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Research Article

Volumetric Modulated Arc Therapy *Versus* 3D Conformal Planning Technique for Esophageal Cancer: Should Field Based Planning Be the Universal Standard?

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Abstract

Carcinoma of the esophagus is among the most rapidly increasing cancers in incidence. With the use of aggressive bimodality and trimodality treatment strategies, the reduction of treatment toxicity is of prime importance [1]. Radiotherapy plays a key role in definitive, adjuvant and neoadjuvant treatment for carcinoma of the esophagus. Due to extensive vascular and lymphatic drainage, and therefore tendency to present at an advanced stage, the volumes required to adequately cover gross disease are substantial. Other critical organs in close proximity are therefore at risk for radiotherapy-induced toxicity, including the lung parenchyma, heart, spinal cord, stomach and others.

Conventional 3D conformal radiotherapy techniques (3 field or 4 field) have traditionally been used at our center to provide adequate coverage to the target volume of the esophageal tumor and lymph nodes; however as a consequence doses delivered to these Organs At Risk (OARs) may be high. Intensity Modulated Radiotherapy (IMRT) and Volumetric Arc Radiotherapy (VMAT) has also been considered in the past, however comparisons of these plans have shown variable results in normal tissue sparing. Furthermore these techniques may impart a higher volume of low dose radiotherapy to substantial amounts of normal tissue.

We compared conventional 3D CRT plans with IMRT or VMAT plans for a series of esophageal cancer patients with tumors of varying location at our center to determine the optimal treatment planning strategy.

Materials and Methods

A retrospective analysis was completed of six patients. All patients were simulated with three dimensional Computed Tomography (CT) scans without oral or IV contrast or immobilization. The Gross Tumor Volume (GTV) was identified as any abnormality in the primary tumor and surrounding lymph nodes on planning or diagnostic CT imaging, endoscopy, ultrasound or Positron Emission Tomography (PET) scan. A radial margin of 2 cm circumferentially and 4 cm proximally and distally was used for microscopic disease or Clinical Target Volume (CTV). For Planning Target Volume (PTV), a 1 cm expansion was used in all directions as no compensation for motion was completed at simulation. The planning CT scans were then imported into Pinnacle planning software and 3D conformal (3D CRT) 4 beam arrangement plans were created. Retrospectively, VMAT (5 cases) or IMRT (1 case) were created for comparison. Patients were treated with 3D conformal plans. Dose Volume Histograms (DVH) and dose distributions were reviewed in Pinnacle, and mean values for the six patients' 3D CRT radiotherapy plans were compared with either VMAT (n=5) or IMRT (n=1).

Results

All six patients were male, with T3-4N0-3 (Stage II-III) esophageal cancer between December 2015 and February 2016. Median age was 74 (range 48-80). Patient and disease characteristics are summarized in Table 1.

In patients with both middle and distal esophageal tumors, the mean dose and dose to 95% of the PTV volume (D95) were similar with 3D CRT and VMAT plans, with the exception that mean dose with higher with conformal planning than VMAT (107% vs 101% prescribed). Mean PTV dose was also similar in patient 6 for both IMRT and 3D CRT however the IMRT plan reduced the D95 to 90.7% (compared with 96.5%). Table 2 summarizes the mean PTVs (Planning Target Volume) and OAR values.

Cardiac volume receiving 30Gy and 40Gy (V30, V40) as well as mean dose were lower with VMAT and IMRT plans in all locations; however in middle thoracic tumors cardiac doses were generally low even with 3D CRT. The average mean cardiac dose was higher (19Gy *versus* 15Gy,

Table 1: Patient co-morbidities, disease characteristics amd treatment regimen summary.

Pt	Co-morbidities	Location	Histology	Stage	BT dose and length trated	Procotol	RT	CT	Plan delivered
1	none	Distal (35 cm)	AC	T4N3	600 x 3 (10,11,13 cm)	Cross	4500cGy/25 f	Carboplatin + paclitaxel x 5 cycles	4 field 3D CRT
2	Smoking, HTN	Distal (35cm)	AC with signet ring cells	T3N3	600 x 3 (12,12,12)	Cross	4500cGy/25 f	Carboplatin + paclitaxel x 5 cycles	4 field 3D CRT
3	None	GEJ (36 cm)	AC	T3N2	No	Macdonald	4500cGy/25 f	5 fluorouracil	4 field 3D CRT
4	Smoking, CAD,HTN, CHF,scleroderma	Middle (30 cm)	SCC	T3N0	600 x 3 (8,10, 10)	Herscovic	5000cGy/25 f- 24 completed	Carboplatin + paclitaxel x 5 cycles	4 field 3D CRT
5	Smoking, HTN, HCOL, AS, cirrhosis	Middle (30 cm)	SCC	T2-3N0-1	800 x 2 (10,10)	Cross	4500cGy/25 f	Carboplatin + paclitaxel x 5 cycles	4 field 3D CRT
6	Smoking, COPD, psoriasis	GEJ (36 cm)	AC	T3N1	600 x 3 (12,14,12)	Cross	4500cGy/25 f	Carboplatin + paclitaxel x 5 cycles	IMRT

BT= Brachytherapy, RT= Radiotherapy, CT= Chemotherapy, AC= Adenocarcinoma, SCC= Squamous Cell Carcinoma, GEJ= Gastro Esophageal Junction, cGy= Centigray, f= fractions, HTN= Hypertension, HC= Hypercholesterolemia, AS= Aortic Stenosis, COPD= Chronic Obstructive Pulmonary Disease, CAD= Coronary Artery Disease.

Table 2: Summary of averages dose and volume data for radiotherapy plans by tumor location (middle left, distal/GEJ right).

	MIDDLE 3D CRT (n=2)	MIDDLE VMAT (n=2)	DISTAL/GEJ 3D CRT (vs VMAT) (n=3)	DISTAL/GEJ VMAT (n=3)	DISTAL/GEJ 3DCRT (vs IMRT) (n=1)	DISTAL/GEJ IMRT (n=1)
A.PTV (all %Rx)						
Max	103%	105%	108%	109%	108%	110%
Min	76%	79%	68%	80%	83%	69%
Mean	98%	99%	107%	101%	101%	100%
D95	93%	94%	96.%	97%	96%	91%
D99	8%	91%	89%	92%	95%	86%
B.Heart						
V30 (%)	16%	6.5%	29%	10%	25%	10%
V40 (%)	5.5%	2%	4.7%	4%	10%	4%
Mean dose (cGy)	1602cGy	1197cGy	2452cGy	1779cGy	1890cGy	1559cGy
C.Lungs						
V5 (%)	44%	58%	56%	75%	29%	25%
V10 (%)	28%	26%	42%	46%	22%	14%
V20 (%)	7%	4.5%	24%	14%	14%	7%
V30 (%)	3.5%	2%	7%	5.3%	4%	2%
Mean dose (cGy)	727cGy	721cGy	1139cGy	1149cGy	630cGy	446cGy
D.Trachea						
Max dose (cGy)	811cGy	647cGy	3396cGy	2760cGy		
Mean dose (cGy)	114cGy	84cGy	777cGy	606cGy		
E. Liver						
D 1/3 (cGy)			1976cGy	1737cGy	977cGy	977cGy
D 2/3 (cGy)			673cGy	1096cGy	601cGy	601.cGy
Mean dose (cGy)			1499cGy	1456cGy	1113cGy	1113cGy
V32 (%)			11%	5.3%	8%	8%
F. Spinal Cord						
Maximum dose	3229cGy	2285cGy	2594cGy	2667cGy	2738cGy	3052cGy

A. PTV dose parameters by average of percent prescribed dose for mean, minimum and maximum, and percent of the prescribed dose to 95% and 99% volume (D95, D99 respectively).

B. Volume of heart receiving 30Gy (V30), 40Gy (V40) and mean heart dose.

C. Volume of lung receiving 5,10,20,30 Gy (V5,V10,V20,V30) and mean lung dose.

D. Mean and maximum dose to trachea.

E. Dose to 1/3 and 2/3 of total volume of liver, mean dose and percent of volume receiving 32Gy.

F. Spinal cord maximum dose.

V= Volume, D= Dose, max= maximum min= minimum Rx= Prescription Dose, PTV= Planning Tumor Volume

=p=0.19) and volume receiving 30 Gy (V30) was significantly higher (23% *versus* 8.8%, p=0.02) in 3D conformal compared with VMAT and IMRT plans.

Volume of lung parenchyma receiving 5Gy (V5) was higher for middle and distal locations using VMAT on average, however volume receiving 20Gy and 30Gy (V20 and V30) were decreased, and mean dose was similar. Overall, though not statistically significant, mean V5 was higher (52.7% *versus* 43%, p=0.59), while mean V20 (8.5% *versus* 15%, p=0.31) and average mean lung dose (7.7Gy *versus* 8.3Gy, p=0.82) were lower for patients receiving IMRT or VMAT *versus* 3D CRT respectively.

Dose to the trachea was lower using VMAT in all five patients. The average maximum dose to the spinal cord was lower using VMAT in mid thoracic location, but higher with IMRT in patient 6. The mean dose to the liver on average was similar using 3D CRT and VMAT, or 3D CRT and IMRT plans; however the average dose per volume was variable among patients (dose to one third (D1/3) and dose to two thirds (D2/3) listed in Table 3).

Discussion

Esophageal cancer is increasing in incidence and radiotherapy plays a central role in neo-adjuvant and definitive therapy in these patients. Esophageal tumors are by nature in close proximity to the cardiac muscle, trachea, lung parenchyma and spine, and therefore radiotherapy plans impart a significant risk of normal tissue damage. Historically these patients have poor long term survival so long term effects have not been well studied; yet evidence suggests that patients may still suffer from acute and sub acute complications. Patients may be at risk for peri-operative or post-operative morbidity with subsequent surgery, or additional toxicity risk with cardio-toxic chemotherapy exposure [1].

Esophageal cancer has historically been treated with conventional radiotherapy plans; generally two-field (anterior and posterior), three field (two lateral oblique fields and an anterior beam), or four field (anterior posterior and two less heavily weighted lateral fields) have been used [2]. In recent years, however, IMRT [3] and VMAT

Table 3: Summary of target coverage and OAR doses in commonly cited series reporting VMAT and IMRT versus 3D CRT radiotherapy plans for esophageal cancer.

Study	Patients (n) and tumor location	RT Technique and dose	Target	Heart	Lungs	Stomach, Liver and bowel	Cord
Kole, 2011	N=19 **distal**	IMRT (5B) *vs*. 3D CRT (4B) 50.4 Gy	*__CI__ 1.3 IMRT *vs* 1.56 3D CRT **Mean dose** -ND	**V30** 60.97 IMRT *vs* 24.84 Gy 3D CRT **mean dose** 22.9Gy IMRT *vs* 28.2Gy 3D CRT **RCA dose** 23.8Gy IMRT *vs* 35.5Gy 3D CRT **LCA dose**: no difference	V5 42.6% 3D CRT *vs* 59.8% IMRT V10,V15,V2 - ND	Stomach Mean, V20, V30 ND Liver V20,V30-ND	Max dose ND
Ling, 2014	N=10 **Distal ,** GEJ	IMRT *vs*, 3D CRT *vs* Proton 50.4Gy	**__HI, CI__-ND	LCA dose IMRT 26.9Gy *vs* 31.4Gy 3D CRT	V50 IMRT 1.6% *vs* 3.3% 3D crt V5-V40 ND	Stomach V20-ND V50 IMRT 59.9% *vs* 40.0% 3D CRT Liver D1/3 IMRT 20.99 Gy *vs* 28.89 Gy 3D CRT	
Kumar, 2011	N=45 **upper** (15) **mid** (24) and **distal** (6) thoracic	IMRT (5B) (n=22) *vs* 3D CRT (n=23) 50-50.4Gy	**HI (D5/D95)** IMRT 1.081 *vs* 1.173 3D CRT	NR	**V20** 19.47 cGy 3D CRT *vs* 24.9Gy IMRT **V30** IMRT 8.57Gy *vs* 14.08 Gy 3D CRT **V5,V10-** ND	NR	
Yin 2012	N= 20, cervical (5), upper (5), middle (5), distal (5) thoracic	IMRT (5,7,9 B) *vs* VMAT (1A, 2A) 60Gy	**CI 0.78, 0.8 (1A,2A)** *vs* IMRT 0.62,0.66, 0.73 (5,7,9 B) **HI (D5%-D95%) IMRT 1.09, 1.07 (7,9B)** *vs* VMAT 1.1 1.09 (1A,2A)	VMAT V30 33.5%, ,V40, 36%, V50 39.3% reduction	Upper: V5 5.5-7.7% , V10 10.5-12.6% increase with VMAT V20 2.1-10.7% and V30 13.2-17.3% reduction with VMAT Mid/Distal: VMAT V5 10.6-13.3%, V10 18.4-21.8% increase with VMAT V205-15.5%, V30 13.2-18.2% reduction with VMAT	NR	Max dose - ND
Fenkell 2009	N=5 cervical	IMRT (9B) *vs* 3D CRT 56-70Gy	CI 1.IMRT 1-1.2 *vs* 1.4-1.7 3D CRT **VPTV95 IMRT 97-99% *vs* 85-98% 3D CRT				Max dose spinal cord IMRT 42Gy *vs* 46 Gy IMRT

Wu, 2014	N=8 middle thoracic	IMRT (5B) *vs* VMAT (1A) *vs* 3D CRT 60Gy	***VPTV95 99.9 %IMRT *vs* 98.8% 3D CRT	V25-50 VMAT *vs* IMRT ND V30 IMRT 34.7% *vs* 28.6% VMAT *vs* 58.4% 3D CRT	V5-30 VMAT *vs* IMRT ND V5 47.9% 3D CRT *vs* 78.2% IMRT *vs* 58.6% V30 IMRT 8.6% *vs* VMAT 8.8% *vs* 3D CRT 13.2%	NR	Max dose ND
Chandra, 2005	N=10 distal thoracic	IMRT (4,7,9B) *vs* 3D CRT 50.4Gy	CI and HI improved with IMRT *vs* 3D CRT	V10 10%, V20 5% reduction with IMRT *vs* 3D CRT V5 reduction with IMRT 4B,7B, increase with 9B IMRT *vs* 3D CRT	V45 ND	V30 Liver ND	Max Dose ND
Nutting, 2001	N=5 esophageal	IMRT (4,9) *vs* 3D CRT 55Gy	PTV homogeneity ND	NR	Mean dose 9.5% 4B IMRT *vs* 11.0% 3D CRT V18 IMRT 4B 14.1% *vs* 18.8% 3D CRT *vs* 22.2% 9B IMRT	NR	Max dose ND
Vivekanandan,2012	N=10	IMRT (4B) *vs* VMAT (1A,2A) *vs* 3D CRT 54Gy	CI VMAT 1.01 *vs* IMRT 1.13 *vs* 3D CRT 1.81	Mean dose ND V35 VMAT 1A 4.81% 2A 5.8% reduction *vs* IMRT	V20 VMAT 1A 4.62%, 2A 10.66% reduction *vs* IMRT V30 VMAT 1A 17.83% 2A 17.98% reduction *vs* IMRT	NR	Max dose ND
Van Bnthuysen, 2010	N=14, distal/GEJ	IMRT (7B) *vs* VMAT 50.4Gy	95% coverage of PTV with 100% dose ND	D2/3 18.6Gy VMAT and 18.3Gy IMRT D1/3 28.3Gy VMAT *vs* 28.6Gy IMRT	V5 58.9 Gy IMRT *vs* 60.8Gy VMAT V20 14.6Gy IMRT *vs* 15.7Gy VMAT	Liver D1/3 14Gy VMAT *vs* 15.8Gy IMRT Stomach D2/3 13.4Gy IMRT *vs* 14.9Gy VMAT.	Max dose IMRT 32.4Gy *vs* VMAT 34.5Gy

B= Beam, A= Arc, V= Volume, D= Dose, Rx= Prescribed Dose, NR= Not Reported, CI= Conformality Index, HI= Heterogeneity Index *CI=V95% of Rx dose/ V PTV) **HI=D1-D99/Rx Dose ***VPTV95= PTV volume receiving 95% of prescribed dose.

techniques have been used to minimize high dose to organs at risk, at the expensive of distributing lower dose to normal tissue.

In patients with distal esophageal cancer, the cardiac muscle and vasculature are in close proximity to the target volume, making it challenging to avoid treating these structures. The literature indicates a benefit in cardiac dose reduction with VMAT or IMRT planning *versus* 3D CRT in most cases, however the magnitude varies between studies [1,4,5]. It has been suggested that high cardiac dose to specific regions in particular may increase risk of ischemia and perfusion abnormalities, for example the left anterior descending artery or left ventricle [6,7]. Kole et al found a 40% reduction in V30 when using IMRT planning, a significant finding as cardiac muscle receiving 30Gy has been correlated with risk of myocardial fibrosis and pericardial effusion [1,8-10]. Toxicity has also been associated with the volume of heart receiving 40Gy (V40) I [11]. In our study we found reductions in V30 and V40 favoring IMRT or VMAT over 3D CRT regardless of tumor location.

Intensity-modulated and volumetric-arc radiotherapy may achieve smaller volumes of lung tissue receiving of 20Gy or 30Gy [12], doses which are known to cause pulmonary damage. Kumar et al. reported grade II (74% vs 41%) and grade III (17% vs 5%) symptomatic pneumonitis rates were worse in patients treated with 3D CRT *versus* IMRT planning for esophageal cancers [13]. VMAT techniques may reduce high doses to the lungs in some areas, however the integral dose (for example volume receiving 5Gy) is often significantly higher. IMRT may likewise increase integral dose with increasing number of beams [14]. Wang et al found the only negative predictor of post-operative pulmonary complication was the volume of normal lung spared receiving a dose of less than 5Gy [15]. Alternatively some studies suggest post-operative complication (pneumonia and acute respiratory distress syndrome) rates correlate with V10 of more than 40% [16].

When considering distal tumors, dose to abdominal organs should be minimized where possible. The stomach remnant may serve as the anastomosis with the upper esophagus at surgery, while good liver function is essential for chemotherapy. IMRT and VMAT have the capability to reduce dose and should be considered where appropriate [2]. Ling et al found substantially lower dose to one third of the liver, and lower volume of stomach treated to 50Gy using IMRT *versus* 3D CRT [4].

In general maximum doses to the spinal cord have been reported as similar with 3D CRT, VMAT or IMRT planning among studies [1,17]. Fenkell et al however, reported reduced doses to both the cord and brainstem in cervical esophageal patients [3]. Interestingly, in our series we found VMAT reduced the maximum dose to the spinal cord while there was an increase in maximum dose in patient 6 who received IMRT.

Both IMRT and VMAT have demonstrated utility in achieving coverage while sparing high dose to OARs, however the increase delivery of monitor units and treatment time (IMRT), and higher cost and planning time (VMAT) should also be considered when choosing a preferred technique [18]. A substantial volume of normal tissue may also receive low integral doses of radiotherapy using VMAT. It may be beneficial to consider those with distal thoracic tumors specifically for VMAT planning, where the heart, larger lung

volumes, and trachea may be at higher risk, as demonstrated in our series. Other studies [3,5], however, have also found the use of IMRT beneficial in OAR dose reduction with cervical and middle thoracic tumors.

The optimal treatment planning strategy requires further investigation, as does the clinical impact on those patients treated with radiotherapy for esophageal cancer. While the risk of radiotherapy induced heart disease related death is known to exist in esophageal cancer patients [8], studies have not concluded a survival benefit exists with the use of improved RT techniques [19]. As the incidence of esophageal cancer continues to rise, optimization of radiotherapy techniques for each patient is paramount. Additionally, clinical impact of treatment technique and long term effects require further characterization.

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