ORIGINAL RESEARCH

Contralateral Constrictor Dose Predicts Swallowing Function After Radiation for Head and Neck Cancer

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Background: Radiation therapy can cause long-term dysphagia that seriously affects quality of life for survivors of head and neck cancer. This study evaluates a novel organ at risk, the contralateral pharyngeal constrictor muscles, to find out whether radiation dose to this structure predicts late swallowing function in patients with head and neck cancer.

Methods: The study included patients with head and neck cancer treated with radiation and concurrent systemic therapy at a single institution over 3 years. One-year dysphagia was defined as either the presence of a gastrostomy tube or an abnormal modified barium swallow ≥ 1 year after completion of radiation.

Results: Fifty-five patients met inclusion criteria, of which 46 were alive at 1 year. One-year dysphagia was present in 37% (n = 17) of this population. Contralateral constrictor V60 < 40% was associated with a 1-year dysphagia rate of 6%, compared with 57% in patients with V60 ≥ 40% (P < .001). An uninvolved pharynx mean dose < 45 Gy was associated with a 1-year dysphagia rate of 22%, compared with 52% in patients with an uninvolved pharynx mean dose ≥ 45 Gy (P = .03). Editing the clinical target volume off air cavities was associated with a decrease in 1-year dysphagia from 67% to 12% (P < .001), and with a reduction of contralateral constrictor V60 from 62% to 33% (P < .001). Air cavity editing was not associated with a change in locoregional recurrence or 1-year survival.

Conclusions: This is the first study to report a connection between contralateral constrictor dose and late swallowing function. The correlation between air cavity editing and contralateral constrictor V60 suggests that contralateral constrictor dose may depend partly on technique. Further studies are needed to explore whether these findings can be replicated prospectively and in other practice settings.

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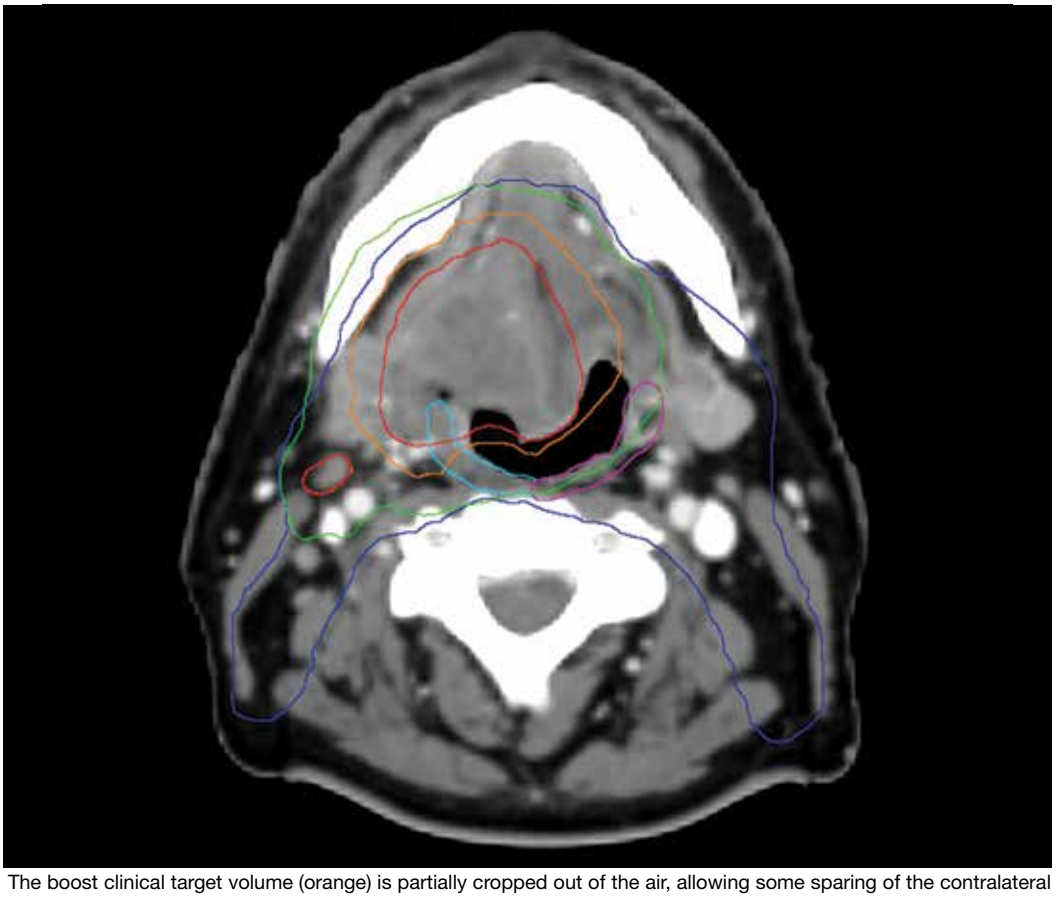
Radiation therapy can cause long-term dysphagia that seriously affects quality of life for survivors of head and neck cancer.[1-3] Numerous studies have linked pharyngeal constrictor dose to long-term dysphagia, but conclusions about the dose distribution that can be safely tolerated have been inconsistent. For example, a group from the Netherlands found that the mean dose to the superior pharyngeal constrictor muscle and the supraglottic larynx were each predictive of dysphagia.[4] A subsequent Vanderbilt study refuted these findings, reporting that these structures were not predictive but that dose to the inferior pharyngeal constrictor muscle was.[5] Other studies have connected late dysphagia with dose to the middle pharyngeal constrictor muscle, total larynx, oral cavity, contralateral submandibular gland, contralateral parotid gland, or a combination of these structures.[6-14] NRG Oncology trials commonly evaluate dose to the "uninvolved pharynx," which is the total pharyngeal constrictor muscle volume minus the planning target volume (PTV) for the lowest dose target volume. NRG head and neck trials 3, 4, 5, 6, 8, and 9 all use uninvolved pharynx mean dose ≤ 45 Gy as a constraint to judge radiation plan quality.

Differences in methodology or patient population may explain the inconsistency of prior studies on dosimetric predictors of dysphagia, but it is possible that these studies did not evaluate the optimal metric for dysphagia. This study evaluates a novel organ at risk, the contralateral pharyngeal constrictor muscle, to determine whether dose to this structure is predictive of late swallowing function. The study also compares a constraint based on this structure to the NRG uninvolved pharynx constraint mentioned earlier.

METHODS

This study is a retrospective review of patients treated at the Richard L. Roudebush Veterans Affairs (VA) Medical Center in Indianapolis, Indiana. Patients were identified by searching the VA Cancer Registry for patients treated for head and neck squamous cell carcinoma between September 1, 2016, and August 30, 2019. Eligible sites included cancers of the nasopharynx, oropharynx, hypopharynx, larynx and oral cavity, as well as head and neck cancer of an unknown primary

FIGURE 1 Radiation Plan With Air Cavity Editing



The boost clinical target volume (orange) is partially cropped out of the air, allowing some sparing of the contralateral pharyngeal constrictor (magenta) at this level.

site. Only patients treated with primary radiation with concurrent systemic therapy were included. Patients were excluded if they had prior surgery or radiation to the head and neck.

The pharyngeal constrictor muscles were contoured per the techniques described by Bhide and colleagues.[11] The contralateral constrictor was defined as the half of the constrictor volume contralateral to the primary site. For midline tumors, the side of the neck with a lower volume of lymph node metastases was judged to be the contralateral side.

Air cavity editing was assessed by making an auto-expansion of the gross tumor volume (GTV) to match the boost volume clinical target value (CTV), then determining whether the size of this CTV was decreased in an air cavity on any axial slice. In patients with air cavity editing, the CTV was not completely cropped out of air, just reduced relative to the expansion used in soft tissue (Figure 1).

One-year dysphagia was defined as having a gastronomy tube (G-tube) in place or an abnormal modified barium swallow (MBS) ≥ 12 months after the completion of radiation. At the study institution, MBS is not routinely done after therapy but is ordered if a patient or clinician has concerns about swallowing function. MBS was considered abnormal if there was laryngeal penetration that reached the level of the glottis or was not ejected from the larynx.

RESULTS

The VA Cancer Registry identified 113 patients treated for head and neck cancer during the study period. Of these, 55 patients met the inclusion criteria. No patients were lost to follow-up. The median follow-up was 29 months. The median age was 67 years (range, 41-83) (Table 1). Oropharyngeal cancer was the most common primary site, accounting for 36 patients (65%).

All patients were treated with intensity-modulated radiotherapy. Patients treated

with a sequential boost had an initial dose of 54 Gy and/or 50 Gy, followed by a boost to a total of 70 Gy at 2 Gy per fraction. Patients treated with a simultaneous integrated boost (SIB) technique received 70.0 Gy in 33 fractions, with elective volumes treated to 54.5 Gy in 33 fractions. Both patients with nasopharyngeal cancer were treated with SIB plans and had an intermediate dose volume of 59.4 Gy.

Systemic therapy was weekly cisplatin in 41 patients (75%) and cetuximab in 14 (25%). Twenty percent of patients receiving cisplatin switched to an alternative agent during treatment, most commonly carboplatin.

Forty-nine patients (89%) had a G-tube placed before starting radiation. G-tubes were in place for an interval of 0 to 47 months (mean, 8.6); 12 (22%) had a G-tube > 12 months. After completion of radiation, 18 patients (33%) had an abnormal MBS. These were done 1 to 50 months (mean, 14.8) after completion of radiation. Abnormal MBS occurred ≥ 12 months after radiation in 9 patients, 5 of whom had their G-tube in place for less than a year.

Forty-six patients (84%) survived more than 1 year and could be evaluated for late swallowing function. One-year dysphagia was seen in 17 (37%) of these patients. Recurrence was seen in 20 patients (36%), with locoregional recurrence in 12 (60%) of these cases. Recurrence occurred at a range of 0 to 15 months (mean, 5.6). Neither recurrence (P = .69) nor locoregional recurrence (P = .11) was associated with increased dysphagia at 1 year.

In patients who could be evaluated for long-term swallowing function, contralateral constrictor V60 ranged from 0% to 100% (median, 51%). V60 was < 40% in 18 patients (39%). With V60 < 40%, there was a 6% rate of 1-year dysphagia compared with 57% for V60 ≥ 40% (P < .001).

Patients with contralateral constrictor V60 < 40 and V60 ≥ 40 both had a mean age of 65 years. χ^2 analysis did not show a difference in T stage or systemic treatment but did show that patients with V60 < 40% were more likely to have N1 disease (P = .01), and less likely to have N2 disease (P = .01) compared with patients with V60 ≥ 40%. The difference in 1-year dysphagia between N0 to N1 patients (27%) and N2 to N3 patients (46%) was not statistically significant (P = .19).

In patients who could be evaluated for long-term swallowing function, the uninvolved pharynx volume median of the total constrictor volume was 32% (range, < 1%-62%). The uninvolved pharynx mean dose ranged from 28 to 68 Gy (median, 45). When the uninvolved pharynx mean dose was < 45 Gy, 1-year dysphagia was 22% compared with 52% with a dose ≥ 45 Gy (P = .03). Table 2 compares constraints based on uninvolved pharynx with a constraint based on the contralateral constrictor.

Air cavity editing was performed in 27 patients (49%). One-year survival was 93% with air cavity editing, and 75% without, which was not statistically significant. Locoregional recurrence occurred in 3 patients (11%) with air cavity editing, and 9 (32%) without, which was not statistically significant. In patients surviving at least 1 year, contralateral constrictor V60 averaged 33% with editing and 62% without editing (P < .001). One-year dysphagia was 12% with air cavity editing and 67% without editing (P < .001).

An SIB technique was done in 26 patients (47%). One-year survival was 85% (n = 22) with SIB and 83% (n = 24) with sequential boost, which was not statistically significant. Locoregional recurrence occurred in 19% with SIB, and 32% with sequential boost, which was not statistically significant. For SIB patients alive at 1 year, the median contralateral V60 was 28%, compared with 66% for patients treated with sequential technique. Seventeen patients (77%) with SIB had V60 < 40%. Nineteen (86%) of SIB plans also had air cavity editing. One patient (5%) with SIB had dysphagia at 1 year compared with 16 (67%) sequential patients (P < .001).

DISCUSSION

This is the first study to link contralateral constrictor dose to long-term dysphagia in patients treated with radiation for head and neck cancer. Editing the boost volume off air cavities was associated with lower contralateral constrictor V60 and with less long-term dysphagia. This may indicate that optimizing plans to meet a contralateral constrictor constraint can reduce rates of long-term dysphagia.

The most useful clinical predictors are those that identify a patient at low risk for toxicity. These constraints are useful because they reassure physicians that treatments will

TABLE 1 Patient Characteristics at Baseline and at 1-Year Follow-up[a]

Characteristics	Baseline, No. (%)	V60 < 40%, No.	V60 ≥ 40%, No.	*P* value
Male sex	55 (100)			
Age				
< 70 y	38 (69)	12	19	.93
≥ 70 y	17 (31)	6	9	.93
Tumor classification				
T0	1 (2)	1	0	.21
T1	8 (15)	3	5	.93
T2	18 (33)	6	10	.73
T3	20 (36)	4	12	.15
T4	8 (15)	4	3	.29
Node classification				
N0	6 (11)	3	3	.55
N1	16 (29)	10	6	.01
N2	28 (51)	4	17	.01
N3	5 (9)	1	2	.83
Primary site				
Nasopharynx	2 (4)	0	2	.25
Oropharynx	36 (65)	13	16	.30
Hypopharynx	5 (9)	0	5	.06
Larynx	9 (16)	3	5	.92
Oral cavity	2 (4)	1	0	.21
Unknown	1 (2)	1	0	.21
Radiotherapy technique				
Sequential boost	29 (53)	17	5	< .001
Simultaneous boost	26 (47)	1	23	< .001
Systemic therapy				
Cisplatin		11	23	.11
Cetuximab		7	5	.11

[a]V60 groups only include the 46 patients (84%) with survival of 1 year or more, as these values were taken at 1-year follow-up.

have a favorable risk/benefit ratio while identifying plans that may need modification before starting treatment.

The contralateral constrictor outperformed the uninvolved pharynx in identifying patients at low risk for long-term dysphagia. This difference could not be overcome by decreasing the threshold of the pharynx constraint, as 17% of patients with dysphagia had a mean dose of < 40 Gy to the uninvolved pharynx, which was not statistically significant. An advantage of contralateral constrictor is that it is independent of PTV size. The uninvolved pharynx structure depends on the PTV contour, so it may obscure a connection between PTV size and dysphagia.

In the context of a clinical trial, only measuring dose to the uninvolved pharynx may allow more plans to meet constraints, but even in NRG trials, physicians have some control over target volumes. For example, NRG HN009, a national trial for patients with head and neck cancer, recommends editing the CTV_7000 (clinical target volume treated to 70 Gy) off air cavities but does not define how much the volume should be cropped or specify protocol violations if the volume is not cropped.[15] Furthermore, constraints used in clinical trials are often adopted for use outside the trial, where physicians have extensive control over target volumes.

The broad range of uninvolved pharynx volume relative to total constrictor volume confounds predictions using this variable. For example, according to the NRG constraint, a patient with an uninvolved pharynx mean dose of 44 Gy will have a low risk of dysphagia even if this structure is only 1% of the total

TABLE 2 Predictors of 1-Year Dysphagia

	Contralateral constrictor, V60 < 40%	Uninvolved pharynx, mean < 45 Gy	Uninvolved pharynx, mean < 40 Gy
1-year dysphagia, %	6	22	17
Meeting constraint, %	39	50	26
P value	< .001	.03	.09

constrictor. The contralateral constrictor is always about 50% of the total constrictor volume, which means that predictions using this structure will not be confounded by the same variation in volume size.

Figure 2 shows a representative patient who met the NRG uninvolved pharynx constraint but developed long-term dysphagia. This patient had an uninvolved pharynx mean dose of only 33 Gy, but this volume was only 31% of his total constrictor volume. This plan shows that on axial slices containing the GTV, nearly the entire constrictor was within the PTV and received at least 60 Gy. These areas of overlap and the dose they receive are not included in the uninvolved pharynx volume. The contralateral constrictor V60 for this patient was 52%, so the patient would have been in the high-risk group for dysphagia based on this structure's constraint.

Pharyngoesophageal stricture is a common cause of dysphagia after intensity-modulated radiotherapy for head and neck cancer.[16] Radiation has been shown to decrease pharyngeal function in patients with head and neck cancer.[17] Sparing one side of the pharynx may allow for better pharyngeal compliance throughout the length of the pharynx, possibly decreasing the rate of pharyngoesophageal stricture. Additionally, constraining the contralateral constrictor may preserve strength on this side, allowing it to compensate for weakness on the side of the primary cancer. An exercise sometimes used for dysphagia involves head rotation toward the affected side during swallowing. This technique has been shown to cause food to move to the unaffected side.[18] Sparing the contralateral constrictor may help such techniques work better in patients with head and neck cancer.

Few studies have commented specifically on dose to swallowing structures contralateral to the primary tumor. Two studies have proposed contralateral submandibular gland constraints for dysphagia (not xerostomia), but neither measured the dose to the contralateral constrictor muscle.[9,10] Although the contralateral submandibular dose may correlate with dose to the constrictor on that side, the submandibular gland may have a less direct impact on swallowing than the constrictor muscle, and its limited dimensions may make constraints based on the gland less robust for cancers outside the oropharynx.

Another study reported improved quality of life in patients who were not treated with elective contralateral retropharyngeal radiation.[19] Although it is likely that doses to the contralateral constrictor were lower in patients who did not receive elective radiation to this area, this study did not measure or constrain doses to the contralateral constrictors.

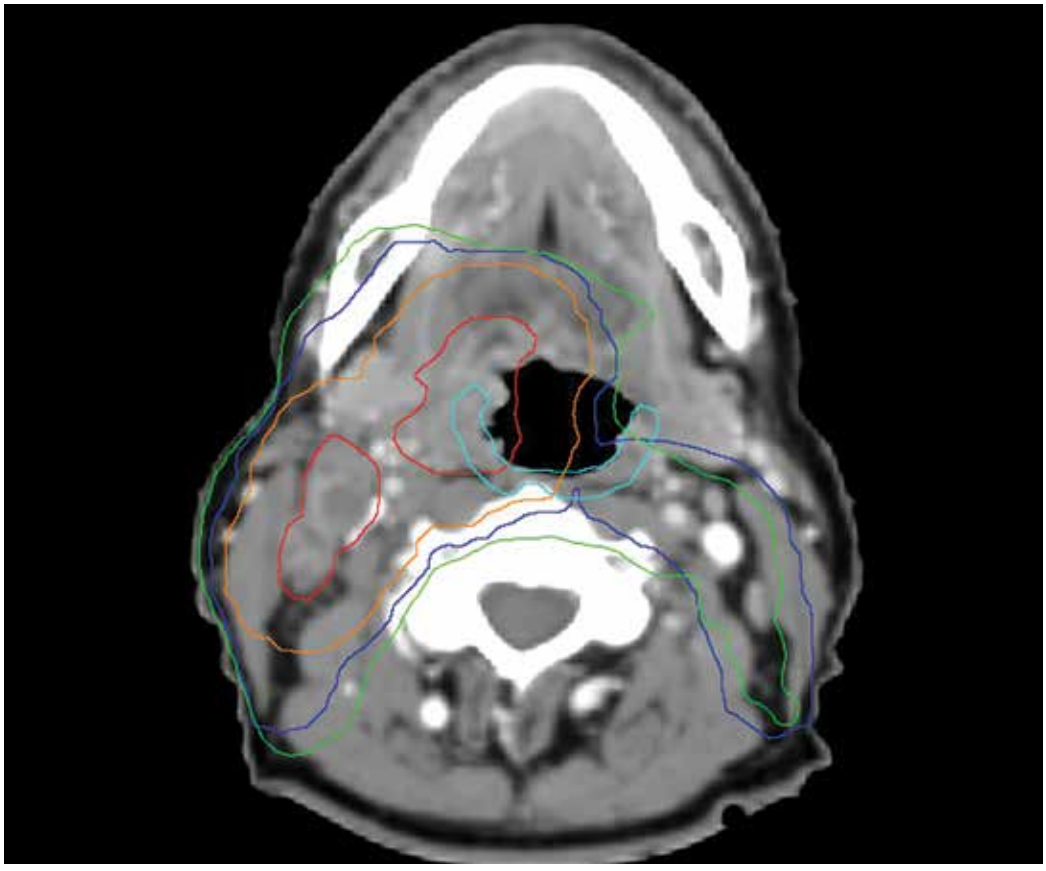
Limitations

This study is limited by its single institution, retrospective design, small sample size, and by all patients being male. The high correlation between air cavity editing and the use of SIB makes it impossible to assess the impact of each technique individually. Patients with contralateral constrictor V60 < 40% were less likely to have N2 disease, but N2 to N3 disease did not predict higher 1-year dysphagia, so the difference in N-category cannot fully explain the difference in 1-year dysphagia. It is possible that unreported factors, such as CTV, may contribute significantly to swallowing function. Nevertheless, within the study population, contralateral constrictor dose was able to identify a group with a low rate of long-term dysphagia.

CONCLUSIONS

Contralateral constrictor dose is a promising predictor of late dysphagia for patients

FIGURE 2 Radiation Plan With Low Uninvolved Pharynx Dose



The patient developed 1-year dysphagia. The 60-Gy isodose line overlapped significantly with the elective planning target volume.

with head and neck cancer treated with radiation with concurrent systemic therapy. Contralateral constrictor V60 < 40% was able to identify a group of patients with a low rate of 1-year dysphagia in this single-center retrospective study. The correlation between air cavity editing and contralateral constrictor V60 suggests that contralateral constrictor dose may depend partly on technique. Further studies are needed to see if the contralateral constrictor dose can be used to predict long-term dysphagia prospectively and in other patient populations.

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Ethics and consent

This research was approved by the Research and Development Committee at the Richard L. Roudebush Veterans Affairs Medical Center and was certified as exempt by the institutional review board at the Indiana University School of Medicine.

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