e-ISSN 2083–4640
ISSN 1507–1367

RESEARCH PAPER

Reports of Practical Oncology and Radiotherapy
2021, Volume 26, Number 2, pages: 259–265
DOI: 10.5603/RPOR.a2021.0039
Submitted: 16.05.2020
Accepted: 08.02.2021

Dosimetric predictors of acute bone marrow toxicity in carcinoma cervix — experience from a tertiary cancer centre in India

Rohith Singareddy[1], Harjot Kaur Bajwa[1], Mahendra M. Reddy[2], Alluri Krishnam Raju[1]

[1]Department of Radiation Oncology, Basavatarakam Indo American Cancer Hospital and Research Institute, Hyderabad, Telangana, India
[2]Department of Community Medicine, Sri Devaraj Urs Medical College, Kolar, Karnataka, India

ABSTRACT

Background: The objective of this study was To determine the dose volume parameters predicting acute haematological toxicity in carcinoma cervix patients undergoing concurrent chemoradiotherapy.

Materials and methods: All patients that presented to the hospital between Jan 2019 and Dec 2019 were prospectively analyzed. Patients diagnosed to have Carcinoma Cervix and planned for concurrent chemoradiation by volumetric modulated arc therapy (VMAT) were included for analysis. Patients were assessed at baseline and every week during treatment for acute haematological toxicities. Dose volume parameters from treatment plans were correlated with RTOG grade of haematological toxicities.

Results: A total of 34 patients diagnosed to have squamous cell carcinoma of cervix were treated by radical radiotherapy by VMAT technique and concurrent chemotherapy. The most common stage of presentation was stage IIB (61.7%). 29 patients (85.2%) completed five cycles of weekly cisplatin. Statistical analysis for sensitivity and specificity of dosimetric parameters was performed using receiver operating characteristic (ROC) curve. The probability of developing bone marrow toxicity was analyzed using T test. Mean dose to bone marrow exceeding 28.5 Gy was significantly associated with bone marrow toxicity (sensitivity — 82.4%, specificity — 70.6%). On analyzing dose volume parameters, volume of bone marrow receiving 20 Gy, 30 Gy and 40 Gy (V20, V30 and V40) more than 71.75%, and 49.75% and 22.85%, respectively, was significantly associated with bone marrow toxicity.

Conclusions: Our study concludes that mean dose to bone marrow exceeding 28.5 Gy has high sensitivity and specificity for predicting bone marrow toxicity in patients receiving IMRT. Volume of bone marrow receiving 20 Gy, 30 Gy and 40 Gy significantly correlated with acute haematological toxicity.

Key words: carcinoma cervix; hematologic toxicity; bone marrow sparing

Rep Pract Oncol Radiother 2021;26(2):259–265

Introduction

Concurrent chemoradiation therapy (CCRT) combined with brachytherapy is the current standard of care for the management of locally advanced carcinoma cervix [1, 2]. More than 40% of active bone marrow is located in the pelvic region which receives varying degree of exposure during pelvic radiotherapy for cervical cancer resulting in acute hematological toxicity [3]. This acute toxicity is more severe with combined therapy compared with radiation therapy alone [4].

Address for correspondence: Dr Rohith Singareddy, DNB Radiation Oncology, Basavatarakam Indo American Cancer Hospital and Research Institute, Road number 10, Banjara hills Hyderabad 500034, Telangana, India, tel: (+91) 9160390945; e-mail: rohithsingareddy@gmail.com

Over the past few years, there has been rising interest in using Intensity Modulated Radiotherapy (IMRT) for the treatment of gynecologic cancers to reduce side effects, mainly related to the bowel and bladder [5, 6]. Non bone marrow sparing IMRT can result in significant volume of marrow receiving low dose of radiation [7]. There is limited data regarding predictors of acute hematological toxicity in carcinoma cervix patients receiving concurrent chemoradiotherapy with IMRT. We report the dose volume parameters associated with increased bone marrow toxicity in that scenario.

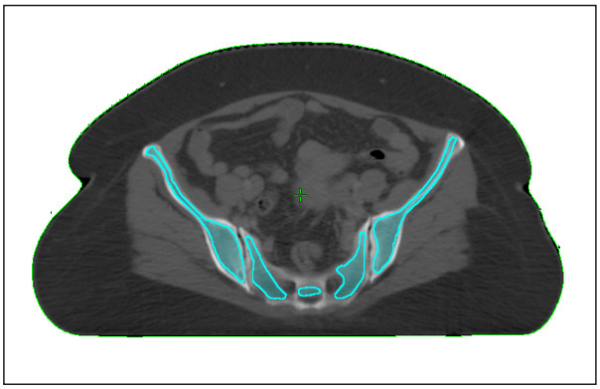

Figure 1. Free hand contouring of the inner cortex of the pelvic bone for bone marrow delineation

Materials and methods

This study was a prospective observational study that included patients treated between January 2019 and December 2019. The study was approved by the institutional scientific and ethics committee. Patients diagnosed to have Carcinoma Cervix and planned for concurrent chemoradiation by IMRT were included for analysis. Patients that required postoperative adjuvant radiation, extended field irradiation and those who had not received chemotherapy were excluded from analysis. Patients were assessed at baseline and every week during treatment for acute hematological toxicities. Bone marrow dose volume parameters from treatment plans (mean dose, V20, V30 and V40) were correlated with RTOG grade of acute hematological toxicities.

Simulation

A CT scan of each patient in the treatment position was obtained using our departmental scanner (Philips Brilliance, Netherlands). The scan parameters consisted of a large field-of-view pelvic protocol with a 3-mm-slice thickness. The CT scans were obtained from the L1 vertebral body to 5 cm below the ischial tuberosities. Intravenous contrast was administered to all patients before CT. In addition, all patients were immobilized with a thermoplastic mask.

Radiotherapy treatment

All patients were treated by the Rapid Arc IMRT technique (Elekta Synergy LINAC). The clinical target volume (CTV) and critical organs were contoured on individual axial CT slices in all patients. The clinical target volume was defined as the gross tumor plus areas containing potential microscopic disease, including the cervix and uterus (if present), the superior third of the vagina (or superior half of the vagina, if clinically involved), the parametria, and the regional lymph nodes. The planning margins consisted of 15 mm around the cervix and uterus, 10 mm around the vagina and parametria, and a 5- to 7-mm margin around the nodal regions. The prescribed dose to the planning target volume (PTV) was 50 Gy in 2Gy daily fractions. The organs at risk included the bladder, bowel, rectum and femur heads. For each patient, freehand contours of the low-density regions inside the bone were contoured as the surrogate for bone marrow (Fig. 1). The window was adjusted to bone range while contouring to bring uniformity. To eliminate inter observer variations, all contouring was done by a single physician and verified by another physician for all patients. The contouring began at 2 cm above the uppermost border of PTV and ended at 2 cm below the lower border of the PTV. No constraint was prescribed to the pelvic bone marrow as the bone marrow was not defined as an OAR. Dose–volume histograms (DVHs) corresponding to the delivered IMRT plan were generated and the volume of bone marrow receiving 20, 30 and 40 Gy (V20, V30, and V40, respectively) was quantified.

Brachytherapy

As per the institutional protocol, all patients received the first fraction of HDR brachytherapy after three weeks from the start of treatment (after 30 Gy EBRT). The total dose prescribed was 21 Gy in 3 fractions, 7 Gy per fraction to point A, one fraction per week. The technique used for brachytherapy was 3 dimensional image guided brachytherapy.

Chemotherapy

All patients were planned to receive weekly cisplatin at a dose of 40 mg/m^2 along with external beam radiotherapy. Cisplatin was typically held under the following conditions: white blood count (WBC) 2.0 × 10^9/L, absolute neutrophil count (ANC) 1.0 × 10^9/L, platelet count 50 × 10^9/L, or creatinine clearance less than 50 mL/min.

Toxicity

Patients were assessed at baseline and every week during treatment for acute hematological toxicities. Dose volume parameters from treatment plans (mean dose, V20, V30 and V40) were correlated with RTOG grade of acute hematological toxicities. Overall toxicity was defined as haematological toxicity manifesting in the form of anemia, leukopenia or thrombocytopenia.

Statistical analysis

Statistical analysis for sensitivity and specificity of dosimetric parameters was performed using an ROC curve. The probability of developing bone marrow toxicity was analyzed using a T test.

Results

A total of 34 patients diagnosed to have squamous cell Carcinoma of Cervix were treated by radical radiotherapy by IMRT and concurrent chemotherapy (weekly cisplatin 40 mg/m^2). The median age was 54 years (39–73 years). The most common stage of presentation was stage IIB (61.7%).

No patient experienced delays or breaks in pelvic RT because of acute toxicity. The median cisplatin dose per cycle was 60 mg. 29 patients (85.2%) completed five cycles of weekly cisplatin whereas four patients received four cycles and one patient received three cycles of chemotherapy. The mean PTV volume was 1248.2 cc and the mean bone marrow volume was 382.3 cc. The mean dose to the bone marrow was 29.5 Gy and the V20, V30 and V40 were 72.85%, 49.76% and 25.24%, respectively.

Hematologic toxicity

The incidence of Grade 1 acute hematologic toxicity was 41% whereas 50% patients developed Grade 2 toxicity during the course of treatment. None of the patients developed Grade 3 or 4 hematologic toxicities. There was a significant difference in the mean dose to the pelvic bone marrow between those who had developed overall haematological toxicity of Grade 2 compared to those who had Grade 0 and Grade 1 toxicity (p = 0.001). The ROC curve showed that a cut-off level of 28.85 Gy mean dose had a sensitivity of 82.4% and a specificity of 70.6% in classifying the overall toxicity level. Similar findings where noted with respect to mean dose to the pelvic bone marrow and anemia and leukopenia (Tab. 1 and 2).

The mean volumes of the bone marrow receiving 20, 30, 40 Gy i.e., V20, V30, V40, respectively, across different toxicity groups, i.e. anemia, leuko-

Table 1. Mean dose to pelvic bone marrow administered across different toxicity profiles (n = 34)

Type of toxicity	Toxicity status (n)	Mean dose administered [Gy] (Mean ± SD)	p-value*
Overall toxicity	Present (n = 17)	31.1 ± 2.8	0.001
	Absent (n = 17)	27.9 ± 2.4	
Anemia	Present (n = 13)	31.4 ± 2.9	0.002
	Absent (n = 21)	28.4 ± 2.5	
Leukopenia	Present (n = 07)	31.8 ± 3.5	0.023
	Absent (n = 27)	28.9 ± 2.7	

SD — standard deviation

Table 2. Cut-off points of mean dose to pelvic bone marrow on toxicity with its sensitivity and specificity

Type of toxicity	Cut-off points (in Gy)	Sensitivity (%)	Specificity (%)
Overall toxicity	28.85	82.4	70.6
Anemia	29.70	76.9	76.2
Leukopenia	29.70	85.7	66.7

Table 3. Distribution of mean irradiated bone marrow volumes across different toxicities (n = 34)

Type of toxicity (n)	Bone marrow volume	Toxicity status	Mean bone marrow volume (Mean ± SD)	p-value
Overall toxicity (Present = 17 Absent = 17)	V20	Present	75.6 ± 5.4	0.004
		Absent	70.1 ± 5.1	
	V30	Present	54.7 ± 7.9	0.001
		Absent	44.0 ± 7.9	
	V40	Present	31.0 ± 11.6	0.003
		Absent	19.5 ± 9.1	
Anemia (Present = 13 Absent = 21)	V20	Present	75.1 ± 5.5	0.096
		Absent	71.5 ± 5.8	
	V30	Present	55.4 ± 8.2	0.004
		Absent	46.3 ± 8.2	
	V40	Present	32.5 ± 11.9	0.003
		Absent	20.7 ± 9.4	
Leukopenia (Present = 07 Absent = 27)	V20	Present	78.8 ± 6.4	0.002
		Absent	71.3 ± 4.8	
	V30	Present	56.8 ± 9.7	0.020
		Absent	47.9 ± 8.3	
	V40	Present	33.1 ± 13.4	0.046
		Absent	23.2 ± 10.7	

SD — standard deviation

penia and overall toxicity is as shown in Table 3. There was a significant difference between the two groups (with toxicity and without toxicity) among all types of toxicity (anemia, leukopenia and overall toxicity) across all the three pelvic bone marrow receiving radiation levels i.e., V20, V30 and V40 except for V20 with anemia.

The obtained cut-off levels with respective sensitivity and specificity in classifying the different toxicity groups with respect to the volume of bone marrow receiving V20, V30 and V40 are as reported in Table 4 (except for V20 with anemia as there was no significant difference between toxicity groups).

With the cut-offs obtained from the ROC curve, relative risk was significant for overall toxicity across V20 and V30 and across V30 for anemia; whereas no significant risk was found for leukopenia (Tab. 5).

Discussion

The increasing use of IMRT in the treatment of carcinoma cervix has resulted in reduced treatment related toxicities and improved quality of life. Various studies have demonstrated the superiority of IMRT in providing reduced bone marrow doses as compared to 3DCRT [8, 9]. In resource limited countries like India, the burden of carcinoma cervix is high and patient affordability is a concern. Most of the patients of carcinoma cervix are treated with conventional four field and few with IMRT. Data is limited regarding the predictors of bone marrow toxicity in patients of

Table 4. Cut-off points of mean irradiated bone marrow volumes on toxicity with its sensitivity and specificity

Type of toxicity	Bone marrow volume	Cut-off points (in %)	Sensitivity (%)	Specificity (%)
Overall toxicity	V20	71.75	82.4	76.5
	V30	49.75	82.4	82.4
	V40	22.85	64.7	64.7
Anemia	V20	–	–	–
	V30	49.75	84.6	71.4
	V40	23.80	69.2	66.7
Leukopenia	V20	72.20	71.4	63.1
	V30	51.20	71.4	66.7
	V40	24.65	71.4	63.0

Table 5. Calculated relative risk (RR) with 95% confidence interval (CI) with cut-offs obtained from receiver operating characteristic (ROC) curve across different toxicities and bone marrow volumes (n = 34)

Type of toxicity	Bone marrow volume	Cut-off points	RR	95% CI	p-value
Overall toxicity	V20	≥ 71.75	4.15	1.45–11.85	0.008
	V30	≥ 49.75	4.67	1.63–13.34	0.004
	V40	≥ 22.85	1.83	0.88–3.82	0.105
Anemia	V20	–	–	–	–
	V30	≥ 49.75	5.50	1.43–21.18	0.013
	V40	≥ 23.80	2.53	0.96–6.65	0.059
Leukopenia	V20	≥ 72.20	3.17	0.71–14.10	0.130
	V30	≥ 51.20	3.57	0.80–15.86	0.094
	V40	≥ 24.65	3.17	0.71–14.10	0.130

carcinoma cervix undergoing concurrent chemoradiation with IMRT.

Our study demonstrated that the cutoff of 28.85 Gy mean dose to bone marrow was significantly associated with Grade 2 or higher hematological toxicity in patients treated with concurrent chemoradiation with IMRT. The cut off values for V20, V30 and V40 were 71.75 Gy, 49.75 Gy and 22.85 Gy, respectively. The incidence of acute grade 2 hematological toxicity was 50% in our study. The percentage of patients developing Grade 2 leukopenia and anemia was 20.5% and 38.2%. Mell et al. [7] reported an association between the volume of whole-pelvis BM receiving low-dose radiation (V10 > 90 Gy and V20 > 75 Gy) and acute hematological toxicity. Overall, 25 patients (67.6%) experienced leukopenia during treatment. The percentage of patients developing Grade 2 or worse leukopenia and anemia was 43.2% and 13.5%, respectively. This was in contrast to our patients who reported a higher incidence of anemia than leukopenia. Only 59.5% patients received all planned chemotherapy, 32.4% had one or more cycles held and 8.1% were noncompliant with the planned chemotherapy course. 85.2% patients received five cycles of weekly cisplatin in our study.

A comparison of two different contouring methods on CT scan by Mahantshetty et al. [10] revealed that free hand contouring of inner cavity of the bone is a better surrogate of active bone marrow compared to whole bone contouring. In our study, we used the free hand contouring method on planning CT. Data is emerging on the identification and sparing of functional bone marrow to further reduce hematologic toxicities. Liang et al. [11] demonstrated favorable outcomes of a functional bone marrow sparing IMRT technique using ^{18}F-FDG-PET, MRI and CT to identify functional BM. Another phase 2 study published by Mell et al. [12] reported reduced incidence of acute neutropenia using PET CT based

bone marrow sparing IG-IMRT. The feasibility of utilizing the above techniques in resource limited settings and high volume centres is limited and needs further evaluation.

Kumar T et al. evaluated the association between pelvic bone marrow dose volume parameters and the probability of acute hematological toxicity in a cohort of cervical cancer patients, receiving definitive chemoradiation plus image-guided adaptive brachytherapy [13]. 114 patients were included of whom 75.4% were treated with 3D radiation therapy and 24.6% with IMRT. In multivariate analysis, grade 4 hematological toxicity was associated with lower pelvis V5 > 95%, lower pelvis V20 > 45%, total pelvic bone V20 > 65%, and iliac crests Dm > 31 Gy. In patients treated by IMRT, G3+ leukopenia correlated with LS bone V30 > 91%, lower pelvis V15 > 65%, lower pelvis V20 > 48%, lower pelvis Dm > 21.7 Gy. Grade 3+ neutropenia correlated with LS bone V30 > 94%, iliac crest V20 > 84%, lower pelvis V15 > 65%. Grade 4 hematological toxicity was associated with lower pelvis V5 > 95% and lower pelvis V15 > 65%. Our patients did not report any Grade 3 or 4 hematological toxicities and we did not divide the bone marrow into different zones so a direct comparison with their results is difficult. We did not find any significant correlation between volume of the bone marrow receiving lower doses of radiation (V5 and V15) and bone marrow toxicity.

Our study is limited by a small sample size and inability to contour functional bone marrow. The strengths of our study are the use of IMRT for all patients and good compliance with chemotherapy. We believe this is the first study to report predictors of hematologic toxicity in carcinoma cervix patients receiving HDR brachytherapy along with chemoradiotherapy. The contribution of brachytherapy to active bone marrow is limited and needs to be evaluated in a prospective setting. These results can serve as a surrogate for carcinoma cervix patients treated with IMRT. This would help in predicting the course of acute toxicities in these patients and treating them effectively.

Conflict of interest

The authors declare no conflict of interest.

Funding

No funding was taken to perform the study.

References

1. Thomas GM. Improved treatment for cervical cancer--concurrent chemotherapy and radiotherapy. N Engl J Med. 1999; 340(15): 1198–1200, doi: 10.1056/NEJM199904153401509, indexed in Pubmed: 10202172.
2. Clinical practice guidelines in oncology. National Comprehensive Cancer Network, Fort Washington 2009.
3. Ellis RE. The distribution of active bone marrow in the adult. Phys Med Biol. 1961; 5: 255–258, doi: 10.1088/0031-9155/5/3/302, indexed in Pubmed: 13726497.
4. Kirwan JM, Symonds P, Green JA, et al. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. Radiother Oncol. 2003; 68(3): 217–226, doi: 10.1016/s0167-8140(03)00197-x, indexed in Pubmed: 13129628.
5. Brixey CJ, Roeske JC, Lujan AE, et al. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2000; 48(5): 1613–1621, doi: 10.1016/s0360-3016(00)00771-9, indexed in Pubmed: 11121668.
6. Brixey C, Roeske J, Lujan A, et al. Impact of intensity-modulated radiotherapy on acute hematologic toxicity in women with gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2002; 54(5): 1388–1396, doi: 10.1016/s0360-3016(02)03801-4, indexed in Pubmed: 12459361.
7. Mell LK, Kochanski JD, Roeske JC, et al. Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy. Int J Radiat Oncol Biol Phys. 2006; 66(5): 1356–1365, doi: 10.1016/j.ijrobp.2006.03.018, indexed in Pubmed: 16757127.
8. Mell LK, Tiryaki H, Ahn KH, et al. Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. Int J Radiat Oncol Biol Phys. 2008; 71(5): 1504–1510, doi: 10.1016/j.ijrobp.2008.04.046, indexed in Pubmed: 18640499.
9. Hui B, Zhang Y, Shi F, et al. Association between bone marrow dosimetric parameters and acute hematologic toxicity in cervical cancer patients undergoing concurrent chemoradiotherapy: comparison of three-dimensional conformal radiotherapy and intensity-modulated radiation therapy. Int J Gynecol Cancer. 2014; 24(9): 1648–1652, doi: 10.1097/IGC.0000000000000292, indexed in Pubmed: 25275663.
10. Mahantshetty U, Krishnatry R, Chaudhari S, et al. Comparison of 2 contouring methods of bone marrow on CT and correlation with hematological toxicities in non-bone marrow-sparing pelvic intensity-modulated radiotherapy with concurrent cisplatin for cervical cancer. Int J Gynecol Cancer. 2012; 22(8): 1427–1434, doi: 10.1097/IGC.0b013e3182664b46, indexed in Pubmed: 22932264.
11. Liang Y, Bydder M, Yashar CM, et al. Prospective study of functional bone marrow-sparing intensity modulated radiation therapy with concurrent chemotherapy for pelvic malignancies. Int J Radiat Oncol Biol Phys. 2013; 85(2): 406–414, doi: 10.1016/j.ijrobp.2012.04.044, indexed in Pubmed: 22687195.
12. Mell LK, Sirák I, Wei L, et al. INTERTECC Study Group. Bone Marrow-sparing Intensity Modulated Radiation Therapy

With Concurrent Cisplatin For Stage IB-IVA Cervical Cancer: An International Multicenter Phase II Clinical Trial (INTERTECC-2). Int J Radiat Oncol Biol Phys. 2017; 97(3): 536–545, doi: 10.1016/j.ijrobp.2016.11.027, indexed in Pubmed: 28126303.

13. Kumar T, Schernberg A, Busato F, et al. Correlation between pelvic bone marrow radiation dose and acute hematological toxicity in cervical cancer patients treated with concurrent chemoradiation. Cancer Manag Res. 2019; 11: 6285–6297, doi: 10.2147/CMAR.S195989, indexed in Pubmed: 31372035.