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Pharyngocutaneous Fistula after Total Laryngectomy: Risk Factors with Emphasis on Previous Radiotherapy and Heavy Smoking

Original Investigation

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Abstract

Objective: In this retrospective cohort study, we aimed to determine the incidence of pharyngocutaneous fistula (PCF) after total laryngectomy (TL) and to define the possible predictors for PCF formation.

Methods: The medical records of 198 patients with laryngeal squamous cell carcinoma who underwent TL were reviewed. After the exclusion of patients with history of free flap reconstruction, previous laryngeal surgery, and previous radiotherapy (RT) for other primary cancers, the risk factors for PCF were analyzed in 183 patients who were included in the study.

Results: The overall incidence of PCF was 20.2%. A history of heavy smoking and previous RT were detected as independent risk factors in both univariate (p=0.004 and p=0.007, respectively) and multivariate (p=0.005) analyses. Preoperative tracheotomy (PT) longer than 14 days was a risk factor for PCF among patients with PT in the univariate analysis (p=0.031). Overall three- and five-year survival rates were statistically indifferent between the PCF and non-PCF groups (p>0.05). However, the overall five-year survival rate was lesser in the persistent PCF group (47%) than in the non-persistent PCF group (83%) (p=0.038).

Conclusion: Heavy smoking and previous RT are independent risk factors for PCF, and the persistence of PCF decreases survival rates. Preventable measures should be taken to decrease the incidence and persistence of this complication of TL in the management of patients with possible risk factors.

Keywords: Laryngeal cancer, pharyngocutaneous fistula, radiotherapy, smoking, total laryngectomy

Introduction

Although indications for total laryngectomy (TL) have considerably declined due to organ preservation protocols and advances in organ-preserving surgeries, it is still the treatment of choice for tumors that are deeply infiltrative or destroying laryngeal cartilages, and in cases of chemoradiotherapy failure. Pharyngocutaneous fistula (PCF) is the leading complication prolonging hospital stay and delaying oral feeding and adjuvant therapy after TL. As it is also a risk factor for major complications such as rupture of the carotid artery, its prevention is crucial (1).

The incidence of PCF following TL is reportedly between 3% and 65% (1, 2). It is associated with a higher incidence of morbidity and higher hospital cost (3). Many studies have been conducted to define possible risk factors for PCF with the aim of reducing its incidence, but there are still different opinions about their impact. For this reason, we aimed to investigate the patient-related, tumor-related and surgical technique-related risk factors for PCF in patients who underwent TL for laryngeal cancer.

Methods

The study was conducted after approval by "Ethical Committee for Non-Invasive Human Research" at Dokuz Eylül University School of Medicine. The records of 198 consecutive patients who underwent TL for laryngeal squamous cell carcinoma at the Department of Otorhinolaryngology Head and Neck Surgery of Dokuz Eylül University Hospital between October 1992 and December 2013 were reviewed. To achieve sample uniformity, after excluding patients with extended pharynge-

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al resection requiring flap reconstruction (four patients), previous partial laryngectomy (five patients), and previous neck radiotherapy (RT) for other primary cancers (six patients), there were 183 patients included in our study group. Written informed consent was obtained from patients who participated or from their relatives.

The planned tumor doses to primary tumors and involved neck for patients who received previous definitive RT were 66-70 Gy. There was only one patient who received previous chemoradiotherapy for laryngeal cancer as she rejected undergoing TL and subsequently she developed PCF.

Patients were given prophylactic antibiotics consisting of cefazolin 1 g and metronidazole 500 mg (clindamycin 900 mg in case of beta-lactam allergy) intravenously at 1 h prior to making a skin incision, repeated every 4 h during surgery, and applied at 8, 16, and 24 h postoperatively. Antibiotics were continued as maintenance treatment until vacuum drainage tubes were removed. Patients were operated by faculty members primarily or under the supervision of them. Three-layer mucosal–muscular–muscular closure of pharyngotomy was done with a 3.0 polyglactin suture material in all but three patients in whom mechanical suturing with staples was performed. Wound care and physical examinations were postoperatively performed twice a day. A definitive diagnosis of PCF was made after wound exploration and fistula tract observation. PCF was accepted as "persistent" if patients did not respond to conservative or surgical treatments within 28 days.

Age of the patient, sex, smoking, additional comorbidities, location of tumor, presence and duration of PT, differentiation of tumor, clinical and pathological primary tumor (T) stage, clinical and pathological regional lymph node (N) stage, surgical margins, presence of concurrent neck dissection, presence of extended pharyngeal mucosal excision and tongue base resection, type of pharyngeal closure, and presence of previous definitive radiotherapy/chemoradiotherapy were investigated for their possible contributions to PCF. Clinical TN and pathological TN staging were done according to the American Joint Committee for Cancer staging form, 2010 (4).

The incidence of and possible risk factors for PCF were analyzed. Two-tailed Fisher's exact test was used to investigate the impact of sex, chronic diseases, surgical margins, pharyngeal resection, tongue base resection, and RT on PCF development. The numerical data were summarized as mean, minimum and maxiumum values and standard deviations (SDs). Pearson's chi-squared test was used to investigate the impact of other categorical variables. The independent samples t-test was used for the analysis of continuous variables among groups. Significant variables were examined by multivariate analysis with binary logistic regression to identify independent risk factors. Odds ratios (ORs) with 95% confidence interval (CI) were calculated. The follow-up periods of patients were considered as the time period from the operation until the last follow-up or death. Survival analysis was performed with Kaplan-Meier analysis and the log-rank test. The level of statistical significance was considered as $p<0.05$. Statistical analysis was performed using Statistical Package for the Social Sciences 20.0 (IBM SPSS Statistics for Windows, Version 20.0. IBM Corp.; Armonk, NY, USA).

Results

There were 183 (173 male and 10 female) patients with a mean age of 58.25 years (range, 36-79 years; SD: 8.996). The overall incidence of PCF was 20.2% (37/183). The categorical descriptive characteristics and the results of univariate analysis are given in Table 1. Risk factors found to be associated with PCF were heavy smoking with a smoking history of 40 or more pack-years (mild: fewer than 20 pack-years, moderate: 30-40 pack-years), previous RT, and prolonged existence of PT for more than 14 days in the univariate analysis ($p=0.004$, 0.007, and 0.031, respectively). Patient age with a cut-off point at 60 years; sex; additional comorbidities consisting of diabetes mellitus, chronic heart disease and chronic pulmonary disease; location of tumor; presence of PT; differentiation of tumor, clinical and pathological TN classification; surgical margins; presence of concurrent neck dissection; presence of extended pharyngeal mucosal excision and tongue base resection; and type of pharyngeal closure were not found to be associated with PCF in the univariate analysis ($p>0.05$) (Table 1).

The associations of "heavy smoking" and "previous RT to larynx+/-neck" with PCF were also confirmed in the multivariate analysis (Table 2), increasing the incidence of PCF by 3.192-fold (95% CI, 1.432–7.115) and 4.281-fold (95% CI, 1.552–11.807), respectively ($p=0.005$ for both). Because the "previous RT to larynx+/-neck" group covered all patients in whom the RT region included the larynx, this group was chosen for the multivariate logistic regression model instead of the "RT only to the larynx" group. The prolonged existence of PT longer than 14 days could not be studied in the binary logistic regression model due to the different sample size. The mean time interval between preoperative definitive RT and TL was 24.5 months (minimum: 4, maximum: 124; SD: 34.896) and it did not differ between PCF (mean: 16.73, SD: 50.725 months) and non-PCF (mean: 34.00, SD: 10.374 months) groups ($p=0.412$).

The mean time from TL to the detection of PCF was 8.07 days (minimum 2 days; maximum 14 days; SD: 2.292) and 11.11 days (minimum 2, maximum 35; SD: 10.517) in primary surgery and salvage surgery patients respectively. The mean healing time from PCF was 43.75 days (minimum 5 days; maximum 300 days; SD: 66.845) in the primary surgery group and 81.67 days (minimum 9 days; maximum 201 days; SD: 77.309) in the salvage surgery group;

Table 1. Categorical variables and univariate analysis of risk factors for PCF formation

Variables	Categories	PCF Group (n)	Non-PCF Group (n)	p
Sex	Female	4	6	0.119
	Male	33	140	
Age (years)	≥60	11	64	0.119
	<60	26	82	
Smoking	Mild–Moderate	11	82	0.004
	Heavy	26	64	
Diabetes mellitus	Yes	4	9	0.302
	No	33	137	
Chronic heart disease	Yes	3	12	0.642
	No	34	134	
Chronic pulmonary disease	Yes	11	37	0.588
	No	26	109	
Tumor location	Supraglottis	11	51	0.550
	Glottis–subglottis	26	95	
cT stage	T1–3	25	95	0.775
	T4	12	51	
cN stage	N0	31	110	0.502
	N1-3	6	32	
Preoperative tracheotomy	Yes	8	25	0,525
	No	29	121	
Duration of tracheotomy	>14 days	8	14	0.031
	≤14 days	0	11	
Tumor differentiation	Well–moderate	29	104	0.384
	Poor	8	42	
pT stage	T2–3	20	78	0.945
	T4	17	68	
pN stage	N0	23	83	0.523
	N1–3	13	60	
Surgical margins	Positive	4	18	1.000
	Negative	33	128	
Neck dissection	Yes	36	143	1.000
	No	1	3	
Neck dissection	Bilateral	16	55	0.511
	Unilateral	20	88	
Pharyngeal resection	Yes	2	4	0.350
	No	35	142	
Tongue base resection	Yes	1	6	1.000
	No	36	140	
Pharyngeal closure type	Horizontal	26	122	*
	Vertical	6	7	
	T-type	3	16	
	Stapler	2	1	
Pharyngeal closure type	Horizontal	26	122	0.171
	Other	9	23	
Previous RT only to the larynx	Yes	7	7	0.009
	No	30	139	
Previous RT to the larynx+/-neck	Yes	9	11	0.007
	No	28	135	
Previous RT to the larynx and neck	Yes	2	4	0.350
	No	35	142	

PCF: pharyngocutaneous fistula; cT: clinical T; cN: clinical N; pT: pathologic T; pN: pathologic N; RT: radiotherapy
*Statistics was not applicable

Table 2. Results of both univariate (chi-square) and multivariate (binary logistic regression) statistical analysis

	Univariate analysis			Binary logistic regression analysis		
Variables	OR	95% CI	p	OR	95% CI	p
Heavy smoking	3.028	1.392–6.587	0.004	3.192	1.432–7.115	0.005
Previous RT to the larynx +/- neck	3.945	1.495–10.410	0.007	4.281	1.552–11.807	0.005

OR: odds ratio; CI: confidence interval; RT: radiotherapy

this difference was not statistically significant (p=0.163). The first explorations were performed at the time of the clinical diagnosis of PCF, and surgical interventions were performed on the day of repetitive explorations, which revealed PCF.

Conservative treatment resulted in the successful control of PCF in 30% (11/37) of the patients. There were nine previously irradiated patients with PCF. The PCF closure rates with conservative treatment were 33% (3/9) and 29% (8/28) in previously irradiated and non-irradiated patients with PCF, respectively. The other six patients with a history of RT to the larynx were also patients with persistent PCF in whom surgical closure of PCF was performed. With respect to cigarette smoking, 18 of 26 (69%) patients with surgical closure were heavy smokers, whereas eight of 11 (73%) patients with the conservative approach were heavy smokers. Fisher's exact test, for analyzing if the requirement of the surgical closure of PCF was related to history of previous RT or heavy smoking, was insignificant for both factors (p>0.05). Although the frequencies of positive surgical margin and metastatic regional lymph node presence were numerically higher in the surgical closure group than in the conservational group (4/26 versus 0/11 and 11/26 versus 2/11, respectively), there were no statistically significant relationships shown between two different approaches with respect to those risk factors, and also other investigated factors defined in Table 1.

Persistent PCF occurred in 19 of the 37 (51%) patients with PCF. All patients with persistent PCF required surgical closure of the fistula in comparison with seven of 18 (39%) patients with non-persistent PCF. There were two patients requiring surgical closure of the fistula with radial forearm free flap: one from primary surgery group and the other from the salvage surgery group. Local random flaps were used for the reconstruction of fistula defects in eight patients. Hyperbaric oxygen therapy was applied to two of six patients undergoing primary closure. One of three patients with persistent PCF had thyroid gland invasion and peristomal recurrence. The second patient developed acute renal failure and pulmonary embolism in addition to flap necrosis, and the last patient, whose surgical margins were reported as positive, also developed flap necrosis. These three patients had persistent PCF for durations of 300, 240, and 200 days until death, and our overall surgical treatment failure rate was 12% (3/26).

In fourteen of 37 (38%) patients with PCF, adjuvant RT could not be started within 8 weeks following TL due to persistence of the PCF. Twenty-six of the 183 (14%) patients developed local–regional recurrences. Five of the 37 (16%) patients with PCF developed local–regional recurrences; among them, four patients had persistent PCF.

The average follow-up period was 64.08 months (range: 2–230 months). The overall 3- and 5-year survival rates for all patients were 77% and 70%, respectively. The overall 3-year survival rates were 70% and 78% in the PCF and non-PCF groups, respectively, and no statistically significant difference was found between the two groups (p=0.172). The overall 5-year survival rates of 65% and 71% in the PCF and non-PCF groups, respectively, were also not statistically different between the groups (p=0.168). There was also no statistically significant difference in the local–regional recurrence-free survival rates between the PCF and non-PCF groups (3-year survival rates: 70% and 78%, respectively, p=0.172; 5-year survival rates: 65% and 70%, respectively, p=0.216). On the other hand, the overall 5-year survival rates were significantly less in the persistent PCF group (47%) than in the non-persistent PCF group (83%) (p=0.038).

Discussion

Although TL is an oncologically safe operation, it carries an inherent risk of pharyngoesophageal reconstruction failure and PCF. Due to prolonged hospitalization time, increased morbidity, and negative psychological impacts on patients, this complication has been the subject of different investigations. Incidences of PCF have been reported as 3% to 65% (1, 2). In a recent study, Benson et al. (5) reported the incidence as 34%. Our incidence of PCF (20.2%), which is still high, lies within the mid-range of previous series (1, 5-8).

Predisposing factors for PCF have been studied for years. In a recent systematic literature review, chronic obstructive pulmonary disease, previous hemoglobin levels<12.5 g/dL, blood transfusion, previous RT or chemoradiotherapy, advanced primary tumor, supraglottic subsite, hypopharyngeal tumor site, positive surgical margin, and neck dissection have been reported as risk factors for PCF formation (3). We did not analyze laboratory results such as preoperative and postoperative hemoglobin levels, albumin levels, or similar biochemical tests because these levels were

kept within normative ranges in our patients. The impacts of prophylactic antibiotherapy on PCF development were also not also analyzed as all patients received the same approach for the management.

In our study, we found that heavy smoking and previous RT to the larynx+/-neck were associated with PCF in the univariate and multivariate analyses within the whole sample; tracheotomy duration longer than 14 days was also a risk factor for patients with PT in the univariate analysis.

Twenty-six of 90 (29%) patients who were heavy smokers developed PCF compared to those who were mild and moderate smokers (12%) (p=0.004). Even tobacco smoke has a diverse toxicity profile depending on the materials within the blaze; the mechanisms of vascular damage from smoking are caused by nicotine and free radicals. Nicotine absorbed by the mucosa stimulates the release of catecholamines; the other products injure the arterial endothelium and promote atherogenesis. Free radicals decrease the endothelial synthesis of nitric oxide, causing the impaired relaxation of arteries. The increased oxidation of low-density lipoproteins in smokers has synergistic effects in promoting monocyte adhesion and migration in the subintimal space and atherosclerosis development (9). Smoking also affects wound healing at the cellular level, reducing fibroblast activity and keratinocyte migration, and potentiates thrombosis at the dysfunctional endothelium by increasing the concentration of plasma fibrinogen and altering the activity of platelets (9, 10). Ejaz and Lim (11) found that different components of 'sidestream whole smoke solutions' may have a cumulative negative impact on wound healing and related angiogenesis.

In a recent study, smokers were reported to develop more local complications (univariate analysis, p=0.05; multivariate analysis, p=0.04). Fifteen of 507 smokers (2.96%) developed PCF, whereas none of 28 non-smokers (0%) developed it (univariate analysis, p=0.01; multivariate analysis, p=0.03) (12). Our results support the negative effects of smoking in terms of local complications including PCF. We suggest conducting further studies as it might be interesting to see whether smoking cessation for a particular period of time before surgery is effective in reducing the incidence of PCF.

In our study, we demonstrated an increased incidence of PCF in patients with preoperative RT, which is in agreement with the majority of literature reports (13-20). While, some studies did not find any association between preoperative RT and PCF formation (5-7, 21, 22). Grau et al. (16) found an increased incidence of PCF in patients with preoperative RT in subgroups where patients had advanced initial T stage and non-glottic primary site laryngeal cancer. In another study, the risk of PCF in patients with preoperative RT was found to be related to the characteristics and site of the primary tumor (23). As a majority of our patients undergoing salvage laryngectomy had recurring glottic or transglottic laryngeal carcinomas, we were unable to make a further analysis in subgroups for tumor site and characteristics within the preoperative RT group. Additionally, as there was only one patient who underwent salvage TL a year after her chemoradiotherapy had finished and who developed postoperative PCF, we could not put use previous chemoradiation as a risk factor.

Dirven et al. (24) reported that patients undergoing salvage surgery within 12 months and who received high-dose RT or concurrent chemoradiation are at a high risk of developing PCF. Scotton et al. (25) reported the time interval between primary RT and salvage laryngectomy as a predictor of PCF formation. The mean time interval between RT and surgery was significantly shorter in their PCF patients than in non-PCF patients, being 19.5 months and 47.0 months, respectively (25). In our study, even the mean time interval between RT and surgery was longer in non-PCF patients than in PCF patients, being 34.0 and 16.7 months, respectively, this difference was not statistically significant. Twenty four percent of our patients with PT and 19% of the patients without PT had PCF, and this difference was not statistically significant. In contrast to two recent studies (3, 6), we did not find the mere presence of PT to be considered as a significant risk factor for PCF formation in agreement with other authors (1, 14, 17, 18). Dedivitis et al. (26) conducted a study on 55 patients, and they found a significantly higher incidence of PCF in patients with previous tracheotomy (60% versus 8%, p=0.012). One of the possible explanations for this was the local contamination developed by tracheal secretion over time, which made us think about not only the presence of prelaryngectomy tracheotomy but also the duration of it (1, 26). The average time interval between tracheotomy and TL was 27.3 days (minimum, 1 day; maximum, 168 days). When longer than 14 days of prior tracheotomy is considered as a risk factor, a 36% incidence of PCF in patients with tracheotomy longer than 2 weeks was statistically higher than a 18% incidence of PCF in patients operated within 2 weeks after tracheotomy (p=0.031).

The stoma is an open surgical wound, and colonization with respiratory flora is inevitable. Occasional cases will develop delayed complications (postoperative period <7 days) such as local infections, which can progress to late complications (postoperative period >7 days) such as spreading cellulitis in case of greater surgical exposure and dissection (27). Based on this information, to cover the complications of tracheotomy related to PCF, we divided patients with PT into two groups depending on whether the duration of tracheotomy prior to surgery exceeded 14 days. The higher PCF risk associated with the prolonged duration of PT might be attributed to the increased bacterial contamination and local infection (1, 27, 28). Further-

more, incoming TL will be advanced to "contaminated" class from "clean-contaminated" class of surgical wounds in the presence of prolonged PT. Consequently, prolonged prior tracheotomy should be kept in mind as an important risk factor for PCF, and every attempt should be made to perform TL as soon as possible.

The incidence of PCF was 31% in patients with diabetes and 19.4% in non-diabetics (p=0.302); other additional comorbidities such as chronic pulmonary disease and advanced age were not also found to be related to PCF formation in our study, which is different from what was found in some reports (6, 15, 29, 30). Likewise our study, Akduman et al. (31) did not detect any significant relationship between the presence of chronic systemic disease and formation of PCF.

In our study, we did not find T_4 stage as a significant risk factor for PCF, in accordance with other studies (1, 22, 29, 33). But some authors (31, 32) declared T_4 stage as a factor significantly associated with PCF formation, in contrary to our study. Supraglottic tumors were speculated to be a risk factor as they require extensive resections and complicate pharyngeal reconstruction (3, 14). This finding was not verified in our study as was done in other studies (5, 17).

In various studies, the potential impacts of suture material and pharyngeal closure technique (horizontal, vertical, or T) on fistula formation have been investigated (6, 14, 30, 33). Tosun et al. (30) revealed an association of T-shaped suturation of the pharynx with the development of postoperative PCF. Soylu et al. (32) demonstrated a higher incidence of PCF with the use of catgut in relation to polyglycolic acid, but no significant difference was shown among manual suturing types such as T, vertical, and horizontal closure. As shown in Table 1, we observed a higher incidence of PCF in patients in whom vertical closure and staples were used for reconstruction (46% and 67%, respectively). Nevertheless, an appropriate statistical analysis could not be applied in our study as data were heterogeneous (mechanical and manual suturing). We used longitudinal mechanical suturing with a linear stapler in only three patients. If patients undergoing longitudinal linear stapler closure were not included in the analysis and the patients were divided into two groups, "horizontal" and "other" according to the pharyngeal manual suturing type, data were still not significantly different (p=0.171).

Basheeth et al. (17) and Dowthwaite et al. (18) did not observe an increase in the incidence of PCF with a primary tracheoesophageal puncture. Ikiz et al. (33) showed significant association of pharyngeal myotomy with PCF. Based on this finding, in our clinic, we left primary tracheoesophageal puncture to avoid a weakened pharyngoesophageal zone. According to some reports, resections of the extended pharyngeal mucosa and tongue base are risk factors for PCF (19). However, we could not indicate an increased incidence of PCF in terms of resection of the pharyngeal mucosa or tongue base because they were performed in a small group of patients. Basheeth et al. (17) showed that concomitant bilateral neck dissection (p=0.02) is a significant risk factor for the development of PCF. However, in our study, we could not find any association of the type and laterality of the neck dissection with PCF.

Overall and local–regional recurrence-free 3- and 5-year survival rates were statistically insignificant between the PCF and non-PCF groups and also between the salvage and primary surgery groups in our study, which is similar to what was found in previous reports (15, 22). However, the overall 5-year survival rate was statistically less in the persistent PCF group (46%) than in the non-persistent PCF group (83%) (p=0.038). This worse survival in patients with persistent PCF may be explained by the inevitable delay in adjuvant RT and supports the requirement of active intervention for PCF before PCF gets to the persistent stage.

Some authors support early intervention in PCF with the purpose of preventing prolonged hospital stay and prolonged enteral feeding (32). Although this opinion has many justifications, the early primary surgical closure of an existing PCF is not always easy and successful. According to our experience, as some PCFs spontaneously close with appropriate treatment, our initial approach was conservative treatment, as reported in other studies (7, 13, 14). However, if 2 weeks of conservative treatment fails, surgical intervention is required to attempt to close the fistula. Repetitive neck explorations are performed to disclose PCF. If PCF becomes persistent despite all efforts, the management of PCF necessitates local or distant flaps. In this series, local flaps were used in eight patients, and two patients required radial forearm free flaps: one in the primary surgery group and another in the previous RT group.

Overall, we believe that precautions should be taken particularly in the presence of heavy smoking and a previous RT history for laryngeal cancer as they increase the risk of PCF by 3.192-fold and 4.281-fold, respectively, in the multivariate analysis. Additionally, as a striking finding, a relationship between PT longer than 14 days and PCF frequency was found (p=0.031), suggesting early definitive surgery after tracheotomy. Even findings regarding survival analysis could not support the importance of PCF for mortality; its persistence was shown to have impacts on mortality.

Finally, we propose the following issue for further research: whether cessation of smoking before a certain time from TL has a positive effect on the prevention of PCF formation and the healing process. Additionally, new studies designed on this topic are needed to contribute to mapping risk factors for PCF and generating a large data pool.

Conclusion

Smoking, a well-known risk factor for head and neck cancer, was found to be a risk factor for PCF in heavy smokers after TL. Preventable measures should be taken for patients with a history of heavy smoking, preoperative RT, and PT during counseling for TL and during the postoperative period to decrease PCF and its persistence.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University Non-Invasive Human Research.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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References

1. Paydarfar JA, Birkmeyer NJ. Complications in head and neck surgery: a meta-analysis of postlaryngectomy pharyngocutaneous fistula. Arch Otolaryngol Head Neck Surg 2006; 132: 67-72. [CrossRef]
2. Thawley SE. Complications of combined radiation therapy and surgery for carcinoma of the larynx and inferior hypopharynx. Laryngoscope 1981; 91: 677-700.
3. Dedivitis RA, Aires FT, Cernea CR, Brandão LG. Pharyngocutaneous fistula after total laryngectomy: A systematic review of risk factors. Head Neck 2015; 37: 1691-7. [CrossRef]
4. Edge SB, Byrd DR, Compton CC, Fritz AG, Green FL, Trotti A, editors. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010.
5. Benson EM, Hirata RM, Thompson CB, Ha PK, Fakhry C, Saunders JR, et al. Pharyngocutaneous fistula after total laryngectomy: a single-institution experience, 2001-2012. Am J Otolaryngol 2015; 36: 24-31. [CrossRef]
6. Boscolo-R P, De Cillis G, Marchiori C, Carpenè S, Da Mosto MC. Multivariate analysis of risk factors for pharyngocutaneous fistula after total laryngectomy. Eur Arch Otorhinolaryngol 2008; 26: 929-36. [CrossRef]
7. Mäkitie AA, Niemensivu R, Hero M, Keski-Säntti H, Bäck L, Kajanti M, et al. Pharyngocutaneous fistula following total laryngectomy: a single institution's 10-year experience. Eur Arch Otorhinolaryngol 2006; 263: 1127-30. [CrossRef]
8. Smith TJ, Burrage KJ, Ganguly P, Kirby S, Drover C. Prevention of postlaryngectomy pharyngocutaneous fistula: the Memorial University experience. J Otolaryngol 2003; 32: 222-5. [CrossRef]
9. Powell JT. Vascular damage from smoking: Disease mechanisms at the arterial wall. Vasc Med 1998; 3: 21-8. [CrossRef]
10. McRobert J. Smoking and its effects on the healing process of chronic wounds. Br J Community Nurs 2013; Suppl: S18, S20-3.
11. Ejaz S, Lim CW. Impact of sidestream whole smoke solutions on the outcome of wound repair and related angiogenesis. Environ Toxicol Pharmacol 2006; 21: 308-16. [CrossRef]
12. Fiorini FR, Deganello A, Larotonda G, Mannelli G, Gallo O. Tobacco exposure and complications in conservative laryngeal surgery. Cancers (Basel) 2014; 6: 1727-35. [CrossRef]
13. Tsou YA, Hua CH, Lin MH, Tseng HC, Tsai MH, Shaha A. Comparison of pharyngocutaneous fistula between patients followed by primary laryngopharyngectomy and salvage laryngopharyngectomy for advanced hypopharyngeal cancer. Head Neck 2010; 32: 1494-500. [CrossRef]
14. Galli J, De Corso E, Volante M, Almadori G, Paludetti G. Postlaryngectomy pharyngocutaneous fistula: incidence, predisposing factors, and therapy. Otolaryngol Head Neck Surg 2005; 133: 689-94. [CrossRef]
15. Klozar J, Cada Z, Koslabova E. Complications of total laryngectomy in the era of chemoradiation. Eur Arch Otorhinolaryngol 2012; 269: 289-93. [CrossRef]
16. Grau C, Johansen LV, Hansen HS, Andersen E, Godballe C, Andersen LJ, et al. Salvage laryngectomy and pharyngocutaneous fistulae after primary radiotherapy for head and neck cancer: a national survey from DAHANCA. Head Neck 2003; 25: 711-6. [CrossRef]
17. Basheeth N, O'Leary G, Sheahan P. Pharyngocutaneous fistula after salvage laryngectomy: impact of interval between radiotherapy and surgery, and performance of bilateral neck dissection. Head Neck 2014; 36: 580-4. [CrossRef]
18. Dowthwaite SA, Penhearow J, Szeto C, Nichols A, Franklin J, Fung K, et al. Postlaryngectomy pharyngocutaneous fistula: determining the risk of preoperative tracheostomy and primary tracheoesophageal puncture. J Otolaryngol Head Neck Surg 2012; 41: 169-75.
19. Timmermans AJ, Lansaat L, Theunissen EA, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Predictive factors for pharyngocutaneous fistulization after total laryngectomy. Ann Otol Rhinol Laryngol 2014; 123: 153-61. [CrossRef]
20. White HN, Golden B, Sweeny L, Carroll WR, Magnuson JS, Rosenthal EL. Assessment and incidence of salivary leak following laryngectomy. Laryngoscope 2012; 122: 1796-9. [CrossRef]
21. Virtaniemi JA, Kumpulainen EJ, Hirvikoski PP, Johansson RT, Kosma VM. The incidence and etiology of postlaryngectomy pharyngocutaneous fistulae. Head Neck 2001; 23: 29-33.
22. Markou KD, Vlachtsis KC, Nikolaou AC, Petridis DG, Kouloulas AI, Daniilidis IC. Incidence and predisposing factors of pharyngocutaneous fistula formation after total laryngectomy. Is there a relationship with tumor recurrence? Eur Arch Otorhinolaryngol 2004; 261: 61-7. [CrossRef]
23. Aarts MC, Rovers MM, Grau C, Grolman W, van der Heijden GJ. Salvage laryngectomy after primary radiotherapy: what are prognostic factors for the development of pharyngocutaneous fistulae? Otolaryngol Head Neck Surg 2011; 144: 5-9. [CrossRef]

24. Dirven R, Swinson BD, Gao K, Clark JR. The assessment of pharyngocutaneous fistula rate in patients treated primarily with definitive radiotherapy followed by salvage surgery of the larynx and hypopharynx. Laryngoscope 2009; 119: 1691-5. [CrossRef]
25. Scotton WJ, Nixon IJ, Pezier TF, Cobb R, Joshi A, Urbano TG, et al. Time interval between primary radiotherapy and salvage laryngectomy: a predictor of pharyngocutaneous fistula formation. Eur Arch Otorhinolaryngol 2014; 271: 2277-83. [CrossRef]
26. Dedivitis RA, Ribeiro KC, Castro MA, Nascimento PC. Pharyngocutaneous fistula following total laryngectomy. Acta Otorhinolaryngol Ital 2007; 27: 2-5.
27. Bodenham A, Bell D, Bonner S, Branch F, Dawson D, Morgan P, et al. Standards for the Care of Adult Patients with Temporary Tracheostomy; Standards and Guidelines. Intensive Care Society Standards 2014: 29-32.
28. Epstein SK. Late complications of tracheostomy. Respir Care 2005; 50: 542-9.
29. Redaelli de Zinis LO, Ferrari L, Tomenzoli D, Premoli G, Parrinello G, Nicolai P. Postlaryngectomy pharyngocutaneous fistula: incidence, predisposing factors, and therapy. Head Neck 1999; 21: 131-8.
30. Tosun F, Gerek M, Birkent H, Özkaptan Y. Total larenjektomi sonrası farengokutanöz fistül; değişik risk faktörlerinin analizi. Türkiye Klinikleri J ENT 2002; 2: 133-9.
31. Akduman D, Naiboğlu B, Uslu C, Oysu Ç, Tek A, Sürmeli M, et al. Total larenjektomi sonrası farengokütanöz fistül: Sıklığı, etkileyen faktörler ve tedavi yaklaşımı. Kulak Burun Bogaz Ihtis Derg 2008; 18: 349-54.
32. Soylu L, Kiroglu M, Aydogan B, Cetik F, Kiroglu F, Akçali C, et al. Pharyngocutaneous fistula following laryngectomy. Head Neck 1998; 20: 22-5.
33. Ikiz AO, Uca M, Guneri EA, Erdag TK, Sutay S. Pharyngocutaneous fistula and total laryngectomy: possible predisposing factors, with emphasis on pharyngeal myotomy. J Laryngol Otol 2000; 114: 768-71. [CrossRef]