Original Research Article

Volumetric modulated arc therapy and concurrent chemotherapy for esophageal cancers: Dosimetric comparison with 3D conformal radiotherapy and early clinical results

Pawar Y.S.[1], Manjula M.V.[2], K. Ramalingam[3], R. S. Ashok[4]

[1]Dr. Y.S. Pawar, Radiation Oncologist, [2]Dr. Manjula M.V., Radiation Oncologist, [3]Mr. K. Ramalingam, Medical Physicist and RSO, [4]Mr. R. S. Ashok, Medical Physicist and RSO; all authors are affiliated with Department of Radiation Oncology, Yashoda Cancer Institute, Hyderabad, India.

Corresponding Author: Dr. Manjula M.V., Department of Radiation Oncology, Yashoda Cancer Institute, Somajiguda, Hyderabad, India. E-mail: samu101107@gmail.com

Abstract

Purpose: Despite Intensity Modulated Radiotherapy being the standard of care for most sites, 3D conformal radiotherapy (3DCRT) is still more widely used in esophageal cancers. This study compares dosimetric results of volumetric modulated arc therapy (RA) with that of 3DCRT and evaluates early clinical results of the patients treated with RA and chemotherapy. **Materials and Methods:** Evaluation of clinical outcomes in 10 patients treated definitively with RA and concurrent chemotherapy for esophageal cancer were included in the study. These patients were retrospectively planned with 3DCRT using antero-posterior portals till 3960cGy followed by obliques to a total dose of 5940cGy. The dose and target in each phase were kept same in both the plans. Dosimetric parameters were compared between the two plans using paired T-test or a Wilcoxon sign-rank based tests of normality on data distribution. **Results:** With a minimum follow-up of 4 months, all the patients tolerated the treatment without grade IV toxicities and treatment interruptions. 7 patients had a complete response and 3 had a partial response of which one patient underwent surgery and is disease free. RA resulted in higher conformity to the target compared to 3DCRT (mean conformity index 1.1 vs.1.8 respectively (p=0.002). RA plans significantly spared lung V15 (32% vs. 40.2%, p=0.003), V20 (22.7% vs. 29.7%, p=0.003), mean lung dose (13.8Gy vs.17.1Gy, p=0.003), heart V30 (46.8%vs.55.2% p=0.002), mean heart dose (24.3Gy vs.28.1Gy, p=0.003), and spinal cord maximum dose (44Gy vs.46.9Gy, p=0.002). The mean V5 and V10 values were similar with either technique. **Conclusion:** Irrespective of site of involvement, the RA resulted in better conformity and better sparing of heart, spinal cord and lungs beyond 15Gy. The dosimetric advantage gained with RA may become clinically relevant in reducing cardio-pulmonary complications especially in multimodality setting.

Keywords: Esophageal Cancer, Volumetric Modulated Arc Therapy, Intensity Modulated Radiotherapy, Chemoradiation, Lung Toxicity

Introduction

Concurrent chemoradiotherapy has been the standard treatment for patients with cancer of esophagus [1-3]. The RTOG 8501 study showed that 5FU based chemotherapy given concurrently with 50.4Gy of radiotherapy yields the best possible outcome compared to all previously reported results [1]. The standard radiotherapy portals consist of antero-posterior portals in the first phase of treatment followed by anterior or posterior obliques in the final phase depending on the location of tumor [1].

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The use of conformal IMRT techniques has not been popular for the treatment of esophageal cancers due to various reasons, the foremost being increased radiation dose to lungs compared to conventional techniques. The non-availability of robust data on clinical benefit of such techniques adds to this apprehension.

Volumetric Modulated Arc Therapy (RA) has been shown to be dosimetrically superior to 3 Dimensional Conformal Techniques (3DCRT) as well as conventional IMRT techniques in the treatment of several sites such as head neck, anal canal, uterine cervix, brain tumors etc [4-7].

In addition, volumetric modulated arc therapy has been shown to reduce the treatment delivery time [4-6,9]. A recent study conducted at our centre has also shown that this technique enhances the clinical throughput in the department [8,9]. This has led RA to be adopted as the standard way to treat patients requiring high precision techniques for several sites at our centre. The use of IMRT as fixed beam or arc therapy in esophageal cancer has not been studied extensively. The apprehensions regarding the dosimetric outcomes in terms of lung or cardiac dose with RA for esophageal cancer has not been verified prospectively using a well-designed dosimetric or clinical study. In our institution, a dosimetric evaluation has been carried out with RA on several of our esophageal cancer patients treated using 3DCRT. Based on initial encouraging results, we decided to conduct a prospective phase II study on the impact of RA techniques on patients with esophageal cancer receiving definitive chemoradiation therapy, with the intention of evaluating the dosimetric outcome, clinical response, toxicity and quality of life parameters. Here we report our dosimetric outcomes on the first 10 patients treated in this protocol, and our experience with standardizing a treatment planning process with RA.

Materials and Methods

The study was approved by institutional review board.10 patients were chosen for this analysis of dosimetric outcomes. Table 1 describes the summary of the study. All the patients were staged according to the AJCC staging system 7th edition. None of the cases chosen had hypopharyngeal or gastro-esophageal junction involvement. This was done deliberately to avoid very large and complex fields. All the plans were retrieved and 3DCRT plans were generated for each patient for comparison.

Table-1: Brief summary of the ongoing phase II study

Inclusion Criteria	Exclusion Criteria
• Patients aged between 18-65 • Must have biopsy-proven primary squamous cell or adenocarcinoma of the esophagus. • Disease confined to the esophagus and peri-esophageal soft tissue. • ECOG 0-1. • Patients included are to be assessed in multidisciplinary clinic by team of medical, surgical, radiation oncologist and surgical gastroenterologists and found suitable for planned treatment • Must sign the study specific informed consent.	• T4b and or patients having tracheoesophageal fistula. • ECOG 2 or above. • Hypopharyngeal and or gastrointestinal junction involvement. • Creatinine clearance of <65ml / min. • Metastatic disease. • Uncontrolled diabetes mellitus, hypertension and cardiac ailments • Pregnant or lactating women. • Previous history of malignancy/radiation to thorax • Unwilling for study.

Primary Objectives:

1. Feasibility of the planned treatment in multidisciplinary institutional setting.
2. Evaluation of acute, sub-acute & late toxicity with respect to esophageal and pulmonary toxicity (RTOG acute & late toxicity scoring criteria).

Secondary Objectives:

1. Estimation of treatment response as assessed at 8 weeks post treatment by an upper gastrointestinal endoscopy and PET-CT.
2. Estimation of local, locoregional control rates and disease specific & overall survival.
3. Quality of life assessment by EORTC QLQC esophageal module ESO18.

Planned Treatment

Eligible patients receive

1. Concurrent weekly cisplatin at a dose of 40 mg/m2 with adequate prehydration.
2. External beam radiotherapy with Volumetric modulated arc therapy to the target to a total dose of 5940cGy in 33 fractions

Patient setup, imaging and target definition: The patients were immobilized in supine position with arms above the shoulder on a vacloc and with a thermoplastic mask on the thorax. A planning CT was obtained in this position with 3 mm slice thickness with oral and intravenous contrast.

All targets were defined on the planning CT by the radiation oncologist based on principles of ICRU 62.The treatment was divided into two phases.

Phase-I: The targets were similar for both plans. All involved nodes were delineated as GTV nodes based on the imaging criteria of mean short axis diameter of more than 1cm.CTV-P was generated by expanding the GTV primary cranio-caudally by 4 cm and laterally 1cm respecting anatomical barriers.to include the corresponding level mediastinal nodes {Michigan University nodal delineation atlas (10)}.

For all the supracarinal lesions, bilateral supraclavicular nodal regions were included apart from upper mediastinal nodes (nodal stations 2-4). Levels 7-9 were included if the CTV was extending up to the corresponding level.

Para-aortic and sub-aortic groups (level 5and 6) were not included unless they were involved (using radiological criteria of more than 1cm). For infracarinal lesions, the corresponding level mediastinal nodes were included after expanding the CTV cranio-caudally. ITV was generated by expanding the CTV by 1cm. PTV was generated by expanding the ITV uniformly by 0.5cm. Typical 3DCRT plans consisted of antero-posterior portals in phase I.

Typical RA plans consisted of two coplanar arcs (179º-181º CW/CCW) with two avoidance sectors (250º-290º & 70º-110º). A non-coplanar arc (330º-30º, couch 90º) was added for 3 patients. PTV was prescribed a dose of 3960cGy in 22 fractions in the first phase.

Phase-II: Phase II CTV was generated by expanding the GTV by 2cm cranio-caudally and 1cm radially. ITV and PTV margins were same as in phase I. Typical 3DCRT plans consisted of 4-6 fields including two oblique portals and sub fields (anterior or posterior depending on the location of the PTV). Typical RA plans for phase II consisted of two coplanar arcs (179º-181º CW/CCW). The phase II dose for both plans was 1980cGy in 11 fractions.

Planning Parameters: Plans were developed to achieve a number of dosimetric aims For PTV, target coverage was aimed to achieve V95 = 100% of prescribed dose and V107 < 3%. For lungs, plans aimed to achieve mean lung dose (MLD) < 12Gy, lung V10 < 45%, V20 < 20%, mean heart dose (MHD) < 26Gy, heart V30 < 46% and spinal cord maximum dose (CMD) < 45Gy.

Rapid Arc plans were optimized with Progressive resolution optimizer (V 8.9.09) and dose calculations were performed using the Anisotropic Analytical Algorithm (V 8.9.09) with a spatial resolution of 2.5 mm. Conformity Index (CI) was defined as ratio of prescription isodose volume to PTV. Dose Homogeneity Index (HI) was defined as ratio of dose received by 95% of the target volume to dose received by 5% of the target volume.

The summed plans (RA phase I+II and 3DCRT phase I+II) were used for the quantitative comparison. Quantitative assessment of plans was performed based on Dose Volume Histogram (DVH) analysis. Several parameters were compared for PTV and Organs at risk (OAR) using paired T-test or a Wilcoxon sign-rank based tests of normality on data distribution. Daily KV imaging and thrice weekly Cone Beam Computed Tomography (CBCT) was done to verify treatment setups. The ITV and PTV margins used were found adequate in all the patients.

Results

Histology, length of lesion and other details of the patients included in the study are provided in table 2. Median length of esophageal lesion was 7cm (5-11cm). Mean PTV volume in phase I and phase II was 696.8cc (520.1-1089.8) and 253.1cc (202-276.8cc) respectively.

Four patients had a total lung volume to PTV ratio equal to or more than 3. The total lung volume was measured on the available CT scan that was used for planning and consequent plan evaluation.

Table-2: Patient details & treatment related toxicity. (M=male, F=female, PS=performance score, SCC= sqamous cell carcinoma, AC= Adenocarcinoma)

Pt.	Age	Sex	PS ECOG	Site	Histology	GTV Length (cm)	Total lung volume to PTV ratio (TLV/PTV)	Esophagitis (RTOG toxicity grade)	Need for Nasogastric Tube Feed	Radiation Pneumonitis (RTOG toxicity grade)
1	58	M	1	Mid	SCC	7	4.5	II	No	I
2	62	M	1	Lower	AC	11	1.9	III	Yes	II
3	55	F	1	Upper	SCC	10	3.5	III	Yes	II
4	57	F	1	Upper	SCC	7	3	II	No	0
5	70	M	1	Mid	SCC	7	5.5	II	No	I
6	52	F	1	Lower	AC	6	2.3	II	No	0
7	61	M	1	Upper	SCC	5	2.9	II	No	0
8	59	M	1	Upper	SCC	5	4.2	II	No	0
9	65	F	1	Mid	AC	8	4.3	III	Yes	I
10	63	M	1	Lower	AC	9	2	III	Yes	I

PTV analysis- DVH analysis performed on PTV for all patients in terms of V95%, V107%, D2 and D98 were similar in both plans for all patients (table 3) however RA resulted in higher conformity compared to 3DCRT {mean conformity index 1.1(±0.076) vs.1.8(±0.191) respectively, p=0.002}. Homogeneity Index (HI) did not differ between RA and 3DCRT {0.91(+0.022) vs. 1(+0.242) respectively, p=0.327}.

Table-3: 3DCRT vs. RA for PTV parameters (SD- standard deviation)

	3DCRT	RA
PTV (39.6 Gy) Volume [cm3] = 696.8 ± 216.8 Range [cm3] = [520.1-1089.8]		
D_{mean}[%]	54.2±2.6	55.0±1.2
SD [Gy]	7.0±1.4	6.5±0.3
$D_{1\%}$ [Gy]	62.0±0.8	62.2±0.5
$D_{99\%}$ [Gy]	38.6±1.5	40.3±0.9
PTV boost (59.4 Gy) Volume [cm3] = 253.1 ± 27.8 Range [cm3] = [202.00-276.8]		
D_{mean} [%]	59.6±0.4	60.1±0.3
SD. [Gy]	1.2±0.3	1.1±0.1
$D_{1\%}$ [Gy]	62.1±0.8	62.0±0.0
$D_{99\%}$ [Gy]	56.5±1.2	56.5±0.5
$V_{90\%}$ [%]	99.9±0.2	100.0±0.0
$V_{95\%}$ [%]	98.6±2.2	99.0±0.5
$V_{105\%}$ [%]	0.1±0.3	0.0±0.0
Healthy tissue Volume [cm3]= 24472 ± 4621 Range [cm3]= [18288; 29036]		
Mean [Gy]	9.7±1.5	8.7±1.3
V_{10Gy} [%]	24.8±4.7	25.8±4.8

Organs at risk analysis: RA plans significantly spared lung volumes beyond 15Gy (V15, V20, V40), MLD, heart volume receiving 30Gy (HV30), MHD and CMD as shown in table 4. Mean lung V5 and V10 values were similar with either technique with no statistically significant difference.

Table-4: Statistical analysis for comparison of RA vs. 3CRT for OAR.

Parameter	3DCRT Mean+/-SD	RA Mean+/-SD	Per cent Benefit with RA	P value (2-tailed)
V5	68±7.39%	69.7±10.15%	-2	0.163
V10	48.8±8.16%	45±11.18%	8	0.150
V15	40.2±8.35%	32±7.055%	20	0.003
V20	29.7±7.37%	22±5.27%	26	0.003
V40	15.9±2.76%	5.82±0.92%	63	0.000
MLD	17.16±2.28 Gy	13.83±2.32 Gy	19	0.003
HV30	55.2±16.66%	46.8±18.17%	15	0.002
MHD	28.15±6.9 Gy	24.3±6.23 Gy	13	0.003
CMD	46.95±1.57Gy	44.05±0.76 Gy	6	0.002

We found that the ratio of the total lung volume and PTV volume (TLV/PTV) affected the quality of RA plans. In 4 patients with TLV/PTV of 3 or more, there was a 10-30% improvement in RA with respect to mean V10 doses. This advantage was not seen in patients with smaller TLV/PTV ratio.

Initial plans of RA using higher priority to V20 and CMD resulted in inferior plans with respect to V5 and V10. Better RA plans were obtained after optimization with a higher priority to V10 instead of V20 and relaxing priorities to CMD and MHD. The final plans resulted in a 26% improvement in V20 which was highly significant. Similarly, MLD was improved by about 20%. Although priorities during optimisation were relaxed to achieve planning goals on lungs and heart, the dose to these organs was significantly lower with RA leading to additional sparing of about 15% with respect to 3DCRT. Smaller but statistically significant improvement was observed for spinal cord (only 6%) despite relaxed priorities.

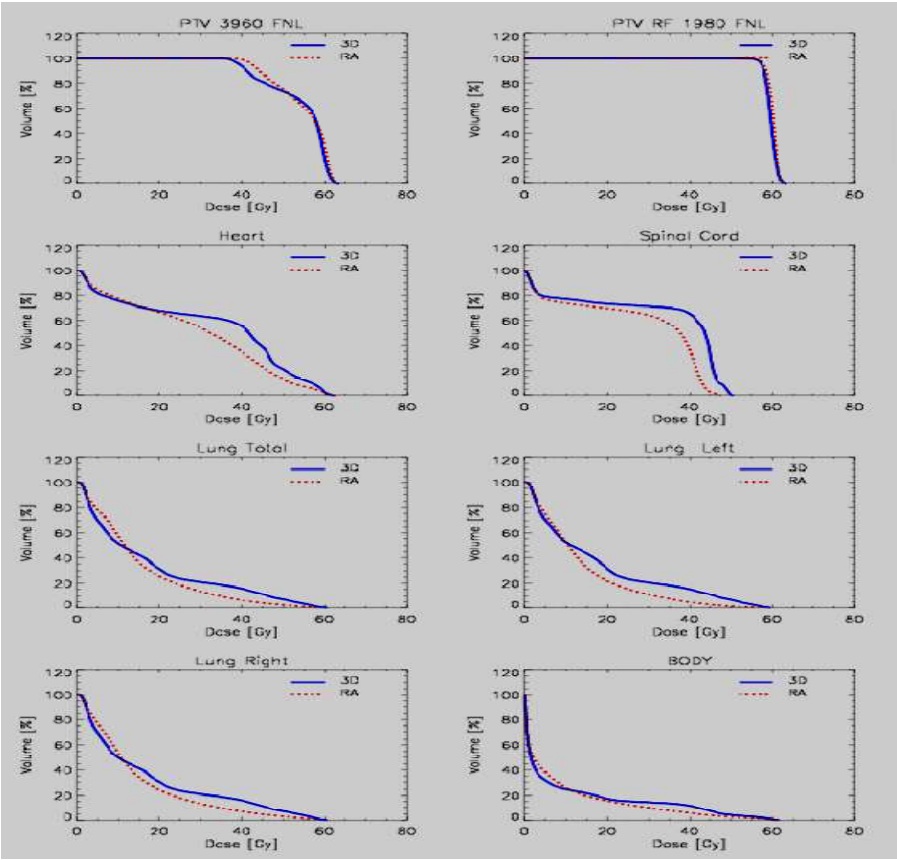

Fig-1(a-h): Comparison of RA vs. 3DCRT with respect to Cumulative Dose volume histogram for PTV 3960cGy(a), PTV 1980cGy (b), heart (C), spinal cord (d), lung total (e),

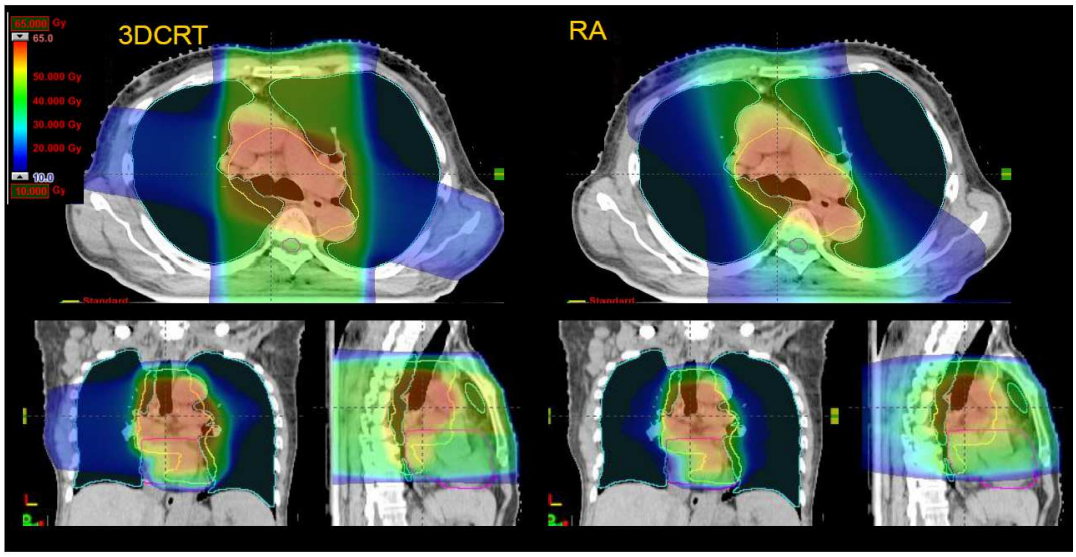

Fig-2: Dose color wash depicting 10Gy volume in 3DCRT and RA plan.

Early Toxicity and Response to Treatment: An initial evaluation for the first 10 patients revealed that none of the patients had treatment interruptions due to acute toxicity. All patients tolerated the treatment well with none of the patients developing grade IV mucosal toxicity (table 2) and $\geq$ grade III hematological toxicity. None of the patients developed clinically symptomatic pulmonary toxicity (grade 2 or more toxicity as assessed with RTOG acute pulmonary toxicity scoring criteria). After a minimum follow up of 4 months (range 4-12 months) for the last patient, 7 patients had a complete response, and 2 patients had a partial response on upper gastrointestinal endoscopy which was done 8 weeks after chemoradiation. Two of the patients are currently undergoing adjuvant chemotherapy and the other patient underwent transthoracic esophagectomy. The loco-regional control rates, survival, late toxicity and quality of life will be reported on completion of the phase II study.

Discussion

Despite RTOG studies [1,2] showing lack of benefit with dose escalation beyond 50.4Gy with concurrent chemotherapy for esophageal cancers, the dose used to treat this site in radical setting at our institution is 59.4Gy. In our experience with 59.4Gy and concurrent weekly cisplatinum, tolerance among our patients has been satisfactory and hence has been the standard institutional protocol for esophageal cancers.

Cylindrical target in esophageal cancer is not ideally suited for IMRT as it does not give a significant benefit compared to more concave targets.

Moreover, traditionally esophagus is not a preferred site for IMRT because of relative lack of consensus on target delineation (especially with respect to elective inclusion of mediastinal/upper abdominal and supraclavicular nodes), lack of reliable data on ITV margins (which takes into account inter-fraction and intra-fraction esophageal motility) and apprehension that large volumes of lung will receive low dose of radiation that may have an adverse effect in the form of pulmonary complications (especially with the advent of multimodality management in these patients).

Owing to this, there have been only a handful of reported dosimetric and clinical studies [11-21] evaluating IMRT for esophageal cancer. Our study is the first clinical study to evaluate RA for this site.

For cervical esophagus, all the studies showed that the conformity to the target, V20, MLD was better with IMRT and hence was superior to 3DCRT as was shown in our study. In the study by Fu et al, the authors found that 5 beam IMRT was best compared to 7 or 9 beam plans [11]. However study from Canada found that 9 beam IMRT provided a better PTV coverage and lesser doses to organs at risk [12]. Our study showed that for upper third lesions, where bilateral supraclavicular nodes were treated electively, the RA was superior to 3DCRT in terms of V15, V20, MLD, MHD, V30H and CMD. For middle and lower third tumors, majority of the studies found that IMRT can reduce dose to organs at risk such as spinal cord, lungs and heart while ensuring similar or better target coverage compared to 3 DCRT. Study by Nutting et al showed that for mid third lesions, 9-field IMRT was found inferior in terms of V18 with similar MLD and target conformity compared to 3DCRT and 4-field IMRT [13].

The 4-field IMRT was dosimetrically the best among the three plans. The study from MDACC reported by Chandra et al evaluated IMRT for 10 patients of distal esophageal cancer [15]. This study showed that IMRT gives a significant benefit over 3DCRT in terms of V20 and MLD as was shown in our study despite the fact that our study included patients of mid third esophagus where the target volume encompassed larger portion of adjacent lung. The absolute values of MLD, V10 and V20 noted in our study was higher compared to study from MDACC owing to differences in target volume and higher prescribed dose.

Unlike in the study from MDACC, our study did not show a statistically significant benefit in V10. This probably could be explained because of difference in 3DCRT plans apart from the differences in target volume. The majority of patients included in MDACC study were treated with 4 field obliques from the beginning, whereas in our study the patients were treated with antero-posterior portals till 3960cGy resulting in better lung sparing.

In our study, a significant benefit with RA could not be achieved in terms of V10 probably because of a better 3DCRT plan, which already spared a larger percentage of lung. In our study, RA plans achieved statistically significant benefit for doses above 15Gy for lung. However in patients with larger lung volumes in comparison with the PTV (TLV/PTV $\geq$3), RA plans had l0-30% lower V10 values compared to 3DCRT. Higher was the total lung volume, higher was the chance for it to be spared and higher was the benefit with RA.

There is no single most consistent lung DVH parameter that can predict post treatment pneumonitis and there is no sharp dose threshold below which there is no risk**.** This is also complicated by the fact that various studies have used different radiation doses, techniques, varied chemotherapy agents and dose schedules as well as incorporation of surgery in some of the studies. Another factor is presence of pre-existing pulmonary co-morbidities that cannot be quantified and hence cannot be compared between the studies. MLD and V20 are the most widely used lung parameters to predict pulmonary toxicity (22), both of which have been found superior in RA plans.

Initially in our study, a higher priority was used for reducing the V20 and CMD. This resulted in plans that delivered much higher V10 and similar V20 compared to 3DCRT plans. In the plan comparison DVH, the crossover between the two lung DVH curves for RA and 3DCRT occurred between 20 and 25Gy.

Because a larger volume of lung received 10Gy and 20Gy in RA plans compared to 3DRCT, patients were re-planned with a higher priority to reduce V10 rather than V20 and relaxing the dose constraints to spinal cord and heart.

The obtained plans with the new dose volume objectives resulted in lower or similar V10 and slightly higher cord and heart dose. The crossover between the combined lung DVH in these plans occurred close to 10Gy. Despite a higher total dose in our study, compared to many others [11,13,15,17], the V10 of <45% was achieved in 7/10 patients.

As shown in our study as well as in the study from MDACC, the obtained dose volume histogram is dependent on the set priorities and objectives as well as is highly dependent on the interaction of planner with the treatment planning system.

Aggressive dose constraints need to be applied to achieve a significant lung sparing. Although there was a statistically non-significant higher V5 in RA plans compared to 3DCRT, the clinical significance is unknown and needs to be explored.

In our experience the lung doses could have been further reduced but with a reduction in PTV conformity and higher heart and cord doses. In the 3 patients who were planned with additional non-coplanar arc, V10 was further reduced by 6-10% with 2-3% increase in HV30. Final accepted RA plans struck a balance between the two competing objectives: the PTV conformity/coverage and lung/heart doses.

Traditionally, dose to heart was not a priority during treatment of esophageal cancer patients owing to poor survival rates.

With the advent of multimodality management and recognition of potential long-term survivors, the heart dose is certainly a significant parameter to compare plans. As for lung, there is no single consistent heart dose volume level that predicts cardiac toxicity. In our study the aim was to limit the MHD below 26Gy and HV30 below 46%, and was achieved in all the patients.

The dosimetric benefits identified in our study and other reports describing IMRT plans for esophageal cancer, must be corroborated with clinical outcomes before being widely used in clinical practice. The initial clinical outcomes from a limited set of patients in our study have been encouraging. The final outcomes will be reported after completion of accrual and sufficient follow-up.

Conclusion

Our initial result of a dosimetric comparison of RA and 3DCRT plans for definitive chemoradiation in esophageal cancers demonstrates superiority in target coverage and in the sparing of OARs with volumetric modulated arc therapy. There is a significant reduction in MLD and V20, while low-dose volumes (e.g. V5 and V10) were not significantly different.

This provides an encouraging basis for controlled clinical testing of technologies like RA in esophageal cancer. There is a learning curve associated with developing an effective institutional planning protocol in order to meet quite stringent dosimetric objectives. Novel approaches like the use of non-coplanar arcs may be tried for incremental improvements in dosimetric outcomes.

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