

ORIGINAL RESEARCH

Late laryngeal dysfunction in head and neck cancer survivors

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Abstract

Objectives: Head and neck cancer (HNC) survivorship issues are areas of increasing research interest. Laryngeal dysfunction in HNC patients is particularly important given the importance of the larynx in voice, swallowing, and airway protection. The objective of our study is to characterize late laryngeal dysfunction in a cohort of long-term HNC survivors.

Methods: HNC survivors who were at least 2 years post-treatment were recruited prospectively for standard collection of videolaryngoscopy findings, videofluoroscopic swallowing studies, and assessment of clinical outcomes. Descriptive statistics were performed and clinical presentation and outcomes were compared between survivors >10 years and <10 years post-treatment. Additional factor analysis to correlate clinical outcomes with clinical variables was performed.

Results: Thirty participants were analyzed with a mean age of 66 years. The majority were male (80%) patients treated for oropharyngeal squamous cell carcinoma (67%). Within the cohort, 43% underwent primary chemoradiation therapy and had 13% radiation alone. Common presenting symptoms included swallowing dysfunction (83%), voice change (67%), and chronic cough (17%). Laryngeal findings on video laryngoscopy include vocal fold motion abnormalities (VFMA) in over half of participants (61%) and mucosal changes in 20%. A weak correlation was found between time since treatment and laryngeal dysfunction ($r = .182, p = .34$), and no correlation was found between age, sex, time since treatment, or primary site and the presence or absence of VFMA, G-tube status, or tracheostomy-tube status.

Conclusion: Late laryngeal dysfunction in HNC survivors contributes to significant morbidity, is difficult to treat, and remains static decades after treatment for their original cancer.

Lay Summary: The voice-box, or the larynx, plays an important role in voice, swallowing and airway protection. It is particularly vulnerable to radiation-related damage and changes. This study demonstrates the sequelae of long-term damage of the larynx in head and neck cancer survivors.

Level of Evidence: IV.

KEYWORDS

cancer survivors, laryngeal dysfunction, radiation

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1 | INTRODUCTION

The incidence of head and neck cancer is increasing worldwide, and this is attributed to the increase in human papillomavirus (HPV)-related oropharyngeal head and neck cancers.¹⁻³ Patients undergo a variety of treatment protocols depending on primary site which can include surgical resection, chemotherapy, radiation therapy, and increasingly, immunotherapy.^{4,5} Significant advances in radiation planning and delivery with the hope of organ-preservation have improved oncologic results, but the burden of short and long-term post-radiation changes to the larynx remain.^{6,7}

The larynx plays an integral role in protecting the lower airways, pulmonary toileting, and phonation.⁸ Direct radiation-related changes to the larynx include soft tissue edema, perichondritis, cartilage necrosis, and fibrosis and result in functional impairment, including dysphonia and dysphagia as well as pulmonary comorbidities.⁹⁻¹³ Of great concern is an increased risk of aspiration, which is major a cause of morbidity and mortality in these patients. Unfortunately, these long-term radiation changes can be progressive and debilitating for patients, and higher radiation doses result in late effects for several decades after initial treatment.¹⁴ In particular, older radiation techniques have been associated with severe dysfunction.¹³ While early laryngeal dysfunction has been well characterized after radiation therapy, long-term effects require further characterization. In addition, laryngeal dysfunction in HNC patients with non-laryngeal primary is poorly described.

We aim to describe the clinical presentation and outcomes of laryngeal dysfunction in a cohort of long-term head and neck cancer survivors. We also sought to identify clinical factors associated with worse function and the need for intervention.

2 | MATERIALS AND METHODS

2.1 | Study ethics

This is a retrospective review of prospectively collected data. Health research ethics board approval was obtained through the University of Alberta Research Ethics Office (HREBA.CC-21-0469).

2.2 | Participant selection

Patients were prospectively recruited through a tertiary laryngology practice over a 3-year period (2019–2022). Consent for participation was obtained at the time of initial consultation for a laryngeal complaint. Specific inclusion criteria included: adult head and neck cancer survivors at least 2 years from treatment, which included radiotherapy in the primary or adjuvant setting, and free of active disease or recurrence at the time of assessment. Although there is no universally agreed upon timeline for early versus late toxicity effects of radiation therapy, cut-offs range from several months to years.¹⁵⁻¹⁹ Here, we assessed patients at least 2 years from treatment to ensure we only

assess for and encompass mostly late effects. Exclusion criteria included: non-head and neck primary, patients with active disease or local recurrence, or concurrent laryngeal dysfunction by another pathophysiology (e.g., status post-thoracic surgery).

2.3 | Data collection and analysis

All patients underwent a complete clinical evaluation including in-office laryngoscopy with videostroboscopy and were offered video-fluoroscopic swallowing evaluation for dysphagia symptoms, if present. Clinical data was collected prospectively using Microsoft Excel (Microsoft Corporation, 2021) and further data collection and verification was performed through a review of electronic medical records. Demographic data collected included age and biologic gender. Oncologic treatment details included time from treatment, primary malignancy type, and modality of treatment(s) received. We recorded patient presenting symptoms, laryngoscopic examination findings, and video-fluoroscopic swallowing study (modified barium swallow). A combination of patient-reported symptoms and in-office clinical examination findings were used to define laryngeal dysfunction. As a literature search revealed no current grading system of laryngeal dysfunction on endoscopy, we modified the Chandler Classification and applied the grading assessment to each laryngeal exam.²⁰ The original Chandler Classification grading system was drafted in 1979 for laryngeal radionecrosis, with grade 0 designating normal findings; grades I and II representing expected changes from ionizing radiation including hoarseness, dryness, edema, erythema and impairment of cord mobility; and grades III and IV describing complications requiring treatment, including odynophagia, dysphagia, severe impairment in vocal cord movement, skin changes, possible respiratory distress, weight loss, fistula, obstruction and/or toxicity. We modified this grading system to describe endoscopy findings for grades I–IV. We added possible early stricture and functional findings of voice or swallowing dysfunction to grade II, possible presence of hypopharyngeal stenosis to grade III, and severe stenosis and functional outcomes of G-tube and/or tracheostomy dependence to grade IV.

The severity of dysphagia on videofluoroscopic swallow studies was graded using the Waxman Dysphagia severity rating scale.²¹ Subsequent treatment outcomes and therapeutic interventions were recorded. All patients were followed for at least 12 months with a range of up to 3 years.

Basic descriptive statistics were performed for patient clinical characteristics. To compare outcomes by duration from treatment, the patients were stratified into those less than 10 years of treatment of their malignancy, and those beyond 10 years post-treatments. Proportions were compared using Chi-Squared analysis, and ordinal categorical data was compared using Mann-Whitney *U* test. Pearson correlation was used to assess association between parametric variables of age, time since treatment, Dysphagia Severity rating scale, and laryngeal dysfunction grade. Logistic regression analysis was performed to assess for the correlation between variables including patient age, time since treatment, sex, and oropharynx site of the

TABLE 1 Patient demographics.

Total patients, <i>n</i>	30	
Mean age at presentation, years \pm SD (range in years)	66 \pm 10 (49–86)	
Sex, <i>n</i> (%)	Male	24 (80%)
	Female	6 (20%)
Head and neck cancer subsite, <i>n</i> (%)	Oral cavity	1 (3.3%)
	Oropharynx	20 (66.7%)
	Hypopharynx	1 (3.3%)
	Larynx	3 (10%)
	Nasopharynx	1 (3.3%)
	Other	4 (13.3%)
Type of treatment, <i>n</i> (%)	Primary radiation	4 (13.3%)
	Primary chemoradiation	13 (43.3%)
	Postoperative radiation	5 (16.7%)
	Postoperative chemoradiation	2 (6.7%)
Mean time from treatment, years \pm SD (range)	13.6 \pm 10.5 (2–40)	
Mean radiation therapy dose, Gys \pm SD (range)	57.2 \pm 12.5 (60–65)	

primary malignancy with the presence or absence of vocal fold motion abnormalities, hypopharyngeal stenosis, and gastric tube (g-tube) status.

3 | RESULTS

3.1 | Patient demographics

A total of 30 participants met inclusion criteria (Table 1). Most patients were male (80%), and the most prevalent cancer subsite was the oropharynx (67%), followed by the larynx (10%). Of these patients, most of them were treated with primary chemoradiation therapy for their malignancies (43%), followed by surgery and postoperative adjuvant therapy (23%), and primary radiation therapy (13%). The mean duration from treatment was 13.6 years with a range of 2–40 years post-treatment.

3.2 | Presenting symptoms of late laryngeal dysfunction

Commonly reported symptom of laryngeal dysfunction included dysphagia symptoms (83%), followed by dysphonia (67%). Airway symptoms included increased chronic cough (17%) and airway restriction or dyspnea (13%) (Table 2). When comparing those less than 10 years

TABLE 2 Presenting symptoms and treatments offered to cohort patients.

	Overall patients	(%)
Neck symptoms, <i>n</i> (%)	11	37%
Voice change, <i>n</i> (%)	20	67%
Chronic cough, <i>n</i> (%)	5	17%
Swallowing dysfunction, <i>n</i> (%)	25	83%
Airway restriction, <i>n</i> (%)	4	13%
Dietary modification, <i>n</i> (%)	8	27%
Treated with surgical intervention, <i>n</i> (%)	24	80%
Treated with medical therapy, <i>n</i> (%)	5	17%
Received voice and/or swallowing therapy, <i>n</i> (%)	20	67%

from treatment with those greater than 10 years from treatment, there was no statistical difference between the two groups in terms of presenting symptoms or grade of dysfunction (Figure 1 and Table 3). Of this patient cohort, 3% had a g-tube placed as primary mode of nutrition and 7% were chronically tracheostomy-dependent (Table 3). We found a weak correlation between time since treatment and laryngeal dysfunction ($r = .182$, $p = .34$) that was not statistically significant. There were no significant correlations between time since treatment and Dysphagia Severity rating scale ($r = .11$, $p = .56$). Furthermore, there was no correlation between age and Dysphagia Severity rating scale ($r = .06$, $p = .76$) nor laryngeal dysfunction grade ($r = .119$, $p = .53$).

3.3 | Laryngeal findings on endoscopy

On laryngoscopy with or without video-stroboscopy, over half the participants had some form of vocal fold motion abnormalities (61%), whether unilateral (37%) or bilateral (20%) (Table 3). Laryngeal stenosis was present in 30% of participants, as well as laryngeal sicca in 17%. There was no statistical difference in frequency of these laryngeal findings when comparing participants less than 10 years from treatment with those greater than 10 years from treatment. Overall, we report no significant correlations between age, time since treatment, sex, or oropharyngeal primary site with any dichotomous variables of presence/absence of vocal fold motion abnormality, laryngeal stenosis, or g-tube/tracheostomy-tube status.

3.4 | Treatment and outcomes

Management of late laryngeal dysfunction included surgical intervention in 80% of participants (Table 2), which included operative laryngoscopy, injection laryngoplasty, and dilations. Speech language pathology intervention for voice and/or swallowing therapy occurred

FIGURE 1 Grading of late laryngeal dysfunction. Grade of dysfunction determined by clinical findings on endoscopy and patient function, as modified from the the Chandler Classification.²⁰

Grade	Clinical Findings	Function
<i>I</i>	Minimal mucosal changes, edema, telangiectasias	Minimal voice, airway, or swallowing complaints
<i>II</i>	Above with unilateral hypo- or immobility or early stricture	Voice or swallowing dysfunction, no airway involvement
<i>III</i>	Unilateral immobility or bilateral hypomobility, hypopharyngeal stenosis	Airway symptoms or moderate to moderate-severe dysphagia
<i>IV</i>	Severe laryngeal or hypopharyngeal stenosis, absent hyolaryngeal motion	G-tube and/or tracheostomy dependence

TABLE 3 Laryngeal function status in patients compared by time since treatment.

	Overall patients	≤10 years post treatment (N = 12)	>10 years post treatment (N = 18)	p value
G-tube status (n%)	3.3%	0%	5.6%	.412
Tracheostomy-tube status (n%)	6.6%	8.3%	5.6%	.081
Mucosal abnormalities (n%)	20.3%	8.3%	27.8%	.198
Vocal fold motion abnormalities (n%)	61.4%	41.7%	66.7%	.437
Mean dysphagia severity score (score ± SD)	3.7 ± 1.6	3.7 ± 1.7	3.7 ± 1.6	.121 (Z score=−1.55)
Mean laryngeal dysfunction grade (grade ± SD)	2.1 ± 0.83	1.7 ± 0.9	2.3 ± 0.7	.06 (Z score=−1.86)

in 67% of patients. The mean Dysphagia Severity score was 3.7 ± 1.6 and dietary modifications were recommended in 27% (Tables 2 and 3). When comparing the distribution in further management options pursued by groups within 10 years of their treatment and those further out, there was no statistical difference between the two groups.

4 | DISCUSSION

Overall, this study reports clinical characteristics and outcomes of a cohort of head and neck cancers survivors with long-term laryngeal dysfunction. Consistent with emerging epidemiology of HNC, three-quarters of our patients were male^{1,22,23} and the most prevalent subsite was the oropharynx.^{4,24} The majority of patients underwent concurrent chemotherapy, highlighting the major role of organ-preservation protocols in managing patients with head and neck cancers. After these treatments, patients presented with functional impairment in their voice, swallowing, and other neck symptoms on average almost 14 years after treatment, and vocal fold motion abnormalities were found in over half of participants.

Direct laryngeal irradiation has shown to cause pathologic findings of increased collagen content, fibrosis, mucositis or dry mucosa, and edema of the vocal folds, as well as muscle atrophy, endothelial damage of vessels, ultimately impairing function in irradiated vocal

folds.^{25–27} Animal studies have also characterized the molecular changes in irradiated vocal folds.^{28,29} The severity of patient reported symptoms of dysphagia and aspiration due to these radiation changes has been correlated with radiation doses to the larynx and subglottic region.^{30–32} Our study highlights that laryngeal dysfunction occurs even in patients who did not receive primary laryngeal irradiation. In addition to radiation to the larynx, increased radiation doses to the oral cavity, pharyngeal constrictor muscles, and contralateral parotid and submandibular glands were similarly associated with difficulties with swallowing, chewing, voice and speech production, coughing, choking, mucus in mouth, and dry mouth. Similarly, a higher mean superior pharyngeal constrictor radiation dose provided to patients has been associated with lower cranial neuropathies.³³

Other studies of late-effects also reported speech and swallowing difficulties in some patients who underwent various radiation modalities, including induction chemotherapy followed by radiation, concomitant therapy, surgery/radiation, and just radiation therapy (RT) alone, after 1–10 years following treatment.^{15,34–37} Additional late effects in patients undergoing various organ-preserving radiation therapy strategies included dependence of tracheostomy (7%–11%),³⁸ enteral feeds (3%–18%, up to 25% at the one-year mark),^{16,36–41} or both.^{42,43} Furthermore, skin fibrosis, laryngeal edema, radiation mucositis, laryngitis, dysgeusia, hyposalivation, neck pain, as well as liquid penetration and aspiration were also reported as late effects.^{16,17,44–49} The rates of

late adverse effects appear to be similar between concomitant therapy and just RT, the former of which serves as the standard of practice where applicable.^{15,50-52} However, a finding of increased unexplained deaths unrelated to malignancy in this high-dose concomitant therapy group suggest possible serious late effects not detected with monitoring.¹⁵ Here, the importance of recognizing late radiation effects and developing robust methods for monitoring remains important during the trajectory of these patient's lives following their treatment for HNC.

While multidisciplinary discussion at head and neck tumor board increasingly emphasizes the importance of laryngeal organ preservation,^{53,54} laryngeal protection and dosage optimization during intensity modulated radiation therapy to the swallowing structures of the head and neck improves overall quality of life.⁵⁵ A retrospective meta-analysis of patients from three separate Radiation Therapy Oncology Group (RTOG) trials found significant association of severe late toxicity effects with increasing age, T stage and tumor sites of the larynx and hypopharynx, but did not find significant association between the cumulative radiation or chemotherapy dosing and late toxicity.¹⁹ Associations between increased age during initial treatment and severe late dysphagia has also been reported.³⁵ Studies have found dose-volume parameters of radiation therapy to be associated with late dysphagia, aspiration risk, and serve as a prognostic factor of long-term enteral feed dependence,^{40,46,56} while others did not have the statistical power to report a significant relationship between radiation dose to swallowing structures and the development of late dysphagia.⁴⁵ All of these factors play an important role in formulating treatment plans.

The severity of laryngeal dysfunction in our patient cohort highlights late survivorship issues as well as the need to screen for those at risk of complications of laryngeal dysfunction, including chronic aspiration and airway narrowing. Ultimately, identifying patients with late-radiation effects earlier in their trajectory may facilitate initiation of therapeutic interventions. Our study shows that there is significant variability in late laryngeal dysfunction that can occur post-treatment, and while various head and neck cancer survivorship guidelines have been released that comment on the importance of addressing dysphagia and dysphonia, no clear guidance regarding timelines and duration of follow-up are included.^{32,33}

There are several limitations to our study. Our sample size remains small as late laryngeal dysfunction remains an uncommon phenomenon. This limits our ability to perform subgroup analysis by sex, site, and dosing. Furthermore, in our study, the lack of significant statistical difference in clinical characteristics and outcomes between patients more than and less than 10 years from treatment may be due an under-powered sample size. However, our results add to the growing body of knowledge assessing for late-effects noted years to decades after organ-preserving radiation treatment.

Additionally, there is also significant bias as study participants all presented to a tertiary laryngology practice and thus were more likely to have severe symptoms and require treatment. There may be patients with subclinical laryngeal dysfunction who do not present to the health care system for assistance or may experience diagnostic delay due to non-presentation. Many patients in the community may

ultimately present with a complication, such as aspiration pneumonia. Finally, we did not prospectively collect any standard patient reported outcomes or questionnaires, which may also provide further insight and perspectives into the sequelae of their disease.

5 | CONCLUSIONS

Overall, our study provides insights into the challenges of late laryngeal dysfunction in head and neck survivors requiring them to seek further management and follow-up with otolaryngologists. Awareness of the prevalence of late laryngeal dysfunction following chemoradiation treatment for head and neck cancer suggests the role for early screening for voice, swallowing, and pulmonary symptoms in these patients at both the primary care level and in hospital to prevent complications that add to the mortality and morbidity in this unique patient population.^{57,58} Additionally, laryngeal protection during therapy may also provide improvement to overall quality of life of head and neck cancer survivors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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