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Original Article

Results of radiotherapy in squamous cell laryngeal cancer: A tomotherapy center experience

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Abstract

Background: Laryngeal cancer is a common type of head and neck cancer (HNC). Radiotherapy (RT) is a mainstay for curative treatment. Intensity-modulated RT (IMRT) is a standard technique today, as it provides of higher survival and local control and lower normal tissue toxicity. One of IMRT devices is helical tomotherapy (HT). The HT treatment results of HNC patients have been reported in few studies. We aimed to investigate the results of squamous cell laryngeal carcinoma patients treated with helical tomotherapy.

Methods: Forty-five laryngeal cancer patients were selected according to the inclusion criteria. Radiotherapy (RT) plans were set in the Hi-Art HT planning system. Image-gated RT (IGRT) technique was used. Appropriate patients received simultaneous cisplatin. Treatment response rates were evaluated at the post-RT third and sixth months. Survival times were calculated with the Kaplan–Meier method. The factors affecting the treatment results were evaluated using Log-rank and Cox regression tests. A P value of less than 0.05 was accepted as statistically significant.

Results: The median age was 65 (28–84) years. The median symptom duration was 6 (1–60) months. The RT dose for the early and the locally advanced disease was median 63 Gy (60.75–66) and 66 Gy (60–70), respectively. The RT interruption was median two (0-20) days. The patients were followed up to 25 (1–45) months. Grade 2 xerostomia and dysphagia rates were 55% and 7%, respectively. The 3-year estimates of overall survival (OS), disease-free survival (DFS), metastasis-free survival (DMFS), and locoregional recurrence-free survival (RRFS) were 71.7%, 60.4%, 84.9%, and 68.5%, respectively. In univariate analysis, the presence of N2 disease was a negative prognostic for DFS ($P = 0.05$) and DMFS ($P = 0.003$). RT interruption >2 days was a negative prognostic for OS ($P = 0.005$), DFS ($P = 0.02$), and RRFS ($P = 0.023$). In the multivariate analysis, symptom duration >6 months was found to be the only significant factor for DFS ($P < 0.05$).

Conclusion: Intensity-modulated radiation with HT achieved comparable clinical outcomes with acceptable toxicity in laryngeal carcinoma.

Keywords:
Helical tomotherapy, laryngeal cancer, radiotherapy, retrospective analysis, treatment results

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Introduction

Laryngeal cancer is a common type of head and neck cancer (HNC).[1] Radiotherapy (RT) is a mainstay for curative treatment for early and locally advanced laryngeal cancers. Intensity-modulated RT (IMRT) is standard today, as evidenced by higher survival rates, locoregional control, and lower salivary gland toxicity compared to conventional and conformal techniques.[2-6]

One of IMRT devices is helical tomotherapy (HT). HT is a modality for delivering IMRT plans using a rotating linear accelerator mounted on a continuously moving slip ring gantry in a synchrony with the couch motion. The HT treatment results of HNC patients have been reported in a few studies.[4,7-11] For this reason, we aimed to investigate the treatment outcomes and to evaluate the factors determining them, in patients with laryngeal carcinoma.

Materials and Methods

Patient selection

Forty-five laryngeal cancer patients who met the inclusion criteria were evaluated retrospectively. The inclusion criteria are given in Table 1. RT was applied to all patients in TomoTherapy® Hi-ART®.

The pretreatment evaluation consisted of history and physical examination (PE), pan-endoscopy, complete-blood count, liver and renal function tests, chest X-rays, dental evaluations, and computed tomography (CT) and magnetic resonance imaging (MRI) of the HN region. Positron emission tomography (PET-CT), bone scans, chest CT, and abdomen CT were obtained when in the presence of a clinical indication. The staging was performed with the American Joint Committee on Cancer (AJCC) TNM-staging system (7th edition). Patients treated with definitive RT were staged clinically, while postoperative cases staged pathologically.

Treatment planning and delivery

Patients were immobilized in the supine position with both arms by their sides, and a thermoplastic IMRT mask was used to cover the HN region and shoulders (type-S thermoplastic-based system CIVCO, Civco Medical Solutions, Kalona, IA, USA). CT images were taken with 3 mm slice thickness by using a contrast agent. The organs-at-risk volumes (OAR) and the target volumes were delineated in the focal contouring system V.4.62 (Elekta, Stockholm, Sweden). The spinal cord, brainstem, parotid glands, submandibular glands, mandible, cochlea, oral cavity, and esophagus were delineated as OAR. Gross tumor volume (GTV) was contoured with the help of the patient's PE findings, and existing images. Involved lymph nodes were defined as any lymph nodes >1 cm or those with a necrotic center. Clinical target volumes (CTVs) were generated, including the primary tumor and lymphatics in the neck. CTV-gross disease was defined as GTV tumor or positive lymph nodes plus 1-2 cm margin. For the postoperative patients, the CTV-tumor bed was defined as the surgical tumor bed at risk for harboring microscopic residual disease. For both definitively and postoperatively treated patients, the high-risk CTV (high-risk subclinical region) subclinical region was created for the involved cervical lymphatics and supraclavicular neck. The low-risk CTV (low-risk subclinical region) subclinical region included the prophylactically treated uninvolved neck. A 3-5 mm planning target volume (PTV) margin was given to the CTV. HT plans were made with the IMRT technique in the Hi-Art HT planning system (Accuray Inc., Madison, USA). For all cases, a jaw setting of 2.5 cm, a pitch of 0.287, and an initial modulation factor of 2 were selected. The optimization parameters were set to deliver the prescription dose to 95% of the PTVs [Figure 1]. RT was performed with the simultaneous integrated boost (SIB) technique by using 6 MV X-ray beams and image-gated RT (IGRT). Patients who had a good general condition and blood tests received 100 mg/m^2/day of cisplatin in every three weeks or 40 mg/m^2/day of cisplatin in every one week, simultaneously.

Evaluation of the response and follow-up protocol

Treatment response rates were evaluated at the post-RT third and sixth months. RT-induced side effects were rated according to the radiation therapy

Table 1: Selection criteria

Inclusion criteria	Exclusion criteria
Histologically confirmed squamous cell laryngeal carcinoma	Diagnosed with non-laryngeal HNC or non-squamous cell laryngeal carcinoma
Treatment with RT for definitive or adjuvant purposes	Treatment with RT for palliative purpose
The good general condition with a performance status of ≤2 in ECOG	The performance status is ECOG 3 or 4
No previous head and neck irradiation	Reirradiation of the head and neck region
No distant metastasis	Disease with metastatic stage
No comorbidities to prevent the completion of treatment	

HNC: Head and neck cancer, ECOG: the Eastern Cooperative Oncology Group classification, RT: Radiotherapy

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Key Message

The clinical outcomes for laryngeal carcinoma obtained with helical tomotherapy were comparable to the other series reporting on intensity-modulated radiotherapy and volumetric arc therapy. The negative effect of symptom duration on disease-free survival was shown for the first time.



Figure 1: RT dose distribution of a locally-advanced laryngeal cancer patient (PTV70 is in red, PTV66 for larynx is in light-blue, PTV66 for lymph node is in dark-blue, PTV63 for the right neck is in pink, and PTV63 for the left neck is in green). RT: Radiotherapy, PTV: Planning target volume

oncology group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) scale.[12] The follow-up of the patients was performed every 3 months in the first 2 years and every 6 months up to the 5th year.

Ethics

This study was approved by the Erzurum Regional Education and Research Hospital Ethics Committee of Clinical Trials (Erzurum BEAH KAEK 2018/12-121).

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 18.0 (SPSS Inc., Chicago, USA). Survival times and rates were examined with the Kaplan–Meier method. Overall survival (OS) was calculated from the day of diagnosis. Disease-free survival (DFS), locoregional recurrence-free survival (RRFS), and distant metastases-free survival (DMFS) were calculated from the last day of RT to the time of death, relapse or last follow-up. The factors affecting the treatment results were evaluated using Log-rank and Cox regression tests. A *P* value of less than 0.05 was considered statistically significant.

Results

The median age of 45 men diagnosed between 2013 and 2017 was 65 (28–84) years. The median symptom duration was 6 (1–60) months. A total of 80% of the patients were staged with PET-CT. In total, 97.7% of the patients were diagnosed with primary tumor biopsy; the remaining patients underwent lymph node biopsy. In early-stage disease, the median prescribed dose was 63 Gy (60.75–66). In locally advanced disease, the median total dose was 66 Gy (60–70) for the high-risk PTV; 54 Gy (54–59.4) for the low-risk PTV. The median duration of RT completion was 46 days (32–105). The median for RT interruption was 2 (0–20) days. The other characteristics of the patients and disease are given in Table 2.

Table 2: Patient and disease characteristics n (%)

		n (%)
Symptoms	Hoarseness	30 (66.7)
	Hoarseness and dyspnea	10 (22.2)
	Hoarseness and dysphagia	3 (6.7)
Smoking history		36 (80)
T Category	T1	14 (31.1)
	T2	9 (20)
	T3	6 (13.3)
	T4a	15 (33.3)
	T4b	1 (2.2)
N Category	N0	27 (60)
	N1	7 (15.6)
	N2a	1 (2.2)
	N2b	2 (4.4)
	N2c	8 (17.8)
M Category	M0	45 (100)
	M1	0 (0)
Staging	Stage I	12 (26.7)
	Stage II	4 (8.9)
	Stage III	6 (13.3)
	Stage IVA	22 (48.9)
	Stage IVB	1 (2.2)
Performance status	ECOG 0	6 (13.3)
	ECOG 1	24 (53.3)
	ECOG 2	15 (33.3)
Treatment purpose	Radical RT/CRT	32 (71.2)
	Adjuvant RT/CRT	13 (28.8)
CT purpose	Neoadjuvant CT	4 (8.9)
	Concomitant CT	22 (48.9)

Min: Minimum, Max: Maximum, ECOG: the Eastern Cooperative Oncology Group classification, RT: Radiotherapy, CT: Chemotherapy, CRT: Chemo-radiotherapy

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In our study, the median follow-up period was 25 (1–45) months. Treatment response rates to radical RT are given in Table 3. Four patients had undergone salvage surgery because of local recurrence. Three of these patients were alive at the time of analysis with no evidence of disease. One of the patients who underwent salvage surgery died 15 days after the operation. Thirty-two patients received RT to the neck region. Late salivary gland side effects were seen in 27 of 32 patients who were followed up for more than 6 months. Three out of the five patients who died before the 6th month after treatment had no treatment response and two patients died from pneumonia. According to the RTOG scale,[12] 7 (26%) of 27 patients had grade 0; 5 (19%) of them had grade 1, and 15 (55%) of them had grade 2 salivary gland side effect. Three of the patient population had grade 2 dysphagia. There was no grade 3-4 salivary gland and esophageal side effect. The most common site of distant metastasis was the lungs (three patients) followed by the liver (one patient), and distant lymphatic metastasis (one patient). The early mortality rate (deaths occurred during treatment or in one or two months after treatment) was 4.4%. Chemo-radiotherapy (CRT) was applied to both patients who died early after treatment. One of these patients died of progression at one-month post-treatment. The latter patient died due to acute exacerbation of chronic obstructive pulmonary disease (COPD) in the first month after CRT. At the time of analysis, 29 (64.4%) patients were disease-free, three (6.6%) had the disease, and 10 (22.2%) deaths occurred due to disease, and three (6.7%) deaths occurred due to non-tumor related causes. Among the entire patient population, a total of 10 (22%) patients experienced locoregional progression/recurrence with a median interval of 24 months (1–45 months). Median OS and DFS time were 29 (3 - 50) months, and 20 (1–45) months, respectively. The survival rates are given in Table 4. In the univariate analysis, the presence of N2 disease was a negative prognostic factor for DFS (P = 0.05) and DMFS (P = 0.003). RT interruption > 2 days is a negative prognostic factor for OS (P = 0.005), DFS (P = 0.02), and RRFS (P = 0.023). The time for completion of RT >45 days is a factor that reduces DFS (P = 0.059) and RRFS (P = 0.042). In both univariate and multivariate analyses, symptom duration >6 months was found to be an only significant factor for DFS (P < 0.05).

Discussion

IMRT is the standard RT technique in HNC treatment today.[2-5] The main advantage of IMRT is to confine the higher doses to the target volumes and lower doses to the adjacent healthy tissue, and therefore, offer better protection of surrounding OAR.[13] This fact results in decreased RT-induced morbidity and improvement in locoregional control.[14] HT plans provide a sharper dose gradient than the “step and shoot” IMRT plans. Thus, the theoretical reduction in the probability of RT-induced toxicity is in favor of HT plans when compared to “step and shoot” IMRT plans.[15] In the literature, treatment results of HNC cancer patients who underwent RT with HT have been reported in a few studies.[4,7-11] For this reason, we report our experience with squamous cell laryngeal carcinoma patients treated with HT in combination with surgery (28.8%) or CT (57.8%)

Table 3: Response rates after the radical treatment*

	3rd-month evaluation			6th-month evaluation		
	Stage I-II	Stage III-IV	Total Group	Stage I-II	Stage III-IV	Total Group
	n=14 (%)	n=18 (%)	n=32 (%)	n=14 (%)	n=15 (%)	n=29 (%)
Partial response	1 (7.1)	8 (44.4)	9 (28.2)	0 (0)	3 (20)	3 (10.3)
Complete response	13 (92.9)	9 (50)	22 (68.7)	13 (92.9)	9 (60)	22 (75.9)
Progression	0 (0)	1 (5.6)	1 (3.1)	1 (7.1)	3 (20)	4 (13.8)

*Post-operative patients and the patients who died early before the analysis time were excluded from this analysis

Table 4: Survival rates (%)

	Overall survival (OS)			Disease-free Survival (DFS)			Distant Metastasis-free Survival (DMFS)			Loco-regional recurrence-free Survival (RRFS)		
	Stage I-II	Stage III-IV	Total Group	Stage I-II	Stage III-IV	Total Group	Stage I-II	Stage III-IV	Total Group	Stage I-II	Stage III-IV	Total Group
1 year	93.8	79	84.3	75.5	77.1	83	100	86.7	91.7	93.3	80	90.4
2 year	93.8	62	80.7	60	59	65.1	100	76.2	84.9	78	72	79.1
3 year	93.8	60	71.7	60	59	60.4	100	76.2	84.9	62	55	68.5

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Generally, the comparison of the present HT data to prior data from the literature is challenging. Today IMRT for HNC is applied with step and shoot IMRT, HT, and volumetric arc therapy (VMAT). The absence of randomized trials comparing these techniques, the selection of heterogeneous patient populations, and the varying assessment and scoring of toxicity - both acute and late, can be listed as factors that make the comparison of the studies challenging.[16] Our study presents homogeneous data on laryngeal cancer treatment results in contrast to the studies presenting heterogeneous data on HNC in the literature.

Chen *et al*. evaluated 77 HNC patients and found 2-years OS, DFS, and LRC rates of 82%, 71%, and 77%, respectively.[7] Survival and local control rates in our study were consistent with this study. In a study of 63 HNC patients treated with HT by Farrag *et al*., 2-year OS, LRC, and DFS were 66%, 77%, and 54%, respectively.[11] A more recent study conducted by Gestel *et al*. consisted of a larger patient population, and examined 147 HNC patients. Two and 3-year OS, LRC, and DFS rates were 72%, 82%, 65% and 66%, 80%, 59%, respectively.[9] Compared to Farrag *et al*., we achieved a higher 2-year OS and DFS in our study, and we have slightly higher OS but a similar DFS rate compared to the study by Gestel *et al*. The stage distribution of the patients and the inclusion criteria of patients with HNC other than laryngeal cancer in these studies may have a role in the different survival rates. The rate of early-stage (Stage I-II) disease in our study was 10% higher than the other studies. In the study by Yao *et al*., more promising results were reported; a 2-year OS rate was 85% in a population presenting locally advanced stages in 85.4% of the patients studied.[17]

Our 4.4% early mortality is in concordance with the 0-6% early death rates, as reported in the data of Gestel *et al*., and the cross-comparison of clinical trials in the study by Schlumpf *et al*.[9,18]

In our study, the locoregional relapse rate was 22% in the median 24 months, similar to the study by Cruz *et al*., which reported a 21% locoregional relapse rate. These relapses occurred in the median 14th month.[10] The Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) group published the data of a more extensive and heterogeneous group of patients, a part of whom received a postoperative IMRT treatment (46%) and a part of whom (37.5%) received concurrent CT in 2012. In this study, 12.2% of the locoregional recurrence rate was observed at a median follow-up of 25.3 months.[19] The locoregional recurrence rates of the GORTEC group are lower compared to our data. This difference may be due to the high proportion of patients with adjuvant irradiation in the GORTEC group.

Previous studies found that the majority of locoregional failures (range from 56% to 82%) occur in high-dose regions.[7,10,11] This analysis was not performed in our study. However, the majority of in-field relapses shown in other studies may indicate a radiobiological resistance like the disease. Future work on the dose escalation to the high-risk regions or the other strategies that increase the efficacy of RT is needed.

In the literature, it has been seen that the most common metastatic sites are lungs and liver.[7,10,11] The distribution of metastatic disease in our study is consistent with these studies.

Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT) trial showed that parotid-sparing IMRT could reduce long-term xerostomia, and therefore, broadly improve the patient's quality of life.[2] However, it is difficult to evaluate the xerostomia objectively. Numerous rates of dry mouth have been reported in the literature. Chen *et al*. reported 74% of xerostomia without grading.[7] Gestel *et al*. found 40% of grade $\geq$2 xerostomia.[9] When grade 1 and grade 2 side effects were evaluated in combination, the result was equivalent to the rate of dry mouth reported by Chen *et al*. However, our rate of grade 2 xerostomia, which was 55%, was higher than that in the study by Gestel *et al*. Additionally, there was no grade 3-4 xerostomia in our study. It was concluded that the difference between xerostomia rates in these studies was due to the subjective assessment of xerostomia degree and not based on objective techniques.

Following HNC irradiation, some cases develop dysphagia. Also, the radiation can cause the muscles and mucosal lining of the mouth, throat, and esophagus to become stiff and deformed.[20] Grade 3-4 esophageal toxicity reported in the literature was 7–21%.[7,9,10] Grade 3–4 esophageal toxicity was not present in our patients. Our grade 2 toxicity rate was 7%.

Several studies have indicated that the overall treatment time (OTT) has a significant impact on outcome in HNC.[21,22] In our study, half of the patients had RT interruption for >2 days and completed RT over 45 days. Similarly, in the study by Gestel *et al*., this rate was 54%. In the study by Gestel *et al*. and Cruz *et al*., no relationship was found between RT interruption length and survival.[9,10] In our study, the negative prognostic effect of RT interruption length on OS, DFS, RRFS, and the time for completion

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of RT >45 days on DFS, RRFS in the univariate analysis has lost its significance in the multivariate analysis. Studies with a more extensive patient population are needed to demonstrate the survival disadvantage of interrupting RT.

One of the main risk factors for laryngeal cancer is tobacco consumption.[23] Gestel *et al*. showed a negative effect on the OS in their study with a smoking rate of 87% (P = 0.04). Additionally, the prognostic meaning of the severity of smoking was found to be significant in both the univariate and multivariate models (P = 0.00).[9] Cruz *et al*. did not demonstrate the negative prognostic effect of smoking on DFS.[10] Similarly, in our study, although the smoking rate was very high, no negative effect on survival was shown.

In our study, the negative effect of symptom duration on DFS was shown for the first time. This result may indicate that the diagnosis and staging procedures should not prolong the pre-treatment period in the presence of symptoms and signs related to HNC. Other studies should support this finding.

Since the studies in the field of HNC usually report heterogeneous disease data, the number of patients in our study presenting a homogeneous data is higher than the number of patients with laryngeal cancer included in many other studies. The retrospective nature of the study and the inclusion of multimodal treated patients in heterogeneous stages constitute the limitations of our study. To evaluate the nature of the disease and the factors affecting the treatment in a more detailed way and to increase the success of the treatment, studies involving homogenous patient data with more extended follow-up periods are needed.

Conclusions

The clinical outcomes for laryngeal carcinoma obtained with HT were comparable to other series reporting on IMRT and VMAT.

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Conflicts of interest
The authors declare that they have no conflict of interest.

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