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Comparison of Carotid Artery Dose in Early-Stage Glottic Cancer Treated with 3D-Conformal, Helical-IMRT and VMAT

Research Article

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Abstract: Background: The aim of this study was to compare the dosimetry of carotid arteries (CAs) using three radiation therapy (RT) techniques, three-dimensional conformal RT (3D-CRT), helical tomotherapy-intensity-modulated RT (HT-IMRT), and volumetric modulated arc therapy (VMAT), in patients with early-stage glottic cancer.

Patients and Methods: A retrospective analysis of 28 patients was performed, and the right and left CAs were delineated. Mean and maximum dose (Dmax) values were compared across the three treatment techniques.

Results: The results indicate that 3D-CRT plans had the highest mean and maximum doses to CAs, while VMAT plans had the lowest doses.

Conclusions: Our study demonstrates the feasibility of sparing CAs with newer RT modalities. Further clinical studies are needed to determine if these techniques can reduce carotid stenosis-related events.

Keywords: *Glottic Cancer • Carotid Arteries Dose • 3D-CRT • HT-IMRT • VMAT*

1. Introduction

Early-stage glottic larynx cancer treatment aims to provide high tumor control rates, larynx preservation, and minimal morbidity[1]. Radiation therapy (RT) and surgery are both viable treatment options, but there is no conclusive evidence that one is superior as a single modality of treatment[2]. Local RT alone for early glottic cancer has shown 5-year local control rates of 80%–90%[1-4]. Therefore, there is an opportunity to customize RT delivery specifically to the glottic target in these patients, as the glottic subregions of the larynx are considered low risk for regional or distant metastasis due to their minimal vocal cord lymphatic drainage system[2,3].

However, these patients have long survival outcomes and may potentially suffer from late toxicities of RT[1]. Therefore, attention to carotid dose reduction through advanced conformal RT techniques is necessary. The relationship between radiation and injury to carotid arteries (CAs) is well established, and survivors of head and neck carcinomas undergoing neck irradiation have reportedly increased transient ischemic attacks and stroke[3-7].

In addition to the risk of cerebrovascular events, high radiation doses to CAs may impact the re-irradiation of patients with second primary head and neck malignancies or neck recurrences due to the potential risk of CA injury or hemorrhage[4,6]. New radiation techniques, such as intensity-modulated RT (IMRT), have demonstrated the ability to reduce CA doses to lower levels without negatively impacting the target dose coverage in patients with early-stage laryngeal carcinoma[4,9,10].

Therefore, this study aims to compare the dosimetric characteristics of CAs in T1/T2 glottic carcinoma patients undergoing three-dimensional conformal RT (3D-CRT), helical tomotherapy-intensity-modulated RT (HT-IMRT), and volumetric modulated arc therapy (VMAT). The goal is to identify the most effective radiation technique for minimizing CA doses.

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2. Patients and Methods

2.1. Patient Selection

The medical records of patients who received radiotherapy for early glottic cancer between January 2019 and September 2022 at IPO Coimbra, Portugal, were retrospectively reviewed. A total of 28 patients with early glottic squamous cell carcinoma were included in this study, comprising two cases of Tis N0, 20 cases of T1 N0, and six cases of T2 N0. The T2 cases did not extend to the supraglottis and subglottis. Clinical stage was determined according to the American Joint Committee on Cancer staging system, 8th Edition, 2017[11]. Treatment was targeted to the larynx without elective nodal irradiation.

2.2. Delineation Details

The Gross Tumor Volume (GTV) was defined based on clinical examination and imaging exams.

The Clinical Tumor Volume (CTV) typically included the entire hemilarynx affected by the disease, extending 5–10 mm in all directions from GTV, while considering anatomic barriers. In cases where tumors extended to the anterior commissure, CTV also encompassed the anterior part of the contralateral vocal cord. For tumors involving both vocal cords, CTV was further expanded to encompass the entire larynx[12].

The Planning Target Volume (PTV) was created by expanding CTV by 3–5 mm. Subsequently, the right and left CAs were retrospectively delineated individually within an area extending approximately 2–2.5 cm cranially and caudally to PTV.

2.3. Treatment Planning

During treatment planning, patients were positioned in a supine position and immobilized using a five-point thermoplastic mask. A 1.5-mm slice CT simulation scan was performed, and the data was transferred to a volume delineation system and radiotherapy planning system. Three radiation therapy techniques were compared: 3D-CRT, HT-IMRT, and VMAT. Before treatment delivery, daily image guidance was performed using kilovoltage (kV) or megavoltage (MV) cone beam computed tomography (CT) images.

The prescribed dose ranged from 60 to 66 Gy in 27–33 fractions with daily fractions of 2–2.25 Gy, aiming for a V95% >95% for PTV. Mean dose and maximum dose for the right and left CAs were the dosimetric values of interest for this study.

2.4. Statistical Analysis

Statistical analysis was conducted using IBM Statistical Package for the Social Sciences (SPSS) ver. 29.0. A significance level of $p < 0.05$ was used to determine statistical significance. To assess the difference within each planning technique, a parametric one-way analysis of variance (ANOVA) was employed after confirming normality using the Shapiro–Wilk test. If normality could not be assumed, the Games–Howell test was utilized. In addition, considering the small sample size and, consequently, reduced power of the parametric tests, the results were further validated using the nonparametric Kruskal–Wallis test.

3. Results

During the study period, 28 patients with early glottic cancer underwent radiotherapy at our department. The median age at diagnosis was 66.5 years (range 48–84), and 26 patients (92.9%) were male.

Among the patients, 50% were treated with 3D-CRT (Siemens ONCOR Avant-Garde®), 28.6% with HT-IMRT (Accuray TomoTherapy TomoHD®), and 21.4% with VMAT (Varian Halcyon®). The majority of patients (50%) received a total dose of 66 Gy in 33 fractions (2 Gy per fraction), while 28.6% of patients received 63 Gy in 28 fractions (2.25 Gy per fraction). Table 1 provides an overview of patient demographics and disease and treatment characteristics for each treatment cohort.

Results showed that the mean right CA dose was significantly lower in the VMAT plan compared to the 3D-CRT plan (mean difference 14.3 Gy, *p*-value 0.001) and the HT-IMRT plan (mean difference 11.0 Gy, *p*-value 0.002) (Figure 1). Similarly, the Dmax values were significantly lower in the VMAT plan than the 3D-CRT (mean difference 19.8 Gy, *p*-value 0.006) and HT-IMRT (mean difference 18.0 Gy, *p*-value 0.009) plans, as illustrated in Figure 2. While the left CA also showed differences in favor of the VMAT plan, these results were not statistically significant (Table 2).

4. Discussion

The main goal of treating T1/T2 laryngeal cancer is to cure the disease while preserving the function of larynx,

Table 1: Summary of the patients' demographics and disease and treatment characteristics for the three different radiotherapy techniques utilized in this study.

Characteristics	Treatment technique			Significance
	3D-CRT (*n* = 14) (%)	HT-IMRT (*n* = 8) (%)	VMAT (*n* = 6) (%)	
Sex				$p = 0.7$
Female	1 (7.1)	1 (12.5)	0 (0.0)	
Male	13 (92.9)	7 (87.5)	6 (100.0)	
Age at diagnosis				$p = 0.1$
<60 years	3 (21.4)	1 (12.5)	4 (66.7)	
≥60 years	11 (78.6)	7 (87.5)	2 (33.3)	
Performance status				$p = 0.1$
ECOG 0	14 (100.0)	6 (75.0)	6 (100.0)	
ECOG 1	0 (0.0)	2 (25.0)	0 (0.0)	
Prognostic stage groups				$p = 0.3$
Stage 0	2 (14.3)	0 (0.0)	0 (0.0)	
Stage I	11 (78.6)	5 (63.5)	4 (66.7)	
Stage II	1 (7.1)	3 (37.5)	2 (33.3)	
Tumor location/target treatment volume				$p = 0.4$
Both vocal cords	4 (28.6)	3 (37.5)	1 (16.7)	
Right vocal cord	4 (28.6)	2 (25.0)	0 (0.0)	
Left vocal cord	6 (42.9)	3 (37.5)	5 (83.3)	
Mean ± SD total radiation dose (Gy)	64.9 ± 1.7	62.4 ± 5.4	64.4 ± 1.5	$p = 0.2$
Mean ± SD no. of fractions received	31.2 ± 2.5	29.3 ± 4.3	29.8 ± 2.5	$p = 0.3$
Mean ± SD dose per fraction (Gy)	2.1 ± 0.1	2.2 ± 0.2	2.2 ± 0.1	$p = 0.4$

especially voice function and quality. Previous research has commonly considered RT as the primary treatment for such patients[13]. With technological advancements, radiation oncologists have access to new treatment approaches that reduce the dose to uninvolved nontarget tissues.

In this study, we retrospectively compared three common RT modalities for early-stage glottic larynx cancer in a cohort of 28 patients. Our objective was to assess the ability of each modality to limit nontarget organ dose. Our analysis revealed that the mean dose of CAs was lower with HT-IMRT plans than with 3D-CRT, and with VMAT plans than with both HT-IMRT and 3D-CRT plans. The differences in maximum dose were less significant.

As anticipated, the location of the tumor had a significant impact on the results obtained. The distribution of dose to CAs was markedly influenced by the affected side, as well as whether one or both sides of the vocal cord were involved, consequently affecting the target volume of either the hemilarynx or the whole larynx. Specifically, treating only the ipsilateral hemilarynx resulted in reduced carotid doses, especially for the contralateral side. On the other hand, when treating the entire larynx, this reduction in carotid doses might not be as prominent. Our study verified this phenomenon, as we did not observe a significant difference in dose distribution to the left carotid (in contrast to the right). This observation could potentially be attributed to the absence of tumors in the right vocal cord treated with VMAT. However, it is worth noting that we also noticed a trend toward reducing the mean dose received by the left CA with VMAT, which was consistent with the results observed on the right side, as indicated by the nonparametric test.

The findings of our study were in agreement with the existing literature. Yurday et al. also investigated the dosimetric outcomes of CAs in 11 patients with T1N0M0 glottic carcinoma who underwent HT-IMRT and 3D-CRT with lateral opposed field (LOF). They reported significantly lower mean doses (20.7/21.5 vs. 48.7/50.5 Gy) and Dmax (53.6/52.0 vs. 67.4/67.7 Gy)

Table 2: Comparison of dosimetric characteristics among the three treatment techniques.

Parameter	Treatment technique			Significance
	3D-CRT (n = 14)	HT-IMRT (n = 8)	VMAT (n = 6)	
Right carotid artery				
Mean dose, Gy (range)	30.9 (15.8–47.4)	27.6 (23.2–34.6)	16.6 (13.0–47.4)	$p = 0.01$
Dmax, Gy (range)	51.7 (24.6–68.9)	49.9 (32.2–62.4)	31.9 (26.1–48.2)	$p = 0.02$
Mean volume delineated, ml (range)	5.0 (3.6–6.4)	3.9 (2.8–5.8)	4.2 (2.6–6.5)	$p = 0.1$
Left carotid artery				
Mean dose, Gy (range)	31.0 (20.1–43.7)	28.2 (19.0–43.2)	23.4 (15.5–30.1)	$p = 0.1$
Dmax, Gy (range)	54.0 (30.4–67.1)	49.7 (30.4–66.2)	48.4 (31.5–60.9)	$p = 0.6$
Mean volume delineated, ml (range)	4.7 (3.1–6.2)	4.0 (3.0–5.8)	4.0 (2.5–5.6)	$p = 0.3$

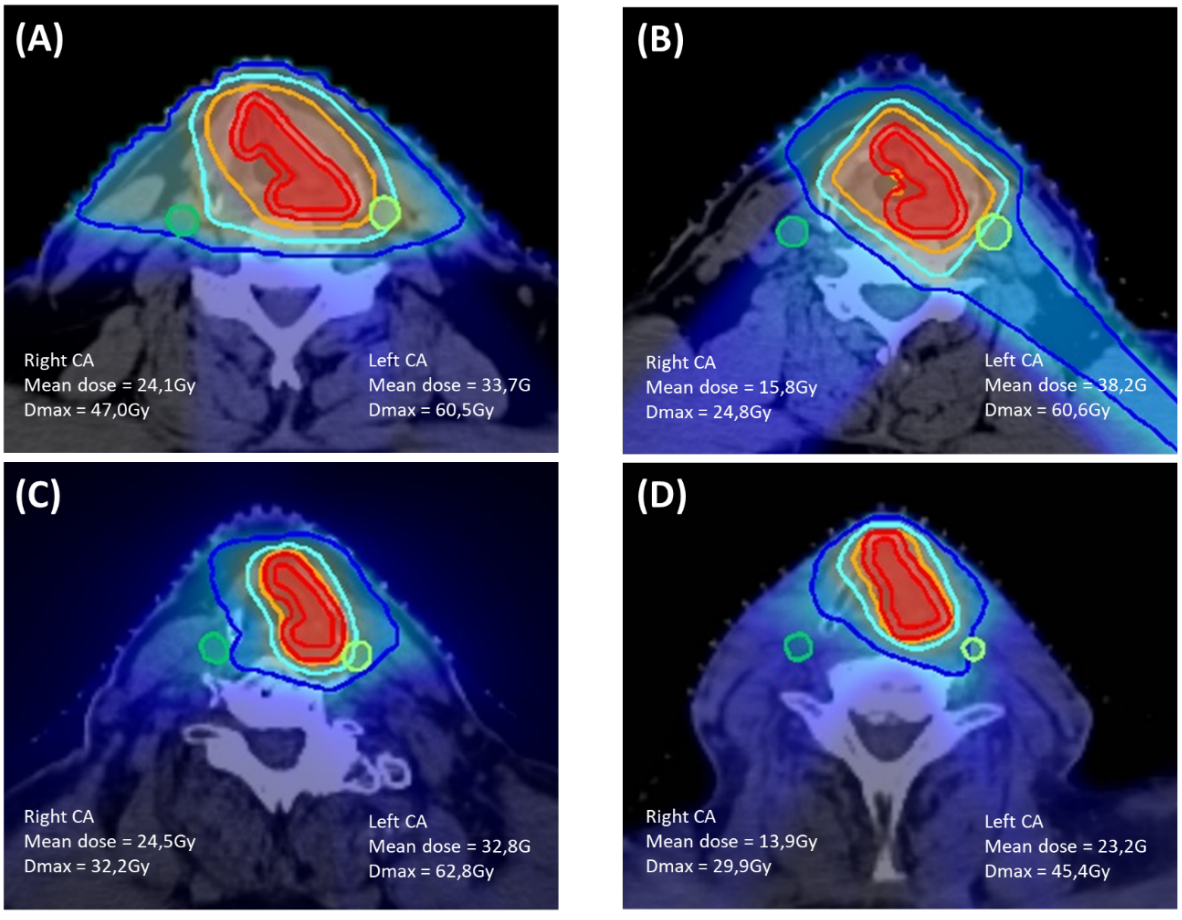


Figure 1: Dose distribution with prescribed isodose curves (50% in dark blue, 80% in light blue, and 95% in orange) for four patients with T1–2 left glottic squamous cell cancer, who underwent radical radiotherapy at a dose of 63–65.25 Gy in 28–29 fractions over 5.6–5.8 weeks. The red volumes represent the clinical target volume (CTV) and the planning target volume (PTV). Axial slices of representative cases were planned using (A) 3D-conformal radiotherapy with opposed lateral fields, (B) 3D-conformal radiotherapy with oblique beams, (C) helical tomotherapy-intensity-modulated radiotherapy, and (D) volumetric modulated arc therapy.

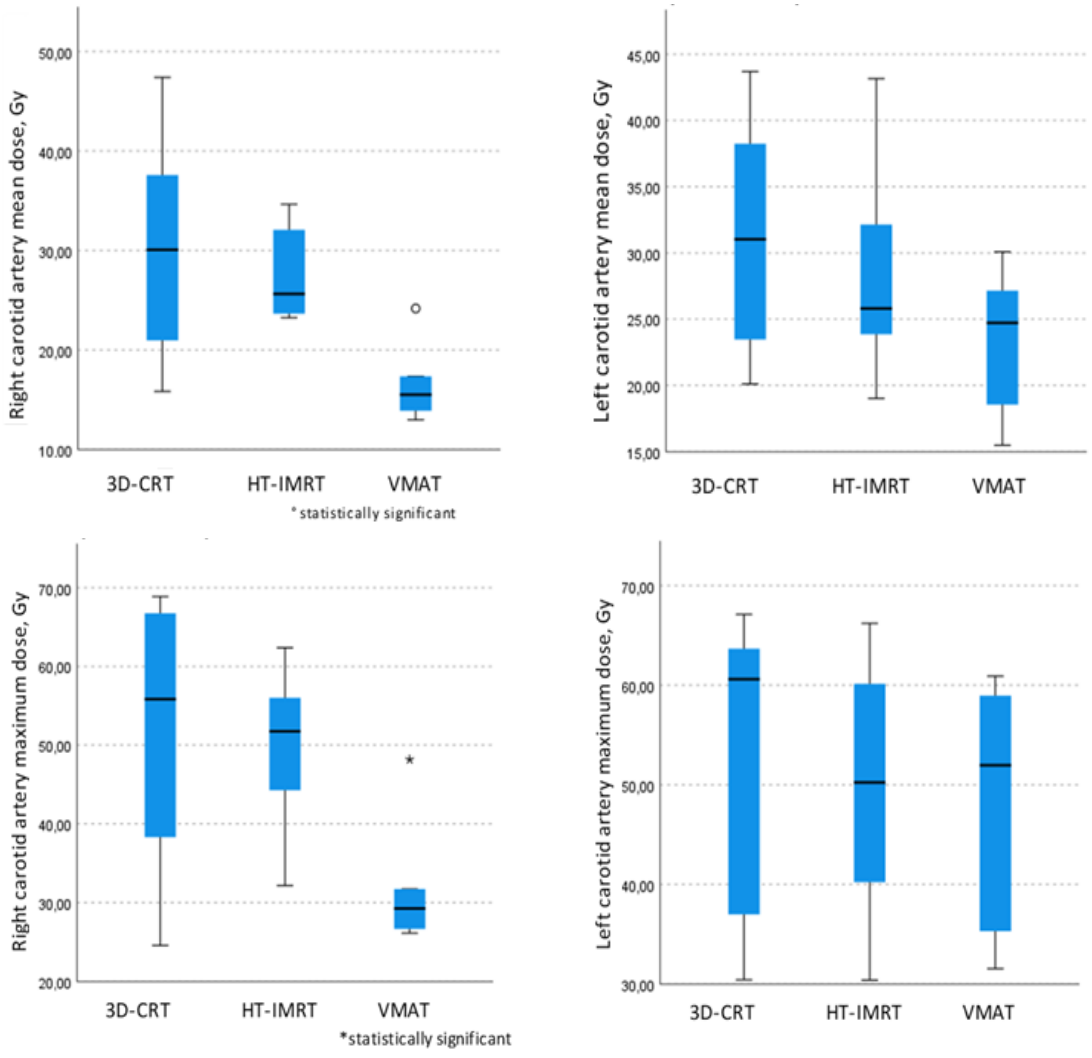


Figure 2: Verification of differences in mean and maximum doses (Gy) to carotid arteries among treatment techniques using the nonparametric Kruskal–Wallis test.

in HT-IMRT ($p < 0.05$) for the right/left CA dosimetric outcomes, respectively[4]. Similarly, Choi et al. conducted a study to evaluate the dosimetric differences in carotid-sparing IMRT and LOF techniques in 10 patients with early-stage glottic carcinoma. Their findings showed a significant reduction in the mean CA dose in the IMRT plans compared to the LOF plans (14.7 vs. 53.9 Gy, $p < 0.001$)[14].

The literature on the use of VMAT for early glottic cancer is limited. Young Suk et al. carried out a study on 21 patients with early glottic cancer who had undergone definitive radiotherapy. The study found that the mean doses to CAs were 49.0, 23.9, and 22.2 Gy for 3D-CRT (using lateral parallel opposed photon fields plus the anterior photon field), IMRT, and VMAT, respectively. The study also demonstrated that the mean doses to CAs in double-arc VMAT were reduced by 6.8% compared to fixed-field IMRT ($p < 0.001$).[15] Matthiesen et al. performed a study to compare the effectiveness of IMRT, RapidArc (RA) VMAT, proton therapy, and 3D-CRT (opposed lateral fields) in treating early-stage glottic laryngeal carcinoma. Their results showed that the new technologies, including IMRT, RA VMAT, and proton therapy, significantly reduced the doses to CAs ($p = 0.002$). Moreover, RA VMAT was found to be superior to the other new techniques, such as IMRT, in preserving normal structures, with a significantly lower mean CA dose ($p = 0.002$)[16].

It is worth noting that significant efforts have been made to move away from conventional radiotherapy for early-stage glottic cancer and toward alternative planning techniques such as IMRT or VMAT[17-19].

Our study reveals that the use of 3D-CRT with oblique beams, as opposed to conventional techniques with opposed lateral fields, produces results that approach those of IMRT.

Advanced radiation therapy techniques present promising opportunities for preserving CAs, thereby reducing the risk of cerebrovascular events associated with circulatory problems. Radiation-induced vascular injury (RIVI) can occur through various mechanisms, including a) ischemic necrosis, resulting from the occlusion of the vasa vasorum, which are the blood vessels supplying the outer arterial wall layer (adventitia); b) extrinsic compression due to adventitial fibrosis; c) acceleration of classical atherosclerotic processes; and d) necrosis and fibrosis in the media and adventitia layers as a consequence of inflammation of endothelial cells. Chronic radiation vasculopathy from RT is characterized by the progressive development of hemodynamically significant stenosis over time, with the time interval from RT representing a significant risk factor related to RIVI. The manifestation of the disease is the result of combined radiation damage to the intima media (endothelium) and the vasa vasorum (adventitia) [2, 20].

Despite this understanding, the specific clinically established radiation doses required to mitigate these risks remain unknown. In a retrospective analysis of a large prospective study cohort comprising 750 head and neck cancer patients, van Aken et al. investigated the relationship between radiation dose to CAs and the risk of ischemic cerebrovascular events (ICVE). The study revealed a significant independent dose–effect relationship, wherein the absolute volume (cm^3) of CAs receiving a radiation dose of at least 10 Gy emerged as the most critical prognostic factor for ICVE. Therefore, further clinical studies are necessary to confirm whether reducing irradiation to CAs offers any clinical benefit[2, 21].

On the other hand, when considering carotid-preserving treatments, the potential for local tumor failure must also be taken into account. Chatterjee et al. investigated the safety of carotid-sparing intensity-modulated radiotherapy (CSIMRT) using helical tomotherapy in 18 patients with early glottic cancer. While no significant differences in carotid intimal thickness were observed between the CSIMRT group and the control group, four patients in the CSIMRT group experienced local recurrence between 8 and 39 months posttreatment. Notably, in all cases, the recurrence was located at the anterior part of the larynx. The 5-year local recurrence-free survival rate was 75.1% in the CSIMRT group, compared to 97.1% in the control group ($p = 0.01$)[22].

These findings underscore the importance of carefully balancing the potential benefits of carotid-sparing techniques against the risks of reduced local tumor control. It is crucial to recognize that tumor spread beyond the vocal cord frequently occurs through invasion of the anterior commissure. Therefore, carotid preservation techniques must ensure optimal visualization of the anterior commissure to maintain the high efficacy of treatment. In specific cases, the placement of a bolus may be necessary to achieve adequate anterior coverage of the tumor, particularly for tumors involving the anterior commissure. Daily imaging for positioning verification plays a critical role in this context. The significance of understanding motion was highlighted in a previous study, which showed that the local control rates after RT delivered by matching to vertebral anatomy were inferior compared to using laryngeal cartilages[2].

Furthermore, additional strategies, such as instructing patients not to swallow if possible, can be employed to minimize potential uncertainties in laryngeal motion. However, it is vital to ensure an optimal selection of PTV margins based on the specific attributes of the radiotherapy technique, as well as the patient's and tumor's characteristics. Each approach should be tailored to ensure the best possible outcomes while mitigating potential risks.

This study has several limitations that should be acknowledged. Firstly, its retrospective nature might introduce potential biases and limitations in data collection and analysis. Secondly, the study relied on data from a single institution, which could limit the generalizability of the findings to other populations or treatment settings. The small sample size is another limitation, which may impact the statistical power and precision of the results.

A significant limitation in this study is the unequal distribution of tumor locations among the treatment arms. This imbalance in tumor location could confound the comparison of treatment techniques and their impact on carotid sparing.

In addition, the study did not assess the long-term clinical outcomes of carotid sparing, such as the occurrence of stroke or transient ischemic attack. Evaluating these clinical endpoints would require extended follow-up periods and detailed monitoring of patients, which were beyond the scope of this study.

To address these limitations and provide more robust evidence, future studies should consider enrolling a larger and more diverse patient cohort from multiple institutions. Randomized controlled trials with balanced tumor location distribution among treatment arms would enable more reliable comparisons of

different techniques. Furthermore, long-term follow-up is necessary to assess the impact of carotid sparing on patient outcomes.

In conclusion, the optimal treatment decision for early-stage laryngeal cancer should be carefully made, taking into account various factors such as technical capabilities and disease-specific characteristics. Notably, tumor location and vocal cord involvement play crucial roles in determining the most suitable treatment approach.

While advanced treatment techniques have shown promise in preserving CAs and reducing the risk of RIVIs, their full potential and efficacy require further investigation. Future studies could explore the use of ultrasound to measure vessel wall thickening as a means to prevent hemodynamically significant stenosis.

As we strive to improve patient outcomes and enhance their quality of life, it is essential to conduct more research in this field. Advancing our understanding of the benefits and limitations of different treatment techniques will enable us to offer better and more personalized treatment options for individuals with early-stage laryngeal cancer.

Abbreviations and Acronyms

CAs: Carotid arteries
RT: Radiation therapy
3D-CRT: 3-Dimensional conformal radiation therapy
HT-IMRT: Helical tomotherapy-intensity-modulated radiation therapy
VMAT: Volumetric modulated arc therapy
Dmax: Maximum dose
IPO: Portuguese Institute of Oncology
GTV: Gross Tumor Volume
CTV: Clinical Tumor Volume
PTV: Planning Target Volume
CT: Computed tomography
kV: Kilovoltage
MV: Megavoltage
LOF: lateral opposed field
RA: RapidArc
RIVI: Radiation-induced vascular injury
ICVE: Ischemic cerebrovascular events
CSIMRT: Carotid-sparing intensity-modulated radiotherapy

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