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Research Article

# Comparative Analysis of Treatment Outcomes and Toxicity in Cervical Cancer Patients: Three-Dimensional Conformal Radiotherapy vs. Intensity Modulated Radiotherapy

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## Abstract

**Introduction:** The global burden of cancer remains substantial, with millions of new cases and deaths annually. Cervical cancer ranks prominently among these statistics. In India alone, cervical cancer accounts for a significant number of cases and is a considerable public health concern. The established therapeutic approach for locally advanced cervical cancer involves a combination of external beam radiotherapy (EBRT) with concurrent chemotherapy followed by brachytherapy. The widely adopted Three-Dimensional Conformal Radiation Therapy (3DCRT) for EBRT, while effective, has been associated with noteworthy side effects when used concomitantly with chemotherapy.

**Methods:** This study focuses on a cohort of cervical cancer patients treated at the Department of Radiation, State Cancer Institute, Indira Gandhi Institute of Medical Science, Patna, between January 2022 and July 2022. The research examines two distinct treatment techniques: 3DCRT (FIF technique) utilized in 50 cases, and Intensity-Modulated Radiotherapy (IMRT) employed in another 50 cases. All patients received treatment with curative intent, combining EBRT with chemotherapy, and were selected based on Karnofsky scores above 70. A comprehensive review of clinical records was conducted.

**Results**: The patient cohort primarily consisted of individuals over 50 years of age, predominantly diagnosed with squamous cell carcinoma. The staging distribution, according to the International Federation of Gynecology and Obstetrics (FIGO) classification, indicated a prevalence of stage IIIA and IIIB cases. Hemoglobin levels ranged from

7.5 to 9.5 g%, and a subset of patients (17%) necessitated blood transfusions during treatment.

**Conclusion:** Comparative analysis between 3DCRT and IMRT techniques revealed that Intensity-Modulated Radiotherapy offers the advantage of precise dose distribution to tumor sites while minimizing exposure to critical organs at risk (OAR), such as the bladder, rectum, bowel, and bones. This approach holds promise in reducing the incidence of side effects associated with traditional treatment methods.

**Keywords:** Cervical Cancer; External Beam Radiotherapy (EBRT); Three-dimensional conformal Radiation Therapy (3DCRT); Intensity modulated Radiotherapy

## Introduction

Cervical cancer remains a substantial global health challenge, as highlighted by the statistics from GLOBOCAN 2020. The worldwide prevalence of new cancer cases reached an alarming 18,078,957, resulting in 955,5027 cancer-related deaths. Notably, the corresponding incidence and mortality rates were 197.9 and 101.1 per 100,000 population, underscoring the urgent need for effective interventions [1].

Within this context, cervical cancer emerges as the second most prevalent malignancy and ranks seventh among both genders. In 2018, an estimated 569,847 new cases were reported among wom-

en globally, constituting 3.2% of all newly diagnosed cases. Geographically, Asian countries bore a significant burden, accounting for 55.3% (315,346 cases) of cervical cancer incidences and 54.1% (168,411 deaths) of associated mortalities. India, in particular, recorded 96,922 new cervical cancer cases, reflecting an incidence rate of 14.7 per 100,000 population. Additionally, 60,078 deaths were attributed to cervical cancer, corresponding to a mortality rate of 9.2 per 100,000 population [2].

Evaluating the regional distribution of cervical cancer within India, major cancer registries report varying incidence rates. Notably, Mumbai recorded an incidence rate of 19.0 (2012), Barshi reported 16.1 (2013), Chennai documented 15.9 (2012-13), and Bangalore observed 15.3 (2012) [3]. Significantly, Indian women face a cumulative lifetime risk of 2.5% for developing carcinoma cervix and a cumulative death risk of 1.4% due to this disease [4]. The age-specific incidence of carcinoma cervix typically escalates between 30 and 34 years, reaching its zenith within the 55-65 age groups, with a median age of 38 years [5].

To address this formidable health concern, the established treatment protocol for locally advanced cervical cancer involves a multimodal approach encompassing external beam radiotherapy (EBRT) combined with concurrent chemotherapy and subsequent brachytherapy [6]. Although three-dimensional conformal radiation therapy (3DCRT) is the prevailing method for delivering EBRT, it is accompanied by noteworthy side effects. These encompass genitourinary and gastrointestinal symptoms, alongside bone marrow suppression, particularly when combined with concurrent chemotherapy [7].

EBRT can be delivered by Two-Dimensional Radiotherapy(2DRT). Which is older method three-dimensional conformal radiotherapy or by intensity modulated radiotherapy. IMRT techniques is associated with more accurate dose distribution to tumor and reduce dose reviewed by organ at risk resulted reduce side effect of urinary bladder, Rectum, bowel and pelvic bone [3-6,8-11].

Worldwide various clinical trials have been done to validate the most preferred treatment by comparing tumor dose and dose to organ at risk, magnitude of side effects and overall survival. The current study was conducted to compare the dosimetric parameter and acute toxicities between three-dimensional conformal radiotherapy and intensity modulated radiotherapy [9-20].

## Methods and Material

### Patient cohort

A total of 100 women with histologically confirmed stage IIIA to IVA carcinoma cervix were retrospectively reviewed. The study period from January 2022 to July 2022.

Out of 100 patients, 50 received 3DCRT (3-Dimensional Conformal radiotherapy) and the other 50 received IMRT (Intensity Modulated Radiotherapy). All patients were newly diagnosed and had not undergone previous chemotherapy or radiotherapy.

Staging was performed using gynecological and radiological examination, blood tests, and in stage IVA cases, cystoscopy.

### CT Simulation

Patients followed specific bladder and bowel protocols prior to simulation. Immobilization was achieved by positioning patient's supine and using thermoplastic sheets for pelvic cavity alignment. Intravenous contrast was administrated, and CT simulation was done on Revolution EVO (GE ) with 3-5mm slice thickness from T10 to mid- thigh, covering the abdomen and pelvis.

### Contour delineation

After reconstructing of planning CT Images, these DICOM images was imported into Varian soma vision (Version 16.0.1, Varian Medical systems, Palo Alto, CA) where the target delineation encompasses the Gross Tumor volume (GTV), Clinical Target Volume (CTV) and Planning Target Volume (PTV). Additionally, the delineation included Organ At Risk (OARs) structures such as Urinary Bladder, Rectum, Both Femoral Head and Bowel, following the guidelines of Radiation Therapy Oncology group (RTOG) protocol. The GTV volume consisted of the visible tumor on CT images, while the CTV covered the remaining cervix, uterus, parametrium and upper vagina (or extended 2cm below vaginal involvement) along with lymphatic chains, common external iliac, and obturator lymph nodes.

### Treatment planning

The entire treatment plan generated using Eclipse Treatment Planning Systems (TPS) (Version 16.0.1, Varian Medical systems, Palo Alto, CA) for the dose of 50Gy in 25# delivered over 5# per week's schedule using 3DCRT and IMRT techniques. The TPS was configured for the True Beam SVC linear accelerator (Varian Medical systems, Palo Alto, CA) featuring photon energies of 6, 10 and

15 mega voltage (MV) as well as electron energies of 6, 9, 12 and 15 mega electron volt (MeV). The linear accelerator is equipped with Millennium 120 multi leaf collimator (MLC) system.

For the 3DCRT plans, Four field box techniques were utilized with photon beams of 6MV, 10 MV. IMRT plans generated using seven fields (0°, 51°, 102°, 153°, 204°, 255°, and 306°) with a 6MV Photon beam. All the plans were optimized and calculated using Photon Optimizer and Analytic Anisotropic Algorithm (AAA) dose calculation algorithm. Additionally, all Patients received weekly cisplatin concurrently with external radiation radiotherapy.

### Concurrent chemotherapy

All patient were administered Cisplatin 40 mg/m2 weekly during external beam radiotherapy with 2-2.5 liters of extra fluid and supplemented with potassium chloride and magnesium sulphate during chemotherapy has been administered an hour before radiotherapy weekly.

### Plan evaluation

All the plans were compared and evaluated for PTV Target Coverage, Homogeneity index (HI), conformity index (CI) for 95% of Prescription Dose (PD) and also Doses to OAR were also compared in both the techniques. For bladder and rectum values of D15, D35 and D50 (dose to 15%, 35% and 50% of organ volume); femoral heads, values of Dmax; bowel (small and large intestine) V45Gy (volume receiving 45 Gy) is calculated for both the techniques.

The HI and CI were calculated according to the formulae given below; CI95% = Total volume receiving 95% of PD/PTV Volume

HI95% = D 5/D95; where, D 5 and D95 are the doses received by 5% and 95% of PTV. The value of CI = 1.0 (one) and HI = 1.0 (one) is considered the ideal.

### Toxicity assessment and follow-up

Weekly clinical examination and CBC and KFT were performed to assess chemo radiation-induced acute toxicities.

Toxicity within 90 days of starting radiotherapy was considered for acute toxicity and Common Terminology Criteria for Adverse Events version 4 (CTCAE v4) for grading toxicities. Patients were followed up monthly up to three-month post-completion of radiation treatment. During each follow-up, the response evaluation was performed by clinical assessment. The three-month response evaluation was performed clinicoradiologically (CECT Whole abdomen and pelvis) using the RECIST 1.1 criteria.

### Statistical analysis

Statistical Analysis was performed with using SPSS version 20 (SPSS 20, IBM, United States of America) and med Calc version 20.118. The median age of the patients was compared using student's t- test.

A Tumor marker levels (CA125, CA19.9, CEA) were analyzed using Wilcoxon rank –sum test (Mann-Whitney U-test) and Kruskal-Wallis rank test (multiple sample statistics). Confidence intervals (95%) were calculated based on histopathology and demographics. A significance level of p-Value < 0.05 was used for all statistical comparison.

## Results

Table 1 represents the characteristics of patients treated with 3DCRT and IMRT was compare highlighting differences in age, addiction, chief complaints parity, histopathological examination results and pelvic lymph node involvements.

The study involved patients with a Mean age exceeding 50 years, and a majority of cases were diagnosed with squamous cell carcinoma. According to the FIGO (International Federation of gynecology and obstetrics staging majority of patients were IIIA, IIIB. Hemoglobin levels of the patients ranged from 7.5-9.5gm %. During treatment about 17% of patients required blood transfusion. The baseline characteristics are summarized in table 1. Median duration of treatment was 5 weeks. Some patients required treatment break due to low hemoglobin level and diarrhea, vomiting.

Table 2 summarizes the distribution of stages and menopausal status among patients treated with 3DCRT and IMRT.

Table 2 represents there was no significance difference in maximum dose (Dmax) delivered by both techniques, with value of 53.39Gy (3DCRT) and 53.86Gy (IMRT, p = 0.606). while IMRT exhibits a lower minimum dose (Dmin) of 38.08Gy compared to 3DCRT 42.37 Gy this difference was not statistically significant (p = 0.84). The D99% dose is 44.83Gy (3DCRT) and 46.86Gy (IMRT, p = 0.24). D95% dose is 48.6Gy (3DCRT) AND 48.27Gy (IMRT. p = 0.537), again showing no significance difference.

| Age | 3DCRT (30) | IMRT (30) |
|---|---|---|
| Mean | 4.5 ± 10.5 | 4.82±10.7 |
| Median | 50 | 52 |
| Addiction | | |
| Smoking | 5/30 (16%) | -4/30 (13%) |
| Tobacco chewing | 3/30 (10%) | 1/30 (3.3%) |
| Chief Complaints | | |
| White discharge per vaginal | (80% ) 24/30 | 86% (26/30) |
| Bleeding per vaginal | (70%) 21/30 | 70% (21/30) |
| Pain in abdomen | (-56%) 17/30 | 56% (17/30) |
| Backache | (-26%) 8/30 | 30% (9/30) |
| Parity | | |
| Nulliparous | 2/30 (6.6%) | 0/30 |
| Multiparous (3-9 Children) | 28/30 (93.3%) | 30/30 (100%) |
| HPE | | |
| Keratinizing SG cell Ca SCC | -56.6% (17/30) | (-53.3%) 16/30 |
| Non-Keratinizing SG cell ca SCC | -40% (12/30) | (46.6%) 14/30 |
| Adeno Squamous | 3.3% (1/30) | 0% |
| Pellvi Lymph Node (Pelvic Lymph node) | 65% | 68% |

**Table 1:** Comparison of Patient Characteristic in 3DCRT and IMRT.

3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; SCC, squamous cell carcinoma; HPE, histopathological examination

| Stage | 3DCRT | IMRT |
|---|---|---|
| Stage III A | 12/30 (40%) | 15/30 (50%) |
| Stage III B | 16/30 (50%) | 9/30 (30%) |
| Stage IV A | 3/30 (10%) | 6/30 (20%) |
| Menopausal | | |
| Postmenopausal | 25 (83.3) | 2.2 (73.3%) |
| Premenopausal | 5 (16.6) | 8 (26.6%) |

**Table 2:** Comparison of Patient Distribution by Stage and Menopausal status in 3DCRT and IMRT.

| PTV Parameter | 3DCRT | IMRT | P-value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Dmax (Gy) | 53.39 ± 0.8815 | 53.86 ± 0.752 | 0.606 |
| Dmin (Gy) | 42.37 ± 5.47 | 38.08 ± 348 | 0.84 |
| D99% (Gy) | 44.83 ± 10.34 | 46.86 ± 0.673 | 0.24 |
| D95% (Gy) | 48.6 ± 0.901 | 48.27 ± 0.553 | 0.537 |
| CI | 1.04 ± 0.089 | 1.02 ± 0.016 | 0.028 |
| HI | 1.07 ± 0.032 | 1.06 ± 0.013 | 0.696 |

**Table 3:** Comparison of Dosimetric parameters between 3DCRT and IMRT techniques for PTV. Dx (% of PD), % of PD to X % of PTV; Dmax, maximum dose in % of PD; Dmin, minimum.

Dose in % of PD; HI, homogeneity index; CI, conformity index; IMRT = intensity-modulated radiotherapy; 3DCRT = three-dimensional conformal radiotherapy

The Conformity index (CI) was significantly higher in 3DCRT (1.04) than IMRT (1.02, p = 0.028). No significant difference was seen in the Homogeneity Index (HI), with values of 1.07 (3dcrt) and 1.06 (IMRT, p = 0.696.

Table 4 demonstrated, the bladder and rectum significant differences are observed between the two techniques. The dose levels at various percentages (D15%, D35%, D50%) are consistently lower for IMRT compared to 3DCRT (p < .001), indicating that IMRT of-

| OAR Parameter | 3DCRT | IMRT | P-value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Bladder | | | |
| D15% (Gy) | 50.99 ± 1.06 | 49.65 ± 0.57 | < .001 |
| D35%(Gy) | 50.53 ± 0.984 | 47.72 ± 1.63 | < .001 |
| D50%(Gy) | 50.29 ± 0.943 | 44.86 ± 3,28 | < .001 |
| Rectum | | | |
| D15% (Gy) | 50.64 ± 0.90 | 49.46 ± 0.75 | < .001 |
| D35%(Gy) | 50.26 ± 0.930 | 48.34 ± 1.79 | < .001 |
| D50%(Gy) | 49.84 ± 1.05 | 47.17 ± 2.95 | < .001 |
| Right Femural Head | | | |
| Dmax (Gy) | 49.09 ± 11.27 | 46.90 ± 10.89 | 0.539 |
| Left Femural Head | | | |
| Dmax (Gy) | 49.21 ± 11.30 | 47.75 ± 11.06 | 0.68 |
| Bowel | | | |
| 195cc (Gy) | 485.83 ± 176.42 | 413.02 ± 110.56 | 0.262 |

**Table 4:** Comparison of OAR parameters between 3DCRT and IMRT techniques.

Dx, Dose to x% of volume; V45, volume receiving 45 Gy; Dmax: Maximum Dose; IMRT: Intensity-Modulated Radiotherapy; 3DCRT: Three-Dimensional Conformal Radiotherapy

| Acute toxins | | 3DCRT | IMRT | P-Value |
|---|---|---|---|---|
| Genitourinary | Grade | -30 | -30 | |
| | 1 | 10 (33.3%) | 6 (20%) | 0.003 |
| | 2 | 3 (10%) | 1 (3.3%) | 0.052 |
| | 3 | 0 | 0 | |
| Gastrointestinal toxicity | 1 | 9 (30%) | -7 (23.3%) | 0.141 |
| | 2 | 6 (20%) | 2 (6.6) | 0.023 |
| | 3 | 1 (3.3%) | 0 | |
| Anemia | 1 | 14 (46.6%) | 11 (36.6%) | 0.146 |
| | 2 | 8 (26.6%) | 5 (16.6%) | 0.256 |
| Neutropenia | 3 | 2 (6.6%) | 1 (3.3%) | 0.034 |
| | 1 | 4 (13.3%) | 1 (3.3%) | 0.382 |
| | 2 | 4 (13.3%) | 0 | |
| | 3 | 2 (6.6%) | 0 | Missing value |
| Thrombocytopenia | 1 | 15 (6.6%) | 3 (10%) | 0.029 |
| | 2 | 2 (6.6%) | 0 | |
| | 3 | 0 | 0 | |

**Table 5:** Toxicity profile of Patients.

3DCRT: ThreeDimensional Conformal Radiotherapy; IMRT: IntensityModulated Radiotherapy

fers better sparing of these critical structures. However, the maximum doses for the right and left femoral heads do not show significant differences (p = 0.539 and p = 0.68, respectively). In terms of bowel irradiation, IMRT again exhibits a trends of lower dose (195cc) compared to 3DCRT, although the difference was not statistically significant (P = 0.262).

Table 5 demonstrated, in terms of genitourinary toxicity, IMRT displays a statically significant reduction in Grade 1 toxicity (p = 0.003) and a trends towards reduced Grade 2 toxicity (p = 0.052) compared to 3DCRT. For gastrointestinal toxicity, there was trends towards lower Grade 2 toxicity with IMRT (p = 0.023). Aneamia and thrombocytopenia show no significant differences, but a slight reduction in Grade3 anaemia with IMRT was observed (p = 0.034). Neutropenia demonstrated no significant differences across grades.

## Discussion

In our study the target coverage with D99, D95, Dmax and Dmin achieved by both techniques was better in IMRT than 3D CRT Because IMRT can deliver treatment to target organs And reduce the volume and dose to normal structure it has several advantages over conventional techniques for treatment of malignancies [21].

Various studies have shown the effects of IMRT in reducing irradiated Volumes of rectum, bladder bone marrow and small bowels [22-36]. Because of use of multiple beams angles and optimized intensity beams.

During optimisation these beams are decided into small beamlets Resulted modification of intensity by using multi leaf collimator to get the highly conformal dose distribution to target and surrounding normal tissue.

In 3D CRT, four fields with uniform intensity were planned. Due to uniform intensity OAR and target in path of each field also received the dose. In cross sectional view, all for field makes rectangular shape of field. This area covers irregular shaped target area and organ at risk which resulted high dose to surrounding structure.

In our study IMRT shown advantage over 3D CRT with reduction dose to organ risk specially to bladder, rectum, small bevels and femoral heads.

Van de Bunt., *et al*. compared between [36] two techniques in Ca cervix and results shown that IMRT was superior in sparing of normal structures with adequate Coverage of target volumes and IMRT shown superior after 30 Gy with external beam radiotherapy despite reduction of tumor size and internal organ motion.

Naik., *et al*. shown IMRT has significantly better target coverage and CI than 3D CRT Sharma., *et al*. shown similar target coverage in both technique IMRT and 3D CRT in terms D99, D95, Dmax and Dmin. CI and were same in both treatment arms mell., *et al.* [38]. Compared IMRT and 3D CRT with concurrent chemoradiotherapy for treatment of carcinoma cervix shown reduction of dose to bone marrow and bladder was less impressive as compare to bone marrow and small bowel doses forest., *et al*. compared IMRT and 3D CRT showed reduction of doses to dose to organ at risk at V50, V45, V40 and V30 with difference of 84% to bladder 50% for small bowel, 54% to sigmoid Colon and 84% to rectum for V50 in most of patients with adequate coverage of target area.

Sharma., *et al*. [39] showed reduced dose to D15, D35, D50 of rectum in IMRT arm as compare to 3DCRT arm and shown similar grade I and fewer grade II acute bowel toxicities than 3DCRT treated patients Naik., *et al*. [9] showed result of carcinoma cervix treated with 3DCRT and IMRT Rectal parameters D15, D35 and D50 were significantly comes in IMRT than in 3DCRT.

Fumeiki., *et al*. compared IMRT and 3DCRT with treatment of carcinoma cervix shown statistically significant reduction of V45 of bowel volume, 89ml was in 3DCRT as compared to 485 ml in IMRT Mark it also shown V45 in bowel bag was 227ml in 3DCRT as compare to 132ml in IMRT.

Gandhi., *et al*. also shown significant reduction of both grade II and III toxicities of acute and late gastrointestinal toxicities in patients of carcinoma cervix treated with IMRT as compared to 3DCRT.

Sharma., *et al*. shown bowel volume of 45 Gy was < 490ml in both the arrows.

Young., *et al*. shown results of meta analysis of 13 dosimetric studies comparing IMRT and 3DCRT 17.3% reduction of V45 of small bowel. No statistically significant reduction of dose to rectum and bladder in IMRT than in 3DCRT arm.

Mundl., *et al*. shown lower rate of chronic gastrointestinal toxicities at 11.1% compare to 50% in 3DCRT grade I toxically 30%, V5 8.3%, Grade II 16.7% V5 2.8% and grade 3 (3.3% V50%) toxicities.

Naik., *et al*. shown IMRT has significant advantages of reduced dose to bladder in D15 (2.09%), D35 (14.62%) and D50 (32.5%)

Brixey., *et al*. shown hematological toxicity was were higher in 3DCRT as compared to IMRT concurrent chemoradiotherapy.

Sharma., *et al*. shown significant reduction in D15, D35 and D50 in bladder dose in IMRT as compare to 3DCRT.

In our study shown the reduction of dose to urinary bladder, rectum Bilateral femoral Heads and Bowel bag. Although it was not statistically significant. Result of an study Were similar to study done by Sharma., *et al*. and naik., *et al*. and mundl., *et al*.

Our study shown the patients treated with either IMRT and 3DCRT have almost same dose distribution CI and CT to target. While with genitourinary toxicity grade I, II toxicities seen in IMRT than 3DCRT, No grade 3 toxicity shown in both arm. In gastrointestinal toxicities grade 1, 2, 3 toxicities were less in IMRT arm. In haematological toxicities less toxicities shown in IMRT arm as compare to 3DCRT arm.

## Conclusion

IMRT intensity modulated radiotherapy is associated with more accurate dose distribution to tumors and reduce dose to normal time (OAR) thus reducing the side effects of bladder, rectum, bowel and bones.

IMRT shown several advantages over 3DCRT radiotherapy in treatment of locally advanced carcinoma cervix. There is reduction of irridated volume organ at risk bladder, Rectum, Small bowel both femoral with IMRT as compare to conformal Radiotherapy. Reduction of volume resulted gastrointestinal, genitourinary and haematological toxicities.

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