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Functional Outcomes after Chemoradiotherapy of Laryngeal and Pharyngeal Cancers

Katherine A. Hutcheson, PhD and **Jan S. Lewin, PhD**
Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Abstract

Organ preservation regimens that combine chemotherapy and radiotherapy (chemoradiotherapy) are increasingly used as the primary treatment of laryngeal and pharyngeal cancers. Meta-analytic data show a survival benefit with combined modality therapy, but the functional sequelae can be significant. Dysphagia is recognized as a common and often devastating late effect of chemoradiotherapy. This review examines functional outcomes after chemoradiotherapy for laryngeal and pharyngeal cancers, with a particular emphasis on dysphagia. Topics examined include the burden of dysphagia after chemoradiation, pathophysiology of dysphagia, baseline functioning, recommendations to improve long-term function, and voice outcomes.

Keywords

Chemoradiotherapy; Larynx; Pharynx; Function

Introduction

Laryngeal and pharyngeal cancers accounted for approximately 50% of head and neck cancers diagnosed in 2010 [1]. Moreover, combined regimens of chemotherapy and radiotherapy (chemoradiotherapy) are increasingly used as the primary treatment of advanced-stage laryngeal and pharyngeal cancers [2, 3]. Meta-analytic data demonstrate a survival benefit after combined modality treatment [4], but a high incidence of acute toxicity (e.g., mucositis) is commonly acknowledged [5]. In recent years, there has also been a growing awareness of the potential long-term functional sequelae of chemoradiotherapy. The larynx is responsible for voice production and is integral to the process of swallowing. These vital functions are at risk for impairment after chemoradiotherapy, and various mechanisms of neuromuscular injury underlie these complications. The purpose of this review was to critically evaluate and summarize the results of recently published studies on functional outcomes after chemoradiotherapy of laryngeal and pharyngeal cancers. The review will focus on swallowing outcomes after chemoradiotherapy because there is general

Send reprint requests to Katherine A. Hutcheson, PhD, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1445, Houston, TX 77030, U.S.A. Telephone: 713-792-6513, Fax: 713-794-4662 karnold@mdanderson.org.

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consensus that the adverse impact on swallowing is more pronounced than the effects on other functions.

Methods of Assessment of Swallowing and Voice Outcomes

A recent review published in this journal underscored the need for a common nomenclature to document functional outcomes among head and neck cancer (HNC) clinicians and researchers [6]. The author suggested the use of the World Health Organization (WHO) International Classification of Functioning, Disability, and Health (ICF) HNC Core Sets to provide consensus on what functional outcomes to measure in HNC patients [7]. The HNC Core Set recommended 19 core domains of functioning to measure, but did not define which outcome measures to use. Currently, a number of functional outcome measures are reported in published literature.

The method of evaluating and measuring swallowing and voice dysfunction after chemoradiotherapy greatly impacts outcomes reported in clinical studies. Instrumental assessments (e.g., videofluoroscopic swallowing studies, endoscopic swallowing studies, and laryngeal videostroboscopy) directly observe physiologic functioning during swallowing or voice production. Validated measures taken from instrumental examinations are considered the gold-standard by many because they are not confounded by subjective factors related to patient-reported metrics. However, a number of psychometrically validated patient-reported outcome measures (e.g., MD Anderson Dysphagia Inventory [MDADI] [8], MD Anderson Symptom Inventory [MDASI] [9], University of Washington Quality of Life Scale [UW-QOL] [10], and Functional Assessment of Cancer Therapy–Head and Neck [FACT-HN]) are available to assess functioning after chemoradiotherapy and provide a complementary perspective and a lower cost option. Finally, global indicators of functional status (e.g., diet level, gastrostomy dependence, and tracheostomy dependence) are commonly recorded from clinical records as a surrogate measure of function and are simple to collect and interpret. This review will summarize functional outcomes using the range of outcome measures reported in recent literature.

Dysphagia Burden after Chemoradiotherapy

Population-Based Estimates

To date, most estimates of functional outcomes have been derived from clinical studies. In 2010, however, Francis et al. [11] published population-based estimates of swallowing outcomes from linked SEER-Medicare data in 8,002 patients with oral, pharyngeal, and laryngeal squamous cell carcinomas. The rates of the 3 primary swallowing outcomes (dysphagia, 64%; stricture, 12%; and pneumonia, 15%) were highest among those treated with chemoradiotherapy in comparison to other modalities, including surgery with adjuvant radiotherapy. In adjusted models, chemoradiotherapy patients were 44% more likely to develop pneumonia after treatment than were patients who underwent surgery alone. The authors acknowledged the limitations of analyzing administrative data, particularly the unknown sensitivity of diagnostic and procedural codes to capture asymptomatic dysphagia (e.g., silent aspiration). Nonetheless, the results of this study provide, for the first time,

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population-level evidence that suggests that swallowing outcomes in HNC survivors are more adversely affected by chemoradiotherapy than by other treatment modalities.

Feeding Tube Dependence

The prevalence of dysphagia after chemoradiotherapy depends on the duration of follow-up and outcome measure reported. The most common swallowing outcome reported in clinical literature is the rate of feeding tube dependence. Feeding tube dependence may, however, underestimate the burden of dysphagia because patients often eat despite evidence of dysphagia or aspiration on instrumental examination. Rates of feeding tube dependence were reported in 6 published phase II and III clinical trials of chemoradiotherapy for HNC, identified by a MEDLINE search over the past 5 years (2006-2011, Medical Subject Heading [MeSH] terms: “drug therapy” and “radiation”, and “pharyngeal neoplasms” or “laryngeal neoplasms”) [12-17], with only 2 clinical trials during the same period reporting the distinct findings of instrumental swallowing studies [13, 16, 18]. Table 1 shows rates of feeding tube dependence after chemoradiotherapy from clinical trials and cohort studies (2006-2011). Most clinical trials reported rates <10% at 1 year and <5% at 2 years, with the exception of RTOG-9914 (concurrent cisplatin with concomitant boost radiation fractionation), which found 41% and 22% of patients tube dependent at 1 and 2 years, respectively [12-17]. In general, higher rates of gastrostomy dependence were reported in cohort studies: 19% to 26% at 1 year and 10% to 14% at 2 years [19-22]. Differences in gastrostomy dependence between clinical trials and cohort studies might be related to favorable selection of patients for participation in clinical trials, but this warrants further investigation.

Aspiration after Chemoradiotherapy

Aspiration rates are also commonly reported in clinical studies on the basis of instrumental swallowing evaluations (e.g., modified barium swallowing studies). It is important to consider, however, that methodological variations affect the interpretation of published aspiration rates. The use of instrumental examinations can detect both sensate and “silent” episodes of aspiration in patients who are unaware they are aspirating and therefore do not complain of or report this problem. Despite this advantage, many authors only perform instrumental swallowing studies in “symptomatic” patients who complain of dysphagia after chemoradiotherapy resulting in a misclassification bias in the analysis of results. There is general agreement that aspiration rates are likely underreported in studies that evaluate only symptomatic patients using instrumental assessments because silent aspiration has been observed in at least one-third of aspirators after chemoradiotherapy [20, 23, 24]. Aspiration rates of 24% to 31% have been reported in studies in which only symptomatic patients were evaluated using instrumental swallowing studies after chemoradiotherapy [20, 21]. In contrast, studies that examine all patients (both symptomatic and asymptomatic) with instrumental swallowing evaluations report higher aspiration rates of 30% to 62% [25, 26]. Interestingly, notably low aspiration rates (<10% overall, 6 months: 6%, 12 months: 3%, and 24 months: 8%) were reported by Kies et al. on the basis of MBS studies conducted in all stage IV HNC patients enrolled in a phase II single-institutional trial of induction paclitaxel, carboplatin, and cetuximab, followed by risk-based local therapy [13]. Further investigation is warranted to explain the favorable swallowing outcomes in this recent chemoradiotherapy

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trial, but small primary tumors in a majority of patients and risk-based treatment selection might have led to favorable swallowing outcomes.

Pharyngoesophageal Stricture after Chemoradiotherapy

Pharyngoesophageal stricture is an important contributor to dysphagia after chemoradiotherapy for laryngeal and pharyngeal cancers. While physiologic impairments that reduce the range of motion of swallowing structures are more common than stricture [23], stricture greatly compounds the functional impairment and often leads to prolonged gastrostomy dependence. Stricture rates after chemoradiotherapy for laryngeal and pharyngeal cancer range from 12% to 37% [11, 21, 27-29]. Previous studies have found an elevated risk of stricture in patients treated for hypopharyngeal disease and after concurrent chemoradiotherapy regimens with twice-daily radiation fractionation [11, 28]. A recent analysis of oropharyngeal cancer patients treated with a uniform protocol of concurrent chemoradiotherapy sought to identify patient-specific factors that predispose to stricture formation by eliminating the confounding effects of varied treatment regimens and disease sites [27]. In adjusted models, duration of mucositis was identified as an independent risk factor for stricture (32% increased risk of stricture with each week of mucositis). Furthermore, the authors identified 15 weeks of mucositis as a potential threshold beyond which the risk of stricture greatly increased.

Composite Functional Endpoints after Chemoradiotherapy

Dysphagia manifests in a variety of ways after chemoradiotherapy. HNC survivors may present with impaired airway protection leading to aspiration and risk of pneumonia, or diet limitations owing to reduced swallowing efficiency or stricture. As such, enumerating the individual impairments (e.g., aspiration or stricture) or markers of dysfunction (e.g., pneumonia, diet level, gastrostomy dependence, or tracheostomy dependence) may lead to underreporting of the overall burden of dysphagia. For this reason, researchers have used composite measures of functional impairment in recent years [14, 21, 30, 31]. Composite endpoints group various functional outcomes (e.g., feeding tube, aspiration, tracheostomy, or pneumonia), and in clinical trials, these endpoints often aggregate survival outcomes with markers of functional status. Recently, an international consensus panel recommended that future phase III clinical trials of larynx preservation in patients with locally advanced laryngeal and hypopharyngeal cancer use a primary endpoint that captures both survival and function [32].

Table 2 describes outcomes using composite functional endpoints reported in the recent literature. The rate of “functional” progression-free survival at 3 years in patients treated with chemoradiotherapy for advanced-stage disease was 40% to 57% [14, 30, 31]. Only 1 study reported a composite measure of swallowing function that did not account for survival [21]. This retrospective analysis of long-term dysphagia used a novel composite endpoint to estimate the prevalence of dysphagia more than 1 year after definitive radiation-based treatment of stage III and IV HNC. A high prevalence of dysphagia (38.5%) was reported, as defined by chronic gastrostomy dependence, aspiration on MBS, aspiration pneumonia, and/or stricture (per MBS or endoscopy). No statistically significantly associations were found between component variables. That is, gastrostomy and stricture were not

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significantly associated with each other, nor were they significantly associated with evidence of aspiration on MBS studies. Hence, solely reporting rates of gastrostomy dependence (as is the standard in many studies) does not sufficiently capture dysphagia outcomes in HNC survivors who eat despite aspiration or stricture.

Etiology of Dysphagia after Chemoradiotherapy

Fibrosis has long been considered a primary source of late chemoradiotherapy-induced dysphagia. Dysregulation of normal wound healing mechanisms, coupled with regional oxidative stress, may lead to overproduction of transforming growth factor β (TFG-β1), which is a commonly studied regulator of the fibrotic process [33]. The process of fibrosis is self-inducing and may spread to adjacent regions, accounting for the chronic and often progressive clinical presentation of fibrosis after radiotherapy. In addition, neuropathy can occur as the result of neural tumor infiltration, chemotoxicity, or as a late effect of radiotherapy, but in clinical practice it has been considered a less common source of dysphagia. Preliminary data from the NIH Laryngeal Study Section has helped expand our understanding of the neuromuscular etiology of chronic dysphagia after chemoradiotherapy [34]. The authors found electromyographic evidence of at least partial denervation of the suprahyoid musculature (geniohyoid and mylohyoid) and the thyrohyoid muscle, required to achieve supraglottic closure and upper esophageal opening, in 90% of nonsurgical patients enrolled in a trial for chronic dysphagia after radiotherapy or chemoradiotherapy for HNC. In addition, intramuscular stimulation at rest induced hyolaryngeal movement similar to that of healthy controls, implying that the muscles in these dysphagic HNC patients were not completely stiffened and fibrotic. Rather, a combination of denervation and muscle fibrosis was suggested. The etiology of neuropathy after chemoradiotherapy is not fully understood, but brainstem neurotoxicity, peripheral devascularization, and compressive injury from adjacent fibrosis have been suggested [34, 35].

Effect of Baseline Functioning on Survival and Functional Outcomes

Impaired baseline functioning has been shown to portend suboptimal functional outcomes after organ preservation. In recent years, authors have reported high levels of posttreatment gastrostomy or tracheostomy dependence in patients who present with baseline aspiration of thin liquids [23] or vocal fold fixation [36, 37] before radiation-based treatment. Two retrospective studies evaluated the effect of baseline vocal fold fixation on functional and survival outcomes after chemoradiotherapy [36, 37]. The rate of chronic gastrostomy or tracheostomy dependence was 35% to 56% in patients with baseline vocal fold fixation versus 6% in patients without fixation. In addition, recovery of vocal fold mobility after chemoradiotherapy was reported in 65% (52% full recovery and 13% partial recovery) of patients with baseline fixation [37]. Recovery of vocal fold mobility after chemoradiotherapy was associated with significantly higher 5-year overall survival and local control, and lower rates of persistent gastrostomy or tracheostomy dependence. The authors suggested that chemoradiotherapy was feasible in patients with baseline vocal fold fixation but emphasized the need for close surveillance in those with persistent immobility after treatment because their outcomes suggest that this is a negative prognostic indicator for long-term survival and functioning. In addition, baseline tracheostomy has been found to be

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a poor prognostic marker of survival after chemoradiotherapy [38], but no association between baseline tracheostomy and functional outcomes has been described. The prognostic significance of baseline functioning supports the routine use of instrumental examination using laryngeal videostroboscopy and a modified barium swallowing study prior to chemoradiotherapy.

Recommendations to Improve Swallowing Outcomes after Chemoradiotherapy

The reduction of late effects and functional impairment is a key priority in the contemporary management of HNC. Risk reduction may be achieved by de-escalating treatment intensity in cancers with favorable survival rates. Various methods have been considered to reduce treatment intensity, including risk-based treatment planning, targeted therapy, and IMRT. Promising functional outcomes have been reported after sequential chemoradiotherapy regimens using a risk-based method to select definitive management [13]. Recent studies have also demonstrated an association between dose and volume coverage to key structures after IMRT (i.e., oral cavity, superior pharyngeal musculature, and larynx) and swallowing outcomes [29, 39, 40]. These findings may ultimately be useful for IMRT planning to decrease radiation dose to swallowing-critical structures. Regardless of the method used to de-intensify therapy, instrumental swallowing examinations are needed to comprehensively evaluate posttreatment swallowing outcomes.

The benefit of early swallowing intervention is increasingly supported in published literature as a technique for improving functional outcomes after chemoradiotherapy. Preventive swallowing therapy encourages the ongoing use of the swallowing musculature during treatment by avoiding periods of no oral intake (NPO periods) and maintaining targeted swallowing exercises [20, 21, 41, 42]. Preventive swallowing exercise regimens have been associated with superior swallowing-related quality of life scores [43], better base of tongue retraction and epiglottic inversion [44], larger post-radiotherapy muscle mass (genioglossus, mylohyoid, and hyoglossus) and T2 signal intensity on magnetic resonance imaging [45], and shorter duration of gastrostomy dependence after radiotherapy [46]. Referral to a speech and swallowing pathologist prior to chemoradiotherapy is considered an integral component of functional preservation through multidisciplinary HNC management.

Voice Outcomes after Chemoradiotherapy

The consensus recommendations for functional assessment in laryngeal preservation trials suggest the use of simple, validated scales to assess vocal outcomes [32]. Two commonly used tools are the Voice-Related Quality of Life (VR-QOL) and the Voice Handicap Index (VHI), or its abbreviated version, the VHI-10 [47, 48]. In 2009, a cross-sectional study [49] compared voice outcomes in of 137 laryngeal cancer patients using these two scales along with the clinician-rated GRBAS (Grade, Roughness, Breathiness, Asthenia, Strain) scale [50]. Early glottic cancers (81% T1 or T2 and 77% glottic primaries) comprised most of the sample, and outcomes were stratified for comparison into 4 groups by final treatment modality (radiotherapy alone, radiotherapy with concurrent platinum chemotherapy, laser surgery, or total laryngectomy). At a median of 38 months, a similar trend was seen across

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the 3 voice outcome measures (VHI-10, VR-QOL, and GRBAS). Patients treated with radiotherapy and chemoradiotherapy had similar results on each outcome measure. Superior voice outcomes were identified in patients treated with radiotherapy alone and chemoradiotherapy, followed by laser surgery. Voice outcomes were uniformly lowest in patients treated with total laryngectomy. Clinically meaningful differences were likely detected, particularly on VHI-10, which showed 2-fold higher median impairment after laser surgery and 4-fold higher median impairment after total laryngectomy, relative to both radiation-based treatment groups, for all disease sites and stages. The authors considered the effect of time after treatment and found that few patients treated with radiotherapy or chemoradiotherapy experienced significantly diminished vocal functioning as a late effect of treatment.

Conclusions

Functional preservation is a key focus of contemporary HNC management. Current evidence clearly documents a high prevalence of dysphagia after chemoradiotherapy for laryngeal and pharyngeal cancers but suggests favorable voice outcomes compared with conservation surgery for glottic cancers or total laryngectomy. Further comparison of functional outcomes between chemoradiotherapy regimens remains difficult because of the variety of metrics used to evaluate functional outcomes and the need to control for confounding factors such as baseline functioning. Analysis of functional outcomes should be included in phase III organ preservation trials to allow reliable comparisons between treatment regimens. Meanwhile, growing evidence supports the benefit of preventive swallowing therapy to reduce the burden of dysphagia after chemoradiotherapy.

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Table 1

Rates of gastrostomy dependence reported in the clinical literature

Study design (N)	Tumor and treatmentM*	Prevalence of feeding tube dependence after CRT				"Chronic" tube dependence time to removal
		Ever	Early (≤6 mos.)	1 yr.	2 yrs.	
Clinical trials						
Phase II (N=49) [12]	III or IV Phx, Lx	86%	NR	NR	NR	Final tube: NR Median removal: NR
Phase II (N=47) [13]	IV OC, Phx, Lx Sequential CRT	70%	15%	9%	3%	Final tube: 4% (median, 33 mos.) Median removal: 3.6 mos.
Phase III (N=450) [14]	II or IV Lx, HP Induction v. alternating CRT	NR	NR	NR	NR	Tube in place >3 mos.** Induction arm: 25% Alternating arm: 20%
Phase II (N=76) [15]	III or IV OC, Phx, Lx	83%	NR	41%	22%	Final tube: 14% (median, 2.9 yrs) Median removal: NR
Phase II (N=111) [16]	III or IV Lx, OP Sequential CRT	40%	NR	3%	NR	Final tube: NR Median removal: NR
Phase III (N=163) [17]	IV Phx (OP, HP) Concurrent w/BID RT***	100%	20%	8%	4%	Final tube: NR Median removal: NR
Cohort studies						
Retrospective cohort (N=32) [51]	III or IV HNC Concurrent CRT	NR	NR	NR	NR	Final tube: 6.3% (median, 44 mos.) Median removal: NR
Prospective cohort (N=104) [19]	II or IV HNC Concurrent CRT	NR	NR	26%	NR	Final tube: 26% (mean, 3.1 yrs) Median removal: NR
Prospective cohort (N=59) [20]	III or IV OC, Phx, Lx Sequential CRT	100%	37%	19%	10%	Final tube: 3% (median, 48 mos.) Median removal: 21 wks
Retrospective cohort (N=122) [21]	III or IV HNC Sequential (16%) or concurrent (69%)	NR	NR	25%	14%	14% (median 32 mos.) Median removal: 8 mos.
Prospective cohort (N=66) [22]	III or IV OP	32%				Final tube: 3% (median, 64 mos.) Median removal: NR

Abbreviations: CRT, chemoradiotherapy; Phx, pharynx; Lx, larynx; NR, not reported; OC, oral cavity; HP, hypopharynx; OP, oropharynx

* Sequential: Induction chemotherapy, followed by concurrent chemoradiotherapy; Alternating: chemotherapy alternated with radiotherapy (20 Gy, 2 wks) between chemotherapy cycles

** Rates in patients with intact larynx

*** Comparison arm, BID radiotherapy alone (g-tube rates for this arm excluded from this table)

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Table 2

Composite functional outcome measures reported in the clinical literature

Study design	Tumor and treatment	Definition composite functional endpoint	Outcome
Composite endpoint (survival with function)			
EORTC 25954, randomized phase III trial [14]	• Advanced Lx (T3-4) or HP (T2-4) • Induction → sequential (control) or alternating (experimental) RT	"Survival with a functional larynx" • Events: Death from any cause, local progression or relapse, tracheotomy (>3 mos.), feeding tube insertion (>3 mos.), gastrostomy, or laryngectomy, whichever occurred first	3-yr survival with functional larynx: • Sequential arm: 39.5% (95% CI: 33.0%-45.8%) • Alternating arm: 45.4% (95% CI: 38.8%-51.8%) • Hazard ratio: 0.85 (95% CI: 0.68%-1.06%)
Prospective case series, single institution* (N=139) [30]	• Stage III or IV OC, OP, Lx, HP • Sequential: induction → concurrent CRT	"Functional PFS" • Events: radical surgery, permanent PEG, permanent tracheotomy, recurrence, progression, death	3-yr functional PFS: 57% (95% CI: 44%-69%) • Significantly worse functional PFS associated with: ○ T4 (p=0.0002), ○ N2-3 (p=0.010), and ○ Pre-treatment hemoglobin <13 g/dL (p=0.0003) • NS better functional PFS in oropharyngeal SCCA patients (p=0.058) NOTE: 3-yr PFS 62% (95% CI: 50%-74%)
Retrospective study, single institution (N=44) [31]	• Stage III or IV OC, OP, Lx, HP • Sequential: induction → concurrent CRT • Restricted inclusion: age > 65 yrs.	"Functional PFS" Events: Radical surgery, permanent PEG, permanent tracheotomy, recurrence, progression, death	3-yr functional PFS: 57% (95% CI: 40%-74%)
Composite endpoint (function only)			
Retrospective cohort, single institution (N=122) [21]	• Stage III or IV HNC • Definitive RT (88% chemotherapy)	"Objective signs of severe dysphagia" • Events: PEG dependence last F/U, or aspiration on MBS, or diagnosis of aspiration pneumonia, orpharyngoesophageal stricture on MBS or endoscopy with subsequent need for dilation	Prevalence of dysphagia by composite outcome measure >12 months post-RT: 38.5% (47/122) • Significantly higher prevalence of long-term dysphagia associated with: ○ Lx, HPx, or BOT compared with other sites (adjusted OR: 2.7, 95% CI: 1.2-6.1), ○ concurrent CRT (adjusted OR: 9.0, 95% CI: 1.8-46.1), and

Study design	Tumor and treatment	Definition composite functional endpoint	Outcome	
				○ age >55 (adjusted OR: 1.1, 95% CI: 1.0-1.1)

Abbreviations: Lx, larynx; HP, hypopharynx; OC, oral cavity; OP, oropharynx; CRT, chemoradiotherapy; PFS, progression-free survival; PEG, percutaneous gastrostomy tube; NS, non-significant; F/U, follow-up; HNC, head and neck cancer; MBS, modified barium swallow study; OR, odds ratio

* Note: Overlapping cohorts cited.

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