Süleyman Demirel Üniversitesi Fen Edebiyat Fakültesi Fen Dergisi
Süleyman Demirel University Faculty of Arts and Sciences Journal of Science
2022, 17(1): 65-71
DOI: 10.29233/sdufeffd.1016027
Atıf için / For Citation: S. Alay, E. O. Göksel, K. Özkaya Toraman, M. Okutan, B. Demir, "Treatment Planning Comparison of Intensity Modulated Arc Therapy and CyberKnife Techniques in Early Stage Glottic Larynx Radiotherapy", *Süleyman Demirel Üniversitesi Fen Edebiyat Fakültesi Fen Dergisi*, 17(1), 65-71, 2022.

Research Article

Treatment Planning Comparison of Intensity Modulated Arc Therapy and CyberKnife Techniques in Early Stage Glottic Larynx Radiotherapy

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(Alınış / Received: 02.11.2021, Kabul / Accepted: 24.01.2022, Yayımlanma / Published: 27.05.2022)

Abstract: We aimed to compare two radiotherapy techniques (the robotic-based linear accelerator Stereotactic Body Radiotherapy (SBRT) and linear accelerator-based Intensity Modulated Arc Therapy (IMAT)) dosimetrically on Early Glottic Larynx Cancerx (EGL) treatment plans in the terms of target volume and critical organ doses. The computerized tomography (CT) images of 15 patients treated with EGL diagnosis were used retrospectively. The Planning Target Volumes (PTV) was generated with a margin of 0.5 cm from the laryngeal volume. The PTV dose was defined as 45 Gy delivered in 10 fractions within each of treatment plans. At least 95% of PTV treatment volumes ($D_{95\%}$) were to receive the treatment dose**.** The average PTV volume was 95.56 cm^3 (range: 68.8 cm^3 - 142.6 cm^3). The average $D_{98\%}$, $D_{2\%}$ and D_{mean} values of PTV were lower in IMAT plan than in CK plan. In CK plans, the mean of the spinal cord maximum dose (D_{max}) for all patients was statistically significantly lower than in IMAT plans. D_{max} and D_{mean} values for the right and left carotid arteries was significantly lower in IMAT plans. Also, the D_{mean} value of thyroid gland was significantly lower in IMAT plans. Our dosimetric comparison study made using images of 15 EGL cancer patients shows that the desired critria for the critical organ doses can not reached with CK plans, especially when the treatment volume is large.

Key words: Larenks Cancer, Radiotherapy, IMAT, CyberKnife, Dozimetry

Erken Evre Gloktik Larenks Radyoterapisinde Yoğunluk Ayarlı Ark Tedavisi ve CyberKnife Tekniklerinin Tedavi Planlarının Karşılaştırması

Öz: Erken Evre Glottic Larenks (EEGL) Kanseri tedavi planlarında iki radyoterapi tekniğini (Robotik tabanlı lineer hızlandırıcı Stereotaktik Beden Radyoterapi (SBRT) ve lineer hızlandırıcı tabanlı Yoğunluk Ayarlı Ark Tedavisi (YAAT)) dozimetrik olarak, hedef hacim ve kritik organ dozları açısından kıyaslamayı amaçladık. EEGL tanısı ile tedavi edilen 15 hastanın

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retrospektif bilgisayarlı tomografi (BT) görüntüleri kullanıldı. Planlanan tedavi volümü (PTV), larinkse 0.5 cm'lik bir marj vererek oluşturuldu. Her iki tedavi planında da 10 fraksiyonda toplam 45 Gy tedavi dozu tanımlanmıştır. PTV tedavi hacimlerinin %95'inin ($D_{\%95}$) tedavi dozunu alması amaçlanmıştır. Ortalama PTV hacmi 95.56 cm^3 (68.8 cm^3 - 142.6 cm^3) idi. $D_{\%98}$, $D_{\%2}$ ve D_{mean} değerleri IMAT planında CK planına göre daha düşüktü. CK planlarında ortalama spinal kord maksimum dozu (D_{max}), istatistiksel olarak anlamlı derecede düşüktür. Sağ ve sol karotid arterler için D_{max} ve D_{mean} değerleri, IMAT planlarında CK planlarına göre anlamlı derecede düşüktür. Ayrıca tiroid bezinin D_{mean} değeri, IMAT planlarında CK planlarına göre anlamlı derecede düşüktür. 15 EGL hastasının görüntüleri ile düzenlenmiş tedavi planlarının dozimetrik kıyaslamasında CK planlamasıyla kritik organ dozlarında, özellikle de tedavi hacminin büyük olduğu tümörlerde istenen kriterlere ulaşılamadığı gösterilmiştir.

Anahtar kelimeler: Larinks Kanseri, Radyoterapi, IMAT, CyberKnife, Dozimetri

1. Introduction

According to GLOBOCAN 2012 data, larynx cancer accounts for 1.1% of all cancer cases and 1.9% of cancer cases seen in men. It is a particularly common cancer among men with a male/female ratio of 7/1 [1]. A total of 13,150 larynx cancers were diagnosed, including 10,490 in men and 2,660 in women, according to a research by the American Cancer Society in the United States in 2018 [2]. Glottic cancers consist of 65% of all laryngeal cancers, and most of them are in the early-stage at the time of diagnosis. Due to scarce of lymphatic collectors in the glottis, the nodal metastasis risk of early-stage glottic (EGL) cancers is under 5%, which makes elective node irradiation unnecessary and local treatment usually sufficient [3].

The treatment of EGL aims to ensure the local control of disease, preserving laryngeal functions as much as possible. This goal can be obtained by either radiotherapy or surgery (such as endoscopic laser-surgery, open-partial-laryngectomy) without any difference in local control rates but with relatively different advantages and disadvantages. While laser surgery is a one-day-treatment with low morbidity, which enables the patient to return their daily life in a short time, the conventional radiotherapy regiment is a total of 66-70 Gy in 33-35 fractions with 2 Gy per fraction, which takes weeks of each patient. Many studies have shown the higher than 2 Gy/daily fraction regiments yield local control advantage without any additional toxicity risk. Some recent clinical studies evaluated the safety and efficacy of 3,3-8 Gy/daily fraction doses, aiming better patient compliance due to a shorter treatment [4,5].

Stereotactic body radiotherapy (SBRT) techniques aim to irradiate the tumor with high conformity. Cyberknife (CK) used for SBRT can give radiation from over 1200 points, enables maximum protection of surrounding tissue with a rapid dose fall-off at the field edge. However, an important disadvantage of Cyberknife treatment is the longer delivery time. Longer delivery time can also cause patient-discomfort and intra-fractional positioning errors. With the fast-dose-rate of the Intensity Modulated Arc Therapy (IMAT) technique, the dose delivery can be completed in minutes, resulting in a lower patient movement related uncertainty. It also has higher set-up precision because of pre-implementation imaging with the Cone-Beam CT.

Our study is aimed to compare the SBRT techniques, IMAT and CK treatment plans dosimetrically by the means of critical organ and treatment volume doses using 15 EGL patients' computerized tomography images.

2. Material and Method

Digital Imaging and Communications in Medicine (DICOM) sets of 15 previously treated early glottic laryngeal cancer (T1-T2, N0, M0) male patients were obtained from the archives of our clinic. The study was approved by the Ethics committee before the start (Date: 24.11.2017, Registration number: 2017/1360). Images for planning were performed using Philips Big Bord 4DCT (Philips Healthcare, Cleveland, OH) of 1 mm slice thickness in all patients.

2.1 Treatment Plans

Treatment volumes (Gross Target Volume-GTV, Planning Target Volume-PTV) and critical organs (Organ at Risk-OAR) (spinal cord, carotid arteries and, thyroid gland) were contoured by a radiation oncologist according to the guidelines of our clinic. We created two target volumes: PTV_{63Gy} and PTV_{70Gy}. PTV_{63Gy}: Larynx+0.5 cm and PTV_{70Gy}: GTV+1 cm (Figure 1). PTV_{70Gy} (range: 68.8 cm^3 - 142.6 cm^3) average volume values are 95.56 cm^3. The patients entered the treatment from the IMAT plan with Simultaneous Integrated Boost (SIB) with a fraction dose of 2 Gy per day, with a dose of PTV_{70Gy}.

For our study, the Biological Effective Dose for 2Gy (BED_{2Gy}) value corresponding to the PTV_{70Gy} dose value was calculated and found to be equivalent to a total dose of 45 Gy in 10 fractions. A total 45 Gy treatment doses with a 4.5 Gy per fraction in 10 fractions were defined for both treatment plans (IMAT and Cyberknife). 45 Gy was given to PTV_{70Gy} in 10 Fractions in these plans. The reference isodose (95%) was given a therapeutic dose of 45 Gy.

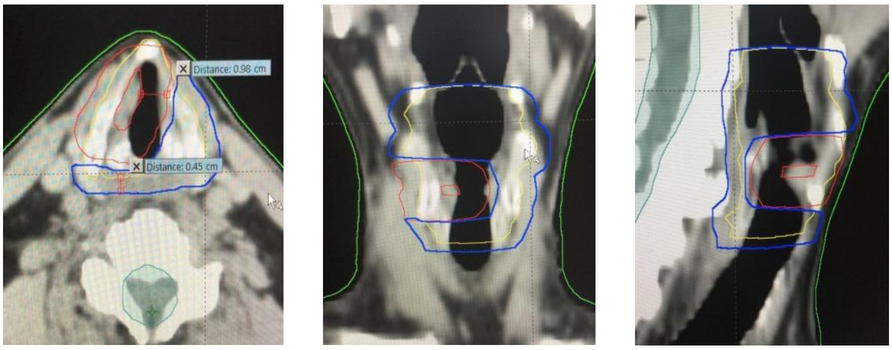


Figure 1. Transverse, coronal and sagittal sections of a patient's PTV_{63Gy}, PTV_{70Gy} and larynx volumes. PTV_{63Gy} is shown in blue, PTV_{70Gy} in red and Larynx in yellow.

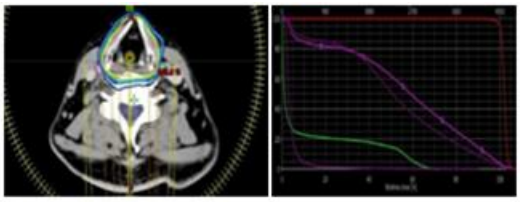
The planning goals for critical structure in the optimization process are given below:
For Spinal cord; D_{max}< 20 Gy,
For Carotid Arteries; D_{mean}<35 Gy,
For the Thyroid Gland; D_{mean}<30 Gy.

6 MV photon beam was used for all treatment plans. The same GTV, PTV_{63Gy}, PTV_{70Gy} and OAR volumes were created for all plans. Thus, the same tumor volumes were irradiated in all plans.

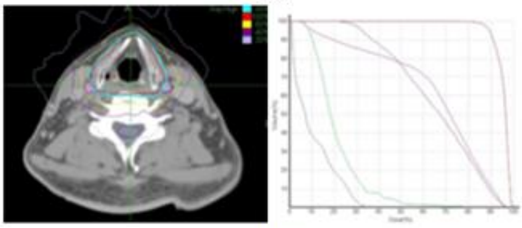
IMAT plans were performed using an Eclipse treatment planning software version 15.6 (Varian Medical Systems Inc., Palo Alto, CA). Two full arcs were used in the IMAT plans. The first arc was between 180.1^0 - 179.9^0 angles and the other arc were set to rotate on the same plane in the opposite direction (179.9^0-180.1^0) ~~of the first arc~~. To avoid the interleaf leakage radiation, the primary and secondary fields were given a 300^0 and 330^0 collimation angle, respectively. Analytical Anisotropic Algorithm (AAA) dose calculation algorithm was used for IMAT plans. Photon

Optimizer (PO) and Progressive Resolution Optimizer (PRO) algorithms were utilized for the IMAT.

CK plans were prepared using Multiplan version 4.0 (Accuray Inc., Sunnyvale, CA, USA) treatment planning system. The plans were prepared using two fixed collimators depending on PTV_{63Gy}. The dose rate was 800 cGy / MU. The dose distribution and dosevolume histogram (DVH) in the transverse section of a patient is shown in Figure 2.



a)



b)

Figure 2. The dose distributions in the transverse section of a patient and its dose-volume histogram (DVH) **a)** IMAT plan **b)** CK plan

2.2 Treatment Plan Parameters

$D_{2\%}$ (near-max), $D_{98\%}$ (near-min) and $D_{50\%}$ (dose-mean) were analyzed in evaluation of PTV volumes (doses received by 2%, 98% 50% of the treatment volumes) as described in ICRU 83 guidelines. For Homogeneity Index (HI); $HI=(D_{\%2} - D_{\%98})/ D_{\%50}$ formula and for Conformity Index (CI); $CI=V_{ri}/TV$ formula (Where V_{ri} is the volume of reference isodose and TV is the treatment volume covered by reference isodose line) were used. HI values approximating to zero indicate a more homogeneous dose distribution in the target volume. The ideal CI value is equal to 1 [6].

2.3 Statistical Analysis

The IBM SPSS 24.0 version (SPSS Inc., IL, USA) was applied for statistical comparison. Nonparametric binary comparison Wilcoxon Signed Rank Test was used to compare 2 different techniques and it was looked at which groups were different. The p-value of <0.05 is considered statistically significant.

3. Results

3.1 Evaluation of Treatment Plan Parameters for PTV

Table 1 shows $D_{98\%}$, $D_{2\%}$ and D_{mean}, CI, HI and, MU (Monitor Unite) values for PTV according to two different Radiotherapy planning techniques for all patients. When the IMAT and the CK plans were compared, there was no significant difference between them for $D_{2\%}$ ($p=0.158$) (Table 1). But, the average $D_{98\%}$, and D_{mean} values of PTV were found to be lower in IMAT plan than in CK plan. In the IMAT and the CK plans, a significant difference was found between $D_{98\%}$ and D_{mean} ($p=0.001$) (Table 1).

The HI value of PTV (HI=1.09) was significantly lower (p=0.001) in the IMAT plans. Although the CI value in the IMAT plan (CI=1.03) was also lower (1.03±0.03 vs. 1.07±0.01) it did not reach statistical significance (p>0.05).

The average for MU was observed to be in the lowest for IMAT plans and the highest for CK plans. A statistically significant difference was observed for MU when planning was compared (p=0.001 in Table 1).

Table 1. $D_{2\%}$, $D_{98\%}$, D_{mean}, HI, CI and, MU values for PTV_{45Gy} and their statistical results. (The values are the average data of 15 patients)

Parameters		IMAT		CK		IMAT vs. CK p*
		Mean	Std. D.	Mean	Std. D.	
PTV_{45Gy}	$D_{2\%}$	38.91	±1.34	40.04	±1.72	>0.05
	$D_{98\%}$	49.62	±0.53	52.22	±1.80	0.001
	D_{mean}	46.16	±0.21	48.75	±0.36	0.001
HI		1.09	±0.01	1.15	±0.01	0.001
CI		1.03	±0.03	1.07	±0.01	>0.05
MU		1216.7	±146.7	62681.2	±11866.7	<0.001

** >0.05 statistically not significant*

3.2 Evaluation of OAR Doses Parameters

The statistical comparison of the critical organ dose values, D_{max} and D_{mean}, obtained by 2 different techniques are given in Table 2. The mean spinal cord maximum dose (D_{max}) for all patients was statistically significant as the lowest in CK plans (p=0.001 in Table 2). D_{max} and D_{mean} values for the right and left carotid arteries are statistically significantly lower in IMAT plans than in CK plans. And, the D_{mean} value of thyroid gland is statistically significantly lower in IMAT plans than in CK plans.

Table 2. OAR dose parameter values and their statistical results for two treatment techniques. (The values are the average of 15 patients' data)

Parameters		IMAT		CK		IMAT vs. CK p*
		Mean	Std. D.	Mean	Std. D.	
Spinal Cord.	D_{max} (Gy)	32.27	±1.33	19.91	±2.29	0.001
Right Carotid A.	D_{max} (Gy)	46.93	±4.19	49.28	±3.13	0.002
	D_{mean} (Gy)	20.06	±3.20	27.84	±4.66	0.001
Left Carotid A.	D_{max} (Gy)	46.78	±3.03	49.50	±1.78	0.001
	D_{mean} (Gy)	18.77	±3.96	27.01	±4.06	0.001
Thyroid Gland	D_{mean} (Gy)	14.82	±9.42	22.63	±8.90	0.001

** >0.05 statistically not significant*

4. Conclusion and Comment

According to National Comprehensive Cancer Network (NCCN) Guidelines, voice protection treatment options for early-stage glottic cancer include CO_2 laser excision, hemilaryngectomy and definitive radiation therapy [7]. The use of laser excision has gained popularity in the treatment of early stage (carcinoma in situ or T1) lesions to achieve good voice results. Laser ablation involves removal of the observable tumor with minimal margins but anterior commissure involvement and excision of larger T2 lesions are difficult. And, there is a higher risk of local recurrence and / or sound disturbance [8]. Radiotherapy is a historically preferred non-operative treatment as it provides equivalent disease control with potentially better functional voice results [9].

In radiotherapy of 15 EGL patients, Ding C. et al. [10] compared the results of the hypofractioned SBRT treatment plans with CK and 13-field Intensity Modulated Radio Therapy (IMRT) treatment plans made for standard carotid artery protection. In their study, a total treatment dose of 45 Gy was defined as the treatment dose from a dose of 4.5 Gy per fraction. Treatment volumes in the study included the CTV anterior commissure and 2 mm of the adjacent contralateral vocal cord for lesions located within 2 mm of the anterior commissure or involving the anterior commissure, and the PTV volume was created by giving the CTV a 3 mm margin in each direction [10]. For T2 lesions, CTV contains the entire ipsilateral vocal cord and, ipsilateral paraglottic cavity and PTV is formed again by giving a 3 mm margin to CTV. The average PTV volume was determined as 8.63 ± 5.69 cm^3. In our study, the PTV volume obtained by giving a 5 mm margin to the larynx was used in accordance with the protocol in our clinic to be treated traditionally. In our study, the average PTV volume was 95.56 cm^3. The most obvious difference between their study and our study is the PTV volume difference (Our volumes are about 10 times their PTV volumes). Unlike the work of Ding C., we considered the entire larynx as the target. The volume difference in the PTV occurs for this reason. In this study, D_{mean} doses of PTV were found more statistically significant in CK technique than in the IMRT technique.

Zhang et al. [11] in their study with 10 patients created PTV volumes by giving a 3 mm margin to CTV. The average PTV volume for 10 patients was 4 cm^3. They selected the treatment dose as 42.5 Gy in 5 fractions. In the plans in which they compared Volumetric Modulated Arc Therapy (VMAT) and CK plans, they found the dose of D_{max} for PTV was greater in the CK plan as in our study.

Thyroid gland D_{mean} doses, right and left carotid artery D_{max} doses and D_{mean} doses were significantly higher in CK technique in studies conducted by both Ding [10] and Zhang [11]. The dose of spinal cord D_{max} was found to be lower in CK technique in our study as in these two studies [10,11]. Longer CK treatment times (62681 MU) are the result of irradiation with small cones. However, tumor movements during treatment with CK may be less sensitive to intra-treatment tumor movements due to the long treatment time. It has also been emphasized in the literature that higher dose rate could potentially increase the incidence of normal tissue toxicity for laryngeal SBRT from a radiobiological point of view [12].

In our study, SBRT treatment plans (IMAT and Cyberknife) created using CT images of 15 patients with EGL cancer who were previously treated with the IMAT technique were evaluated dosimetrically and the differences between the techniques were investigated. For EGL patients treated with a total dose of 70 Gy using the SIB technique in our clinic, When SBRT-IMAT and SBRT-CK plans performed for only this study were compared, considering the same volumes, it was found that CK plans were not suitable for other OARs except for the spinal cord. Thus EGL radiotherapy with SBRT is a method that is still the subject of research and needs more patient studies.

Author Statement

Serdar Alay: Methodology, Theoretical Calculations, Investigation.
Evren Ozan Göksel: Theoretical Calculations, Investigation.
Murat Okutan: Conceptualization, Methodology, Original Draft Writing, Review and Editing, Investigation.
Kubra Özkaya Toraman: Resource/Material/Instrument Supply, Review and Editing
Bayram Demir: Conceptualization, Investigation, Review and Editing

Conflict of Interest

As the authors of this study, we declare that we do not have any conflict of interest statement.

Ethics Committee Approval and Informed Consent

As the authors of this study, we declare that we have an ethics committee approval (Date: 24.11.2017, Registration number: 2017/1360).

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