Original Article

Clinical significance of geographic miss when using conventional four field radiotherapy technique in treatment of locally advanced carcinoma cervix

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Abstract

BACKGROUND: Although conventional four- field radiotherapy based on bony landmarks has been traditionally used, areas of geographical miss due to individual variation in pelvic anatomy have been identified with advanced imaging techniques. **AIMS:** The primary aim of this study is to evaluate the geographical miss in patientswhen using the conventional four-field planningplanning and to find out the impact of 3-D conformal CT based in patients with locally advanced carcinoma cervix. **MATERIALS AND METHODS:** In 50 patients, target volume delineation was done on planning computed tomography (CT) scans, according to guidelines by Taylor *et al.* Patients were treated with modified four field plan, except for the superior, where field border was kept at L4-L5 interspace A dosimetric comparison was done between the conventional four-field based on bony landmarks and the target volume delineated on computed tomography. The disease free survival, pelvic and para aortic nodal free survival, distant failures free survival were calculated using Kaplan Meir Product Limit Method. **RESULTS:** Patients were followed-up for a median period of 11 months. The median V95 for conventional and modified extended four field plans were 89.4% and 91.3% respectively. Patients with V95 for modified extended pelvic fields less than 91.3% had a trend toward inferior disease free survival (mean DFS 9.8 vs. 13.9 months) though the difference was not statistically significant log rank test. **CONCLUSIONS:** Our preliminary data shows trend toward lower DFS in patients with inadequate target volume coverage. We recommend routine use of CT based planning for four field technique.

Key Words: Carcinoma cervix, four field technique, geographic miss

Introduction

External beam radiotherapy (EBRT) with concurrent chemotherapy followed by brachytherapy is the treatment of choice in patients with locally advanced cervical cancer. EBRT portals includethe whole pelvis, whereas, the central disease (cervix, vagina and medial parametria) is further boosted by intracavitary brachytherapy. Conventionally EBRT is delivered using a four field box technique defined on bony landmarks. Over the past decade, the increased use of sectional imaging has raised doubts over adequate coverage of the taget volume by the conventionally defined radiation portals.

Studies have shown that wide anatomical variation including varying levels of aortic bifurcation, altered sacral curvature and varying course of pelvic vessels may occur which may result in a geographical miss of the target with conventional portals defined on the basis of bony landmarks.[1-3]

With the advent of conformal techniques like three-dimensional (3D) conformal radiotherapy and intensity modulated radiotherapy, the issue of proper delineation of target volume has assumed utmost importance. Significant inter and intra observer variations have been found in image segmentation, which can have a significant impact on dose reporting as well as outcome.[4] As a result, several authors have attempted to formulate a set of guidelines for target delineation. At the time of inception of this study, a literature review identified two guidelines, one by Taylor *et al*. and the other by Small *et al*. regarding the delineation of pelvic nodal clinical target volume (CTV).[5,6] Both authors recommend pelvic vessels with a margin of 7 mm as a surrogate for nodal CTV delineation. Although Small *et al*. have recommended that the Common Iliac nodal volume should be delineated from 7 mm below the L4-L5 interspace to the level of bifurcation of common iliac into external and internal iliac arteries, Taylor *et al*. have recommended that common iliac nodal CTV should be delineated from the level of bifurcation of aorta up to the common iliac artery bifurcation.

In addition, the external iliac nodal volume delineation according to Small *et al*. is recommended to be taken from the level of bifurcation of common iliac artery to the level of superior aspect of the femoral head with 7 mm margins around vessels, while Taylor *et al*. recommends 7 mm margin around vessels and extending the anterior border by 1 cm anterolaterally along iliopsoas muscle, to cover outlying group of external iliac lymph nodes.

No formal comparisons are available between outcomes when patients are treated with these different volume delineation guidelines. Furthermore, using the guidelines by Taylor *et al*., target volume delineation may result in a much larger irradiated volume than that seen in conventional planning, which can potentially increase the normal tissue toxicity. In the absence of data showing the superiority of volumetric planning in terms of local control and survival, integration of volumetric planning in routine practice needs to be evaluated in resource constrained settings due to the increased cost and manpower requirements. This study was designed with an aim to estimate the inadequacies in target volume coverage when using traditional bony landmarks based planning compared with volumetric planning.

Materials and Methods

A total of fifty previously untreated biopsy proven patients of carcinoma cervix Stage II-III seen at our institute were included in the study from January to December 2009. A baseline work up done for all patients which included a complete blood count, assessment of renal function, HIV status and an X-ray chest to rule out lung metastasis. After a thorough clinical examination, the patients were planned for external radiotherapy with 3-D conformal technique. Patients age ranged from 32 to 75 years (median 55 years) and 32 patients (64%) belonged to Stage IIB and 18 (36%) were of Stage IIIB. All patients were

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planned for radical radiation 46 Gy/23#/4.5 weeks and 78% of patients received concomitant chemotherapy with weekly cisplatin at a dose of 40 mg/m^2. After EBRT, all patients received intracavitary brachytherapy.

CT simulation and treatment planning

All patients underwent a planning computed tomography (CT) acquired on the CT simulator Light Speed; VFX-16 (GE Health Care Ltd, Waukesha, WI, USA). Computed tomography (CT) simulation was performed for all patients after oral, rectal and IV contrast for proper delineation of target volume. Slices were taken from T12 to L1 level up to the level of the lesser trochanter of the femur, with the slice thickness of 3.75 mm. Patients were excluded if they had positive paraaortic nodes (nodes enlarged >1 cm). Patients with significantly enlarged lymph nodes were treated with IMRT with simultaneous integrated boost to the involved lymph nodes.

The contouring was done on Advantage Sim Workstation 4.3 (GE Health care Ltd, Waukesha, WI, USA). The primary tumor, along with the whole uterine corpus, cervix, upper third of the vagina and parametrium were included in the (CTV tumor) of the tumor. The nodal CTV included the presacral, obturator, external and internal iliacs and common iliac lymph nodal groups (CTV nodal). Nodal CTV was delineated from the bifurcation of the aorta and according to the atlas by Taylor *et al*. as an aid for target volume definition of the pelvic nodal regions.[5] Furthermore, the organs at risk including bladder, rectum and small bowel were delineated. As, the uterus is a highly mobile organ, a margin for movements was separately defined for it as internal target volume (ITV uterus).[7] Target volume was defined as CTV total (CTV tumor + CTV nodal + ITV uterus).

The initial plan was to treat the patients according to the standard four field box marked on bony landmarks.For AP fields, the superior border was taken at L4-L5 intervertebral space and the inferior border was taken at the lower border of the obturator foramen. The lateral borders were taken 2 cm on either side of the widest part of the pelvic brim. For the lateral fields, the superior and inferior borders were the same as the AP-PA fields. The posterior border was taken to cover the sacral hollow. The anterior border was taken at the anterior edge of the pubic symphysis and ensuring at least 2.5 cm margin from the anterior aspect of the L5 vertebral body.

However, it was felt that it would not be justifiedto treat patients with bony landmark based planning when we were seeing that the target volume as defined above was being excluded. Therefore, the protocol was modified to extend the fields so that the fields covered the target volume laterally (for AP-PA fields) and AP (for lateral fields). In addition during the planning phase it was apparent that the aortic bifurcation often occurred higher up than L4-L5, which would have resulted in a sharp increase in the irradiated volume. To limit the potential increase in normal tissue toxicity and the resultant reduction in treatment tolerance, the superior border was kept at L4-L5 interface and nodal CTV extending above the L4-L5 interspace was excluded from the treatment field. The decision for modifying the field borders were taken in accordance with the guidelines given by Small *et al*., who have advocated that the nodal CTV for common iliac vessels should be restricted to 7 mm below the L4-L5 intervertebral space. Patients were treated using this modified plan. Correlation of dosimetric parameters with failure was done using the dose distributions obtained from this modified field as patients were treated using this plan.

Planning was done on the eclipse treatment planning system (Varian Medical Systems, Paolo Alto, CA, USA). In order to quantify the extent to which the target volume was being missed with standard four field plans, a four field box plan was generated using the bony landmarks outlined above. The target volume delineated was then projected onto the digitally reconstructed radiograph and using the Beam's eye view the distance of the target volume from the edges of the field was measured [Figure 1]. The volume of the target receiving at least 95% of the prescribed dose was calculated (V95) [Figure 2]. The V95 was subtracted from the total target volume to calculate the volume that would have been missed in conventional planning based on bony landmarks. Furthermore, uterine version was noted and divided into three categories; anteverted, straight and reteroverted. The distance of the uterine fundus from the sacral promontory was measured as a measure of the bulk and version of the uterine corpus. For this, a vertical tangent was drawn at the anterior most extent of the uterine fundus and the distance was measured from sacral promontory to

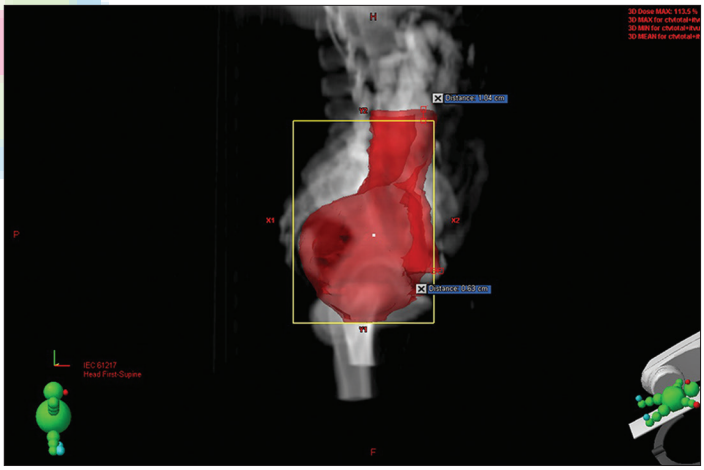

Figure 1: Measurement of extent of miss of target volume at various borders

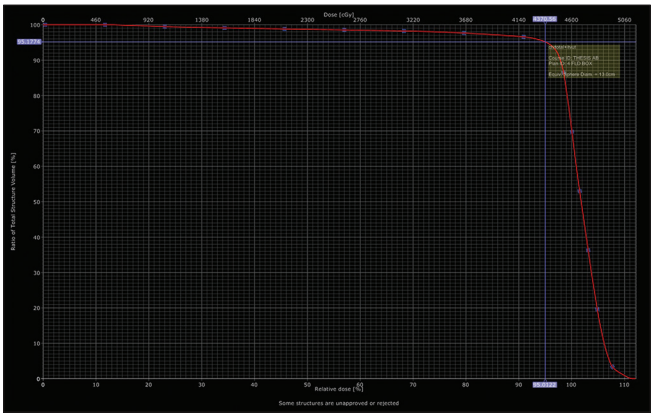

Figure 2: Dose volume histogram, showing volume of target receiving 95% of prescribed dose (V95)

the point of intersection of this tangent with the line joining sacral promontory with the symphysis pubis [Figure 3].

Three-dimensional conformal planning was done on the Eclipse treatment planning system (v. 8.6, Varian Medical Systems, Paolo Alto, CA, USA) and all the patients were treated on a linear accelerator with 15 MV energy. A dose of 46Gy in 23 fractions was delivered over 4.5 weeks with weekly concurrent cisplatin (40 mg/m^2). The patients were assessed for brachytherapy towards end of treatment and two sessions of high dose rate brachytherapy (HDR) were delivered one week apart. The dose per fraction was 9Gy (HDR). The patients were followed up regularly every two months for the first one year and three monthly thereafter. The follow up ranged from -15 months. A detailed clinical examination along with a pelvic examination was done at each visit. A CT scan of the chest abdomen and pelvis was done in case a recurrence was suspected and was correlated to the treatment fields used. The late rectal and bladder toxicities were analyzed according to CTCAE version 4.1. The failure pattern was analyzed and disease free survival for local, pelvic, para aortic and distant failures was determined.

Statistical analysis

Descriptive statistics including mean, median and 95% confidence intervals of the mean were derived for parameters related to miss and same correlated against disease related parameters. Actuarial probability of the DFS, pelvic nodal free survival, paraortic nodal failure free survival and distant failure free survival were calculated using Kaplan Meir Product Limit method. For the purpose of calculation of DFS any disease recurrence was considered as an event. Patients were censored at the time of last follow-up or death as applicable. The log rank test was used to compare the difference in DFS according to the variables related to inadequacies in target volume coverage for the modified four field plans. Owing to the small number of events multivariate analysis was not attempted.

Results

In only two patients out of 50, the standard four field box covered the whole of the target volume. The mean and median V95 for standard plans were 88.95% and 89.4% respectively (95% confidence intervals of means 87.25-90.66%). The median miss at the superior border of the fields was 2.95 cm and the maximum miss was up to 7.27 cm above the L4-L5 interspace. Lateral borders of the anterior fields encompassed the target in 46% (n = 23) patients. The median miss at the lateral borders was 0.27 cm and the maximum was 2.62 cm. The miss at the lateral borders of the anterior fields, was due to the external iliac nodal contours, in all cases. In 41 patients (82%) the target volume extended beyond the anterior borders of the lateral fields, the median miss was 1.05 cm and maximum was 4.91 cm [Table 1]. In majority of the patients the miss at the anterior borders of the lateral fields was due to delineation of the outlying group of the external iliac nodal volume, however in 10/41 patients (24.39%) the miss was due to bulky anteverted uterus.

The median distance of the uterine fundus from the sacral promontory in patients with anteverted uterus (n = 36) was 6.33 cm. Patients with increased anteversion had a bulkier uterus with associated hydropyometra. The follow-up period ranged from 4 to 15 months. Out of total 50 patients, 5 patients (10%) had failed at the time of analysis. There were 2 patients who had infield failure. 4 patients failed in the paraortic region, one of whom also had an infield failure and two also developed distant metastasis.

On comparing the mean irradiated volume receiving 95% and 50% of the prescribed dose by the four-field technique using bony landmarks and the modified four field technique, it was found that there was a statistically significant increase in the volume of tissue irradiated while using the modified plan [Table 2]. Furthermore, the mean dose to the bowel and bone marrow was increased significantly in the modified plan when compared with the standard four field plan [Table 2].

The local and paraaortic failure free survivals were 87% [Figure 4] and 84% [Figure 5] respectively, at 12 months. The distant DFS was 88.8% [Figure 6]. Although, there was not statistically significant influence of parameters related to dosimetric miss using the modified field plans a trend toward inferior outcomes was noted for those with an inferior coverage [Table 3 and Figures 7 and 8].

Patients with inferior coverage of target volume (V95 < 89.7%) had a higher, but statistically insignificant chance of para-aortic nodal failure. At 1 year, the actuarial probability of para-aortic

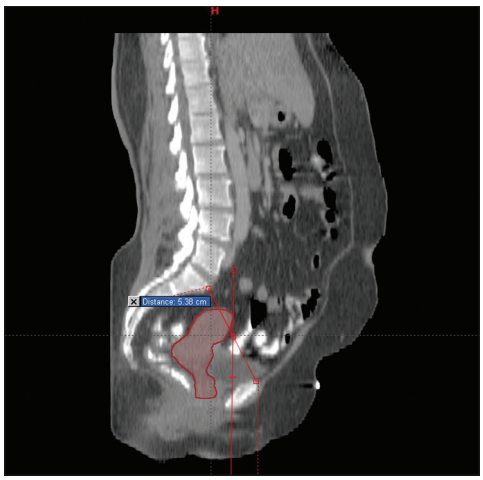

Figure 3: Measurement of uterine fundus distance from sacral promontory

Table 1: Pattern of target volume missed with conventional four field box technique

	No. of patients with TV extending outside (% of total cases)	Length of TV outside the border (cm)	
		Median (cm)	Range (cm)
AP-PA fields			
Superior border	48 (96)	2.95	0-7.27
Lateral border	27 (54)	0.27	0-2.62
Lateral fields			
Anterior border	41 (82)	1.05	0-4.91

TV=Target Volume; AP-PA=Anteroposterior and posteroanterior

Table 2: Comparison of few dosimetric parameters between two plans

	Mean		95% confidence interval		*P* value (*t*-test)
	Four field	Modified field	Four field	Modified field	
Vol. receiving 95% of prescribed dose (cu cm)	2851.41	3155.66	2732.11-2971.71	3046.03-3215.28	<0.001
Vol. receiving 50% of prescribed dose (cu cm)	7505.36	7771.09	7145.58-7865.14	7426.55-8115.64	<0.001
D mean bowel (% of prescribed dose)	51.38	55.74	46.80-55.98	51.23-60.25	<0.001
D mean bone marrow (% of prescribed dose)	91.02	91.87	90.06-91.99	90.84-92.89	<0.001

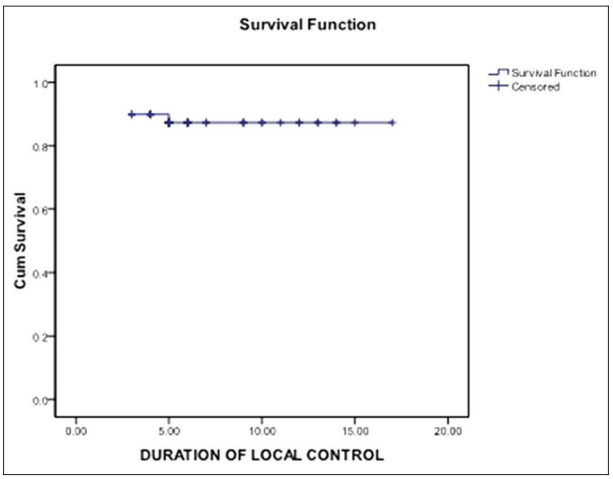

Figure 4: Local failure free survival

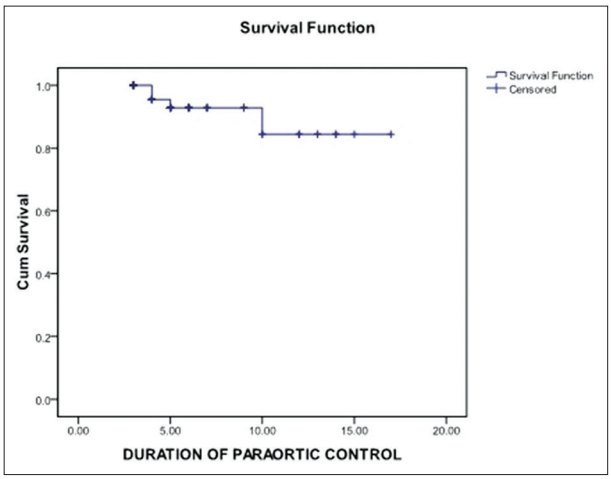

Figure 5: Paraaortic failure free survival

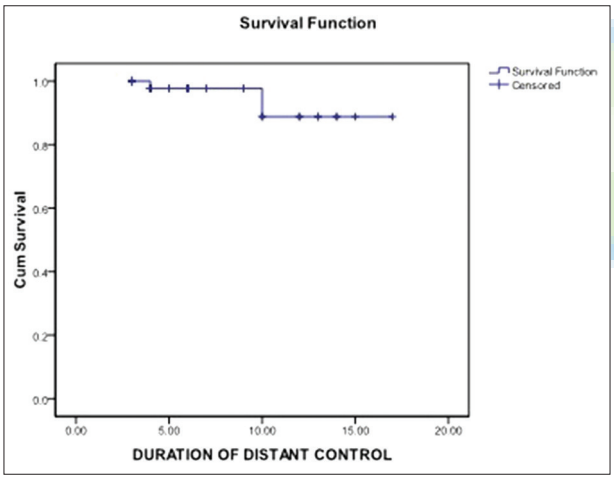

Figure 6: Distant disease free survival

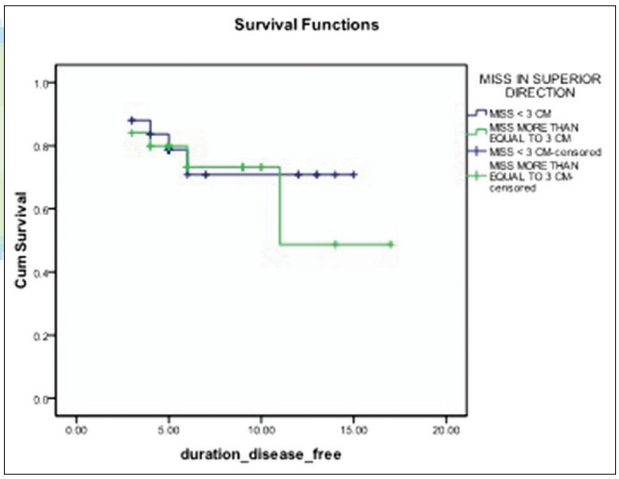

Figure 7: Correlation of miss in superior direction with disease free survival

failure was 10% in patients with V95 > 89.7% and 14% in patients with V95 < 89.7% ($P = 0.22$).

Discussion

The standard four field technique has been used tradionally and has resulted in good locoregional control and acceptable clinical toxicity.[8-10] Over the years, with the increase availabi, ity of sophisticated imaging modalities, radiotherapy planning has also witnessed drastic changes from 2D planning to 3D and now 4D planning. In order to improve the therapeutic ratio with increase inloco regional control withlower normal tissue toxicity, clinicians are gradually shifting from conventional to conformal planning. Although the target volume is more or less agreed upon, precise localisation of structures for target delineation and their anatomic boundaries remainsa debatable issue.[4] Due to economic and logistic constraints in developing countries, routine implementation of 3D planning remains problematic despite these countries accounting for bulk of patients with carcinoma cervix. Without clear cut clinical data showing the comparative efficacy of 3D planning and dose delivery over conventional techniques, routine implementation in the clinic is problematic.

Earlier, Zunino *et al*. have assessed, by means of magnetic resonance imaging (MRI), lymphangiography and anatomic studies on cadavers, whether the four field radiotherapy technique involved the planning target volume (PTV).[11] Authors have concluded that the design of the lateral fields of the four field technique for the irradiation of the uterine cervix carcinoma based on anatomic bone references failed to encompass the PTV in a significant number of patients. However, it is necessary to bear in mind that it is not possible to establish comparisons between anatomical

Table 3: Correlation of dosimetric coverage with DFS

Variable	Cut-off	Mean DFS	*P* value
Distance between superior border and superior extent of the target volume	<2.6 cm	11.87	0.74
	≥2.6 cm	12.01	
V95	<89.7%	9.8	0.28
	≥89.7%	13.95	
Distance from sacral promontory to uterine fundus	<6.3 cm	11.47	0.72
	≥6.3 cm	12.64	
	Retroverted	12.1	

DFS=Disease free survival

features observed in intraoperative studies and studies in cadavers with anatomy of living human beings.

Russell *et al*., reported on the value of pelvic MRI in the design of pelvic fields of the box technique.[12] MRI was used primarily to define the treatment volume required to encompass the primary disease and its direct regional extensions and only secondarily to assess the presence or absence of lymph node metastases. The saggital scans revealed that use of "conventional" or "standard" lateral radiation portals would have resulted in a failure to encompass all gross cancer extensions (marginal miss) in 24% patients as compared with 82% in our study. The difference may be due to use of a margin for ITV uterus by us. However, in developing countries where there is a higher incidence of carcinoma cervix cases, more so in the lower socio economic class women, the costly techniques like MRI are out of reach for many patients.

Our study indicates the need for target volume delineation by using CT based planning while using conventional four field box technique, in patients with locally advanced carcinoma cervix. However, one of the major difficulties lies in the definition of the CTV components. While there is general agreement on what constitutes the CTV, defining these different components for delineation is problematic.

The conventional belief of bifurcation of the aorta at L4-L5 level is also challenged by the observation in our study that in 48 out of 50 patients the level of bifurcation was above the L4-L5 level. Hence, if target volume was delineated according to guidelines for CTV pelvic nodal basins by Taylor *et al*., our target coverage would have been inadequate in all except two patients. The disadvantage of delineating by the guidelines proposed by Taylor *et al*. however lies in the excessive volume of small bowel and bone marrow that can potentially get irradiated [Table 2]. Using conventional fields without shielding using multileaf collimators or customized blocks can further increase the volume. As these patients receive concurrent chemoradiation tolerance to such extended fields remains questionable. Further the delineation of the lateral external iliac nodal volume often results in significant lateral extension of the target volume, which can result in inclusion of a large volume of iliac crest and femoral heads.

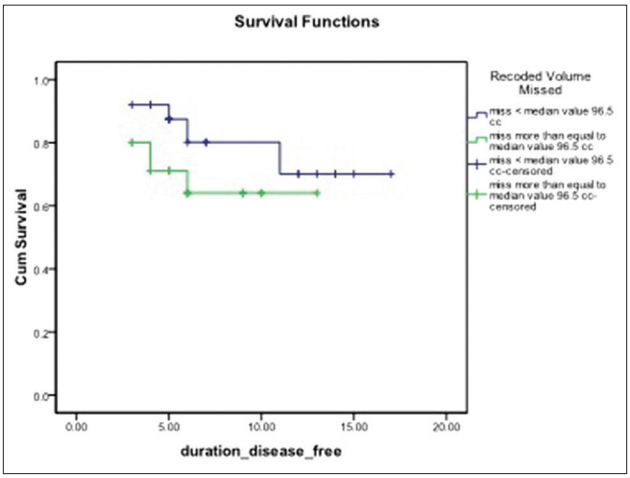

Figure 8: Correlation of volume of target volume missed with disease free survival

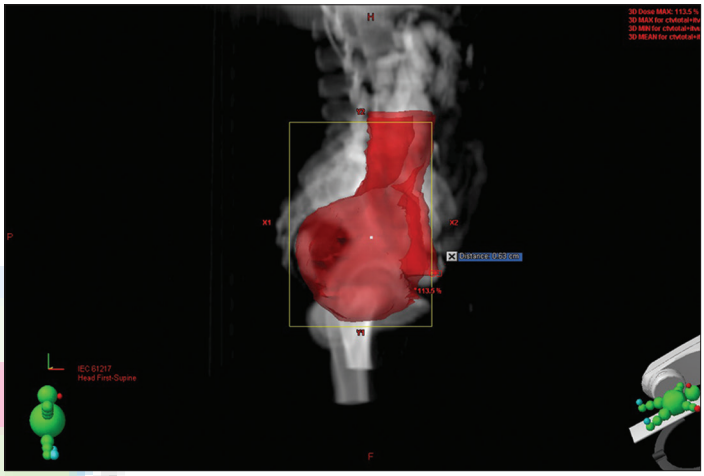

Figure 9: Target volume missed at various borders, with no planning target volume margin

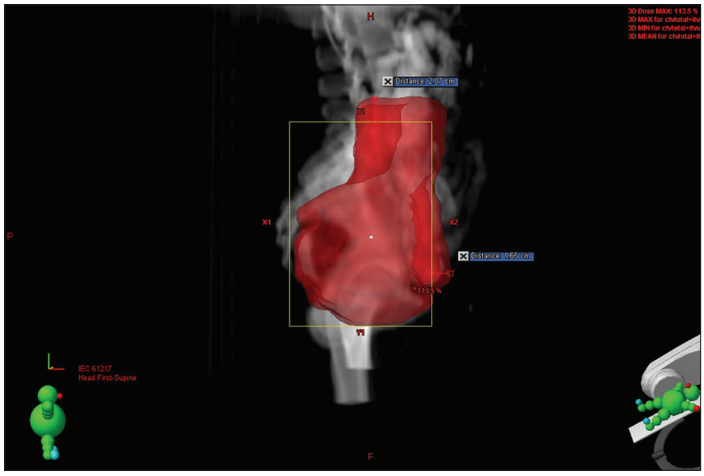

Figure 10: Target volume missed at various field borders if planning target volume margin is given

The irradiated volume would have been grossly increased if we had tried to cover the entire target volume, mainly at the superior aspect. It was also realised that the target could be missed at the lateral borders of the anterior fields too since a further margin for setup errors in the form of PTV was not given [Figures 9 and 10]. However, this decision was taken anticipating excessive acute toxicity mainly due to increased volume of small bowel irradiation and risking unplanned treatment breaks which could be detrimental for tumor control.

The present study shows early trends in the outcome of treatment and points to increased failures secondary to inadequate target coverage, but longer follow-up of the study group is required to determine the clinical significance of the need for coverage of target volume by extending field borders, or by other means like conformal radiotherapy.

With a longer follow-up, the present study can find out the significance of missed common iliac nodal volume at the superior border, but the significance of target volume missed with conventional four-field technique at other borders cannot be determined as we had extended the, field borders were extended to include the target volume.

We recommend CT based treatment planning for locally advanced cases of carcinoma cervix based on our observation of the target volume miss in 48 out of 50 cases**.** The clinical significance of geographic miss of target volume in the common iliac nodal region is to be ascertained and longer follow-up of the study cohort is required.

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