LOCALLY ADVANCED CERVICAL CANCER THERAPY **Original Article**

Dosimetric comparison between conventional and conformal radiotherapy for carcinoma cervix: Are we treating the right volumes?

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Abstract

Background and Purpose: Conventional portals, based on bony anatomy, for external beam radiotherapy for cervical cancer have been repeatedly demonstrated as inadequate. Conversely, with image-based conformal radiotherapy, better target coverage may be offset by the greater toxicities and poorer compliance associated with treating larger volumes. This study was meant to dosimetrically compare conformal and conventional radiotherapy. **Materials and Methods:** Five patients of carcinoma cervix underwent planning CT scan with IV contrast and targets, and organs at risk (OAR) were contoured. Two sets of plans-conventional and conformal were generated for each patient. Field sizes were recorded, and dose volume histograms of both sets of plans were generated and compared on the basis of target coverage and OAR sparing. **Results:** Target coverage was significantly improved with conformal plans though field sizes required were significantly larger. On the other hand, dose homogeneity was not significantly improved. Doses to the OARs (rectum, urinary bladder, and small bowel) were not significantly different across the 2 arms. **Conclusion:** Three-dimensional conformal radiotherapy gives significantly better target coverage, which may translate into better local control and survival. On the other hand, it also requires significantly larger field sizes though doses to the OARs are not significantly increased.

Key words: Conventional radiotherapy, conformal radiotherapy, carcinoma cervix, dosimetric comparison

Introduction

Carcinoma cervix is the commonest cancer in females in the developing world, and radiotherapy is the cornerstone of treatment of cervical cancer at all stages. The history of radiotherapy for cervical cancer is a rich and successful one. The bulk of data on radiotherapy for cervical cancer is gleaned from studies based on traditional X-ray-based simulation on bony anatomy, though at present, the focus has shifted to conformal radiotherapy. This has necessarily created a demand for proper guidelines for tumor delineation, and much important work has been published in this regard of late. Guidelines for contouring of the pelvic lymph nodal stations have already been published by the RTOG. While these guidelines have been derived from a variety of imaging modalities, in practice, conformal radiotherapy in cervical cancer requires contouring on axial CT slices, which have their own limitations in structure delineation. For one, the cervix itself and the vagina are poorly visualized on CT, and contouring of the gross tumor volume presents a challenge-fusion with MRI is often resorted to, especially for image-guided brachytherapy, but for external beam radiotherapy, the variability of bowel and bladder filling and organ motion make accurate fusion difficult. On the other hand, estimation of the PTV margin can be exaggerated due to the same uncertainties. What this means is that very often, while contouring for conformal RT in cervical cancer, we tend to err on the side of caution, and the resulting treatment volumes are significantly larger than would have been the case for conventional radiotherapy.

This study is not meant to opine on the success or failure of the recent contouring guidelines-multiple studies are ongoing worldwide based on the same, and only the long-term clinical data from these studies, when available, can tell us the answer. The potential dosimetric advantages of better target coverage may well be offset by the greater toxicities and poorer compliance associated with treating larger volumes, especially as concurrent chemotherapy is now a standard of care. For the moment, it is important to record the dosimetric differences between conformal and conventional radiotherapy, and this is what this small study intends to do.

Materials and Methods

Five patients of biopsy-proven carcinoma cervix in stage IIIB with moderate anteroposterior (20-25 cm) and lateral (25-30 cm) separations were taken up for the study. All patients were positioned supine without thermoplastic

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mould, with knee rest for immobilization and underwent planning CT scan with IV contrast, taking 3 mm thickness slices. Fiducials were placed at the expected isocenter, approximately halfway between the umbilicus and the symphysis pubis in the midplane.

After imaging, contouring was done based on clinical findings for the primary and standard RTOG guidelines for the pelvic nodes. The primary and nodal CTVs were fused, and expansions of 1 cm in craniocaudal and 0.7 cm in other directions were given to arrive at the final PTV.

All patients were planned on the PLATO Sunrise (v. 2.7.7) planning system (Nucletron BV). For each patient, two sets of plans were generated. Each patient was treated by 4-field technique, using appropriate energies (6 MV or 15 MV). The prescribed dose was 50 Gy/25# to the PTV (for conformal plans) or to the isocenter (for conventional plans). Corner blocks were placed in the AP/PA fields for all patients, using MLCs for the conformal plans and traditional 5 HVL blocks for the conventional plans.

Conformal plans were generated for optimal PTV coverage ensuring that 95% of the PTV received 95% of the prescribed dose and that no part of the PTV received more than 107% of the prescribed dose. Isocenter was placed at the fiducials, and asymmetric fields were generated. Dose was normalized at a separate dose normalization point. Subsequently, the field sizes were recorded, and the dose volume histograms (DVHs) were analyzed for PTV coverage and sparing of the organs at risk (urinary bladder, rectum, small bowel, femoral heads).

For the conventional plans, the isocenter was placed at the fiducials, and asymmetric fields were generated based only on the bony digitally reconstructed radiograph (DRR) akin to X-ray simulator-based planning, placing the borders according to tradition as follows:

- Upper border → L4-L5 interspace
- Lower border → lower border of obturator foramen or inferiorly extended to ensure adequate coverage of vaginal disease (radio-opaque marker placed) extension with proper margins
- Lateral border →2 cm from pelvic brim
- Anterior border → at anterior cortex of symphysis pubis
- Posterior border → at S2-S3 junction.

Dose was prescribed at the isocenter, and beams were weighted equally as is done for conventional planning. Field sizes were recorded. Subsequently, the volumes of interest (VOIs) were turned on in the TPS, and DVHs were again analyzed for target coverage and OAR sparing.

The two sets of plans were compared on the basis of PTV coverage and OAR sparing. The field sizes and definitions were also compared to analyze how far the conformal field arrangement matched the conventional one.

Data was analyzed on the SPSS software (v13.0). The 2 sets of plans were compared using the Wilcoxon matched pairs signed-ranks test.

Results

Field sizes used for the 3DCRT plans were significantly larger than those used for the conventional plans ($P = 0.043$ for AP fields and $P = 0.042$ for lateral fields). Field sizes for AP field ranged from 19.6 × 20.8 cm^2 to 17.2 × 21 cm^2 in the 3DCRT arm, whereas it was between 13.6 × 16.8 cm^2 and 16.9 × 19.4 cm^2 in the conventional arm. Field sizes for the lateral field ranged from 15.4 × 17.7 cm^2 to 14.1 × 21 cm^2 in the 3DCRT arm, whereas it was between 13.5 × 19.5 cm^2 and 10.7 × 19.5 cm^2 in the conventional arm [Table 1].

Target coverage was significantly improved using 3DCRT as compared to conventional RT ($P = 0.043$ for dose to 95% of PTV). [Table 2]

On the other hand, dose homogeneity within the PTV was not significantly better with 3D CRT ($P = 0.08$ for average dose to the PTV) [Table 2].

Doses to the organs at risk (rectum, urinary bladder, and small bowel) were not significantly different across the 2 arms. Doses to the rectum were not significantly higher for the 3DCRT arm as compared to the conventional arm ($P = 0.225$ for dose to 25% of rectum and $P = 0.138$ for average rectal dose) [Table 3].

Doses to the urinary bladder were not significantly higher for the 3DCRT arm as compared to the conventional arm ($P = 0.5$ for dose received by 25% of urinary bladder and $P = 0.138$ for average dose received by urinary bladder) [Table 3].

Doses to the small bowel were not significantly higher for the 3DCRT arm as compared to the conventional arm ($P = 0.893$ for average dose received by small bowel) [Table 3].

Discussion

Even with the advent of 3DCRT, the standard of care in carcinoma cervix radiotherapy remains the 4-field box

Table 1: Relative field sizes

Patient no	AP (cm)		Lateral (cm)	
	3D (X*Y)	Conventional (X*Y)	3D (X*Y)	Conventional (X*Y)
1	17.5*20.2	13.6*16.8	14.6*20.3	12.1*16.8
2	19.2*19.8	16*18.4	14.4*20	12.9*18.4
3	19.6*20.8	16.9*19.4	14.9*21	10.7*19.5
4	17.2*21	15*19.7	14.1*21	12.9*19.7
5	19.2*17.7	15.1*19.5	15.4*17.7	13.5*19.5

Table 2: PTV coverage

Patient no	PTV 95% (cGy)			PTV average (cGy)		
	3D	Conventional	*P*	3D	Conventional	*P*
1	4893	4183	0.043	4998	4850	0.08
2	4796	4473		4952	4868	
3	4928	4306		5035	4928	
4	4861	4817		5026	5012	
5	4937	4912		5059	5066	

PTV 95%=Dose received by 95% of the planning target volume,
PTV average=Average dose to the planning target volume

Table 3: OAR sparing

Pt no	Dose to 25% of rectum (cGy)			Average rectum dose (cGy)			Dose to 25% of urinary bladder (cGy)			Average urinary bladder dose (cGy)			Average small bowel dose (cGy)		
	3D	Conventional	*P*	3D	Conventional	*P*	3D	Conventional	*P*	3D	Conventional	*P*	3D	Conventional	*P*
1	4979	5055	0.225	4497	4626	0.138	4987	5012	0.5	4950	4970	0.138	2567	2238	0.89
2	5012	5045		4870	4998		4977	4959		4962	4943		2270	2536	
3	4981	4990		4793	4836		5008	5007		4876	4967		3528	2853	
4	4973	4948		4943	4891		4861	4878		4773	4850		4389	4660	
5	5016	5017		4834	5000		5148	5159		5116	5124		3970	4727	

OAR=Organs at risk, Pt no=Patient no

arrangement. Conventional portals based on bony anatomy as seen on X-ray simulation, used for pelvic irradiation in carcinoma cervix, have been repeatedly demonstrated to be inadequate in comprehensive nodal coverage. Earlier studies were based on intra-operative and lymphangiographic studies.[1-6] Greer *et al*.,[3] in their lymphangiographic study found that in 87% of the patients, the common iliac nodes were located proximal to the L5-S1 bifurcation, the conventional upper border of the pelvic portals and recommended that if coverage of the common iliac nodes is desired, the upper border should be moved to the L4-L5 junction. In an intra-operative study using surgical clips, McAlpine *et al*.[4] recommended that the superior border would need to be even higher at the L3-L4 junction to properly cover the common iliac nodes and also discovered that 26% of patients would have inadequate lateral coverage on the AP/PA portals. Other lymphangiographic studies by Zunino *et al*.[1] and Bonin *et al*.,[6] on the other hand, found that lateral coverage of the external iliac nodes was insufficient on the AP/PA portals and recommended going 2.5 cm and 2.6 cm, respectively, beyond the pelvic brim. Pendlebury *et al*.[5] also found that 62% of patients required alteration of the conventional pelvic portals based on lymphangiographic findings, with most requiring enlargement of one/more portals while in 20% patients, portals could actually be reduced. They found that the lateral border of the AP/PA portals and the anterior border of the lateral portals were most often inadequate and recommended 2.5 cm margin from the pelvic brim for the former and 0.5 cm margin anterior to the symphysis pubis for the latter so as to cover 90% of the pelvic nodes.

With the advent of CT simulation, it is possible to identify and contour the pelvic blood vessels, and these can then be used as surrogates for localizing the adjacent lymphatics and lymph nodes.

Using non-contrast CT images, a study by Finlay *et al*.[7] found that had conventional portals alone been used for radiotherapy planning, the majority (95.4%) of subjects would have had at least one inadequate margin, the majority located superiorly though in around half the subjects, at least one margin would have been generous (>2 cm beyond the blood vessel), usually the lateral borders of the AP/PA portal.

Different studies have come up with different recommendations regarding how far the actual lymphatic structures are located relative to the blood vessels. In one study based on pelvic lymphangiograms, Chao and Lin[8] recommended at least 1.5 cm margin around the common iliac and 2 cm around the external iliac vessels, to cover the majority (82.3%) of pelvic nodes. On the other hand, in a recent study by Tayor *et al*.,[9] using MRI imaging after injection of the novel contrast agent USPIO (ultra small super paramagnetic iron oxide), observed that 7 mm expansion beyond the blood vessels allowed coverage of 97% of the pelvic lymph nodes.

Although outcome of carcinoma cervix treated by radiotherapy are quite satisfactory in early-stage disease and have also been greatly improved beyond the historical 30-40% survival rate for advanced-stage disease also, by addition of concurrent chemoradiation, it is still likely to be further improved by superior delineation and coverage of the pelvic lymph nodes. Geographic miss of the pelvic lymph nodes has serious consequences, especially in advanced-stage disease. In a study by Beadle *et al*.,[10] it was found that the majority (66%) of pelvic nodal failures were marginal; 71 out of 119 patients recurred above the treatment field, 2 had inguinal nodal failures while 2 other patients had recurrences both above the treatment field and in the inguinal lymph nodes. This was one of the first studies to correlate the site of regional recurrence with respect to the treatment portals.

In our study, use of CT simulation allowed superior visualization of the pelvic lymph nodes and improved the PTV coverage, mainly by reducing the chances of geographical miss to a minimum. This may translate into superior loco-regional control and even superior survival.

Concurrently, large field sizes were called for, which could have led to inferior sparing of the organs at risk. However, this was not the case, even with this simple beam arrangement, chiefly because, just as PTV coverage is improved by nodal visualization, so also is the OAR sparing, allowing much tighter blocking than would be deemed safe in terms of disease control for conventional planning.

Conclusion

Three-dimensional conformal radiotherapy gives significantly better PTV coverage, which may translate into better local control and survival. On the other hand, it also requires significantly larger field sizes though doses to the OARs are not significantly higher compared to the conventional plans. Thus, the improved delineation of the target, especially pelvic nodes, and the improved target coverage make 3DCRT an attractive tool. However, it remains to be seen whether this will have a clinical benefit given that the toxicity profile of 3DCRT is no better than conventional RT.

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