard deviation; *, Significant at p<0.05

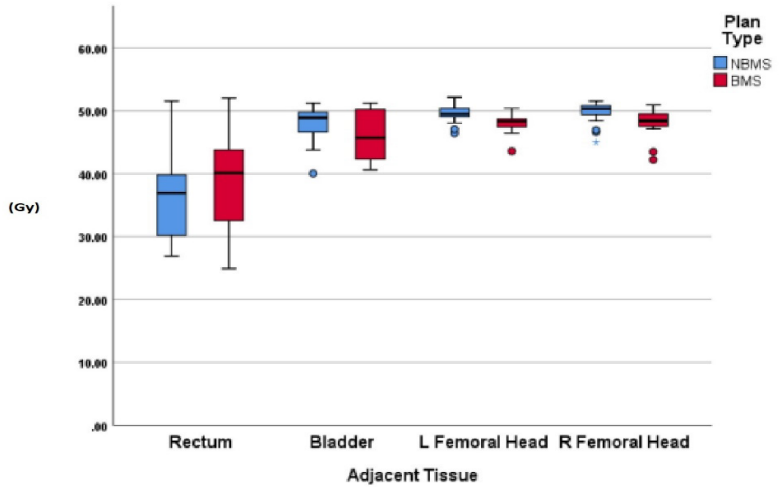

Figure 2. Dose to Bladder, Rectum and Femoral Heads in Presence and Absence of BMS Constraint

PTV 95% of prescribed dose coverage among the patients in presence and absence of BMS constraint. The gamma pass results of 3%, 3mm on both NBMS and BMS plans showed >95%. And NTID did not show any significant difference between two plans ($p>0.05$).

Discussion

Cervical cancer has been ranked third among the most common cancer affecting females globally and second in case of India. It has been reported to be most prevalent among females of underdeveloped nations (Ferlay et al., 2013). Concurrent chemoradiation is the current standard of treatment for cervical cancer patients. In the eras when conventional planning was used, much effort in reducing the BM dose concentrated on shielding femoral heads and iliac wings. The technique of delivering radiotherapy has improved from the box field to CT based highly conformal modalities. In a study by Brixety et al., (2002), it was reported that IMRT effectively helps in reducing the haematological toxicity, even in absence of BMS constraints (Brixey et al., 2002). With the advent of newer techniques like IMRT it is now possible to treat the malignancies with highly conformal approach to decrease the radiation dose to normal surrounding structures without decreasing coverage to target volume (Rose et al., 2011). Pelvis comprises of 40-50% of BM (John et al., 1996).

Irradiation causes suppression of radiosensitive tissues like BM stem cells (Mauch et al., 1995). Clinical studies reported the magnitude of injury of BM due to radiation is dependent on the irradiated BM volume as well as dosage (Mell et al., 2008). Patients receiving RT to pelvis develop high grade of haematological toxicities like anaemia, leukopenia and thrombocytopenia (Cao et al., 2011). Mell et al., (2008) showed that the amount of haematological toxicity increases when V10>90% in entire pelvic BM. It also showed grade 2 or more leukopenia (11.1% vs 73.7%) and grade 2 or more neutropenia (5.6% vs 31.6%) with higher BM dose (Mell et al., 2006). RTOG 0418 has

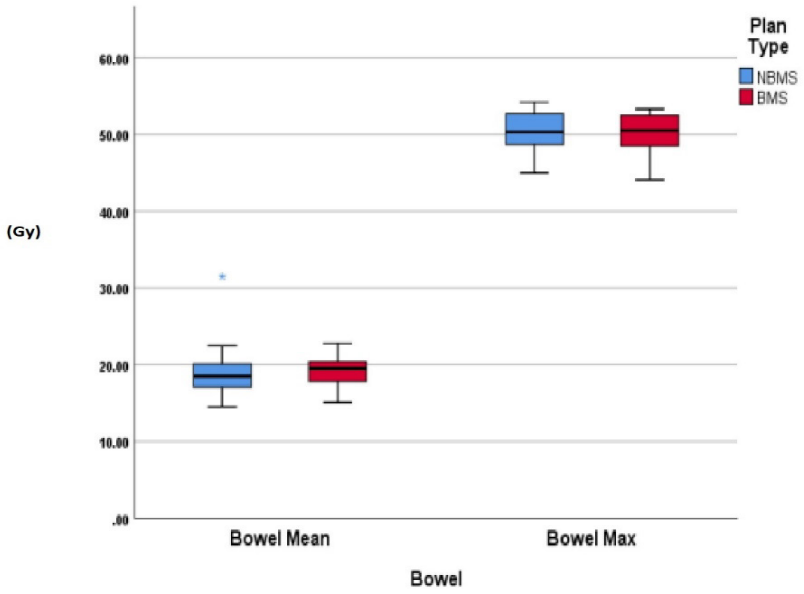

Figure 3. Mean and Max Bowel in Presence and Absence of BMS Constraint

shown that in patients receiving more than 40 Gy dosages in BM volume show haematological toxicity with grade 2 and above (Mell et al., 2008; Mell et al., 2006).

Rose et al., (2011) estimated the probability of the adjacent tissue complexity for BM complications in carcinoma cervical cancer patients. They deduced in their investigation, that endeavors to keep up V10 < 95% and V20 < 76% could essentially diminish hematological toxicity (Rose et al., 2011). Albuquerque et al observed moderate to severe toxicity in 67.5% of patients receiving whole pelvic radiotherapy. The author suggested constraint of V20<80% for bone marrow. The studies have reported that IMRT reduces the irradiated BM volume due to increased dosage and decreasing the effect of haematological toxicity (Albuquerque et al., 2011). Additionally, IMRT showed decrease in acute toxicities. In a study by Portelance et al., (2011) in cervical cancer patients treated by chemoradiation, only 22.5% of patients developed grade 2 and above GI toxicity as compared to the predicted 40%.

Similarly some of the reports described that BM volume due to irradiation dose of 30 to 50 Gy required increased recovery time as well as damages that are non-recoverable (Mauch et al., 1995; Sacks et al., 1978). Meta-analysis published in 2012 concluded that IMRT reduced the percentage of mean BM volumes irradiated for al dosage of radiation, but without a statistical significance (Yang et al., 2012).

In our analysis we extended the effect of IMRT, using rapid arc technique to create plans with BM sparing and compared with pelvic radiation plans without the BM sparing constraints.

Mahantshetty et al., (2010) showed that with Rapid Arc® technique distribution of dosage to the point of application was adequate with increased homogeneity of target sufficient enough to reduce the risk of damage to healthy regions (Mahant Sheety et al., 2010). Highly conformal dose distributions with improved target-volume coverage and normal tissues sparing can be achieved in RA (Bucci et al., 2005;Guy et al., 2013).

In our study all patients who were prescribed BM constraint were analysed and based on mean value of patients DVHs, doses in the entire pelvic BM were observed to be less significantly in comparison to that without BMS constraint. This study supports the ability of rapid arc technology to deliver BM sparing plans without compromising the coverage of PTV and not increasing the radiation dose to other normal structures (Bladder, Rectum, Bowel, Femoral heads). Our study data depicted that there is significant decrease in the dose to BM compared to the plans where constraints to BM was not given. With BM sparing, the mean dose achieved was less than Gy.

It has been observed from the present study that there was a significant dosage reduction to TP V10, TP V20 and TP V40 with addition of BMS constraint which was found to be consistent with that reported by Christopher et al., (2018) where it was reported that in presence of BMS constraint the pelvic BM dose decreased significantly for various dosimetric points (Platta et al., 2013). The study also reported that there were no significant bladder, rectum and small bowel changes in dosage were observed which was consistent with the findings of our study. Similar findings were also reported by Bao et al., (2019) where it was presented that the IMRT procedures in presence of BMS sparing showed promising outcome without effecting the adjacent tissues.

Previous studies have demonstrated that the occurrence of hematological toxicity is associated with the volume of bone marrow irradiated (Jodda et al., 2017; Jodda et al., 2019; Jadda et al., 2020). Therefore, bone marrow sparing radiotherapy is considered an effective way to reduce hematological toxicity in pelvic radiotherapy. Many studies have focused on functionally active bone marrow sparing using functional imaging. As this is not available with our institution, we explored the optimal dose limiting strategy and rapid arc technique in bone marrow sparing pelvic radiotherapy to cervical cancer patients. In our institution we are in the process of analyzing the hematological toxicity and grade of toxicity leading to, if any treatment interruptions in cervical cancer patients undergoing chemo -radiation therapy. However, ffurther studies need to be continued to analyse the correlation between the achieved dosimetric results with complete blood test results of every week of treatment. The functional BM has to be delineated to achieve better conformal sparing and identifying the association between dose volume and haematological toxicity grade.

In conclusion, toxicity in the BM due to exposure of pelvis to radiation can be reduced which is evident from the fact that there is a correlation among the amount of irradiated pelvis BM and the amount of hematological toxicity. In the treatment of cervical cancer, the RA technique can deliver highly conformal dose to the target with better OARs sparing. It can help to reduce hematological toxicity by reducing the BM irradiation dose and volume to avoid the treatment gaps.

Author Contribution Statement

Data collection, analysis and interpretation of results by RA, SS, MS, KS, DS, VM. Preparation of manuscript and draft editing by RA and PM. All authors reviewed the results and approved the final version of the manuscript

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Conflict of interest

The authors report no conflict of interest.

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