Comprehensive Head and Neck Radiotherapy Dose-Volume Constraints Do Not Apply to Smaller Volumes

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Abstract. *Aim: To investigate the impact of definitive radiation therapy (RT) in the management of early glottic cancer on clinical RT-induced dysphagia (RID) and carotid vasculopathy (RICV). Patients and Methods: This is a single-institution retrospective study. From January 1997 to 2010, 253 patients, with early glottic cancer, underwent RT with ^{60}Co or LINAC-6 MV photons. RT fields with wedge pair and daily 5-mm bolus were applied in all patients treated with 6-MV photons to avoid under-dose of the anterior laryngeal structures. The whole larynx (LX), pharyngeal constrictors (PCs), and carotid arteries (CA) were contoured and dose-volume histograms (DVHs) were generated to assess the delivered dose. The median age of patients was 65 years (range; 28-93), Caucasians were 80%, males were 87%, and 23% had T2 lesions. Results: After a median follow-up of seven years (range; 1.5-12), the median dose and fraction size delivered to the LX were 63 and 2.25 Gy, respectively. The mean doses to the LX, PC, and CA were 57 Gy delivered to 34 cm^3, 54 Gy to 15 cm^3, and 60 Gy to 4 cm^3, respectively. The LX, PC and CA V60 and V65 were (77 and 71), (70 and 52) and (84 and 51), respectively. Patients with acute dysphagia grades 1, 2, and 3 or more were 81, 19%, and zero, respectively; none had clinically RID or RICV. Conclusion: Small-volume RT up to 67.5 Gy at 2.25 Gy per fraction, is not a predictor of RID or RICV. Separate delineation of the aforementioned critical structures, as well as others, may better identify dose tolerances to maintain function and further prioritize the importance of structures in RID and RICV.*

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Multiple studies report on radiation therapy (RT) dose values that cause permanent radiation-induced dysphagia (RID) (1-6) and cerebrovascular disease (RICV) (7-12). The dose values that these studies report are important because they are being used to support recommendations to change treatment such as surgery in place of RT, a different RT technique, and/or different prescribed doses of RT. The purpose of this study was to test the hypothesis that the dose values that have been correlated with swallowing and vascular problems are not applicable to patients who are treated with RT-alone for early true vocal cord cancer.

Patients and Methods

Patients. This study represents a single institution's, retrospective investigation performed at our head and neck comprehensive cancer center, and fully-approved by our institutional review board. From January 1997 to 2010, 253 patients with squamous cell carcinoma (SCC) of the true vocal cord (glottic larynx) treated definitively with RT were identified. Patients were excluded if they had less than 12 months of follow-up, were previously treated with definitive surgery or RT, or did not have an available RT treatment plan. Characteristics of the 253 evaluable patients are listed in Table I. The Eastern Cooperative Oncology Group (ECOG) performance status was interpreted based on the patient condition at the time of RT.

Structures. Anatomical structures were investigated based on the proximity to and involvement in the RT field. Structures were bilateral carotid arteries, middle and inferior pharyngeal muscle constrictors (PC), and the whole larynx (Figure 1).

In general, PCs structures were contoured as described by Eisbruch *et al*. (2). The whole larynx was contoured as a single structure from the supra and infrahyoid epiglottis to the inferior aspect of the cricoid cartilage. The PCs were contoured from the superior border of the hyoid bone through the inferior edge of the cricoid cartilage and were divided into the middle pharyngeal constrictor (superior to inferior portions of hyoid bone), and inferior pharyngeal constrictor (inferior portion of hyoid bone to inferior edge of cricoid cartilage). As both

Table I. *Patients' and tumor characteristics.*

Race	Value
Caucasian	203 (80%)
Hispanic	23 (9%)
African Americans	17 (7%)
Asian	10 (4%)
Median age	65 (28-93) Years
Gender	
Male	220 (87%)
Female	33 (13%)
AJCC 7th edition	
(T1) Stage I	195 (77%)
(T2) Stage II	58 (23%)
ECOG	
0	231 (91%)
1	22 (9%)
Median follow-up, years	7 (1.5-12)
Diagnosis to RT, days	35 (14-207)
RT duration, days	41 (34-68)
Total Dose, Gy	
T1	63 (60-66)
T2	66 (63-72)
Fractionation size , range of fractions	(%)
225 cGy x (28-30)	182 (72%)
200 cGy x (31-36)	68 (27%)
180 cGy x (35)	3 (1%)

the middle and inferior PC were included in the planning target volume (PTV), the decision was made to consider both as one critical structure (PC) for dosimeteric analysis. Bilateral carotid arteries were contoured from the level of the suprahyoid epiglottis to the inferior aspect of the cricoid cartilage.

Outcomes and treatment. The two primary end-points were RID and RICV in addition to exploring dose and functional outcomes in the context of definitive single-modality laryngeal sparing RT in the management of early glottic cancer. Criteria for coding were: clinically present or not. This is followed by further grading *via* modified barium swallow (MBS) and carotid ultrasound (US) for RID and RICV respectively. Treatment characteristics are listed in Table I. No (PEG) tubes were placed before, during, or after RT in the whole cohort of 253 patients (100%). All patients were immobilized with a thermoplastic head-and-neck mask. Fifty-one patients (20%) underwent CT simulation and CT-based planning. Planning in patients was carried out with the Varian Eclipse treatment-planning system (Palo Alto, CA, USA) with 6-MV photons. Parallel opposed wedge paired fields were used and daily 5-mm bolus was applied in all patients treated with 6-MV photons to avoid under-dosing of the anterior laryngeal structures. The gross tumor volume (GTV) was defined as the primary tumor as shown on the physical examination including: indirect mirror and laryngoscopic examination, CT, and positron emission tomography (PET) imaging. The clinical tumor volume (CTV) was defined as the GTV plus microscopic spread (10 mm). No elective nodal volume was included. The CTV was then expanded by 20 mm to construct a PTV to account for setup error and laryngeal motion during swallowing. No sparing of any of the aforementioned critical structures was attempted. Of note, all critical structures were contoured retrospectively for dosimetric analysis in a very consistent manner by one radiation oncologist (WM).

Table II. *Dosimetric analysis for the DVH of larynx, pharyngeal constrictors, and carotid arteries.*

DVHs	PCs Median, Range	LX Median, Range	CA Median, Range
Median volume/cm^3	15 (11-24)	34 (15-50)	4 (3-7)
Mean dose Gy	54 (37-67)	57 (45-70)	60 (36-63)
Max. dose Gy	66 (61-73)	67 (65-74)	68 (21-69)
V40	84 (57-100)	86 (67-100)	89 (50-96)
V50	81 (55-100)	83 (63-100)	88 (47-95)
V60	70 (45-99)	77 (57-100)	84 (43-90)
V65	52 (12-92)	71 (37-95)	51 (25-73)

Follow-up. All the patients were examined by LBH or KSH. The Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 was utilized to grade dysphagia and vascular problems. Statistics; logistic regression was planned to determine predictors of each outcome including patient, tumor, and treatment characteristics noted previously, as well as to assess the relationship between each dosimetric variable, swallowing and cerebrovascular outcomes, while controlling for significant clinical variables. A significance level of $p<0.05$ was considered statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 253 patients were treated with single modality definitive laryngeal RT, 202 patients (80%) underwent 2-D clinical simulation, while 51 patients (20%) were treated with 3-D conformal treatment after CT simulation and CT-based planning. The median age for the whole cohort was 65 years, (range; 28-93 years). The breakdown for males and females was 87% and 13%, respectively. T1 (stage I) represented 77% of all patients while T2 (stage II) was 23%. The median dose delivered to the whole larynx (extending from the supraglottic superiorly to the subglottic larynx inferiorly) was 63 Gy (range; 60-72 Gy) with a median fraction size of 2.25 Gy (range; 1.8-2.25 Gy). The median duration of RT was 41 days, (range; 34-68), and the median follow-up of the whole cohort was seven years (range; 1.5-12 years). All patients were treated with once-daily fractionation.

Dosimetric analysis for dose-volume histogram (DVH) DVH (Table II) revealed that the median dose delivered to the whole LX was 57 Gy, to a median volume of 34 cm^3. Furthermore, the LX median V40, V50, V60, V65 were 86, 83, 77 and 71 Gy, respectively. The median dose delivered to the PCs (combined middle and inferior) was 54 Gy to a median volume of 15 cm^3. The PCs' median V40, V50, V60 and 65 were 84, 81, 70 and 52 Gy, respectively. The median

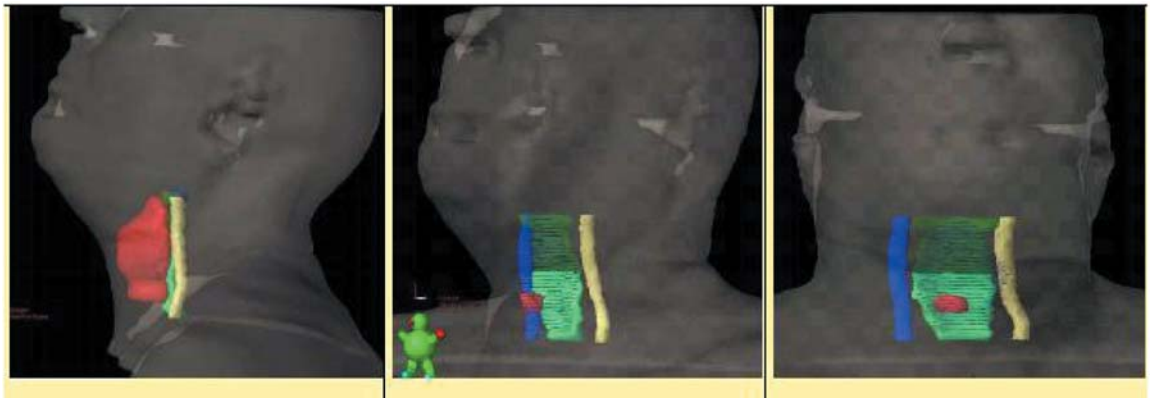

Figure 1. *The gross target volume (small lesion in red), supraglottic, glottic, and subglottic larynx in red and in segmented blue. Right carotid is in blue, left carotid in yellow, middle pharyngeal constrictor (dark green), and inferior pharyngeal constrictor (light green).*

dose delivered to the CA was 60 delivered to a median volume of 4 cm^3. The CA V40, V50, V60 and V65 were 89, 88, 84, and 51 Gy, respectively.

Two objective signs of late dysphagia were examined: clinical symptoms and aspiration as observed on MBS evaluation. MBS was performed at the discretion of the physician, based on the patients' symptoms, complaints and the highest PCs doses according to the DVHs. After a median follow-up of seven years, no patients needed PEG tube placement and no patients were clinically symptomatic. Moreover, no aspiration was seen in any of the patients who underwent MBS [n=10 (4%) patients]. The proportion of patients with acute dysphagia (*i.e.* grades 0 and 1) was 81%, and for grade 2 was 19% with no grade 3 or 4 changes. Chronic dysphagia and long-term impaired swallowing were not seen in any patient. Also, none of the 253 patients have developed any RICV to date.

Discussion

Studies correlating RT doses to different organs with long-term vasculopathy and swallowing function outcomes in patients treated for head and neck cancer patients have resulted in conflicting data. Structures implicated in previous studies mainly include the pharyngeal constrictor muscles (superior, middle and inferior), as well as the larynx. However, other structures may play important roles in swallowing. Due to the use of concurrent chemotherapy, altered fractionation and escalated RT, the rates of long-term dysphagia have significantly increased (1). Generally, dosage exceeding tolerance of the constrictor muscles and larynx is thought to be a major etiology for long-term dysphagia. Multiple studies have shown that patients with locoregionally advanced head and neck cancer treated with definitive RT, with or without chemotherapy or biological agents, demonstrate late severe dysphagia in up to 40% of cases. Authors have advocated that both laryngeal and pharyngeal constrictor doses are responsible and predictive for the development of late severe dysphagia (2-6). There is sufficient data that high-dose RT to the neck and carotid arteries can lead to RICV. These studies have shown that RT to the neck increases the risk of RICV to a statistically significant level but to a small magnitude (7-12). This retrospective review included patients with early glottic SCC for whom the general institutional policy was to treat with definitive RT with once-daily fractionation. Dosimetric parameters of the main anatomic structures (bilateral carotid arteries, supraglottic, glottic, subglottic, middle and inferior PCs) involved in the RT fields were analyzed to assess RID and RICV.

RID. Our data show that RT doses to the whole larynx (supraglottic, glottic, and subglottic), and PCs (middle and inferior) do not result in long-term dysphagia. Of note, the linear-quadratic model was used to determine the biological equivalent dose (BED) for RT using BED= nd [1+ (d/α/β)]. It was found that 67.5 Gy at 2.25 × 30 is BED to 76 Gy at 2 Gy × 37 and 84 Gy at 1.8 Gy × 47. This calculation was based on an α/β ratio of 3 and 10 for late and early tissue respectively (13). This finding suggests that RT dose cut-off values should be re-assessed for an association with the likelihood of long-term dysphagia. This may be due to the small tumor volume, consequently small RT field, the absence of chemotherapy and its chemosensitization effect. None of the patients in the current study initially had any swallowing impairment before RT and they continued to do very well despite RT with a high dose per fraction to the larynx and PCs.

Pauloski *et al*. reported that patients with laryngeal and pharyngeal tumors complaining of dysphagia were significantly more likely to have aspiration (up to 30%)

Table III. *Summary of RID studies*.

Author (ref)	Organs of interest	DVH threshold	Mean dose
Eisbruch *et al*. (2)	Lx, SGL, PC	V50 >50%	Lx >60Gy
Feng *et al*. (3)	Lx, SGL, PC	PC V50 >80% PC V60 >70% PC V65 >50%	PC >66 Gy
Caglar *et al*. (4)	Lx, inf PC	Lx V50 >21% Inf PC V50 >51%	Lx >48.2 Gy inf PC >54 Gy
Caudell *et al*. (5, 6)	Lx, inf PC	Lx V60 >24% Inf PC V60 >12% Sup PC V65 >33% Mid PC V65 >75%	Lx >41 Gy
Jensen *et al*. (15)	Lx, SGL, inf PC	Lx, SGL, Inf PC ≥V60	Lx, SGL, inf PC <60
Levendag *et al*. (16)	Sup PC, mid PC	N/A	Sup or mid PC >55 Gy
Doornaert *et al*. (28)	Pharyngeal mucosa & PC	N/A	45 Gy
O'Meara *et al*. (29)	Inf. Hypopharynx	N/A	50 Gy
Dornfeld *et al*. (30)	SGL	N/A	50 Gy
Van der Molen *et al*. (31)	Sup, Mid, Inf PC	Inf PC V40	50 Gy
Machtay *et al*. (34)	Age and Inf. Hypopharynx	RT ≤60 *vs*. >60 Gy to the inferior hypopharynx had 40% *vs*. 56%, respectively.	Older age (p=0.0021) and RT received by the Inf. hypopharynx (p=0.016)
Mourad *et al*. (35)	Lx, SGL, mid & Inf PC	No RID despite* Lx + SGL: V50=83 V60=77 V65=71 Mid-Inf PC: V50=81 V60=70 V65=52	No RID despite* Lx=57 Gy/34 cm^3 Mid-Inf PC=54Gy/15 cm^3

Adapted with modification from Rancati and Galloway *et al*. (32, 33). Pharyngeal constrictor (PC), superior (sup), middle (mid), inferior (inf), larynx (Lx), supraglottic larynx (SGL), and radiation-induced dysphagia (RID). *All the patients underwent RT alone at 2.25 Gy/fraction {*i.e*. 67.5 Gy (2.25×30), which is biological equivalent dose of 76 Gy (2 Gy × 37) and 84 Gy (1.8 Gy × 47)} while in the other studies patients underwent comprehensive head and neck irradiation with different RT doses and fractionation sizes with and without chemotherapy or biological agents.

versus those without complaints (≤5%), suggesting that this may be a reasonable approximation of the true incidence of aspiration (14).

Other institutional studies examining the association of doses to normal structures and risk of dysphagia found that up to 47% of patients had developed aspiration (2-6, 15, 16). Clinical factors associated with aspiration included primary site, advanced T-stage, larynx and inferior pharyngeal constrictor doses. The studies have shown that a mean dose up to 48 Gy to the larynx results in no aspiration issues (3-6). Using a different laryngeal anatomical definition, the Danish group found that V60 and V65 were associated with aspiration (15). Larynx V55 through V70 was also associated with aspiration (15), whereas in both the Michigan and Harvard experience, larynx V50 was found to be most significant (3, 4).

The threshold percentage for larynx V60 and V65 of 77% and 71% respectively in our study was much higher than the larynx V50 threshold of 21%, 26%, and 32%, reported by other investigators (3-6). Dissimilar to Caglar *et al*. (4) and Caudell *et al*. (5) we found that the dose to the PCs was not a predictor of dysphagia. Whereas they found V50, V60, and V65 to be significant, we found volumes irradiated to higher (V50, 60 and 65) doses not to be associated with any long-term dysphagia (4, 5). Table III summarizes the most important studies on RID. The difference in results may be the result of variances in patient populations, treatment modality, and structure delineation.

RICV. Smith and Loewenthal, in 1950, were the first to report on the adverse impact of RT on elastic arteries in irradiated mice (17). It was later reported by other groups that RT induced atheromatous lesions in the arterial wall of irradiated vessels (18-20). Clinically, this was first reported by Glick, who reported a case of bilateral carotid occlusive disease following RT for vocal cord cancer (21). This was followed by other reports that confirmed the existence of RICV (22-27). Recent reports have shown that RT to the

Table IV. *Summary of RICV studies*.

Author ref	Institution	Nature of study	Outcome
Dorresteijn *et al*. (8)	Netherlands Cancer Institute, 2002	Retrospective study of 367 patients	14 Ischemic strokes. RR 5.6 15-year cumulative risk of stroke of 12%.
Smith *et al*. (11)	M.D. Anderson Cancer Center, 2008	SEER and Medicare study	9% Increase in 10-year incidence of cerebrovascular events with RT (35%) *vs*. surgery (26%), no significant increase with surgery and adjuvant RT
Huang *et al*. (12)	Mt. Sinai Medical Center, 2008	SEER and Medicare study	2.5% Increase in 10-year stroke incidence rate with RT (10%) *vs*. (7.5%) without RT (p=0.01), no significant difference in stroke mortality
Mourad *et al*. (35)	BIMC, 2011	Retrospective study of 253 patients.	No RICV with RT after median follow up of seven years (1.5-12 years)

Beth Israel Medical Center; BIMC. Surveillance, Epidemiology, and End Results; SEER. Radiation induced carotidvasculopathy; RICV. Radiation therapy; RT, Relative risk; RR.

head and neck may cause carotid artery stenosis and increase the risk of ischemic stroke (7-12). The European group, Netherlands Cancer Institute, performed a retrospective study on 367 patients who underwent definitive RT with and without chemotherapy for head and neck tumors, of whom 162 patients had cancer of the larynx (8). Dorresteijn and colleagues reported that 14 ischemic strokes were identified and RT had a statistically significant relationship with ischemic stroke in patients with cancer larynx, with a 15-year cumulative risk of stroke of 12% (8).

More recently, the MD Anderson group performed a Surveillance, Epidemiology, and End Results (SEER)–Medicare cohort study by Smith *et al*. (11). These authors investigated the risk of a cerebrovascular event in patients older than 65 years who had previously received head and neck RT. The authors found that the 10-year incidence of cerebrovascular events was 34% in patients treated with RT-alone, compared to 25% and 26% in patients treated with surgery-alone and surgery-plus-adjuvant RT, respectively. However, there was no significant increase in cerebrovascular events in patients treated with surgery with or without adjuvant RT (11). Another (SEER database and Medicare claims records) study by the Mount Sinai group reported a statistically significant increase in stroke incidence in head and neck cancer patients treated with RT, but there was no significant difference in stroke mortality: the 10-year rate of stroke was 10% with RT *vs*. 7.5% without RT (p=0.01) (12). Table IV summarizes the recent RICV studies.

In summary, controversial and contradictory data continue to exist as the results reported herein suggest that the doses to the carotid artery, larynx and PC (middle and inferior) muscles were of limited significance in development of sequlae. It is possible that differences in the patient population, treatment modality and techniques, as well as delineation of various structures, could change the emphasis of various analyses with respect to the significance of dose constraints as noted previously. Our study contradicts those previously published because our patients did not develop problems at the doses that prior studies reported to be problematic. We surmise that the reason for this difference is that complication risk is sensitive to treatment volume in a way that is not taken into account by the typical DVH analyses. We treated only the larynx and our patients did not develop the problems reported when regional nodes and larger volumes of the larynx are treated. This finding is important because it means that the DVH thresholds for clinical complications are only applicable to the specific situations in which the data were generated. Changing the treatment volume will likely change the dose thresholds for complications and the rate of complications at a given dose. Therefore, reducing the treatment volume is likely to be an important strategy for reducing treatment toxicity, independent of other factors.

Of note, all the previous and current DVH values are based on static (initial CT simulation and planning) dosimetry. Given the fact that there are daily variations in patient setup, weight loss, inter- and intrafraction organ motion mainly during swallowing, and tumor shrinkage, we could not ascertain how much dose was deposited to the critical structures reported in our study. This problem is currently being resolved as we have implemented the usage of daily image-guided radiation therapy. This has enabled daily contouring of the structures of interest *via* on-board imaging, cone-beam CT, to calculate the actual delivered doses for the critical structures. We hope this strategy will be beneficial in determining normal tissue tolerances.

Lastly, the strengths of our study include single-institution experience, a sufficient number of patients, and management of treatment by two radiation oncologists (LBH and KSH).

In addition, all contours were drawn by one radiation oncologist (WFM), and an independent statistician (RAS) who was not involved with the data abstraction performed all the statistical analyses.

The caveats of the study include it is a non-randomized retrospective analysis and vulnerability to selection bias. An additional factor is the dependence on accurate documentation. All previously reported studies have shown DVHs from comprehensive head and neck RT with and without chemotherapy or biological agents. However, in the current study, all patients were treated with small-field larynx-only RT. Moreover, there was no pre-RT carotid study to compare to post-RT changes, if any.

RICV was evaluated primarily on a clinical basis and from medical chart review. Furthermore, only 4% of patients agreed to be evaluated by MBS due to lack of symptoms. Four percent is certainly a very small number to draw any conclusion from but in the absence of symptoms, we could not justify the extra cost and radiation exposure due to MBS for all the 253 patients in our cohort. We selected the patients (4%) who received the highest dose to the larynx and constrictors. Lastly, the current study has a relatively short follow-up (median of seven years), which may not be sufficient for development of RICV.

Conclusion

Our study shows that definitive single-modality radiotherapy up-to 67.5 Gy at 2.25 Gy/fraction, to the carotid, larynx and PC (middle and inferior) is not a predictor of long-term RID or RICV. The tolerance of these structures should be examined in further studies based on the actual RT doses delivered and in relation to the irradiated volume. This could be achieved by using daily cone-beam CT to calculate the cumulative daily DVHs which represent the actual dose delivered. The separate delineation of these structures, as well as others, may better-identify dose tolerance in order to maintain swallowing function and further prioritize the importance of these structures in causing RID and RICV.

Conflicts of interest

None.

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