Meta-Analysis of the Incidence of Pharygeocutaneous Fistulas In Laryngectomized Patients

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Abstract

Background: Laryngeal cancer is the seventh most common cancer worldwide, with significant morbidity and mortality. Treatment often involves total laryngectomy, leading to complications such as

Pharygeocutaneous fistulas (PCF) in 10-20% of cases. PCFs impede recovery and worsen patient outcomes, with risk factors including nutritional status, surgical techniques and pre-operative radiotherapy.

Methods: A retrospective analysis of 19 studies including over 5000 patients was conducted to evaluate the incidence of PCF in laryngectomized patients. The study focused on laryngectomies performed for laryngeal carcinoma. Examining risk factors such as age, nutritional status and deficiencies, radiotherapy and surgical techniques. Studies unrelated to oncological treatment or those published before 2000 were excluded.

Results: No significant difference in the rate of PCF was found between oral feeding and feeding via a Nasogastric tube (NGT). Hypoalbuminemia was a notable risk factor in the development of PCF. Advanced tumour stages (T3 and T4) were linked to a higher incidence of PCF, though statical significance varied. Continuous suturing and mechanical sutures showed reduced PCF risk compared to interrupted and manual sutures.

Conclusion: PCF are the most common complication post-laryngectomy, with factors like hypoalbuminemia, low haemoglobin and preoperative radiotherapy increasing the risk. Pre-operative optimization of the nutritional and haematological status is recommended to lower PCF incidence and improve patient outcomes and quality of life.

Key words: Laryngeal carcinoma, Pharygeocutaneous fistula, NGT and feeding

Introduction

Laryngeal cancer (LC) accounts for a considerable number of total head and neck cancers and is the 7th most common type of cancer worldwide, making It a major cause of morbidity and mortality and reduced quality of life.

Risk factors can be grouped into non-modifiable risk factors such as age - those over the age of 55 are at greater risk, family history, male gender. The majority of cases are associated with modifiable risk factors such as the smoking or chewing of tobacco as well as second hand smoke exposure, alcohol, beetle nut chewing, gastro-oesophageal reflux disease (GERD) and Infection with Human Papilloma Viruses (notably subtypes 16 producing oncogene E6 and subtype 18 producing oncogene E7). The majority of laryngeal cancers are squamous cell carcinoma and found in the glottic region, other less common types of neoplasms of the larynx include salivary gland carcinoma, adenocarcinoma and lymphoma.

The treatment of Laryngeal carcinoma varies based on the stage of the disease, T0 (Carcinoma in Situ)

T1 and T2 are usually managed with radiotherapy or trans-oral laser surgery whereas stages T3 and T4 are managed with concurrent chemotherapy and radiotherapy or total laryngectomy for bulky T4 disease and salvage. Evidence of metastatic spread to cervical lymph nodes may also require neck dissection. Surgical intervention aims to remove malignant tissue and prevent metastatic spread and disease progression. The procedure can cause iatrogenic complications including, acute blood loss, transient hyperthyroidism and hypoparathyroidism, surgical site infections and Pharygeocutaneous fistula.

Pharygeocutaneous fistula (PCF) are the most common complication of laryngectomies and can severely impede wound healing, patient recovery and quality of life. Post-surgical complications also exacerbate existing problems of a lack of finances and resources in the public care sector, this is

because of prolonged occupation of beds and the increased burden of monitoring patients.

Fistulisation occurs at the level of surgical incision or around the tracheostoma to create a connection between the digestive tract and the cervical skin.

Many risk factors have been linked with PCF such as hypoalbuminemia (<3.5g/L) and pre-surgical malnutrition, haemoglobin concentrations less than

120g/L, serum Amylase concentrations, previous neck irradiation, surgical technique and suture material, age and timing of postoperative feeding.

Diagnosis is based on the presence of salivary secretions on the surface of the neck, localised erythema, oedema and pain are also indicative of infection of the fistula tract. Patients fitted with a tracheostomy tube may develop an abnormal connection between the trachea and posteriorly situated oesophagus, Tracheoesophageal fistula (TOF). TOF may become apparent due to secretions on to the cervical skin when coughing and the aspiration of stomach and oesophageal content into the trachea.

This is a very severe complication with a poor prognosis.

Hallmarks of infection such as leucocytosis and elevation of acute phase proteins and lactate are also likely to be seen on blood works. Although clinical presentation is usually adequate for the diagnosis of PCF, imaging techniques such as a Barium swallow fluoroscopy may be used to confirm the size and location of the fistula tract.

This is especially useful if surgical intervention is required.

Other diagnostic methods include the Methylene blue swallow test, the presence of the blue dye on the surface of the neck may be highly suggestive of the formation of a fistula tract. The size of the fistula can be categorised using the Zbar and Funk classification:

- Pharygeocutaneous fistula - An Anomalous connection between the pharynx and skin of the neck.
- Pharyngeostoma - A direct opening between the pharynx and skin, usually accompanied by necrosis of the cervical skin

Pharygeocutaneous fistula can also be categorised based on how long the fistula persists:

- Acute - Less than 2 weeks
- Subacute - Between 2 weeks and 3 months
- Chronic - Beyond 3 months

Most fistulae resolve with conservative intervention such as packing of the fistula tract and drainage. Broad spectrum antibiotics with aerobic and anaerobic coverage are recommended to prevent infection and associated complications.

Complicated or persistent fistulae may require surgical intervention - detrimentalto the patients recovery, quality of life and disease prognosis

Complications of PCF are seen in 10-20% of patients, this can include nosocomial surgical site infection, notably with Methicillin-Resistant Staphylococcus Aureus (MRSA) and Pseudomonas Aeruginosa, fistula recurrence, Carotid Artery blowout haemorrhages, pharyngeal stenosis, hypoparathyroidism and hypocalcaemia, aspiration pneumonia and mediastinitis.

The aim of our study was to consolidate the current data available on the incidence of PCF's in laryngectomised patients and examine their associated risk factors.

Methods

As part of our retrospective analysis a number of different databases were used: PubMed, Google Scholar, ScienceDirect and Elsevier Scopus, a total of 20 relevant studies were identified with over 5000 subjects participating

To narrow our search we set inclusion criteria to include studies reporting the incidence of Pharygeocutaneous fistula after laryngectomy and only those studies which were done on patients who had laryngectomies to manage laryngeal carcinoma. Risk factors we analysed included age, neoadjuvant radiotherapy, preoperative malnutrition, previous neck irradiation, surgical and suturing methods and post-operative feeding regimes and post-operative serum amylase concentrations.

Studies were excluded if laryngectomy was not performed as part of cancer treatment. Studies published before the year 2000 were also omitted.

Results: different factors

I. Oral Feeding Vs NGT Feeding:

The timing and methodology of feeding laryngectomised patients is highly debated amongst clinicians with some in favour of physiologically correct oral feeding to also minimise demands on staff and resources. While others favour the placement of a NGT to reduce mechanical stress on the suture line.

A meta-analysis of 602 laryngectomised patients was conducted by Süslü Et Al 2015. Of these patients, 582 were fed orally and only 20 were fed via an NGT. 69/582 orally fed patients developed PCF (11.80%) compared to 3/20 in the patients with an NGT (15.00%). No statistical difference for the formation of PCF was found in these two groups, P = 0.722. Although there was no identified statistic difference, tumours which had spread to include the base of the tongue were significantly more likely to cause PCF. Similar conclusions were made by a number of different authors including Aswani Et Al 2008: 79 patients were included In this study, 39/79 received oral feeding, 6 of whom developed PCF (15.40%) and 40/79 who had a NGT placed with 8 going on to develop PCF (20.00). No statistical difference was found between the two groups, P = 0.592.

The works of Bulgurcu Et Al 2018 also compared oral feeding and feeding via a NGT. Although no statistical difference was found between the two groups (P>0.05), preoperative hypoalbuminemia (Albumin < 3.50g/Dl) was found to be a significant factor (P = 0.001) in the formation of a fistula tract. Preoperative hypoalbuminemia is associated with malnutrition and inadequate protein intake. This may be caused by the reduced desire to eat in patients with throat and neck neoplasms often due to symptoms such as dysphagia and globus sensation In the throat. The lack of statistical significance between these two groups was reinforced by the findings of Sharifian Et Al 2008. 25 patients underwent total radical laryngectomy for the treatment of squamous cell carcinoma of the larynx 13/25 were fed orally and 12/25 were fed by NGT. Only 1 case of PCF was observed in each of these groups, with the development of fistula found to be insignificant.

Seven Et Al 2003 compared oral feeding to feeding via a Trans-esophageal puncture (TEP), opposed to an NGT. Seven's control trial found that 2/32 (6.20%) orally fed subjects developed PCF and 3/33 (9.00%) subjects with TEP formed a PCF. This shows a lack of statistical significance between the two groups. Seven proposed that TEP is less likely to irritate the suture line opposed to NGT. However, no data of significance was provided on this matter and may need to be investigated in subsequent studies.

II. Pre-operative Malnutrition:

Numerous studies have identified hypoalbuminemia (serum Albumin concentration <3.50g/Dl) and hypohaemoglobinaemia (Males < 130g/l and in Females < 120g/l) as major risk factors in the development of PCF.

Birkmeyer Et Al 2006 identified post-operative hypohaemoglobinaemia as an important risk factor in the formation of PCF with a relative risk of 2.10 (RR 2.10). This indicates that laryngectomised patients with low haemoglobin concentrations are more than twice as likely to develop PCF than patients with normal blood haemoglobin concentrations.

Hemdan Et Al 2022 conducted a multivariate analytic study which included 203 patients who underwent a total laryngectomy with neck dissection for the treatment of laryngeal squamous cell carcinoma. A profound correlation between prealbumin, albumin, and transferrin levels with PCF development. In a multivariate logistic regression analysis, preoperative prealbumin emerged as the strongest independent nutritional predictor of PCF (P value <0.001 and an odds ratio of 11.951 (95% CI 3.686-38.749). Preoperative albumin was the next significant predictor (P value of 0.006 and an odds ratio of 3.985 (95% CI 1.485-10.694.

Mattioli et al 2015 conducted a retrospective study involving 69 patients who underwent laryngectomy between January 2008 and January 2012. Among these, 24 patients developed a Pharygeocutaneous fistula (PCF), indicating an incidence rate of 34.8%. The study cohort included 59 males (85.5%) and 10 females (14.5%).The study identified a significant correlation between pre-operative albumin levels below 3.5 g/dL or pre-albumin lev-

els below 20 mg/dL and the development of PCF. As illustrated in Figure 1, 53.6% of patients who developed PCF had pre-operative albumin levels below 3.5 g/dL or pre-albumin levels below 20 mg/dL. This correlation was statistically significant, with a p-value of 0.005.

Other risk factors of significance which were identified by Mattioli include Diabetes Mellitus (P=0.004)

III. Tumour Size and Location:

The size & location of laryngeal tumours in patients that undergo laryngectomy is debated as a common risk factor in the development of Pharygeocutaneous fistula, post laryngectomy. Many clinicians argue that the more advanced the tumour, the greater the risk of Pharygeocutaneous fistula development. Early detection of malignant tissue transformation is of utmost importance in limiting

Risk factor	% patients with fistula	% patients without fistula	p value
G1	50	50	0.18
G2	22.2	78.8	
G3	48.5	51.5	
Gx	16.7	83.3	
T1	66.7	33.3	0.51
T2	34.3	65.7	
T3	25	75	
T4	38.1	61.9	
N+	75	25	0.41
N-	30	70	
R1	31.2	68.8	0.7
R0	36.5	63.5	
AJCC stage I	50	50	0.42
AJCC stage II	40	60	
AJCC stage III	18.8	81.2	
AJCC stage IV	42.5	57.5	
Previous RT	40	60	0.72
No previous RT	34.5	65.5	
Primary surgery	41.2	58.8	0.06
Savage surgery	16.7	83.3	
Previous tracheostomy	40	60	0.56
No neck dissection	22.2	77.8	0.26
Monolateral neck dissection	31.8	68.2	
Co-morbidity			
Diabetes	77.8	22.2	0.004
No diabetes	28.3	71.7	
Vasculopathy	42.9	57.1	0.41
No vasculopathy	31.3	68.7	
Preop Hb < 12.2 g/dl	45	55	0,14
Preop Hb > 12.2 g/dl	30.6	69.4	
Preop albumin < 3.5 g/dl or prealbumin < 20 mg/dl	53.6	46.6	0.005
Preop albumin > 3.5 g/dl or prealbumin > 20 mg/dl	120	180	
Albumin during hospitalisation			0.4
Decrease	80	20	
Increase	35.3	64.7	
Unchanged	50	50	
Hb during hospitalisation			0.34
Decrease	34.6	65.4	
Increase	44.4	55.6	

Fig 1.

Univariate analysis of the impact of predisposing factors on fistula formation

disease progression, metastasis and improving patient prognosis and quality of life. Many clinicians have proclaimed that surgical intervention to remove advanced tumours (T3/T4) may be more likely to promote the establishment of Pharygeocutaneous fistula opposed to the removal of less advanced tumours.

Saydam Et Al 2002, conducted an analysis on 48 patients that underwent total laryngectomy, of which 45 had T3 or T4 tumours and 3 had T1 or T2 tumours. The incidence of PCF was seen in a total of 6 (12.5%) patients, all of whom had T3 or T4 tumours. Although the difference between the group that developed PCF and the non-fistula group was not statistically significant (P = 0.66), the association between advanced tumour stage and the development of PCF has been observed by several researchers, including Fitzgerald et al., who conducted a retrospective cohort study involving 550 patients after laryngectomy. Of these patients, 264/550 (51%) had T1 or T2 tumour and 242/550 (48%) patients had T3 or T4 tumour. 127/550 (23%) of patients developed PCF. Fitzgerald's univariable analysis found that the T3 & T4 tumours required wider anatomical resections, which left less tissue available for pharyngeal closure, which impaired anastomotic healing thus leading to PCF.

Dedivitis Et Al 2007 conducted a retrospective study comparing 55 patients who underwent total laryngectomy and compared a range of risk factors associated with PCF development. 36/55 had T1 or T2 tumours and 12/55 had T3 or T4 tumours. 7/55 patients developed PCF, of whom 4 (25%) had T3 or T4 tumours and 3 (7.7%) had T1 or T2 tumours, however there was no statistical significance P = 0.926, between the two groups.

A meta-analysis of 2446 patients who underwent total laryngectomy was conducted by Rao Et Al in 2022. 8/131 (6.11%) patients with T1 or T2 tumours developed PCF, in comparison to 140/1054 (13.28%) patients with T3 or T4 tumours. P = 0.481 further highlighting the statistical insignificance between tumour stage and the occurrence of PCF.

In Süslü Et Al 2016 analysis, 264 (51%) of the patients had T1 or T2 tumour and 242 (48%) had T3 or T4 tumour. 127 (23%) patients developed PCF. Once more, there was no statistical significance between results P = 0.722, Süslü found that tumours that had metastasised to involve the base of the tongue were significantly more likely to cause PCF development.

IV. Suturing Techniques:

The most common type of suturing technique used in total laryngectomy is simple interrupted suture. In pharyngeal closure, continuous Connell suture is used. Recently, newer techniques such as the zipper suturing have been implemented to reduce PCF development post laryngectomy. Different suturing techniques have been shown to increase risk of Pharygeocutaneous fistula development post laryngectomy.

Deniz Et Al 2015 conducted a retrospective study which included 20 patients who underwent total laryngectomy for stage 4 laryngeal carcinoma. 4/20 patients developed PCF. 13/20 patients had cushing type continuous sutures and none developed PCF in the postoperative period. The remaining 7 patients underwent interrupted sutures, of which 4 (57.14%) developed PCF. There was a statistically significant difference between the two different suture groups and PCF development, P=0.007.

Goncalves Et Al 2008 compared formation of PCF in patients who underwent total laryngectomy with either manual or mechanical sutures. The study included 60 patients, 30 with mechanical linear stapler sutures & 30 with manual sutures. 2/30 (6.70%) developed PCF, both cases were concluded to be due to failure of surgical technique. 11/30 (36.70%) of patients who had manual sutures developed PCF. There was a statistically significant difference between the two different suturing groups, P = 0.0047. Mechanical suturing methods are used more frequently as they are easier to learn, & allow for watertight closure of the pharynx, reducing the risk of contamination and infection of the surgical field and reduced risk of PCF development.

Rao Et Al 2022 meta-analysis found that of the 504 patients that underwent total laryngectomy with vertical T type closure, 112/504 (22.22%) developed PCF. The other 55 patients that underwent total laryngectomy with horizontal closure, 16/55 (29.09%) developed PCF. There was no statistically significant difference between the two different closure groups, P = 0.385.

Algargaz Et Al 2022 conducted a study where a total of 59 patients underwent total laryngectomy, 22 had stapler suturing and 37 had manual suturing. 60.5% of patients who underwent stapler suturing developed PCF and 59.9% of patients that underwent manual suturing developed PCF. Although there was no statistically significant difference between the two groups P = 0.83, there was a reduced risk of PCF development in patients with stapler suturing in comparison to manual suturing.

V. Age and Sex:

The age and sex of a patient is debated as a potential risk factor for PCF development post total laryngectomy. It's noted in several studies that an increase in age is often associated with a significantly increased risk of

Pharygeocutaneous fistula development. In Devivitis 2007 Et Al study of the different risk factors associated with PCF development, including sex and gender, he found that there was no statistically significant association between PCF development and sex, P=1.00. In addition to this Devitis analysis found that elderly patients over the age of 60 years had a statistically significant increased risk for PCF development P = 0.051.

However, Fitzgerald Et Al 2022 study found that there was no statistically significant association between age at diagnosis P = 0.12, nor was there any association between sex & PCF development, P = 0.46.

The lack of statistical significance between sex, age and PCF development was further reiterated in the retrospective cohort study conducted by Aslier Et Al 2016. 183 patients underwent total laryngectomy as treatment for laryngeal squamous cell carcinoma. 10/183 were female, and 173/183 were male - 6 females, & 140 males developed PCF, however there wasn't a statistically significant difference between the two sex's P = 0.119. 75/183 patients were over 60 years of age and 108/183 were under the age of 60. Of those aged 60 and above, 64 developed PCF and of those below the age of 60, 82 developed PCF. Again there was no statistically significant difference between the two age groups P = 0.119.

Kilic Et Al 2015 conducted a retrospective study on 166 patients who underwent total laryngectomy for the treatment of laryngeal carcinoma. 32/166 (19.2%) of patients developed PCF, all of which were over the age of 61. There was a statistically significant difference between age and increased risk of PCF, P = 0.003. Kilic did not identify any significant association between sex and PCF development. Rao Et Al 2022 didn't find any increased risk associated with age, sex & PCF development. 300 patients under the age of 65 underwent total laryngectomy and of these only 33/300 (11%) developed PCF. 145 patients over the age of 65 underwent total laryngectomy, & 17/145 (11.72%) developed PCF. There was no statistically significant difference between patients over the age of 65 or those under the age of 65 and PCF development. Rao also found no increased risk associated with either sexes and PCF development - 1113 males underwent total laryngectomy and 119/1113 (17.88%) developed PCF. Only 73 females underwent total laryngectomy and 9/73 (12.3%) developed PCF. Overall there was no statistically significant difference between the two sex's P = 0.684.

VI. Radiotherapy:

Postoperative and preoperative radiotherapy has been known to cause late complications, such as Pharyngocutaneous fistula development post total laryngectomy. Advanced laryngeal cancers are often treated by combining radiation with concurrent chemotherapy for larynx preservation and total laryngectomy for bulky T4 disease or salvage.

Dirven Et Al 2009 conducted a retrospective review of 152 patients that received surgical treatment for primary laryngeal squamous cell carcinoma. Following previous definitive radiotherapy treatment 38 patients underwent salvage surgery and 114 patients underwent primary surgery with curative intent. Dirven found that 75% of patients who had received radiotherapy within 4 months of laryngectomy developed PCF, compared to 25% who underwent surgery after 4 months of radiotherapy treatment. There was a statistically significant difference between the two groups, P = 0.034. Dirven also found that there was a statistically significant difference between PCF development based on the dose of radiotherapy given prior to total laryngectomy, patients who received a median dose of 70

Gy. had a significantly higher risk of PCF development, P = 0.001.

Grau Et Al 2003 conducted a survey with 472 patients that underwent post-irradiation salvage laryngectomy. 89/472 patients developed PCF. Grau found an increased incidence of PCF development in subgroups where patients had advanced initial T stage and non-glottic primary site laryngeal cancer.

In Fitzgerald Et Al analysis 383/550 (70%) patients received radiotherapy prior to total laryngectomy, of which 81 developed PCF. This finding was not statistically significant P = 0.14. In contrast, Goncalves Et Al 2009 analysis, found that neoadjuvant radiotherapy is closely associated with an increased risk of PCF. Goncalves found that there was a statistically significant difference between the use of mechanical sutures that reduced the incidence of PCF in patients who previously received radiotherapy in comparison to those who had manual suturing, P = 0.0048. Mattioli Et Al conducted a retrospective study in 2015 regarding the risk factors associated with PCF development in laryngeal cancer patients post laryngectomy. 69 patients underwent total laryngectomy and 24/69 (34.8%) developed PCF. 40% of the patients that developed PCF had received previous radiotherapy.

Although there was no statistical significance P = 0.72, it's thought that previous radiotherapy can increase the incidence of PCF development due to the decreased healing capacity, secondary to fibrosis and hypo-vascularization.

Conclusion

There is no significant statistical data linking the formation of PCF with NG feeding tube or early transoral feeding. There is a correlation between stage of the disease and the probability of forming PCF. There is a strong connection to suturing techniques of the neo hypopharynx and formation of postoperatively PCF. Preoperative radiotherapy leads to a higher risk of forming early or late PCF. As a prognostic method we can evaluate the serum levels of amylase ,the patients BMI and his serum albumin levels. Patients with preoperative malnutrition and low levels of albumin are factors that lead to higher levels of forming PCF. They can be used as prognosis markers. Low haemoglobin level preoperatively can be used as a prognostic tool as well. Based on the scientific data we recommend evaluating the preoperatively the patients levels of haemoglobin, albumin , BMI, amylase. In patents whose results are not desirable, it is preferable to compensate the patients levels to opt for prophylaxis of PCF. In most. Of the cases PCF is treated with compression bandaging, but if the tissues allow it there is a way to repair the defect with regional flaps or flee flaps. Different conservative and surgical approaches should be adopted according to the acute, subacute and chronic stages of PCF, and condition of the locoregional tissues.

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