Original Article

An evaluation of three dimensional conformal radiation therapy versus intensity modulated radiation therapy in radical chemoradiation of esophageal cancer: A dosimetric study

Soumik Ghosh, Rakesh Kapoor, Rajesh Gupta[1], Divya Khosla, Rakesh Kochhar[2], Arun S. Oinam, Reena Sharma, Suresh C. Sharma

Departments of Radiotherapy and Oncology, [1]Surgical Gastroenterology, [2]Gastroenterology, Institute of Medical Education and Research, Chandigarh, India

ABSTRACT

Aims: To evaluate the feasibility whether intensity-modulated radiotherapy (IMRT) can be used to reduce doses to normal thoracic structures than three-dimensional conformal radiotherapy (3DCRT) in treating esophageal cancer and to compare normal tissue complication probability (NTCP) for lung between two treatment plans. **Materials and Methods:** A prospective study was carried out from 2009 to 2011, in which 15 inoperable patients of esophageal cancer who were suitable for radical chemoradiation were enrolled. All patients were treated with 3DCRT. In first phase, patients were treated with external beam radiation therapy (EBRT) dose of 36Gy in 20 fractions in 4 weeks, along with concurrent weekly chemotherapy with cisplatinum and 5-fluorouracil (5 FU). In second phase, boost dose of 18Gy in 10 fractions in 2 weeks was given. An IMRT plan was generated for each patient. Plan sum of both the 3D CRT and IMRT plans were compared. Doses to critical structures and NTCP for lung were compared between 3DCRT and IMRT plans. **Results:** The mean lung dose and volumes of lung receiving 20 Gy, 10 Gy, and 5 Gy (V20, V10, and V5) were significantly lower with 3DCRT plans as compared to IMRT plans. The mean dose to heart and spinal cord was higher in 3DCRT arm. There was no difference in dose distribution to the liver between the 3D CRT and IMRT techniques. The NTCP for lung was lower with 3D CRT than IMRT. **Conclusion:** IMRT technique needs further dosimetric study as well as further clinical trials before implication of this technique replacing 3D CRT technique with escalated dose for the treatment of esophageal cancer in our setup. IMRT using seven fields provided no improvement over 3DCRT.

Keywords: Conformal radiotherapy, dose escalation, esophageal cancer, intensity-modulated radiotherapy, normal tissue complication probability

INTRODUCTION

Treatment of esophageal cancer, which has a 5-year overall survival rate of 20–25%, traditionally involves chemoradiation for inoperable or unresectable disease or preoperative chemoradiation for operable disease.[1-3]

Access this article online	
Quick Response Code:	Website: www.ccij-online.org
	DOI: 10.4103/2278-0513.99565

Because the locoregional persistence or failure rate after chemoradiation is approximately 50%,[1,3] better local treatment through radiotherapy may be needed to improve the overall treatment outcome. The goal of radiotherapy for esophageal cancer is to ensure appropriate coverage of the targeted structures while minimizing irradiation of normal tissues. Despite the combined treatment modalities of chemoradiation, locoregional recurrence clearly emphasizes the necessities for improvements in local control, initiating the need for delivering higher radiation doses for better local tumor control.[4] The therapeutic ratio for esophageal radiotherapy can only be maintained if higher doses can be delivered without an increase in late normal tissue damage; the lung parenchyma and spinal cord being of particular concern. After chemo-radiation, a significant number of patients may survive for 5 years or more, and so the clinical

Address for correspondence: Dr. Rakesh Kapoor, Department of Radiotherapy and Oncology, Regional Cancer Centre, Post Graduate Institute of Medical Education and Research, Chandigarh - 160 012, India. E-mail: drkapoor.r@gmail.com

consequences of normal tissue damage must be taken into account when designing new treatment techniques. The radiation technique delivered by conventional method use to irradiate a large volume of lung, causing more restriction to dose escalation to avoid radiation-induced lung toxicity.

Delivery of escalated radiation doses for overall better tumor outcome has introduced the necessity of dose-restriction within the normal tissue tolerance for the surrounding vital structures *viz*. lung, spinal cord, and heart; thus introducing various newer conformal techniques of radiation therapy like three dimensional conformal radiation therapy (3-DCRT), intensity modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT) etc. The delivery of radiation doses while planning for external radiation in esophageal cancer is technically difficult when dose escalation is done as the planning target volume (PTV) is central. It is close to spinal cord and is almost completely surrounded by lung, a radiosensitive organ, with a relatively low radiation tolerance. With the encouraging results of increasing dose to increase in local control in esophageal cancer, care for the normal tissue toxicity, mainly for lungs and spinal cord, emerged the necessity for an evaluation of IMRT technique.

In the treatment of esophageal cancer, it is hoped that IMRT might offer the potential to improve the uniformity of tumor irradiation and reduce the dose delivered to lung parenchyma. Hence, this study aims to evaluate the reduction in radiation doses to the normal thoracic structures through the use of 3DCRT and comparing the treatment plans with IMRT-generated plans. Dose–volume histograms (DVHs) for lungs, liver, and spinal cord were used as endpoints, as well as the normal tissue complication probability (NTCP) for lung. To the best of our knowledge, this is the first dosimetric comparative study between 3DCRT and IMRT in esophageal cancer from India.

MATERIALS AND METHODS

Patients

It is a prospective study from 2009 to 2011, in which 15 inoperable patients of esophageal cancer who were suitable for radical chemoradiation were enrolled. The inclusion criteria for study were: Inoperable disease, histologically-proven squamous cell carcinoma, stage II and III as per American Joint Committee on Cancer staging criteria, and Karnofsky performance status ≥ 70. The pretreatment workup included clinical examination, complete blood counts and hemoglobin levels, kidney function tests, barium swallow, fiberoptic upper gastrointestinal endoscopy, and contrast-enhanced computed tomography (CT) of chest, abdomen, and pelvis. All patients signed a written informed consent prior to participation in the study. Ethical clearance for the conduction of the study was obtained from the institutional ethics committee prior to the inception of the study.

Treatment delivery

Treatment was delivered in 2 phases. In first phase, external beam radiotherapy (EBRT) of 36 Gy in 20 fractions in 4 weeks was delivered with weekly concurrent chemotherapy with cis-platinum 30 mg/m^2 and 5-fluorouracil 325 mg/m^2. The first phase was immediately followed by the second phase without any treatment gap. In second phase, EBRT boost was given with 18 Gy in 10 fractions over 2 weeks with three field 3DCRT technique without any chemotherapy.

Treatment planning

All planning CT were helical scans with 2.5 mm slices, acquired in the Light Speed VFX-16 CT simulator (GE Medical Systems, Waukesha, WI, USA). Patients were simulated in supine position with both arms raised, forearms kept under the head, and hands to touch the opposite elbow. This helped to keep the arms and forearms away from the radiation field. Treatment planning was done on Eclipse treatment planning system version 8.6 (Varian Medical Systems, Palo Alto, CA, USA). The gross tumor volume (GTV) was defined by taking into consideration the endoscopy and barium swallow reports in conjunction with CT scan data obtained. Any esophageal wall thickening more than 5 mm was considered pathological. Any lymph node more than 1 cm in its shortest diameter was taken into consideration. Clinical target volume (CTV) was taken considering the microscopic extension of the disease. In first phase, for CTV, a margin of 5 cm proximally and distally and a radial margin of 15 mm was added to GTV, and in second phase, a margin of 2 cm proximal and distal and radial margin of 5 mm was added to GTV. The CTV in both the phases was excluded from the vertebra, heart, aorta, and liver. A three-dimensional margin of 1 cm was added to the CTV in both the phases to account for movement and uncertainty in target definition, creating the planning target volume (PTV). The spinal cord, lungs, liver, and heart were delineated. Multileaf collimators were used to conform the PTV.

In first phase, 3DCRT plan constituted of two equally weighted parallel-opposed Antero-Posterior and Postero-Anterior (AP-PA) portals. In second phase, 3DCRT plan constituted of one anterior and two posterior oblique fields at selected Gantry angles so that the spinal cord was excluded out and the beams were weighted so as to obtain homogenous dose distribution throughout the PTV. Plan modification was done according to the necessity to optimize the dose distribution. This was done by changing the gantry angles of the posterior fields, rearranging the positions of multi-leaf collimators, and changing the

weightage of the beams of the fields. Dose distributions were prioritized in the following sequences—PTV, lung, spinal cord, heart, liver. A 7 beam IMRT plan was generated for each patient considering the same contouring as in first and second phase. Plan sum of both the 3D CRT and IMRT plans were made. Dose constraints are specified in Table 1.

Statistical analysis

Statistical significance of each comparison was assessed using Wilcoxan Signed Rank test. Normal tissue complication probability of both the 3D CRT and IMRT arms were compared by paired *t* test.

RESULTS

The clinical profile of patients is given in Table 2. The average tumor size was 8.9 cm. A plan sum was made for both 3D CRT and IMRT plan adding first and second phase plans. Both the plans of 3D CRT and IMRT were evaluated dosimetrically. The dose homogeneity within the PTV was comparable for both techniques.

Doses to organs at risk

The mean dose to spinal cord with 3D CRT and IMRT was 23.72 Gy and 19.30 Gy, respectively. These mean values clearly signified higher irradiated dose to spinal cord in 3D CRT arm ($P = 0.001$). The dose to the 2cc volume was 43.84 Gy and 44.84 Gy for 3D CRT and IMRT arm, but the difference was not statistically significant ($P = 0.46$). The minimum, maximum, and mean dose distribution to the heart and liver in both 3D CRT and IMRT plans were calculated and compared as shown in Table 3. The minimum, maximum, and mean dose to the heart was higher in 3D CRT arm, but not exceeding the dose constraints. The liver doses did not show any statistically significant difference for 3D CRT and IMRT arms though the individual data for lower thoracic esophageal cancer had higher dose of irradiation for IMRT arm [Figure 1].

The lung doses were calculated from the cumulative DVH in terms of the percentages of the lung volumes receiving 5 Gy, 10 Gy, and 20 Gy demarcated as V5, V10, and V20, respectively. The values of V20, V10, and V5 in 3D CRT plans were 20.72%, 39.36%, and 62.45%; whereas in IMRT plans, the values were 36.23%, 73.21%, and 85.93%, respectively. This dose-volume evaluation of V5, V10, and V20 in 3D CRT technique showed markedly lesser lung volume irradiation as compared to the similar IMRT plans with *P*-value of 0.001

Table 1: Dose constraints

Structure	Constraint
PTV	95% - 107%
Lungs	V20 - ≤35%
	V10 - ≤ 45%
	V5 - ≤ 65%
Spinal cord	45Gy to the whole spinal cord with not more than 2% of the spinal cord over 50Gy
Heart	V40 - ≤ 50%
	V50 - ≤ 30%
Liver	V30 - ≤ 50%
	V50 - ≤ 30%

Table 2: Clinical profile

Structure	Profile
Age (years)	
Range	25-62
Median	48
Site of tumor	
Cervical	2
Upper Thoracic	3
Mid Thoracic	9
Lower Thoracic	1
Stage	
IIA	1
IIB	6
III	8
Histology	
Well - differentiated	4
Moderately - differentiated	6
Poorly - differentiated	5

Table 3: Comparison of minimum, maximum and mean doses to heart, liver and lungs between 3D CRT and IMRT

Organ	3D CRT (Gy)	IMRT (Gy)	*P* value
Heart			
Minimum dose	1.58	3.98	0.012
Maximum dose	51.74	51.33	0.027
Mean dose	29.26	22.42	0.001
Liver			
Minimum dose	0.14	0.13	0.76
Maximum dose	33.70	30.12	0.65
Mean dose	4.33	5.12	0.19
Lungs			
Minimum dose	0.51	0.97	0.053
Maximum dose	57.04	55.34	0.004
Mean dose	14.52	18.31	0.011

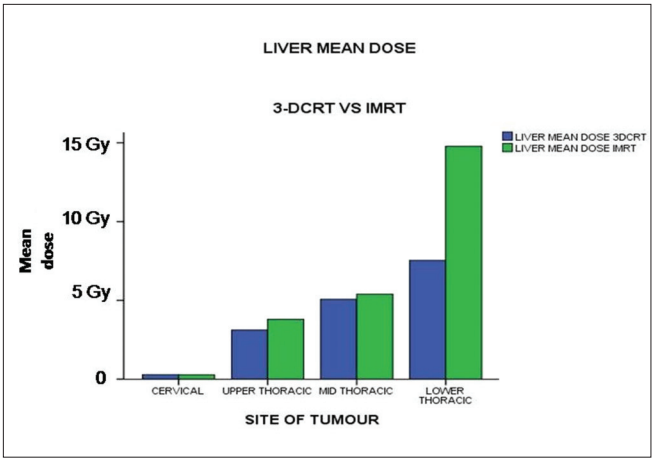

Figure 1: Mean dose to liver by 3DCRT and IMRT according to site of tumor (X axis depicting site of tumor and y axis showing mean dose in Gy)

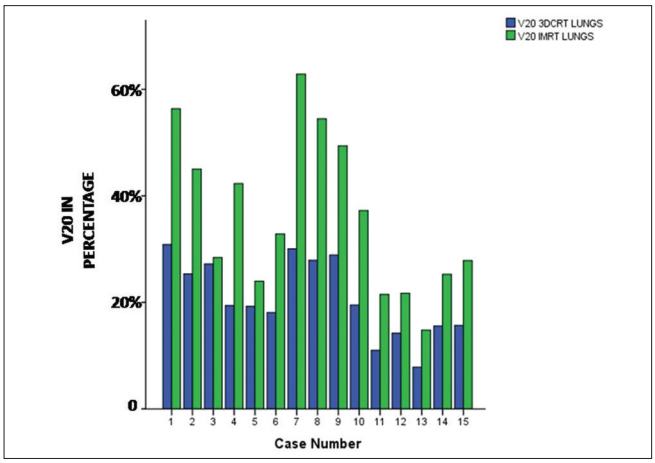

Figure 2: Comparison of V20 values for each patient in 3D CRT and IMRT plans

in each dosimetric parameter. The comparative study of V20 values for each patient in 3D CRT and IMRT plans has been shown in Figure 2, where V20 values are constantly higher in IMRT technique in comparison to 3D CRT technique in each patient. The minimum, maximum, and mean dose values of the lung with 3D CRT and IMRT plans were also calculated and compared. Though the maximum value was marginally higher in 3D CRT arm (57 Gy) than IMRT arm (55.34 Gy) (P = 0.004), both the minimum and mean dose values were higher in IMRT arm [Table 3].

Radiobiological comparison

Radiotherapy treatment plan evaluation relies on an implicit estimation of the normal tissue complication probability (NTCP) arising from a given dose distribution.[5] The NTCP i.e. probability of complications in normal tissue was calculated for IMRT and 3DCRT plans using the phenomenologic Lyman–Kutcher-Burman (LKB) (Eq.1) model.[6] Lyman's formula models the sigmoid-shaped dose response curve of NTCP as a function of dose (D) to a uniformly irradiated fractional reference volume (v_{ref}).

$$NTCP = \frac{1}{\sqrt{2\neq}} \int_{-\infty}^{t} \exp(-\frac{t^2}{2})\, dt \quad (1)$$

where t is defined as

$$t = \frac{D - TD_{50}(v)}{m.TD_{50}(v)} \quad (2)$$

and

$TD_{50}(v) = TD_{50}(1).v^{-n}$

The normal tissue complication probability (NTCP) for lung was estimated from the DVH of each plan. The value of NTCP was lower in 3D CRT arm (0.0196%) than IMRT arm (0.224%), though both the arms had a value < 1.0%. The difference between the NTCP values of 3D CRT and IMRT arms was found statistically significant with P-value of 0.001, with lower value in 3D CRT arm.

DISCUSSION

The median survival after radiotherapy for carcinoma of the esophagus is approximately 9 months. The 2-year survival rate is around 10%, and the 5-year survival rate is less than 5%,[7] although selected series report a 5-year survival rate of 21%, demonstrating the potential of radiotherapy as a curative modality.[8] In recent years, concomitant chemo-radiation schedules have produced encouraging results in randomized trials, with up to 25–30% of patients surviving for 5 years or more, and this is now considered as standard treatment.[1,9-11]

Clinical studies have shown that chemoradiation used alone or preoperatively to treat esophageal cancer can result in severe complications.[1-3] Besides good clinical rationale, evidence exists that suggests that minimization of the volume of lung irradiated to low doses could results in fewer pulmonary complications.[12] Our study addressed whether IMRT for esophageal cancer can be used to reduce the volume of lung irradiated even at low doses of 10–20 Gy. IMRT offers the greatest benefit when the tumor is concave.[13] For esophageal carcinoma, where the PTV is approximately cylindrical, the benefit is, therefore, expected to be small. The results of this study are in accord with this expectation, with a small benefit in terms of sparing of spinal cord and heart but no benefit in lung sparing being demonstrated with IMRT technique. The problem of increased volumes of healthy tissue receiving low doses has also been documented when IMRT is compared with 3D-CRT.[14] In cases of IMRT *vs.* 3D-CRT, IMRT is capable of better conforming higher doses to the treatment volume. The improved conformality is achieved with an increased number of beams and, therefore, a greater volume of healthy tissue receiving the dose.

From clinical point of view, in our Indian population, patients of esophageal carcinoma presents with large sized tumor; as in our study, the average tumor size was 8.9 cm. And, the microscopic disease spread may occur as far as 8 cm cranio-caudally. As per the clinical practice, we consider 5 cm cranio-caudally safe margin to include microscopic disease.[15] This gives a large PTV as well as the large surrounding organs at risk, mainly lung and spinal cord.

In this dosimetric study, an IMRT plan was generated for each patient treated with 3D CRT to evaluate the feasibility of IMRT in esophageal cancer in our setup. Nutting *et al.*,[16,17] in their study, used 9 beam equispaced IMRT plans and compared it with 3D CRT, which concluded no benefit in reduction of dose to lung in IMRT plan. In our study, we used 7 beam IMRT plan where the beams were not equispaced, but were carefully chosen according to the best possibility to cover PTV and to save OARs. As per the

results obtained in our study, spinal cord is always better saved by IMRT technique. Similarly, heart being a midline structure, gets more exposed to prescribed dose of PTV in 3D CRT. It can also be spared well in IMRT technique. If chemoradiation treatment modality with higher radiation dose can prolong the overall survival period, then the late toxicity of the heart will become a major factor for treatment failure/ decreased survival rate. Hence, the dose constraint for heart must not be ignored while planning EBRT for esophageal cancer. Liver surrounds almost two-third of the PTV circumferentially. It is important to avoid this organ in the lesion of mid and lower thoracic esophagus where PTV mostly comes at the level of liver. So, the more coplanar beams used, more dose will reach to the liver. Our results correlated the fact. There was only one case of lesion in lower thoracic region in our study and marked higher dose was delivered to the liver in IMRT arm in this particular case [Figure 1]; whereas the mean, maximum, and minimum doses of the entire sample size failed to find out any difference in between the 3D CRT and IMRT plans.

Lung is one of the most challenging organs at risk, which restricts escalation of dose to esophageal cancer. The irradiated lung volumes in terms of V20, V10, and V5 were significantly higher with IMRT. This was more prominent in case of lower dose level with V5. The maximum dose delivered to the lung was higher in 3D CRT. But, the mean lung dose was significantly low in 3D CRT plan ($P = 0.011$). Our study followed the trend of the study by Nutting *et al*,[16] but results obtained were different from those of Chandra *et al*.[18] where they found lesser lung volume irradiation in V5, V10, and V20. This may be explained by the location of the tumor at lower thoracic esophagus and gastroesophageal junction; and moreover, the dose delivered was 50.4 Gy. In our study, 10 out of 15 cases were of mid thoracic esophageal cancer. Also, the PTV volume in both the phases was larger than the study because of larger tumor size (average 8.9 cm) in our patient population.

The values of the NTCP of both arms were within safe limit for radiation therapy. But, the NTCP calculations did not incorporate the concurrent chemotherapy factor. Therefore, it can be assumed that the actual NTCP should be higher than the calculated value in our study.

Though it was not a part of this study, still we collected data for evaluation of the patient compliance in 3D CRT technique to assess the normal tissue toxicity with chemoradiation by our treatment regimen. Four cases had grade-II dysphagia, and 5 patients complained of grade-I dysphagia during 2nd and 3rd week of treatment. These subsided within 6 weeks from the date of treatment completion. Only 1 patient presented with grade-II pneumonitis on follow-up in 3rd month of treatment completion, and it was resolved within 1 month. Only 1 local failure was seen. There was no cardiac toxicity. Two out of 15 patients died. One was due to lung metastasis and progressive local disease. The other death was due to surgical anastomotic leak, as the patient underwent surgery by his own from outside after completion of radical chemoradiation course.

CONCLUSION

No clinically and dosimetrically meaningful differences between the 3DCRT and IMRT plans were observed with respect to dose given to spinal cord, heart, and liver, but IMRT technique fears more chance of lung toxicity. Conformal radiotherapy techniques offer the prospect of decreasing lung dose in combined chemo-radiation for esophageal cancer. IMRT technique needs further dosimetric study as well as further clinical trials before implication of this technique replacing 3D CRT technique with escalated dose for the treatment of esophageal cancer in our setup. Detection of disease at an early stage may have an impact to the dose distribution to the OARs due to smaller GTV.

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Cite this article as: Ghosh S, Kapoor R, Gupta R, Khosla D, Kochhar RK, Oinam AS, *et al*. An evaluation of three dimensional conformal radiation therapy versus intensity modulated radiation therapy in radical chemoradiation of esophageal cancer: A dosimetric study. Clin Cancer Investig J 2012;1:65-70.

Source of Support: Nil, **Conflict of Interest:** No.