Original Article

Adaptive radiation therapy for cervical esophageal cancer: dosimetric and volumetric analysis

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Background: Cervical esophageal cancer (CEC) patients may suffer from significant anatomical changes due to tumor shrinkage or weight loss during radiotherapy. The aim of the study is to evaluate the volumetric and dosimetric changes in the target and critical volumes of CEC patients by using adaptive radiotherapy (ART) technique.

Methods: Seven CEC patients treated in helical tomotherapy (HT) unit was analyzed. All patients had a replanning CT simulation at 3rd (CT2) and 5th (CT3) weeks in addition to the initial CT (CT1). Volumetric and dosimetric changes of target and organs at risk (OAR) were evaluated.

Results: The average weight loss of the patients was 9.03%. The major changes of the planning target volume (PTV), PTV boost, right and left parotid volumes were 4.74%; 15.93%; 26.82% and 26.64%, respectively. Using ART software was evaluated with first planning values (CT1) and pre-CT2-CT3 verification values. The correlation was decrease of the D95 and increase of the Dmax was statistically significant. When evaluated the varying values of the new CTs, there was no significant change between the initial PTV and adapted PTV's. But a significant decrease was observed at the summation plan for left and right parotids ($P<0.05$). The mean dose reductions of left and right parotid were 2.48 and 2.49 Gy, respectively.

Conclusions: Our results showed that using ART technique was beneficial to ensure adequate doses to the target volumes and safe doses to the OARs for the patients who need replanning during RT in uncommon CEC patients.

Keywords: Cervical esophageal cancer (CEC); adaptive radiation therapy; dosimetric and volumetric analysis

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Introduction

Cervical esophageal cancer (CEC) is rarely seen and accounts for 2–10% of all esophageal cancers (1,2). Treatment methods and the results of CEC differs from thoracic or abdominal esophageal cancers. RT is the primary treatment modality for CEC (3). Studies are suggesting that high dose radiation should be given in the treatment of CEC similar to the head and neck (HN) cancers (4).

The use of modern RT techniques allows treatment of CEC with low toxicity (5). Intensity-modulated radiotherapy (IMRT) has become the standard technique for the treatment of many cancers (6). One of the optimal techniques for CEC is typically IMRT. Increased of coverage, conformality and decreased dose to organs at risk (OARs) such as medulla spinalis (MS), brainstem, oral cavity, and parotid glands can be obtained with IMRT plans (7). When the image-guided RT (IGRT) is added to

Table 1 Patient characteristics

Case	Gender	Age	Type	Stage	RT dose (boost dose) (Gy)	Fraction dose (boost dose) (Gy)	Concurrent chemotherapy	Total weight loss (%)
1	F	63	SCC	IIB	64.8 (14.4)	1.8 (1.8)	Yes	11.8
2	M	47	SCC	IIIA	64 [19]	1.8 (2.11) (SIB)	No (patient rejected)	6.5
3	M	50	SCC	IIIC	64.8 (14.4)	1.8(1.8)	Yes	8.5
4	M	57	SCC	IIIB	64.8 (14.4)	1.8 (1.8)	Yes	6.7
5	F	61	SCC	IIIA	64.8 (14.4)	1.8 (1.8)	Yes	8.2
6	M	44	SCC	IIB	64 [19]	1.8 (2.11) (SIB)	Yes	9.6
7	M	54	SCC	IIIC	64.8 (14.4)	1.8 (1.8)	Yes	11.9

F, female; M, male; SIB, simultaneous integrated boost; SCC, squamous cell carcinoma.

the IMRT method; organ movement and set-up changes can be easily detected (8).

Helical tomotherapy (HT) (Accuray Inc., Madison, WI, USA) has daily megavoltage computed tomography (MVCT) which is used for pretreatment patient positioning to decrease setup errors and see anatomical changes (9). But there may be differences between the planning dose and the verification dose, depending on the patient's postures and anatomical changes during treatment and it may lead to under dosage or overdosage in target and OARs (10,11). The IG-IMRT technique does not allow dose and contour change while the treatment is going on. So the adaptive radiotherapy (ART) technique started to be used. Owing to the ART, daily dosing can be calculated considering daily anatomical changes and the comparison of the planning and verification dose can be done. ART is an important approach to make the correction of the daily tumor and OAR's variations through streamlined online or offline modification of original planning volumes and plans (12). The offline ART modification is widely used and is based on the principle of new CT extraction during treatment. These new CT images are used for recontouring and replanning (13).

Volumetric and dosimetric changes may occur in CEC patients during 6–7 weeks of RT treatment. The aim of the study is to evaluate the volumetric and dosimetric changes in target and OARs in CEC patients by using ART technique.

Methods

Patient selection

Seven patients who had radical RT in HT device between February 2015 and January 2018 for the treatment of CEC and needed ART planning because of the tumor shrinkage or weight lost causing in volumetric and dosimetric changes in the RT field were selected for the study. Our study was approved by the Erzurum Regional Education and Research Hospital Ethics Committee of Clinical Trials, Turkey (Erzurum BEAH KAEK 2019/04-37). Study was a retrospective review so subject informed consent was not obtained.

Patient characteristics are shown in *Table 1*.

Simulation, delineation and radiotherapy planning

Patients were immobilized with a supine position with both arms by their sides and using a thermoplastic IMRT mask covering the HN and shoulders (type-S thermoplastic-based system CIVCO, Civco Medical Solutions, Kalona, IA, USA). CT images were taken with 3-mm slice thickness throughout the entire HN and thorax regions. Second and third CT scans were performed with a new thermoplastic mask used same baseplate and head support during the course of treatment at 3rd (CT2) and 5th (CT3) weeks for all patients. The weight of each patient was recorded before CT1, CT2, and CT3. CT images were transmitted to the contouring workstation through Digital Imaging and Communications in Medicine (DICOM). The OARs (brain, brainstem, MS, parotid and submandibular glands, oral cavity) were delineated first at the Focal Sim (ver.4.80) contouring workstation. The gross tumor volume (GTV) was contoured according to the findings at the staging tests (upper gastrointestinal endoscopy, diagnostic tomography, PET-CT). A 3–5 cm craniocaudal margin was given for clinical target volume (CTV). Also, the bilateral cervical lymphatic regions, supraclavicular

Table 2 The volumetric comparisons between first plans (CT1) and replans (CT2, CT3)

Volume parameters	CT1 (mean ± SD) (cc)	CT2 (mean ± SD) (cc)	CT3 (mean ± SD) (cc)	CT1-CT2 percent difference (%)	CT1-CT3 percent difference (%)	P value
PTV	790.86±51.69	777.00±56.31	764.39±53.20	1.79±0.82	3.39±1.09	0.018
PTV boost	278.93±114.43	262.63±109.93	256.03±105.33	5.97±3.31	8.23±4.71	0.027
Right parotid	21.64±1.93	19.77±2.82	18.52±2.60	8.91±6.62	14.55±7.38	0.009
Left parotid	20.44±1.80	18.57±2.49	17.65±2.73	9.40±6.06	13.79±7.47	0.012

PTV, planning target volume.

and upper mediastinal lymph nodes are included to the CTV. The margin for planning target volume (PTV) was 5 mm. After all volumes were constructed the CT images and structures were transferred to tomotherapy planning system (TPS) (Accuray Inc., Madison, USA).

Twenty-one IMRT plans were performed in initial CT (CT1), 3rd and 5th weeks CT (CT2, CT3) in TPS (Accuray Inc.). For all plans, a field width of 2.5 cm, a pitch of 0.287 and a modulation factor of 2.0 was used during optimization and dose calculation. Total 64.8 Gy doses were defined for cases 1, 3, 4, 5 and 7. Total 60 Gy doses were defined for cases 2 and 6. A daily dose of 1.8 Gy was given to gross PTV. Simultaneous integrated boost (SIB) technique was adopted in cases 2 and 6. For this case 64 Gy total dose was planned and daily doses of PTV and PTV boost was 1.8 and 2.11 Gy, respectively.

Adaptive planning and analysis of the recalculated dose distributions

All patients have been treated using daily MV image guidance in HT. The ART software (Accuray Inc., Madison, WI, USA) module allows dose to be recalculated based on the MVCT. Daily MVCT images were used for the offline ART modification to determine how the daily positioning and anatomical changes of each fraction affect the target coverage and OAR's dose difference. In this system, the dose is calculated according to daily anatomy and DVH is obtained. In this study, an off-line ART plan was performed pre-CT2 and CT3. The DVH of the treatment plan and daily DVH are compared and evaluated. Volumetric and dosimetric differences in PTV and OAR's were analyzed.

Statistical analysis

Percentage differences were calculated by volume comparison (PTV, PTV boost, right parotid, and left parotid) between CT1, CT2, and CT3. Dosimetric comparison of the PTV's D95, D50 and Dmax between CT1 and ART before verification of CT2 and ART before verification of CT3 values were performed. The analyzed variables were D95, Dmean, Dmin, Dmax for PTV and Dmean and Dmax for OARs. Wilcoxon Singed Ranks Test was used to compare the PTV and OAR's doses between CT1, CT2, and CT3. A value of $P<0.05$ was considered significant. All statistics were calculated by using SPSS 18.0 statistical software (SPSS Inc., Chicago, USA).

Results

The patients who will benefit most from replanning are decided with MVCT imaging analysis and daily ART's DVH analysis in our clinic. Tumor shrinkage and weight loss during treatment are the most important factors in ART decision. In the present study, we investigate the volumetric and dosimetric changes in CEC, which is a rare type of esophageal cancer by using ART technique. Volumetric and dosimetric [V(cc), D95%, Dmean, D50, Dmin, Dmax] changes of target and OARs (parotid glands, MS, brainstem and oral cavity) values were evaluated.

The volumetric changes between first plans and recalculated plans

The average weight loss of the patients during the treatment period was 9.03%. Statistical analysis revealed a significant decrease in PTV, PTV boost, left parotid and right parotid volume values ($P<0.05$). The major volume changes were 4.74% for PTV, 15.93% for PTV boost, 26.82% for right parotid and 26.64% for left parotid. Volumetrically, the CT1-CT3 percent differences values were greater than CT1-CT2. The details of the volumetric comparisons are given in *Table 2*. The volumetric changes

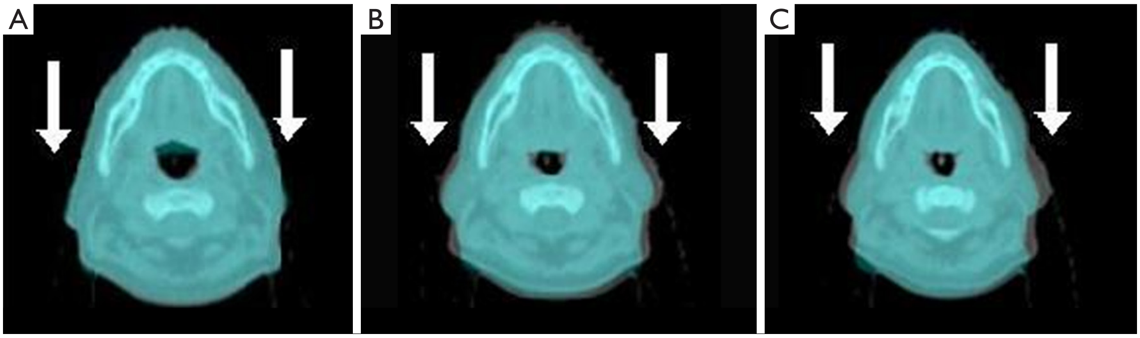

Figure 1 The change of the treatment volume during the treatment course for case 1 (registration of kVCT and MVCT images). The kVCT image is shown in gray and the MVCT image is shown in blue. (A) First plans (CT1); (B) before replanning CT2; (C) before replanning CT3. The arrows indicate the external volume change. kVCT, kilovoltage computed tomography; MVCT, megavoltage computed tomography.

Table 3 The dosimetric comparison of the targets between the CT1 values and CT2-CT3 ART before verification values

Index	PTV planning values of CT1 (Gy)	PTV verification values of pre-CT2 (Gy)	PTV verification values of pre-CT3 (Gy)	P value (CT1-CT2)	P value (CT1-CT3)
D95	64.994±0.419	64.886±0.573	64.782±0.474	0.345	0.043
D50	65.868±0.404	66.009±0.293	65.977±0.451	0.150	0.499
Dmax	68.286±0.749	69.881±1.636	70.014±1.758	0.018	0.018

D95, dose received by 95% volume; D50, dose received by 50% volume. ART, adaptive radiotherapy; PTV, planning target volume.

in the irradiation field during the treatment course for case 1 showed in *Figure 1*.

Analysis of ART

Using ART planning DVH was evaluated with first planning PTV values (CT1) and PTV values of pre-CT2 and CT3 shown in *Table 3*. The decrease of D95 (CT1-CT3) and the increase of Dmax values (CT1-CT2 and CT1-CT3) were statistically significant ($P<0.05$).

The dosimetric changes between first plans (CT1) and recalculated plans (CT2 and CT3)

Impact of anatomical changes in PTV and OARs (brainstem, MS, parotid glands, oral cavity) on dosimetric outcome was evaluated. *Table 4* showed the dose difference of PTV and OARs between CT1, CT2, and CT3. When the dose differences of CT3-CT1 was evaluated, the maximum decrease of the left parotid was 19.01% and right parotid was 16.04%. The mean dose reductions of left and right parotid were 2.48 and 2.49 Gy, respectively. These decreases were significant for both parotid glands ($P<0.05$). No significant correlation was observed between CT1-CT2 and CT1-CT3 summation plan values of PTV (D95, Dmean, Dmin, and Dmax) and Dmax values of MS, brainstem and oral cavity.

Discussion

Patients who are receiving RT and concurrent chemotherapy may experience weight loss due to dysphagia, odynophagia, mucositis, taste disorders, nausea, vomiting, diarrhea, increased catabolism and depression. In the present study, we found the average weight loss of the CEC patients during the treatment period was 9.03%. In addition, a mean volume reduction of 3.76% and 8.19% was observed for PTV and PTV boost during the 5–7 weeks treatment period, respectively. In the literature, volumetric and dosimetric changes during treatment were examined especially for HN cancers. In the study of Bando *et al.* there was a 7% reduction in the weight of the patients during the first 3 weeks of the treatment, a 28% reduction in the target volume and an 11% reduction in the neck volume in HN RT (14). In Yip and colleagues' study, there was a decrease of 4.7% in PTV1 volume and 11.5% in

Table 4 The dosimetric evaluation of the target and OAR's doses for the first plans (CT1) and replans (CT2, CT3)

Parameters	Index	CT1-CT2 (Gy) (mean ± SD)			CT1-CT3 (Gy) (mean ± SD)		
		CT1	CT2	P value	CT1	CT3	P value
PTV	D95	63.74±2.52	63.90±2.62	0.128	63.74±2.52	63.81±2.46	0.307
	Dmean	64.47±2.35	64.37±2.52	0.866	64.47±2.35	64.46±2.54	1
	Dmin	60.25±2.63	57.87±3.61	0.063	60.25±2.63	57.71±4.66	0.128
	Dmax	67.08±2.40	66.49±4.32	1	67.08±2.40	67.33±2.43	0.128
Right parotid	Dmean	21.37±3.14	19.42±2.62	<0.05	21.37±3.14	18.04±1.73	<0.05
Left parotid	Dmean	20.95±4.56	19.01±4.39	<0.05	20.95±4.56	18.04±4.52	<0.05
MS	Dmax	41.29±2.04	41.30±2.57	0.735	41.29±2.04	40.84±2.20	0.499
Breinstem	Dmax	28.07±19.76	28.38±21.20	0.612	28.07±19.76	28.23±21.10	0.398
Oral cavity	Dmax	38.02±19.12	36.91±16.82	0.499	38.02±19.12	35.03±16.76	1

SD, standard deviation; Dmax, maximal dose; Dmin, minimal dose; Dmean, mean dose; D95, dose received by 95% volume; OAR, organs at risk; MS, medulla spinalis; PTV, planning target volume.

PTV2 volume (15).

Weight loss, the shrinkage, and deformation of the target and OAR are expected during RT (16). Several studies have documented significant volumetric change in parotids during RT for HN cancers. In the study of Ho *et al.*, a weight loss of 6.5 kg was found in the treatment process. They found that ipsilateral and contralateral parotid lesions showed a mean decrease of 29.7% and 28.4%, respectively (17). In the study of Yip *et al.*, a decrease of 10.4% in the single parotid volume and 12.1% decrease in total parotid volume were determined (15). In another study, mean parotid gland volume reduction on the 3rd week of the treatment, at the end of the treatment and second month after treatment were 20%, 26.9%, and 27.2%, respectively (18). In a similar study, the parotid glands showed a progressive mean volume reduction of 22% at 5th day CT and 30% at 25th day CT (19). In our analysis, we found that right and left parotid volumes showed a mean decrease of 14.40% and 13.80 % respectively.

The change of the patients' external contour causes different dose distributions to the target and critical structures. Anatomical changes during the treatment can result in a high dose to the OARs than expected (20). Our findings consistent that the mean dose reductions of left and right parotids were 2.48 and 2.49 Gy, respectively. The HN study of O'Daniel *et al.*, showed that parotid gland doses were found 5–7 Gy higher in 45% of patients (21). Robar *et al.* found in their study that the change in mean dose to the parotids was 2.6% (22). Schwartz *et al.* noted mean parotid dose sparing by 3.9% and 3.8% in contralateral parotid and by 2.8% and 9% in ipsilateral parotid with single and two ART planning, respectively (23). In the study of Wang *et al.* found that there was a 1% decrease in the mean dose of left parotid and 1.3% decrease in right parotid and Ahn *et al.* found a 24% reduction in parotid volume with ART and a 22% increase in parotid conservation with re-planning (24,25). Castadot *et al.* reported that reduction in mean parotid dose after 1, 2 and 6 weeks replanning by 3%, 5%, and 6%, respectively (20).

In our study, when we compare the first CT plan and the replanning data, no significant correlation was observed between CT1-CT2 and CT1-CT3 summation plan values of MS, brainstem and oral cavity. Similarly in the study of Beltran *et al.*, showed that no significant dose changes were found in the OARs (oral cavity, brainstem, MS, optic chiasm, optic nerves) (19).

In the treatment process, the target and the volumetric changes in the critical organs require a change in the treatment planning. ART consists of evaluating the dose distribution during treatment and replanning if necessary, depending on the patient's anatomical changes (26). With ART, daily changes in the treatment plan can be observed. In this study, we found a significant dosimetric change of the targets between the CT1 planning values to CT2-CT3 ART before verification values.

The limitation of the present study is containing a small number of patients, and thus further studies with a larger patient population are needed to consolidate the importance of ART planning in CEC patients.

Conclusions

The ART technique is feasible and should be considered in the RT of CEC patients who are at risk of volumetric changes during the treatment due to the weight loss like any other HN cancer patient. Our volumetric and dosimetric results showed that using ART technique was beneficial to ensure adequate doses to the target volumes and safe doses to the OAR for the patients who need replanning during RT in a rare form of esophageal cancer.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Our study was approved by the Erzurum Regional Education and Research Hospital Ethics Committee of Clinical Trials (Erzurum BEAH KAEK 2019/04-37). Study was a retrospective review so subject informed consent was not obtained.

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