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Clinical and functional outcomes after total laryngectomy and laryngopharyngectomy: Analysis by tumor subsite, salvage status, and extent of resection

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Abstract

Background: Outcomes following surgical intervention for laryngeal and hypopharyngeal tumors are dependent on several factors. In the present study, we sought to determine whether tumor subsite, salvage status, and extent of resection influenced postoperative outcomes.

Methods: Retrospective review of 107 patients at a single institution who underwent total laryngectomy or partial/total laryngopharyngectomy.

Results: Hypopharyngeal subsite and total laryngopharyngectomy subgroups had inferior speech and swallow outcomes compared to their respective cohorts ($P < .05$). Salvage patients had inferior 3-year overall survival ($P < .05$) and swallow outcomes ($P < .001$). Previously radiated patients had increased fistula rates (29.9% vs 10%, $P = .02$), and the use of tissue coverage in salvage total laryngectomy had a protective effect on fistula formation (10% vs 37%, $P = .04$).

Conclusions: By stratifying patients across multiple subgroups, we provide a detailed narrative in surgical outcomes that can be incorporated into treatment planning. Further prospective studies are needed to compare surgical outcomes to those of organ preservation therapy.

KEYWORDS
hypopharyngeal cancer, laryngeal cancer, laryngopharyngectomy, salvage surgery, total laryngectomy

1 | INTRODUCTION

Advanced (stage III/IV) laryngeal and hypopharyngeal squamous cell carcinomas (SCCs) have an estimated 5-year overall survival (5y OS) of approximately 50%[1] and 35%,[2] respectively. With increasing use of organ preservation therapy (OPT) over the past several decades, surgical intervention has traditionally been reserved for patients with extra-laryngeal extension, compromised laryngeal function and/or those developing disease recurrence. Although certain series have demonstrated laryngeal preservation rates as high as 88% in OPT,[3] an estimated 35%-40% of patients undergoing OPT will ultimately have locoregional failure and only 35%-50% of these treatment failures will be candidates for salvage surgery.[4,5] Furthermore, hypopharyngeal patients who fail OPT are less likely than their laryngeal counterparts to undergo salvage interventions (42% vs 26%)[5] in part due to the higher rates of distant metastasis (30%) relative to laryngeal SCC (19%).[6]

In addition to oncologic outcomes, functional considerations such as speech and dietary rehabilitation should be an

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integral component of treatment planning. Patients with hypopharyngeal cancer have been shown to have worse objective speech outcomes following surgical intervention compared to their laryngeal counterparts, but differences among dietary outcomes have not been shown to be statistically significant.[7] Comparing the extent of surgical intervention, total laryngopharyngectomy (TLP) patients—which largely represent those with hypopharyngeal primaries—have similarly been shown to have worse objective speech outcomes relative to total laryngectomy (TL) patients,[8,9] whereas comparisons of dietary outcomes have been more inconsistent.[7,9] For TLP defects, various reconstructive options are available for the necessary circumferential pharyngeal repair. Anterolateral thigh (ALT) and radial forearm free flaps (RFFFs) represent the two more commonly used reconstructive options for TLP defects. RFFFs are considered to have superior speech outcomes relative to ALT, whereas swallow outcomes between the two are considered more equivocal.[10] Actual rehabilitative rates in the literature among TLP or partial laryngopharyngectomy (PLP) patients are highly variable, however, with successful rehabilitation of speech and swallow ranging anywhere from 40% to 90%.[9,11-14] Additionally, there have been few attempts to compare functional outcomes among primary vs salvage groups. Gadepalli et al[7] found prior radiation to have no effect on subsequent postoperative functional outcomes. Given the paucity of studies and variability of data currently available, more clarity is needed regarding factors that impact functional outcomes following surgical intervention for laryngeal and hypopharyngeal tumors.

Finally, salvage operations are considered more technically challenging than their respective primary interventions, yet complication rates have not consistently shown to be increased within salvage groups.[12,15] Pharyngocutaneous fistula (PCF) is a well-studied complication in this setting, with an overall incidence of approximately 15%-35%.[12,16] Prior radiation therapy (XRT) has been associated with an increased risk for PCF in some series[16] but not in others.[12,15] Significant attention has been given to various closure techniques and their effect on PCF formation. Certain studies have demonstrated lower PCF rates in the salvage setting with the use of pectoralis major coverage[17] or free tissue grafts,[18] whereas others have shown similar[19] or even increased[15] rates of PCF with these coverage techniques in comparison to primary closure. Thus, further data are needed to provide additional insight into the effects that salvage status and closure technique have on the development of PCF.

In the present retrospective study, we describe the clinical and functional outcomes in a large surgical patient population of laryngeal and hypopharyngeal SCC within a single institution. Our main objectives are to stratify outcomes by tumor subsite, salvage status, and extent of surgical resection. We also provide an analysis of risk factors for PCF and investigate whether tissue coverage offers a protective effect for preventing PCF formation. By providing this needed narrative, we aim to allow for more accurate patient counseling in regard to appropriate clinical and functional expectations as patients navigate decision making between available treatment regimens.

2 | PATIENTS AND METHODS

2.1 | Patients and data collection

Retrospective chart review was performed on all patients with supraglottic, glottic, or hypopharyngeal SCC who underwent definitive surgical intervention at our institution between the years 2009 and 2016. Any of four institutional surgeons performed all operations. Institutional Review Board approval was obtained at the initiation of the study. Exclusionary criteria included: age <21 or >90, prior surgical intervention to the primary tumor site (eg, transoral laser microsurgery), prior history of head and neck cancer, synchronous or metachronous tumors, prior history of radiation to the head and neck for non-SCC cancers, non-oncologic (functional) resections, and patients lost to follow-up prior to 12 months for reasons other than mortality. Demographic information, clinical history, and details of surgical interventions were obtained from review of institutional electronic medical records. Patients were stratified into primary vs salvage surgical intervention. None of the patients received only chemotherapy prior to surgical intervention. TNM classification was identified at the time of initial diagnosis. For primary tumors with extension across multiple subsites (eg, hypopharyngeal primary with extension to glottis), tumor epicenter as determined by the operating surgeon was used for subsite classification. Surgical resections were classified into three categories: TL, PLP, or TLP. PLP was defined as a subtotal pharyngeal resection with a remaining native mucosal connection between resection margins. TLP was defined as a complete circumferential pharyngeal defect between resection margins. Reconstructions were classified as following: primary closure, pec overlay, patched ALT or RFFF microvascular reconstruction, tubed ALT or RFFF microvascular reconstruction, and jejunal free tissue transfer with microvascular reconstruction. Postoperative complications were compiled by reviewing inpatient records during the initial hospital stay as well as any subsequent admissions. Tracked complications included wound infection, PCF, flap loss, and carotid blowout. Smoking status was determined by review of clinical records; anyone with a prior smoking history and associated pack years was grouped as having a smoking history.

2.2 | Survival analysis

Patients were stratified into the following survival categories: no evidence of disease, alive with disease, or mortality (dead of disease or death from other causes). Date of surgical intervention served as the initial time point for survival calculations. Estimated 3-year OS (3y OS) and 5-y OS was calculated using MedCalc software (Ostend, Belgium) and its associated Kaplan-Meier survival analysis.

2.3 | Functional outcomes

Speech modalities were stratified into the following groups: none, tracheoesophageal voice prosthesis (TEP), electrolarynx (EL), or esophageal speech. For patients utilizing multiple modalities, the primary method at the time of most recent assessment was used for analysis. Regardless of speech method, patients were characterized as intelligible or unintelligible. Intelligibility of speech was at the discretion of the treating head and neck surgeon and classification at the time of most recent clinical assessment was used. Patients using any form of speech in an unintelligible fashion or those who did not use any voicing method were considered unintelligible. Dietary status was stratified into the following groups: full *per os* (PO), partial PO, or gastrostomy-tube (G-tube) dependent. We did not differentiate between dietary consistencies for patients taking full PO diets due to lack of sufficient data on our retrospective intake. Dietary status at the time of most recent clinical follow-up was used for functional classification.

2.4 | Statistical analysis

Survival statistics were calculated using Kaplan-Meier survival analysis as described above. Descriptive statistics were used for calculating demographic information. For comparison of means among three groups, one-way analysis of variance (ANOVA) was used with an alpha of .05. When necessary, post hoc Student's *t* test was used for direct comparisons between two groups using an alpha of .05. For analyses involving binary outcomes (eg, TEP usage), a chi-square test of independence was used to determine intergroup differences with post hoc direct group comparisons when differences were present. Statistical significance was defined as $P < .05$ for all analyses.

TABLE 1 Patient and disease characteristics

Demographics	Frequency
Sex (n = 107)	No. (%)
Men	85 (79.4)
Women	22 (20.6)
Age at surgery (y)	
Mean	62.4
Range	43-82
Tumor subsite	
Glottis	37 (34.6)
Supraglottis	48 (44.9)
Hypopharynx	22 (20.5)
Prior treatment	
XRT	22 (20.5)
CRT	45 (42.1)
None	40 (37.4)
Surgical intervention	
Salvage	67 (62.6)
Primary	40 (37.4)
T classification at diagnosis	
T1	8 (7.5)
T2	7 (6.5)
T3	34 (31.8)
T4	58 (54.2)
N classification at diagnosis	
N0	60 (56.1)
N1	12 (11.2)
N2	33 (30.8)
N3	2 (1.9)
Overall stage at diagnosis	
Stage I	7 (6.5)
Stage II	6 (5.6)
Stage III	24 (22.4)
Stage IV	70 (65.4)

Abbreviations: CRT, chemoradiation therapy; XRT, radiation therapy.

3 | RESULTS

3.1 | Patient demographics and treatment overview

A total of 107 patients met inclusion criteria (Table 1). Median follow-up for the entire group was 28.8 months. The most frequent tumor subsite was the supraglottis (44.9%). The majority of cases were salvage operations (62.6%), with 20.5% of patients receiving prior XRT and 44.9% receiving prior chemoradiation therapy (CRT). The majority of patients had advanced tumors (86%), defined as either T3 (31.8%) or T4 (54.2%). Overall, 87.8% of patients had either stage III (22.4%) or stage IV (65.4%) disease.

3.2 | Tumor subsite analysis

Patients were stratified based upon primary tumor subsite (Table 2). There were intergroup differences present for both prior XRT ($X^2(2,107) = 10.44$, $P = .005$) and CRT ($X^2(2,107) = 6.51$, $P = .04$). Patients with glottic primaries

TABLE 2 Tumor subsite variables and outcomes

	Glottis (n = 37)	Supraglottis (n = 48)	Hypopharynx (n = 22)	*P* value
Mean age (y)	63.1	60.0	66.5	.43
Treatment (TX)	No. (%)			
Prior XRT	14 (37.8)	6 (12.5)	2 (9.1)	**.005**
Prior CRT	11 (29.7)	20 (41.7)	14 (63.6)	**.04**
No prior TX	12 (32.4)	22 (45.8)	6 (27.3)	.34
Adjuvant XRT	10 (27.0)	7 (14.6)	6 (27.3)	.29
Adjuvant CRT	8 (21.6)	23 (47.9)	8 (36.4)	**.04**
No adjuvant TX	19 (51.4)	18 (37.5)	8 (36.4)	.32
No prior or adjuvant TX	1 (2.7)	0	0	.75
Both prior + adjuvant TX	7 (18.9)	8 (16.7)	8 (36.4)	.16
Surgical intervention				
Salvage	25 (67.6)	26 (54.2)	16 (72.7)	.34
Primary	12 (32.4)	22 (45.8)	6 (27.3)	.34
TL	35 (94.6)	39 (81.3)	7 (31.8)	**<.001**
PLP	0	5 (10.4)	2 (9.1)	.14
TLP	2 (5.4)	4 (8.3)	13 (59.1)	**<.001**
T stage at diagnosis				
T1	4 (10.8)	1 (2.1)	3 (13.6)	
T2	3 (8.1)	3 (6.3)	1 (4.5)	
T3	10 (27.0)	17 (35.4)	7 (31.8)	
T4	20 (54.1)	27 (56.2)	11 (50)	
Average	3.2	3.5	3.2	.62
Overall stage at diagnosis				
Stage I	4 (10.8)	1 (2.1)	2 (9.1)	
Stage II	3 (8.1)	2 (4.2)	1 (4.5)	
Stage III	8 (21.6)	13 (27.1)	3 (13.6)	
Stage IV	22 (59.5)	32 (66.7)	16 (72.7)	
Average	3.3	3.6	3.5	.63
Dietary outcomes				
Total G-tube dependence	11 (29.7)	17 (35.4)	12 (54.5)	.15
Partial PO diet	14 (37.8)	15 (31.3)	9 (40.9)	.69
Full PO diet	12 (32.4)	16 (33.3)	1 (4.5)	**.03**
Average time to full PO diet (mo)	5.8	7.8	9	.29
Speech outcomes				
TEP	27 (73.0)	40 (83.3)	6 (27.3)	**<.001**
EL	7 (18.9)	6 (12.5)	1 (4.5)	.28
Esophageal	1 (2.7)	0	1 (4.5)	.38
Unintelligible	2 (5.4)	2 (4.2)	14 (63.6)	**<.001**
Clinical outcomes				
Average OS (mo)	55.5	58.8	47.9	.62
Average LRC (mo)	36.6	34.0	31.2	.77

(Continues)

TABLE 2 (Continued)

	Glottis (n = 37)	Supraglottis (n = 48)	Hypopharynx (n = 22)	*P* value
3y OS (%)	60.6	59.4	44.4	NS[a]
5y OS (%)	56.6	51.4	44.4	NS[a]

Note. Included *P* values represent those for intergroup differences; those for two group comparisons are included in the text.
Abbreviations: CRT, chemoradiation therapy; EL, electrolarynx; LRC, locoregional control; NS, not significant; OS, overall survival; PLP, partial laryngopharyngectomy; TEP, tracheoesophageal puncture; TL, total laryngectomy; TLP, total laryngopharyngectomy; XRT, radiation therapy.
[a]Refers to text for 95% confidence interval.
Bold font was meant to emphasize *p*-values that represented statistical significance ($p < 0.05$).

were more likely to receive prior XRT ($P = .007$ vs supraglottic; $P = .02$ vs hypopharyngeal), whereas hypopharyngeal primaries were more likely to receive prior CRT compared to the glottic ($P = .01$) but not supraglottic ($P = .09$) groups. Differences in salvage rates were not statistically significant across all groups. There was an intergroup difference among patients receiving adjuvant CRT ($X^2(2,107) = 6.24$, $P = .04$), with supraglottic patients more likely to receive adjuvant CRT relative to glottic patients ($P = .01$). The proportion of patients receiving both prior and adjuvant therapy was highest in the hypopharyngeal group (36.4%) and nearly twice that of the other subsites, but this difference did not reach statistical significance ($P = .16$).

A summary of functional outcomes by subsite is displayed in the lower portion of Table 2. Hypopharyngeal patients had the highest rate of G-tube dependence (54.5%) but the intergroup difference was not statistically significant ($P = .15$). There was a significant intergroup difference for rates of full PO diet ($X^2(2,107) = 7.14$, $P = .03$) with hypopharyngeal patients significantly less likely to resume a full PO diet (4.5%) relative to the glottic ($P = .01$) and supraglottic ($P = .01$) groups. Hypopharyngeal patients were significantly less likely to achieve intelligible TEP usage and significantly more likely to be unintelligible relative to their glottic and supraglottic peers ($P < .001$ for all four direct comparisons). Survival data by subsite are also summarized in Table 2 and depicted in Figure 1A. Differences in both estimated OS and locoregional control between the three subsites did not reach statistical significance.

3.3 | Outcomes by salvage status

Table 3 summarizes functional and clinical outcomes by salvage status. Patients undergoing surgical salvage were more likely to be G-tube dependent and less likely to achieve a full PO diet compared to patients undergoing primary surgical intervention. Survival data for the two groups are described in Table 3 and displayed in Figure 1B. Estimated OS between the two groups were not statistically significant (mean OS [$P = .08$]: 65.4 months [95% CI, 52.5-78.4] for primary group vs 49.3 months [95% CI, 39.1-59.4] for salvage group). There was a statistically significant difference in estimated 3y OS but not at 5 years (3y OS [$P < .05$]: 74.6% [95% CI, 60.0%-89.1%] in the primary group vs 47.0% [95% CI, 34.8%-59.3%] in the salvage group; 5y OS: 60.1% [95% CI, 41.1%-79.0%] in the primary group vs 47.0% [95% CI, 34.8%-59.3%] in the salvage group).

To investigate the relative temporal effects of XRT on functional outcomes, subgroup analyses were performed comparing patients who received preoperative radiation (n = 44), postoperative radiation (n = 39), or both (n = 23). There was a statistically significant intergroup difference in rates of G-tube dependence ($X^2(2,106) = 24.40$, $P < .001$); patients who received both preoperative and postoperative XRT displayed the highest rates of G-tube dependence (78.3%; all intergroup comparisons: $P < .03$). Similarly,

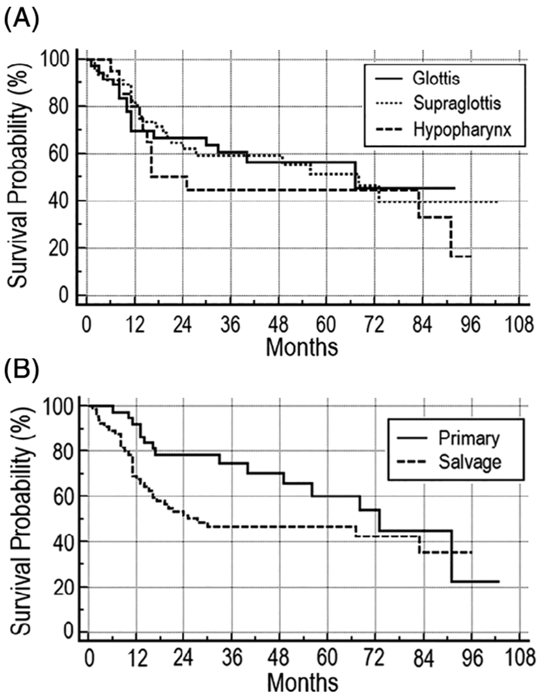

FIGURE 1 Survival outcomes. A, Overall survival (OS) data among subsite subgroups. OS not significantly different ($P = .62$). Please refer to Table 3 for 3-year and 5-year survival data. B, OS data among primary vs salvage interventions. OS not significantly different ($P = .08$). Please refer to Table 4 for 3-year and 5-year survival data

TABLE 3 Clinical and functional outcomes by salvage status

Outcomes	Primary surgery (n = 40)	Salvage surgery (n = 67)	*P* value
Dietary outcomes	No. (%)		
Total G-tube dependence	6 (15.0)	34 (50.7)	**<.001**
Partial PO diet	15 (37.5)	23 (34.3)	.74
Full PO diet	19 (47.5)	10 (14.9)	**<.001**
Average time to full PO diet (mo)	6.7	9.2	.48
Speech outcomes			
TEP	30 (75.0)	43 (64.2)	.29
Unintelligible	5 (12.5)	13 (19.4)	.36
Clinical outcomes			
Average OS (mo)	65.4	49.3	.08
3y OS (%)	74.6	47.0	**<.05**
5y OS (%)	60.1	47.0	NS[a]

Abbreviations: NS, not significant; OS, overall survival; TEP, tracheoesophageal puncture.
[a]Refers to text for 95% confidence interval.
Bold font was meant to emphasize *p*-values that represented statistical significance ($p < 0.05$).

rates of attaining a full PO diet were significantly different across groups ($X^2(2,106) = 16.14$, $P < .001$), with the postoperative therapy group exhibiting the highest rates (48.7%; comparisons between the postoperative and other groups: $P < .007$). There was also a significant intergroup difference in rates of unintelligibility ($X^2(2,106) = 15.16$, $P < .001$), with the preoperative and postoperative therapy group displaying higher rates (43.5%) than the preoperative therapy (6.8%, $P < .001$) and postoperative therapy (12.8%, $P = .007$) groups. Differences between the preoperative and postoperative therapy groups were not statistically significant ($P = .36$).

3.4 | Outcomes by surgical intervention

Patients were stratified by surgical intervention and closure/reconstruction types (Table 4). Complication rates were not significantly different across groups. The overall fistula rate across the entire study was 22.4%. Patients within the TLP group were less likely to achieve a full PO diet relative to the TL and PLP groups ($X^2(2,107) = 6.05$, $P = .05$; TLP vs TL: $P = .02$; TLP vs PLP: $P = .02$) and more likely to be G-tube dependent relative to the TL group ($X^2(2,107) = 6.95$, $P = .03$; TLP vs TL: $P = .009$). The TLP group was less likely to attain intelligible TEP usage relative to the TL group ($X^2(2,107) = 15.57$, $P < .001$; TLP vs TL: $P < .001$), whereas both the TLP and PLP groups were less likely to obtain any intelligible speech method relative to the TL group ($X^2(2,107) = 34.47$, $P < .001$; TLP vs TL: $P < 0.001$; PLP vs TL: $P < .001$). To determine whether type of surgical intervention had an effect on functional outcomes within the hypopharyngeal subsite group (data not shown), speech and dietary outcomes were compared between hypopharyngeal patients undergoing TLP (13 of 22) vs those who did not (9 of 22). There was not a significant difference in G-tube dependence (TLP: 61.5%, TL/PLP: 44.4%; $P = .44$), full PO diet (TLP: 8.3%, TL/PLP: 0%; $P = .41$), or rates of unintelligibility (TLP: 76.9%, TL/PLP: 44.4%; $P = .12$).

Twenty-one patients underwent subtotal ($n = 2$) or total ($n = 19$) circumferential pharyngeal free flap reconstruction. The vast majority of these cases (16 of 21) were salvage. The most commonly used reconstruction was the tubed ALT (16 of 21) followed by tubed RFFF (3 of 21) and jejunum (2 of 21). In all, 33.3% of patients resumed some form of PO diet (tubed ALT: 4 of 16; tubed RFFF: 1 of 3; jejunum: all of 2). TEP usage rates were 33% across the entire subgroup (tubed ALT: 3 of 16; tubed RFFF: all of 3; jejunum: 1 of 2); 7 of 8 patients who underwent TEP placement used it intelligibly.

3.5 | Risk factors for PCF and effects of tissue coverage

Across the entire study, 24 of 107 patients (22.4%) developed PCFs postoperatively. Subgroup analyses were carried out as shown in Table 5. The fistula rate among salvage cases (29.9%) was three times greater than the rate among primary surgical interventions (10.0%; $X^2(1,107) = 5.62$, $P = .02$). Group comparisons are visually depicted in Figure 2.

Subgroup comparisons were made to determine whether the utilization of tissue coverage (either pec overlay or free tissue transfer) conferred any protective benefit against PCF formation in TL patients. A 34.6% of all TL repairs utilized tissue coverage (28 of 81). As previously shown in Table 4, 22 of 28 of these repairs utilized pec overlay whereas 6 of 28 used either patch RFFF or ALT free flaps. To determine whether the tissue coverage group was biased toward containing patients more at risk to develop PCF, we compared the rates of smokers and previously radiated patients between the two groups. Both groups had >90% smokers ($P = .73$), and although there was a higher proportion of previously radiated patients within the tissue coverage group (71.4% vs 50.9%), this difference did not reach statistical significance ($P = .07$). The overall fistula rate within the entire TL cohort was not significantly different between patients who did (14.2%) and did not (22.6%) receive tissue coverage ($P = .37$). However, when comparing fistula rates only among those exposed to prior radiation, those receiving tissue coverage were nearly four times less likely to develop PCF (10.0% vs 37.0%; $X^2(1,47) = 4.32$, $P = .04$).

TABLE 4 Surgical intervention: variables and outcomes

Variables/outcomes	Overall (n = 107)	TL (n = 81)	PLP (n = 7)	TLP (n = 19)	*P* value
Tumor subsite	No. (%)				
Glottis	37 (34.6)	35 (43.2)	-	2 (10.5)	**<.005**
Supraglottis	48 (44.9)	39 (48.1)	5 (71.4)	4 (21.1)	**.04**
Hypopharynx	22 (20.5)	7 (8.6)	2 (28.6)	13 (68.4)	**<.001**
Mean age (y)	62.4	61.8	63.4	64.3	.74
Surgical intervention					
Primary	67 (62.6)	34 (42.0)	2 (28.6)	4 (21.1)	.21
Salvage	40 (37.4)	47 (58.0)	5 (71.4)	15 (78.9)	.21
Repair type					
Primary closure	56 (52.3)	53 (65.4)	3 (42.9)	-	
Pec overlay	26 (24.3)	22 (27.2)	2 (28.6)	2 (10.5)[a]	
Free flap	27 (25.2)	6 (7.4)	2 (28.6)	19 (100)	
Patched RFFF	5/27	5/6	-	-	
Patched ALT	1/27	1/6	-	-	
Tubed RFFF	3/27	-	-	3/19	
Tubed ALT	16/27	-	2/2	14/19	
Jejunum	2/27	-	-	2/19	
Complication rates					
Total complications	36 (33.6)	25 (30.9)	3 (42.9)	8 (42.1)	.56
Fistula	24 (22.4)	16 (19.8)	2 (28.6)	6 (31.6)	.41
Infection	15 (14.0)	12 (14.8)	2 (28.6)	1 (5.3)	.29
Carotid blowout	3 (2.8)	2 (2.5)	-	1 (5.3)	.72
Flap loss	1/27 (3.7)	1/6	0/2	0/19	
Outcomes					
Median LOS (d)	9	8	8	12	.43
Any PO diet	67 (62.6)	56 (69.1)	4 (57.1)	7 (36.8)	**.03**
Full PO diet	29 (27.1)	25 (30.9)	3 (42.9)	1 (5.3)	**.05**
Partial PO diet	38 (35.5)	31 (38.3)	1 (14.3)	6 (31.6)	.41
G-tube dependent	40 (37.4)	25 (30.9)	3 (42.9)	12 (63.2)	**.03**
TEP	73 (68.2)	63 (77.8)	4 (57.1)	6 (31.6)	**<.001**
Any intelligible speech	89 (83.2)	77 (95.1)	4 (57.1)	8 (42.1)	**<.001**

Note. Included *P* values represent those for intergroup differences; those for two group comparisons are included in the text.

Abbreviations: ALT, anterolateral thigh; PLP, partial laryngopharyngectomy; RFFF, radial forearm free flap; TEP, tracheoesophageal puncture; TL, total laryngectomy; TLP, total laryngopharyngectomy.

[a]Both pec overlays in TLP group were used in conjunction with free flap reconstruction. Note that the summation of individual complication rates is greater than total complication rate as several patients had multiple complications. Bold font was meant to emphasize *p*-values that represented statistical significance ($p < 0.05$).

4 | DISCUSSION

4.1 | Functional outcomes by tumor subsite and surgical intervention

Gadepalli et al[7] previously found that surgical patients with hypopharyngeal primaries had significantly worse objective speech outcomes relative to those with laryngeal primaries, whereas differences in dietary outcomes were not significant. The authors acknowledge that this is largely a result of hypopharyngeal patients receiving total or sub-TLP more often than their laryngeal counterparts, with TLP patients having worse speech and dietary outcomes relative to the TL and PLP group. Similarly, Mahalingam et al[8] found that patients undergoing TLP had significantly worse objective

TABLE 5 Risk factors for pharyngocutaneous fistula

Risk factors	Fistula	No fistula	P value
	No. (%)		
Overall	24/107 (22.4)	83/107 (77.6)	
Prior XRT or CRT	20/67 (29.9)	47/67 (70.1)	**.02**[a]
XRT	7/22 (31.8)	15/22 (68.2)	**.03**[b]
CRT	13/45 (28.9)	32/45 (71.1)	**.03**[c]
No prior XRT or CRT	4/40 (10.0)	36/40 (90.0)	
Diabetes mellitus			
Yes	6/23 (26.1)	17/23 (73.9)	.55[d]
No	17/83 (20.5)	66/83 (79.5)	
Smoking history			
Yes	24/98 (24.5)	74/98 (75.5)	.09[e]
No	0/9	9/9 (100.0)	
Average pack years	40.2	40.3	.99
Bilateral neck dissection			
Yes	19/80 (23.8)	61/80 (76.3)	.50[f]
No	5/27 (18.5)	22/27 (81.5)	

Abbreviations: CRT, chemoradiation therapy; XRT, radiation therapy.
[a]Comparing prior XRT or CRT group vs no prior CRT or XRT group.
[b]Comparing prior XRT group to no prior CRT or XRT group.
[c]Comparing prior CRT group to no prior CRT or XRT group.
[d]Comparing diabetic vs non-diabetic groups.
[e]Comparing smokers vs non-smokers.
[f]Comparing bilateral neck dissection group to unilateral neck dissection group.
Bold font was meant to emphasize *p*-values that represented statistical significance ($p < 0.05$).

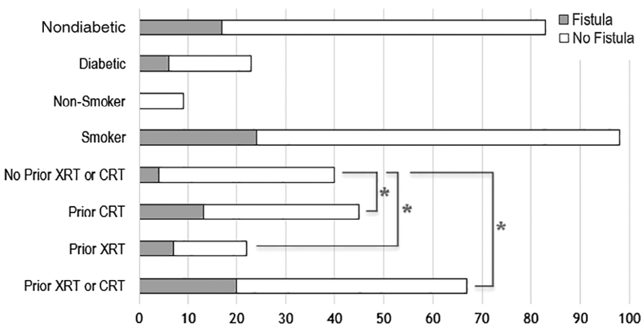

FIGURE 2 Comparison of risk factors for pharyngocutaneous fistula. *X*-axis denotes total number of patients within each subgroup. CRT, chemoradiation therapy; XRT, radiation therapy. *$P < .05$ between two subgroups denoted by respective brackets

speech and dietary outcomes compared to their TL peers. Conversely, Ward et al[9] compared dietary outcomes among TL and TLP cohorts and found similar rates of PO intake 3 years postoperatively.

Our present data demonstrate significantly worse speech and dietary outcomes in patients with hypopharyngeal primaries. This differs slightly from prior studies showing only inferior speech outcomes.[7] TLP patients were similarly found to have worse speech and dietary outcomes relative to the TL group which is congruent with prior reports[7,8] but differs from the dietary outcomes reported by Ward et al.[9] As expected, hypopharyngeal patients had the highest TLP rate (59%), and 68% patients in the TLP group were from the hypopharyngeal subgroup. When comparing functional outcomes among hypopharyngeal patients who underwent TLP vs those who did not, there was not a significant difference in speech or dietary outcomes which suggests that the extent of surgical intervention alone does not explain the poorer outcomes seen in our hypopharyngeal group. However, the relatively few patients in each of these subgroups may have limited our ability to detect a true difference between these conditions. The hypopharyngeal subsite also exhibited the highest proportion of salvage cases (72.7%) and the highest rate of patients who received both preoperative and postoperative radiations (36.4%). Our findings that both salvage status and the combination of preoperative and postoperative radiations were associated with worse dietary outcomes may partly explain the predisposition for hypopharyngeal patients to exhibit poorer functional outcomes. Conversely, the fewer number of patients undergoing TLP and receiving both preoperative and postoperative radiations in the glottic and supraglottic groups likely explains the better functional outcomes seen in these subsites relative to hypopharyngeal patients. Possible mechanisms underlying these findings include fibrosis and loss of sensory feedback to muscles of deglutition seen with additive radiation, as well as scarring and stenosis at the pharyngoesophageal anastomosis following TLP.

4.2 | Functional outcomes by salvage status

Few studies have attempted to investigate the effects of prior XRT on functional outcomes in laryngeal and hypopharyngeal SCC patients undergoing surgical intervention. Gadepalli et al[7] did not find a significant difference in postoperative functional outcomes when stratifying by salvage status. However, the authors acknowledged that their laryngopharyngectomy group had a relatively low proportion of salvage patients (20%). Clark et al did not find a difference in G-tube dependency rates among salvage (18%) and primary (15%) surgical patients.[20] In our present study, the overall proportion of salvage interventions was 62.6%. Patients undergoing salvage intervention had a significantly higher rate of postoperative G-tube dependence (50.7% vs 15.0%) and lower attainment of a full PO diet (14.9% vs 47.5%) relative to primary surgical interventions. Interestingly, speech outcomes between the two groups were similar with respect to both TEP utilization and rates of unintelligibility. Thus, our results contradict previous reports[7,20] by demonstrating worse dietary outcomes in the salvage group while also establishing that speech outcomes are conversely unaffected by salvage status. A high proportion of salvage cases in our current study compared to those above may explain these contradictory findings, as well as a relatively high rate of patients receiving both preoperative and postoperative XRT. Although we did not specifically analyze rates of pharyngeal/esophageal stricture, we expect this postradiation phenomenon to account for the worse dietary outcomes in salvage cases while being less detrimental to speech outcomes.

The subgroup of patients in our study who were exposed to both preoperative and postoperative XRT (21.5%) had significantly worse functional outcomes than those exposed to only one condition, whereas patients receiving only postoperative radiation had superior swallowing outcomes and equivalent speech outcomes relative to the preoperative radiation group. These findings differ from those provided by de Casso et al[21] who did not find functional differences between TL patients receiving preoperative vs postoperative radiation. Due to a limited number of patients in these subgroups, we were unable to stratify the effect of additive radiation by tumor subsite. Our findings that salvage status is associated with worse dietary outcomes should raise caution when interpreting functional outcomes in the literature, as salvage rates often vary greatly across studies. Ultimately, further work is needed to compare functional outcomes among patients undergoing organ-preservation therapy and those receiving primary surgical intervention. Given the high rates of surgical salvage in advanced laryngeal and hypopharyngeal tumors treated initially with organ-preservation therapy,[4,5] coupled with our findings that salvage status portends worse functional outcomes, future comparisons of initial CRT vs primary surgical intervention will help elucidate whether any functional deficit is seen in patients receiving up-front surgery.

4.3 | Survival outcomes

We did not find a statistically significant difference in average OS or estimated 3y OS and 5y OS rates in our subsite analysis. However, these numbers are similar to previously published reports[1,2] and likely represent the higher end of the spectra for subsite survival data given that our patient population excluded CRT failures who did not receive salvage intervention. We also did not find a significant difference in average OS between salvage (49.3 months) and primary (65.4 months) surgical groups, although the observed difference could be considered clinically significant. An inherent bias in these calculations is the consideration of surgical intervention as time zero, as the initial timeframe of diagnosis among salvage patients was not uniformly available on our retrospective review. This again highlights the need for future studies prospectively evaluating patients in organ preservation and primary surgical arms.

4.4 | Functional outcomes following pharyngeal reconstruction

Rates of successful speech and swallowing rehabilitation following subtotal or total circumferential pharyngeal reconstruction are widely variable in the literature. Most studies report success rates in the 40%-90% range, but comparisons across studies are limited by varying outcome definitions as well as utilization of different reconstructive options. In a cohort of 27 patients with circumferential pharyngeal defects repaired with tubed ALTs, Lewin et al[13] report successful TEP usage in 8 of 9 who underwent TEP placement and a return to PO diet in 90%. In a series of 114 patients undergoing ALT reconstruction after TLP or PLP, Yu et al[22] reported successful TEP utilization in 41% of those undergoing primary TEP and 81% of those undergoing secondary TEP, whereas 91% of patients were able to return to a PO diet. van der Putten et al[11] demonstrated a 38% TEP utilization rate and an 80% return to PO diet in a series of 136 patients with total or subtotal pharyngeal defects. The wide variation in success rates is likely attributable to pooling of TLP and PLP patients, surgeon and rehabilitative staff experience, incorporation of G-tube use into dietary stratification, and exclusionary criteria within the surgical cohorts.

In our series, 21 patients underwent free flap reconstruction for total or subtotal circumferential pharyngeal defects. Overall, 33% were able to resume some form of PO diet. Thirty-three percent used TEP for phonation whereas 57% remained unintelligible at the last clinical follow-up. Seven of 8 patients who underwent TEP placement were able to use it intelligibly. Our subgroup population was not large enough to make statistical comparisons across circumferential reconstructive techniques. Our speech and swallow outcomes are slightly inferior to those referenced above, likely in part due to the relatively higher proportion of patients undergoing salvage intervention. Given our findings that both the salvage condition and the combination of preoperative and postoperative XRT were associated with significantly worse functional outcomes, the high proportion of such patients within our circumferential repair subgroup may in part explain their outcomes. Prior studies have demonstrated high success rates in patients who ultimately undergo TEP placement.[13,22] The relatively low TEP placement rates in our cohort is likely due to prior radiation status serving as an historical barrier to TEP candidacy. Recent reports have shown the suitability of TEP placement in previously radiated patients,[23] however, and this has been less of a perceived barrier at our institution in recent years.

4.5 | Risk factors and prevention of PCFs

Development of PCF is a well-studied phenomenon following TL and laryngopharyngectomy. Most studies describe PCF rates in the range of 15%-35%, although some series have reported rates as high as 50%.[12,16,24] Preoperative XRT has been demonstrated by some authors to increase the risk for PCF[16,25] whereas others have suggested that the addition of chemotherapy to preoperative radiation further increases risk.[24] Other studies have not shown salvage status to impact the risk for PCF.[12] Our overall fistula rate in the present study was 22.4%. Patients undergoing preoperative XRT had a higher fistula rate compared to those who did not (29.9% vs 10.0%). Neither the addition of preoperative chemotherapy nor the presence of diabetes increased the risk for fistula.

Several authors have demonstrated that the use of either pec overlay or free tissue transfer results in a decreased incidence of PCF. Withrow et al[18] reported lower PCF rates in salvage laryngectomy patients receiving free flap coverage compared to those undergoing primary closure (18% vs 50%). Patel et al[17] found decreased fistula rates with the use of either free tissue transfer (25%) or pec overlay (15%) compared to primary closure (34%). Conversely, Benson et al[15] found increased fistula rates in patients receiving pec overlay coverage (25%) compared to primary closure (11%), but this difference was not significant. Chepeha et al[26] recently demonstrated reduced fistula rates in hypopharyngeal closures with the use of vascularized tissue augmentation. However, the use of muscle in this augmentation seemingly had a negative impact on postoperative functional outcomes. When we stratified previously radiated patients undergoing TL into those who did and did not receive tissue coverage, we found nearly a four times lower fistula rate in those receiving tissue coverage. In fact, with the use of tissue coverage in radiated patients, the fistula rate was equivalent to those without preoperative radiation exposure (Table 5, 10%). Thus, our findings strongly support the use of tissue coverage (either pec overlay or free tissue transfer) in salvage cases. Our data set did not contain enough free flap patients within the TL group (n = 6) to draw comparisons of protective effects relative to pec overlay.

4.6 | Limitations

Our study was subject to several limitations. Functional assessment of speech and dietary outcomes was at the discretion of the attending surgeon and thus subjective. Stratification of dietary consistencies and incorporation of objective data such as modified barium studies or formal speech pathologist assessments would have allowed for more uniform and descript functional assessments but would not have been uniform across patients. Baseline assessment of functional performance in both the salvage and primary surgical groups (eg, preoperative G-tube dependence) would have allowed for more controlled postoperative assessments but these data were not uniformly accessible within our retrospective review. Although we tracked overall TEP placement in our circumferential repair cohort, we only monitored successful TEP usage in the remainder of the study and thus did not have an accurate assessment of patients who may have had remote TEP placement; these patients would have been classified as unintelligible if they did not demonstrate intelligible speech with any method at the time of most recent clinical follow-up.

5 | CONCLUSIONS

The stratification of patients by subsite, salvage status, and surgical intervention allowed for an in-depth analysis of factors contributing to postoperative clinical and functional outcomes in patients undergoing TL or laryngopharyngectomy. To the best of our knowledge, this study is the first to associate the hypopharyngeal subsite with both inferior speech and swallow outcomes and the first to demonstrate inferior dietary outcomes in salvage cases. Our data also provide further evidence that salvage cases are associated with increased rates of PCF and support the use of tissue coverage in salvage cases. The circumferential repair subgroup had relatively low functional outcomes compared to previously published data, which may in part be explained by the high salvage rates. Given the functional deficit seen with salvage cases in our present study, further prospective work is needed to compare functional outcomes between patients undergoing organ-preservation therapy and those undergoing primary surgical intervention. Such work will clarify whether up-front surgery confers long-term functional disadvantages relative to nonsurgical patients, particularly those with hypopharyngeal primaries who may be more predisposed to inferior functional outcomes. Additionally, the incorporation of subjective perception of functional outcomes into future prospective analyses will provide useful information in regard to therapeutic comparisons and patient counseling.

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