

## Research Article

# Dosimetric Comparison and Clinical Toxicity in Cervical Cancer Patients Treated with Intensity-Modulated and Three-Dimensional Conformal Radiotherapy: Real-World Data

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## Abstract

**Background:** Predominantly used in external beam radiotherapy (EBRT) are intensity modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3DCRT). However, the superiority between these two techniques remains inconclusive. This study aim to evaluate the late clinical toxicity of cervical cancer patients treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiation therapy (3D-CRT) and dosimetrically compare the planning target volume (PTV) plan of 3D-CRT to the PTV plan of IMRT based on target coverage and bladder and rectum doses at different volumes.

**Methods and Materials:** From September 2011 – December 2015, 146 patients with International Federation of Gynaecology and Obstetrics (FIGO) stage IB2-IIIB squamous cell carcinoma of the cervix were analysed retrospectively. The patients received EBRT of 50 Gy in 25 fractions of the whole pelvic delivered with IMRT or 3D-CRT. Seventy-five (75) patients received 3D-CRT and seventy-one (71) patients received IMRT.

**Results:** The 2 years' overall survival (OS) was 92% in the IMRT group and 88% in the 3D-CRT group (p-value = 0.073). The disease-free survival outcome (DFS) was 83% and 80% in IMRT and 3D-CRT group respectively (p-value). Acute genitourinary (GU) and gastrointestinal (GI) toxicity were lower in IMRT patients compared to 3D-CRT patients (GU, 21.1% vs. 37.3%, p-value = 0.179; GI, 46.5% vs. 49.3%, p-value = 0.436). The mean coverage of the prescribed dose in IMRT and 3D-CRT techniques was  $50.02 \pm 0.10$  Gy and  $50.10 \pm 0.23$  Gy respectively with a non-significant p-value of 0.005 for 95 percent ( $D_{95}$ ) of the PTV. Also, the mean coverage of 5% ( $D_5$ ) of the PTV was  $52.66 \pm 0.39$  Gy and  $53.89 \pm 0.76$  Gy of the prescribed dose in IMRT and 3D-CRT techniques respectively with a significant p-value of 0.0001.

**Conclusion:** Patients treated with IMRT had a lower dose to bladder and rectum, a lesser rate of late toxicity and comparable clinical outcome than 3D-CRT. We admonish larger sample size studies and longer follow-up in subsequent studies to affirm our results.

**Keywords:** Cervical cancer; IMRT; 3D-CRT; Rectum; Bladder

## Introduction

Cancer has become a significant public health problem in China since 2010 due to increasing incidence and mortality, making it the number one cause of death in the country [1,2]. External beam radiotherapy (EBRT) is a vital method of treatment for cervical cancer management. Most often than not EBRT and brachytherapy in addition to chemotherapy are often used when treating and managing locally advanced cancer of the cervix. The primary goal of EBRT is in the delivering of maximum radiation to the malignant tissue, with

minimum radiation to healthy organs. This treatment can be noxious, and about 20-25% of patients are reported to have severe side effects [3]. Hence, reliable dose-response knowledge in malignant lesions and organs at risk (OAR) is therefore very vital. Before advancement into new treatment planning and imaging technique, most cervical cancer patients were treated using 2D (Two-dimensional) planning. In 2D treatment planning, the contour of the patient is captured with x-ray using lead wire, and bony landmarks and is transcribed on a graph paper sheet with an identified reference point, [4] which results in the target volume being inadequately uncovered. With the

limitation of 2D planning, 3D treatment planning and conformal radiotherapy became the standard for EBRT in the 90ths [5]. This treatment planning uses computer tomography (CT) scan images with patients required to be positioned in the planning set-up and requires a computerised treatment planning system (TPS). 3D-CRT is a form of EBRT which uses computers and unique imaging technologies to optimize the radiation beams precisely in order to reduce radiation to surrounding healthy tissues; and was started to be used for effective management of patients since it could give a maximum target coverage and also has the tendency for dose optimization to normal healthy tissues. It makes use of several high photon beams to amply deliver a high dose to a centrally located target volume with minimum dose to superficial structures in the pelvis. Intensity-modulated radiation therapy (IMRT) allows radiation to be more precisely shaped to fit the target volume by using heterogeneous fluences beams from different directions thereby optimises high radiation dose to the target volume and also limiting the amount of radiation received by the normal healthy organs. With IMRT, the beam intensity is able to be optimised as it orients around the patients using computer algorithms [6]. The 'inverse method' in treatment planning forms the basis of this process hence able to generate significant dose gradients in the adjacent structures and target volume to accomplish dose-volume prescription [7]. In IMRT, many beams with varying intensity levels are used in treating the tumour while 3D-CRT uses uniform intensity radiation beams hence the constraint of the latter is evident whenever a tumour is wrapped around an organ. Many experts indicated that IMRT is capable of reducing doses to the bone marrow, rectum and bowel and are linked with reduced levels of haematological, gastrointestinal (GI) and genitourinary (GU) toxicity compared to conventional radiation therapy. Nevertheless, these studies were usually defined by small sample sizes and the absence of clinical outcome data. Additionally, brachytherapy patients were involved in their selection criteria and this could influence toxicity. Retrospective reviews comparing IMRT and 3D-CRT technique for cervical cancer patients treated by radiotherapy are deficient, and also there has been inconsistency finding in dose to OAR. The purpose of this study was to analyse retrospectively the clinical toxicity of cervical cancer patients treated with IMRT compared to 3D-CRT and secondly, to compare the PTV plans of 3D-CRT to the PTV plan of IMRT on the basis of target coverage and doses to bladder and rectum at different volumes.

## Materials and Methods

### Patient Selection

146 stage IB2-stage IIB cervical cancer patients were treated from September 2011-December 2015. The eligibility criteria were [8]:

- i. Biopsy confirmation of squamous cell carcinoma or adenocarcinoma.
- ii. Cytological /histological diagnosis of cervical cancer.
- iii. No previous surgery, chemotherapy or radiation.
- iv. No evidence of distance metastasis.
- v. KPS performance score 70-80.

### Pre-Treatment Evaluation

The pre-treatment workup included a comprehensive medical history, vagina-recto-abdominal examination. Radiological studies like CT-scan of the abdomen-pelvis, chest x-ray and MRI in a few selected patients. Laboratory studies included a complete blood count (CBC), Liver function test (LFT), Blood Chemistries, BUN/Cr, SCC blood test. The clinical-stage was defined according to the International Federation of Obstetrics & Gynaecology (FIGO) staging system.

### CT-Simulation

All patients were immobilised with a thermoplastic sheet and underwent CT simulation for planning in a supine position. Philips CT scanner was used for simulation and 3 mm slice images of the abdomen and pelvis area were obtained. The Pinnacle treatment planning system (TPS) (Version 9.2) was used for planning and target contouring.

### Treatment Planning

The clinical target volume (CTV) and organs at risk (OAR) were contoured using the concept and definition of volume targets from ICRU reports [9,10]. The gross tumour volume (GTV) and clinical target volume (CTV) were contoured on each single axial CT slice. The CTV included palpable tumour and areas expected to be affected with subclinical tumours. Therefore, the CTV included the pelvic lymph node (external, internal and common iliac), cervix, vagina upper section and uterus. A margin of 10 mm was generated around the CTV to define the planning target volume (PTV). Four fields (two lateral and PA-AP fields) with zero-degree (0°) couch angle were used to generate the 3D-CRT plans (Figure 1). The isocenter was positioned at the PTV's geometric centre. 10 megavolt (MV) photon energy was used for all plans to improve coverage of PTV and reduce dose to the skin. The beam aperture was shaped to the PTV in each beam's eye view and a margin of 0.5 cm in all directions accounting for the beam penumbra. The PTV was prescribed a total dose of 50 Gy (2Gy per fraction). The bladder and rectum were protected with a 4-cm central shield after 40 Gy. IMRT plans were generated using 10 megavolt energy with six coplanar fields (Figure 2). Patients had whole pelvic radiotherapy prescribe to 50 Gy with either 3D-CRT or IMRT in 1.8-2 Gy per fractions from Monday – Friday. Chemotherapy involving cisplatin (25 mg/m<sup>2</sup>) was given concurrently to all patients from second to fifth week during radiotherapy treatment. None of the patients received high dose rate-intracavitary brachytherapy.

### Plan Evaluation

All plans were passed and accepted after more than 95% of the PTV received more than 95% of the dose prescribed (PD). The dose-volume histograms (DVHs) were used in evaluating the PTV coverage, rectum and bladder between 3D-CRT and IMRT plans. The parameter analysed for bladder and rectum included D<sub>15</sub>, D<sub>50</sub>, D<sub>80</sub> (dose to 15%, 50% and 80% of organ volume) while PTV coverage was based on D<sub>5</sub> and D<sub>95</sub> (Dose to 5% and 95% of the PTV respectively). The conformity index (CI) and homogeneity index (HI) was calculated in both techniques using the formulae below.

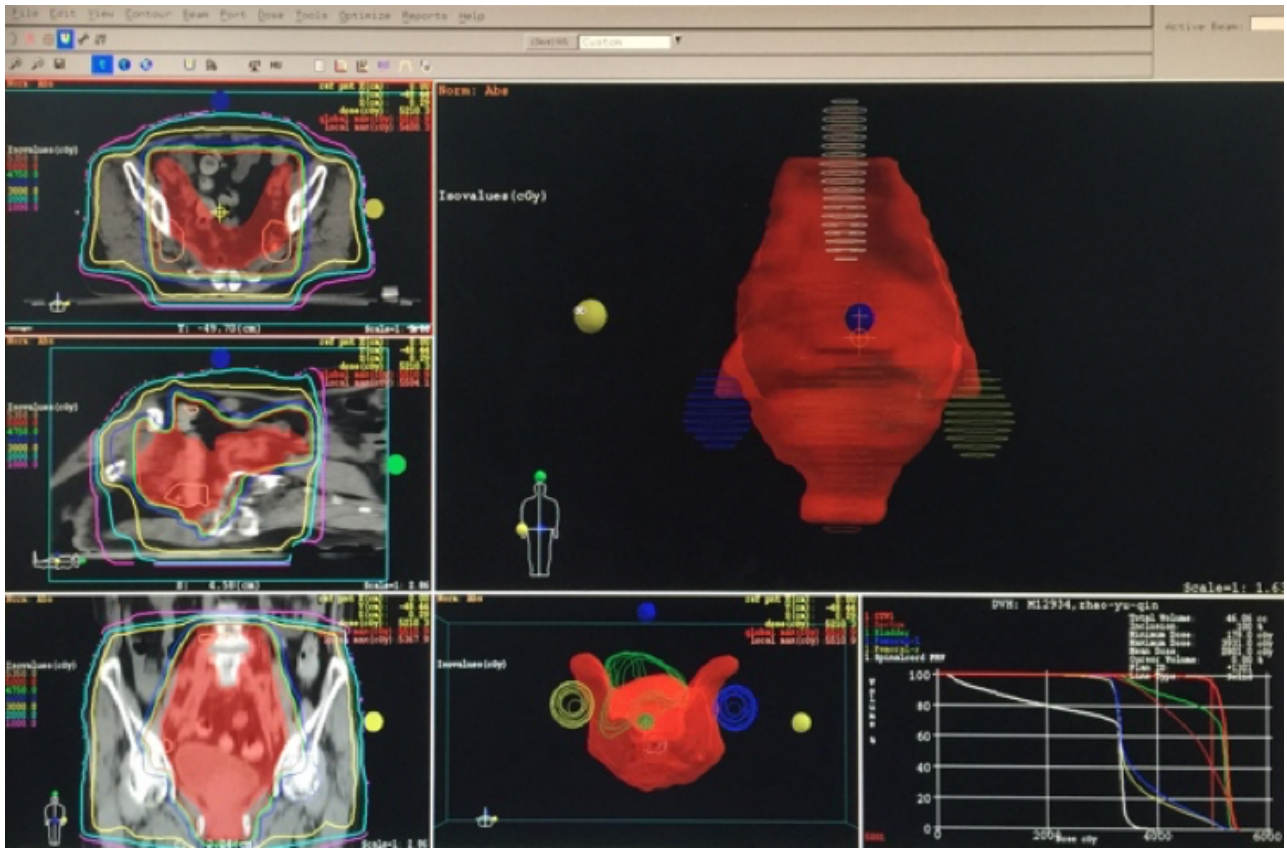


Figure 1: Shows the 4-field beam arrangement and isodose curve in 3D-CRT.

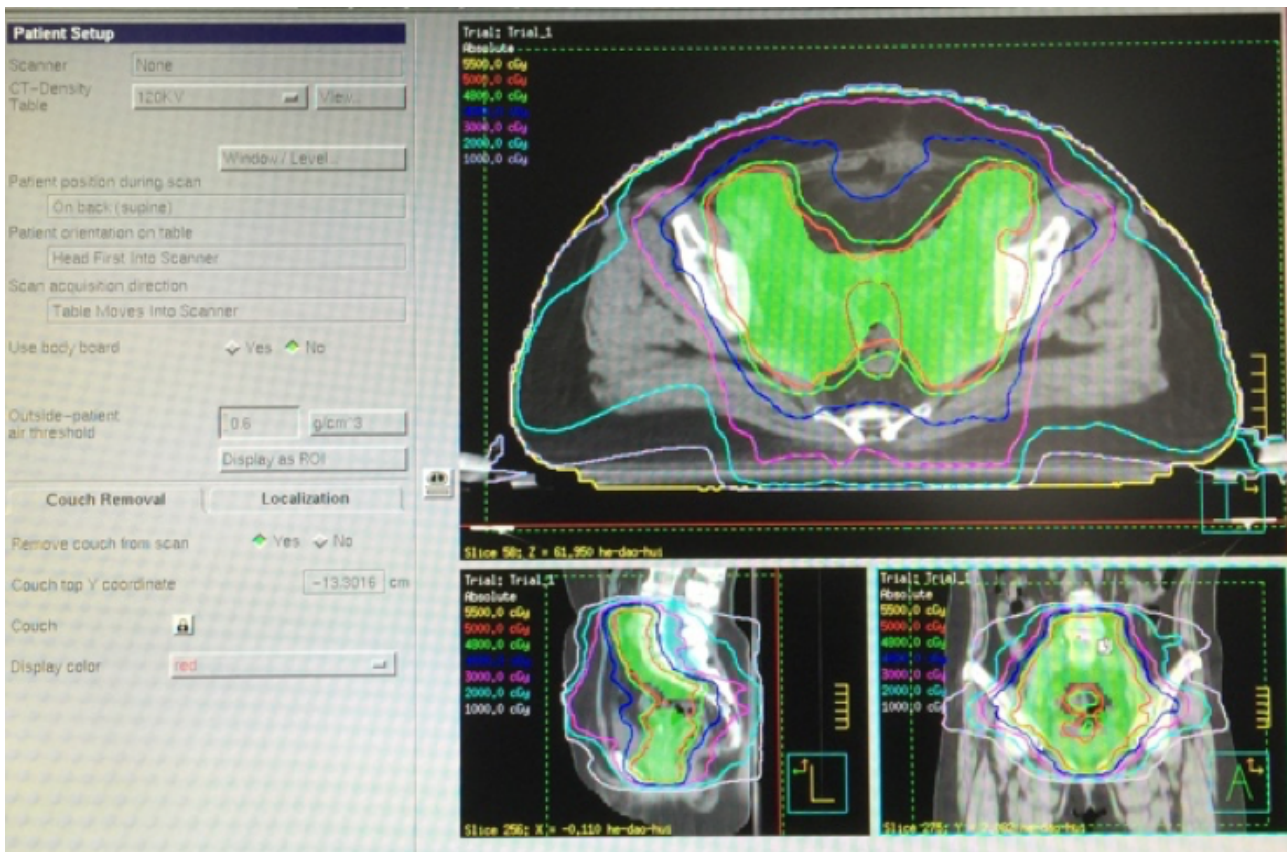


Figure 2: Shows the beam arrangement and isodose curve in IMRT technique.

$HI_{95\%} = D_5/D_{95}$ ; where  $D_5$  is the minimum dose of 5% of the target volume indicating the maximum dose, and  $D_{95}$  is the maximum dose of 95% of the target volume indicating the minimum dose. The Homogeneity Index (HI) is an accurate method for analysing the homogeneity of the target volume dose distribution. HI, therefore, demonstrates in all terminology the ratio between both the minimum and maximum dose in the target volume and the lower value demonstrates a more homogeneous distribution of the dose within this volume.

The ideal value is 1, and it increases as the plan become less homogeneous.

$CI_{95\%} = \text{Total volume receiving 95\% of prescribed dose/planning target volume}$ . The ideal value is 1.

### Statistical Analysis

All statistical analyses were carried out using SPSS 18, and a substantial difference in each set of dosimetric variables was determined using an independent sample test and chi-square. The rate of survival was evaluated after treatment was completed. The Kaplan – Meier method was used to calculate overall survival (OS) and disease-free survival (DFS). With the aid of the log-rank test, the significance of the difference was analyzed and a p-value < 0.05 was considered significant statistically.

### Follow-Up

One month after treatment, patients had a gynaecological examination and pelvic CT/MRI. Afterwards, they were followed at a regular interval of 3 months for the first 2 years and at an interval of 6 months thereafter and then once a year. Version 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE) was used in evaluating chronic and acute toxicity.

## Results

### Characteristics and Treatment of patients

146 stage IB2-stage IIB cervical cancer patients were treated from September 2011-December 2015. Seventy-five (75) were treated with 3D-CRT and the median age was 50 years (range, 39-68). Seventy-one (71) were also treated with IMRT and the median age was 53 years (range, 32-78). The squamous cell carcinoma histology type was seen in one hundred and thirty-seven (137, 93.8%) patients and nine (9, 6.2%) patients with adenocarcinoma. Table 1 shows a summary of the patients' characteristics.

### Dose-Volume Histogram (DVH) Outcomes

The 95% PTV mean value was  $50.02 \pm 0.10$  Gy and  $50.10 \pm 0.23$  Gy of the prescribed dose in IMRT and 3D-CRT techniques respectively with a significant p-value of 0.005. Also, the mean coverage of 5% of the PTV was  $52.66 \pm 0.34$  Gy and  $53.89 \pm 0.76$  Gy of the prescribed dose in IMRT and 3D-CRT techniques respectively with a significant p-value of 0.001. Hence the target coverage was esteemed satisfactory and appropriate in both groups.

The HI mean value was  $1.052 \pm 0.008$  and  $1.083 \pm 0.021$  in IMRT and 3D-CRT plans respectively, and the p-value 0.001, indicates the statistical significance of HI in both plans. The CI mean value was 1.330

$\pm 0.103$  and  $1.109 \pm 0.214$  in IMRT and 3D-CRT plans respectively, with a significant 0.001 p-value. Table 2 shows the outcomes of the CI, HI and target coverage in both treatment technique.

The dose received by 15% ( $D_{15}$ ), 50% ( $D_{50}$ ) and 80% ( $D_{80}$ ) of the bladder in IMRT was 51.30Gy, 46.79 Gy and 38.69 Gy respectively while that of 3D-CRT was also 52.96 Gy, 51.30 Gy and 41.95 Gy at  $D_{15}$ ,  $D_{50}$  and  $D_{80}$  respectively. The dose difference between these two techniques at  $D_{15}$ ,  $D_{50}$  and  $D_{80}$  was highly significant with p-value 0.0001 at all level. Furthermore, dose received by 15% ( $D_{15}$ ), 50% ( $D_{50}$ ) and 80% ( $D_{80}$ ) of the rectum in IMRT was 51.04 Gy, 48.82 Gy and 43.72 Gy respectively while that of 3D-CRT was also 52.24 Gy, 50.99 Gy and 48.08 Gy at  $D_{15}$ ,  $D_{50}$  and  $D_{80}$  respectively. The dose difference between these two techniques at  $D_{15}$ ,  $D_{50}$  and  $D_{80}$  was highly significant with p-value 0.001 at all level. Table 3 shows the detailed values of rectum and bladder dose at  $D_{15}$ ,  $D_{50}$  and  $D_{80}$ .

Table 1: Patients clinical characteristics.

Characteristics	IMRT	3D-CRT	p-value
<b>Age</b>			
Median	53	50	
Range	32-78	39-68	
<b>Histology type</b>			
SCC	64 (93.8%)	73 (97.3%)	
Adenocarcinoma	7 (9.9%)	2 (2.7%)	0.071
<b>Stage</b>			
IB2	6 (8.5%)	7 (9.3%)	
IIA1	29 (40.8%)	44 (58.7%)	
IIA2	2 (2.8%)	2 (2.7%)	0.131
IIB	34(47.9%)	22 (29.3%)	
<b>Grade</b>			
1	8 (11.3%)	12 (16.0%)	0.166
2	59 (83.1%)	53 (70.7%)	
3	5 (5.6%)	10 (13.3%)	
<b>Tumour Size</b>			
<4 cm	45 (63.4%)	50 (66.7%)	0.677
≥ 4 cm	26 (36.6%)	25 (33.3%)	
<b>LVSI</b>			
Yes	30 (42.3%)	39 (52.0%)	0.238
No	41 (57.7%)	36 (48.0%)	
<b>Pelvic Node</b>			
Yes	19 (26.8%)	17 (22.7%)	0.540
No	52 (73.2%)	57 (76.0%)	

Table 2: Outcomes of the CI, HI and target coverage in both treatment technique.

Dosimetric Parameters	IMRT	3D-CRT	P-value
$D_5$	$52.66 \pm 0.39$	$53.89 \pm 0.76$	0.001
$D_{95}$	$50.02 \pm 0.10$	$50.10 \pm 0.23$	0.005
CI	$1.330 \pm 0.103$	$1.109 \pm 0.214$	0.001
HI	$1.052 \pm 0.008$	$1.083 \pm 0.021$	0.001

### Survival Outcome and Failure Patterns

The 2 years' overall survival (OS) was 92% in the IMRT group and 88% in the 3D-CRT group with a non-significant p-value of 0.073 and the median follow-up time was 28 months. The disease-free survival outcome (DFS) was 83% and 80% in IMRT and 3D-CRT group respectively. Locoregional failure was noticed in 5 patients. Three (3) from the 3D-CRT group and 2 from the IMRT group. Distant metastasis was observed in one patient in the three-dimensional conformal radiotherapy group in addition to the locoregional failure. Six (6) death rate was recorded during the follow-up, two (2) from the IMRT group and 4 from the 3D-CRT group. The causes of death were pulmonary embolism (1 patient), heart failure (3 patients) and natural death (2).

### Clinical Toxicity Outcome

Table 4 shows the percentage of patients with acute genitourinary (GU), haematological and gastrointestinal (GI) toxicity and their grades. Less acute genitourinary (GU) and gastrointestinal (GI) toxicity were noticed in the IMRT patients compared to the 3D-CRT patients (p-value = 0.436 and 0.179 respectively). None of the patients experienced grade 4 genitourinary (GU) and gastrointestinal (GI) toxicity in both groups. Two patients in the IMRT category developed

oedema while 12 patients in the 3D-CRT category experienced the same effect. None significant statistical difference was noticed between the two groups when the various clinical toxicity was considered.

### Discussion

Previous epidemiological studies have shown that most cervical cancer patients mostly report to the hospital in advance stages of the disease. The public, accepted management for locally advanced cervical cancer (LACC) is brachytherapy with concurrent cisplatin chemoradiotherapy. Conventional radiotherapy continues to be the golden standard for LACC. There has been a reduction in the clinical outcomes and toxicities of IMRT compared with 3D-CRT from preliminary studies. The utilisation of IMRT for gynaecologic tumours including locally advanced cervical cancer has upsurge over these years even though there is insufficient retrospective randomised data to support its usage. From our results, both techniques attained the desired target coverage since 95% of the PTV had above 95% of the prescribed dose (PD). Also, there was better CI, HI and PTV coverage in IMRT compared to 3D-CRT because IMRT uses computer optimised intensity beams and multiple beam angles. Secondly, by using computer algorithms, the intensity of the beam can be optimised in IMRT as it orients around the patient, therefore, allowing radiation to be more precisely shaped to fit the target volume. The results of previous studies, when compared to this present study, confirmed that both IMRT and 3D-CRT are useful in PTV coverage hence no difference in our PTV coverage when compared with previous studies. Van De Bunt et al. [11] reported that IMRT is superior to conformal and conventional treatment in sparing critical organs with ample target volume coverage and also stated that IMRT remains superior after EBRT of 30 Gy regardless of internal organ movement and tumour deterioration.

Mell et al. [12], reported IMRT that there was a reduction in doses to the bone marrow and small bowel when patients were treated with IMRT. A study by Naik et al. [13], reported that doses to organ volume of bladder and rectum were reduced in IMRT patients compared to 3D-CRT. Fiorino et al. [14] concluded that IMRT was superior regarding bowel sparing for doses above 30Gy and also a correlation exists between toxicity and the amount of radiation received by an organ. Central target volume boost is possible with IMRT for patients whom brachytherapy is not possible due to a reduction in doses to OAR thereby allowing higher dose up to 66-70 Gy to be delivered using IMRT. Retrospective studies have accounted that decrease in dose to healthy organs may present a clinical benefit in clinical toxicities reduction. Jereczek – Fossa et al. [15] examined 317 postoperative endometrium carcinoma patients and reported that there was a statistically significant correlation between late and acute bowel reactions. The morbidity and complications among cervical cancer patients after a long-term treatment survivor was assessed by Kamal et al. [16] and reported that the rate of obstruction of the small intestines was comparable in IMRT and 3D-CRT with no significant p-value in both groups. Ajeet et al. [17] reported grade 2 diarrhoea, tenesmus and constipation in patients treated with 3D-CRT compared to a lower grade in IMRT patients. Avinash et al. [18] concluded that there were no differences in both techniques when

Table 3: Summary of rectum and bladder dose.

Dosimetric Parameters	IMRT	3D-CRT	P-value
Bladder			
D <sub>15</sub>	51.300.39	52.96 ± 0.88	0.001
D <sub>50</sub>	46.79 ± 2.28	51.30 ± 1.72	0.001
D <sub>80</sub>	38.69 ± 3.63	41.95 ± 6.14	0.001
Rectum			
D <sub>15</sub>	51.04 ± 0.52	52.24 ± 0.89	0.001
D <sub>50</sub>	48.82 ± 0.97	50.99 ± 0.75	0.001
D <sub>80</sub>	43.72 ± 2.59	48.08 ± 2.97	0.001

Table 4: Clinical toxicity between IMRT and 3D-CRT.

Toxicity	Grade	3D-CRT arm, n (%)	IMRT arm, n (%)	χ <sup>2</sup>	p-value
Hematologic	0	43 (57.3%)	47 (5.3%)	1.834	0.608
	1	21 (28.0%)	18 (25.4%)		
	2	8 (10.7%)	4 (5.6%)		
	3	3 (4.0%)	2 (2.8%)		
GI	0	47 (62.7%)	56 (78.9%)	4.907	0.179
	1	22 (29.3%)	12 (16.9%)		
	2	5 (6.7%)	2 (2.8%)		
	3	1 (1.3%)	1 (1.4%)		
GU	0	28 (37.3%)	22 (31.0%)	2.726	0.436
	1	33 (44.0%)	31 (43.7%)		
	2	10 (13.3%)	16 (22.5%)		
	3	4 (5.3%)	2 (2.8%)		
Edema	Yes	12 (16.0%)	2 (2.8%)	7.311	0.007
	No	63 (84.0%)	69 (97.2%)		

the grade of haematological toxicities was considered every week even though there was a statistically significant difference between IMRT and 3D-CRT during the second week when the total count and Neutrophils count were assessed. Our results showed that less acute genitourinary (GU) and gastrointestinal (GI) toxicity was noticed in the IMRT patients compared to the 3D-CRT patients (p-value = 0.436 and 0.179 respectively). None of the patients experienced grade 4 genitourinary (GU) and gastrointestinal (GI) toxicity in both groups. Two patients in the IMRT category developed oedema while 12 patients in the 3D-CRT category experienced the same effect. In general, lower clinical toxicities were observed in the IMRT patients than the 3D-CRT patients even though there wasn't any statistical significance between the two techniques.

Past studies [19-27] in postoperative patients treated with IMRT have normally shown suitable survival outcomes. Chen et al. [28] analyzed 35 patients receiving four-field radiation therapy and 33 patients receiving intensity-modulated radiotherapy and concluded that IMRT improved locoregional control. An update of the study of the Gynaecologic Oncology Group showed 3-year overall survival and progression-free survival rates of 88% and 86% respectively in stage IB cervical cancer patients. Results from the Radiation Therapy Oncology Group 0418 study, involving 48 patients showed an estimated 2-year OS and DFS rates of 94.6% and 86.9% respectively with a median follow-up duration of 2.68 years. In Folkert et al. [29] studies involving 34 patients, the 3 years OS was 91.1% and the 5 years DFS was 91.2%. Our findings were similar to this study.

Our study's major limitation is the short follow-up period. Furthermore, using bone marrow-sparing methods could reduce the higher rates of haematological toxicity recorded in treated patients with intensity-modulated radiotherapy. In addition, more focus should be given to the target margin in order to leave an adequate margin in IMRT planning for PTV expansion.

## Conclusion

In conclusion, patients treated with IMRT had a lower dose of bladder and rectum, a lesser rate of clinical toxicity and comparable clinical outcome than 3D-CRT. We admonish larger sample size studies and longer follow-up in subsequent studies to affirm our results.

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