Original Investigation

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Dosimetric Comparison of Radiotherapy Techniques for Treating Early-stage Glottic Larynx Cancer

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ABSTRACT

Objective: As early-stage larynx carcinoma is considered curable, we have investigated the possible differences among treatments with the contribution of advanced technology for maximum prevention of the development of secondary malignancies, and for the long-term quality of life. We compared the doses to the organs at risk, the Conformity indexes (CI), and the total monitor units of patients with early-stage glottic laryngeal cancer with the patients' physical planning for 3-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and volumetric modulated arc radiotherapy (VMAT) using the Eclipse treatment planning system.

Methods: Radiotherapy planning tomography sections of patients with early-stage (T1N0M0) glottic larynx cancer who underwent only radiotherapy were used. The sections were used for target volume and critical organ descriptions. Plans for 3DCRT, VMAT, 5-field IMRT, and 7-field IMRT were made and were compared after the procedures. The patients did not receive elective nodal irradiation. A total of 63 Gy in 28 fractions was described for all patients for the planning target volume (PTV).

Results: There was no difference between the mean PTV dose for VMAT and 5-field and 7-field IMRT. VMAT had the best results for the heterogeneity index and CI; 7-field IMRT had the best results for the mean dose and carotid artery volume receiving (V35 Gy) values. Although very low doses were detected for the medulla spinalis for 3DCRT, the doses of the other three plans were acceptable.

Conclusion: Due to the higher conformality and better protection of the critical organs, VMAT or IMRT is more appropriate rather than 3DCRT in RT treatment of early-stage glottic larynx cancer. The use of 7-field IMRT yields positive results, particularly for the carotid arteries.

Keywords: Dosimetric comparison, early-stage glottic larynx cancer, volumetric arc radiotherapy, intensity-modulated radiotherapy

INTRODUCTION

Larynx cancer constitutes 2% of all cancers and is the second most common cancer after skin cancer in the head-neck region (1). Tobacco use greatly influences the development of larynx cancer (2). Larynx cancers are most frequently detected in the glottic region. The primary treatment of early-stage glottic larynx cancer is surgical treatment or radiotherapy (RT). RT is a singly performed primary treatment in early-stage glottic larynx cancer. It has the advantages of organ protection and enables better voice quality compared to the surgical treatment (3-6). Recently, there has been increased use and preference for treatments that enable larynx protection with increased quality of life. Owing to the functional importance of the larynx, completing treatment with minimal function loss in cancer control has become one of the most important treatment targets (7,8). Factors such as anterior commissure involvement, tumor field size, daily fraction and total dose, total treatment time, beam energy, male gender, and pre-treatment hemoglobin level determine the tumor control of RT in larynx cancer (9-11). RT causes acute and chronic toxicities based on the treated region. To decrease these toxicities, RT for treating

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larynx cancer targets the regions in critical structures neighboring the larynx, such as the carotid arteries, thyroid gland, and medulla spinalis, and normal tissue regions exposed to the radiation dose. Here, we evaluated patients who received only RT for early-stage glottic larynx cancer to identify the approach that would yield the best appropriate tumor and critical organ dose. New volumes were created and physical plans were made using four planning techniques, and the plans were compared on system-recorded computed tomography (CT) sections of patients with pathologically and clinically proven early-stage larynx cancer and who received only RT. We evaluated a total of 20 patients who had been diagnosed with early-stage (T1N0M0) glottic larynx cancer. The study was planned as a prospective study. To enable 63 Gy in 28 fractions for each patient for planning target volume (PTV), we made physical plans that were compatible with 3-dimensional conformal RT (3DCRT), 5-field intensity-modulated radiotherapy (IMRT), 7-field IMRT, and volumetric modulated arc RT (VMAT). A total of 80 plans were prepared. The patients received no elective nodal irradiation.

METHODS

Ethics committee approval was received for this study from the Ethics Committee of Okmeydanı Training and Research Hospital (approval number: 524, date: 25.10.2016). This is a retrospective study. Patient data were taken from the files.

Twenty patients (1 woman, 19 men) with pathologically proven squamous cell epithelial carcinoma larynx cancer with early-stage glottic tumor, and who received only RT indication for treatment between 2013 and 2015 at Okmeydanı Training and Research Hospital Clinic of Radiation Oncology were included in the study. The patients had not received previous treatment, and CT images performed for RT planning were recorded in the system. The mean patient age was 55 (minimum: 33, maximum: 69) years. A prospective study method was planned.

The staging of the patients was conducted after direct laryngoscopy, CT, or magnetic resonance imaging scanning. All patients were diagnosed with T1N0M0 larynx cancer. The CT images previously recorded in the system were used in the study. Each patient was immobilized using thermoplastic head-neck masks when obtaining the images. The CT planning data were obtained using a Philips Brilliance wide-bore, 16-slice CT scanner (Philips Healthcare, Stockholm, Sweden). Image sections were taken from the vertex to underneath the clavicle at 3 mm intervals. Then, the images were transferred to the Eclipse 10.0 treatment planning system. Each patient was drawn compatibly with the following newly identified volume protocols:

- Clinical target volume (CTV): Cricoid cartilage, arytenoid cartilage, false vocal cords, anterior and posterior commissures, true vocal cords, and 1-1.5 cm of subglottis from above the hyoid bone to the end of the cricoid cartilage,

- PTV: CTV + symmetric 0.7 cm safety margin in each direction,

Dose: 63 Gy/28 fractions.

The carotid arteries (right and left), medulla spinalis, and thyroid gland were contoured as the organs at risk (OAR). The medulla spinalis and carotid arteries were drawn in the space determined via the addition of 1 cm to the upper and lower borders of the PTV. The thyroid gland was described to involve the entire organ. In addition, the body sections outside the PTV receiving doses of 5 Gy (D5) and >5 Gy were described. Four plans were prepared using the RapidArc Millennium 120 MLC device on the Eclipse 10.0 system to provide 63 Gy/28 fractions to all of the patients. The 3DCRT used two opposite lateral fields; IMRT planning used 5- and 7-field techniques; VMAT planning used the double arc method. All plans used a 6-MV photon beam. The data were obtained using dose-volume histograms.

Statistical Analysis

The data were prepared using the Microsoft Excel 2013 program. We compared the OAR doses; total treatment times; tumor dose coverage; Conformity index (CI); Homogeneity index (HI); total monitor units administered; and the low, median, and high dose volumes of the normal tissues rather than the target volume among the four dosimetric plans. The statistical analyses were performed using the SPSS 22 program.

RESULTS

Target Volume Dose Contents

The PTV63 volume levels were between 71.4 and 89.3 mL (mean: 77.4 mL). There was a statistically significant difference between the mean PTV and mean dose measurements of the RT techniques ($p=0.003$).

The mean PTV and D5 (Gy) of VMAT was significantly lower than that of 5-field IMRT ($p=0.000$), 7-field IMRT ($p=0.000$), and 3DCRT ($p=0.000$) ($p<0.05$). There was no statistically significant difference between the mean PTV and D5 (Gy) of 5-field IMRT and 7-field IMRT ($p>0.05$). There was no statistically significant difference between the mean PTV and D5 (Gy) measurements ($p=0.837$). There was a statistically significant difference between the mean PTV of the methods and the HI ($p=0.001$) and between the mean PTV and the CI of the methods ($p=0.001$) (Table 1, 2).

Doses in Organs at Risk

The carotid arteries, medulla spinalis, and thyroid gland involved in the treatment region were described as the OAR and were evaluated.

Carotid Arteries

The mean carotid artery doses and the mean dose measurements were statistically significantly different ($p=0.001$).

There was a statistically significant difference between the mean carotid artery dose and minimum dose (Gy) measurements ($p=0.001$). Paired comparisons showed that the mean carotid artery dose and the minimum dose (Gy) of 3DCRT were significantly higher than those of VMAT ($p=0.000$), 5-field IMRT ($p=0.000$), and

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7-field IMRT (p=0.000) (p<0.05). The mean carotid artery dose and the minimum dose (Gy) of VMAT were significantly higher than those of 7-field IMRT (p=0.003) (p<0.05). The mean carotid artery dose and minimum dose (Gy) of the 5-field IMRT and 7-field IMRT were not statistically significantly different (p>0.05). The mean carotid artery dose and the minimum dose (Gy) of the 5-field IMRT and VMAT were not statistically significantly different (p>0.05).

There was a statistically significant difference between the mean carotid artery dose and the maximum dose (Gy) measurements of the RT techniques (p=0.001). Paired comparisons demonstrated that the mean carotid artery dose and the maximum dose (Gy) measurement of 3DCRT were significantly higher than those of VMAT (p=0.000), 5-field IMRT (p=0.019), and 7-field IMRT (p=0.000) (p<0.05).

There was a statistically significant difference between the mean carotid artery dose and the V35 (cm^3, volume receiving 35 Gy) measurements (p=0.001) and between the mean carotid artery dose and the V50 (cm^3) measurements (p=0.001) of the RT techniques (Table 3, 4).

Table 1. **The evaluation of the planning target volume measurements**

	VMAT	IMRT 5-field	IMRT 7-field	3DCRT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
PTV - mean dose	65.14±0.74	65.52±0.2	65.51±0.27	66±0.56	[1]0.003*
PTV - D5 (Gy)	66.41±0.41	67.26±0.18	67.17±0.32	67.88±0.49	[1]0.001*
PTV - D95 (Gy) (median)	62.95±0.06 (63)	62.97±0.05 (63)	62.96±0.05 (63)	62.96±0.05 (63)	[2]0.837
PTV - HI (median)	0.047±0.007 (0.05)	0.061±0.005 (0.06)	0.059±0.005 (0.06)	0.068±0.009 (0.07)	[2]0.001*
PTV - CI (median)	0.97±0.05 (1)	1.21±0.13 (1.2)	1.27±0.16 (1.2)	2.22±0.31 (2.2)	[2]0.001*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, PTV: planning target volume, SD: standard deviation, HI: Heterogeneity index, CI: Conformity index

Table 2. **The evaluation of the compatibility of planning target volume measurements to the plans**

	VMAT/IMRT 5-field	VMAT/IMRT 7-field	VMAT/3DCRT	IMRT-5 field/ IMRT-7 field	IMRT 5-field/3DCRT	IMRT 5-field/3DCRT
[1]PTV - mean dose	0.378	0.210	0.002*	1.000	0.022*	0.004*
[1]PTV - D5 (Gy)	0.000*	0.000*	0.000*	1.000	0.000*	0.000*
[2]PTV - HI (median)	0.000*	0.000*	0.000*	0.157	0.007*	0.000*
[2]PTV - CI (median)	0.000*	0.000*	0.000*	0.221	0.000*	0.000*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, PTV: planning target volume, HI: Heterogeneity index, CI: Conformity index

Table 3. **The evaluation of the measurements of the carotid artery**

	VMAT	IMRT 5-field	IMRT 7-field	3DCRT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Carotid artery - mean dose	32.69±3.79	35.51±5.58	29.2±3.72	61.99±1.30	0.001*
Carotid artery - min dose (Gy)	4.53±0.51	4.45±0.96	4.09±0.46	26.16±4.14	0.001*
Carotid artery - max dose (Gy)	64.59±1.51	66.84±1.01	65.78±1.04	67.73±0.81	0.001*
Carotid artery - V35 (cm^3)	3.47±1.16	3.98±1.54	3.14±0.84	7.74±1.62	0.001*
Carotid artery - V50 (cm^3)	1.11±0.57	1.7±1.38	1.01±0.34	7.11±1.6	0.001*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, SD: standard deviation

Table 4. **The evaluation of the compatibility of the carotid artery measurements to the plans**

	VMAT/ IMRT 5-field	VMAT/ IMRT 7-field	VMAT/ 3DCRT	IMRT 5-field/ IMRT 7-field	IMRT 5-field/ 3DCRT	IMRT 5-field/ 3DCRT
Carotid artery - mean dose	0.297	0.034*	0.000*	0.000*	0.000*	0.000*
Carotid artery - min dose (Gy)	1.000	0.003*	0.000*	0.321	0.000*	0.000*
Carotid artery - max dose (Gy)	0.000*	0.033*	0.000*	0.065	0.019*	0.000*
Carotid artery - V35 (cm^3)	0.111	0.765	0.000*	0.020*	0.000*	0.000*
Carotid artery - V50 (cm^3)	0.137	1.000	0.000*	0.172	0.000*	0.000*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy

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Thyroid Gland and Medulla Spinalis

There was a statistically significant difference between the mean thyroid gland dose and the mean dose measurements of the RT techniques (p=0.001). Paired comparisons showed that the mean thyroid gland dose and the mean dose of 3DCRT were significantly higher than those of VMAT (p=0.000), 5-field IMRT (p=0.000), and 7-field IMRT (p=0.000) (p<0.05). There was no statistically significant difference between the mean thyroid gland dose and the mean dose measurements of VMAT, 5-field IMRT, and 7-field IMRT (p>0.05).

There was a statistically significant difference between the mean medulla spinalis dose and the maximum dose measurements of the RT techniques (p=0.001). Paired comparisons showed that the mean medulla spinalis dose and the maximum dose of 3DCRT were significantly lower than those of VMAT (p=0.000), 5-field IMRT (p=0.000), and 7-field IMRT (p=0.000) (p<0.05). There was no statistically significant difference between the mean medulla spinalis dose and the maximum dose of VMAT, 5-field IMRT, and 7-field IMRT (p>0.05) (Table 5, 6).

Organs at Risk Outside the Planning Target Volume

Evaluation of the low and median doses of normal tissues outside the PTV63 exposed to radiation revealed a significant difference for V5, V10, V20, V30, and V40 (Table 7).

Monitor Unit Values

There was a statistically significant difference between the mean monitor unit measurements of the RT techniques (p=0.001). As expected, the mean monitor unit values of the 3DCRT plans were significantly lower than those of the VMAT, 5-field IMRT, and 7-field IMRT plans (Table 8).

Treatment Times

There was a statistically significant difference in the mean treatment times of the RT techniques (p=0.001). The mean treatment time of the VMAT, 5-field IMRT, 7-field IMRT, and 3DCRT plans was 2.6±0.29 minutes, 2.62±0.19 minutes, 2.83±0.21 minutes, and 2.52±0.19 minutes, respectively. However, data obtained using QA for the total treatment times showed that

Table 5. The evaluation of the thyroid gland-mean dose, and medulla spinalis-max dose measurements

	VMAT	IMRT 5-field	IMRT 7-field	3DCRT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Thyroid gland - mean dose	20.54±4.83	22.91±4.52	21.05±3.42	34.41±5.93	0.001*
Medulla spinalis - max dose	24.96±2.93	24.67±4.75	26.88±3.45	4.23±1.2	0.001*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, SD: standard deviation

Table 6. The evaluation of the compatibility of the medulla spinalis and thyroid gland measurements in accordance with the plans

	VMAT/ IMRT 5-field	VMAT/ IMRT 7-field	VMAT/ 3DCRT	IMRT 5-field/ IMRT 7-field	IMRT 5-field/ 3DCRT	IMRT 5-field/ 3DCRT
Thyroid gland-mean dose	0.351	1.000	0.000*	0.066	0.000*	0.000*
Medulla spinalis-max dose	1.000	0.215	0.000*	0.450	0.000*	0.000-

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy

Table 7. The evaluation of the the means of the organs at risk (CC) measurements in accordance with the plans

OAR volume	VMAT	IMRT 5 field	IMRT 7 field	3CRRT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
V5	17.17±4.83	16.54±4.52	17.32±5.02	11.03±3.93	0.001*
V10	9.73±1.68	12.51±2.95	12.78±3.15	10.21±1.93	0.001*
V20	3.83±1.21	7.66±1.89	6.84±1.67	5.31±1.44	0.001*
V30	2.5±0.87	3.15±1.11	3.19±1.14	4.2±1.35	0.002*
V40	1.81±0.7	2.03±0.74	2.07±0.76	3.64±1.16	0.001*

OAR: organs at risk, VMAT: volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, SD: standard deviation

Table 8. The evaluation of the means of the monitor unit measurements in accordance with the plans

	VMAT	IMRT 5-field	IMRT 7-field	3CRRT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Monitor unit	503±45.6	792±114.4	941±139.4	271±23.5	0.001*

VMAT: Volumetric modulated arc radiotherapy, IMRT: intensity-modulated radiotherapy, DCRT: dimensional conformal radiotherapy, SD: standard deviation

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the 3DCRT plans were superior. The total treatment times were as follows: VMAT plans, 3.69±0.31 minutes; 5-field IMRT plans, 6.92±0.61 minutes; 7-field IMRT plans, 8.21±0.74 minutes; and 3DCRT plans, 2.82±0.22 minutes.

DISCUSSION

The primary aim of treatment of early-stage glottic larynx cancer is protecting the larynx function in particular, and protecting voice quality (11,12). Therefore, RT has become the first treatment option in early-stage glottic larynx cancer, considering the relatively lower toxicity with good tumor control, and the organ-protective approach as compared to the surgical treatment (13,14). Over time, RT techniques that reduce the potential adverse effects and morbidity risk have become research areas of interest (15,16).

In early-stage glottic larynx cancer, RT treatment with two opposite fields enables greater tumor control. Patients have been treated with this method for years. However, there has been increased prevalence of atherosclerosis, carotid artery wall thickening, and cerebrovascular accident, as the carotid arteries are innately located in the treatment field. In recent years, the convenience of novel RT techniques such as IMRT and VMAT for treating early-stage glottic larynx cancer has been investigated. The main aim in these advanced technologies is to enable more conformal dose distribution in the target volumes and maximum protection of the surrounding tissues. Modern techniques with higher conformal RT planning and administration systems have the potential to decrease the early and late adverse effects that result from the limitation in tumor dose determination by reducing the dose to which the carotid arteries and surrounding tissues will be exposed. In addition, tumor control may be increased by enabling an increased dose to the target field using more conformal RT techniques.

IMRT provides dose distribution that may create a concave/convex isodose line in the target tissues. The benefit of this modality is the possibility of reducing the early and late adverse effects by decreasing the distribution of high doses to the critical organs.

Many researchers have investigated VMAT for treating local advanced larynx cancer; however, the number of studies investigating VMAT for treating early-stage glottic larynx cancer is inadequate.

The publications on early-stage glottic larynx cancer in which VMAT is used are scarce (17,18), as are comparison studies investigating VMAT and IMRT (19-22).

One advantage of VMAT is the shorter treatment time (23). There is no time loss in the form of a waiting period for the gantry to reach the expected state, as the radiation in VMAT is administered when the gantry is mobile. However, there is a waiting time for IMRT, which is a significant reason for the longer treatment periods (23,24). Rosenthal et al. (25) showed that the treatment times for IMRT and 3DCRT are similar (26).

Lower doses may be obtained in VMAT, as the shorter treatment time will reduce organ movement. Atalar et al. (22) reported that VMAT had the shortest treatment time and lowest carotid artery dose.

However, the shortest treatment time recorded in the present study was for 3DCRT; VMAT had shorter treatment times compared to 5-field and 7-field IMRT. The advantage of the rapid treatment time is that the risk of missing the field is reduced by minimizing organ movement.

In the present study, double arc VMAT was preferred. Comparison studies of single and double arc VMAT have reported higher PTV involvement and critical organ protection rates in favor of double arc VMAT (27). Moreover, a study using double arc VMAT reported better parotid gland protection (28). However, discussion of the accurate VMAT technique is ongoing.

Maximum doses of decrease to the medulla spinalis may be enabled by identifying the angles of the IMRT regions from the anterior surface of the larynx; however, this increases the doses to the carotid artery (22,29).

Although the medulla spinalis doses were within the tolerance doses for VMAT and IMRT, they were higher compared to 3DCRT ($p<0.001$).

The primary aim of the present study was to identify the PTV involvement rate and to identify a limit dose for the critical organs (30). The lowest mean dose for the carotid arteries was, in the order of lowest to highest, from VMAT, IMRT, and 3DCRT. Thus, using VMAT would reduce the risk of cerebrovascular accident. However, it is unclear which dose limitations should be used in RT treatment of the carotid arteries. Therefore, it is possible that more prospective clinical studies will identify the clinical benefit of such dose reduction.

Rosenthal et al. (25) have recommended that decreased carotid artery doses are required, particularly in young patients with carotid artery pathology.

Martin et al. (31) found that a carotid artery vascular wall dose of ≥35-50 Gy was significant. The values obtained in their study were higher than those of other studies. The reason could be the 7 mm safety margin given to the CTV in PTV identification.

Similar to carotid arteries, the thyroid gland is anatomically located in the neighboring region of the PTV. The use of RT for treating head-neck cancers may cause adverse effects such as hypothyroidism, Graves' disease, and various thyroid malignancies (32).

CONCLUSION

RT treatment of head-neck cancers gives rise to risk factors for carotid artery atherosclerosis, cerebrovascular accident, and thyroid dysfunction.

Here, using planning images, we devised 3DCRT, 5-field IMRT, 7-field IMRT, and VMAT plans for patients with early-stage glottic larynx cancer who were treated using only RT. Then, the plans were compared using dosimetric parameters. The 7-field IMRT was

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the best for protecting the carotid arteries; however, the VMAT plan was the best for the CI and HI. These dosimetric advantages may be useful for patients with a history of ischemic stroke with atherosclerotic changes in the carotid arteries. The best technique for medulla spinalis doses was 3DCRT, and the doses obtained for the other three techniques were at acceptable levels. The mean thyroid gland doses were higher in 3DCRT compared to the doses in the other three plans. The 3DCRT plans were the best for treatment times and total monitor units, and VMAT plans enabled shorter treatment times, treatment with monitor units, and better patient comfort compared to the IMRT plans (5- and 7-field).

RT planning systems such as IMRT and VMAT, which were developed after 3DCRT, currently provide better results for both dose distribution and dosimetrically. However, the efficacy, applicability, and dosimetric superiority of the systems in accordance with the treated region are controversial. In addition, there may be differences in CTV contouring among clinicians. In such cases, changes are expected for the dosimetric results.

The main advantage of the IMRT and VMAT plans is the possibility of high-level protection for the surrounding OAR in addition to enabling high doses to the target tissue. Similar studies are required for planning the options for patients with early-stage glottic larynx cancer in clinics that have both planning systems. The best option for RT is treatment conducted using the best available plan.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Okmeydanı Training and Research Hospital (approval number: 524, date: 25.10.2016).

Informed Consent: This is a retrospective study. Patient data were taken from the files.

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