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DOSIMETRIC COMPARISON BETWEEN 3-DIMENSIONAL CONFORMAL RADIATION THERAPY AND INTENSITY MODULATED RADIOTHERAPY IN CARCINOMA ESOPHAGUS

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ABSTRACT

Background: The management of loco regional or locally advanced esophageal or gastro esophageal junction cancer has shifted from surgery or radiation single modality approaches to tri modality approach with the addition of chemotherapy.[1] This Multimodality approach can cause various treatment-related complications.[2-4] Despite improved local, regional, and distant control and increased survival, roughly 50% of patients treated with chemoradiation will have persistent local disease or recurrence.[5] Hence better local treatment through radiotherapy may be needed to improve the overall treatment outcome.

Aims and objectives

- To compare Planning Target Volume (PTV) coverage and doses to normal structures between 3DCRT and IMRT plans for esophageal carcinoma patients.
- To evaluate if Dose Escalation is possible by using IMRT.

Methods: A total of 30 patients presenting to department of Radiation Oncology with non-metastatic Carcinoma Esophagus of any subsite with less than or equal to 10 cms were enrolled to the study. Patients were treated with 3DCRT to a dose of 5040cGy in 28 fractions. Three IMRT plans were generated on the same CT images. First plan of dose 5040cGy was compared with 3DCRT plan for PTV coverage and doses to organs at risk using DVH. Two more plans were generated to check feasibility of dose escalation to 6040cGy and 7040cGy with respect to organs at risk. **Results:** In our study IMRT had a better PTV coverage and Conformality Index (CI) when compared with 3DCRT. Doses to normal structures like Spinal cord and Heart were significantly spared with IMRT ($p < 0.001$) while Lung doses were higher in IMRT. Dose escalation to 6040cGy and 7040cGy was feasible with IMRT as the organs at risk did not exceed tolerable limits. **Interpretation & Conclusion:** IMRT offers the opportunity to sculpture radiation dose by improving target homogeneity while sparing normal organs by taking advantage of a sharp dose gradient except lung. Hence Hybrid technique of combining 3DCRT and IMRT is recommended to take advantage of both the techniques.

KEYWORDS: 3DCRT, IMRT, Carcinoma Esophagus.

INTRODUCTION

Esophageal carcinoma accounts for approximately 6% of all gastrointestinal malignancies.[6] With an annual incidence of 572034 new cases Esophageal carcinoma is the eighth most common cancer worldwide and sixth most common cause of cancer-related deaths (508585).[7]

Radiotherapy is a major treatment modality for esophageal carcinoma as more than 60% of the patients are diagnosed at an advanced stage which are deemed unresectable.[8] Traditionally, cancers of the esophagus have been treated using Antero Posterior/ Postero Anterior (AP/PA) field arrangement up to cord tolerance dose, followed by an off-cord boost. Other beam arrangements include 4-field box technique with less weightage on the lateral beams in an effort to reduce lung dose and 3-field technique with an AP field and 2 posterior oblique fields. Treatment planning and delivery for esophageal cancer has progressed rapidly over the past 5 years. 3D Conformal Radiation Therapy (3D-CRT) was the planning method of choice for many years.[9] Innovative technologies in radiation delivery such as Intensity-Modulated Radiotherapy (IMRT) offer the potential for improved tumor coverage, while reducing the doses delivered to the surrounding normal tissues.[10]

IMRT is capable of generating significant dose gradients between the target volume and adjacent tissue structures to accomplish the intended dose–volume prescription.

Several critical organs are usually in close proximity to the tumor which makes radiation therapy a very challenging task. Radiation to esophageal cancers typically involves part of the spinal cord, heart and lung leading to late effects such as dysphagia, pneumonitis and cardiac injury. Pericarditis is the most prevalent late side effect of treating esophageal cancer with conventional techniques. With the advent of 3DCRT, the doses to these organs could be reduced. IMRT holds promise to provide excellent loco-regional control while sparing dose to normal structures. Hence we have undertaken this study in our institution to explore the possible advantages of IMRT to further reduce the doses to the organs at risk and dose escalation to tumor and its clinical applications.

AIMS AND OBJECTIVES

- To compare Planning Target Volume coverage and doses to normal structures between 3DCRT and IMRT plans for esophageal carcinoma patients
- To evaluate if Dose Escalation is possible by using IMRT.

MATERIALS AND METHODS

This dosimetric study was carried out on 30 consecutive non metastatic esophageal cancer patients presenting to the department of Radiation Oncology, Vydehi Institute of Medical Sciences. The study was a prospective nonrandomized observational study.

RADIOTHERAPY DETAILS

All the patients were treated with 3-Dimensional Conformal Radiation Therapy. Intensity Modulated Radiation therapy plans were generated on the same set of CT images.

STEPS

CT Simulation

Patient was set up in supine position with arms raised above. Immobilisation was done with a wing board and thermoplastic mask using room lasers. Based on the location of the esophageal cancer 5mm thickness CT scan images were acquired with fiducial markers placed at appropriate location.

Planning

The planning CT images were transferred to the Varian Eclipse treatment planning system V.11. A 3DCRT plan for a dose of 5040cGy in 28 fractions and 3 IMRT plans for doses of 5040cGy, 6040cGy & 7040cGy respectively were generated. For Calculation AAA (Anisotropic Analytical Algorithm) and Grid size of 0.25cm were used. For Optimization PRO (Progressive Resolution Optimization) was used.

Study Design

Volumes: The following volumes were defined (Fig 1)
Gross Tumor Volume (GTV) was delineated for the Primary lesion & involved lymph nodes (GTV N) visualized on contrast enhanced diagnostic CT scan and upper GI endoscopy & PET CT if present. Clinical Target Volume (CTV) includes GTV plus the subclinical disease (regional lymph nodes & submucosal) which was derived by giving a proximal & distal margin of 4cm & radial margin of 1.5cm. Planning Target Volume (PTV) includes CTV + 0.5cm & PTV Boost includes GTV + 4 cm proximal & distal margin & radial margin of 1.5cm. Organs at risk included were Spinal cord, Heart and Lungs.

3 Dimensional Conformal Radiation Therapy (3DCRT)

Phase I – Dose of 3600cGy in 20 fractions, 180cGy per fraction, 5 fractions per week was prescribed to PTV1 using AP/PA fields (Fig 2)

Phase II – Dose of 1440cGy in 8 fractions, 180cGy per fraction, 5 fractions per week was prescribed to PTV Boost. In the boost phase the fields differed in the following ways to reduce doses to OARs.

Upper third esophagus – Two anterior oblique fields
Middle third esophagus – One anterior field and two oblique posterior fields (Fig 3)
Lower third esophagus – One anterior field and one or two posterior fields

Intensity Modulated Radiation Therapy (IMRT)

Three IMRT plans were generated. The plans were made for sequential delivery.

- **Plan 1**

Phase I: Dose of 5040Gy in 28 fractions, 180cGy per fraction, 5 fractions per week was prescribed to PTV 1 using 5-7 non coplanar fields (Fig 4)

- **Plan 2**

Phase I: Same as in plan 1.
Phase II: PTV Boost defined as GTV + 3 cm margin both proximally, distally and radial margin of 1.5cm. Additional dose of 1000cGy in 5 fractions, 200cGy per fraction, 5 fractions per week was prescribed to PTV Boost using 5-7 non coplanar fields escalating the Total Dose up to 6040cGy.

- **Plan 3**

Phase I: Same as in plan 1 and 2.
Phase II: PTV Boost defined as GTV + 2 cm margin both proximally, distally and radial margin of 1.5cm. Additional dose of 2000cGy in 10 fractions, 200cGy per fraction, 5 fractions per week was prescribed to PTV Boost using 5-7 non coplanar fields escalating the Total Dose up to 7040cGy.

Plan comparison

Dose volume Histogram (DVH) tool was used for comparison of 3DCRT and IMRT (5040cGy) plans. The plans were compared in terms of PTV coverage, CI and Homogeneity Index(HI). IMRT plans for 6040cGy and 7040cGy were generated to see the feasibility of dose

escalation without exceeding the tolerance limits of organs at risk. All the plans were aimed to achieve a minimum dose >95% and a maximum dose <110% of the prescribed dose. The primary objectives with regard to the OARs were defined as follows:
Spinal cord- Dmax <45 Gy.
Lung: V33 - 33% Volume of total lung should not receive more than 20 Gy
Mean lung dose(MLD): ≤ 20 – 23 Gy
Heart: V67 - 67% Volume of total heart should not receive more than 40 Gy
Mean cardiac dose: < 26Gy (<15% pericarditis)

Statistical Analysis
Our study is a Non randomised prospective observational dosimetric study. The Statistical analysis was performed by STATA 11.2 (College Station TX USA). Shapiro wilk test were used to check the normality. Students independent sample t-test were used to find the significant difference between the age, maximum and mean dose to spinal cord, Lung V3 and MLD, Heart V63 and MCD, volume of PTV(V95), D5, D95, Prescribed Dose (Dp) - Minimum, maximum and Mean doses, CI and HI to compare between the two groups and is expressed as mean and standard deviation. P value <0.05 was considered statistically significant.

Significant Figures
Suggestive significance (P value: 0.05 to <0.10)
Moderately significant (P value: 0.01 to ≤ 0.05)
Strongly significant (P value: ≤0.01)

RESULTS
The patients age ranged from 43 to 67 years. The median age was 57.3 yrs. There were 17 male patients (57%) and 13 female patients (43%).

Comparison with respect to PTV coverage (Table: 1)
IMRT plan showed significant difference in terms of V95, D5, D95, CI (p <0.001 to p<0.005). There was no significant difference in Volume, Minimum, maximum and mean prescribed doses.

Table 1: PTV coverage for 3DCRT and IMRT (5040cGy).

	3DCRT	IMRT		P-Value
	Mean ± SD	Mean ± SD	Mean Difference	
Volume of PTV (cc)	346.41 ± 39.06	346.41 ± 39.06	0	1.000
V95 (cc)	572.17 ± 51.89	419.74 ± 51.80	152.43	<0.001
D5 (cGy)	5147.34 ± 69.58	5186.70 ± 25.26	39.36	0.005
D95 (cGy)	4384.95 ± 47.84	4878.22 ± 52.43	43.27	0.002
Dp (cGy)	5040	5040	0	
Min Dose (cGy)	4442. 49 ± 172.05	4194.51 ± 408.30	227.98	0.023
Max Dose (cGy)	5310.96 ± 69.86	5302.53 ± 55.08	8.42	0.606
Mean Dose (cGy)	5048.23 ± 42.17	5047.95 ± 24.04	0.279	0.975
CI	1.66 ± 0.11	1.21 ± 0.07	0.44	<0.001
HI	0.06 ± 0.02	0.06 ± 0.01	0.0008	0.827

Comparison with respect to OAR'S(Table:2)
Maximum and Mean doses to spinal cord were significantly reduced in IMRT plan (p<0.001). V33 and MLD were lesser in 3DCRT plan (p<0.001). Heart region was better spared by IMRT plan (p<0.001)

Table 2: Comparison with respect to OAR'S (Spinal Cord, Heart and Lungs).

SPINAL CORD	3DCRT Mean ± SD	IMRT Mean ± SD	Mean Difference	P-Value
Max Dose (cGy)	4284.86 ± 85.29	3270.91 ± 219.54	1013.95	<0.001
Mean Dose (cGy)	3770 ± 331.77	1787.59 ±347.63	1982.77	<0.001
LUNG				
V33 (cc)	1382.40 ± 209.72	1799.34 ± 142.15	416.94	<0.001
MLD (cGy)	1379.68 ± 233.77	1560.16 ± 191.02	180.48	0.112
HEART				
V67 (cc)	3860.74 ± 660.92	2294.51 ± 637.79	1566.23	<0.001
MCD (cGy)	3476.21 ± 382.28	2904.54 ± 538.83	571.66	0.006

Comparison with respect to PTV coverage in Dose Escalation plans using IMRT for 6040cGy and 7040cGy (Table: 3)

Table 3: Details of Tumor coverage in IMRT for 6040cGy & 7040cGy.

IMRT	**6040cGy**	**7040cGy**
	Mean	Mean
Volume of PTV (cc)	167	148
V95 (cc)	283.6	251.0
D5 (cGy)	6191.08	7213.9
D95 (cGy)	5888.06	6837.44
Dp (cGy)	6000	7000
Min Dose (cGy)	5394	6161.7
Max Dose (cGy)	6270.40	7307.4
Mean Dose (cGy)	6090.4	7090.4

Comparison with respect to OAR'S in Dose Escalation plans using IMRT for 6040cGy and 7040cGy (Table:4)

Table 4: Doses to Heart, Lung and Spinal Cord.

HEART	6000cGy	7000cGy
	Mean	Mean
V67 (cc)	2551.73	2764.33
MCD (cGy)	3339.6	3687.1
LUNG		
V33 (cc)	1824.77	2018.08
MLD (cGy)	1572	1728
SPINAL CORD		
Mean	1477.3	1724
Max	2836.8	3453

DISCUSSION

D95 (Fig 5) was better in IMRT than 3DCRT plans (4878.22cGy vs. 4384.95). Maximum, minimum and mean doses were similar in both the plans. CI (Fig 6) was significantly better in IMRT (1.21) than with 3DCRT (1.66) [p<0.001]. HI was comparable with both the techniques. Louis fenkell[9] et al compared IMRT and 3DCRT with respect to Conformality of target coverage and normal tissue sparing in cervical esophagus. The study showed that IMRT provides superior target volume coverage and Conformality, with decreased dose to normal structures.

Spinal cord (Fig 7) was better spared with IMRT than 3DCRT plan (p<0.001). Maximum and Mean doses were 3270cGy & 1787cGy with IMRT and 4284cGy and 3770cGy with 3DCRT respectively. Lung V33 (Fig 8) was 1382cGy in 3DCRT and 1799cGy in IMRT (p<0.001). Lungs were better spared with 3DCRT than IMRT. This is due to multiple beam arrangement in IMRT delivering lower doses to more lung volume.[11] The MLD (Fig 9) were similar in both modalities. Emami[12] et al. concluded that dose to the spinal cord should be limited to 45 Gy (1.8–2.0 Gy daily). V20 of bilateral lung should be limited to 33% as probability of pneumonitis increases rapidly when V20 > 33%. Heart was better spared with IMRT than 3DCRT (p<0.001). V67 (Fig 10) and MCD were 2294cGy and 2904cGy with IMRT whereas with 3DCRT, V67 and MCD (Fig 11) were 3860cGy and 3476cGy respectively. Byhardt[13] et al. concluded that V40 of the heart should be limited to 50% or less, and the dose to the entire heart should be limited to 30 Gy.

As a secondary objective we estimated the feasibility of dose escalation to 6040cGy and 7040cGy with IMRT. DVH was used to determine the doses to organs at risk in both the plans. In the 6040cGy plan, MCD was 3339cGy and V67 was 2551cGy. MLD was 1572cGy and V33 was 1824cGy. Spinal cord received a maximum dose of 2936cGy. In the 7040cGy plan, Heart received a mean dose of 3687cGy and V67 was 2764cGy. MLD was 1728cGy and V33 was 2018cGy. Spinal cord received a maximum dose of 3453cGy. In a study done by James Welsh[14] et al the use of SIB-IMRT has shown to selectively increase the dose to the GTV while simultaneously reducing the dose to the normal heart, lung, and liver. Our dosimetric study showed a better target coverage and significantly lesser dose to heart and spinal cord with IMRT than 3DCRT plan. Furthermore, dose escalation to 6040cGy and 7040cGy was possible without exceeding tolerance limits to the organs at risk with IMRT plans. Clinical data is needed to validate these results.

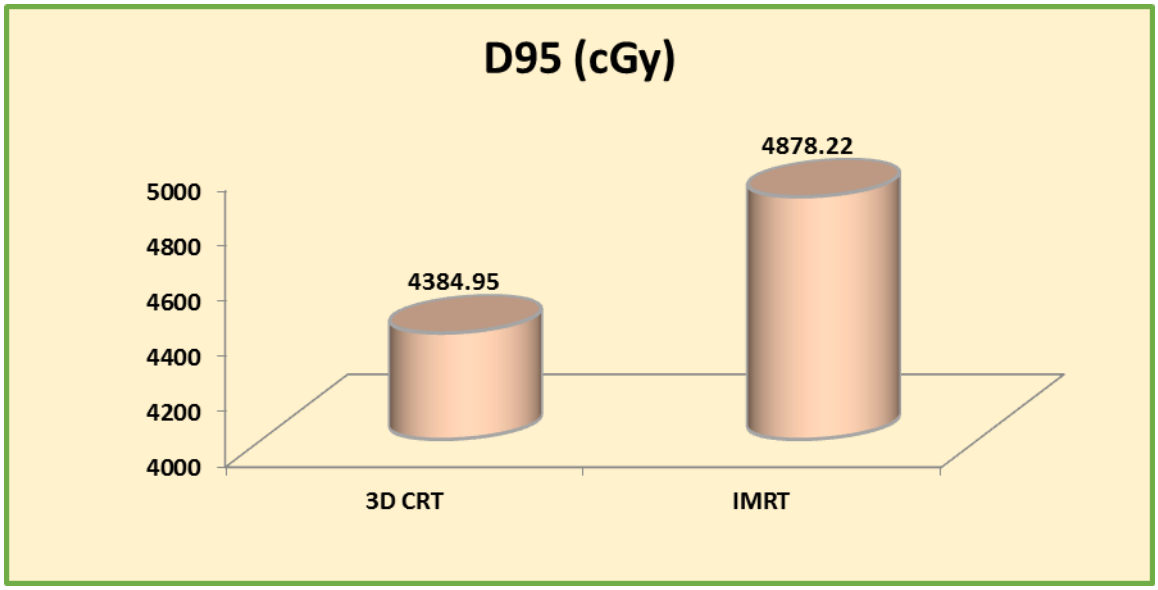

Figure 5: Bar graph Comparing Dose received by 95% of volume in both modalities.

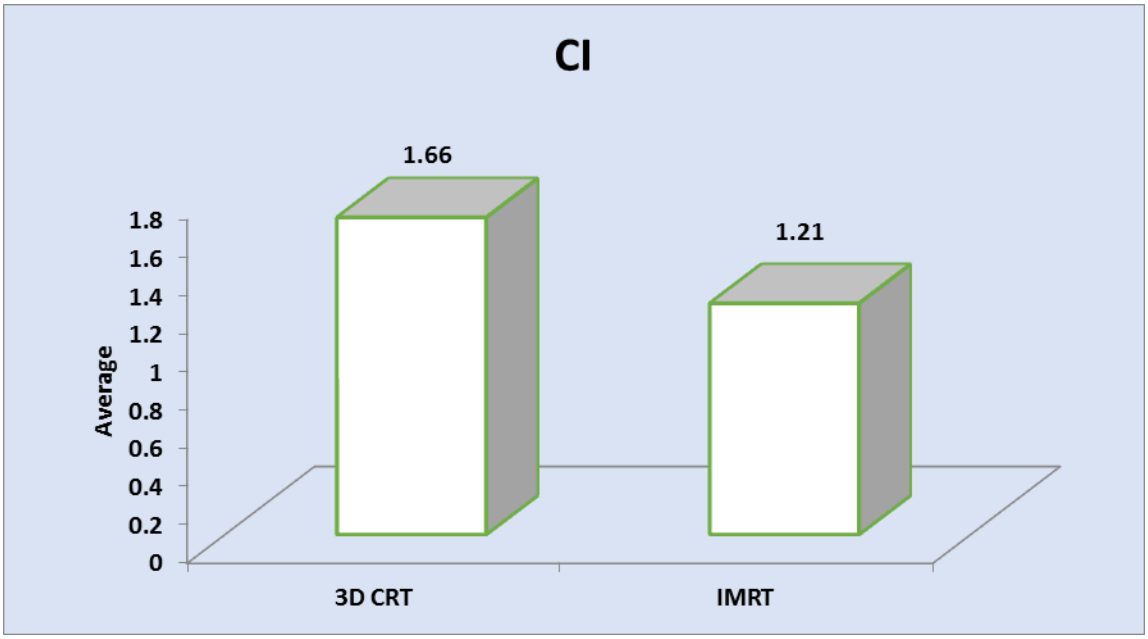

Figure 6: Bar graph showing Conformality Index in both modalities.

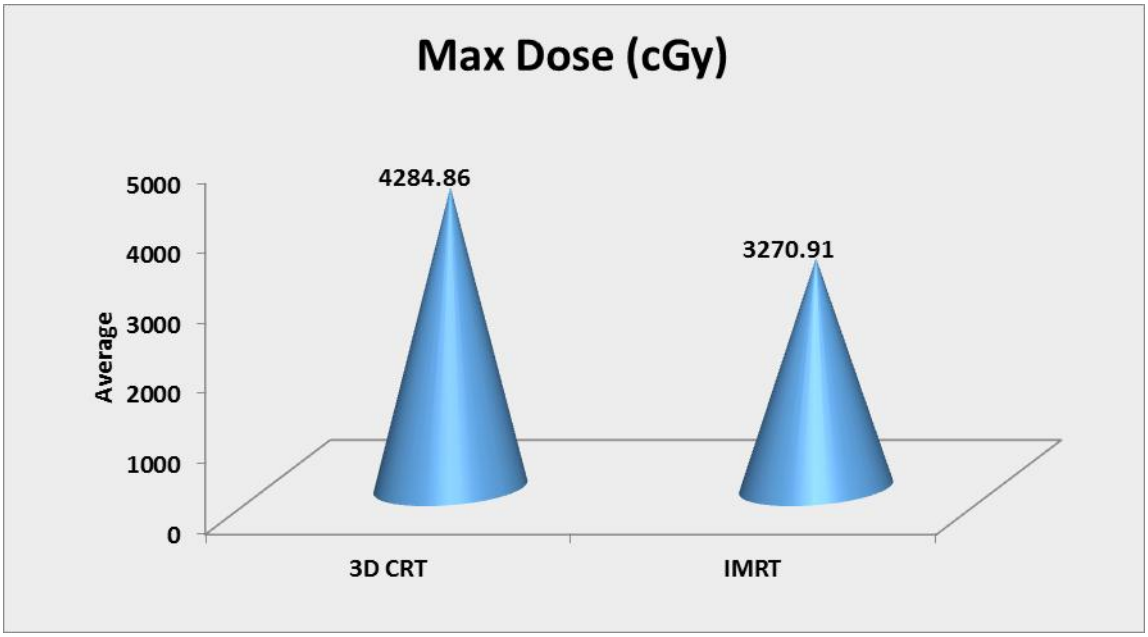

Figure 7: Bar graph showing Maximum dose to spinal cord.

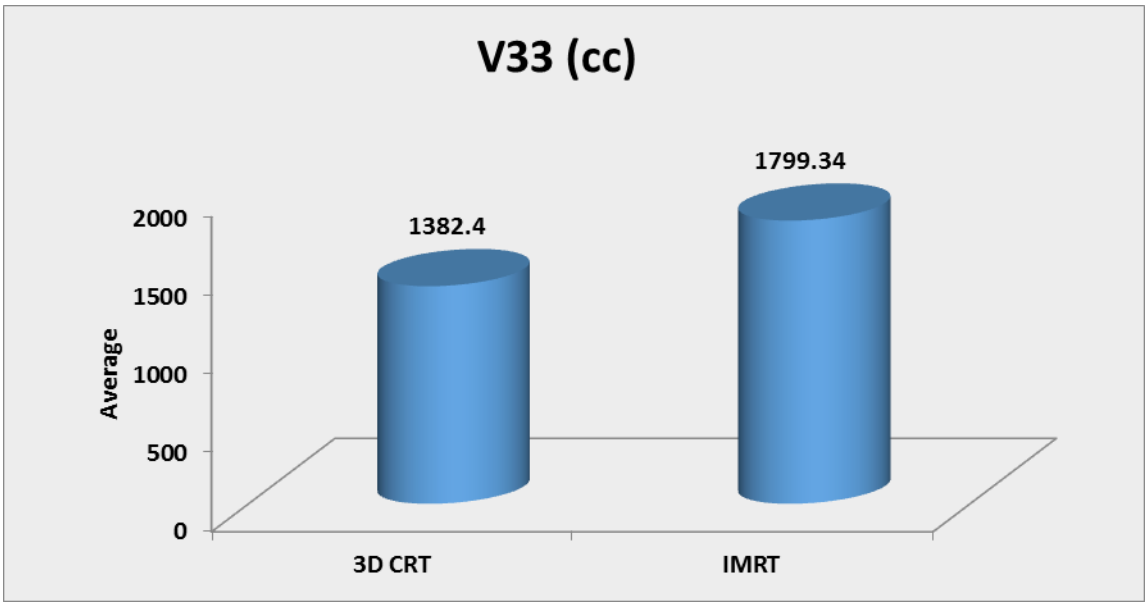

Figure 8: Bar graph showing dose received by 33% volume of lung in both modalities.

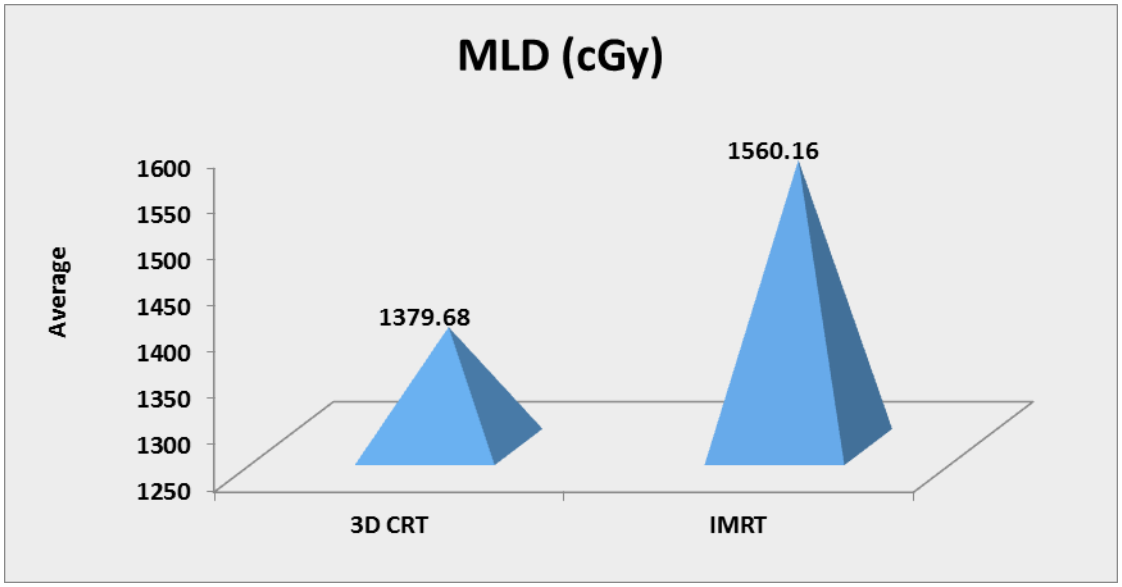

Figure 9: Bar graph showing Mean lung dose in both modalities.

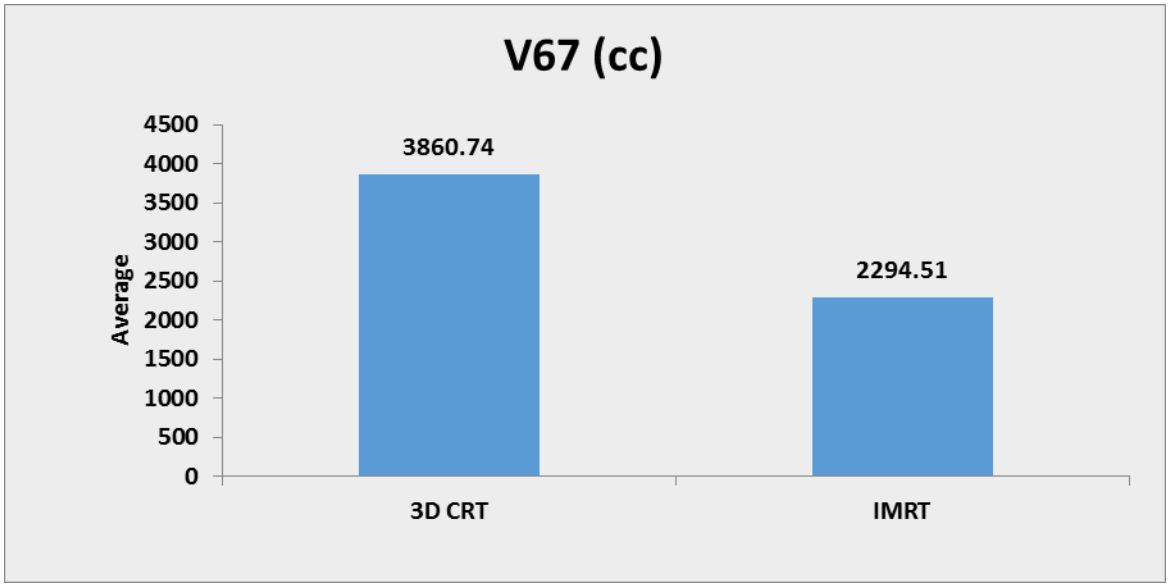

Figure 10: Bar graph showing dose received by 67% volume of heart in both modalities.

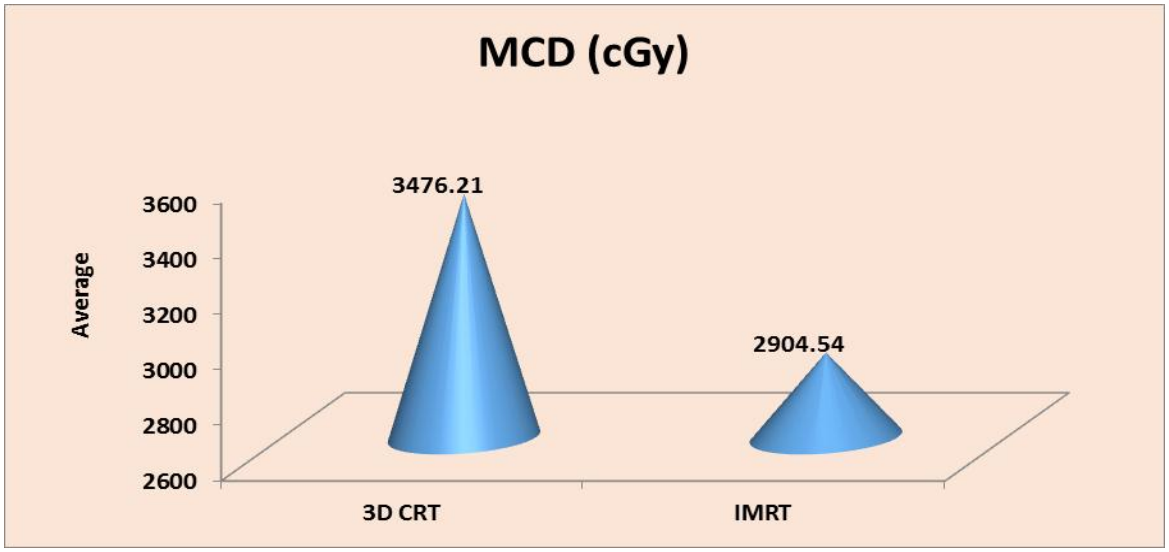

Figure 11: Bar graph showing Mean cardiac in both modalities.

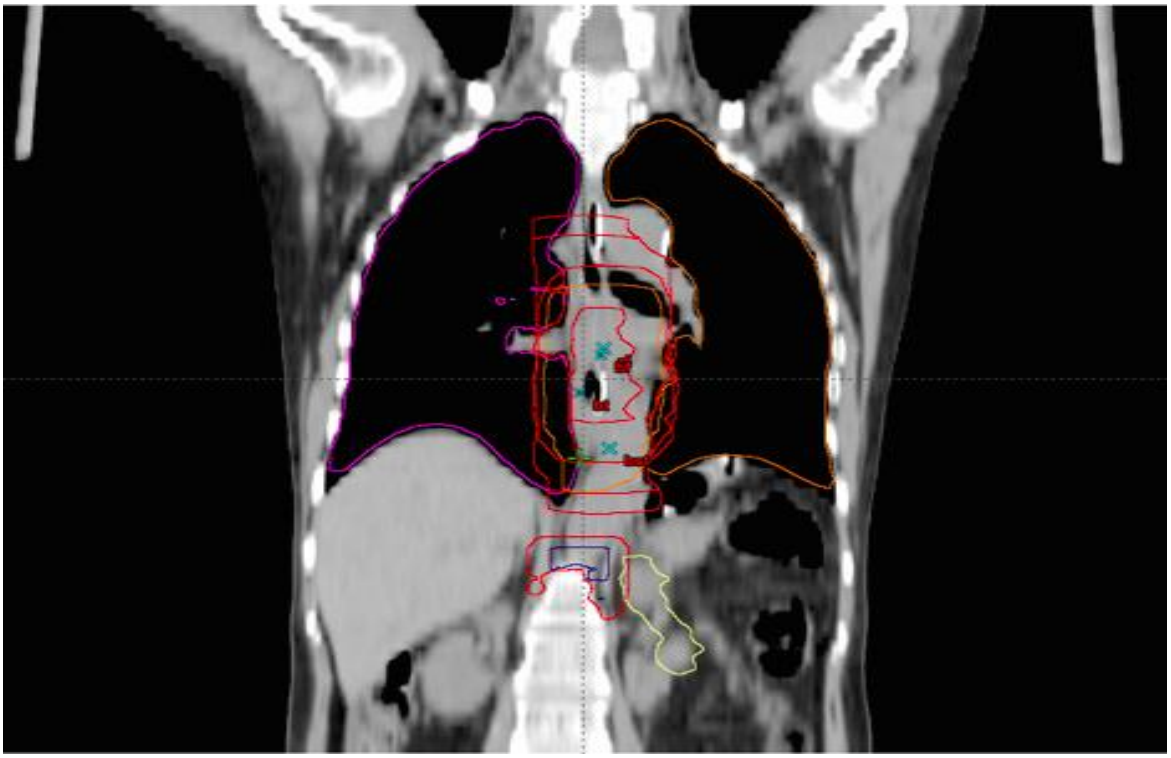

Figure 1: Volumes contoured in mid one third Esophageal Carcinoma.

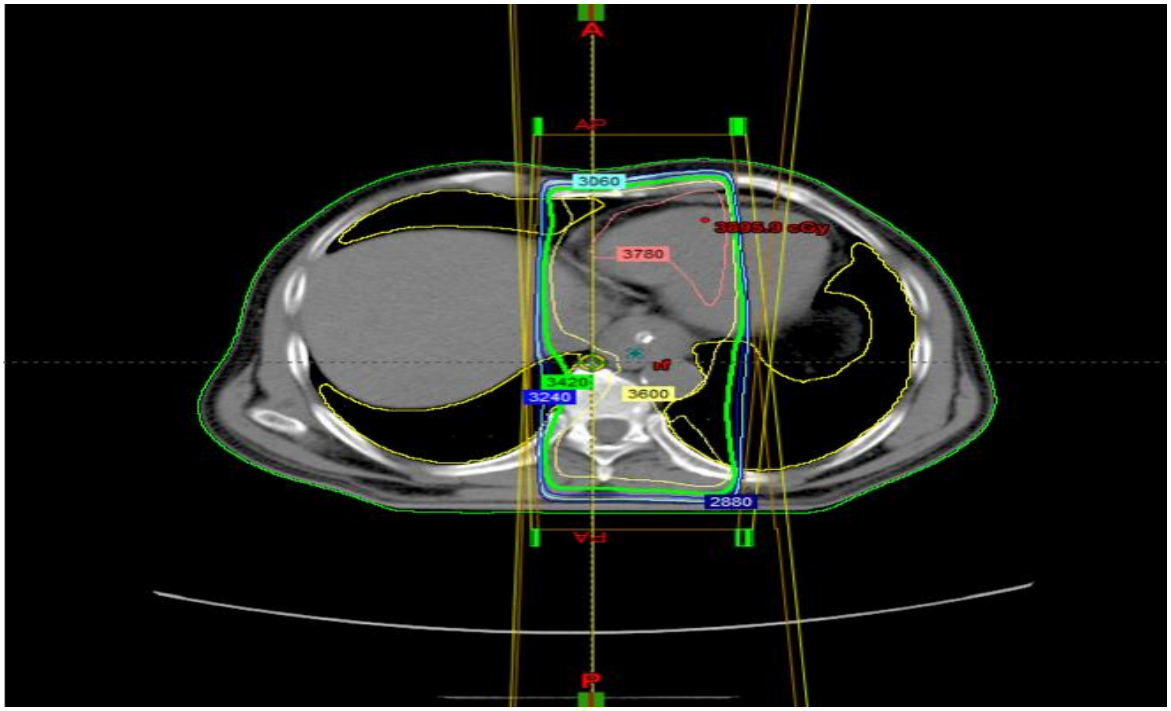

Figure 2: Typical AP/PA Field for 3DCRT.

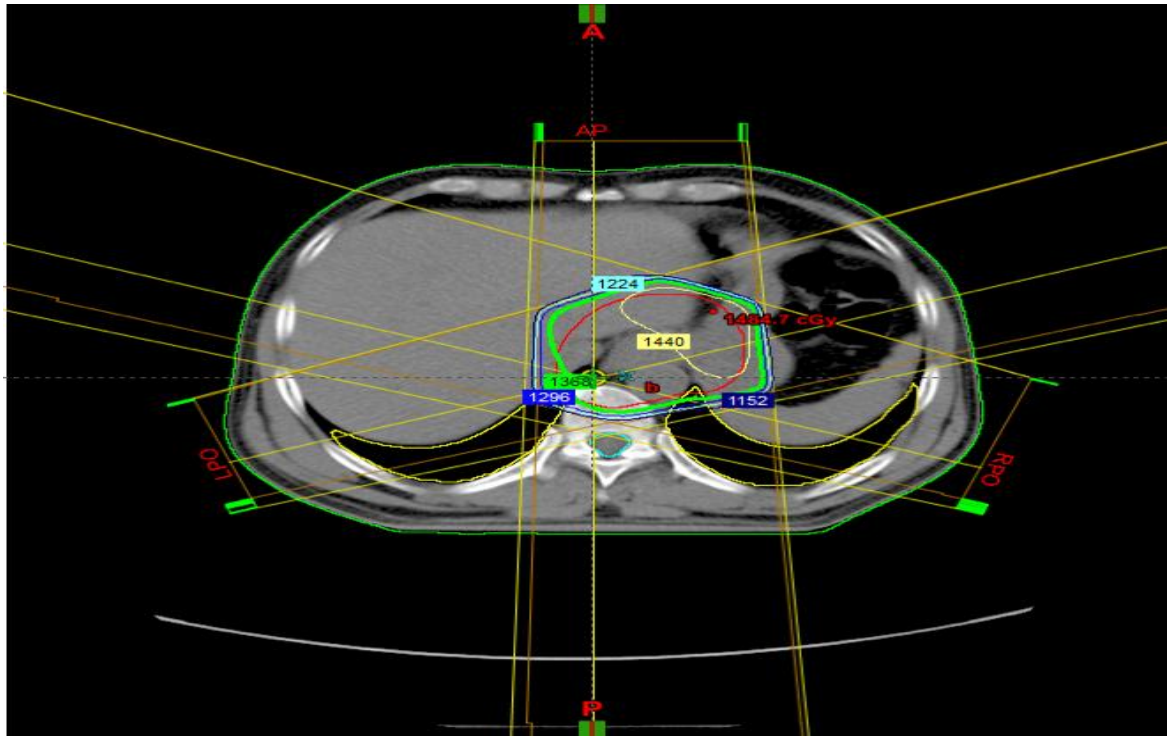

Figure 3: Typical Oblique fields for 3DCRT.

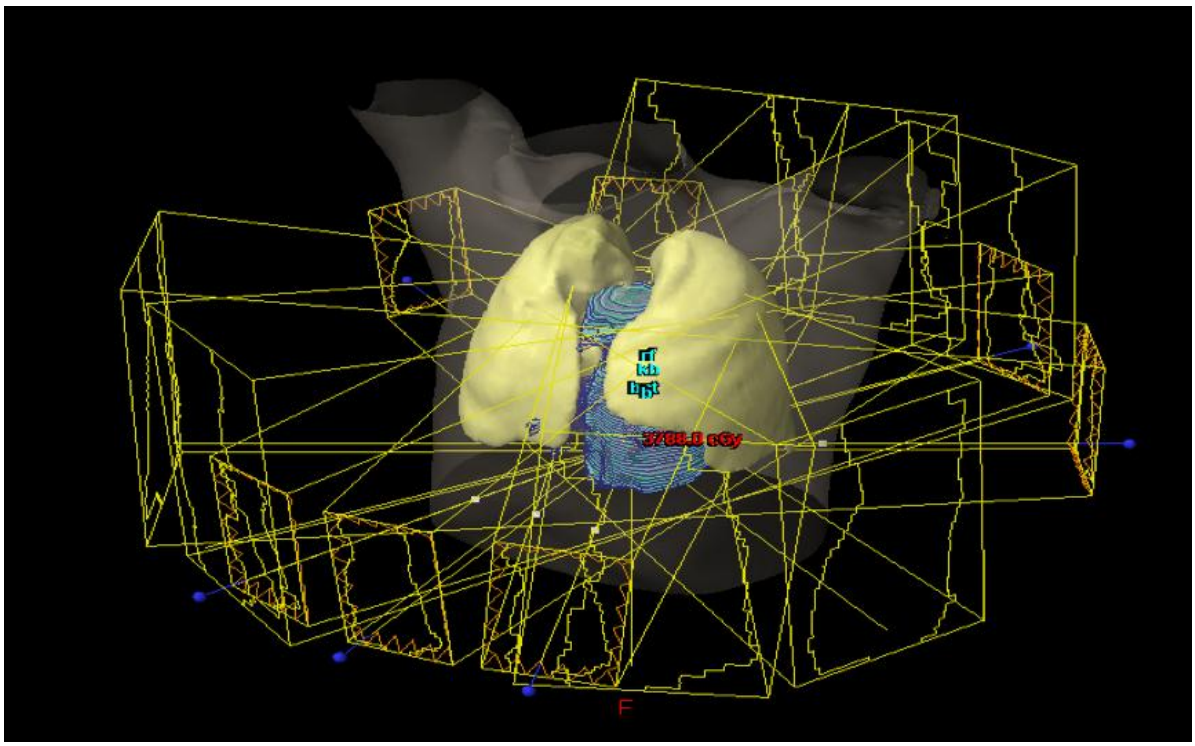

Figure 4: Seven field IMRT Plan.

CONCLUSION

IMRT definitely had a better tumor coverage when compared with 3DCRT. Though IMRT increased lung dose it has shown better sparing of spinal cord and heart. As there was better sparing of organs at risk even at higher doses, dose escalation to 7040cGy is feasible with IMRT and the clinical reflection of such dosimetric escalation is a subject of further investigation. Furthermore, by taking the advantages of both the techniques, a hybrid technique by combining 3DCRT and IMRT can be evaluated.[15]

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