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"A comparative dosimetric evaluation of radiotherapy planning techniques in cervical cancer: A treatment planning study."

Dr Deepali B. Patil[1], Dr. Mukesh zope[2], Dr Shraddha Raj[3], Dr Seema Devi[4], Dr. Rajesh singh[5]

[1,2]*Department of Medical Physics, State cancer institute, Indira Gandhi Institute of Medical Sciences, Patna-14, Bihar*

[4,5]*Department of Medical Physics, State cancer institute, Indira Gandhi Institute of Medical Sciences, Patna-14, Bihar*

Author for correspondence: *Dr Mukesh Kumar Zope, [2]Department of Medical Physics, State Cancer Institute, Indira Gandhi Institute of Medical Sciences, Patna-14, India-800014, tel: (+91)-9771811037; e-mail:zopeigims27@gmail.com*

Running title: "Cervical Cancer Radiotherapy Comparison".

Abstract

Aim*:*

This study aimed to assesses the dosimetric parameters of Rapid Arc plans, Intensity-Modulated Radiotherapy (IMRT), and Three-Dimensional Radiotherapy field (3DCRT) planning techniques in cervical cancer.

Materials and methods:

We created treatment plans for 15 previously treated cervical cancer patients using their CT scan data sets in this observational comparative analysis. With a prescribeded dose of 50 Gy in 25 fractions, we planned three separate approaches using the Eclipse treatment planning system (version 16.1). The conformity index (CI), uniformity index (UI), homogeneity index (HI), conformation number (CN), dose spillage, monitor units (MUs), and organ-at-risks (OARs) factors for each approach were all evaluated.

Results:

Our results show that, in comparison to IMRT and rapid arc at 97.91%, 96.71%, and 96.39%, $p<0.01$ (ANOVA), 3DCRT obtained considerably lower Dmax at 52.69Gy, 54.09Gy, and 54.05Gy, along with greater D95%. Significantly better CN and dosage Spillage Index were shown by rapid arc ($p<0.01$, ANOVA). In comparison to IMRT (47.29Gy,85.52%,141.40cc) and 3DCRT (49.58,95.69%,260.78cc), it effectively lowered OAR doses, rectum Dmean and V45 (46.91Gy and 82.92%), and minimized bowel D45Gy (128.10cc), $p<0.05$ (ANOVA), indicating greater bladder sparing. In comparison to IMRT, 3DCRT and fast arc required fewer MUs.

Conclusion:

Rapid Arc offers superior dosimetrically, improved conformance, less dose leakage, and greater OAR sparing in external beam radiation treatment (EBRT) for cervical cancer, suggesting potential benefits. According to these results, it may prove to be a beneficial therapeutic choice for cervical cancer.

Keywords:

Cervical cancer, Rapid Arc, IMRT, 3DCRT, dosimetric parameters, External Beam Radiotherapy (EBRT).

I. Introduction:

Cervical cancer is still a major global health concern. It is currently the eighth most prevalent cancer globally and the fourth most common cancer in women worldwide [1]. It is the second most common malignancy in women in India, affecting more than 20 out of every 100,000 women [1]. Depending on the disease's stage, treatment for cervical cancer often consists of a variety of methods including primary surgery, radiotherapy and chemotherapy. Radiation therapy has a significant role and should be used in up to 60% of patients [2]. Concurrent chemoradiotherapy is the chosen treatment option since most patients in developing countries receive their diagnosis at an advanced stage [3].

Treatment planning was traditionally done using plain film X-rays and two-dimensional conventional radiotherapy (2DRT). Nevertheless, a higher frequency of complications resulted from this 2-field or 4-field approach's inadequate accounting for the presence of the bladder or bowel in the irradiation field [4].

Three-dimensional conformal radiation therapy (3DCRT) was introduced with the use of computed tomography (CT) for treatment planning. It provided enhanced organ-at-risk (OAR) sparing and target volume delineation. Using standard conventional beams, 3DCRT reduced radiation and toxicities while improving dose conformity [5, 6].

Subsequently, Intensity-modulated radiation treatment (IMRT) was then used to improve target volume coverage even more while protecting OARs [7]. Rapid Arc, a type of Volumetric Intensity-Modulated Arc Radiotherapy (VMAT), is notable for its capacity to provide highly conformal dose distributions at the same time as reducing the treatment time and monitor units [9, 11]. Our goal in this study is to thoroughly evaluate PTV coverage, dosimetric parameters,doses to OARs and investigate potential low radiation dose spread for patients with cervical cancer.

II. Material and Methods:

1. Patient selection and CT Simulation:

Fifteen patients with histopathologically confirmed cervical cancer (FIGO stages IIB to IVA) and eligible for definitive treatment planning were included in this retrospective study. A GE Revolution EVO scanner (2.5 mm slice thickness) was used to obtain CT scans, with and without intravenous contrast, covering the area from T10 to mid-thigh. Thirty minutes prior to treatment, the patient was given 500 milliliters of water and placed in a supine position with both arms elevated above the chest in order to achieve equal bladder capacity and position during the CT scan and treatment separation. Every patient has regular bowel habits as well.

2. Contouring and Treatment Planning:

CT images were imported into Varian SomaVision (version 16.0.1, Varian Medical Systems, Palo Alto, CA) after reconstruction using DICOM planning. Target delineation followed Radiation Therapy Oncology Group (RTOG) protocol recommendations, using organ structures at risk (OAR) in addition to gross tumor volume (GTV), the target volume clinical (CTV) and planning target volume (PTV) [18] .

Using the Eclipse treatment planning system (TPS,version 16.0.1, Varian Medical Systems, Palo Alto, CA), comprehensive treatment planning was carried out on a True Beam SVC linear accelerator that was fitted with a Millennium 120 multileaf collimator (MLC). 50 Gy in 5 fractions over 5 weeks was the prescribed dose. The Analytical Anisotropic Algorithm (AAA) was used to calculate the final dose. For each patient in the retrospective, new IMRT and RA plans were created. Using Photon Optimizer (PO), inverse optimization was used to optimize IMRT and RA (version 13.6.23). Treatment planning strategies have been employed in the treatment of patients with cervical cancer. A 3D-CRT plan was created using four fields with gantry angles of 0°, 180°, 270°, and 90° using 6 MV and 10 MV photon beams. In the IMRT plan, seven equidistant gantry angles were used, such as 0°, 51°, 102°, 153°, 204°, 255°, and 306° and RA plans includes two full arcs, a counterclockwise 179°–181° with a collimator angle of 330° and a clockwise 181°–179° with a collimator angle of 30° using 6MV photon beam. In order to encompass the entire tumor and reduce the tongue and groove impact of MLCs during arc rotation, collimator rotation was applied.

In every plan, the main goal was to minimize OAR doses while making sure that at least 95% of the recommended dose got 95% of the PTV. OAR doses and volumes followed certain guidelines, such as maximum doses to the bladder (Dmax<52.5Gy, V40<60%, V45<55%), rectum (Dmax<52.5Gy, V40<100%), femoral heads (Dmax<52Gy, V30Gy<15%), and bowel volume (V45Gy below 195cc [18].

3. Dosimetric Parameters :

We performed a dosimetric evaluation utilizing metrics like Uniformity Index (UI), Conformity Index (CI), Homogeneity Index (HI), Grandient Index (GI), Uniform Dosimetry Index (UDI), and Conformation Number (CN) in order to determine the most clinically acceptable treatment plan employing each technique. In addition, we assessed the recorded eclipse gradient (GM) data, the high dosage spillage index (beyond the PTV), and the dose spillage index (R50%). Table 1 summarizes the quality and efficacy of the treatment plan, which is ensured by this assessment.

Table 1: Various dosimetric parameters and definitions

Parameters	Formula	Interpretation
Uniformity Index (UI)	UI = D5% / D95%	UI close to 1 indicates more uniform dose distribution as per ICRU REPORT 83.
Conformity Index (CI)	95% CI = TV95% (cc) / TV	CI ideal value is one. As per RTOG 90-05 protocol [21].
Homogeneity Index (HI)-1	HI = (D2% - D98%) / D50%	A value of zero is ideal; closer to zero indicates better homogeneity as per ICRU REPORT 83.
Homogeneity Index (HI)-2	HI = Dmax / PD	Closer to 1 indicates better homogeneity. Acceptable range: 1-1.5., as per RTOG protocol [19].
Conformation Number (CN)	CN = (TVRI / TV) * (TVRI / VRI)	Maximum value for CN is 1, corresponding to perfect PTV coverage as per RTOG 90-05 protocol [21].
Coverage	Coverage = Dmin / PD	Acceptable range for target volume coverage: 90% to ±10% deviation[20].
Dose Gradient Index (GI)	GI = PTVPD / PTVPD50%	Lower GI implies steeper dose fall-off and better conformity [21].
Unified Dosimetry Index (UDI)	UDI = CN * CI * HI-2 * GI	UDI value near 1 is preferable [22].
Dose Spill Outside of PTV	Volume of 105% spilling outside the PTV = (Volume of 105% in Body) - (Volume of 105% in PTV)	Evaluates dose spillage outside the PTV[23,24].
Dose Spillage Index (R50%)	R50% = 50% isodose volume / PTV volume	Lower R50% ratio indicates better dose conformity around PTV [23,24]
TPS Gradient Measure (GM)	GM = rEqSphVIDC50% - rEqSphVIDC100%	Smaller GM value indicates a steeper dose gradient [7,10].

D2%, D5%, D50%, D95% and D98% were doses delivered to specific percentage of Target Volume, TV95%(cc) :the target volume covered by the reference isodose (RI) (95%) in cubic centimeters, and TV is target volume, Dmax: maximum target dose, Dmin: Minimum target dose PD: Prescription dose, TVRI & VRI: Treatment volume & total Volume at the RI, PTVPD: Planning Target volume coverage at PD, rEqSphVIDC50% &rEqSphVIDC100% are the radii of spheres that match the volume of 50% & 100% isodose coverage, respectively.

4. Statistical Analysis:

IBM SPSS version 29.0.1.0 for Windows was used to conduct the statistical analysis. To find out significant differences between the three groups, a one-way ANOVA was employed. Then, individual differences were examined using the paired t test. The threshold for statistical significance was set at $p<0.05$.

III. Results:

Table 2 presents the significant findings from the examination of dosimetric parameters for three planning techniques (3DCRT, IMRT, and Rapid Arc) inside the Planning Target Volume (PTV). In particular, the minimum doses (Dmin) for IMRT (38.96±2.09) and Rapid Arc (41.08±3.37) were much lower than those of 3DCRT (43.83±3.36), with IMRT and Rapid Arc showing no difference ($p=0.027$). In contrast, IMRT (54.09±0.98) and Rapid Arc (54.05±0.68) had considerably greater maximum doses (Dmax) than 3DCRT (52.69±0.27). With IMRT and Rapid Arc lower than 3DCRT, there was a significant difference ($p<0.001$) in the mean doses (Dmean) and the 95% PTV dosage (D95% PTV). Figure 1 presents comparative instances of dose distribution within the PTV, while Figure 2 displays the cumulative dosage volume histogram for the PTV and OARs across the three delivery techniques. All techniques had equivalent values ($p>0.05$) for UI, HI-1, and 95%CI. There were notable variations between the methods (3DCRT, IMRT, Rapid Arc) for dosimetric parameters (Table 2, $p<0.001$). The Gradient Index (GI) and Ultimate Dose Index (UDI) were lower for IMRT and Rapid Arc ($p<0.001$). For IMRT and Rapid Arc, the 100% Conformal Index (100%CI) was lower ($p<0.01$). On the other hand, the Homogeneity Index-2 (HI-2) was lower for 3DCRT ($p<0.001$). While Conformation Number (CN) was higher in IMRT and Rapid Arc ($p<0.001$), Coverage was higher in 3DCRT ($p=0.001$).

Significant differences were found for the Dose Spillage Index (R50%) (Table 2, $p<0.001$), where 3DCRT was higher than IMRT and Rapid Arc. Regarding the TPS Gradient Measure ($p=0.3954$) and Dose Spill Outside of the PTV ($p=0.1108$), no significant changes were seen. Table 2 demonstrates that although 3DCRT (1595.7±119.41), Rapid Arc (578.15±40.2), and IMRT (281.81±15.65) required less Monitor Units (MU) than the latter two. Table 2 shows that IMRT had the longest treatment time (TT), whereas 3DCRT had the shortest, followed by Rapid Arc.

Table 2: PTV parameters comparison among 3DCRTFIF, IMRT and Rapid Arc techniques.

PTV Parameters	3DCRTFIF	IMRT	Rapid Arc	ANOVA	Pair-wise comparison		
	Mean±SD	Mean±SD	Mean±SD	p-value	*p*-value		
	A	B	C		A vs. B	A vs. C	C vs. D
Planning Target Volume (PTV)							
Dmin	43.83±3.36	38.96±2.09	41.08±3.37	0.0005	0.001	0.004	0.027
Dmax	52.69±0.27	54.09±0.98	54.05±0.68	<0.001	<0.001	<0.001	0.841
Dmean	50.81±0.322	49.94±0.152	49.87±0.129	<0.001	<0 .001	<0 .001	0.157
D95%	97.91±1.12	96.71±0.6	96.39±0.62	<0.001	0.003	<0.001	0.026
UI	1.06±0.013	1.06±0.01	1.06±0.008	0.5708	0.395	0.407	0.735
HI-1	0.075±0.01	0.084±0.01	0.081±0.01	0.0963	0.085	0.237	0.326
CN	0.62±0.037	0.91±0.012	0.92±0.002	<0.001	<0.001	<0.001	0.005
Coverage	0.88±0.07	0.78±0.04	0.82±0.07	0.0005	0.001	0.004	0.027
HI-2	1.05±0.01	1.08±0.02	1.08±0.01	<0.001	< .001	< .001	0.841
100%CI	1.09±0.32	0.50±0.06	0.48±0.05	<0.001	<0.01	<0.01	0.624
95%CI	0.99±0.01	0.95±0.12	0.98±0.01	0.2844	0.225	0.015	0.376
GI	0.94±0.26	0.49±0.05	0.45±0.13	<0.001	<0 .001	<0 .001	0.322
UDI	0.88±0.29	0.39±0.08	0.38±0.29	<0.001	<0 .001	<0 .001	0.778
Dose spillage index (R50%)	5.32±0.82	3.13±0.25	2.91±0.18	<0.001	<0.001	<0.001	<0.001
Dose Spill Outside of the PTV	1.6±3.13	1.53±0.32	0.42±0.31	0.1108	0.74	0.162	0.005
TPS Gradient Measure	4.74±0.77	4.62±0.42	4.44±0.46	0.3954	0.423	0.103	0.06
MU	281.81±15.65	1595.7±119.41	578.15±40.27	<0.001	<0.001	<0.001	<0.001
TT	0.55±0.07	3.19±0.24	0.96±0.07	<0.001	<0.001	<0.001	<0.001

Dmax: Dose of Maximum, Dmin: Dose of minimum, Dmean: Dose of mean, D95%: Dose received by 95% volume, UI-Uniformity Index, HI-1 &2: Homogeneity Index, CI: Conformity Index, CN: Conformation number, GI: Gradient index, MU: Monitor Unit, TT: Treatment time, SD: Standard Deviation.

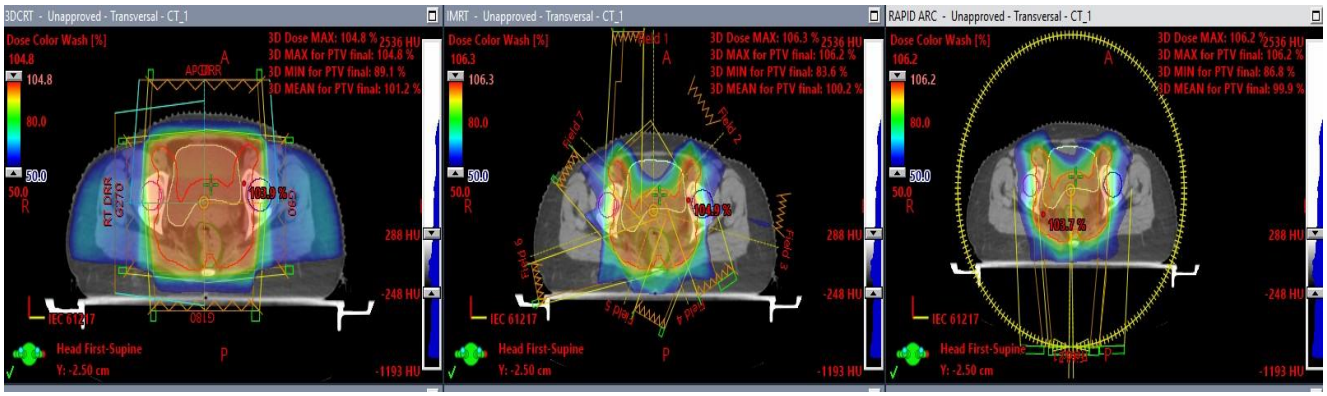

Figure 1 shows the colour wash dose level from 50% of the prescribed dose to maximum dose for the 3DCRTFIF, IMRT and Rapid Arc treatment plans in Transverse view, respectively.

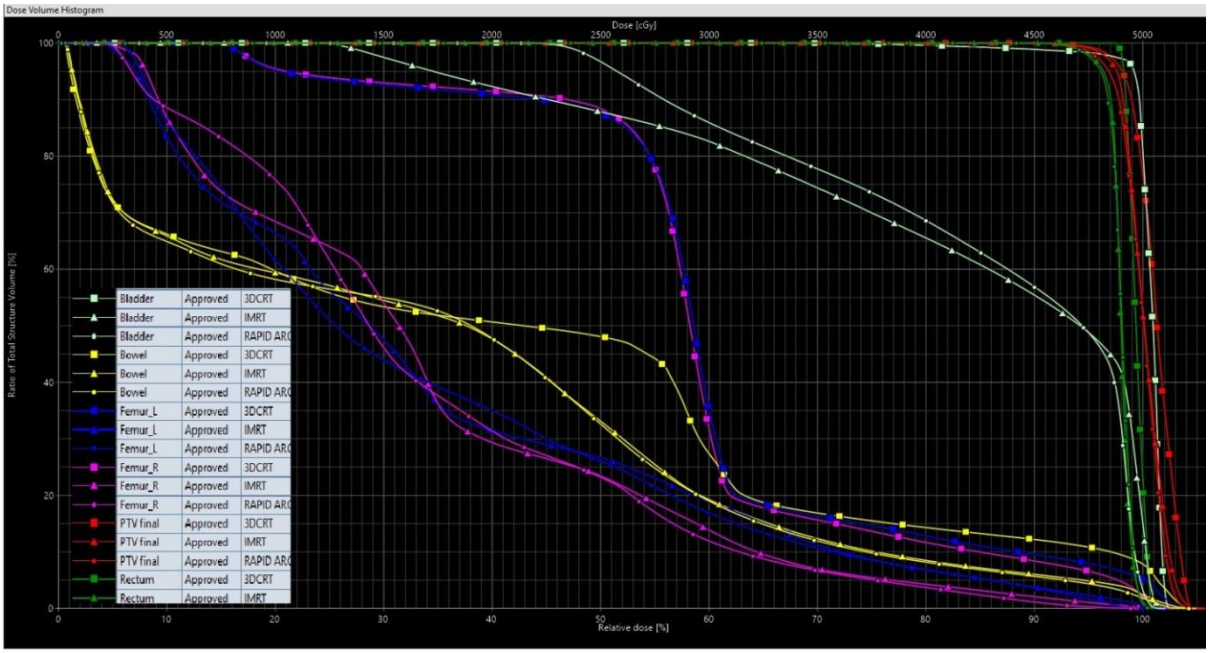

Figure 2: Dose-volume histogram comparison of different techniques for planning target volume and Organ at Risk.

Table 3 compares characteristics such as Dmax, Dmean, and V30, V40, and V45 for the bladder, rectum, femoral head, and bowel to show the effects of radiation treatments (3DCRT, IMRT, and RapidArc).

Bladder and Rectum:

An ANOVA analysis of the bladder revealed a highly significant difference in Dmean ($p < 0.01$) and a substantial difference in Dmax ($p = 0.0037$) between approaches. bladder volume exposed at V30 (%), V40 (%), and V45 (%) varied significantly, with the exception of V45 (%) where IMRT was exposed instead of RapidArc. ANOVA results for the rectum revealed that there was no significant difference in Dmax ($p = 0.26414$), but there was a significant change in Dmean ($p = 0.00348$), with a greater mean dose resulting from 3DCRT. Furthermore, there were extremely significant differences across approaches for V40 (%) and V45 (%) ($p = 0.06668$ and 0.0146, respectively).

Femoral Head and Bowel:

Significant differences in Dmax and Dmean were seen among all technique pairings in the study of the right and left femoral heads ($p < 0.05$), indicating the influence of the technique. Additionally, all pairings of approaches showed highly significant differences in V30(%) ($p < 0.001$). For the bowel, Dmax did not change significantly ($p = 0.30058$, ANOVA); however, D45Gy, which represents the dosage to the 195cc volume, showed highly significant differences ($p = 0.00132$) across all pairings of procedures, highlighting the significance of taking D195cc into account.

Table 3: Comparative Analysis of Organ At Risk (OAR) parameters among 3DCRT, IMRT and Rapid Arc techniques.

OAR	3DCRT	IMRT	RapidArc™	ANOVA	Pair-wise comparison		
	Mean±SD	Mean±SD	Mean±SD	p-value	*p*-value		
	A	B	C		A vs. B	A vs. C	C vs. D
Bladder							
Dmax	52.21±0.35	51.76±0.69	51.54±0.48	0.0037	0.024	0.001	0.383
Dmean	49±1.66	42.52±1.82	43.11±1.94	<0.001	<0.001	<0.001	0.037
V30(%)	99.2±1.73	84.95±6.40	87.08±6.40	<0.001	<0.001	<0.001	0.032
V40(%)	91.3±8.65	69.27±8.02	71.15±9.25	<0.001	<0.001	<0.001	0.205
V45(%)	88.98±9.92	59.28±8.88	61.98±9.68	<0.001	<0.001	<0.001	0.045
Rectum							
Dmax	51.67±0.6	51.49±0.45	51.32±0.65	0.26414	0.402	0.118	0.297
Dmean	49.58±1.41	47.29±2.41	46.91±2.58	0.00348	<0.001	<0.001	0.464
V30(%)	98.78±3.05	97.19±4.71	96.42±5.29	0.34383	0.016	0.04	0.469
V40(%)	97.24±4.95	91.61±9.7	89.16±12.2	0.06668	0.001	0.005	0.313
V45(%)	49.58±1.41	85.52±13.4	82.92±14.8	0.0146	<0.001	<0.001	0.351
Right femoral Head							
Dmax	51.62±0.59	48.35±4.71	48.73±1.63	0.00662	0.019	<0.001	0.768
Dmean	31.31±3.67	15.46±2.84	15.35±2.26	<0.001	<0.001	<0.001	0.76
V30(%)	67.35±29.18	10.93±5.58	9.91±3.37	<0.001	<0.001	<0.001	0.272
Left femoral Head							
Dmax	51.40±0.70	49.35±2.56	48.68±1.94	0.00088	0.008	<0.001	0.118
Dmean	30.65±3.82	15.33±3.04	15.31±2.33	<0.001	<0.001	<0.001	0.972
V30(%)	64.65±23.66	14.77±13.31	10.69±3.53	<0.001	<0.001	<0.001	0.275
Bowel							
Dmax	52.49±0.25	52.82±1.23	48.76±13.52	0.30058	0.311	0.309	0.268
D45Gy	260.78±131.64	141.40±83.99	128.10±74.21	0.00132	<0.001	<0.001	0.588

Dmax: Dose of Maximum, Dmean: Dose of mean, Vxx: XX Gy dose recived by % of the volume, D45Gy: volume (cc) received in 45Gy dose.SD: Standard Deviation

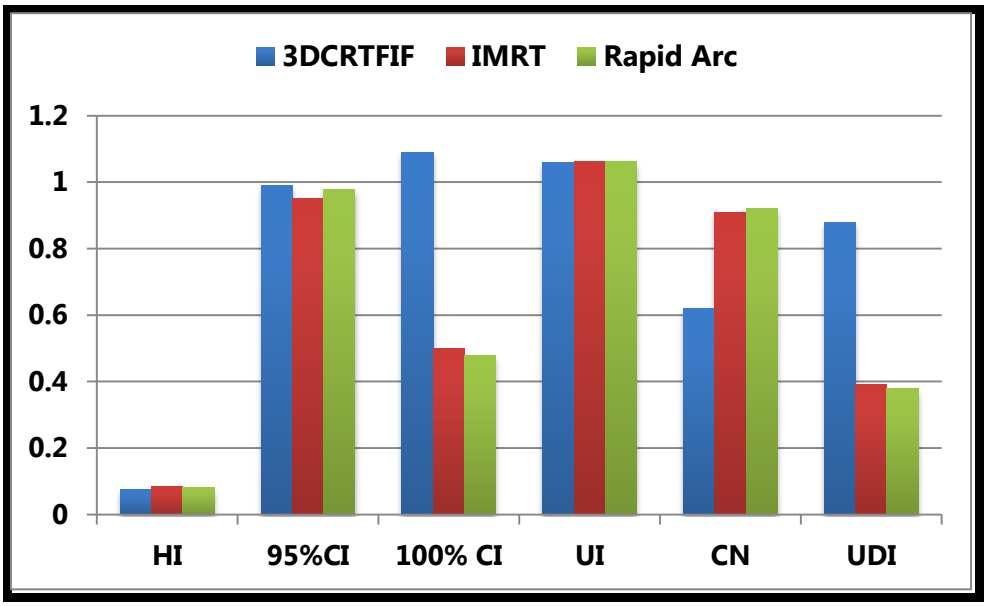

Figure 3: The variation in the Homogeneity Index (HI), conformity Index (CI) at 95% and 100%, Uniformity Index (UI) and the conformation Number (CN) for three different Techniques.

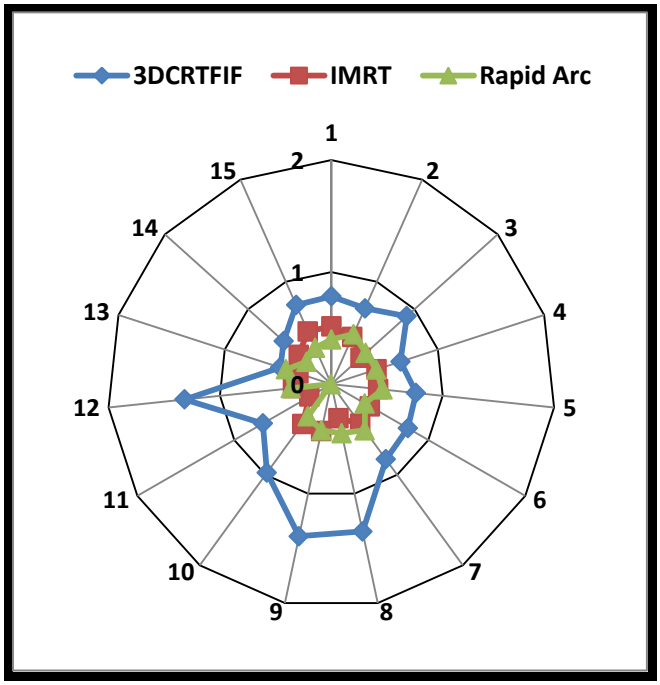

Figure 4: The Unified Dosimetry Index score of each patient across three different techniques

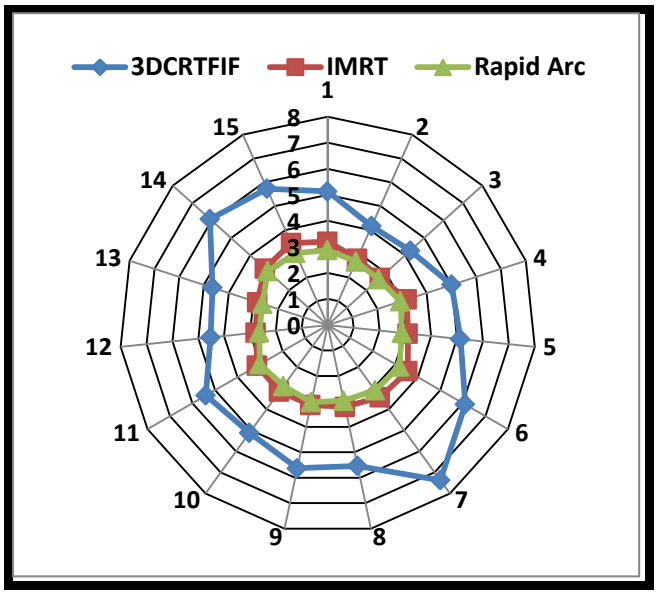

Figure 5a: The R50% Dose Spillage index of each patient, across three different techniques.

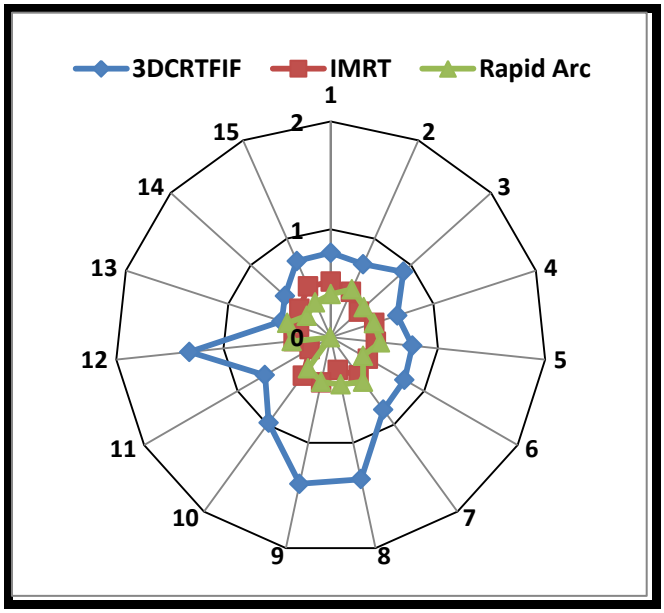

Figure: 5b: The Dose Spill Outside of the PTV of each patient, across three different techniques.

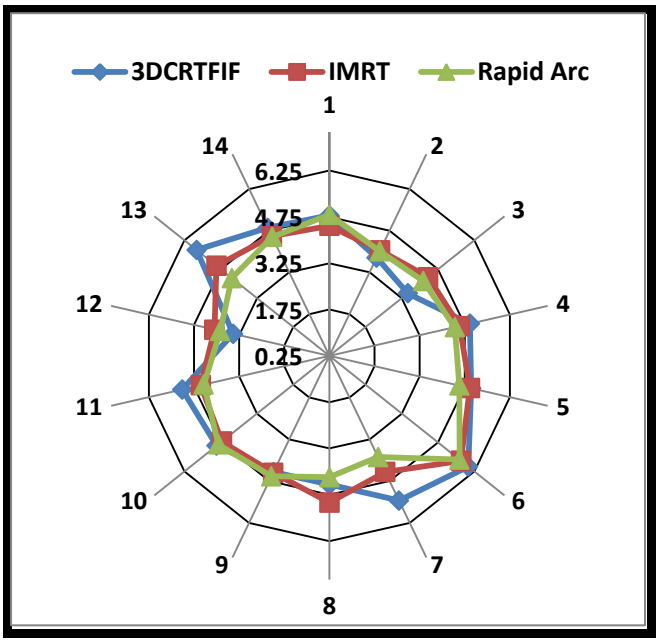

Figure: 5c: The TPS Gradient Measures of each patient, across three different techniques.

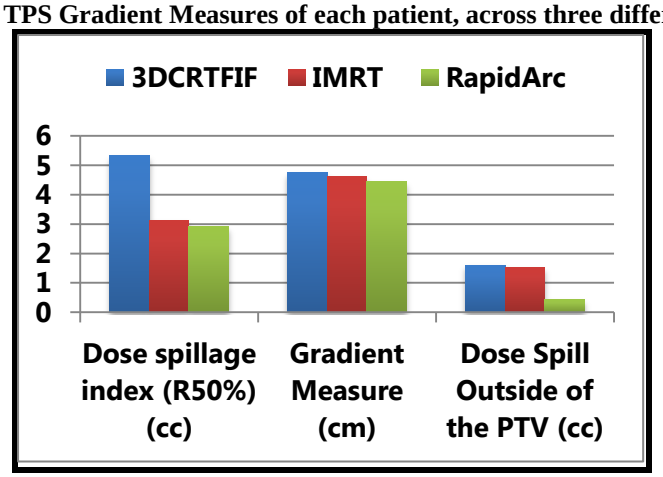

Figure 5d: The mean variation in the Dose spillage Index at 50%, Gradient Measure and outside PTV for three different Techniques

IV. Discussion:

In line with other studies, we verified in our study that IMRT and Rapid Arc are superior to 3DCRT [25–28]. For each of the three approaches, Figure 3 showed the average variances in key indices such as the Conformation Number (CN), Uniformity Index (UI), Homogeneity Index (HI), and Conformity Index (CI) at 95% and 100%. Increased protection of normal tissue, better dosimetry consistency, and increased treatment precision were all made possible by IMRT and Rapid Arc. Better coverage at 95% of the prescribed dosage (D95%), a lower maximum dose (Dmax), a greater minimum dose (Dmin), and enhanced target coverage were among the benefits of 3DCRT. In our investigation, the three techniques—Rapid Arc at 0.92, IMRT at 0.91, and 3DCRT at 0.62—all attained comparatively high conformance levels.

The significant benefits of VMAT in cervical cancer radiation therapy were emphasized by Huang et al. (29) and Nguyen et al. (30). These benefits included improved organ protection, highly conformal dose distribution, and superior target dose homogeneity. Higher Conformity Number (CN) values were shown by IMRT and RapidArc in our investigation, indicating enhanced conformance and accurate tumor targeting with less radiation exposure to nearby healthy tissues. Volumetric-Modulated Arc Therapy (VMAT) was consistently shown to provide superior dose homogeneity, reduced dose spillage outside the Planning Target Volume (PTV), and improved Gradient Measure (GM) values in a combined analysis of studies by Huang et al. (29) and Nguyen et al. (30). VMAT is useful in the treatment of cervical cancer because of its precise and conformal dose distribution.

The Uniformity Dose Index (UDI) was one of the additional dosimetric metrics that our study examined between the three radiation therapy techniques. Better plans are indicated by lower UDI scores. When

comparing Rapid Arc and IMRT, Atiq et al.'s study found that Rapid Arc had a marginally higher average UDI score (1.26 against 1.48). In contrast to IMRT (0.39±0.08) and Rapid Arc (0.38±0.29), 3DCRT had a substantially higher mean UDI score (0.88±0.29) in our study (Table 1 & Figure 3). As can be shown in Figure 4, Rapid Arc had a marginally lower UDI score than IMRT for every patient, although the difference was not statistically significant. According to Atiq et al. [21], every technique satiated the outstanding plan UDI score requirement.

The research also investigated unplanned dosage spillage indices, such as the High dosage Spill Index (Outside PTV) and the Intermediate Dose Spill Index (R50%). We looked into the direct effects of treatment efficiency on the Treatment Planning System (TPS) Gradient measure. As demonstrated in Figure 5a, IMRT and RapidArc considerably decreased Dose Spillage R50%, which is essential for reducing radiation exposure to critical structures. Figure 5d showed the differences between IMRT and Rapid Arc, with Rapid Arc demonstrating superior dose spill control outside PTV and 3DCRT demonstrating higher dosage spill. Figure 5b showed high dose spillage outside PTV for each patient. Additionally, our investigation revealed differences in Gradient Measure (GM) between RapidArc and IMRT. The individual patient radar graph in Figure 5c and the superior GM values of RapidArc at the 95% level indicate that IMRT performed better at the 100% level, better aligning with the target volume.

The rectum is one of the important organs at risk (OARs) that must be protected during cervical cancer treatment. Studies on the effects of VMAT and IMRT on rectal irradiation at 40 Gy (V40) were conducted by Cozzi et al. [9], Qiao et al. [30], and Guo et al. [31]. The dosimetric benefits of IMRT and Rapid Arc over 3DCRT were the main topic of our investigation. When compared to 3DCRT, IMRT and Rapid Arc consistently produced lower rectal doses (Dmean) and decreased exposure to high radiation dose levels (V40Gy and V45Gy). These cutting-edge methods consistently lowered Dmean and limited rectal exposure to 40 Gy or more and 45 Gy or more, minimizing the likelihood of rectal problems, even though variations in maximum dose (Dmax) were not statistically significant. Radiation therapy for cervical cancer also requires bladder safety. Rapid Arc and IMRT. With lower Dmax, IMRT and Rapid Arc outperformed 3DCRT; Rapid Arc also showed greater promise for bladder preservation. The mean dose (Dmean) was consistently decreased by both methods, reducing the possibility of radiation-related problems. In comparison to 3DCRT, they also greatly reduced bladder exposure to particular radiation doses (V30, V40, and V45). For bladder Dmean, V30, and V45, IMRT outperformed Rapid Arc in the comparison. These results are consistent with earlier research conducted by Guy et al. [32] and Marjanovic et al. [26].

V. Conclusion:

We found that Rapid Arc was consistently the better option. It showed better conformance to the target volume, less dose spillage, and required fewer monitor units, which made it a viable option for reducing radiation exposure to healthy tissues. Furthermore, both IMRT and Rapid Arc showed benefits over 3D-CRT in terms of protecting vital organs like the bladder and rectum, which lowers the possibility of problems. Furthermore, these sophisticated methods shown potential advantages in reducing bowel toxicity, with Rapid Arc being particularly effective in this regard. All things considered, our research suggests that Rapid Arc is the most effective EBRT technique for enhancing cervical cancer treatment outcomes.

ETHICAL APPROVAL:

This study conducted with valid Ethical approval at Indira Gandhi Institue of Medical Sciences, Patna-14, Bihar, India.

Conflict of interest statement:

None

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