

COMPARISON OF DOSE VOLUME HISTOGRAMS OF GASTROINTESTINAL TRACT AND ITS TOXICITY IN CARCINOMA CERVIX PATIENTS TREATED WITH 3-DIMENSIONAL CONFORMAL RADIOTHERAPY VERSUS INTENSITY MODULATED RADIOTHERAPY

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INTRODUCTION

Carcinoma cervix is the 4th most commonly diagnosed cancer in women and 10th overall worldwide. There were 569,847 new cases and 311,365 deaths from cervical cancer worldwide which accounts for 7.5% of total number of cancer deaths in women.¹ Cervical cancer is the 2nd most common cancer among Indian women aged 15-44 years with an estimate of 1,23,000 incident cases and 67,000 deaths in 2013.² The choice of treatment depends on staging. Treatment planning i.e. Radiotherapy for cervical cancer consists of EBRT (external beam radiotherapy) along with concurrent chemotherapy followed by Intracavitary irradiation (ICRT).³ External beam radiotherapy can be provided in the form of conventional (2 D), 3 dimensional conformal and intensity modulated techniques.

In late 1990s, the technique of 3D-CRT emerged as a preferred treatment for gynaecological malignancies. It uses information obtained from computed tomography scanning to identify visible tumour and organs at risk (bowel, bladder, rectum & bones). 3D-CRT is also known as forward planning as after delineation of target and organs at risk & dose prescription, the set-up of initial beam arrangement is done to deliver adequate dosage to target while respecting the dose constraints for the organs at risk. Thus, it gives a better target coverage and significantly reduces the radiation exposure to organs at risk especially urinary bladder as compared to conventional technique. However, studies showed that this technique did not appreciably reduce the amount of radiation exposure to the intestine or rectum.⁴

In contrast to 3D-CRT, which uses uniform fields, IMRT generates non-uniform fields to achieve better planning target volume coverage, while decreasing unnecessary radiation exposure to normal organs; also called inverse planning.⁵⁻⁷ IMRT provides tighter dose gradients to targets and reduces toxic and undesirable side effects to the rectum, bladder, small bowel and pelvic bones.⁸⁻¹¹ Therefore IMRT is increasingly being used for whole pelvic radiotherapy.

While the method has been applied to cervical and endometrial cancers as well¹²⁻¹³, the reported findings on its utility and safety in these patients have been controversial.

Thus, in late 2000s, the National Comprehensive Cancer Network (NCCN) reported that IMRT treatment for gynaecologic malignancies was not sufficiently well-established for general recommendation.¹⁴

Pelvic radiotherapy is recommended for patients with high-risk cervical cancer because it significantly improves local control. The improvement in locoregional control, however, is at the expense of increased acute and late gastrointestinal and genitourinary toxicity.¹⁵

Current literature suggests that 60% of women experience acute Grade 1 to 2 GI toxicity following EBRT to pelvis with 20% continuing to experience chronic GI symptoms at five years. Acute Grade 3 to 4 complications are seen in 3% of patients.¹⁶ Problems cited with IMRT were the facts that the target site and parameters of posture immobilization remained to be precisely defined, and that repeatability of an IMRT plan remained to be demonstrated.¹⁴ This could affect the doses to both the target and organs at risk.

Nonetheless, the previous success of IMRT in other cancer patients have promoted significant research interest to evaluate its promise for treating gynaecologic malignancy patients.¹⁷

With the aim of resolving inconsistencies present study, first research project on this topic in Punjab, aims to compare the Dose Volume Histograms of Gastrointestinal Tract and its Toxicity in Carcinoma Cervix Patients Treated With 3-Dimensional Conformal Radiotherapy versus Intensity Modulated Radiotherapy. This study will evaluate the volumetric dose distribution and gastrointestinal toxicity profile in both arms. In the new era of conformal radiotherapy, IMRT can pave the path to less normal tissue toxicity and better tolerated radiotherapy treatments for cervical cancers.

AIMS & OBJECTIVES

1. To compare dose volume histograms of gastrointestinal tract in carcinoma cervix patients treated with 3-dimensional conformal radiotherapy and Intensity Modulated Radiotherapy.
2. To compare grades of Gastrointestinal Tract Toxicity in carcinoma cervix patients treated with 3-dimensional conformal radiotherapy and intensity modulated radiotherapy.
3. To correlate dose volume histogram with gastrointestinal tract toxicity in patients treated with 3-dimensional conformal radiotherapy and intensity modulated radiotherapy

MATERIAL AND METHODS

60 biopsy proven cases of carcinoma cervix were randomized into ARM- A 3D-CRT & ARM-B IMRT after taking a written informed consent. Patients included were FIGO stage IIB - IIIB. All patients received 50 Gy/ 25 # EBRT with concomitant cisplatin 50mg weekly followed by 9.5 Gy/# *2 ICRT. For planning CT patients were made to lie supine on the couch in Simulator CT (Simulix-Nucletron). Patients were immobilised using a thermoplastic cast with four-point fixation. Oral contrast was given as 20 ml urograffin dissolved in 1 litre water given over 1 hour before CT scan. Rectal contrast was given by dissolving 20 ml urograffin in 50 ml normal saline. Patients were advised to keep a full bladder, so as to ensure a consistent and reproducible bladder protocol. For IV contrast 100 ml of omnipaque was

used according to the Cross Method of intravenous contrast administration. CT scan was taken from T10 to mid-thigh with a slice thickness of 3 mm. These images were then transferred to Elekta treatment planning system (CMS-Xiao) and contouring was done using modified Taylor's Guidelines & RTOG Guidelines.

Patients were assessed for rectal and bowel bag dose volume parameters at the beginning of the treatment. The volume of each of these regions receiving 10Gy, 20Gy, 30Gy, 40Gy, 45Gy and 50Gy (V10, V20, V30, V40, V45 and V50 respectively) was assessed before beginning of treatment.

These dosimetry parameters were designated as follows:

A. Bowel Bag – volumes – BV10, BV20, BV30, BV40, BV45 & BV50

B. Rectum- volumes- RV10, RV20, RV30, RV40, RV45 & RV50.

The RTOG toxicity grading was used to assess subjective response weekly during EBRT and thereafter monthly for 6 months.

RESULTS

Our study showed that the mean irradiated volumes of Bowel Bag receiving 40 Gy, 45 Gy and 50 Gy were lower in Arm B as compared to Arm A with a significant p value < 0.005.

Our study showed that the mean irradiated volumes of rectum receiving 30 Gy, 40 Gy, 45 Gy and 50 Gy were lower in Arm B as compared to Arm A with a significant p value < 0.005.

Most patients in our study developed grade 2-3 gastrointestinal toxicity during week 2-3.

In our study the gastrointestinal toxicities assessed weekly and monthly thereafter, using RTOG criteria in the two arms, were comparable with a non – significant p value > 0.005. The patients treated by 3DCRT showed comparable Grade 2 – Grade 3 toxicities to the patients treated by IMRT.

The comparison of irradiated bowel bag and rectal volumes in both arms show a significant difference with lower irradiated volumes for patients treated with IMRT technique. The p value for the same is < 0.005 which is significant in favour of Arm B.

This significant reduction in bowel bag and rectal volumes did not translate into a lower GIT toxicity in Arm B as compared to Arm A in our study.

DISCUSSION

The mean age of diagnosis in our study was 55.87 years in Arm A and 52.73 years in Arm B. In our study 33 patients (55%) were in fifth – sixth decade. The mean \pm SD in Arm A was 55.87 ± 6.12 and in Arm B was 52.73 ± 7.25 . Similar results were seen in another study that most cervical cancers in India occurred in 45-60 years of age.¹⁸

Another study found that the average age at diagnosis to be 57 years.¹⁹ These results are comparable with our study.

In this study the patients in Arm A presented with a mean duration of symptoms of 5.17 ± 2.05 months whereas in Arm B the mean duration of symptoms before presentation was 4.50 ± 1.57 months. Patients with longer duration of symptoms presented with advanced stage and has poor prognosis.²⁰

In our study 65% patients had an ECOG PS of 1, they were able to carry out work of a light or sedentary nature, e.g., light house work, office work but, they were restricted to perform any kind of physical strenuous activity due to emaciation, weight loss and blood loss.

The acute gastrointestinal radiation toxicities were graded according to RTOG criteria. Most patients had grade 2 gastro-intestinal toxicity. Diarrhoea was the commonest symptom

observed in either group. The next common symptom was abdominal pain followed by nausea.

During the first week of EBRT, in our study, 1 (3%) patient in Arm A and no patient in Arm B showed Grade 0 toxicity. In Arm A 29 (97%) patients and 30 (100%) patients in Arm B showed Grade 1 toxicity. {p value of 0.313}.

In our study, during the second week of EBRT, 2 (7%) patient in Arm A and no patient in Arm B showed Grade 1 toxicity. In Arm A 18 (60%) patients and 18 (60%) patients in Arm B showed Grade 2 toxicity. In Arm A 10 (33%) patients and 12 (40%) patients in Arm B showed Grade 3 toxicity. {p value of 0.336}

In our study, during the third week of EBRT, 4 (13%) patient in Arm A and no patient in Arm B showed Grade 1 toxicity. In Arm A 15 (50%) patients and 17 (57%) patients in Arm B showed Grade 2 toxicity. In Arm A 11 (37%) patients and 13 (43%) patients in Arm B showed Grade 3 toxicity. {p value of 0.117}

During the fourth week of EBRT, 1 (13%) patient in Arm A and no patient in Arm B showed Grade 1 toxicity. In Arm A 17 (57%) patients and 14 (47%) patients in Arm B showed Grade 2 toxicity. In Arm A 1 (3%) patients and no patient in Arm B showed Grade 3 toxicity. {p value of 0.359}

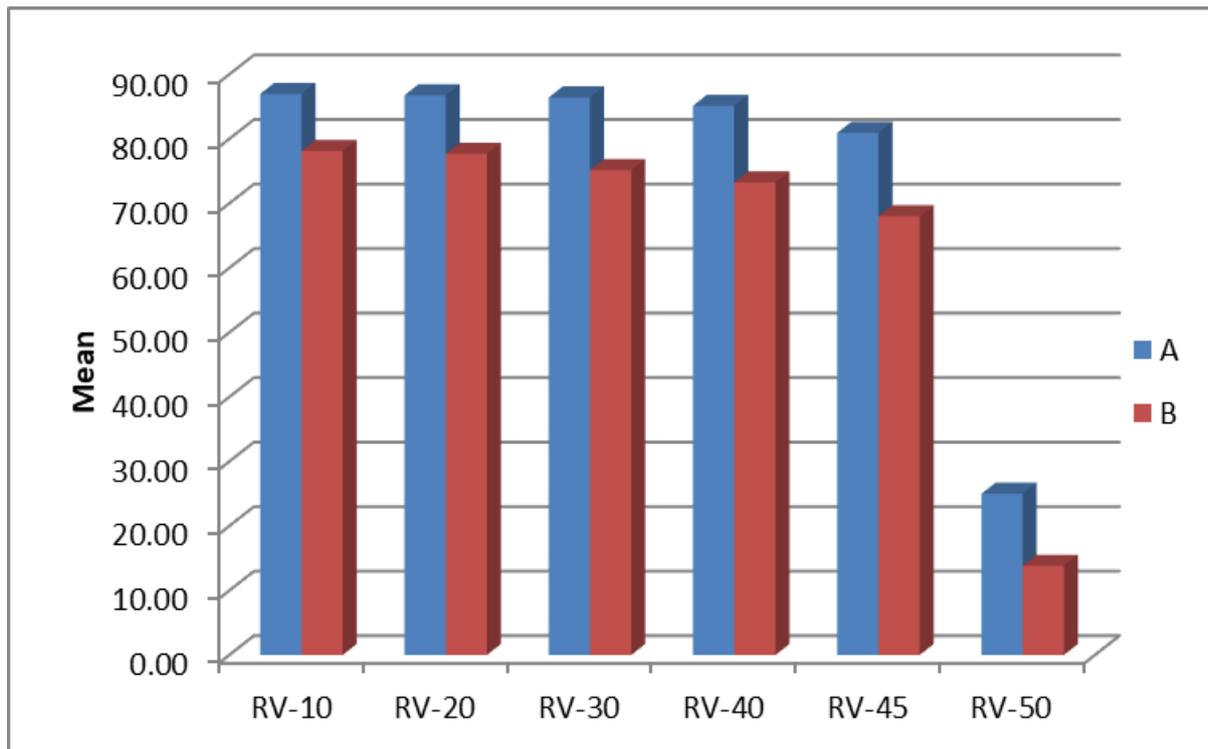
The fifth week of EBRT showed, 9 (30%) patient in Arm A and 8 (27%) patient in Arm B showed Grade 0 toxicity. In Arm A 18 (60%) patients and 21 (70%) patients in Arm B showed Grade 1 toxicity. In Arm A 3 (10%) patients and 1 (3%) patient in Arm B showed Grade 2 toxicity. {p value of 0.525}

During monthly follow up, patients in both arms showed Grade 0-1 Gastrointestinal toxicity. A study evaluated toxicity experienced by locally advanced cervical cancer patients. Stage II B – III B cervical cancer patients were treated with IMRT followed by ICRT. The IMRT plans consisted of 3-7 coplanar fields with 6 MV photons beams. The prescription doses to cover 95% of PTV were 45-50 Gy. The incidence of Gastrointestinal toxicities reported were 8.3 % Grade 3 and 25% Grade 2 toxicity.²¹ Similar results were shown other studies.²²⁻²³

Our study compared the mean bowel bag volumes for the two arms: TABLE 1

BOWEL BAG VOLUMES	A-3DCRT		B-IMRT		p-value
	Mean (cc)	SD	Mean (cc)	SD	
BV-10	1098.41	315.34	994.76	212.83	0.141
BV-20	979.94	256.48	864.47	192.43	0.053
BV-30	594.55	165.41	595.97	175.91	0.974
BV-40	481.47	169.20	375.70	152.63	0.014
BV-45	370.03	140.45	280.99	149.70	0.021
BV-50	192.08	109.50	60.29	55.35	0.000

Here is a bar diagram representing the above-mentioned data- FIGURE 1



RECTAL VOLUMES	A -3DCRT		B-IMRT		p-value
	Mean (cc)	SD	Mean (cc)	SD	
RV-10	86.97	24.74	78.14	21.64	0.147
RV-20	86.76	24.83	77.69	21.43	0.135
RV-30	86.43	25.07	75.15	20.27	0.050
RV-40	85.13	25.11	73.25	20.73	0.050
RV-45	80.92	25.85	68.01	23.89	0.049
RV-50	24.99	14.78	13.83	14.85	0.005

Our study compared the mean rectal volumes for the two arms: TABLE 2

Here is a bar diagram representation of the above-mentioned data: FIGURE 2

A study reported that IMRT at doses 30 Gy, 40 Gy, and 45 Gy significantly reduced the irradiated volume of rectum as compared to 3D-CRT.²⁴ These findings are consistent with our study.

According to a study when patients received 70% of the prescribed dose with IMRT, the average percent volume of irradiated rectum was significantly less ($p < 0.05$).²⁵

However, another study found no significant reduction in average percent volumes at the same doses.²⁶

In our study the gastrointestinal toxicities assessed weekly and monthly thereafter, using RTOG criteria in the two arms were comparable with a non – significant p value > 0.005 . The patients treated by 3D-CRT showed comparable Grade 2 – Grade 3 toxicities to the patients treated by IMRT.

The comparison of irradiated bowel bag and rectal volumes in both arms show a significant difference with lower irradiated volumes for patients treated with IMRT technique. The p value for the same is < 0.005 which is significant in favour of Arm B.

This significant reduction in bowel bag and rectal volumes did not translate into a lower GI toxicity in Arm B as compared to Arm A in our study. More studies need to be undertaken to reach a consensus regarding GI sparing effects of these novel techniques in the management of gynaecological malignancies.

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