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ORIGINAL ARTICLE

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Outcomes of carotid sparing intensity-modulated radiotherapy for early stage glottic cancer in 201 patients: Multicenter study of Turkish Radiation Oncology Society/ TROD-01-007

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Abstract

Background: To assess and report clinical outcomes after carotid sparing intensity-modulated radiotherapy for early stage laryngeal cancer.

Methods: We retrospectively analyzed 201 patients with early stage glottic laryngeal cancer treated with carotid sparing intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) techniques in six TROD centers.

Results: After a median follow-up of 31 months the actuarial 1- and 3-year local and locoregional control rates were 99.4% and 94.7%, 98.4% and 93%, respectively. T classification, anterior commissure involvement, IMRT technique, and type of fractionation were not found to be prognostic for local control. Overall, eight patients had lost their organ function due to recurrence or toxicity. Grade 3 and 4 acute laryngeal edema was seen in eight (4%) and one (0.5%) of patients, respectively. Grade 3 and 4 late laryngeal edema developed in two (1%) and one patient (0.5%), respectively.

Conclusion: Oncologic outcomes of patients treated with carotid sparing IMRT were excellent; comparable with historical series, with acceptable side effects. Longer follow-up is needed to estimate long term effect on stroke.

KEYWORDS

carotid sparing, glottic cancer, IMRT, radiotherapy

1 | INTRODUCTION

Laryngeal cancer is one of the most common cancers in males in Turkey. The standardized tobacco smoking prevalence is 28.7% in Turkey, leading to a laryngeal cancer incidence rate of 8.4 per 100 000, more than double the world incidence, with nearly half of the patients being diagnosed at an early stage.[1] Two modalities, namely transoral laser excision (TLE) and radiotherapy (RT), are used for treatment in early stage glottic cancer.[2] There are no conclusive clinical study results as to which treatment modality (TLE vs. RT) gives better outcomes in

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terms of local control (LC) and overall survival (OS).[3–7] Although RT can be an attractive option it has its pitfalls.

The risk of carotid artery stenosis and cerebrovascular accidents increased by 9%–12% in long term follow-up in patients who received radiotherapy to the neck region due to head and neck cancer.[8–11] Similarly, Dorresteijn et al.[12] reported that the risk of stroke was 5.6 times higher in patients who had undergone neck radiotherapy compared to patients who had not. Therefore, carotid sparing treatment techniques have come to the fore in order to reduce the carotid artery dose in early stage laryngeal cancer. With the development of new techniques, such as intensity-modulated (IMRT) and volumetric modulated arc therapy (VMAT) and the recognition of carotid artery as an organ at risk, the risk of stroke in irradiated patients could be reduced.[13,14] There is no large prospective data comparing the effect of conformal and IMRT/VMAT on local control in early stage laryngeal cancer. However, retrospective studies comparing the two modalities in terms of local control have also shown similar results.[13]

While there are few studies comparing conformal and IMRT techniques[13–16] in early glottic cancer in terms of toxicity and disease control, there are no studies with large number of patients to our knowledge that estimate treatment results in patients treated exclusively with IMRT/VMAT.

This is retrospective multicenter study led by the head and neck study group (HNSG) of the Turkish Radiation Oncology Society (TROD). In this study we aimed to assess patient, disease, treatment characteristics and dosimetric parameters affecting local control, regional control, overall survival, and toxicity in patients treated with carotid sparing IMRT/VMAT using conventional or hypofractionated fractionation regimes.

2 | MATERIALS AND METHODS

2.1 | Patients and treatment characteristics

A retrospective analysis was carried out to identify patients with early stage glottic laryngeal cancer treated with IMRT/VMAT in six TROD centers between 2012 and 2019.

Inclusion criteria were (1) histologically proven in situ or squamous cell carcinoma, Tis-T1-T2 N0 M0 glottic larynx cancer according to AJCC 8th edition staging system; (2) being treated with definitive external radiotherapy, with either IMRT or VMAT techniques; (3) detailed dosimetric data.

Exclusion criteria were: (1) <18 years of age; (2) Eastern Cooperative Oncology Group (ECOG) performance score higher than 2, (3) previous history of radiotherapy of the neck area, (4) secondary malignancy at the time of treatment, (5) less than 3 months of follow-up, (6) high-risk T2 laryngeal cancer with bulky tumor in need of extended RT fields and/or concomitant chemotherapy.

In all patients, physical examination, fibreoptic laryngoscopy, contrast-enhanced neck computed tomography (CT), tissue biopsy, bidirectional chest radiography/CT were routinely performed, and in some patients, magnetic resonance imaging/18-fluorodeoxglucose positron emission tomography was used.

Study was approved by the ethics committee of University of Health Sciences, Kartal Dr Lutfi Kirdar City Hospital 2019/514/160/2.

2.2 | Radiotherapy technique

All patients were immobilized in the supine position with a thermoplastic head and neck mask and CT images were taken from the vertex to the sternoclavicular joint with <3 mm slice thickness.

Target volumes were delineated as follows: "GTV: either primary tumor visible on CT/endoscopy or whole cord involved with tumor," "CTV: entire larynx (false and true vocal cords, arytenoid cartilages, 1–1.5 cm of subglottis, anterior–posterior commissure, ventricular band; superior hyoid; inferior cricoid cartilage or 4 cm × 4 cm/5 cm × 5 cm field)," "PTV: 3–5 mm margin was applied to CTV."

Bilateral carotid arteries and spinal cord were delineated at least 2-cm superior and inferior to thyroid cartilage. If the carotid arteries overlapped with PTV, PTV was manually or automatically modified to exclude the carotid arteries. Most centers did not define PRV for carotid arteries (only 18 patients had been given PRV 2–3 mm).

The IMRT plan was designed as three to nine fields technique and VMAT plan was designed as 2–4 arc technique. Plans were normalized so that 100% of the PTV received more than 95% of the prescription dose. Dose constrains commonly used by centers for carotid arteries were either as low as possible or V35 < 50% and for spinal cord were as low as possible or maximum point dose <45 Gy. Centers used different fractionation schemes (total dose/fractions/dose per fraction); (66–70 Gy/33–35 fr/2 Gy); (69.3 Gy/33 fr/2.1 Gy); (66 Gy/30 fr/2.2 Gy); (63–65.25 Gy/28–29 fr/2.25 Gy), respectively.

Treatment area accuracy was evaluated by performing image guided radiotherapy using kV–kV images and/or cone beam CT every day or every other day throughout the entire treatment period.

TABLE 1 Patient, tumor, and treatment characteristics

Characteristic		*n*	%
Median age (years, range)		64 (39–87)	
Sex	Male	188	93.5
	Female	13	6.5
Smoking	Yes	174 (active 48)	86.6 (23.9)
	No	27	13.4
Alcohol	Yes	78 (active 43)	38.8 (21.4)
	No	123	61.2
Previous treatment	Biopsy	163	81.1
	Stripping	31	15.4
	Cordectomy	7	3.5
T classification AJCC 8th	T0 (Tis)	28	13.9
	T1a	136	67.7
	T1b	17	8.5
	T2	20	10
Differentiation	Well differentiated	79	39.3
	Moderately differentiated	27	13.4
	Poorly differentiated	2	1
	Not specified	93	46.3
Anterior commissure invasion	Yes	47	23.4
	No	154	76.6
Radiotherapy technique	IMRT	27	13.4
	VMAT	174	86.6
Dose per fraction	≥2.25	95	47.3
	<2.25	106	52.7
Dose per fraction, median (range)		2.2 Gy (2–2.25 Gy)	
Total dose, median (range)		66 Gy (63–70 Gy)	
Homogeneity index (HI), median (range)		0.09 (0.02–0.96)	
Conformity index (CI), median (range)		1.01 (0.16–1.98)	

2.3 | Dosimetry

For the PTV volume in all plans, Dmean, D2, D5, D50, D95, D98, Homogeneity Index (HI), Conformity Index (CI) data were evaluated. The Conformity and Homogeneity index were calculated with the formula given by the International Commission on Radiation Units and Measurements (ICRU83).[17] V35, V50, mean, and maximum doses were evaluated for bilateral carotid arteries.

2.4 | Follow-up statistical analysis

During the treatment period acute toxicities were assessed weekly. Patients were examined at 1 and 3 months after the completion of radiotherapy for treatment-related toxicities, and every 3 months thereafter. Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) scales were used to assess acute and late side effects.[18]

Data analysis was performed with IBM SPSS Statistics for Macintosh, version 17.0 (IBM, Armonk, NY). Local progression free survival (LPFS), regional progression-free survival (RPFS), progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS) rates were calculated using the Kaplan–Meier method. The LPFS, RPFS, PFS rates were calculated from the last day of RT until either disease recurrence or progressive disease or death. OS was calculated from diagnosis until death or censoring at the last follow-up visit. Disease-specific survival was calculated from diagnosis until death proven to be due to laryngeal cancer. Cox univariate regression analysis was performed to identify

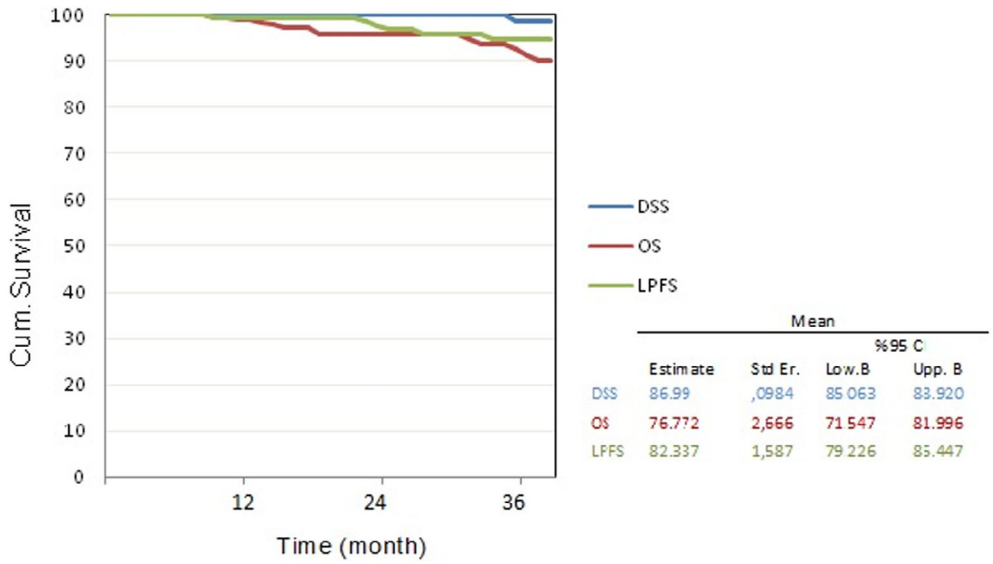


FIGURE 1 Kaplan–Meier survival curves for entire study cohort. DSS, disease-specific survival; LPFS, local progression-free survival; OS, overall survival. [Color figure can be viewed at wileyonlinelibrary.com]

factors affecting survival. Statistical significance was set at $p < 0.05$.

3 | RESULTS

There were 201 patients identified and included in this analysis. Two patients were excluded because they had a follow-up of less than 3 months, no patient was excluded due to missing dosimetric data. Patients and treatment characteristics are summarized in Table 1. Thirty-two patients had hypertension, 36 coronary artery disease, and 26 diabetes mellitus. Median follow-up was 31 months (range: 6–88.4 months).

3.1 | Overall survival

Eighteen patients had died at the time of the analysis, only two patients died due to laryngeal cancer. Sixteen patients had died due to causes unrelated to laryngeal cancer (six patients had second primary cancer, nine had cardiovascular events, one patient died of an unknown cause with primary tumor under control at last control). Of the nine patients who died due to cardiovascular events, four had coronary artery disease, three had no history of cardiovascular disease, and two patients had no information at baseline. Median time of death from second primary and cardiovascular events was 32.6 (4.57–60.76) months. OS and DSS rates were 92.5% and 98.7%, respectively, at 3 years (Figure 1). The estimated 5-year OS was 84.5%. Three- and 5-year OS according to T classification were Tis; 88.6% and 81.3%, T1; 92.1%and 86.2%, T2; 90% and 78.8%, respectively.

OS was significantly lower in patients developing secondary cancers and patients who already had or later developed cardiovascular disease (3 year survival in patients with second primary cancer was 78.1% versus 94.2% in other patients, $p = 0.024$). None of other treatment related factors or disease characteristics had a significant impact on OS (sex, age, anterior commissure involvement, stage, differentiation, total dose, fraction dose; $p > 0.05$ for all comparisons).

Second primary cancers were seen in 19 (9.4%) cases. Most common secondary cancers were lung (six cases, 3%), prostate (four cases, 2%), and colorectal (two cases, 1%) cancer.

3.2 | Disease control

Isolated local recurrence was detected in six (3%) patients, both local and regional recurrence in one (0.5%) patient and isolated regional recurrence in three (1.5%) patients. Distant metastasis was detected in three (1.5%) patients, two of which occurred after regional recurrence. The 3-year progression-free survival was 92.9%. Three-year local and local-regional progression-free survival rates were 94.7% and 93%, respectively. LPFS was similar for patients treated with 2.25 Gy per fraction vs other fractionations (94.1% vs. 94.7%, $p > 0.05$).

None of the patient, tumor and treatment factors were found to be prognostic on local control. Three-year LPFS was 89.1% in patients with anterior commissure involvement and 96.4% in patients without anterior commissure involvement, $p > 0.05$. Three-year LPFS according to stage was; Tis 100%, T1 95.4% (T1a 94.7%, T1b 100%), T2 82.5%, respectively, $p > 0.05$. Patient who

TABLE 2 Recurrence sites and salvage treatments applied

Recurrence site	Number	Treatment	Last status
Local alone	6	1PL, 5TL	All ANED
Local + regional	1	TL + LND	Death
Regional alone	3	LND	2 ANED, 1 death
Total	10	10	8 ANED, 2 death

Abbreviations: ANED, alive with no evidence of disease; LND, lymph node dissection; PL, partial laryngectomy; TL, total laryngectomy.

had undergone surgery prior to radiotherapy had a 3-year LPFS of 100% as compared to 93.5% in patient whose primary treatment was radiotherapy.

Similarly, anterior commissure involvement, stage, differentiation, fraction size had no statistically significant effect on regional progression-free survival ($p > 0.05$ for all comparisons).

3.3 | Salvage therapy

The majority of patients with isolated local recurrence underwent total laryngectomy (TL) (five out of six patients) and one patient underwent partial laryngectomy (PL) (Table 2). The 3-year laryngeal preservation rate was 96.5%. One patient with local and lymphatic recurrence treated with TL and lymph node dissection (LND) and three other patients with isolated regional recurrences underwent LND.

3.4 | Carotid artery sparing (OAR)

Different approaches were used according to the centers, and the most common carotid artery dose *constraint was mean 35 Gy* and the second most frequent approach was as low as possible. The mean ipsilateral and contralateral carotid artery doses were 20.87, 18.78 Gy, respectively. The median dose and range were 18.56 Gy (6.36–60.9) for the ipsilateral carotid artery and 17.37 Gy (4.92–58.6) for the contralateral carotid artery.

3.5 | Side effects

Nine patients (4.5%) experienced Grade 3 acute laryngeal edema and three (1.5%) patients experienced Grade 3 late laryngeal edema. Fraction size, treatment time, total dose, or smoking status did not affect occurrence of neither early nor late edema. Four (33%) out of 12 patients with acute or late laryngeal edema underwent either temporary or permanent tracheostomy due to dyspnea. The treatment details of four patients who underwent tracheostomy (Table 3) were also given. Patient, treatment, and dosimetric characteristics of four patients who underwent tracheostomy were analyzed; however, no significant factor causing trachesotomy was found. No patient had a laryngectomy due to complications. Grade 3 dysphagia requiring IV fluid support was observed in three patients (1.5%) during treatment. None of the patients needed long-term enteral feeding. No transient ischemic attack or stroke was observed during the follow-up period.

4 | DISCUSSION

The increased risk of cerebrovascular accidents due to damage of carotid artery after conventional radiotherapy had led to pursuit of alternative, safer, and effective RT techniques. Rosenthal et al.[19] first reported their carotid sparing IMRT for early glottis cancer and in their series of 11 cases of T1-T2 glottic cancer, carotid-sparing IMRT significantly reduced radiation doses in the carotid arteries compared to the conventional technique. In a subsequent retrospective study of the same group, treatment results for 62 patients treated with carotid sparing IMRT versus 153 conventional radiotherapy were compared.[13] While no difference was found in local control between two techniques, the cerebrovascular events were reported in four cases after conventional radiotherapy, whereas no patients in the IMRT group. They had concluded that they transitioned to IMRT as the standard treatment of patients with early stage laryngeal cancer, as the local control results obtained with IMRT were excellent and IMRT allowed carotid sparing. Many studies have shown that the carotid artery dose can be reduced with the IMRT technique.[15,18,19]

There are no clearly defined dose constraints for carotid arteries in the literature. In the overview of Gujral et al.,[20] carotid artery dose constraints were reported in only two studies, Zumsteg et al.[15] mean carotid artery dose <52 Gy and Riegel et al.[21] as low as possible. Martin et al. reported that the intimal-medial thickness was a dose response threshold that was statistically significant only at doses above 35–50 Gy.[22]

TABLE 3 Patients' treatment and dosimetric characteristics of four patients with tracheostomy

Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Age, sex	69, M	62, M	62, M	56, M
Dose (Gy)	2	2.1	2	2.25
Fraction number	35	33	33	28
Total dose (Gy)	70	69.3	66	63
Field size (cm × cm)	7.7 × 8	5 × 5.5	7 × 7.5	6.3 × 5.7
Treatment technique – MV	2 ARC – 6 MV	6 F dimrt – 6 MV	3 ARC – 6 MV	2 ARC – 6 MV
Use of bolus			0.5 cm	
Closest distance between PTV and skin	3 mm	3 mm	1 mm	9.8 mm
PTV margin (mm)	All: 3–5 mm	CC: 7 mm Others: 5 mm	All: 5 mm	All: 3 mm
Treatment planning algorithm	AAA	AAA	AAA	AAA
Time interval RT – tracheostomy (months)	12	6	4	2
Last status of tracheostomy	Permanent/exitus	Temporary/closed	Temporary	Temporary/closed
Smoking during RT	No	No	No	Yes
PTV_MEAN (Gy)	71.42	71.4	67.81	64.48
PTV_D2 (Gy)	73.06	73.1	69.15	66.57
PTV_D5 (Gy)	72.77	72.8	68.86	65.98
PTV_D50 (Gy)	71.51	71.5	67.92	64.51
PTV_D95 (Gy)	69.86	69.7	66.42	63
PTV_D98 (Gy)	68.73	68.5	65.33	62.1
DMAX (%)	105.8	107	107.4	107.5
HI	0.06	0.06	0.05	0.07
CI	1	0.7	0.88	1.08

In our retrospective study, we aimed to investigate the toxicity profile and disease control after carotid sparing IMRT/VMAT for early stage glottic laryngeal cancer. After a median follow-up of 3 years the overall and disease-specific survival were 92.5% and 98.7%, respectively (5-year OS 84.5%). Five-year OS for T1 was 86.2% in our study and it compares with conformal RT results which range between 79% and 89%, and TLE ranging between 84% and 92%.[3] Likewise, 5-year OS for T2 was 78.8%, similar to previous studies including patients treated with RT (OS range 53%–91%) or TLE (OS range 68.2%–93%).[6] Patients with Tis, although they had 100% disease-specific survival, local and regional control their OS was 81.3%, much lower than expected, because of high rate of death due to secondary cancers and cardiovascular disease. High rate of disease-specific survival in the cohort (only two patients died due to laryngeal cancer) made it impossible to draw any conclusion related to the impact of laryngeal cancer related risk factors such as stage, anterior commissure involvement or differentiation.

The rate of secondary cancers was 9.4% (19 patients), with tobacco related malignancies being the most frequent; lung and upper gastrointestinal (GI) tract cancers followed by prostate. These results are similar with the retrospective study by Gowda et al., where 18 out of 200 patients with T1 glottic cancer developed second primary cancers, most of which were lung, GI, and prostate.[23]

In our study, 3- and 5-year local control for the whole group was 94.7% and 92.3%, respectively. Patients with Tis had a high rate of LPFS with no local recurrence. Patients with T1a or T1b tumor, which comprised the majority of our cohort, had a local control comparable with older series in which patients treated with either RT or TLM achieved local control rates ranging between 69% and 96%.[3] T2 glottic cancer is known to have lower local control as compared to Tis and T1. Our study showed a similar trend but because of a low number of events it failed to reach statistical significance.

None of our patients had any cerebrovascular accident, similar to the cohort of patients treated with IMRT in the study by Mohamed et al.,[13] implying that respecting constraints to the carotid arteries may protect from arterial injury.

In our series, there were four patients (2%) who suffered from severe laryngeal edema or necrosis that led to tracheostomy. In a few studies in the literature,

laryngeal chondroradionecrosis rates after laryngeal radiotherapy have been reported between 1% and 5.3%.[24,25] Chondroradionecrosis was detected at a lower rate in our series, with only one patient (0.5%) suffering from it. Factors causing local trauma (continuity of smoking, infection, diabetes, laryngopharyngeal reflux) and treatment-related factors (RT dose, RT technique, RT portals, and RT frequency) may predispose to the development of laryngeal chondroradionecrosis.[24–26] We could not find any clear relation to any variable with the need for tracheostomy due to toxicity; however, three of the four patients were treated with conventional/near conventional fractionation while the fourth patient who was treated with hypofractionation was a heavy smoker during and after the treatment. Continued smoking is a known factor related to higher risk of complications after radiotherapy.[27] We cannot exclude the possibility that the remaining three patients continued smoking even after RT.

To the best of our knowledge our series includes one of the largest number of patients in the literature who received carotid-sparing radiotherapy with IMRT/VMAT technique. The retrospective nature of the study is the main limitation, which may have led to selection bias. Also, we did not do any survey to the patients regarding the perceived voice quality.

In conclusion, patients with Tis-T2 glottic cancer can be treated with carotid sparing IMRT/VMAT technique which can lead to local control and organ preservation comparing favorably with historical series treated with conformal radiotherapy or other modalities, with less and acceptable side effect. Secondary cancers and comorbidities are the main cause of mortality in this cohort. Longer follow-up is needed to estimate the impact of carotid sparing IMRT/VMAT on stroke. Prospective clinical trials are needed to evaluate the effect of carotid sparing IMRT/VMAT on local control and adverse effects in early stage laryngeal cancer compared to conventional techniques.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data were available for the health professionals.

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REFERENCES

1. World Health Organization (WHO). *Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region, 2000–2019*. World Health Organization; 2020 who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death
2. Silver CE, Beitler JJ, Shaha AR, Rinaldo A, Ferlito A. Current trends in initial management of laryngeal cancer: the declining use of open surgery. *Eur Arch Otorhinolaryngol*. 2009;266(9):1333-1352.
3. Vaculik MF, MacKay CA, Taylor SM, et al. Systematic review and meta-analysis of T1 glottic cancer outcomes comparing CO_2 transoral laser microsurgery and radiotherapy. *J Otolaryngol Head Neck Surg*. 2019;48(1):44.
4. Mo HL, Li J, Yang X, et al. Transoral laser microsurgery versus radiotherapy for T1 glottic carcinoma: a systematic review and meta-analysis. *Lasers Med Sci*. 2017;32(2):461-467.
5. Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1-T2 glottic carcinomas. *Cancer*. 2004;100(9):1786-1792.
6. Warner L, Lee K, Homer JJ. Transoral laser microsurgery versus radiotherapy for T2 glottic squamous cell carcinoma: a systematic review of local control outcomes. *Clin Otolaryngol*. 2017;42(3):629-636.
7. Warner L, Chudasama J, Kelly CG, et al. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. *Cochrane Database Syst Rev*. 2014;12:CD002027.
8. Haynes JC, Machtay M, Weber RS, Weinstein GS, Chalian AA, Rosenthal DI. Relative risk of stroke in head and neck carcinoma patients treated with external cervical irradiation. *Laryngoscope*. 2002;112(10):1883-1887.
9. Brown PD, Foote RL, McLaughlin MP, et al. A historical prospective cohort study of carotid artery stenosis after radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys*. 2005;63(5):1361-1367.
10. Smith GL, Smith BD, Buchholz TA, et al. Cerebrovascular disease risk in older head and neck cancer patients after radiotherapy. *J Clin Oncol*. 2008;26(31):5119-5125.
11. Choi HS, Jeong BK, Jeong H, et al. Carotid sparing intensity modulated radiotherapy on early glottic cancer: preliminary sudy. *Radiat Oncol J*. 2016;34(1):3326-3335.
12. Dorresteijn LD, Kappelle AC, Boogerd W, et al. Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. *J Clin Oncol*. 2002;20:282-288.
13. Mohamed ASR, Smith BD, Smith JB, et al. Outcomes of carotid-sparing IMRT for T1 glottic cancer: comparison with conventional radiation. *Laryngoscope*. 2020;130(1):146-153.
14. Matthiesen C, Herman TDLF, Singh H, et al. Dosimetric and radiobiologic comparison of 3D conformal, IMRT, VMAT and proton therapy for the treatment of early-stage glottic cancer. *J Med Imaging Radiol*. 2015;59(2):221-228.
15. Zumsteg ZS, Riaz N, Jaffery S, et al. Carotid sparing intensity-modulated radiation therapy achieves comparable locoregional control to conventional radiotherapy in T1-2N0 laryngeal carcinoma. *Oral Oncol*. 2015;51(7):716-723.
16. Sert F, Karakoyun-Celik O, Esassolak MA. Can carotid-sparing radiotherapy approaches replace with conventional techniques

for the patients with T1 glottic larynx cancer? *Kulak Burun Bogaz Ihtis Derg*. 2012;22(5):267-274.
17. International Commission on Radiation Units and Measurements. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT): ICRU Report 83; 2010.
18. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31(5):1341-1346.
19. Rosenthal DI, Fuller CD, Barker JL Jr, et al. Simple carotid-sparing intensity-modulated radiotherapy technique and preliminary experience for T1-2 glottic cancer. *Int J Radiat Oncol Biol Phys*. 2010;77:455-461.
20. Gujral DM, Long M, Roe JWG, Harrington KJ, Nutting CM. Overview standardisation of target volume delineation for carotid-sparing intensity-modulated radiotherapy in early glottis cancer. *Clin Oncol*. 2017;29(1):42-50.
21. Riegel AC, Antone J, Schwartz DL. Comparative dosimetry of volumetric modulated arc therapy and limited-angle static intensity-modulated radiation therapy for early-stage larynx cancer. *Med Dosim*. 2013;38(1):66-69.
22. Martin JD, Buckley AR, Graeb D, Walman B, Salvian A, Hay JH. Carotid artery stenosis in asymptomatic patients who have received unilateral head-and-neck irradiation. *Int J Radiat Oncol Biol Phys*. 2005;63(4):1197-1205.
23. Gowda RV, Henk JM, Mais KL, Sykes AJ, Swindell R, Slevin NJ. Three weeks radiotherapy for T1 glottic cancer: the Christie and Royal Marsden Hospital experience. *Radiother Oncol*. 2003;68(2):105-111.
24. Sebelik ME. Chondroradionecrosis of the larynx in patients treated with organ preservation therapy. *Otolaryngol Head Neck Surg*. 2004;131(2):63-64.
25. Melo GM, Souza PD, Filho LCB, et al. Laryngeal chondroradionecrosis following radiotherapy. *Rev Col Bras Cir*. 2017;44(4):374-382.
26. Varghese BT, Paul S, Elizabeth MI, Somanathan T, Elizabeth KA. Late post radiation laryngeal chondronecrosis with pharyngooesophageal fibrosis. *Indian J Cancer*. 2004;41(2):81-84.
27. Van der Voet JC, Keus RB, Hart AA, et al. The impact of treatment time and smoking on local control and complications in T1 glottic cancer. *Int J Radiat Oncol Biol Phys*. 1998;42(2):247-255.

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