

Dosimetric Evaluation of 4 Field Three-Dimensional Conformal Radiation Therapy and 7 Field Intensity Modulated Radiation Therapy in Esophageal Cancer Treated with Definitive Chemoradiation

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Abstract

Background: The present study aimed to evaluate dosimetrically and correlate the lung and heart dose volume histogram (DVH) of the 4 field three-dimensional conformal radiotherapy (3DCRT) with 7 field intensity modulated radiotherapy (IMRT) in patients with oesophageal cancers.

Method: This retrospective dosimetric study considered 20 oesophagus cancer patients treated with definitive chemoradiation with IMRT technique. In the 7 field IMRT technique, the first phase delivered a dose of 36Gy/18fr followed by 18Gy/9fr in two weeks in the second phase. In the 3DCRT technique, the first phase was planned with 4 field technique with two parallel opposed and two posterior oblique fields, followed by the 3 field technique in the second phase. The assessments of the techniques were performed using differential DVH analysis of the right and left lungs, heart, and the spinal cord. The values of the mean dose, V20 (volume receiving 20 Gy), and V30 (volume receiving 30 Gy) were assessed for any correlations.

Results: The DVH of V20 in IMRT showed 5% less lung volume irradiation compared with the 3DCRT plans and over 20% less V30 for irradiated heart volume. The study demonstrated a statistical advantage of using 7 field IMRT over 4 field 3DCRT in reducing the mean percentage dose to both lungs, heart, and spinal cord.

Conclusion: 7 field IMRT is superior to 4 field 3DCRT plans in significantly reducing the average percentage of irradiated volume of both the lung and heart in esophageal cancer radiation therapy.

Keywords: Esophageal neoplasms, Radiotherapy, Conformal, Intensity-modulated, Radiation dosimetry, Heart

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Introduction

Esophageal cancer (EC), being the eighth most prevalent cancer with an estimated 0.45 million new cases in the world, accounts for the sixth leading cause of cancer-related death with an estimated 0.4 million worldwide cancer deaths (4.9% of all cancer deaths) in 2012.¹ Since EC manifests typical clinical symptoms late, it is generally diagnosed only at advanced stages and the 5-year overall survival rate of patients is only 15 to 25%.²⁻⁴ Treatment of EC involves chemoradiation for unresectable or inoperable diseases and preoperative chemoradiation followed by surgery for operable diseases.⁵⁻⁷

Radiotherapy is believed to be one of the most effective treatment modalities for EC and plays an important role in both resectable and unresectable cancer treatments.^{8,9} The goal of radiation therapy is to provide adequate coverage of the target tumor volumes while minimizing irradiation of normal surrounding tissues. Despite the combined treatment modalities of chemoradiation, a high locoregional recurrence necessitates improvements in local control, initiating advancement in radiotherapy planning techniques and treatment delivery.¹⁰ The radiation technique delivered by conventional method irradiates a large volume of both lungs, causing restriction to dose escalation to avoid radiation-induced late lung toxicity. The therapeutic ratio for esophageal radiation therapy could be maintained, if higher doses can be delivered

without a substantial increase in late normal tissue damage to lung parenchyma, heart, and the spinal cord. Several advanced radiotherapy techniques, including three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), image guided radiotherapy (IGRT), tomotherapy, intensity-modulated arc therapy, and volumetric modulated arc therapy, have evolved during the last few decades to increase the conformal dose delivery to target areas and to minimize the toxicity to normal organs.^{11,12}

The presence of spinal cord and the surrounding lung tissues in close proximity to the centrally located planning target volume (PTV) makes it very challenging to deliver the escalated radiation dose. Given the increased benefit of local disease control by dose escalation, the optimal care for the lungs and spinal cord can be best achieved by IMRT technique than by 3DCRT techniques.

This study aimed to dosimetrically evaluate the correlation between lung and heart dose volume histogram (DVH) of the 4 field 3DCRT with 7 field IMRT in patients suffering from carcinoma esophagus with an objective to evaluate the superior conformity indices.

Materials and Methods

In this retrospective dosimetric study on 20 histologically proven squamous cell carcinoma with American joint committee on cancer staging criteria (AJCC) stage II and stage III oesophagus

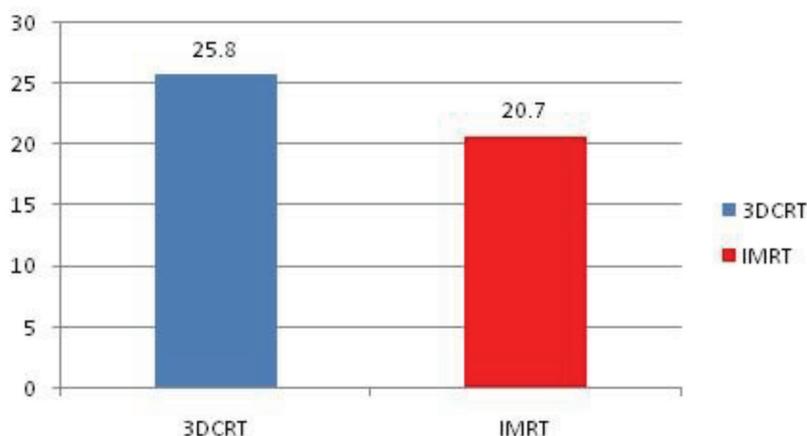


Figure 1. This figure shows the mean volume of the right lung receiving 20 Gy (V20) in 3DCRT and IMRT techniques. 3DCRT: 3-dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy

cancer patients were treated at the Department of Radiotherapy, Father Muller Medical College, Mangalore, Karnataka, India. Definitive chemoradiation were considered after institution of ethical clearance (Father Muller Institutional Ethical Committee, FMFC/FMIE/4450/2018) and the participants signed the informed consent. The radiation was planned for a total dose of 54 Grays to be delivered in 18 fractions over five weeks along with weekly concurrent radiosensitizer using cisplatin ($40\text{mg}/\text{m}^2$) administered weekly for five weeks. In the first phase, the patients received a dose of $36\text{Gy}/18\text{fr}$ for four weeks followed by $18\text{Gy}/9\text{fr}$ for two weeks. All the 20 patients were treated by definitive radiation therapy using 7 field IMRT technique.

The patients were immobilized in supine position with both arms raised and forearms kept under the head to avoid the arms coming in the radiation field. All the patients underwent a planning computed tomography (CT) with proper chest immobilization. The gross tumor volume (GTV) was delineated through the upper endoscopy findings and the diagnostic CT scan images. Clinical target volume (CTV) of around 2 cm radial margin and 5cm superior and inferior to GTV was delineated to account for microscopic spread of the disease. PTV of 0.5cm margin around CTV was considered as per institution protocol to account for movement and uncertainty in target delineation.

Planning via 3DCRT technique

The initial 3DCRT plan had a 4 field technique with two parallel opposed fields and two posterior oblique fields with gantry an angle of between 130 to 230 degrees for right post-oblique and left posterior oblique fields. The 4 field technique was utilized for obtaining adequate PTV coverage using the 6 MV linear accelerator as the patient thickness was more than 16-18 cm in the AP-PA field. The optimal coverage was achieved employing MLC fitted around PTV with the help of digitally reconstructed radiographs (DRR), thereby sparing higher dose to the spinal cord. In the second phase, the 3 field technique was applied with one anterior field contributing 35% dose to spinal cord and two posterior oblique fields at selected gantry angles in order to avoid the spinal cord with the optimal weightage of the beams.

Planning via IMRT technique

The IMRT planning was done on eclipse 13 version of Varian medical system with equal gantry angulations and optimized using Analytical Anisotropic Algorithms (AAA). In phase 1, a dose of $36\text{Gy}/18\text{fr}$ using 7 field sliding window dynamic IMRT was delivered by 6MV photon using 80 millennium MLC of 10 mm leaf width at isocenter by inverse planning technique on ECLIPSE 13 version planning software with the gantry angles selected equally with 52 degrees in each field with coplanar beams. The electronic

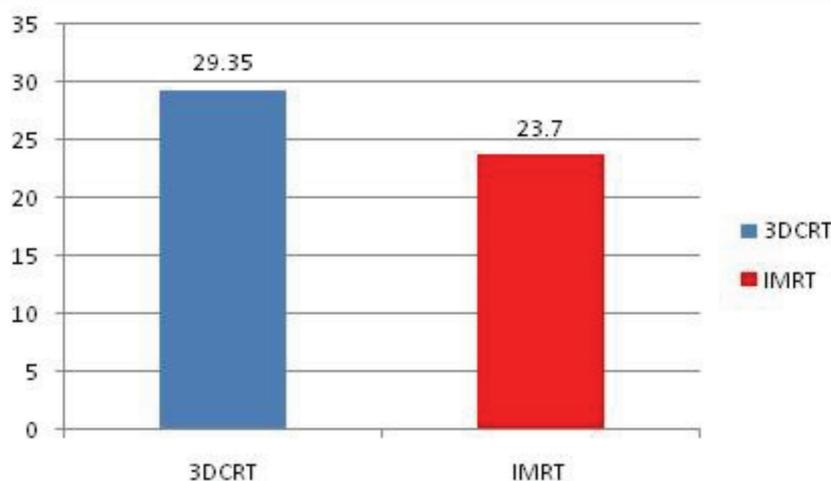


Figure 2. This figure shows the mean volume of the left lung receiving 20 Gy (V20) in 3DCRT and IMRT techniques. 3DCRT: 3-dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy

portal images (EPID MV images) were taken during the first treatment fraction and subsequently repeated twice weekly during the entire course of the treatment. In phase 2, the PTV changed and replanning for 7 field IMRT was done for a dose of 18Gy in nine fractions. All the IMRT plans had complete PTV coverage with 95% of dose prescribed with an acceptable dose maximum of 107% to 108% of the dose prescribed.

Plan and statistical assessment

The assessments of all the plans was performed using differential DVH analysis to the average of the standard DVHs for the right and left lungs, heart, and the spinal cord. The values of the mean dose, V20 Gy (percentage volume receiving 20 Grays dose), and V30 Gy (percentage volume receiving 30 Grays dose) were investigated for various target volumes. The conformity of the plans were assessed by conformity index (CI) which was defined as $CI_{RTOG} = VRI/TV$, where VRI = Reference isodose volume and TV = Target volume (acceptable deviation 0.95-1.0).¹⁸ The mean doses for left lung, right lung, and heart were calculated and also the cumulative values of all V20 and V30 received by both the lungs and the heart were recorded. The maximum spinal cord dose was received and analyzed. All the parameters obtained in the 7 field IMRT plan were compared to those in the 4 field 3DCRT plan. The correlation between the 3DCRT and IMRT arms for all the parameters was analyzed by paired T tests and Wilcoxon Signed Ranks

Tests.

Results

A plan summation of both phases in the 3DCRT and IMRT plans were obtained. We also carried out the dosimetric evaluation of both combined plans. The dose homogeneity within the PTV were comparable for both the techniques.

The doses to both lungs were calculated from the cumulative DVH in terms of percentages of lung volumes receiving 20 Gy, which is demarcated as V20. The values of V20 for the right lung for all the 20 patients in 3DCRT and IMRT plans were 25.8 % (standard deviation (SD) \pm 8.32) and 20.7% (SD \pm 5.18), respectively (Figure 1). The comparative evaluation of V20 values of all the patients showed constantly higher values in 3DCRT technique in comparison with those in IMRT technique. The dose volume evaluation of V20 in IMRT technique showed less lung volume irradiation as compared with the 3DCRT plans with a statistically significant *P* value of 0.002. Similarly the values of V20 for the left lung for all the 20 patients in 3DCRT and IMRT plans were 29.35 % (SD \pm 6.86) and 23.7% (SD \pm 4.44), respectively (Figure 2). The comparative evaluation of V20 values of all the patients also showed constantly higher values in 3DCRT technique in comparison with those in IMRT technique. The dose volume evaluation of V20 in IMRT technique indicated less lung volume irradiation as compared with the 3DCRT

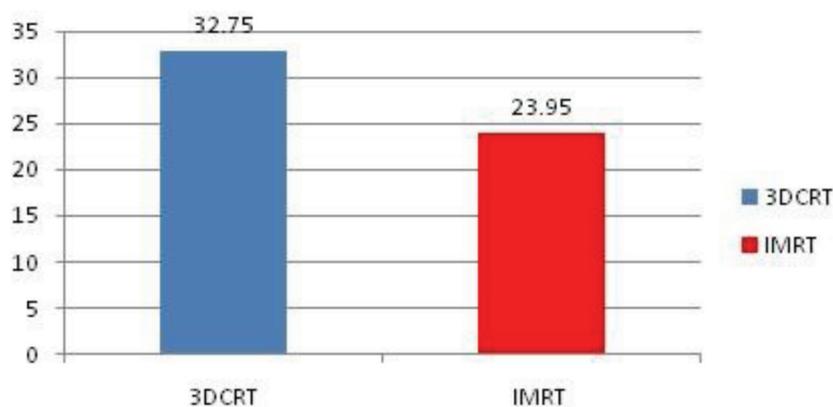


Figure 3. This figure shows the mean dose received by the heart in 3DCRT and IMRT techniques. 3DCRT: 3-dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy

plans with P value of 0.018, which was statistically significant.

The mean dose to the heart in 3DCRT plan was 32.72 Gy (SD \pm 9.63) with a median dose of 31.5 Gy and a maximum dose of 48 Gy. The mean dose to the heart in IMRT plan was 23.95 Gy (SD \pm 7.00) with a median dose of 25.0 Gy and a maximum dose of 65 Gy. The mean median dose to the heart was higher in 3DCRT plan than that in IMRT plan with a statistically significant P value ($P < 0.001$) (Figure 3). However, the maximum point dose was higher in the IMRT technique.

The values of V30 for heart in 3DCRT and IMRT plans were 51.3 % (SD \pm 17.86) and 30.65% (SD \pm 14.91), respectively (Figure 4). The comparative evaluation of V30 values of all the patients showed constantly higher values in 3DCRT in comparison with those in IMRT technique. The dose volume evaluation of V30 in IMRT technique showed less heart volume irradiation as compared with 3DCRT plan with a statistically significant P value ($P < 0.001$).

Similarly, the mean values of the maximum spinal cord dose for all the 20 patients in 3DCRT and IMRT plans were 44.55Gy (SD \pm 2.37) and 40.5Gy (SD \pm 2.66) respectively (Figure 5). The comparative evaluation of the maximum heart dose of all the patients also showed constantly higher values in 3DCRT technique in comparison with those in IMRT technique with a P value of

0.008, which was statistically significant.

The median CI for all the subjects in 3DCRT plan was 0.9250; whereas, that in IMRT plan was 0.965. The paired test correlation showed a P value of 0.068, which revealed a difference, yet not statistically significant.

Discussion

Our study suggested that 7 field IMRT is superior to 4 field 3DCRT plans in significantly reducing the average percentage of irradiated volume of both lungs resulting from >20 Gy doses and of the heart receiving 30Gy in EC patients under chemoradiation.

The irradiated lung volumes of both lungs in terms of V20 were significantly higher with 3DCRT plan than that with IMRT plan in our study. Ghosh et al. showed no significant dosimetrical differences between 5 field 3DCRT and IMRT plans, but indicated a higher chance of lung toxicity in IMRT arm.¹² Minimizing the volume of lung irradiated to very low doses could result in less pulmonary toxicity.¹³ IMRT provides a greater benefit when the tumor is concave.¹⁴ Various studies have shown different results regarding the benefit of IMRT technique in reducing the lung, heart, and spinal cord doses. Fenkell et al. reported an increased volume of normal tissues receiving low radiation doses with IMRT technique compared with 3DCRT.¹⁵ Xu et al., in their systematic review and meta-analysis

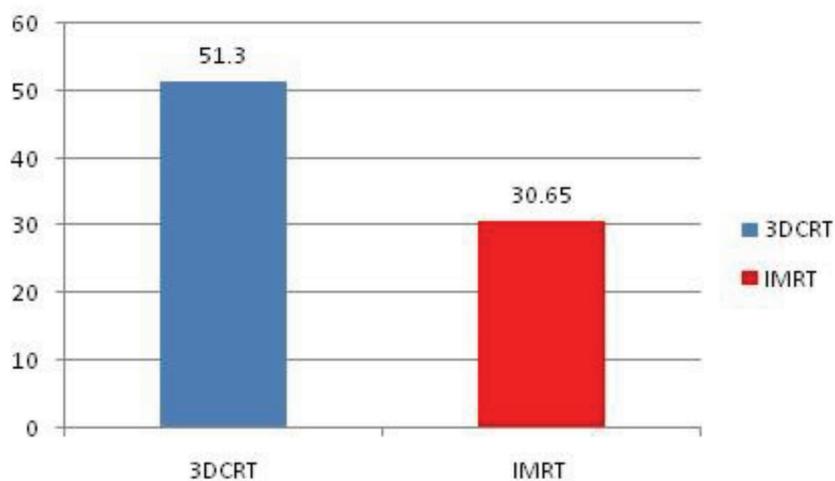


Figure 4. This figure shows the mean volume of heart receiving 30 Gy (V30) in 3DCRT and IMRT techniques. 3DCRT: 3-dimensional conformal radiotherapy.; IMRT: Intensity modulated radiotherapy

of seven various studies, suggested that IMRT is clinically superior to 3D-CRT in the overall survival of ECs and could significantly reduce the mean percentage of irradiated volume of both lungs resulting from >20 Gy doses and of the heart from 50 Gy; meanwhile, they found it to have no clinical advantages in reducing the incidence of radiation-induced pneumonitis and esophagitis.¹⁶

Our study also addressed whether 7 field IMRT provides lower lung and heart toxicity, when compared with the 4 field 3DCRT. The results of the study are in accordance with the meta-analysis, demonstrating a statistically significant advantage of using IMRT over 3DCRT in reducing the mean percentage of dose to lungs, heart, and spinal cord.

The lung is the most challenging organ at risk, which restricts dose escalation to EC. The irradiated lung volumes of both lungs in terms of V20 was significantly higher with 3DCRT plan in our study. The maximum dose delivered to both the lungs were also higher in 3DCRT technique. These results were in line with the study by Chandra et al., where they found lower lung volume irradiation in V10 and V20 in IMRT techniques.¹⁷

In our dosimetric study, the 4 field 3DCRT plan was generated in all the patients with 4 fields in phase 1 in order to achieve better conformity in delivery of dose in a low energy 6MV linear accelerator considering the patients' higher anterior

posterior chest thickness of 16-18 cm. This was in contrast to many other studies that used only 2 fields (AP-PA) during phase 1 in the 3DCRT plan. The addition of two more fields (2 posterior obliques) during phase 1 in the 3DCRT plan provided better target volume conformity, but resulted in higher dose percentages in both lungs and heart tissue. Through the use of 7 field IMRT technique, the bilateral lungs and heart will be saved significantly with a reduction in their irradiated dose percentages in comparison with the 4 field 3DCRT technique. The 7 field IMRT had gantry angles, which were selected equally with 52 degrees in each field with coplanar beams to have the best possibility to cover the PTV and save the organs at risk.

Our study revealed a higher mean and median dose to the heart in the 3DCRT plan than in those in IMRT plan. The dose volume evaluation of V30 in IMRT technique showed lower heart volume irradiation as compared with the 3DCRT plans with a statistically significant *P* value of <0.001. These results were also confirmed in the study by Ghosh et al., where the minimum, maximum, and mean dose distribution to the heart was higher in the 3DCRT plan, yet not exceeding the dose constraints.¹² Xu et al., in a meta-analysis, showed that the irradiated volume of heart in patients treated with doses <50 Gy showed no significant differences between the two radiotherapy techniques; meanwhile, when doses were >50 Gy, it resulted in significantly

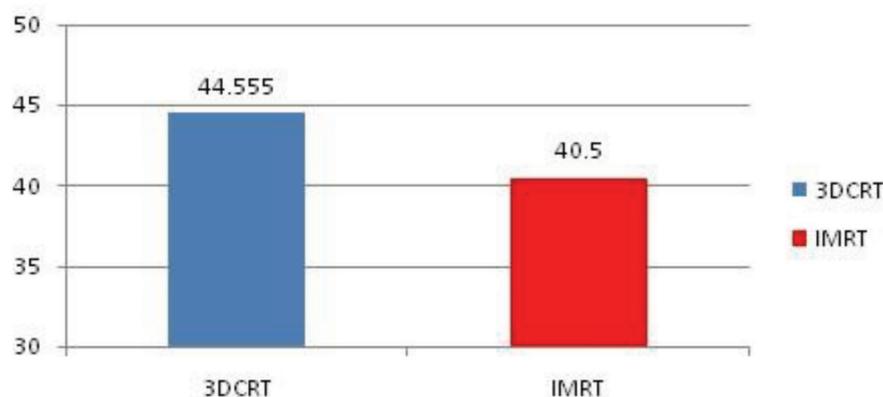


Figure 5. This figure shows the maximum dose received by spinal cord in 3DCRT and IMRT techniques. 3DCRT: 3-dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy

higher irradiated heart volumes for 3D-CRT than those in IMRT.¹⁶ Higher radiation dose delivered in the setting of definitive chemoradiation prolongs the overall survival period. The late toxicity of heart becomes a major factor for treatment failure or decreased survival rate, which necessitates a dose constraint for heart during planning external beam radiation.

The current study had a median CI for all the patients in 3DCRT plan and IMRT plan of 0.9250 and 0.965, respectively. Wu et al. also demonstrated a relatively higher overall mean CI with the IMRT plans with a CI of 0.62, while those for the forward and inverse 3DCRT were less (0.57 and 0.55, respectively) in carcinoma esophagus patients.¹⁸ The logical basis of using conformal radiation treatment is to shape the prescribed isodose volume perfectly around the PTV so as to achieve a CI of 1.0. However, certain factors, like irregular PTV shapes and close proximity of organs at risk, pose a challenge to achieve the desired CI. Our usage of further fields in both techniques helped us to achieve much higher conformity indices.

The present work is the first study comparing a 4 field 3DCRT plan in phase 1 to 3 field in phase 2; however, we encountered a few limitations. Primarily, the included sample number was limited and further prospective studies are needed to draw a reliable conclusion. Secondly, the study did not have a clinical correlation with respect to the patients' follow-up in order to estimate the treatment-related locoregional disease control assessment and overall survival statistics.

Conclusion

Our study suggested that 7 field IMRT is superior to 4 field 3DCRT plans in significantly reducing the average percentage of irradiated volume of both lungs resulting from >20 Gy doses and of the heart receiving 30Gy in EC patients under chemoradiation. Further larger prospective studies are needed on the study design and clinical correlation with the related toxicity and survival parameters to confirm the advantages of 7 field IMRT to those of 4 field 3DCRT concerning the

treatment of ECs.

Conflict of Interest

None declared.

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