ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

Med J SDU / SDÜ Tıp Fak Derg ▶ 2021:28(1):15-22 doi: 10.17343/sdutfd.623353

THE EFFECT OF RADIOTHERAPY TECHNIQUE ON CAROTID ARTERY DOSE IN PATIENTS WITH EARLY STAGE GLOTTIC LARYNX CANCER

ERKEN EVRE GLOTTİK LARENKS KANSERLİ HASTALARDA RADYOTERAPİ TEKNİĞİNİN KAROTİS ARTER DOZU ÜZERİNE ETKİSİ

Beyza ŞİRİN ÖZDEMİR[1], Zeynep Rukiye Özge CAN[2]

[1] Department of Radiation Oncology, Akdeniz University School of Medicine, Antalya, Turkey
[2] Department of Radiology, Akdeniz University School of Medicine, Antalya, Turkey

Cite this article as: Sirin Ozdemir B, Can RO. The Effect of Radiotherapy Technique on Carotid Artery Dose in Patients with Early Stage Glottic Larynx Cancer. Med J SDU 2021; 28(1): 15-22.

Öz

Amaç

Bu çalışmanın amacı, erken evre glottik larenks kanser tanılı hastalarda iki radyoterapi (RT) tekniğinin karotis arter dozları açısından karşılaştırılmasıdır.

Gereç ve Yöntem

Bu çalışmaya, 10 erken evre (T1 / 2) glottik larenks kanser tanılı hastayı dahil ettik. Her bir hasta için hem yoğunluk ayarlı radyoterapi (YART) hem de 3 boyutlu konformal radyoterapi (3BKRT) tedavi planları hazırlandı. Tüm hastalar için tedavi volümleri (CTV, PTV) oluşturuldu. Tüm larinks, gerçek ve yalancı vokal kordlar, anterior-posterior komissürler, aritenoidler, aryepiglottik kıvrımlar, subglottik bölge dahil edilecek şekilde klinik hedef volüm (CTV) olşturuldu. PTV'ye 28 -29 fraksiyonda (fraksiyon başına 225 cGy) 6300-6525 cGy doz tanımlandı. Planlanan hedef volümü (PTV) oluşturmak için, tüm yönlerde CTV'ye 5 mm eklenirken, karotis arter ve spinal kordu korumak adına posterolateral yönde 3 mm'lik marj verildi. Spinal kord ve karotis arterler kritik organlar (OAR) olarak konturlandı. Hedef hacim dozları, OAR hacimleri, homojenlik indeksi (HI), konformite indeksi (CI) karşılaştırıldı.

Bulgular

3BKRT'ye kıyasla YART, karotis arterde yüksek doz hacimlerini (V30, V35, V50) belirgin olarak düşürürken ($p < 0.001$), düşük doz hacimleri (V10) her iki teknikte de yüksek seyretti. Her iki teknikte de CI benzer olup (0.9 vs. 0.9, $p = 0.3$), HI 3BKRT'de daha iyiydi (0.1 vs. 0.08, $p < 0.001$). Spinal kord maksimum dozları 3BKRT'de daha düşüktü (18 Gy vs. 44Gy).

Sonuç

IMRT, T1 / T2 glottik kanserli hastalarda karotis arterin korunması açısından üstün bir RT tekniğidir.

Anahtar Kelimeler: Radyoterapi, glottik laringeal kanser, karotis arter, 3BKRT, IMRT

Abstract

Objective

The aim of this study was to compare two radiotherapy (RT) techniques in early-stage glottic laryngeal cancer patients in terms of radiotherapy doses to which the carotid artery was exposed.

İletişim kurulacak yazar/Corresponding author: beyza@akdeniz.edu.tr
Müracaat tarihi/Application Date: 23.09.2019 • **Kabul tarihi/Accepted Date:** 20.12.2019
ORCID IDs of the authors: B.Ş.Ö. 0000-0001-9724-7875; Z.R.Ö.C. 0000-0003-3460-8746

Material and Methods
In this study, we included 10 early-stage (T1/2) glottic larynx cancer patients. Both intensity-modulated radiotherapy (IMRT) and 3-dimensional conformal radiotherapy (3DCRT) treatment plans were prepared for each patient. Treatment volumes (CTV, PTV) were created for all patients. The entire larynx was described as CTV to include both false and true vocal cords, anterior-posterior commissures, arytenoids, aryepiglottic folds, subglottic region. The prescription dose was 6300-6525 cGy in 28 -29 fractions (225 cGy per fraction) to the PTV. For planning target volume (PTV), while 5-mm was added to CTV in all directions, 3-mm margin was given to protect the carotid artery and spinal cord posterolaterally. Spinal cord and carotid artery were contoured as the organs at risk (OAR). The doses of the target volumes, the OAR volumes, the homogeneity index (HI), conformity index (CI) were compared.

Results
IMRT in comparison to 3DCRT significantly reduced the high-dose volumes (V30, V35, V50) of carotid artery ($p < 0.001$). However, the V10 parameter did not significantly decrease in any technique. CI was similar (0.9 vs. 0.9, $p = 0.3$) compared to 3DCRT. However, HI was significantly improved with 3DCRT (0.1 vs. 0.08, $p < 0.001$). The maximum dose of spinal cord was lower in 3DCRT compared to IMRT (18 Gy vs. 44Gy).

Conclusion
IMRT is a RT technique in patients with T1/T2 glottic cancer in terms of protecting carotid artery.

Keywords
Radiotherapy, glottic laryngeal cancer, carotid artery, 3DCRT, IMRT

Introduction

Laryngeal cancer is the most common cancer of the head and neck region. Laryngeal cancers account to around 2% of all cancer cases in the world (1). The incidence in Turkey is 2.6%. It is among the top ten most common cancers in men due to the higher frequency of tobacco and alcohol use (2). There is also an increased risk in former smokers (3). The larynx is divided into three anatomic regions: the supraglottis, glottis, and subglottis. Glottic, supraglottic and subglottic cancers represent approximately two-thirds, one-third and two percent of laryngeal cancers, respectively (4).

Glottic laryngeal cancers are usually diagnosed at early stage (T1N0M0, T2N0M0). The pattern of lymphatic-hematogenous spread is extremely rare because the glottic region is relatively poor in lymphatic and vascular vessels (5, 6).

For early-stage (stage I-II) laryngeal cancer, definitive radiation therapy (RT) and larynx-sparing surgery (transoral laser surgery and open partial laryngectomy) generally offer equivalent local tumor control and survival. The optimal treatment maximizes both survival outcomes and functional consequences considering the importance of maintaining the function of the larynx (voice, swallowing, and airway protection and patency) (7, 8). RT is a primary treatment approach for stage I laryngeal cancer and the local control rate is 84 - 95%. During RT, it is necessary to protect critical organs and healthy tissue as much as possible while giving the sufficient tumor dose to target for local control. Tumor control is closely related to the dose given to the target volume. Therefore, the dose should be given at the correct rate and with the appropriate RT technique (9, 10). Various RT techniques have certain advantages. For instance, 3D-CRT is used in order to provide better dose distribution with computerized imaging, while IMRT and the Volumetric Arc Therapy Technique (VMAT) are used in order to produce better solutions in complex geometric structures (11).

Increased incidences of stroke and other cerebrovascular events have been reported in patients who have survived over 10 years since undergoing treatment for early-stage glottic cancer. In particular, the risk of ischemic stroke increases 10-fold in patients undergoing traditional RT for early-stage glottic cancer if younger than 60 years of age. As such, the dose administered to the carotid artery during RT is an important parameter of patient outcome in early-stage glottic cancer (12, 13).

In the present study, we compared 3DCRT and IMRT in terms of their dosimetric characteristics for early-stage glottic laryngeal cancer. We aimed to investigate the dose suffered by critical organs and especially the carotid artery in patients with early-stage glottic laryngeal cancer.

Materials and Methods

In this study, we included 10 early-stage (T1/2) glottic larynx cancer patients treated and followed between January 2017 and May 2018.

The current study was conducted according to the principles put forth by the Helsinki Declaration and Good Clinical Practice guidelines.

All patients underwent computed tomography (CT) (2.5-mm slice thickness) after being immobilized in the supine position using thermoplastic masks. Each patient's CT image dataset was transferred to the treatment planning system (TPS), and the clinical target volume (CTV), planning target volume (PTV), spinal cord, and both carotid arteries were delineated. Whole larynx, including true and false vocal cords, anterior-posterior commissures, arytenoids, aryepiglottic folds and the subglottic region, were contoured as CTV. In patients with T2 stage cancer, the lower border of treatment field was kept wider due to subglottic extension. To prevent irradiation of the spinal cord and carotid, a 3-mm margin was created in the posterolateral and 5-mm margins were used in all other directions. Spinal cord and carotid artery were contoured as organ at risk (OAR).

Treatment Planning

A total of 10 patients were studied with the 3DCRT technique. Photon energies were as follows: 6 MV for lateral areas, 4 MV for the anterior-posterior (AP) field (Figure 1). The prescribed dose of the anterior commissure and 1/3 anterior of the vocal cord was better provided by the addition of the AP field. All plans were normalized so that 95% of the PTV received 100% of the desired dose.

The same patients' CT slices were used for IMRT planning with 7 angles (Figure 2). 6 MV photon energy was used. All plans were normalized so that 95% of the PTV received 100% of the treatment dose.

We compared 3DCRT and IMRT in terms of their dosimetric characteristics.

Comparison of Dosimetric Characteristics

Dose-volume histograms (DVHs) for PTV, carotid artery and spinal cord were evaluated for all plans and CI and HI were calculated for each plan.

CI is defined as follows (ICRU 62):

CI= TV (95% Target volume) / PTV (Planning target volume)

HI is defined as follows (ICRU83):

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}}$$

IMRT and 3DCRT were planned by using TPS with the Elekta Precise Pencil Beam algorithm. Linear accelerator devices (Synergy Platform model) were used in the treatment. The prescription dose in those with T1 stage cancer was 6300 cGy in 28 fractions (225 cGy per fraction) to the PTV. The prescription dose in those with T2 stage cancers was 6525 cGy in 29 fractions (225 cGy per fraction) to the PTV. TPS datas were analyzed with IBM SPSS v20 program. Mann Whitney U test was used for comparisons and p <0.05 was considered significant.

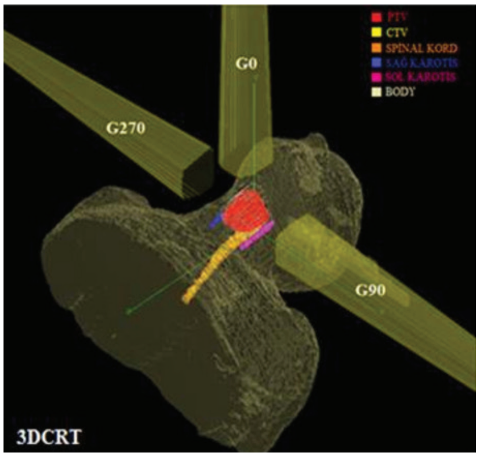

Figure 1
AP-lat fields in 3DCRT technique

technique

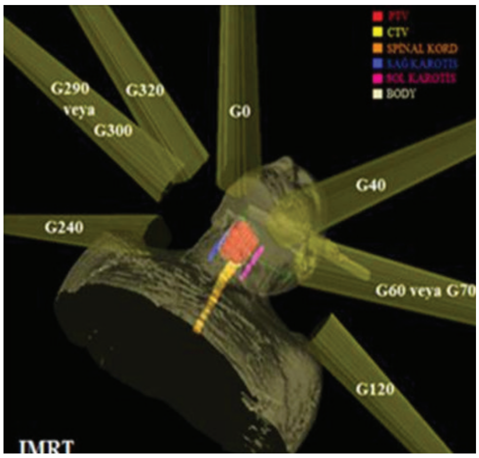

Figure 2
7 angled fields definition in IMRT

Results

One female and 9 male patients were included in the study. Six of the patients included in the study were T1 stage and 4 were T2 stage.

Dose Coverage
Figure 3 shows the dose distribution of two plans in a patient.

The dose distributions in 3DCRT and IMRT
Average mean doses for PTV were 6663.4cGy and 6610.3 cGy for the IMRT and 3DCRT plans, respectively. The average maximum and minimum PTV doses were 7230,3 and 5371,5 cGy for IMRT, and 7016,3 and 6065,7 cGy for 3DCRT plans, respectively. No statistically significant differences were observed between mean doses for IMRT vs 3DCRT. However, statistically significant differences were observed for minimum and maximum doses (Table 1).

In 3DCRT plans, the HI value was found to be closer to 0 (Figure 4). This means that the 3DCRT plans resulted in a more homogenous dose distribution. A significant difference in HI was observed between the two planning techniques ($p<0.001$).

Regarding the CI values, no significant difference was observed between 3DCRT and IMRT planning techniques (Figure 5).

In both planning techniques, the CI value was between 0.9 and 1 (Table 2).

When the T1 and T2 stage patient groups were compared, it was seen that there was a significant difference in PTV and CTV volumes in regard to cancer stage. However, there was no significant difference between the T1 and T2 stages in terms of doses (Tables 3, 4).

Carotid Arteries And Spinal Cord
In 3DCRT plans, PTV and CTV target volumes accounted for 95% of the dose, while the maximum dose of spinal cord (Dmax) did not exceed about 1800 cGy, but it was found that carotid arteries could not be preserved. In the IMRT plan, the target volume of the PTV was 95% of the defined dose, while the Dmax of the spinal cord was approximately 4500 cGy and there was a significant decrease in high-dose volumes of the carotid arteries ($p <0.001$). (Tables 5)

There was a significant decrease in V30, V35, V50 of the carotid artery with the IMRT plans ($p<0.001$). However, the V10 parameter of the carotid artery did not significantly decrease in any technique. (Table 6)

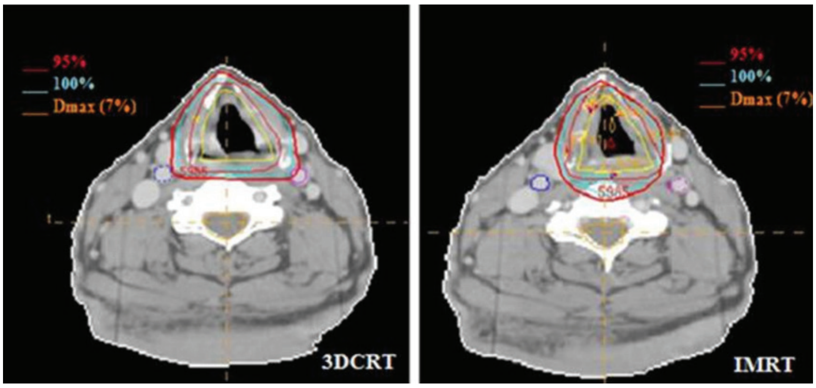

Figure 3
The dose distributions in 3DCRT and IMRT of a patient

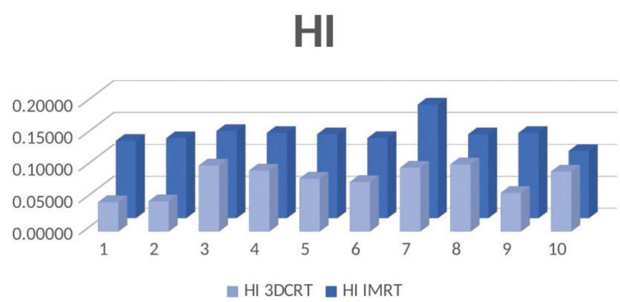

Figure 4
HI in 3DCRT and IMRT techniques

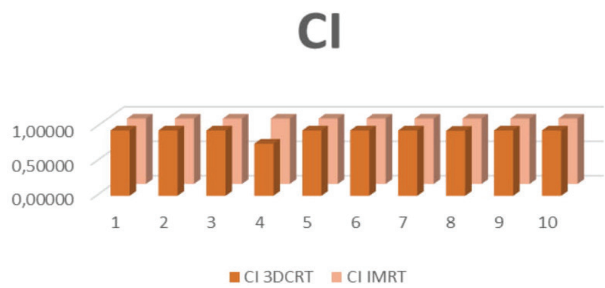

Figure 5
CI in 3DCRT and IMRT techniques

Table 1 Dmin, Dmax and Dmean values of PTV and CTV target volumes

	PTV (cGy)			CTV (cGy)		
RT	**Dmin**	**Dmax**	**Dmean**	**Dmin**	**Dmax**	**Dmean**
3DCRT	6065,7±68,7	7016,3±76,4	6610,3±53,6	6372,5±48,2	7011,4±76,8	6631,8±56,4
IMRT	5371,5±90,7	7230,3±40	6663,4±44,1	6093,1±110	7163±66,4	6727,8±60,2
p	<0,001	0,027	0,454	0,032	0,162	0,26

Table 2 HI and CI values of the target volume (mean)

	HI	CI
3DCRT	0,08±0,007	0,9±0,19180
IMRT	0,1±0,006	0,9±0,00001
p	<0,001	0,306

Table 3 D95 values of PTV and CTV according to stages

STAGE	PTV D95(cGy)		CTV D95(cGy)	
	3DCRT	**IMRT**	**3DCRT**	**IMRT**
T1	6311,1±96	6362,1±99,9	6381±98,7	6396±121,6
T2	6589,8±21,5	6579,3±94,3	6634,1±70	6597,3±95
p	0,011	0,033	0,011	0,033

Table 4 Dmean value for carotid arteries, Dmax value for spinal cord

STAGE	RIGHT CAROTID Dmean(cGy)		LEFT CAROTID Dmean(cGy)		SPINAL CORD Dmax(cGy)	
	3DCRT	**IMRT**	**3DCRT**	**IMRT**	**3DCRT**	**IMRT**
T1	5254±666,6	2416,7±310,1	5136,8±653,3	2405,8±317,1	1804,7±231,9	4475,7±337,9
T2	5339±371,6	2640±271,4	5606±431,5	2633,3±284,6	2046,5±284,6	4591,3±70,1
p	0,831	0,201	0,286	0,201	0,286	0,831

Table 5 Dmax and Dmean values for OARs

	RIGHT CAROTID (cGy)		LEFT CAROTID (cGy)		SPINAL CORD (cGy)
RT	**Dmean**	**Dmax**	**Dmean**	**Dmax**	**Dmax**
3DCRT	5288±171,7	6751,8±76,5	5324,5±189,2	6517,7±232,7	1901,4±81,2
IMRT	2506±95,5	5008,3±112	2496,8±98,3	4972±129	4521,9±82,8
p	<0,001	<0,001	<0,001	<0,001	<0,001

Table 6 Percentages of volumes corresponding to specific doses for carotid artery

	RIGHT CAROTID (%)				LEFT CAROTID (%)			
RT	**V10**	**V30**	**V35**	**V50**	**V10**	**V30**	**V35**	**V50**
3DCRT	97,7±1,2	92,1±2,5	89,8±2,8	71,4±5,4	97,5±1,3	91,9±2,3	89,4±2,5	69,4±7,1
IMRT	97,3±1,2	27,6±3,5	14,7±2,5	0,3±0,1	96,8±1,4	28±3,5	15,5±2,4	0,2±0,1
p	0,518	<0,001	<0,001	<0,001	0,620	<0,001	<0,001	<0,001

Discussion

Definitive RT has been one of the main treatment options for early-stage (T1 / T2) glottic laryngeal cancer for many years. Compared with surgery, local-regional control rates were similar and acute-chronic complication rates were very low (14, 15).

Khan et al., in their retrospective study involving 141 patients with early-stage laryngeal cancer, emphasized the importance of definitive RT (16). In the study, definitive RT provided excellent LC and cause specific survival for early-stage glottic carcinoma, with excellent voice preservation and minimal long term toxicity. 73% of the patients reported significant improvement, while only 8.5% reported a chronic worsening of their voice. In our hospital, the primary treatment method in patients with T1 / T2 glottic cancer is definive RT.
RT application in early stage glottic laryngeal cancers can be performed with different techniques. In the literature, there are studies comparing different RT techniques in terms of normal tissues and target volumes. The carotid artery is an important structure located in the surroundings of the larynx. Vascular injury due to RT is a late complication. In the literature, the definition of atherosclerosis due to RT was first described in 1959 (17). Vascular changes in patients receiving RT to the head and neck region begin after 6 months (18). In a study evaluating patients undergoing RT with the diagnosis of nasopharyngeal cancer, carotid intima media thickness was shown to increase linearly after RT (19). In addition, the study by Gujral et al. in 2016, indicated that the increase in carotid artery intima media thickness may be an important marker for the detection of radiation-induced atherosclerosis (20).

Gomez et al., compared 3 different techniques (2-dimensional conventional, 3DCRT and IMRT) in patients with early-stage larynx cancer and found that IMRT was superior in terms of mean carotid doses (21). In this study, our first goal was to compare two RT techniques (3DCRT and 7-area IMRT) in terms of carotid artery dose in patients with early-stage glottic laryngeal cancer. As expected and consistent with the literature the carotid artery doses were lower in the IMRT technique.

In the literature, there is no consensus on target volume definitions in carotid artery protective IMRT. In a review, it was reported that the greatest variability was in the definition of CTV, and in most studies, IMRT with three to seven fields were used (22). Similar to our study, the majority of studies in this field did not utilize GTV definitions (12, 23, 24). In most studies, the definition of CTV included the area 1.5 cm below the vocal cords, arytenoids and subglottic region, while PTV was defined with margins ranging between 2-10 mm (12, 21, 25). In a study which was focused on dose-sparing of carotid arteries without PTV margin, Chatterjee et al. performed planning according to CTV and treatments were performed with IGRT (13). In our study, PTV margin was defined and the patients were treated at IGRT.

The carotid artery behaves like a serial organ and so it is the dose of RT to a particular section of artery that is important (26). The effect of RT dose on the carotid artery in development of radiation-induced atherosclerosis is not clear. However, the incidence of 10-year cerebrovascular event in head and neck cancer patients was reported to increase by 9% when treated with radiotherapy (27). In literature, radiation doses were suggested to be limited to the following maximums: carotid artery <35 Gy (22, 28). However, in the study of Vatanen et al., significant subclinical vascular damage has been observed at total body irradiation doses of 10–12 Gy in long-term survivors of high-risk neuroblastomas (29). Some studies have reported that the stenosis of the carotid artery increases the thickness of the intima-media as the radiation dose increases (26, 30).

Atalar et al compared 3DCRT, IMRT and intensity-modulated arc therapy (IMAT) (31). They found the number of hot spots in IMRT and IMAT was significantly higher than 3DCRT. In our study, the number of hot spots in IMRT was higher than 3DCRT. And accordingly, the HI values were affected. HI value closer to zero indicates a more homogeneous dose distribution within the PTV. As can be understood from the formula HI, a high D2 value moves the result value away from zero and brings it closer to 1 ((D2: Minimum dose which receives 2% of the target volume (maximum dose)). As a result, in our study, 3DCRT plans had a more homogeneous dose distribution. However, 3DCRT plans median V35 and V50 values for carotid arteries were significantly higher than IMRT and IMAT. Rosenthal et al compared conventional planning and IMRT (32). Median carotid V35, V50, and V63 values significantly decreased in IMRT. In our study, the high-dose volumes (V30, V35, V50) were significantly higher than IMRT. Choi et al reported IMRT can significantly decrease the dose of carotid arteries (the median V2, V25, V50) (33). But, in the study, dose volume relationship for carotid artery damage from radiation had not yet been established. They suggested that carotid sparing IMRT could reduce the risk of carotid artery damage. In our study, IMRT in comparison to 3DCRT significantly reduced the high-dose volumes (V30, V35, V50) of the carotid artery. However, we could not reduce the V10 value of the carotid artery as we wanted in any technique. In our opinion, this is due to the fact that both the MLC thickness is 1 cm and the present TPS. In conclusion, we suggest that the V10 value of the carotid artery is also kept low since the RT dose causing atherosclerosis in the carotid artery is uncertain.

Conclusion

Considering the frequency of vascular disorders which are not associated with RT, it will be appropriate to examine vital vessels such as the carotid artery with radiological tests before RT application. It is also evident that, for patients at risk (those with high morbidity such as diabetes, high cholesterol, hypertension, cardiovascular disease, etc.), treatment should be planned with the RT technique that has higher dose-sparing ability for vascular structures. Patients should be monitored for local-regional and distant metastases after RT and also cardiovascular controls should be performed.

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