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Dosimetric comparison of whole pelvic radiotherapy for post-operative endometrial cancer using three-dimensional conformal radiotherapy and intensity-modulated radiotherapy technique

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ABSTRACT

Background: The use of intensity-modulated radiation technique is being used increasingly in gynecological patients. It plays an important role in the adjuvant treatment of gynecologic malignancies, particularly in cervical and endometrial cancer. While radiotherapy (RT) has greatly improved local-regional control of primary tumors, it has come at the cost of significant toxic effects on adjacent non-cancerous tissues. **Aims and Objectives:** The purpose of this study was to perform a direct dosimetric comparison between the three-dimensional radiation technique and intensity modulation radiation technique in post-operative endometrial cancer patients and to evaluate the integral dose to organs at risk (OAR). **Materials and Methods:** We selected 49 patients with endometrial cancer undergoing post-operative whole pelvic RT. Plans for three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) were developed for each patient. All plans were normalized to deliver 45 Gy to 95% of the planning target volume. The dosimetry and integral dose to OARs were compared. The significance of differences was tested using a paired Student t-test. **Results:** IMRT had significantly better conformity and reduced mean dose and integral dose to OARs in comparison to 3D-CRT. **Conclusion:** In post-operative endometrial cancer patients IMRT had better dose conformity and reduced integral and mean dose to OARs when compared to 3D-CRT. The clinical significance of these dosimetric differences needs to be further investigated.

Key words: Endometrial cancer; Three-dimensional conformal radiotherapy; Intensity-modulated radiotherapy; Planning target volume; organs at risk; Integral dose; Dose conformity

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INTRODUCTION

Endometrial cancer is the most common gynecologic cancer in women between the ages of 55 years and 85 years in developed countries.[1,2] Radiotherapy (RT) plays an important role in the adjuvant treatment of gynecologic malignancies, particularly in cervical and endometrial cancer. While RT has greatly improved local regional control of primary tumors,[3] it has come at the cost of significant toxic effects on adjacent non-cancerous tissues.[4] According to actual guidelines, standard treatment consists of surgery ±RT± chemotherapy in case of non-metastatic operable cases.[5] Technological advancements in RT made three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated RT (IMRT) techniques available which allows better sparing of the organs at risk (OAR) situated

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in the proximity of target volume from ionizing radiation, therefore reducing the acute and late toxicity.[6] In contrast to 3D-CRT, which uses uniform fields, IMRT generates non-uniform fields to achieve better planning target volume (PTV) coverage, while decreasing unnecessary radiation exposure to normal organs.[7] Conventional WPRT with 3D-CRT exposes most of the contents of the pelvis to the prescribed dose.[8] A significant portion of the small bowel falls into the vacated space in the pelvis after hysterectomy, increasing the volume of bowel treated to a high dose.[9] Because most of the total body bone marrow reserve is located within the lower lumbar spine and pelvic bones, hematologic toxicity is common in gynecologic patients treated with concomitant whole pelvic RT and chemotherapy.[10] The use of IMRT is increasing in gynecological patients.[11] With IMRT and volumetric modulated arc therapy, the radiation dose is delivered more conformally to the target volume, and the dose to the adjacent OARs is reduced, compared to 3D-CRT, without compromising clinical outcome.[12]

Since the beginning of the 2000s, IMRT has tended to replace the standard 3D-CRT as it allows the delivery of a highly conformal treatment without compromising the target volume coverage.[13] A recent Cochrane Database Systematic Review supports these assumptions.[14]

With this background, the purpose of this study is to provide a direct dosimetric comparison of 3D-CRT and IMRT plans in post-operative endometrial cancer patients and to evaluate the integral dose to normal tissues and OARs.

Aims and objectives

To compare the dosimetric outcome in terms of PTV coverage and OAR sparing with IMRT and 3DCRT technique in whole pelvic radiation of post operative endometrial cancer patients.

MATERIALS AND METHODS

After obtaining informed consent and approval from the institutional review board, 49 patients with endometrial cancer who had undergone post-operative WPRT were selected for this study. The sample size was calculated using the formula-$n_0=Z^2\ pq/e^2$ with a 95% confidence interval, where Z=1.96.

p=percentage of PTV receiving 100% of the prescription dose for IMRT=95.6%[19]

q=100–p=100–95.6=4.4%

e=allowable error=6% of p=5.736

n=sample size=49.11

For each patient, a vaginal marker was inserted to indicate the position of the vaginal apex, carefully not to distort the vagina before the simulation scan. All patients were instructed to drink 500 mL water half an hour before simulation and treatment. Then, the patients were immobilized using knee rest and footrest and scanned from T12 vertebrate to mid-thigh, with a slice thickness of 0.25 cm. In addition, i.v. contrast was administrated to all patients before the computed tomography (CT) scan. The image sets were transferred to the Varian Clinic iX treatment planning system (Version 11.0.31) for contouring and planning.

Contour of targets

The clinical target volume (CTV) was delineated according to the consensus guidelines of the radiation therapy oncology group.[15] The CTV included pelvic lymph node regions (common, internal, and external iliac), the proximal 3.0 cm of the vagina, and paravaginal tissues for all the patients. For patients with cervical stromal invasion, the presacral lymph node region was also contoured to the inferior border of S2. A margin of 0.7 cm was added to the "vessels" contour in all dimensions and modified by anatomic boundaries (as clinically indicated for individual patients) to create the nodal CTV, from which the pelvic bones, femoral heads, and vertebral bodies were excluded. The CTV was expanded by 0.5 cm to create the PTV.

Contours of OARs

The OARs contoured include the bladder, rectum, and small intestine. The superior and inferior extents of OARs were outlined on all CT slices in which portions of the PTV existed, as well as at an additional 2 cm superior and inferior to the limits of the PTV. The rectum was contoured from the rectosigmoid flexure to the anus. The small intestine and colon were defined as all individual bowel loops and contoured together as one structure referred to as the "bowel bag."[16] No expansion of all these OARs was made to account for the organs' motion and setup error.[17]

Treatment planning

3D-CRT and static IMRT plans were generated for each patient using the Varian Clinac iX planning system (Version 11.0.31). 3D-CRT four-field box plans were generated using 15-MV photons. The beam aperture was shaped to the PTV in each beam's eye view, with a 0.8 cm margin in all directions to account for beam penumbra. Weights of the individual fields were optimized to maximize homogeneous dose distribution to the PTV and minimize the dose to the OARs. The IMRT plans using 6 MV photons were generated using the rapid arc technique. The typical dose-volume constraints of IMRT, used as input for the inverse treatment planning process, are given in Table 1. A field

Table 1: OARs and dose-volume constraints used in IMRT

Structures	Constraints
PTV	Minimal dose, 41.8 Gy; maximal dose 48.1 Gy; 95% of PTV receives 45 Gy
Bowel	35% of the bowel receives 35 Gy
Bladder	40% of the bladder receives 40 Gy
Rectum	60% of the bladder receives 40 Gy

OARs: Organs at risk, IMRT: Intensity-modulated radiotherapy, PTV: Planning target volume

width of 2.5 cm was used for all plans, along with a pitch of 0.3 and a modulation factor of 3.0.

Dosimetric comparison

For the convenience of comparison, all plans were normalized to deliver 45 Gy to 95% of the PTV. The dose-volume histograms (DVHs) of the 3D-CRT and IMRT plans were compared for the PTV coverage and OAR sparing, and integral dose to OARs and normal tissue. The parameters analyzed included the percentage of PTV receiving 95%, 100%, 105%, and 110% of the prescription dose (PTV_{95}, PTV_{100}, PTV_{105}, and PTV_{110}); the homogeneity index (HI) and conformity index (CI). The HI was defined as D5%/D95% (minimum dose in 5% of the PTV volume that received the most dose/minimum dose in 95% of the PTV volume that received the most dose).[18] Since not all parts of the PTV were covered by the prescribed dose, the CI was calculated as follows: CI=CF (cover factor) × spill factor (SF), where the CF was defined as the percentage of the PTV volume receiving at least the prescribed dose and the SF as the volume of the PTV receiving at least prescription dose relative to the total prescription dose volume.[18] The closer the CI value is to 1, the better the dose conformity. To quantify the dose distribution of OARs and normal tissue in different dose levels, the percentage volume of the OARs and normal tissue receiving a dose of 5 Gy, 10 Gy, 20 Gy, 30 Gy, 40 Gy, and 50 Gy (V_5, V_{10}, V_{20}, V_{30}, V_{40}, and V_{50}) were evaluated and compared for two techniques. The mean dose and integral dose to OAR were also calculated. The integral dose is equal to the mean dose times the volume of each structure.

Statistics

The significance of differences was tested using a paired two-tailed Student's t-test. The threshold for statistical significance was $P<0.05$. All data were analyzed using Statistical Package for Social Science, version 27.0, software (SPSS, Chicago, IL).

RESULTS

Most of the women were menopausal (77.5%) with most of the patients belonging to the age group of 51–60 years with a median age of 60 years (range: 42–89 years). They mostly had a myometrial invasion superior to 50% (73.4%). FIGO stage Ib (44.8%) and grades 1–2 (57.1%) cancers were the most represented in the population. Patients (59.1%) received adjuvant chemotherapy combining paclitaxel and carboplatin with a median number of six cycles. There was no difference between the 3D-CRT and IMRT groups regarding age, histology type, grade, FIGO stage, LVSI status, adjuvant chemotherapy, and brachytherapy. The median dose was 45 Gy in 25 fractions and 54 days (range: 46–60 days) The median interval between WPRT and vaginal brachytherapy was 8 days (range: 7–10 days). Median follow-up was 4 months (range: 3–7 months).

Table 2 summarizes the PTV coverage for the two techniques. The mean conformity index was 0.3 and 0.5 for 3D-CRT and IMRT plans, respectively. IMRT had significantly improved dose conformity compared to 3D-CRT ($P<0.01$). Specifically, the average HI was 1.04 and 1.03, the mean PTV_{110} was 1.1 and 4.2% for 3D-CRT and IMRT plans, respectively. A typical axial dose distribution obtained with 3D-CRT and intensity-modulated RT is given in Figure 1.

OAR's sparing

Receiving 5 Gy, 10 Gy, 20 Gy, 30 Gy, 40 Gy, and 50 Gy, respectively; other abbreviations as in Table 2. The DVHs of OARs are listed in Table 3. For the rectum, the V_{40} and V_{45} were significantly lower in IMRT plans. For the bladder, the percentage volume receiving a dose above 30 Gy was also significantly reduced with IMRT. The V_5 and V_{10} of the bowel were higher in both plans, but the volume of the bowel receiving a dose above 20 Gy significantly decreased in IMRT plan. The mean dose to OARs decreased in IMRT plans.

Integral dose to OARs

The integral dose to OARs by both techniques is summarized in Table 4. IMRT plans resulted in a lower integral dose to the OARs (%, $P<0.05$) compared to 3D-CRT.

DISCUSSION

In this study, we compared two kinds of pelvic radiotherapy treatment planning for postoperative endometrial cancer. IMRT showed to have excellent conformity to PTV, thus proving it's benefit . Figure 2 shows the beam arrangements for 3D-CRT planning. Our results suggest that IMRT has more conformal PTV coverage and better sparing of OARs than does 3D-CRT. Figures 3 and 4 shows the isodose distribution for 3D-CRT and IMRT planning. These results are similar to the data of studies by Lujan AE et al and

Table 2: Summarizes the PTV coverage with 3D- CRT and IMRT techniques

Plan	Item	PTV 95 (%)	PTV 100(%)	PTV 105 (%)	PTV 110 (%)	CI	HI
3D-CRT	Mean	97	72.7	4.6	1.1	3.02	1.04
IMRT	Mean	97.2	90	14.7	4.2	5.53	1.03
	P-value	<0.001	<0.001	<0.001	0.32	<0.001	0.903

3D-CRT: Three-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiotherapy, PTV: Planning target volume, PTV95, PTV100, PTV105: PTV110-percentage of PTV receiving 95%, 100%, 105%, 110% of the prescription dose, respectively, CI: Conformity index, HI: Homogeneity index

Table 3: The DVHs of OARs by 3D-CRT and IMRT techniques

Structure	Technique	Items	V5	V10	V20	V30	V40	V45	D-mean
Bowel	3D-CRT	Mean	94.5	87.2	75.6	51.2	41.6	7.30	30.7
	IMRT	Mean	83.7	76.2	55.7	32.0	7.30	0.278	22.1
		P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Bladder	3D-CRT	Mean	100	100	99.9	99.7	97.3	36.6	44.4
	IMRT	Mean	100	100	99.9	93.1	70.9	46.8	42.4
		P-value	-	-	<0.769	<0.001	<0.001	<0.001	<0.001
Rectum	3D-CRT	Mean	100	100	100	97.3	96.9	35.1	43.8
	IMRT	Mean	100	100	100	96.2	67.4	27.7	43.2
		P-value	-	-	-	<0.001	<0.001	<0.001	<0.001

IMRT: Intensity-modulated radiotherapy, 3D-CRT: Three-dimensional conformal radiotherapy, OARs: Organs at risk, V5, V10, V20, V30, V40, and V50-percentage of organs at risk

Table 4: The integral dose to OARs by 3D- CRT and IMRT techniques

Structure	3D-CRT (mean-Gy/L)	IMRT-mean (Gy/L)	P-value
Bowel	410.43	295.89	<0.001
Bladder	37.49	35.79	<0.001
Rectum	24.02	23.7	<0.001

3D-CRT: Three-dimensional conformal radiotherapy, IMRT: Intensity-modulated radiotherapy

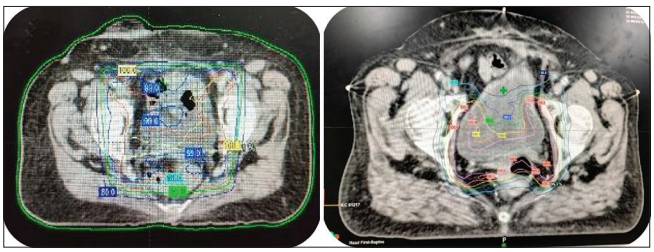

Figure 1: Typical axial dose distributions obtained with three-dimensional conformal radiotherapy, and intensity-modulated radiotherapy. The shown isodose lines included 100%, 99%, 98%, 95%, and 80 % of the dose. The planning target volume is shown in red

Roeske JC et al.[19,20] The integral dose to OARs also showed a significant decrease by IMRT technique in this study.

Aoyama et al.[21] evaluated the integral dose to normal tissue of IMRT plans for prostate cancer. They found that 6 MV-IMRT resulted in a 5.0% lower integral dose to normal tissue than 6MV-3DCRT. Similar results were observed in the publications of Hermanto et al.,[22] and Mock et al.,[23] for glioma and paranasal sinus carcinoma, although it is commonly believed that the large number of beamlets and monitor units used in IMRT leads to an increase in the integral dose to normal tissue.[24] Pirzkall et al.,[25] evaluated the effect of beam energy and number of fields on photon-based IMRT for prostate cancer. They also found that the difference in integral non-target dose was within 5% for all plans. The small difference is likely due to the balance of a greater volume of normal tissue receiving a low dose and a smaller volume receiving a high dose. D'Souza and Rosen[26] reported that the total energy deposited in a patient is relatively independent of treatment planning parameters for deep-seated targets, and the integral dose to normal tissue increases with increasing size of the anatomic region for similar tumor sizes. Whole pelvic IMRT has been reported to reduce the rate of acute[27] and chronic gastric-intestinal toxicity than conventional WPRT.[28] Heron et al. compared the conventional 3D-CRT in the adjuvant treatment of gynecologic cancer patients.[29] They showed that IMRT reduced the treatment volume for the bladder, rectum, and small bowel. The mean volume of all bowel, bladder, and rectum receiving doses in excess of 30 Gy was reduced by 36%, 66%, and 52%, respectively.

Forrest et al. compared the dose to OAR between the conventional four-field whole pelvis plan and IMRT plan for cervical cancer patients.[30] Their study demonstrated a statistically significant difference in DHI between the two plans: 1.05 (4F) versus 1.07 (IMRT). Moreover, they found a significant reduction in the mean V30, V40, V45, and V50

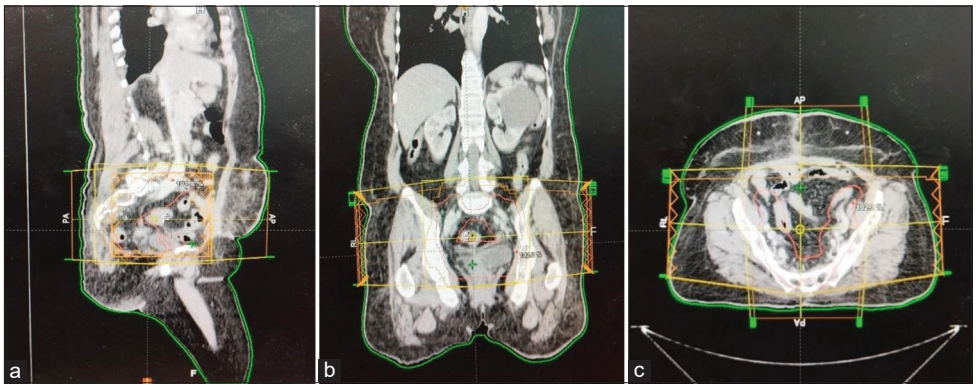

Figure 2: Beam arrangements for three-dimensional conformal radiotherapy planning, (a) coronal view, (b) sagittal view, (c) axial view

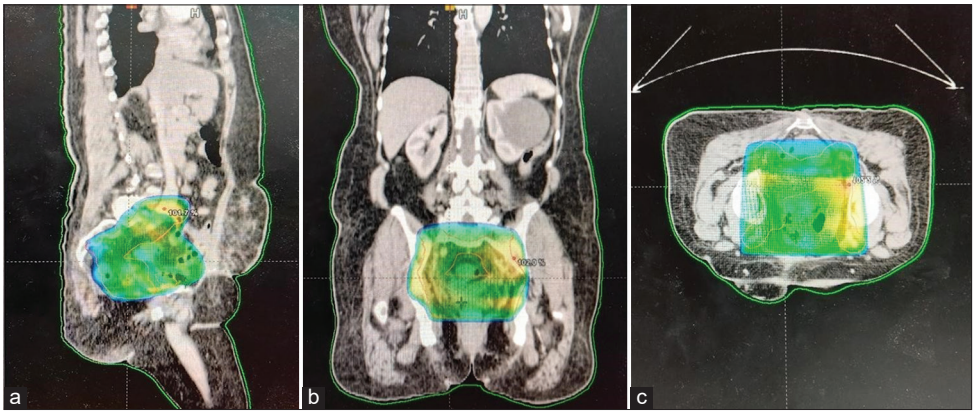

Figure 3: Isodose distributions in color wash for three-dimensional conformal radiotherapy planning; 95% isodose distribution in (a) sagittal view, (b) coronal view, (c) axial view

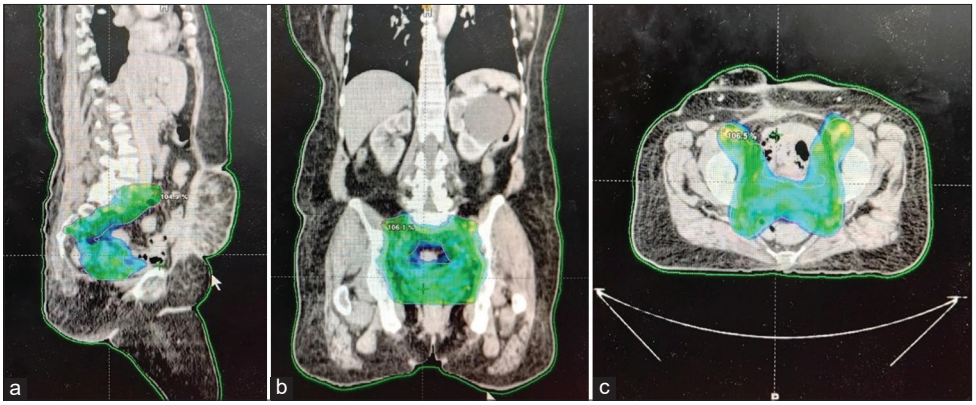

Figure 4: Isodose distributions in color wash for intensity-modulated radiotherapy planning, 95% isodose distribution in (a) sagittal view, (b) coronal view, (c) axial view

for all OARs (except V30 rectum). The minimum dose to the PTV was 2.45 Gy higher for 4F (45.91 Gy; standard deviation 3.67) compared with IMRT (43.46 Gy; standard deviation 2.65). In our study, we also found a statistically significant difference between the two plans in terms of DHI.

Although there are many studies demonstrating the clinical advantage of IMRT in gynecologic patients,[29] some concerns have been raised about the widespread application of IMRT.[14] Due to the presence of steep dose gradients and longer treatment times with IMRT, concerns remain about possible inferior tumor control. Finally, an approximate doubling of the risk of second malignancies with IMRT compared to conventional techniques has been hypothesized[14] due to increased total body dose from leakage radiation and the increased volume of tissue exposed to low-dose radiation.

There are some shortcomings of the current study. First, there is a relative lack of data on organ motion, particularly as

it relates to pelvic and abdominal structures. Organ motion and patient setup uncertainty are important considerations with conformal planning in gynecologic patients. However, the targets for adjuvant RT for gynecologic malignancies are less likely to be mobile. Because the vagina is not attached to the bladder as in the normal state, the movement as a result of bladder filling is likely significantly diminished.[31] Although no consensus planning margins for 3D and IMRT treatment have been created, a 1.0–1.5 cm (or institution-specific) uniform CTV expansion is commonly advocated. We also created the PTVs by expanding the CTV 10 mm isotropically. According to Report 50 of the International Commission on Radiation Units and Measurements,[32] PTV is defined as the volume usually created by extending CTV 0.5–1 cm, accounting for factors such as internal organ motion, set-up variation, and patient movement. Therefore, we have already given the suggested margin to compensate for the internal organ motion. Moreover, we established a treatment protocol to standardize the treatment for these patients. All the patients were treated with a comfortably full-bladder and empty rectum. During daily treatment, we evaluated digitally reconstructed radiographs for each patient by observing the bony anatomy provided by the RT. In our study, all of the structures were delineated using pelvic normal tissue contouring guidelines for radiation therapy atlas.[33] We intentionally did not outline specific loops of the bowel, but instead, we contoured the peritoneal space occupied or potentially occupied by small and large bowel from L4-5 interspace to its lowest extent in the pelvis. This methodology, as others have found, is more likely to overestimate the dose to small bowel as represented in the DVH since the probability of small bowel residing in a specific region of the pelvis is variable from day to day.[34]

CONCLUSION

In post-operative WPRT of endometrial cancer, IMRT resulted in a more conformal dose distribution and lower integral dose to OARs in comparison with 3D-CRT. The clinical significance of this dosimetric difference needs to be further investigated.

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