Association between Acute Hematological Toxicities and Bone Marrow Dosimetric Parameters in Cervical Cancer Patients Undergoing Concurrent Chemoradiation – A Comparison between Three Dimensional Conformal Radiotherapy and Intensity Modulated Radiotherapy

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ABSTRACT

Introduction: Acute hematological toxicities are an important cause of morbidity in patients receiving concurrent chemoradiation to the pelvis in CA cervix. Our objectives were to find out the incidence of acute hematological toxicities in patients undergoing concurrent chemotherapy and three-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) and to evaluate the role of IMRT in reducing dose to bone marrow and hence its impact on reducing acute hematological toxicities.

Methods: Between January 2016 and July 2017,47 patients with FIGO stage IB2 to IIIB ca cervix were randomized to receive 45 to 50.4 Gy in 25 to 28 fractions, delivered via either 3DCRT or IMRT with concurrent weekly cisplatin 40mg/m^2. Pelvic and lumbosacral marrow were delineated as the organ at risk. In the IMRT arm, the constraint was given to reduce dose to bone marrow as per the RTOG 0418 protocol; BM V40≤37%. Acute toxicities were monitored weekly during RT and were graded according to the RTOG acute toxicity grading system.

Results: Of the 47 patients, 25 patients received 3DCRT and 22 patients IMRT. Median age of patients in IMRT and 3DCRT arm were 54 and 52 years respectively. Patients in the IMRT arm experienced significantly fewer grade ≥2 hematological toxicities- 28% vs 72% in 3DCRT (P=0.03) and there was significant reduction in V20, 30, 40 pelvic marrow (P<0.001) and V10, 20, 30, 40 Lumbosacral marrow (P=0.01). Significant reduction in grade 2 or more hematological toxicities were found when V20 pelvic marrow<86%,V30<57%, V40<29% and V40 Lumbo sacral marrow <50.9% (P=0.03).

Conclusion: IMRT reduced the volume of bone marrow getting irradiated to higher doses and the incidence and severity of acute hematologic toxicities in cervical cancer patients undergoing concurrent chemoradiation.

Keywords: Hematological Toxicity, Cervical Cancer, Concurrent Chemoradiotherapy, Three-dimensional Conformal Radiotherapy, Intensity-modulated Radiation Therapy, Bone Marrow

INTRODUCTION

Radiation therapy forms an integral component of the management of cervical carcinoma. The current standard of care for locally advanced cervical carcinoma is cisplatin-based concurrent chemoradiation followed by brachytherapy.[1,2] Five large randomized controlled trials[3–6] have clearly showed the superiority of concurrent Chemoradiotherapy over radiotherapy alone in improving overall survival, but at the cost of excess toxicities especially acute hematological toxicities.[7,8] So compared to RT alone CCRT is associated with more treatment breaks and literature says treatment prolongation of 1 day corresponds roughly to a 1% decrease in local control.[2] Delivery of scheduled cycles of chemotherapy may also get compromised due to neutropenia in routine clinical practice which adversely affects the outcome. Also, it adds to the cost of therapy by requiring the use of growth factors and blood transfusions.[9] Moreover, chronic bone marrow suppression may develop, impairing chemotherapy delivery at the time of relapse.[10,11] Hematologic toxicity has been particularly noted in women undergoing pelvic RT for cervical cancer, compared with other locations, because of the increased radiosensitivity of pelvic bone marrow.[12,13] Development of these acute toxicities depends upon both the dose and volume of bone marrow getting irradiated. Nearly 40% of red marrow resides in pelvic bone and 11% in the lumbar spine. The conventional two-dimensional fields irradiate the large volume of bone marrow which in addition to myelotoxic effects of chemotherapy results in more severe acute hematological toxicities. With the introduction of CT based treatment planning, 3DCRT offers better target coverage but still unnecessarily irradiates large volume of bone marrow. In contrast to 3DCRT, which uses uniform fields, IMRT generates non-uniform fields

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How to cite this article: Ashitha EA, Bindu G, T. Ajayakumar, Janish K, Jayaraman MB. Association between acute hematological toxicities and bone marrow dosimetric parameters in cervical cancer patients undergoing concurrent chemoradiation – a comparison between three dimensional conformal radiotherapy and intensity modulated radiotherapy. International Journal of Contemporary Medical Research 2018;5(11):K1-K5.

DOI: http://dx.doi.org/10.21276/ijcmr.2018.5.11.20

to achieve better planning target volume coverage, while decreasing unnecessary radiation exposure to normal organs including red marrow.[14,15]

Study aimed to evaluate the impact of IMRT in reducing dose to bone marrow and thus the incidence of acute hematological toxicities.

MATERIAL AND METHODS

Patients with biopsy-proven carcinoma cervix stage IB2-IIIB presented to the Department of Radiotherapy, Kozhikode medical college for treatment were selected and randomly assigned to either of the two modalities of treatment (3DCRT or IMRT). All patients received concurrent chemotherapy with cisplatin 40 mg/m2 weekly. Following EBRT to a total dose of 45- 50.4 Gy in 25-28 fractions, 5 fractions a week, all patients underwent HDR brachytherapy,7 Gy delivered weekly once for 3 fractions.

Simulation

All patients were planned by CT simulation. Patients were kept fasting for a minimum of 4 hours before planning CT scan. Patients were asked to void urine 15 min before the CT scan. Similar bladder voiding instructions were given while treating patients. Contrapaque was used as IV contrast. After preparation patients were made to lie supine on the couch in CT simulator. CT scans were obtained from T10-T11 interspace to upper third of femur, with 3mm thickness. These images were transferred to the treatment planning system (TPS), and contouring was done.

Target delineation

Any gross disease identified in the planning CT was contoured as GTV. Clinical target volume (CTV) was divided into CTV1, CTV2 and CTV3. CTV1 was GTV + uterus + cervix (if not already encompassed in the GTV). Parametrial/ paravaginal tissues, parauterine fat, ovaries, and proximal vagina were contoured as CTV2. If there was more extensive vaginal involvement, the entire vagina was included in the CTV 2. CTV3 included common iliac, external and internal iliac nodal regions, and presacral regions. The common iliac and external and internal iliac regions were defined by including the pelvic vessels plus a 7-mm expansion. The 1.7 cm brush was used along the medial pelvic wall medial to muscle to contour the obturator lymph nodes. The presacral area consists of the soft tissues 1cm anterior to the S1–S2 vertebrae. CTV1 was given a 1.5 cm symmetrical expansion to obtain PTV1. CTV2 was given 1cm expansion to obtain PTV2. A 7mm expansion was given to CTV3 to obtain PTV3. Final PTV was obtained by merging PTV1, PTV2 and PTV3.

The organs at risk were delineated, including the small intestine, rectum, bladder and bone marrow (BM) Pelvic and lumbosacral marrow were contoured separately. Marrow cavity was identified in the bone window and the same contoured. Entire pelvic marrow was contoured as the single OAR. Lumbar marrow was contoured from one vertebral body above the upper border of PTV till L5 and entire sacrum were contoured as the single OAR (figure-1).

Treatment planning

The dose of 45-50.4Gy in1.8Gy/ Fraction was prescribed to PTV in both arms. Constraints were given to reduce dose to OAR in the IMRT plan.V40 pelvic and lumbosacral marrow were kept below 37%. All plans were normalized to cover 95% of the planning target volume with 100% of the prescribed dose. After external beam radiation, intracavitary implants using high-dose-rate brachytherapy (192Ir) were given in all cases. Concurrent cisplatin was given at a dose of 40mg/m2 weekly during external beam RT. Patients were monitored by weekly CBC during RT for acute hematological toxicities and were graded as per RTOG acute toxicity grading system. DVH analysis was done to find out V10, V20, V30, V40 pelvic marrow,V10, V20, V30, V40 lumbosacral marrow in both 3DCRT and IMRT arm (figure-2,3).

STATISTICAL ANALYSIS

Statistical analysis was done using the SPSS version 18.0 software, and analyzed with the help of descriptive statistics such as mean, median, standard deviation, frequencies, cross tabs and statistical tests like chi square and t test.

RESULTS

Clinical data

Of the 47 patients,25 patients received 3DCRT and 22 patients IMRT. Median age of patients in IMRT and 3DCRT arm was 54 and 52 years respectively. Among 3DCRT treated patients 1 was IB2 (4%),17 were IIB (68%), 2 were IIIA (8%) and 5 were IIIB (20%). Among the IMRT treated patients, 4 were IIA (18.2%), 10 were IIB (45.5%),1 was IIIA (4.5%) and 7 were IIIB (31.8%).

Table 1 shows the incidence of hematological toxicities in 3DCRT and IMRT. Grade ≥2 HT is only 27.8% in IMRT compared to 72.2% in 3DCRT.Chi square test showed a p value of 0.03 which is statistically significant.

This dosimetric comparison between 3DCRT and IMRT shows that there is reduction in volume of pelvic marrow receiving 10, 20, 30 and 40 Gy in the IMRT plans. Statistical analysis by t-test showed that there is statistically significant reduction in V20, V30, V40 in IMRT and the reduction in V10 was not statistically significant (table-2).

This data analysis shows that there was reduction in V10, 20, 30 and 40 lumbosacral marrow in IMRT plans compared to 3DCRT and this reduction is found to be statistically significant with P value <0.05 in all cases as per T test. So dosimetrically in IMRT plans less volume of marrow is getting irradiated compared to 3DCRT (table-3).

Mean volume of pelvic marrow getting 10 Gy dose in patients with grade <2 hematological toxicity and those with grade ≥2 hematological toxicity is 96.8% and 96.5% respectively. T test done to assess its significance showed a P value 0f 0.8 which is not statistically significant. Hence V10 pelvic marrow is not a factor associated with acute hematological toxicity. Mean V20,V30,V40 pelvic marrow in patients with grade <2 hematological toxicity are 86.6%, 57% and 29% respectively and it is 91.9%,67% and 42.9%

HT grade	RT		Total
	3DCRT	IMRT	
Grade <2	12	17	29
	41.4%	58.6%	100.0%
Grade ≥2	13	5	18
	72.2%	27.8%	100.0%
`Total	25	22	47
	53.2%	46.8%	100.0%

Table-1: Hematological toxicities

Volume/RT	3DCRT	IMRT	P value
	Mean volume% ± SD	Mean volume% ± SD	
V10 pelvic marrow	97.2 ± 3.1	96.1 ± 5.0	0.36
V20 pelvic marrow	93.7 ± 3.7	82.8 ± 9.1	0.001
V30 pelvic marrow	66.8 ± 7.4	54.2 ± 10.2	0.001
V40 pelvic marrow	46.2 ± 9.3	20.9 ± 6.5	0.001

Table-2: Dosimetric Analysis of Pelvic Bone Marrow

Volume/RT	3DCRT	IMRT	P value
	Mean volume% ± SD	Mean volume% ± SD	
V10 LS marrow	83.9 ± 12.3	72.5 ±11.9	0.002
V20 LS marrow	79.7 ± 11.9	69.8 ± 11.5	0.006
V30 LS marrow	73 ± 12.9	64 ± 10.2	0.01
V40 LS marrow	66.6 ± 15.3	43 ± 9.5	0.001

Table-3: Dosimetric Analysis of Lumbosacral Bone Marrow

Volume	Hematological Toxicity Grade <2	Hematological Toxicity Grade ≥ 2	P value
	(Mean volume% ± SD)	(Mean volume% ± SD)	
V10 pelvic marrow	96.8 ± 3.8	96.5 ± 4.7	0.83
V20 pelvic marrow	86.6 ± 9	91.9 ± 7.1	0.03
V30 pelvic marrow	57.1 ± 9.8	67.0 ± 9.7	0.002
V40 pelvic marrow	29.1 ± 12.6	42.9 ± 15.0	0.001

Table-4: Dosimetric Factors Associated With Acute Hematological Toxicities

Volume	Hematological toxicity grade <2	Hematological toxicity grade ≥ 2	P value
	Mean volume % ± SD	Mean volume % ± SD	
V10 LS marrow	75.9 ± 12.4	82.7 ± 13.9	0.08
V20LS marrow	72.7 ± 12.1	78.9 ± 12.8	0.1
V30 LS marrow	67.1 ± 2	72 ± 3.4	0.18
V40 LS marrow	50.9 ± 14.8	63.1 ± 19.1	0.01

Table-5: Correlation of lumbosacral marrow dosimetry and hematological toxicities

respectively in those with grade ≥2 toxicities, t test showing statistical significance with a P value of 0.03,0.002 and 0.001 respectively. So V20, V30, V40 pelvic marrow are factors associated with development of acute hematological

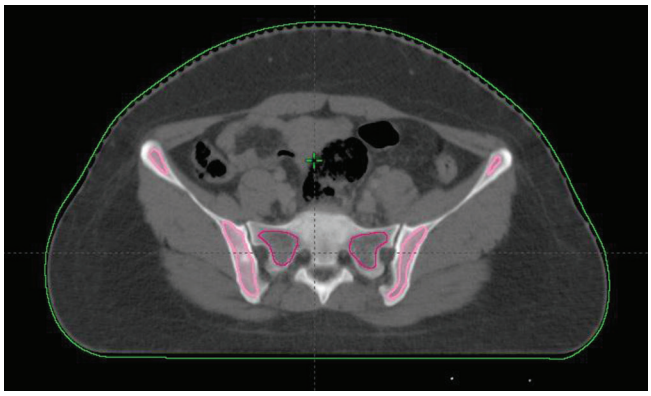

Figure-1: Contour of pelvic and lumbosacral bone marrow

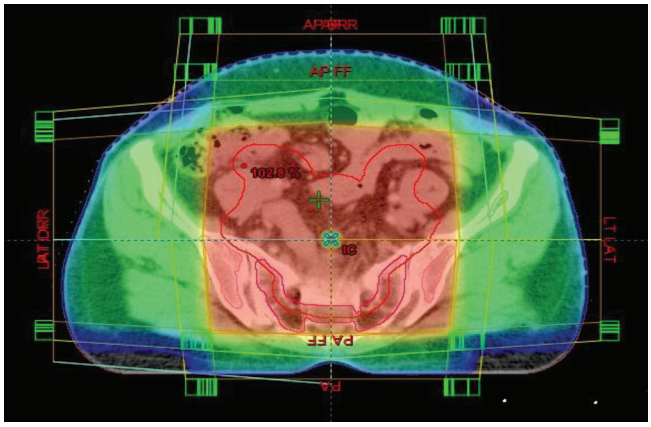

Figure-2: 3DCRT plan

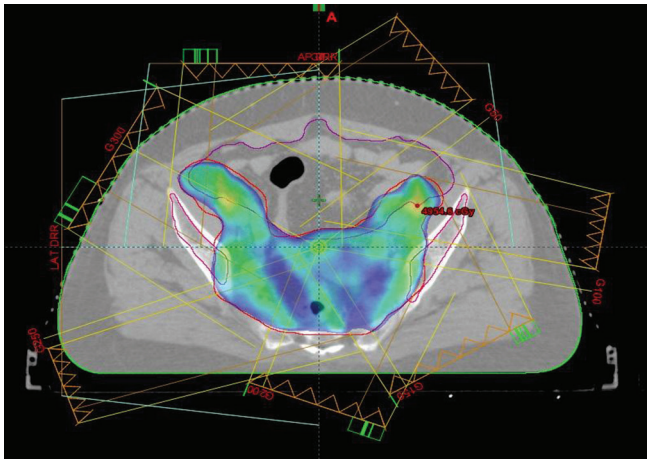

Figure-3: IMRT plan

toxicities (table-4).

In patients with grade <2 hematological toxicities,V10,V20,V30 lumbosacral marrow are 75.9%,72% and 67% respectively and in those with grade ≥2 hematological toxicities it is 82.7%,78.9% and 72% respectively. T test showed a P value of 0.08, 0.1 and 0.1 respectively, which is not statistically significant. So even though there is reduction in V10, V20 and V30 lumbosacral marrow in IMRT, it doesn't correlate with hematological toxicities. This implies V10, V20, V30 lumbosacral marrow cannot be considered as dosimetric factors associated with acute hematological toxicities. Only V40 lumbosacral marrow is related to hematological toxicities (table-5).

DISCUSSION

Acute hematological toxicities are a major problem faced by patients undergoing concurrent chemoradiation for cervical malignancies. Studies have shown that more conformal approaches like IMRT can reduce the volume of bone marrow getting irradiated which in turn result in reduced acute toxicities, thus improves treatment compliance.[16,17] In this study, we have analyzed and compared the incidence of acute hematological toxicities in patients undergoing CCRT for ca cervix in both 3DCRT and IMRT. The data analysis has shown that there is a statistically significant reduction in grade 2 or more acute hematological toxicities in IMRT patients compared to 3DCRT.

Out of 18 patients who developed grade 2 or more acute hematological toxicities,13 patients were in the 3DCRT arm (72%) and only 5 patients (28%) in IMRT arm. This shows that there is a significant reduction in grade ≥2 acute hematological toxicities in IMRT patients. This reduction will improve treatment tolerance of patients, allowing completion of treatment without any breaks and without skipping any weekly cisplatin doses. Even one-day treatment break is significant as far as the cervical cancer treatment is concerned. The literature says,1% reduction in tumor control per day prolongation of treatment beyond 50 days. Also, concurrent chemotherapy is associated with an absolute survival advantage of 10% in ca cervix as per Green meta-analysis.[3] Avoidance of even one cycle of chemotherapy may have a negative impact on survival.[18] So by reducing acute hematological toxicities, IMRT can improve chemo as well as RT tolerance thereby it may produce a positive impact on the outcome.

Dosimetric analysis showed that there is a significant reduction in pelvic marrow V20, 30, 40 Gy and lumbosacral marrow V10, 20, 30, 40 Gy in IMRT plans compared to 3DCRT plans. Mean V20, 30, 40 pelvic marrow in 3DCRT arm were 93.7%, 66.8%, 46.2% respectively, whereas they were 82.8%, 54.2% and 20.9% in IMRT plans. T-test showed a significant p-value of 0.001. But there was no significant difference between pelvic marrow V10 between both arms.

The V10, 20, 30 and 40 lumbosacral marrow in 3DCRT arm were 83.9%, 79.7%, 73% and 66.6% respectively whereas they were 72.5%, 69.8%, 64% and 43% in IMRT plans. T-test showed a significant p-value of <0.05. So in IMRT, there is a significant reduction in the volume of bone marrow irradiated compared to 3DCRT. This finding was consistent with previous studies in this respect. In the analysis of RTOG 0418 data by Ann H Klopp et al., the mean percentage volume of bone marrow getting 10, 20, 30 and 40 Gy were 96%, 84%, 61% and 37% in the IMRT patients.[19] In our study, they were 96%, 82.8%, 54.2% and 20.9% in IMRT plans. So the treatments plans generated in our study were more conformal so that it could reduce the volume of bone marrow irradiated significantly even less than what was achieved in previous studies.

So the previous analysis has shown that dosimetrically IMRT is superior to 3DCRT especially when the normal structures are considered. However, the main question is whether this dosimetric advantage of IMRT can lead to clinically relevant results when compared with conventional external beam RT. Veldeman et al. made a systematic review of 41 comparative clinical studies with the use of IMRT that reported on overall survival, disease-specific survival and treatment-induced toxicity.[20] Their results showed evidence of reduced toxicity for various tumor sites by use of IMRT. So in this study, the incidence of acute hematological toxicities was analyzed concerning the volume of pelvic and lumbosacral marrow getting 10, 20, 30 and 40Gy. The analysis showed that there is no relation between V10 pelvic marrow and V10, 20, 30 lumbosacral marrow and acute hematological toxicities. Among the patients who developed grade <2 acute hematological toxicities, mean pelvic marrow V20 was 86.6%, V30 was 57.1%, V40 was 29.1% and V40 lumbosacral marrow was 50.9%.So pelvic marrow V20, V30,V40, and lumbosacral marrow V40 were significantly correlated to acute hematological toxicities.

The RTOG 0418 phase II clinical trial showed that the hematologic toxicity of Chemoradiotherapy for cervical cancer is related to the BM volume receiving a dose greater than 40 Gy.[19] Conversely, Mell et al. and Albuquerque et al. found that V10 and V20 of the pelvic bone more accurately predicted HT complications, compared to V30 or V40.[2] However, in our study, V20, 30 and 40 pelvic marrow and V40 lumbosacral marrow are related to the incidence of acute hematological toxicities.

CONCLUSION

This study highlights the role of IMRT in the management of carcinoma cervix. Compared to 3DCRT, patients undergoing treatment with IMRT experiences significantly less acute grade ≥2 hematological toxicities. This, in turn, will improve the treatment compliance by avoiding unnecessary treatment breaks owing to toxicities. It will also help patients in completing the prescribed number of concurrent chemotherapy cycles without skipping anyone. Dosimetrically IMRT is associated with less irradiation of bone marrow, and this dosimetric advantage is getting translated to the clinical reduction in the occurrence of acute toxicities. V20, 30 and 40 pelvic marrow and V40 lumbosacral marrow are dosimetric factors related to acute hematological toxicities. Following the ongoing technologic developments of modern radiotherapy, it is essential to evaluate the intensity- modulated techniques on prospective studies of larger scale. Also, functional bone marrow sparing is an emerging option that needs to be considered in reducing acute hematological toxicities while avoiding unnecessary constraining of planning system as in the case of contouring entire bone marrow as OAR.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 15-10-2018; **Accepted:** 09-11-2018; **Published:** 22-11-2018