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Pectoralis Major Myofascial Onlay and Myocutaneous Flaps and Pharyngocutaneous Fistula in Salvage Laryngectomy

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Abstract

Objective—To review the fistula rate in irradiated patients undergoing salvage laryngectomy, compare the effect of closure type on fistula rate, and examine possible perioperative risk factors that might contribute to an increased fistula rate.

Study Design—Case series with chart review.

Methods—We conducted a retrospective review of the University of Pittsburgh head and neck tumor registry and identified 73 patients from 1998 to 2011 who had received prior radiation before total laryngectomy or salvage laryngectomy and who had either primary closure, pectoralis major myofascial flap (PMMF) onlay, or pectoralis major myocutaneous flap (PMMC).

Results—Fistula was more common in patients who underwent initial primary closure (45%) than in patients who had immediate PMMF onlay (10.5%). The fistula rate for patients who underwent immediate PMMC flap was 28.6%, intermediate to primary closure and PMMF flap. Several factors were evaluated for relationship to fistula, but no significant associations were identified. However, patients with fistula tended to have longer inpatient stays and may have been more likely to have a history of cardiovascular or hypoxic disease.

Conclusion—Pharyngocutaneous fistula is a well-established complication of total laryngectomy, and it is especially a concern in patients with a previous history of radiation. Our retrospective review demonstrates pectoralis major myofascial onlay flap appears to be more effective in reducing the rate of fistula compared to primary closure in these patients. Myocutaneous augmentation flaps, in contrast, have a fairly high fistula rate and may be better replaced with alternative closures such as free flaps.

Keywords

laryngeal cancer; radiation; head and neck cancer; fistula; pectoralis major flap

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Introduction

Laryngeal cancer will affect over 12,000 new patients in the United States each year, with an estimated overall prevalence of approximately 89,142 Americans in 2009, and a five-year survival rate of 60.5%.¹ Ever since the landmark Veterans Affairs Laryngeal Cancer Study Group showed that the tumor response rate for chemoradiation alone was equivalent to surgery with adjuvant radiation², total laryngectomy has fallen out of favor as an initial management strategy. This change has led to an increasing number of patients undergoing salvage total laryngectomy whose prior radiation exposure predisposes them to complications after the surgery.

One of the most common complications of total laryngectomy is pharyngocutaneous fistula, and management strategies for its resolution have long been discussed.³ Various techniques have been proposed to reduce the risk of fistula.^{4,5} Pectoralis major myofascial (PMMF) and myocutaneous (PMMC) flaps are two of the standard techniques for reconstruction of head and neck defects.⁶ It has been proposed that patients who are at high risk for pharyngocutaneous fistula should have pectoralis major myofascial flap onlayed on the pharyngeal closure at the time of the salvage laryngectomy to minimize the risk of fistula.⁷⁻⁹ However, the utility of PMMF onlay and PMMC flaps in reducing the rate of pharyngocutaneous fistula following salvage laryngectomy is not fully established.^{7,10-12} It would be helpful to know if operative techniques such as the use of pectoralis major flap can decrease the fistula rate in this population compared to primary closure, and if there are other risk factors that can guide surgical management.

The aim of our study is to review the fistula rate in previously irradiated patients undergoing salvage laryngectomy, compare the effect of closure type on fistula rate, and examine possible pre- or perioperative risk factors that might contribute to an increased fistula rate.

Materials and Methods

This study was approved by the University of Pittsburgh Institutional Review Board. A retrospective review of the University of Pittsburgh head and neck tumor registry revealed 540 patients who received laryngectomies (all types) between 1998 and 2011. We queried this cohort for patients who had had received prior radiation before total laryngectomy or salvage laryngectomy. We also reviewed clinical notes, operative reports, pathology reports, and radiation records. Some patients only presented to our facilities for their recurrences, and in those cases some information regarding the initial laryngeal cancer was unavailable.

We collected information regarding comorbidities at the time of laryngectomy including diabetes, cardiovascular disease, thyroid disease, and report of malnutrition. Baseline demographics were collected, including age at diagnosis, smoking and alcohol history, and gender. We reviewed charts for the development of pharyngocutaneous fistula and the management and/or resolution of fistula. Patients with fistula secondary to persistent disease or grossly positive margins were excluded, as were patients who died within a month after receiving laryngectomy. Furthermore, we excluded patients who received closures other than primary or PMMF or PMMC flap (e.g. radial forearm free flap, jejunal flap, etc.). In all

PMMF cases, the pharynx was closed primarily and the PMMF was onlayed onto the pharyngeal closure. For patients undergoing PMMC, the skin paddle was used to reconstruct the pharyngeal defect. Additionally, due to the retrospective nature of the study, several charts of patients prior to the electronic medical record were either lost or destroyed, necessarily excluding these patients from the study.

Pharyngocutaneous fistula presence was confirmed by the documentation of fistula in the medical chart, by evidence of fistula on esophagram (fistulogram), or by the presence of wound breakdown such as dehiscence or vascular injury/blowout that were likely secondary to salivary/enzymatic damage to the closure.

Statistical Analysis

Logistic regression was used to investigate association with the presence of fistula from a candidate list of 19 covariates. A univariate Wald test was conducted for each covariate. The raw p value was reported along with the Benjamini and Hochberg adjusted p value. Continuous variables were tested for linearity. Model selection was ad hoc. The final model included a test of interaction between covariates. A parsimonious multivariate model was used to predict the probability of fistula. Patient probabilities were used to construct an ROC curve and to estimate the area under the ROC curve. A candidate classifier was chosen at the cutpoint providing the greatest possible classification accuracy. The operating characteristics were evaluated with leave-one-out cross validation. A recursive partitioning model was also attempted but was unable to reduce cross validated misclassification error. Statistical analyses were conducted with R version 2.15.1.¹³

Results

Out of 540 patients with laryngectomy, 174 patients had a prior history of radiation. We excluded patients with fistula secondary to persistent disease or grossly positive disease, patients who died within a month after receiving laryngectomy, and patients who had closure other than primary, PMMF, or PMMC flap. We were able to identify 73 patients who had received prior radiation before total laryngectomy or salvage laryngectomy, and for whom postoperative clinical follow-up data was available in order to document occurrence of fistula. Demographics and putative risk factors by closure type are summarized in Table 1. Overall, as typical for laryngeal cancer, the majority of patients was male and had a prior history of smoking, with age at the time of surgery in the seventh or eighth decade. A history of cardiovascular or pulmonary disease, such as coronary artery disease, hypertension, or COPD was common. The dose of prior radiation was not significantly different between closure types. Eighty-six percent of patients receiving PMMC flaps were treated with chemotherapy compared to 34% and 29% for primary and PMMF flap, respectively ($p = 0.0013$).

Overall, 32% of the patient cohort had documented pharyngocutaneous fistula (Table 2, Figure 1). Fistula incidence differed by closure type (Exact chi square $p < 0.0001$). Fistula was more common in patients who underwent initial primary closure (45%) than in patients who had immediate PMMF onlay, in which the incidence was only 10.5%. The fistula rate

for patients who underwent immediate PMMC was 28.6%, intermediate to primary closure and PMMF flap.

Demographics and previously published risk factors were evaluated for association with fistula occurrence (Table 3). Four variables were continuous (age, tumor size, length of stay and radiation dose); the remaining factors were categorical. Odds ratios and 95% confidence intervals were computed for each covariate. P values were expressed as raw and adjusted for false discovery. Three factors emerged as moderately associated with fistula: closure type, smoking history and length of stay (all adjusted $p = 0.1320$). In particular, the odds of fistula for PMMF was only 0.13 (0.03 – 0.64) relative to primary closure. Additional length of stay of seven days was associated with 61% increased occurrence of fistula (odds ratio = 1.61 (1.05 – 2.47)). Smoking history, scored simply a yes or no, had a contradictory association with a reduced odds of fistula of 0.18 (0.02 – 0.96) for ever smokers compared to never smokers.

Multivariate analysis was performed using variables conceptually associated with fistula, including closure, age, cardiovascular disease/hypoxia, smoking history, transfusion, length of stay, CHF, and CAD. Only 2 variables were selected for significant association with fistula: closure type and smoking history (Table 4, Figure 2). According to this model closure type and smoking history were each associated with fistula.

Length of stay was weakly associated with type of closure (Figure 3). Patients with primary closure had slightly longer length of stay (mean = 15 days) than did PMMC (12 days) or PMMF (9 days) [Kruskal-Wallis $p = 0.0734$] (Figure 3). Furthermore 22 patients with fistula (one patient missing length-of-stay) had an average stay of 18 days versus 10 days for 50 patients without fistula (Figure 3). Therefore length of stay was weakly correlated with both the outcome (fistula) and a predictor (closure). Conditional on closure and smoking history, length of stay was less influential than closure and smoking history and was excluded from the model ($p = 0.138$).

Discussion

Pharyngocutaneous fistula is a well-established complication of salvage laryngectomy which carries the significant risks of postoperative infection, further wound breakdown, and subsequent damage to surrounding vasculature, including potentially catastrophic carotid artery injury.³ Patients with a prior history of radiation are particularly susceptible to wound complications.¹⁴ It has been suggested that PMMF onlay prevents fistula, but data are conflicting. Righini et al. examined 60 patient post-radiotherapy undergoing total laryngectomy or laryngopharyngectomy and found a reduction of 50% to 23% for PMMF versus primary closure, with even better reduction for patients with previous history of diabetes, vascular disease, or poor nutrition.¹¹ In a small study, Patel and Keni showed that none of ten patients undergoing salvage laryngectomy with PMMF developed fistula whereas four out of seven patients with primary closure for salvage laryngectomy developed fistula.⁷ Oosthuizen et al. showed a reduction by half (50% to 25%) for both total laryngectomy and salvage laryngectomy patients with the use of PMMF.¹⁰ A large recent multi-institution study examined 359 patients, all with a previous history of radiation and the

rate of fistula formation with primary closure versus PMMF versus interspersed free flap.¹⁵ Patients with primary closure had a significantly increased fistula rate of 34% versus 15% of those with pectoralis onlay flap. They also found that fistulas closed faster in the pectoralis onlay flap group. Still, other studies show no benefit of PMMF in decreasing fistula formation.^{7,12} In addition, PMMF flaps are not without compromises and drawbacks. Disadvantages are can be reduced neck mobility, the need to rotate the vascular pedicle of the when using the skin paddle to resurface the neck, and the thickness of the flap, which is determined by the amount of subcutaneous fat between the pectoralis muscle and the overlying skin paddle, possibly leading to possible reduced swallowing function.¹⁶

Our study aimed to address the incidence of fistula relative to closure technique in total laryngectomy, specifically in patients with prior radiation, with the idea of helping the surgeon select which closure to perform at the time of surgery. Fistula rates in our study were significantly lower for primary closure with PMMF onlay compared with primary closure alone, lending support to the hypothesis that PMMF is effective in reducing incidence of fistula in this cohort of previously radiated patients. The fistula rates for PMMC were midway between primary closure and PMMF onlay in spite of the fact that patients receiving PMMC flaps had significantly higher rates of prior chemotherapy (85.7%). It is worth noting that patients who received myocutaneous flaps likely did so for pharyngeal defects that could have not been closed primarily, so it may not be appropriate to compare them to primary closure in this way.¹⁷ It is possible that patients needing PMMC for augmentation of a defect may be better served with a different closure, such as a free flap, since the fistula rate is still rather high at almost 30%. Even so, previous studies have compared PMMC to primary closure for pharyngeal reconstruction with regard to fistula prevention and found PMMC to be far superior.¹⁸ In our study, the smallest expected false discovery rate for individual covariates was 12.5%. This small underpowered convenience sample suggests, with a 12.5% false discovery rate, that fistula may be associated with primary closure.

Our study also showed several interesting findings regarding risk factors for fistula formation. In 2006, Paydarfar and Birkmeyer performed a large meta-analysis of over thirty years of studies (1970–2003) of pharyngocutaneous fistula following total laryngectomy.¹⁹ Overall rates were anywhere from 2.6% to 65.5%. Postoperative hemoglobin level, prior tracheotomy, preoperative radiotherapy, and preoperative radiotherapy combined with neck dissection all had increased relative risk of pharyngocutaneous fistula following laryngectomy. The severity of fistula was consistently worse in patients who received preoperative radiotherapy. Interestingly, dose and time of radiotherapy to surgery demonstrated no association with increased fistula incidence. Amongst the confounding variables across studies, however, was type of closure, which was not consistently addressed. Erdag et al. performed a multivariate analysis of risk factors for fistula following total laryngectomy and found associations with perioperative anemia (Hgb<12.2 g/dL), hypoalbuminemia, ipsilateral or contralateral nodal disease, and the use of erythrocyte suspensions for transfusions.²⁰

Aarts et al. performed a literature search for risk factors for pharyngocutaneous fistula in salvage laryngectomy following failed radiotherapy and found the main factor to be the

tumor size and site characteristics, i.e. T-stage.²¹ Dedivitis et al. found fistula rates associated with peri-operative blood transfusion, T stage, and type of neck dissection.²² White et al. performed another large study examining risk factors for fistula following primary or salvage laryngectomy found previous radiation and hypothyroidism found to be significant, although this study did not examine patients with pectoralis major flaps as almost all flap closures were via radial forearm free flap.²³ For this study, it was not clear if hypothyroidism was prior to surgery or if it was related to laryngectomy.

Another study by Boscolo-Rizzo et al. examined a 218 patients who underwent total laryngectomy and found on multivariate analysis increased risk of fistula for diabetics, patients with chronic pulmonary diseases or chronic hepatopathy, and patients with preoperative hypoalbuminemia.²⁴ As mentioned above, Righini et al. found patients in particular with diabetes, vascular disease, and poor nutrition to benefit significantly from PMMF.¹¹ Vanni et al. looked at risk factors for poor healing following pectoralis major myocutaneous flap for general head and neck reconstruction and found older patients with hypopharyngeal defects who had prior surgery plus radiation therapy to be significantly associated with reconstruction failure.²⁵

Based on the above studies and general risk factors for poor healing, we examined a number of preoperative variables for their association with fistula, including age, gender, diabetes, cardiovascular disease or pulmonary disease(broken up by process and combined), history of prior neck surgery, presence of pre-operative hypothyroidism, history of smoking, history of alcohol use, prior chemotherapy, prior tumor resection, tumor size, positive margins, length of stay, dose of prior radiation, and blood transfusion during stay. Some of the factors, e.g. hypothyroidism, were uncommon in our cohort as to not warrant analysis. The majority of these factors showed no association with fistula either in univariate or multivariate analysis. Self-reported never smokers in our study had an increased fistula rate of 66% compared to 26% among ever smokers. This is most likely a type I error since there were only nine self-reported never smokers – a number too small for a stable prevalence estimate. Furthermore, our smoking and alcohol histories may not be reliable since they are casual questions in patient histories that are subject to self-report bias. Length of stay was generally longer for patients with fistula and for patients with primary and PMMC closure. Since these are the closures with the highest rates of fistula, it is likely that length of stay is generally longer for patients with fistula, causing a false association with closure type.

Our study has several limitations. The small sample size provided low statistical power. Furthermore, we conducted hypothesis testing of the effect of closure type when closure type is likely to be dictated by patient conditions and surgeon preference. Thus, results are likely to be quite different in a randomized framework. We did not have reliable data on precisely when fistulas developed or resolved that would have facilitated investigation into factors related to fistula natural history or resolution (such as observation, nutrition, and operative interventions). The effect of radiotherapy, which was identified in other studies, was affected by low variability in dosing. An interesting question would have been to address whether narrow field radiation or IMRT affected the fistula rate differently—unfortunately, data on the exact type of prior radiation was frequently lacking. Finally,

smoking history, recorded as a binary variable (ever/never), was collected casually without scientific rigor or validation and may be compromised by patient recall and subjectivity.

Conclusion

Pharyngocutaneous fistula is a well-established complication of total laryngectomy, and it is especially a concern in patients with a previous history of radiation. Our retrospective review demonstrates pectoralis major myofascial flap appears to be more effective in reducing the rate of fistula compared to primary closure in these patients. Pectoralis major myocutaneous flaps are not significantly better than primary closure but are often required for augmentation in situations of insufficient mucosa to close pharyngeal defects—free flaps may be a better alternative in these situations. Patients with fistula tended to have longer inpatient stays and may have been more likely to have a history of cardiovascular or hypoxic disease. Careful consideration should be made about the risk factors of patients in deciding whether to perform primary closure or pectoralis major myofascial flap.

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Figure 1.
Predicted probability of fistula by closure (univariate)

Figure 2.
Predicted probability of fistula from logistic model

Figure 3.
Length of stay by closure and fistula

Table 1

Data summary/demographics by type of closure

Variable	Closure			Test of Equality ⁽¹⁾	
	Primary	PMMF	PMMC	Raw p	Adjusted p
Total	38	21	14		
Gender				.4916	.682
Male	30 (78.9%)	18 (85.7%)	13 (92.9%)		
Female	8 (21.1%)	3 (14.3%)	1 (7.1%)		
Diabetes	10 (26.3%)	3 (14.3%)	3 (21.4%)	.5604	.682
Cardiovascular/Hypoxic Disease	32 (84.2%)	17 (81.0%)	7 (50%)	.0480	.346
CAD	14 (36.8%)	12 (57.1%)	7 (50%)	.2958	.682
HTN	21 (55.3%)	9 (42.9%)	9 (64.3%)	.4670	.682
COPD	6 (15.8%)	3 (14.3%)	5 (34.9%)	.2259	.682
Arrhythmia	7 (18.4%)	3 (14.3%)	0	.2870	.682
CHF	1 (2.6%)	2 (9.5%)	2 (14.3%)	.2045	.682
Previous Neck Surgery	13 (34.2%)	6 (28.6%)	8 (57.1%)	.2182	.682
Hypothyroidism	3 (8.1%)	3 (14.3%)	0	.3849	.682
Age, median (range)	66.8 (50 – 86)	64.1 (48 – 99)	71.9 (45 – 84)	.2999	.682
Pos. Smoking hx ⁽²⁾	32 (88.9%)	19 (90.5%)	11 (78.6%)	.5701	.682
Pos. Alcohol hx ⁽³⁾	23 (65.7%)	10 (50%)	9 (69.2%)	.4327	.682
Prior Chemotherapy	13 (34.2%)	6 (28.6%)	12 (85.7%)	.0013	.026
Prior Resection	5 (13.2%)	6 (28.6%)	4 (28.6%)	.2307	.682
Tumor size in cm, median IQR	3.0 (2 – 3.5)	2.6 (2 – 3.1)	3.8 (3 – 4.8)	.0346	.346
Pos Margins ⁽³⁾	4 (10.8%)	3 (15%)	4 (28.6%)	.3107	.682
Length of stay (days), median IQR	10.0 (8 – 14)	8.0 (7 – 9)	10.5 (8 – 15)	.075	.375
Prior radiation, median, (IQR) ⁽⁴⁾	6600, (6120 – 6970)	7000 (6800 – 7000)	6630 (6270 – 7125)	.1461	.584
Blood transfusion ⁽⁵⁾	3 (8.1%)	1 (4.8%)	0	.5447	.682

⁽¹⁾ Fisher's exact test for categorical variables. Kruskal-Wallis test for continuous variables (age, tumor size, length of stay, radiation dose)

(2) Two patients were missing smoking history

(3) Two patients were missing margin status

(4) Eleven patients were missing prior radiation dose

(5) Two patients were missing transfusion data

Table 2

Fistula incidence by closure type

		Closure Type			Total
		Primary	PMMF	PMMC	
Fistula	Yes	17 (45%)	2 (10%)	4 (29%)	23 (32%)
	No	21 (55%)	19 (90%)	10 (71%)	50 (68%)
	Total	34	21	14	73

Table 3

Possible risk factors for fistula

	Risk Factor Frequency	Proportion with Fistula	Odds Ratio (95% CI)	Odds ratio reference	Wald Test Raw p	Adj p ⁶
Complete Cohort	73	31.5 %				
Age	—	—	1.82 (.95 – 3.50)	58:73	.0635	.2053
Gender = Male	61	31.1 %	0.91 (.21 – 4.62)		.882	
Diabetes	16	43.8 %	1.97 (.52 – 7.18)		.2418	.5373
Closure = Primary	38	44.7 %			.0126	.1320
Closure = PMMF	21	9.5 %	0.13 (.03 – 0.64)	Primary		
Closure = PMMC	14	28.6 %	0.49 (.13 – 1.86)	primary		
Previous Neck Surgery	27	29.6 %	0.87 (.26 – 2.71)		.7909	.9269
CV/hypoxia	21	37.5 %	4.42 (0.88 – 43.70)		.0327	.1635
Smoking history ¹	62	25.8 %	0.18 (.02 – .96)		.0176	.1320
Alcohol history ²	42	28.6 %	0.64 (.21 – 2.06)		.3991	.6278
Prior chemotherapy	31	29.0 %	0.82 (.26 – 2.49)		.6952	.9269
Prior surgery	15	20.0 %	0.48 (.08 – 2.07)		.2665	.5373
Prior RT ³			0.88 (.65 – 1.18)	6300:7000	.3767	.6278
Tumor size ⁴			1.12 (.53 – 2.36)	2:3.8	.7683	.9269
Transfusion ⁵	4	75.0 %	7.34 (.55 – 405)		.0616	.2053
Positive margin	11	18.2 %	0.42 (.04 – 2.29)		.2528	.5373
Length of Stay	—	—	1.61 (1.05 – 2.47)	7:14	.0066	.1320
CAD	33	21.2 %	0.41 (.12 – 1.28)		.082	.2053
HTN	39	33.3 %	1.20 (.40 – 3.68)		.7187	.9269
COPD	14	28.6 %	0.84 (.17 – 3.43)		.7192	.9269
Arrhythmia	10	40.0 %	1.53 (.28 – 7.36)		.5407	.7724
CHF	5	0 %	0 (0 – 2.33)		.0469	.1876

¹Two patients missing smoking history²One patient is missing alcohol history³Eleven patients are missing prior RT

⁴ Five patients are missing tumor size

⁵ One patient missing transfusion data

⁶ Benjamini-Hochberg adjustment for false discovery, this is the expected false discovery rate associated with a claim of a positive result

Table 4

Final Multivariate Logistic Model (N = 71). Candidates: closure, age, hypoxia, smoking history, transfusion, length of stay, CHF and CAD

Factor	Reference	Odds Ratio	95% CI
Closure = PMMF	Primary	0.11	0.02 – 0.61
Closure = PMMC	Primary	0.35	0.08 – 1.58
Smoking Hx = No	Yes	7.82	1.43 – 42.77