



Dosimetric comparison of the carotid arteries in patients of T1 and T2 N0 M0 carcinoma glottis by three-dimensional conformal radiotherapy versus carotid sparing intensity-modulated radiotherapy technique

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ABSTRACT

Background: Radiotherapy (RT) is a cornerstone in the treatment of early-stage glottic carcinoma (T1 and T2 N0 M0). However, RT can lead to radiation-induced vasculopathy, which increases the risk of cerebrovascular complications. Carotid-sparing intensity-modulated RT (Cs-IMRT) has been proposed to minimize radiation exposure to the carotid arteries while maintaining effective tumor control.

Aims and Objectives: This study aimed to compare the dosimetric impact of three-dimensional conformal RT (3DCRT) and Cs-IMRT on carotid artery exposure in patients with T1 and T2 N0 M0 carcinoma of the glottis. **Materials and Methods:** This prospective comparative study included 30 patients equally divided into 3DCRT and Cs-IMRT treatment arms. Dosimetric parameters, including carotid artery dose exposure (V5Gy, V25Gy, and V50Gy), mean carotid dose, and local control rates, were analyzed. **Results:** The mean carotid artery dose was lower in the Cs-IMRT group (43.2 ± 9.7 Gy) than in the 3DCRT group (46.9 ± 5.3 Gy, $P=0.004$). Cs-IMRT demonstrated a significant reduction in high-dose exposure, with V50Gy being $10.2 \pm 5.8\%$ for Cs-IMRT versus $42.7 \pm 20.1\%$ for 3DCRT ($P<0.001$). Similarly, Cs-IMRT achieved dose constraints more effectively, with 73.3% of patients meeting the V50Gy=0 criterion compared with none in the 3DCRT group. Although Cs-IMRT showed a slight improvement in local control rates, the difference was not significant ($P=0.382$). **Conclusion:** Cs-IMRT showed significant dosimetric advantages over 3DCRT by reducing carotid artery radiation exposure, potentially lowering the risk of radiation-induced carotid artery vasculopathy. While both techniques achieved similar local control, the reduced vascular toxicity associated with Cs-IMRT supports its preferential use in early-stage glottic carcinoma.

Key words: Glottic carcinoma; Radiation therapy; 3D conformal radiotherapy; Carotid-sparing intensity-modulated radiotherapy technique; Dosimetric

INTRODUCTION

Radiation therapy (RT) is the basis for the treatment of early-stage glottic carcinoma, specifically T1 and T2 N0 M0 carcinoma of the glottis. The primary goal of RT is

to eradicate the tumor while preserving the surrounding healthy tissues. However, RT can induce vasculopathy, characterized by radiation-induced acceleration of atherosclerosis. This occurs due to endothelial cell damage, fibrosis of the intima-media layer, and formation of

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atheromatous plaques. These vascular changes can lead to ischemia of the arterial wall, increasing the risk of transient ischemic attacks, amaurosis fugax, and ischemic strokes.¹

Glottic carcinoma is one of the most prevalent types of laryngeal cancer worldwide, predominantly affecting males, particularly in populations with high tobacco and alcohol consumption rates. According to the American Cancer Society, approximately 12,370 new cases of laryngeal cancer were diagnosed in the United States in 2020, with glottic cancer comprising a substantial proportion of these cases. In India, the burden of laryngeal cancer is significant, reflecting the widespread use of tobacco products. Early-stage glottic cancer, which is typically treated with RT, has a high survival rate. In contrast, managing treatment-related complications such as radiation-induced vasculopathy is of paramount importance.²

Globally, laryngeal cancer constitutes a notable proportion of cancer cases worldwide. According to the GLOBOCAN 2022 data, there were approximately 20 million new cancer cases and 9.7 million cancer-related deaths worldwide. Laryngeal cancer accounts for approximately 1% of all cancer diagnoses, with glottic malignancies being the most common subtype. The incidence of laryngeal cancer varies geographically, with higher rates observed in regions with a high prevalence of smoking. While advances in treatment and early detection have improved survival rates in high-income countries, disparities in cancer care persist, particularly in lower-income regions where limited access to healthcare and early diagnostic tools contribute to higher mortality rates.^{3,4}

Radiation-induced vasculopathy is a significant concern in patients undergoing RT for glottic carcinoma. The primary sequelae of carotid atherosclerosis include transient ischemic attacks, amaurosis fugax, and ischemic strokes, all of which can severely impact a patient's quality of life and overall prognosis.⁵ Traditional three-dimensional conformal RT (3DCRT) effectively shapes radiation beams to match the tumor's dimensions. However, this technique may inadvertently expose the surrounding healthy tissues, including the carotid arteries, to substantial radiation doses. In contrast, carotid-sparing intensity-modulated RT (Cs-IMRT) is an advanced technique designed to precisely target the tumor while minimizing radiation exposure to adjacent structures such as the carotid arteries, thereby potentially reducing the risk of radiation-induced vasculopathy.⁶

Previous studies have emphasized the risks associated with neck irradiation. For example, studies have reported an increased likelihood of cerebrovascular events in patients who receive RT to the neck. However, comprehensive dosimetric comparisons explicitly focusing on the carotid

arteries and the dosimetric advantages of advanced RT techniques, such as IMRT, in sparing critical structures remain limited. Further research is necessary to establish the clinical efficacy and long-term benefits of these advanced radiation techniques in reducing the risk of radiation-induced vasculopathy in patients with early-stage glottic carcinoma.⁷

By identifying the dosimetric and clinical benefits of Cs-IMRT, this study could lead to improved treatment guidelines that enhance patient outcomes while minimizing long-term complications. This study aimed to address a critical gap in the understanding of radiation-induced vasculopathy in patients with glottic carcinoma. Through a detailed dosimetric comparison and evaluation of local control rates, we aimed to provide evidence-based recommendations for optimizing RT in this patient population.

Aims and objectives

This study aimed to compare the dosimetric impact of 3DCRT and Cs-IMRT on the carotid arteries in patients with T1 and T2 N0 M0 carcinoma of the glottis.

MATERIALS AND METHODS

This double-arm prospective comparative study included 30 patients, with 15 in each arm. Arm A consisted of patients treated with 3DCRT, while Arm B included patients treated with Cs-IMRT.

Inclusion and exclusion criteria

Patients aged 18–70 years, with histologically confirmed glottic carcinoma staged as T1 or T2 and without nodal (N0) or distant (M0) metastasis, who had an Eastern cooperative oncology group performance status of 0–2, were included in the study. Patients with tumor staging of T3 or T4, metastatic glottic cancer, or nodal involvement classified as N1, N2, or N3 were excluded from the study.

Methods

RT contouring guidelines and assessment

The contouring guidelines included defining the gross tumor volume based on laryngoscopy and imaging. The clinical target volume (CTV) encompassed the entire larynx, including the anterior and posterior commissures and arytenoids. The planning target volume (PTV) was created by applying a 0.5 cm three-dimensional expansion to the CTV, with a margin reduction near the carotid arteries. The carotid artery dose constraints were set as V5Gy <90%, V25Gy <14%, and V50Gy at 0. The prescribed treatment dose was 66 Gy delivered in 33 fractions, with each fraction being 2 Gy. Patients were reviewed weekly during treatment, followed by monthly post-treatment evaluations in the 1st year and periodic assessments thereafter. The

assessment included measuring and comparing the carotid artery dose, along with clinical and radiological evaluation of local tumor control.

Statistical analysis

Data are presented as mean, standard deviation, frequency, and percentage. Categorical variables were compared using Pearson's Chi-square test. Significance was defined as $P < 0.05$ using a two-tailed test. Data analysis was performed using IBM SPSS version 21.0.

Ethical standards

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Madras Medical College (ethics approval number: 09042023). All participants provided informed consent before their inclusion in the study.

RESULTS

The age distribution between the two groups was similar, with no significant difference ($P = 0.754$). The sex distribution was balanced between the two groups, with no significant difference ($P = 0.657$). The body mass index (BMI) distribution did not differ significantly between the two groups ($P = 0.893$). The prevalence of comorbidities was similar between the groups, with no significant difference ($P = 0.914$) (Table 1).

Regarding dose constraints, V5Gy was significantly lower in the Cs-IMRT group (65.4 ± 12.2) than in the 3DCRT group (87.2 ± 10.5 , $P < 0.001$). Similarly, the V25Gy and

V50Gy values were decreased in Cs-IMRT (30.6 ± 12.7 and 10.2 ± 5.8 , respectively) compared to 3DCRT (63.4 ± 15.3 and 42.7 ± 20.1 , respectively). Regarding dose constraints, all patients in the Cs-IMRT group met the V5Gy $< 90\%$ constraint, whereas only 80% of those in the 3DCRT group did ($P < 0.001$). In addition, 60% of the Cs-IMRT patients met the V25Gy $< 14\%$ constraint, compared to only 6.7% in the 3DCRT group. Moreover, 73.3% of patients in the Cs-IMRT group achieved V50Gy=0, whereas none of the patients in the 3DCRT group met this criterion.

The follow-up rates were comparable between the groups at 6 months and 1 year, with 100% of the 3DCRT patients and 93.3% of the Cs-IMRT patients completing follow-up ($P = 0.382$). Regarding dosimetric parameters, the mean carotid dose was significantly lower in Cs-IMRT (43.2 ± 9.7 Gy) than in 3DCRT (46.9 ± 5.3 Gy, $P = 0.004$). The volume receiving 50 Gy (V50) was also significantly lower in Cs-IMRT (2.3 ± 2.5) than in 3DCRT (4.4 ± 2.3 , $P = 0.001$), while no significant differences were observed in the volume receiving 25 Gy (V25) or 35 Gy (V35). In addition, the mean PTV dose was significantly higher in Cs-IMRT (52.3 ± 0.5 Gy) than in 3DCRT (46.2 ± 9.9 Gy, $P < 0.001$) (Table 2).

DISCUSSION

In our study, the age distribution between the two groups was similar, with no significant differences ($P = 0.754$).

Table 1: Comparison of patient characteristics, dose constraints, and dosimetric parameters between 3DCRT and Cs-IMRT

Patient characteristics	3DCRT (n=15)	Cs-IMRT (n=15)	P-value
Age group			
<50	4 (26.7)	3 (20)	0.754
50–60	6 (40)	7 (46.7)	
>60	5 (33.3)	5 (33.3)	
Gender			
Male	12 (80)	11 (73.3)	0.657
Female	3 (20)	4 (26.7)	
BMI range			
<18.5	1 (6.7)	2 (13.3)	0.893
18.5–24.9	8 (53.3)	7 (46.7)	
25–29.9	4 (26.7)	5 (33.3)	
≥ 30	2 (13.3)	1 (6.7)	
Comorbidity			
Hypertension	2 (13.3)	1 (6.67)	0.914
Diabetes	1 (6.67)	1 (6.67)	
Cardiovascular disease	-	-	
None	12 (80)	13 (86.67)	

3DCRT: Three-dimensional conformal radiation therapy, Cs-IMRT: Carotid-sparing intensity-modulated radiation therapy, BMI: Body mass index

Table 2: Dosimetric comparison between 3DCRT and Cs-IMRT

Variables	3DCRT (n=15)	Cs-IMRT (n=15)	P-value
Dose constraint			
V5Gy	87.2 \pm 10.5	65.4 \pm 12.2	<0.001
V25Gy	63.4 \pm 15.3	30.6 \pm 12.7	
V50Gy	42.7 \pm 20.1	10.2 \pm 5.8	
Constraint			
V5Gy <90%	12 (80.0)	15 (100)	<0.001
V25Gy <14%	1 (6.7)	9 (60)	
V50Gy=0	0	11 (73.3)	
Follow-up duration			
6 Months	15 (100)	14 (93.3)	0.382
1 Year	15 (100)	14 (93.3)	
Dosimetric parameter			
Mean dose to carotids (Gy)	46.9 \pm 5.3	43.2 \pm 9.7	0.004
Volume receiving 25 Gy (V25)	5.4 \pm 2.7	5.2 \pm 2.6	0.727
Volume receiving 35 Gy (V35)	5.3 \pm 2.6	4.5 \pm 2.5	0.14
Volume receiving 50 Gy (V50)	4.4 \pm 2.3	2.3 \pm 2.5	0.001
Planning target volume (Gy)	46.2 \pm 9.9	52.3 \pm 0.5	<0.001

3DCRT: Three-dimensional conformal radiation therapy, Cs-IMRT: Carotid-sparing intensity-modulated radiation therapy

Global Burden of Disease Cancer Collaboration et al., emphasized the global burden of cancer and its increasing incidence, which is reflected in the age distribution of our study. This finding suggests that both 3DCRT and Cs-IMRT groups are comparable in terms of age, thus eliminating age as a confounding factor in comparing treatment outcomes.⁸ Mendenhall et al., also noted the importance of demographic factors in treatment planning for laryngeal cancer, emphasizing that understanding the age distribution is critical in tailoring treatment protocols.⁵ Similarly, Chera et al., discussed the demographic distribution in similar patient cohorts, emphasizing the relevance of age-matched studies to ensure balanced comparisons between different treatment modalities.⁹

In our study, sex distribution was balanced between the two groups, with no significant difference ($P=0.657$). Hoffman et al., discussed changes in the demographics of laryngeal cancer, noting a shift in gender patterns over the years.¹⁰ This balance in gender distribution aligns with the findings of Teshima et al., and Smith et al., who observed similar trends in their respective studies.^{2,11,12} Piccirillo emphasized the role of demographic characteristics in influencing treatment outcomes, suggesting that a balanced gender distribution helps mitigate potential biases in treatment efficacy and side effect profiles.¹³ Therefore, the gender distribution in our study ensured that gender-related differences in response to treatment did not skew the comparison between 3DCRT and Cs-IMRT.

We found that the BMI distribution did not differ significantly between the two groups ($P=0.893$). Marshak et al., found that patient characteristics, such as BMI, are critical in predicting treatment outcomes for glottic carcinoma.¹⁴ Aaltonen et al., showed that physical health metrics, including BMI, play a role in post-treatment quality of life.¹⁵ This is supported by findings from Cooper et al., and Fujita et al., on the influence of patient health metrics on treatment outcomes.^{16,17} The similar BMI distribution in our study groups shows that both 3DCRT and Cs-IMRT groups are comparable in terms of physical health, which is vital for evaluating the true impact of the treatment modalities on clinical outcomes without the confounding effects of varying BMI.

In our study, the prevalence of comorbidities was similar between the groups, with no significant difference ($P=0.872$). Piccirillo emphasized the impact of comorbid conditions on the management and outcomes of head and neck cancers.¹³ These findings are consistent with Hoffman et al., who noted that comorbidities must be considered when planning treatment for glottic carcinoma.¹⁰ Smith et al., and Dorresteijn et al., have also emphasized the significance of managing comorbidities in cancer

treatment.^{12,18} The similar prevalence of comorbidities in our study groups ensures that the observed treatment outcomes are not influenced by differences in baseline health conditions, thus providing a more accurate comparison of 3DCRT and Cs-IMRT.

We found that Cs-IMRT significantly reduced the dose to the carotid artery compared with 3DCRT ($P<0.001$). Chera et al., demonstrated the dosimetric benefits of carotid-sparing IMRT in reducing radiation exposure to the carotid arteries.⁹ This aligns with the findings of Matthiesen et al., who emphasized the superiority of advanced RT techniques in sparing healthy tissues. The reduced carotid artery dose with Cs-IMRT potentially lowers the risk of radiation-induced carotid artery disease, a significant complication associated with head and neck RT.¹⁹ Gomez et al., also noted the improved dosimetric outcomes with IMRT compared to conventional techniques, further supporting the use of Cs-IMRT in reducing treatment-related vascular complications.²⁰

Cs-IMRT achieved dose constraints more effectively than 3DCRT ($P<0.001$). Chatterjee et al., reported IMRT techniques to improve morbidity outcomes by better sparing the carotid arteries.²¹ These findings are supported by Gujral et al., who standardized target volume delineation for carotid-sparing IMRT, ensuring precise and effective treatment delivery.²² The guidelines by Hartford et al., and Potters et al., support these findings, emphasizing the importance of advanced planning and delivery techniques in achieving optimal dose distribution while minimizing exposure to critical structures like the carotid arteries.^{23,24}

Local control rates were slightly higher in the Cs-IMRT group, but the difference was not significant ($P=0.382$). Gomez et al., found that IMRT provides better local control rates than conventional RT techniques.²⁰ This is further supported by studies by Teshima et al., and Mendenhall et al., who observed that precision in RT delivery can enhance local tumor control.^{5,11,25} Although the difference in local control rates in our study was not significant, the trend suggests a potential benefit of Cs-IMRT in achieving better tumor control.

In our study, IMRT provided a significant reduction in the dose to the carotid arteries compared to 3DCRT, particularly in the higher dose ranges (V50), while maintaining superior PTV coverage ($P=0.004$ for mean dose, $P=0.001$ for V50, and $P=0.000$ for PTV). Potters et al., discussed the benefits of IGRT in enhancing the precision of RT delivery, supporting our findings.²⁴ Gujral et al., also emphasized the importance of accurate target volume delineation in achieving optimal dosimetric outcomes with IMRT.²² This is further supported by studies from Dobler et al., who

highlighted the advantages of advanced RT techniques in delivering high radiation doses to the tumor while sparing adjacent normal tissues, thus enhancing treatment efficacy and reducing side effects.²⁶

Limitations of the study

In this study, only dosimetric analysis was performed without clinical follow-up to assess carotid artery outcomes. Additionally, the small sample size may limit the generalizability and robustness of the results.

CONCLUSION

Our study shows the significant advantages of Cs-IMRT over 3DCRT in treating early-stage glottic carcinoma. Cs-IMRT significantly reduced radiation exposure to the carotid arteries, which may translate to a lower incidence of radiation-induced vasculopathy in the future. Despite these benefits, both Cs-IMRT and 3DCRT show comparable efficacy in terms of local tumor control. The improved dosimetric profiles and reduced dose to the carotid arteries associated with Cs-IMRT make it a preferable option for preserving critical structures and enhancing patient quality of life. While Cs-IMRT offers clear benefits in reducing radiation-related side effects and improving functional outcomes, long-term follow-up and further studies are necessary to confirm these findings and to establish standardized treatment protocols. The findings of this study support the adoption of advanced RT techniques, such as Cs-IMRT, as the standard of care in the management of early-stage glottic carcinoma to optimize patient outcomes and minimize treatment-related morbidity. However, the benefit of carotid-sparing IMRT is likely to depend on the anatomy of the individual patient.

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