

Original Research Article

A study to evaluate the adequacy of pelvic lymph node coverage in carcinoma cervix patients in Indian population by conventional four field box technique using computerized tomography simulation based pelvic lymph node contouring

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ABSTRACT

Background: Traditionally pelvic External Beam Radiotherapy is delivered with four field box technique in carcinoma cervix patients. The primary aim of this prospective observational study is to determine the adequacy of pelvic lymph nodal coverage by conventional Four Field Box Technique with the help of pelvic lymph node contouring by CT simulation.

Methods: Between January 2013 and August 2015 sixty patients with biopsy proven Carcinoma Cervix were enrolled in this study. Of these fifty-three patients were available for final analysis. CT simulation based Pelvic lymph node contouring was done for each patient. Then two External Beam Radiotherapy plans were generated, one contoured based and the other based on bony landmark based Four Field Box Technique. The number of patients whose contoured lymph nodes lies partly outside the field borders of the bony landmark-based plan and also its extent was determined. D90 of various groups of pelvic lymph nodes obtained from both the plans were compared using 'paired sample t - test'.

Results: It was seen that with Four Field Box Technique there is inadequate coverage of common iliac lymph nodes in 34/53 patients. The difference between the mean D90 of common iliac lymph nodes in two sets of plans was found to be statistically significant.

Conclusions: Pelvic field planning should be individualized. CT simulation-based radiotherapy planning should be done for each individual patient to adequately cover the nodal microscopic disease.

Keywords: CT simulation, Four field box technique, Pelvic lymph node contouring

INTRODUCTION

Carcinoma of the uterine cervix is the one of the leading sites of primary cancer among Indian women. Although in developed countries, the incidence has declined, it remains a major health problem in developing countries,

where no clinically significant reduction in the incidence of cervical cancer has occurred during the past three decades. Moreover, due to lack of proper screening facilities, poverty and ignorance most of the patients present to us in locally advanced stages. Cervix has a rich lymphatic drainage. The cervix and upper vagina drain

laterally to the parametrial, obturator, and external iliac nodes and posteriorly along the uterosacral ligaments to the sacral nodes.¹ Drainage from these primary lymph node groups is upward along the infundibula-pelvic ligament to the para-aortic nodes. Incidence of pelvic and para-aortic lymph node involvement correlates significantly with stage, local volume of the disease and depth of invasion.

Radiotherapy is one of the most important components of treatment of carcinoma cervix. Commonly radiotherapy is delivered by conventional Four Field Box Technique.

Multiple investigators have demonstrated that such an approach may inadequately treat the target tissues. For adequate tumor control in cases of invasive carcinoma cervix, it is important to deliver adequate doses of irradiation not only to the primary tumor but also to the pelvic lymph nodes. With the advent of conformal radiotherapy, several authors have published guidelines emphasizing imaging methods to more accurately define target volumes, including lymph nodes.^{2,3}

The primary objective of this observational study is to evaluate adequacy of pelvic lymph nodal coverage by four field box technique based on bony landmark and at the same time to compare D90 of Clinical Target Volume of each group of lymph nodes using bony landmark based plan with that using contoured lymph node based plan.

METHODS

This is a single institution prospective observational study carried out in the department of Radiotherapy, Medical College Hospitals, Kolkata between January 2013 - August 2015.

Inclusion criteria

- All patients aged between 18 - 70 years with biopsy proven carcinoma cervix attending our radiotherapy outpatient department are eligible for this study.

Exclusion criteria

- FIGO stage IA and IVB
- Evidence of para - aortic nodal involvement as detected on diagnostic CT scan
- History of total hysterectomy or other pelvic or abdominal surgery
- History of radiation therapy for any other reasons
- Uncontrolled comorbid conditions
- Pelvic Inflammatory Disease are excluded from the study.

Sixty biopsy proven cases of carcinoma cervix attending radiotherapy outpatient department during the stipulated time and fulfilling the inclusion criteria of the study are selected for the study. The sample size is based on number

of patients attending radiotherapy outpatient department as per the current epidemiological trends.

Detailed history, physical examination and staging work up of each patient was done. The pros and cons of entering into this study were explicitly explained to them in a language they understood best and they were registered for the study only after they agreed to give informed consent.

Each patient underwent CT simulation before the start of radiation in Philips CT simulator machine (Brilliance CT 16-slice configuration, Philips Health Care). For CT simulation Thermoplastic immobilization device was used to immobilize the lower abdomen and pelvis of the patient. CT simulation was done on flat top couch in supine position with intravenous contrast and appropriate placement of radio-opaque fiducials oriented with machine lasers. Inferior extent of vaginal disease was marked with radio-opaque marker. Intravenous contrast agent used here was Inj. Iohexol in recommended dosage schedules and with preparations to manage hypersensitivity reactions according to the ACR (American college of radiology) manual on contrast media.^{4,6} CT slices were obtained from the level of first lumbar vertebrae to mid-thigh with 3 mm slices. Bladder filling protocol as practiced in institute was followed for each patient. Local quality control assurance of radiation procedures was performed by a radiation oncologist and a medical physicist at each site. The various groups of pelvic lymph nodes were first contoured according to RTOG contouring guidelines (including modification by Taylor et al) on contrast enhanced CT simulation images.^{3,7} 1 cm. margin was added around any grossly involved lymph node. A plan was generated for each patient covering all the contoured lymph nodes with Pinnacle Treatment Planning System. Another plan was generated using the same software but using the bony landmark based Four Field Box technique. The bony landmarks used for the conventional four field technique here were:

Superior border of the AP-PA field and lateral field: L4-L5 vertebral body interspace. L3-L4 junction was taken when common iliac lymph node coverage was indicated.

Inferior border of the AP-PA field and lateral field: inferior border of obturator foramen (in case of vaginal extension the border was 3 cm. below obvious vaginal disease as indicated by radio-opaque marker in CT simulation images).

Lateral border of the AP-PA field: 1-1.5 cm. beyond lateral border of pelvic brim. Anterior border of lateral field: 1 cm. anterior to symphysis pubis.

The posterior margin of lateral field: Usually is designed to cover at least 50% of the rectum in stage IB tumors, and it is extended to the sacral hollow in patients with

more advanced tumors to adequately cover the uterosacral ligaments.

Dose was prescribed covering the target volume delineated by above-mentioned bony landmarks. Now, the borders of the contoured pelvic lymph node groups were compared with the field borders of the bony landmark-based plan - whether they were adequately included within the borders or not. Perpendicular distance between the borders of the contoured lymph nodes and the respective field borders was measured in cases where contoured lymph nodes remained outside the borders of bony landmarks-based plan. Then the distances were analyzed by appropriate statistical methods.

Another plan was generated adequately covering all the contoured lymph nodes. The D90 (i.e. dose received by 90%) of each respective group of lymph nodes in the bony landmark-based plan and that in the contoured lymph node-based plan are compared using Dose Volume Histogram in Pinnacle software. This is purely an observational study and the treatment of the patients was allowed to follow the protocols of our institution. For comparing D90 in bony landmark-based plan and in contour-based plan for each respective group of lymph nodes, 'paired sample t-test' was used. For continuous variables, 95% Confidence Intervals and p value <0.05 were considered significant. All reported p values are 2 tailed. Workflow of the entire procedure is depicted in Figure 1.

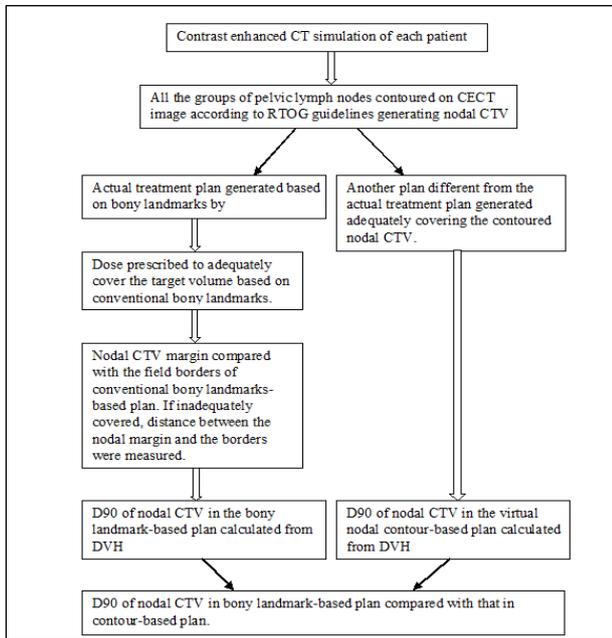


Figure 1: Flowchart of study technique.

RESULTS

Initially, sixty patients were enrolled for the study. Of these, five patients did not turn up for treatment and two more patients were excluded from the study due to noncompliance with study protocol, refusal to undergo

contrast enhanced CT scan. Patient demography is depicted in Table 1.

Table 1: Patient demography.

Characteristics	Frequency	%	
Age	Less than equal to 50 years	25/53	47.2
	More than 50 years	28/53	52.8
	Median	51 years	
Menstrual status	Premenopausal	16/53	30.2
	Postmenopausal	37/53	69.8
Parity	Less than equal to 2	18/53	33.9
	3 - 4	25/53	47.2
	More than 4	10/53	18.9
FIGO stage	IIB	27/53	50.9
	IIIA	06/53	11.3
	IIIB	19/53	35.9
	IVA	01/53	1.9
Histology	Squamous	46/53	86.8
	Adenocarcinoma	04/53	7.5
	Adenosquamous	02/53	3.8
	Clear cell	01/53	1.9
Grade	I	18/53	33.96
	II	31/53	58.5
	III	04/53	7.54

Adequacy of lymph node coverage

It was seen that all the borders of the conventional four field box technique adequately covered the respective pelvic lymph nodes except the superior border. The conventional superior border was inadequate to cover the common iliac lymph nodes in 34 of the 53 patients (64.2%). Of the 44 patients in whom L4-L5 vertebral body inter space was taken as the upper bony landmark, 31 had inadequate common iliac node coverage (70.46%); whereas even among the 9 patients in whom L3-L4 was taken as the superior landmark to account for gross common iliac node involvement, 3 had inadequate coverage of the entire common iliac group (33.33%). Overall, 64.15% (34/53) patients had inadequate coverage. These data on inadequacy of coverage of common iliac nodes by conventional bony landmark-based radiation portals are summarized in Table 2.

Table 2: Frequency distribution of inadequacy of common iliac node coverage by superior border of conventional fields.

	Total no. of patients	No. of inadequate	Percentage
Superior border at L4-L5	44	31	70.46
Superior border at L3-L4	9	3	33.33

Lengths of contoured common iliac lymph nodes remaining outside the borders of bony landmarks were measured for each patient with inadequately covered nodes. Median of the lengths was found to be 2.8 cm. for patients with L4-L5 inter space as the superior landmark; median of the same for patients with L3-L4 inter space as superior landmark was 0.8 cm (Table 3).

Dosimetric comparison of bony landmark-based plan and nodal contour-based plan

D90 (i.e. dose received by 90% of the volume) of each respective group of lymph nodes was measured for bony landmark based plan as well as for nodal contour based plan (which adequately covers the lymph nodal CTV)

from Dose Volume Histogram and plotted in a scatter diagram. D90 of common iliac group of lymph nodes with L4 - L5 as superior border and that with L3 - L4 as superior border is given in Figure 2 and 3 respectively. D90 of internal iliac, external iliac and obturator nodes is given in Figure 4 and D90 of presacral group of nodes is given in Figure 5. The dose is expressed as a percentage of prescribed dose.

In cases with L4-L5 as superior border, mean D90 of common iliac lymph nodes in bony LANDMARK-BASED plan was 78.68% of prescribed dose, whereas the same in nodal contour-based plan was 96.6% of prescribed dose for that subset of patients.

Table 3: Pattern of lymph node miss with conventional bony landmark-based technique.

Bony landmark of conventional radiation portal	No. of patients with inadequate coverage (%-age of all cases)	Length of contoured lymph nodes remaining outside superior border of bony landmarks (cm.)	
		Median	Range
Superior border at L4-L5	31 (70.46)	2.8	1.4-4.1
Superior border at L3-L4	3 (33.33)	0.8	0.6-1.2

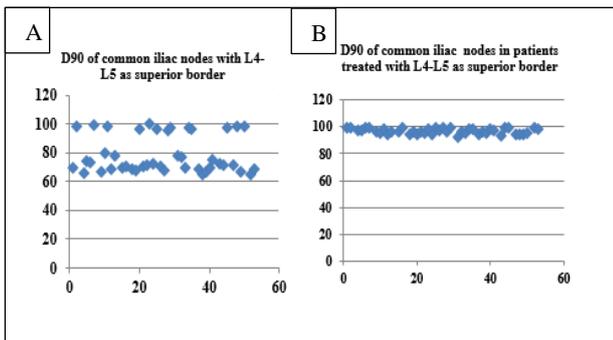


Figure 2: Scatter diagrams comparing D90 of common iliac lymph nodes L4-L5 as superior border in A) bonylandmark-based plan and B) nodal contour-based plan.

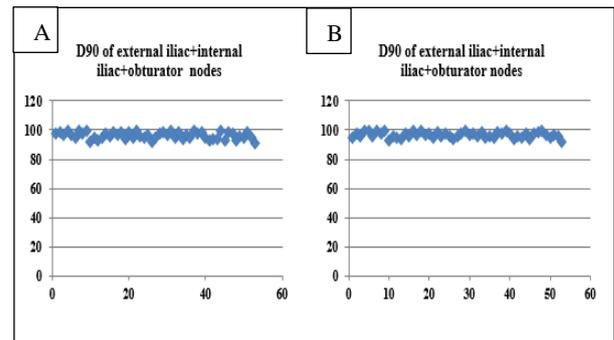


Figure 4: Scatter diagrams comparing D90 of internal iliac, external iliac and obturator group of pelvic lymph nodes in A) bony landmark based plan and B) nodal contour based plan.

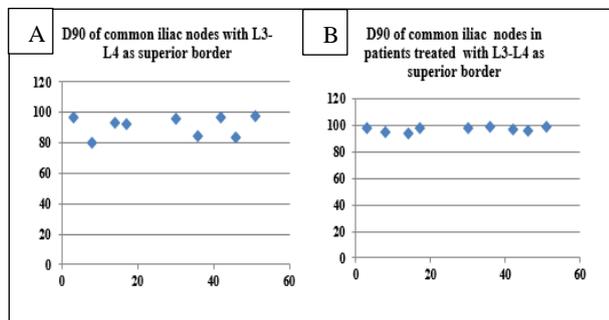


Figure 3: Scatter diagrams comparing D90 of common iliac lymph nodes L3-L4 as superior border in A) bony landmark based plan and B) nodal contour based plan.

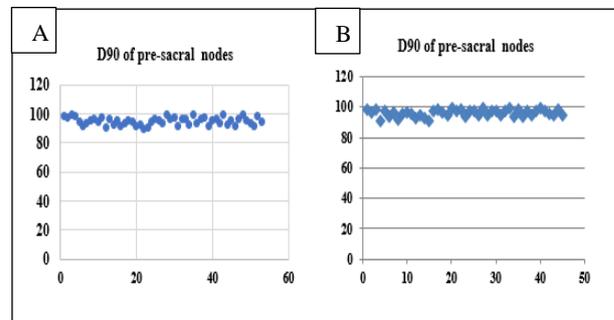


Figure 5: Scatter diagrams comparing D90 of presacral group of pelvic lymph nodes in A) bony landmark based plan and B) nodal contour based plan.

The difference as calculated by Paired t-test was statistically significant (p-value <0.0001). Similarly, in cases with L3-L4 as superior border, mean D90 of common iliac lymph nodes in bony landmark based plan

was 91.14% of prescribed dose, whereas the same in nodal contour based plan was 96.93% of prescribed dose; even here the difference was statistically significant (p-value= 0.023) (Table 4).

Table 4: Dosimetric comparison of Bony landmark-based plan and Nodal contour-based plan.

Lymph node groups	Plans	D ⁹⁰				
		Mean	N	Std. deviation	Std. error mean	p-value (2-tailed)
Common iliac with L4-L5 as superior border	Bony landmark based	78.67509	44	12.941129	1.950949	<0.0001
	Contour based	96.60420	44	1.945965	0.293365	
Common iliac with L3-L4 as superior border	Bony landmark based	91.14200	9	6.677908	2.225969	0.023
	Contour based	96.92956	9	1.622367	0.540789	
External iliac+ internal iliac+ obturator	Bony landmark based	96.20087	53	2.475669	0.340059	0.080
	Contour based	96.59766	53	2.013493	0.276574	
Pre-sacral	Bony landmark based	94.84323	53	2.605801	0.357934	0.786
	Contour based	94.34223	53	13.408476	1.841796	

DISCUSSION

Radiotherapy is used as primary treatment for locally advanced cervical cancer and adjuvant therapy for early disease in many countries. Conventional pelvic fields planned on bony landmarks as indication of lymph node location have been used for several decades. Although the concurrent chemoradiotherapy has recently improved their curative effect to a certain extent, locoregional relapse rates still remain high, especially in pelvic lymph node regions.^{8,9} Optimization of radiation field parameters to improve the cure is crucial.

It was found that an optimal external irradiation to prevent the locoregional relapse required an adequate coverage of pelvic lymph nodes.¹⁰

However, in most cases conventional pelvic fields based on bony landmarks could not provide adequate coverage.

Finlay et al assessed the adequacy of nodal coverage of conventional pelvic radiotherapy fields in 43 cervical cancer patients.¹¹ Pelvic vessels were contoured using CT simulation and used as surrogates for the pelvic lymph nodes.

In 95.4% patients, conventional fields inadequately covered various lymph node groups. In 56% patients, conventional fields and blocks were found to be too generous. In another study conducted on 100 Chinese patients, Xiang Zhang et al, contoured pelvic vessels to evaluate the adequacy of lymph node coverage by conventional pelvic fields based on bony landmarks.¹²

The distance between the conventional field borders and various vessel contours was measured. All patients had at

least one inadequate margin, 97 patients (97.0%) had two, and 22 patients (22.0%) had all the three. Zunino S et al, similarly used three dimensional imaging and found that conventional field and blocking may result in inadequate target coverage in up to 50% of patients, particularly with the placement of the posterior field border of the lateral pelvic field at S2-S3.¹³ Lymph nodes are located along the vessels, especially arteries, so McAlpine et al, placed clips at the bifurcation of the common iliac arteries and the junctions of the deep circumflex vein and the external iliac vein by surgery in 100 patients.¹⁴

They performed an abdominal X-ray examination for each patient postoperatively and compared the conventional pelvic fields with the position of the clips shown on these films. It was demonstrated that a part of common iliac lymph nodes in 39 patients (39%) were out of the radiation fields, and 26% of the patients had inadequate coverage of one or both of the lateral boundaries of pelvic radiation.

In the current study it was seen that overall, in 34/53 (64.15%) patients, the superior border of conventional field did not adequately cover the upper common iliac lymph node group.

On subset analysis, 31/44 (70.46%) patients had inadequate coverage of the common iliac group of lymph nodes when L4-L5 inter space was taken as superior border. Even when L3-L4 inter space was taken as the upper bony landmark, 3/9 (33.33%) patients had inadequate coverage of the common iliac group.

All the other groups of pelvic lymph nodes were seen to be adequately covered by the borders of the conventional

portals. Hence, by using CT simulation, authors confirmed that the conventional radiation fields usually did not have adequate coverage of pelvic lymph nodes, and the inadequate coverage was located at common iliac lymph nodes.

For the common iliac lymph node group, the mean D90 in the conventional plan was 78.68% (D90 is expressed as a percentage of prescribed dose) in patients with L4-L5 as superior bony landmark and 91.14% in those with L3-L4 as superior landmark, whereas the mean common iliac lymph node group D90 in the contour based plan in the two groups of patients were 96.6% and 96.93% respectively. The differences in the mean D90 between the two plans were statistically significant.

The difference in mean D90 between bony landmark-based plan and nodal contour-based plan for other groups of lymph nodes, i.e. external iliac+ internal iliac+ obturator groups and pre-sacral group was not statistically significant.

Limitations of the study was the findings of this study are not conclusive as a result of the small sample size which is a major drawback of this study. Further large multicentric trials are required to establish the use of CT simulation for planning pelvic radiotherapy fields in Indian patients with carcinoma cervix.

Also, the use of more liberal superior borders may result in more radiation related toxicities, especially Gastrointestinal adverse effects. Authors did not address this particular issue as clinical outcomes were beyond the purview of this essentially dosimetric study.

CONCLUSION

Based on the observations of the study, it may be concluded that conventional radiation portals based on bony landmarks are inadequate in treating the nodal target volume in cases of carcinoma cervix. Pelvic field planning should be individualized for each patient. CT simulation may be done to contour pelvic lymph nodes and consequently plan radiation fields for each individual patient to adequately cover the nodal microscopic disease.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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