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Original Article

Preliminary Simulation Study of Carotid Artery and Pharyngeal Constrictor Muscle Sparing-Radiotherapy in Glottic Carcinoma

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Abstract

Background: This preliminary simulation study aimed to compare the dosimetric outcomes of carotid arteries (CAs) and pharyngeal constrictor muscle (PCM) in patients with T1N0M0 glottic carcinoma undergoing helical tomotherapy-intensity modulated radiotherapy (HT-IMRT) and 3-dimensional conformal radiotherapy (3D-CRT) plans. **Methods:** In addition to the clinical target volume (CTV) which was defined as the entire larynx, the CAs and PCM of 11 glottic carcinoma patients were delineated. The CTV was uniformly expanded 5 mm to create a planning target volume (PTV) relative to the PCM and at a distance of 2 mm from the CA. The dosimetric characteristics in HT-IMRT and lateral opposed fields-based 3D-CRT plans were analyzed. **Results:** Median $D_{95\%}$and $V_{100\%}$ of PTV were significantly higher in HT-IMRT ($p < 0.001$) compared to 3D-CRT. The right/left CA dosimetric outcomes, including the mean doses (20.7/21.5 Gy versus 48.7/50.5 Gy), D_{max} (53.6/52.0 Gy versus 67.4/67.7 Gy), V_{30} (25.0/27.1% versus 77.6/80.3%), V_{40} (8.0/7.9% versus 74.6/71.9%), and V_{50} (2.0/1.2% versus 70.0/71.6%) were also significantly lower in HT-IMRT ($p < 0.05$), similar to the mean PCM doses (49.6 Gy versus 62.6 Gy for 3D-CRT;$p < 0.001$), respectively. **Conclusions:** Our present results demonstrated the feasibility of simultaneous sparing of the CAs and PCM in HT-IMRT-compared to 3D-CRT plans in glottic carcinoma patients undergoing definitive radiotherapy.

Keywords

glottic carcinoma, pharyngeal constrictor muscle, carotid arteries, helical-tomotherapy, 3D-conformal radiotherapy

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Introduction

Patients with T1-glottic carcinoma undergoing radiotherapy have a high curability rate, with cancer-specific survival rates over 95%.[1,2] The technique of lateral opposed fields (LOF), which is the most frequently used in conventional radiotherapy, offers simple, fast treatment planning and set-up processes.[3] However, the organs at risk (OARs) adjacent to the larynx, namely the carotid arteries (CAs) and pharyngeal constrictor muscle (PCM), are inevitably exposed to the fully prescribed radiation dose, potentially leading to stenosis of the carotid vessel wall and dysphagia-related disorders, respectively.[3-5]

The relationship between radiation and injury to CAs is a well-established issue, and survivors of head and neck carcinomas undergoing neck irradiation reportedly have increased transient ischemic attacks and stroke.[6] In addition to the risk of cerebrovascular events, exposure of the CAs to high radiation doses 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.[7] In this context, the dosimetric and clinical research on the so-called intensity-modulated radiotherapy (IMRT) or tomotherapy based "carotid-sparing radiotherapy technique" has demonstrated that it was plausible to reduce the CAs doses to meaningfully lower levels with no negative impact on the target dose coverage in early-stage laryngeal carcinoma patients.[2,3,8-12]

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Radiotherapy-induced dysphagia, which may occur as a result of damage to the PCM, as well as the supraglottic and glottic larynx, cricopharyngeal inlet, and cervical esophagus decreases the quality of life (QoL), and leads to chronic aspiration with possible death in survivors of glottic carcinoma patients.[13] The PCM is an important swallow-related structure, and a radiation dose of >50-60 Gy to the PCM has been demonstrated to correlate with dysfunctional swallowing in patients with nasopharyngeal and oropharyngeal carcinomas undergoing chemoradiotherapy.[4,14-17] On the other hand, PCM-sparing radiotherapy (PCM-SRT) for treatment of early-stage glottic carcinoma has been a scarcely addressed issue, with only 1 report published by Ward, et al., who reported on 1 patient undergoing IMRT.[18] A mean dose of 16.3 Gy was achieved for the PCM when the clinical target volume (CTV) and planning target volume (PTV) were delineated to be significantly smaller than the current recommendations.

In absence of similar studies, the present preliminary simulation study aimed to comparatively analyze the dosimetric characteristics of PTV, CAs and PCM (middle and inferior muscles) in T1glottic carcinoma patients undergoing 3D-CRT and simulated helical tomotherapy-intensity-modulated radiotherapy (HT-IMRT) plans.

Methods and Materials

Patient Selection

The electronic records of T1- glottic carcinoma patients treated with standard conformal radiotherapy in our department of XXXXXX between January 2018 and February 2019 were reviewed retrospectively. This pure dosimetric comparison study was approved by the institutional ethics committee before the acquisition of any patient information. The eligibility criteria were: histologically proven squamous cell carcinoma, age between 18–80 years, Karnofsky Performance Score (KPS) $\geq$70, endoscopic/radiological proof of the T1N0M0 disease stage according to the TNM staging system (7th ed.), no prior chemotherapy/RT history and flexible fiberoptic laryngoscopy examinations. According to our institutional standards, we performed18F-fluorodeoxyglucose-positron emission computerized tomography (18-FDG-PET/CT) scans in all patients intended for definitive radiotherapy irrespective of the clinical T-stage, and each likely patient was offered organ preserving surgery as an alternative to radiotherapy.

Delineation Details

Contouring of the target and OARs volumes was performed in 11 patients by 1 radiation oncologist. The CTV included the laryngeal cartilaginous structure covering the thyroid, arytenoids, and cricoid, extending from the superior thyroid notch to the bottom of the cricoid cartilage. The PTV was created by expanding a 5-mm margin in the superior and inferior direction and 2 mm in the remaining directions, keeping a distance of 2 mm between the CAs and the PTV. Besides, overlapping between the PTV contours and the PCM was avoided as much as possible (Figure 1). The OARs were CAs, middle and inferior parts of the PCM, and the spinal cord. Briefly, the right and left CAs were delineated individually; 2 cm superior and inferior to the PTV with no additional margin for the planning at risk volume. The lower edge of the hyoid cartilage and the inferior edge of the cricoid cartilage was referred to as the respective superior and caudal limits of the middle and inferior constrictor muscles.[13] The whole spinal canal between the 2-cm cranial and caudal borders of the PTV was delineated as the spinal cord.

Treatment Planning

Patients were immobilized in the supine position with a thermoplastic mask and contrasted planning CT. A2.5-mm slice was obtained from each patient. Two sets of radiation treatment plans were performed for each patient to assess the dosimetric characteristics: 1) helical tomotherapy (HT)-IMRT using the Accuray planning system (Tomo HDA, version 2.1.2, Accuray, Palo Alto, CA) (Figure 2), and 2) LOF with coplanar or non-coplanar beams were used in 3DCRT. For adequate PTV coverage, the beams were individually weighted and a bolus was utilized for every patient. In all HT plans, a 2.5-cm thick fan beam with a pitch of 0.3 and a modulation factor of 3 was utilized during optimization and dose computation. Photon energy of 6 MV was used in both techniques.

The total dose prescribed was 64.4 Gy in 28 fractions of 2.3 Gy/fraction/day; with the goals of V100% > 95%, V95% > 99%, V105% < 10%, D_{max} < 120%.The dosimetric values of interest in this study were D_{max}, D_{95}, $V_{95\%}$, and $V_{100\%}$for the target volume; mean D_{max}, V_{30}, V_{40}, andV_{50} for the CAs; as well as the mean dose for the PCM and D_{max} for the spinal cord. The D_{max} represented the maximum dose administered to treat the related structure while $D_{95}$was the dose received by at least 95% of the PTV. V_X represented the volume of CA irradiated by at least X Gy.

Statistical Analysis

A paired Student's t-test was utilized to assess differences observed between the techniques. A p-value < 0.05 was considered as statistically significant.

Results

Dosimetric Comparison

PTV coverage. While no difference in D_{max} value was observed between the 2 plans, the median $D_{95\%}$ was significantly higher in the HT-IMRT plan ($p < 0.001$). The median $V_{95\%}$ values were 99.3% (range, 97.3%-100.0%) and 99.9% (range, 98.5%-100.0%) in the HT-IMRT and 3D-CRT plans, respectively, with no significant differences observed. However, the $V_{100\%}$ was significantly higher in HT-IMRT ($p < 0.001$) compared to the 3D-CRT plan (Table 1).

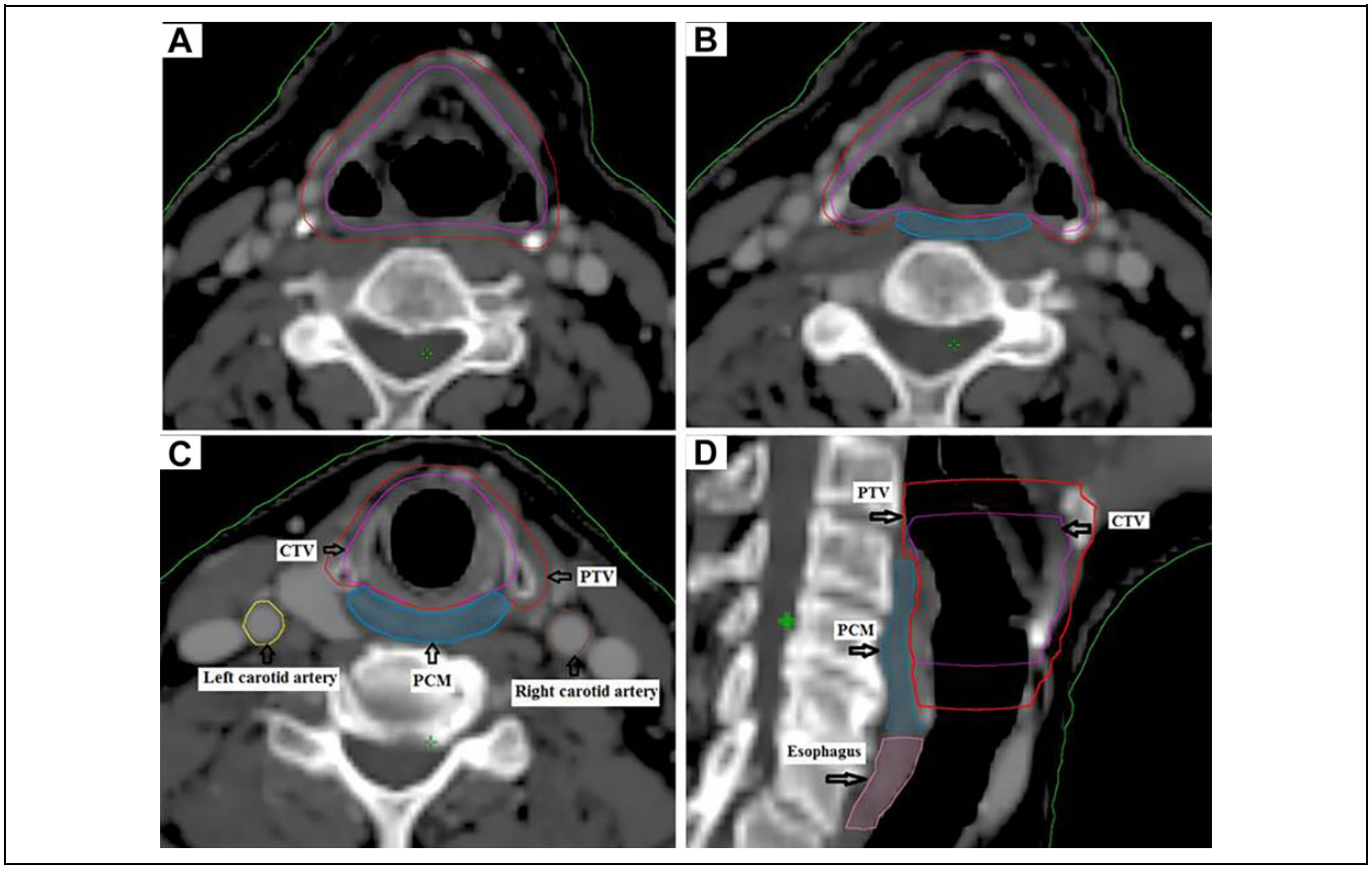


Figure 1. Delineation of target and organ at risk volumes.

Right CA dose. The mean CA dose was significantly lower in the HT-IMRT plan(20.7 Gy; range, 9.2 to 27.6 Gy) than the 3D-CRT plan (48.7 Gy; 36.2 to 65.7 Gy) ($p < 0.001$). Similarly, the D_{max} (53.6 Gy vs. 67.4; $p = 0.003$), V_{30} (25.0% vs. 78.0%; $p < 0.001$), V_{40} (8.0% vs. 75.0%; $p < 0.001$), and V_{50} (2.0% vs. 70.0%; $p < 0.001$)values were significantly lower in the HT-IMRT plans than the 3D-CRT. The left CA was consistent with these results, showing significant differences in favor of the HT-IMRT plan (Table 1).

PCM dose. The mean doses to PCM were significantly lower in the HT-IMRT plans (49.6 Gy vs. 62.5 Gy; $p < 0.001$) with no difference found for D_{max}.

Spinal cord. The mean D_{max} value of the spinal cord was significantly higher in the HT-IMRT plans (31.4 Gy vs. 4.8; $p < 0.001$) compared to the 3D-CRT plan.

Discussion

Our current analysis exhibited that mean dose, Dmax, V30, V40, V50 of the CA ($p < 0.001$ for each), and mean PCM dose ($p = 0.001$) were altogether significantly lower with the HT-IMRT plans than the 3D-CRT opponents. These results revealed the feasibility of sparing bilateral CA and the PCM simultaneously in early-stage glottic carcinoma patients undergoing HT-IMRT.

Interest in better understanding treatment-related drawbacks, including dysphagia, chronic aspiration, and increased cerebrovascular events, has increased in recent years due to the high curability rate in early-stage glottic carcinoma patients.[19] Occurrences of transient ischemic attacks or ischemic stroke have been well-documented due to the atherosclerotic changes observed in the irradiated vessels.[20] The main mechanisms of radiation-induced CAS include direct damage to the vessel, accelerated atherosclerosis, intimal proliferation, necrosis of the media, and peri-adventitial fibrosis.[21,22] Radiation-induced plaque and arterial wall thickening, which is histologically comparable with spontaneous atherosclerosis, tends to develop in the radiotherapy fields and can even occur in the cohort without the other risk factors of atherosclerosis.[21,23] Furthermore, patients older than 60 years who have undergone conventional RT have been reported to exhibit a greater than 10-fold risk of ischemic stroke and a significant tendency to develop ipsilateral CA stenosis in the irradiated neck compared to the radiotherapy-naïve neck.[4,24] These published data encouraged to examine CA-sparing radiotherapy techniques in this cohort. For instance, Choi, et al. evaluated the dosimetric difference of CA in IMRT and LOF techniques in early-stage glottic carcinoma patients and found that the mean CA dose (14.7 vs. 53.9 Gy; $p < 0.001$), V_{25} (13.5 vs. 89.0 Gy;

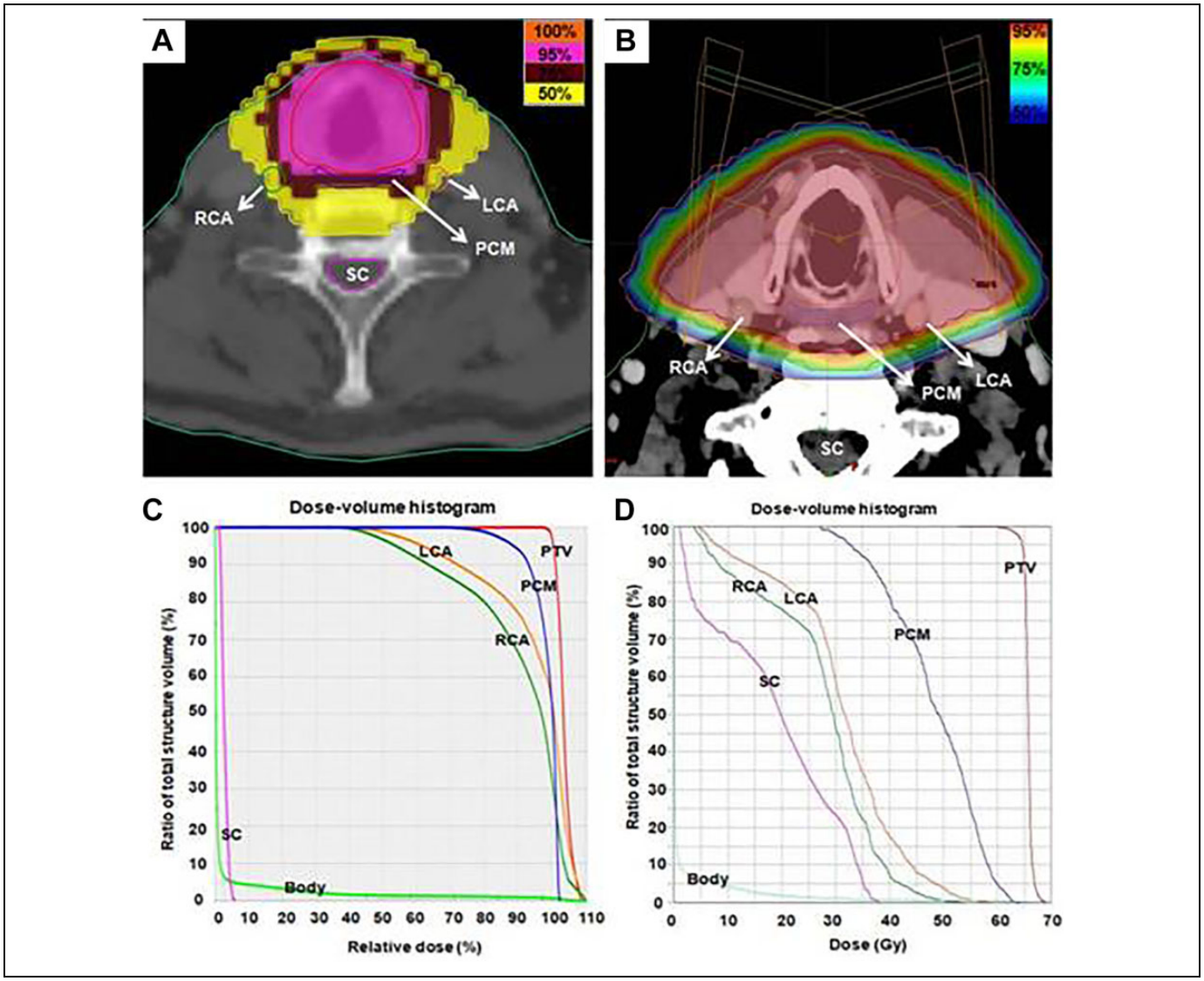


Figure 2. Isodose curves on an axial slice for a representative case planned with (A) helical tomotherapy-intensity-modulated radiotherapy plan. (B) 3D- conformal radiotherapy plan. dose-volume histogram of the planning target volume and organ at risk volumes for 2 treatment modalities (C) helical tomotherapy-intensity-modulated radiotherapy. (D) 3D- conformal radiotherapy. abbreviations: RCA, right carotid artery; LCA, left carotid artery; PCM, pharyngeal constrictor muscle; SC, spinal cord; PTV, planning target volume.

$p = 0.005$), and V_{50} (0.0 vs. 77.3 Gy; $p = 0.005$) were all significantly lower in the IMRT plans.[19] Concordant with these results, our investigation demonstrated that the mean CA dose (20.74 vs. 48.74 Gy; $p < 0.001$), V_{30} (24.97 vs. 77.55 Gy; $p < 0.001$), and V_{50} (1.89 vs. 69.78 Gy; $p < 0.001$) were markedly improved by HT-IMRT. However, the delineation method applied in Choi, et al., namely exclusion of thyroid cartilage from the CTV and expanding the CTV with no posterior margin, may explain the quantitative differences between the 2 studies.

Variations on the definition of CTV and PTV seem to be distinct theoretically for the protection of the CA and PCM. For instance, although the CTV has been defined as the vocal cords, arytenoids, and 1.5 cm of the subglottis in most investigations, while some studies included only the involved cord[25] or the CTV created with adding a 0.3-0.5-cm margin to the true vocal cords.[18] Similarly, numerous definitions of PTV exist, from no expansion[9] to a homogenous 1 cm.[8,12] These variations may be another factor contributing to the heterogeneity of dosimetric outcomes in different investigations. In our study, the entire larynx including the thyroid cartilage was defined as the CTV, and the PTV was generated by expanding the CTV by 5-mm in the superior-inferior directions and 2-mm in the other directions concerning the PCM contour and maintaining a 2-mm distance from the CA. Additionally, the primary goal was to evaluate the ideal mean doses for CA and PCM without sacrificing the dose characteristics of PTV rather than prescribing specific dose limitations for CA and PCM, which could theoretically reduce the doses CA beyond the previously reported doses.

Table 1. Comparisons of Dosimetric Characteristics for 2 Treatment Techniques.

Parameter	HT-IMRT	3D-CRT	p-value
Right carotid artery			
Mean dose, Gy (range)	20.7 (9.2-27.6)	48.7 (36.2-65.7)	<0.001
D_{max}, Gy (range)	53.6 (32.6-67.2)	67.4 (62.4-70.4)	0.003
V_{30} (%)	25.0 (0.6-47.5)	77.6 (55.8-100)	<0.001
V_{40} (%)	8.0 (0.0-15.6)	74.6 (52.8-100)	<0.001
V_{50} (%)	2.0 (0.0-5.3)	70.0 (47.8-98.1)	<0.001
Left carotid artery			
Mean dose, Gy (range)	21.5 (11-30.5)	50.5 (31.5-66.5)	<0.001
D_{max}, Gy (range)	52.0 (38.3-64.5)	67.7 (65-70.5)	<0.001
V_{30} (%)	27.1 (3.3-52.7)	80.3 (49.6-100)	<0.001
V_{40} (%)	7.9 (0.0-20.5)	71.9 (6.4-100)	<0.001
V_{50} (%)	1.2 (0-4.9)	71.6 (42.4-100)	<0.001
PCM			
Mean dose, Gy (range)	49.6 (35.0-57.3)	62.5 (55.3-65.1)	<0.001
D_{max}, Gy (range)	65.6 (59.6-67.5)	66.0 (64.3-68.0)	0.513
PTV			
D_{max}, Gy (range)	69.1 (67.2-71.3)	69.1 (67.4-70.2)	0.864
$D_{95\%}$	64.7 (64.4-66.7)	63.5 (62.4-64.2)	<0.001
$V_{95\%}$	99.3 (97.3-100.0)	100.0 (98.5-100.0)	0.13
$V_{100\%}$	95.2 (95.0-95.5)	84.5 (72.0-93.3)	<0.001
Spinal cord			
D_{max}, Gy (range)	31.4 (21.1-38.3)	4.8 (1.9-19.4)	<0.001

Abbreviations: Gy, gray; HT-IMRT, helical tomotherapy-intensity modulated radiotherapy; 3DCRT, 3 dimensional conformal radiotherapy; PCM, pharyngeal constrictor muscle; PTV, planning target volume; D_{max}, maximum dose; V_D, the percentage of the organ volume that received D Gy or more; D_X, dose received by the X% of the volume.

Besides the injury to the CAs, radiotherapy-induced swallowing dysfunction (RISD) is a common symptom in patients with head and neck carcinoma, which may originate from damage to the larynx, submental muscles, esophageal inlet, and the PCM.[26-30] In addition to dysphagia, chronic aspiration may develop in up to 30% of survivors even with modern radiotherapy techniques, which impacts tolerability of treatment as a life-threatening complication of RISD.[31-33] Given that the larynx is the main target in this cohort, sparing PCM becomes more critical for improving QoL and avoiding these side effects. In support of this statement, administering the mean PCM dose of $\geq$60 Gy and the V_{50} to the superior and middle constrictor muscles correlated with the grade of late dysphagia observed.[34] The link between the radiation dose and swallowing function was previously assessed in oropharyngeal carcinoma patients undergoing IMRT and concurrent carboplatin-paclitaxel by using videofluoroscopy and patient-reported scales.[35] Albeit a neurotoxic impact of paclitaxel on dysphagia couldn't be precluded, patients treated with a mean PCM dose of >60 Gy were reported to be more likely to experience aspiration-related problems. Levendag et al. reported that administration of a mean dose of 33 Gy to the inferior PCM may be the threshold dose associated with a 20% risk of dysphagia.[36] Furthermore, Li et al. demonstrated that a mean dose of <55 Gy and D_{max} <60 Gy to the inferior PCM were associated with lower RISD and less time requiring a gastric tube.[37] Consistent with the current literature, the mean dose administered to the PCM was significantly lower (49.6 Gy vs. 62.5; $p < 0.001$) in our HT-IMRT plan. However, our mean PCM D_{max} of 65.6 Gy was higher than the result reported by Li, et al. Given the fact that the cohort studied by Li, et al. was comprised mostly of patients diagnosed with oropharyngeal carcinomas, the long distance between the inferior PCM and region which received high radiation doses, presumably rendered it possible to reduce the D_{max}. This is in stark contrast with our cases where the PCMs were directly adjacent to the target volume.

Other than the PCM mean dose and the PCM volume receiving a given dose, a D_{max} of 69.1 Gy for PTV in our cohort also should be considered with caution because the larynx (as our target) represents an important structure responsible for swallowing. Correlation between the laryngeal radiation dose and RISD has been reported previously,[37] and the risk of grade 3 vocal toxicity has been reported to be significantly limited when the laryngeal D_{max} was <66 Gy.[38] On the other hand, the use of the D_{max} as an assessment criterion has been an established issue for the dosimetric evaluation of serial organs. The mean dose and percent of the larynx receiving a specific dose reportedly correlate with laryngeal edema, which may underestimate the value of the D_{max} as a laryngeal dose constraint (provided that the $D_{max} < 120\%$) compared with the mean dose and volume associated with a specific dosage range.[39]

While the doses of CA and PCM have decreased significantly, the HT-IMRT modality has also provided more conformal dose distributions with steeper dose gradients and superior target coverage in terms of $D_{95\%}$ (64.7 vs. 63.5 Gy; $p < 0.001$) and $V_{100\%}$ of (95.2% vs. 84.5%;$p < 0.001$) compared with the 3D-CRT plans. Most likely, the use of an integrated CT scan with 51 coplanar beam projections per 360-degree rotation and 64 binary leaves utilized for modulating the slit beam comprised the critical factor affecting the administration of a highly uniform and more homogenous dose to the target in the HT-IMRT.[40]

Present study has certain drawbacks. First, our study was just a preliminary simulation study in a limited patients cohort, therefore, the outcomes introduced here ought to be interpreted with caution until the accessibility of the results of appropriately designed clinical studies uncovering the pros and cons of such technical approach. Second, the use of constrained posterior PTV margin relative to the outer contour of PCM in our study represents a common challenge of any IMRT study aiming to spare CA and PCM, which may serve as a potential source of geographical misses and increased marginal treatment failures due to the unexpected movements of the larynx during swallowing that may reach up to 3.5 cm in the cranial-caudal direction.[25,41]In this context, incorporation of the image guidance during treatment, as practiced herein, may conceivably minimize the technique-related obstacles. Third, absence of the periodical objective clinical assessment of the dysphagia and radiological follow-up information for CAs may appear to be other downsides by some. In any case, our primary aim was to test whether we could spare the 2 CAs and PCMs

simultaneously in a dosimetric manner, instead of its likely clinical consequences, which warrants to be addressed in fittingly designed large-scale investigations.And fourth, the D_{max} of the spinal cord was significantly higher in our HT-plans (31.4 Gy vs. 4.8 Gy; $p < 0.001$) as we primarily aimed the simultaneous protection of the CA and PCM without sacrificing the PTV dose coverage and keeping the OAR doses below the recommended limit.[39,42]Although the reported dose constraints for the spinal cord D_{max} varied from <20 Gy to <45 Gy in different CA-sparing studies, yet it is universally recognized that the risk of permanent spinal injury is very low (range: 0.03% to 0.2%) with conventionally fractionated total doses of 45 to 50 Gy,[43] corresponding to a biologically equivalent dose (BED_2) of 85.5 to 100 Gy_2. Therefore, it is unlikely to experience severe late spinal cord toxicities with a total dose of 31.4 Gy given in 28 fractions that corresponds to a BED_2 of 49 Gy_2, which is far below the above mentioned 85.5 to 100 Gy_2, even if the large recovery capacity of mammalian spinal cord is neglected.[44]

Conclusion

Our study demonstrates the feasibility of sparing CA and PCM simultaneously in early-stage glottic carcinoma patients without sacrificing PTV outcomes. In view of these results, future clinical studies incorporating objective and subjective assessment tools for addressing the potential influence of this technique on CA- and PCM-related complications and clinical outcomes are required.

Declaration of Conflicting Interests

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