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Original Research Article.

Comparison of Acute Toxicities and Clinical Outcome in Locally Advanced Cervical Cancer Patients Treated with 3-Dimensional Conformal Radiotherapy and Bone Marrow Sparing Volumetric Modulated Arc Radiotherapy

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ABSTRACT

Objectives: This study compares acute toxicities and clinical outcome in locally advanced cervical cancer patients treated with 3-Dimensional conformal radiotherapy (3DCRT) and Bone marrow sparing Volumetric modulated arc radiotherapy (VMAT).

Materials and Methods: This prospective study was done in fifty newly diagnosed patients of cervical cancer patients of FIGO Stage IB2–III, treated with 3DCRT or VMAT (25 in each group) and weekly concurrent Cisplatin. External radiotherapy (46 Gy delivered in 23 fractions in 4.5 weeks) was followed by Intracavitary brachytherapy to a dose of 7 Gy HDR in 4 fractions. The endpoints were treatment related to acute toxicities and clinical outcomes. Grade ≥ 2 acute toxicities graded by RTOG (Radiation therapy oncology group) were compared using independent sample T test and Chi square test among two groups. Local control (LC) and overall survival (OS) rates were evaluated by Kaplan Meir method and compared using log rank test.

Results: The median follow up time was 13 months (range = 3–27). The 1 yr LC rates [VMAT = 80% and 3DCRT = 73 %; p = 0.27] and 1 yr OS rates [VMAT = 88 % and 3DCRT = 81 %; p= 0.53] shows no significant difference among the two groups. Patients treated with 3DCRT have significantly higher number of acute hematological and gastrointestinal toxicities compared to VMAT group [28% vs 8 % (p =0.02)] and [28% vs 46% (p = 0.04)] respectively.

Conclusion: VMAT achieves similar LC and OS rates, as achieved by 3DCRT. But acute hematological and gastrointestinal toxicities are significantly lower with BM sparing VMAT compared to 3DCRT.

Key words: 3-Dimensional Conformal Radiotherapy (3DCRT), Bone Marrow Sparing Volumetric Modulated Arc Radiotherapy (VMAT) Carcinoma Cervix, Chemoradiation.

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INTRODUCTION

Radiotherapy for cervical cancer patients consist of external beam whole pelvic radiotherapy (EBRT) and intracavitary brachy therapy. EBRT, traditionally delivered using four-field box technique defined by bony landmarks, is associated with dose-limiting incidence of acute and late toxicity [1]. In addition, conventional planning increases the risk of geographic miss. Over the years, treatment planning has shifted from conventional two-dimensional planning to three-dimensional (3D) planning.

The advent of computed tomography based 3-dimensional conformal treatment planning (3DCRT) has allowed better anatomic visualization and improved target delineation for the dose avoidance of normal structures. In 3DCRT, the treatment volume conforms to the shape of the tumour, allowing a higher dose of radiation delivered to the tumour than conventional techniques, but significant portions of small bowel, rectum and bone marrow still receive the same dose, contributing to toxicity. IMRT (Intensity Modulated radiotherapy) is an advanced type of conformal radiotherapy whereby the use of inverse planning, high doses of radiation are delivered directly to the target volumes much more precisely than is possible with conventional or 3DCRT,

leading to lesser exposure of organs at risk to radiation and therefore reduced toxicity rates [2]. VMAT (Volumetric Modulated arc radiotherapy) is the type of IMRT, where radiation is delivered in arc form. In addition, concurrent chemotherapy with cisplatin further increases chances of acute hematological, genitourinary and gastrointestinal toxicities, leading to treatment interruptions.

In our setup, there is a major load of cervical cancer patients. Till date, most of our patients have been treated with 3DCRT. Since VMAT planning is time consuming and complex than 3DCRT, our study intends to compare the two conformal techniques in terms of acute toxicities and overall response, so that the technique with lesser toxicities and/or better response can be implemented routinely for the treatment of such patients.

MATERIALS & METHODS

The study was conducted as a prospective randomized trial in the Department of Radiation Oncology, Government Medical College, Rajindra Hospital, Patiala, Punjab, India.

Approval from the institutional ethics committee was obtained prior to study. Study is registered with Clinical Trial Registry of India. CTRI registration: CTRI/2020/03/023923.

Fifty patients of previously untreated, biopsy proven squamous cell carcinoma cervix, with FIGO stage IB2- IIIB cancer cervix, with Karnofsky performance scale > 70, age ≤ 70 yrs, normal baseline hematological, renal and hepatic parameters, recruited from June 2020 to December 2021, were randomized into two study groups, based on the computer-generated simple randomization table. 3DCRT group included patients treated by 3-Dimensional conformal radiotherapy technique (3DCRT), and VMAT group included those treated by Bone marrow sparing Volumetric modulated arc radiotherapy (VMAT). All post operative cases, patients with medical contraindication to concurrent chemotherapy, or with uncontrolled co-morbid conditions were excluded from the study. Both these groups were treated with standard regimens of weekly cisplatin at 40 mg/m2 (maximum 70-mg), concurrently with EBRT followed by intracavitary Brachytherapy.

External Beam Radiotherapy (EBRT) Planning

All patients underwent radiotherapy planning CECT (Contrast enhanced computed tomography) scan of pelvis after intravenous contrast for assessment of disease extension, delineation of tumor and normal structures for radiotherapy planning. The patients were advised to take one liter of water within 2 hours before the image acquisition and to empty the bladder and rectum 15 minutes prior to the CT scan. The same was also repeated before the treatment session every day.

Patients were positioned supine on a pelvic board using an immobilization cast for planning. The CT images were acquired on the CT machine GE Light Speed VFX (VARIAN) with 2.5 mm slice interval. The image data set was transferred to the Eclipse treatment planning system (TPS) where treatment target volumes and normal structures at risk were contoured according to standard guidelines [3,4,5,6]. Organs at risk included small bowel, bone marrow, bladder and rectum.

25 Patients in 3DCRT group were planned by four Field technique using Multileaf collimators (MLCs). For another 25 patients, VMAT plans were generated using arc beams. A dose of 46Gy / 23 fractions /4.5 weeks was planned and administered daily (from Monday to Friday) to the PTV Final, with 6 to 15 MV X-rays from a linear accelerator (Varian Clinac; TRUE BEAM, Palo Alto, CA) in both the groups. Table 1 shows the Dose prescription and constraints used for VMAT planning. EBRT was followed by HDR Intracavitary brachytherapy by delivering 7 Gy in 4 fractions using the departmental brachytherapy protocol.

Table 1: Dose prescription and constraints for VMAT planning

Structure	Dose prescription and constraints
PTV46	46Gy/23#/4.5 weeks
	95% of PTV to receive 95% of the prescription dose.
	1% PTV to receive <115% of the prescription dose
CTV46	At least 95% of CTV to receive 100% of prescription dose
Rectum	V40 < 40%
	Dmax < 46 Gy
Bladder	V40 < 40%
	Dmax < 46 Gy
Bowel	V45< 195 cc
	Dmax < 46 Gy
Bone marrow	V10 < 80%
	V20 < 70%
	V40 < 30%
	Dmean < 30 Gy.

PTV and CTV: Planning target volume and clinical target volume respectively
V10, V20, V40: Volume of organ at risk receiving 10, 20, 40 Gy respectively
Dmax: Maximum dose received by organ at risk
Dmean: Mean dose received by organ at risk

Patient assessment and follow up

Patients were assessed for acute toxicity on a weekly basis during the entire treatment, by using acute toxicity grade by RTOG (Radiation therapy oncology group) [7]. The following parameters were studied: Hematological toxicity (anemia, thrombocytopenia and neutropenia), Constitutional (weight loss), genitourinary toxicity (urgency, frequency, retention, cystitis), skin reactions (radiation dermatitis) and gastrointestinal toxicity (nausea, vomiting, diarrhoea, constipation, proctitis). Patients were followed

up at two monthly intervals after the completion of treatment as per departmental protocol. Target Lesion Evaluation was done using CECT Abdomen and Pelvis at 1 year after treatment completion.

Statistical analysis

All the study parameters were coded and entered into SPSS v.17 (Statistical Package for the Social Sciences) for statistical analysis [8]. Descriptive as well as frequency distributions of all parameters was done. Independent T test for means was used to determine any difference in baseline characteristics. Qualitative study outcome parameters were measured as grades of toxicity and were compared among two groups using Chi square test. Local control rates and survival rates were determined using Kaplan Meir Method and Log rank test was used to find any significant difference among the two groups. p- value < 0.05 was considered statistically significant.

RESULTS

The study participants have baseline characteristics as shown in table 2. The two groups are comparable in terms of mean Age, stage and mean baseline weight, as there is no statistically significant difference between the two groups.

Acute RTOG clinical toxicity assessed among two groups is as described in table 3. The mean weight loss is significantly higher in 3DCRT group compared to VMAT by 1.24 Kg (p = 0.02). Also, overall number of patients with acute hematological, genitourinary and gastrointestinal toxicities, are more in 3DCRT group compared to VMAT group. However, when number of patients with Grade ≥ 2 acute toxicities were compared, patients treated with 3DCRT have significantly higher number of acute hematological and gastrointestinal toxicities compared to VMAT group [28% vs 8 % (p =0.02)] and [28% vs 46% (p = 0.04)] respectively. No grade ≥ 2 radiation dermatitis was seen in any group.

Number of patients who had local, nodal and distant failure till last date of follow up are depicted in table 4. All these patients were treated by palliative chemotherapy.

Median follow up time is 13 months (Range = 3 to 27). Figure 1 and 2 shows 1 yr local control rates [VMAT = 80% and 3DCRT = 73 %; (p = 0.27)] and 1 yr overall survival rates [VMAT = 88 % and 3DCRT = 81 %; (p = 0.53)] for the two groups. The log rank test shows no statistically significant difference between the local control rates and overall survival rates among the patients treated with VMAT or 3DCRT.

Table 2: Baseline characteristics of two groups

Variable	3DCRT (n = 25)	VMAT (n = 25)	p
Mean Age (yrs)	54.68 ± 9.91	52.32 ± 7.08	0.13
Stage			-
IIA	1 (4%)	1 (4%)	
IIB	12 (48%)	9 (36%)	
IIIB	12 (48%)	15 (60%)	
Baseline weight (Kg)	58.7 ± 10.33	63 ± 11.13	0.15

P determined by Independent sample T test

Table 3: Acute RTOG clinical toxicity in two groups

Toxicity	3DCRT (n= 25)	VMAT (n = 25)	P
Mean weight loss (Kg)	3.32 ± 7.55	2.08 ± 1.28	0.02
Hematological	10 (40%)	8 (32%)	
Grade 1	3	6	
2	3	2	
3	2	0	
4	2	0	
Grade ≥ 2	7 (28%)	2 (8%)	0.02
Genitourinary	7 (28%)	3 (12%)	-
Grade 1	1	1	
2	2	1	
3	3	1	
4	1	0	
Grade ≥ 2	6 (24%)	2 (8%)	0.08
Gastrointestinal	14 (56%)	12 (48%)	-
Grade 1	1	5	
2	4	4	
3	7	3	
4	2	0	
Grade ≥ 2	13 (46%)	7 (28%)	0.04
Radiation dermatitis	7 (28%)	4 (16%)	
Grade 1	7 (28%)	4 (16%	
Grade ≥ 2	0	0	0.63

p determined by Independent sample T test (for mean weight loss), and chi square test (for grade ≥ 2 toxicities)

Table 4: Local, nodal and distal failures in two groups

	3DCRT (n = 25)	VMAT (n = 25)
Local Failure	3 (12%)	2 (8 %)
Nodal Failure	1 (4%)	1 (4%)
Distant Failure	1 (4%)	0

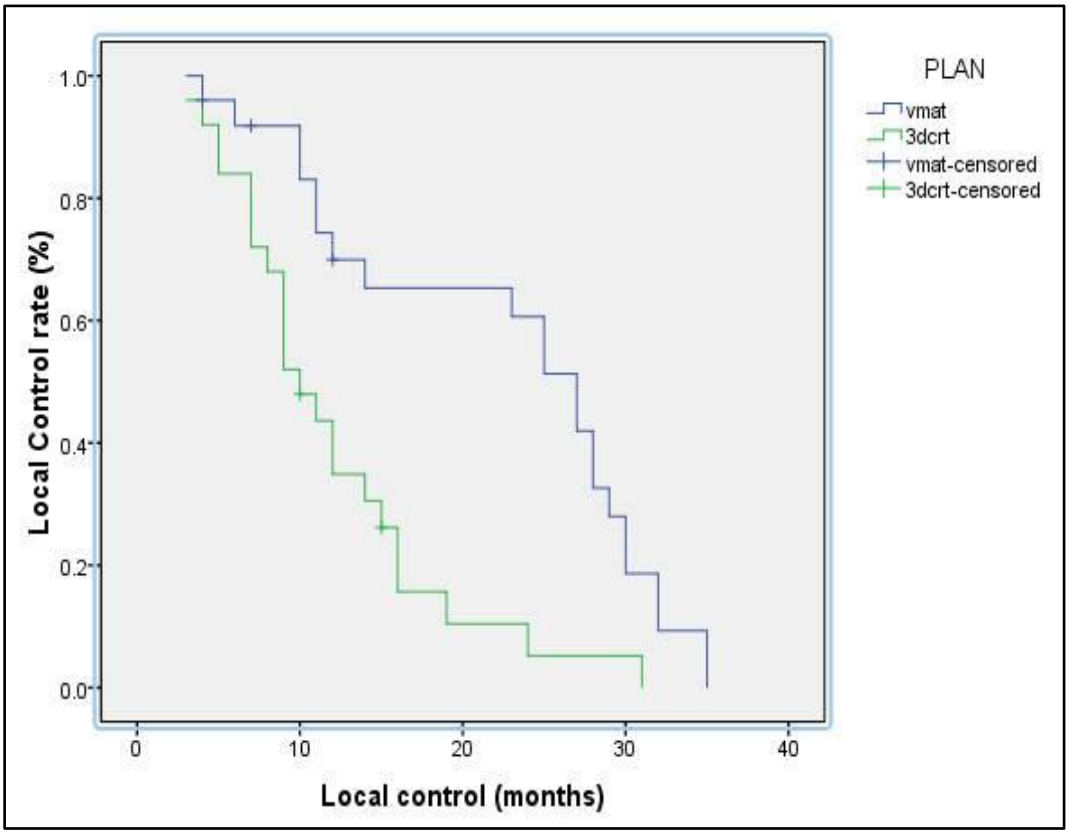

Figure 1: 1 yr local control rates for VMAT and 3DCRT

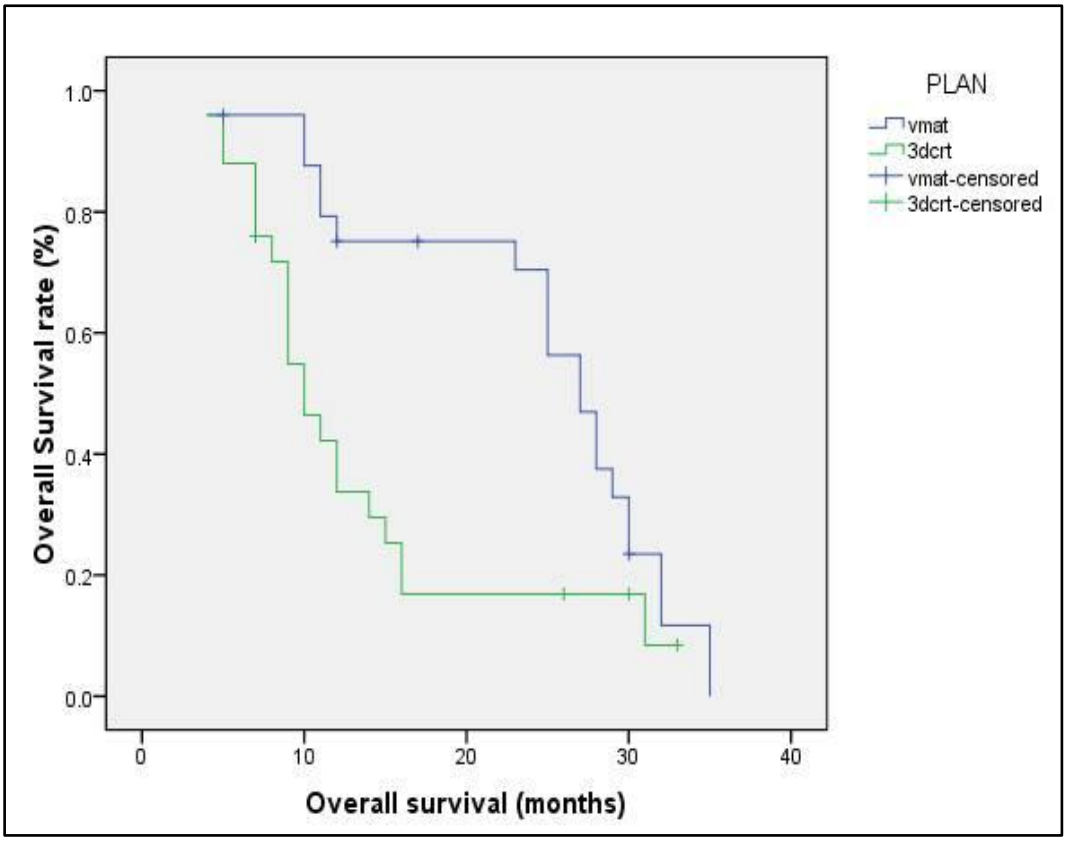

Figure 2: 1 yr overall survival rates for VMAT and 3DCRT

DISCUSSION

With the establishment of concurrent chemoradiation as the standard of care, radiotherapy techniques have evolved from conventional 2-Dimensional planning to 3-DCRT and IMRT. IMRT and VMAT planning have gained popularity because of their ability to better spare doses to the organ at risk (OARs) with the use of MLCs, computerized dosimetry and better treatment accuracy. Though Chemoradiation has improved the local control and overall survival in comparison to radiotherapy alone, it has also increased the treatment related toxicity [9]. Around 45% of intact cervical cancer patients undergoing chemoradiation experience acute gastrointestinal toxicity (≥Grade 2) and approximately one-sixth of patients report genitourinary toxicity (≥Grade 2) [1]. With advancements in treatment came the IMRT technique, and its earlier use by Mundt et al. [2] showed that it significantly improved conformity and decreased doses to the OARs when compared to conventional whole pelvic radiotherapy. The clinical results showed reduction of gastrointestinal (P = 0.001) and genitourinary toxicities (P = 0.38). Since then, the use of IMRT has been extensively studied. Gandhi et al. [10], has compared the toxicities and outcomes in patients with locally advanced carcinoma cervix, treated with whole pelvic four-field conventional radiotherapy or whole pelvic IMRT. Their results showed that IMRT resulted in lower rates of gastrointestinal toxicity and comparable clinical outcomes than did conventional radiotherapy. Reduced doses to the pelvic bone marrow with the use of IMRT have been shown to result in reduced incidences of neutropenia and subsequent treatment breaks. The advantages of IMRT can thus be summarized as dosimetric (reduction in doses to the OARs, dose escalation, improved conformity, ability to achieve concave dose distributions) as well as clinical (decrease in treatment-related toxicities) which meant better compliance to treatment and thereby improved outcomes.

One limitation in literature review is that almost all studies which have attempted to reduce the toxicities using IMRT have compared their results with conventional 4-field box technique. Only one randomized study till date has compared 3DCRT and IMRT techniques in intact cervical cancer patients. Twenty patients each were randomized into two arms, 3DCRT and IMRT. Patients in both arms received concurrent chemoradiation (cisplatin 40 mg/m2 weekly: 50Gy/25 fractions/5 weeks). Except for gastrointestinal toxicities and higher grade genitourinary toxicity, other toxicities were comparable between the two groups. Significant reduction of Grade 2 or more (20% vs 45%; P = 0.058) and Grade ≥3 (5% vs 15%, P = 0.004) acute genitourinary toxicity and Grade ≥2 (20% vs 45%, P = 0.003) and Grade ≥3 (5%vs. 20%, P = 0.004) acute gastrointestinal toxicity was seen, while no significant difference for Grade 2 and 3 or more hematological toxicity was noted in patients treated with IMRT compared to 3DCRT [11].

In our study, acute Grade ≥2 hematological toxicity, genitourinary toxicities and gastrointestinal toxicities were observed in 7 (28%) and 6 (24%), and 13 (46%) patients, respectively in 3DCRT group and 2 (8%) and 2 (8%), and 7 (28%) patients respectively, in VMAT group. Loco-regional control rate in our study was 80% and 73% in VMAT and 3DCRT group respectively after a median follow-up period of 13 months, which was not significantly different (p = 0.27). In the multicentric 'INTERTECC-2' trial treating patients with IMRT, 2-year progression-free survival and overall survival for patients were 78.6% and 90.8%, respectively [12]. Gandhi et al. [10] has reported similar 2-year DFS and OS of 60% and 85.7% respectively, in the IMRT group, which was not significantly different to the conventional WPRT group (79.4% DFS and 76% OS). Our study reported 1-year OS of 88% and 81%, in VMAT and 3DCRT group respectively, which is comparable to these studies.

Previous retrospective data and randomized trials have not shown any survival advantage with the use of IMRT/VMAT technique when compared to conventional 4-field box technique or 3DCRT [13, 14]. Also, IMRT/VMAT involves complex treatment planning – image acquisition using approved institutional protocols, meticulous target delineation, cumbersome planning process and verification, all of which are time-consuming and labor intensive, both for the patient and the health care providers. In addition, image guidance is mandatory to ensure the accuracy of treatment delivery, without which there is a high risk of geographical miss of the target volumes. Therefore, despite showing significant reduction in acute toxicities, IMRT/VMAT have not become the standard of care in gynecological malignancies.

There are some limitations of this study. One is small sample size, because of which, the results cannot be generalized for all locally advanced cervical cancer patients. Second, dosimetric correlation of target volumes and organs at risk with acute toxicity was not done as it was beyond the scope of this study. Third follow up period is less, so late toxicities could not be determined.

CONCLUSIONS

Inspite of above-mentioned limitations, our study has shown that VMAT can be used routinely for locally advanced cervix cancer patients, with an aim to decrease acute grade ≥ 2 hematological, gastrointestinal and genitourinary toxicities, while achieving similar control rates as 3DCRT.

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