HIGHLIGHTING THE PHARYNGOCUTANEOUS FISTULA RISK FACTORS AFTER TOTAL LARYNGECTOMY

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Abstract:

Pharyngocutaneous fistula (PCF) is a major complication after total laryngectomy involving prolonged hospitalization, additional discomfort and increased treatment costs. This retrospective study, conducted over a 5 year period, included 118 patients that underwent total laryngectomy after larynx carcinoma. Various factors influencing PCF development are discussed. Statistical analisys of the results show an important role of smoking and alcohol abuse, tumor stage and extension, pre-operative radiotherapy and local complications. In studying PCF developing risk factors, multicenter studies are absolutely necessary.

Keywords: *carcinoma, larynx, laryngectomy, fistula*

Introduction:

Pharyngocutaneous fistula (PCF) can be defined as a pharyngeal mucous dehiscence through which saliva can flow and thus communicates with the skin[1]. This major complication of total laryngectomy involves prolonged hospitalization, additional discomfort and, from the economic point of view, increased treatment costs[2].

Through the 1970's and 1980's, various studies reported PCF prevalence to vary between 5% and 65%. However, from 2000 up until 2010, a 9% to 25% drop in prevalence was observed [3].

Treating patients with PCF requires prolonged antibiotic treatment and additional surgical maneuvers (such as gastrostomy, flap fistula closure, etc) that may result in physically and psychological stress, all leading to major complications such as, sepsis, mediastinitis, pneumonia and carotid artery rupture or to minor complication such as pharyngeal stenosis.

Also the moment for the usefulness complementary treatments, radiotherapy and chemotherapy is delayed if post-surgical complications occur.

Although numerous factors have been implicated in the development of PCF, no consensus has been reached regarding the most significant risk factors[4,5].

Various authors have incriminated: pharynx tumoral resection extension[6,7], tumor location[8,9,10], radiotherapy[3,5,11-14], associated systemic diseases[3,5], neck dissection[5,6], positive resection margins[3,11,15], gastroesophageal reflux[16], decreased hemoglobin value[17], hypoalbuminemia [13], tumor recurrence[10], chronic congestive cardiac diseases[17], suture material[9], smoking[18], chronic pulmonary disease[18], patient age[15], alcohol consumption[19] and surgeon's experience[19].Therefore, the risk factors can be grouped in the following categories:

- patient related factors: sex, age, smoking, alcohol consumption, associated systemic diseases (cardiac, pulmonary, gastroesophageal reflux,

low hemoglobin, hypoalbuminemia, other diseases);
- tumor related factors: stage, tumor location;
- required treatment: quality of therapy

Material and method:

This retrospective study was conducted over a 5 year period (2011-2015). The number of patients included in this study who underwent total laryngectomy totaled 118. The study was conducted in the Ear Nose Throat (ENT) Clinic in the Clinical Rehabilitation Hospital in Iasi and had the acceptance of the Ethics Commission.

The main independent variables of the study were: age, sex, tumor stage and location. The rest of the variables such as: associated diseases, blood constants, postoperative evolution, preoperative and postoperative tumor excision margins based on microscopic results, the existence of ganglion invasion and if any preoperative radio or chemotherapy was done; were considered dependent variables. The following indicators have been calculated: prevalence (%), odds ratio (OR-the relative estimated risk) and its confidence interval (CI 95%) and the risk factor attributable risk (AP).

The results of the sex distribution lot analysis were: 112 (94,92%) were men and 6 (5,08%) women. Mean age in the lot was 64 years.

Among the 118 patients, 76 (64,41%) had total laryngectomy, 38 (32,20%) had total laryngectomy and glossectomy and partial pharyngectomy, 3 (2,54%) total pharyngo-laryngectomy and 1 (0,84%) total pharyngo-laryngectomy with partial glossectomy.

For all patients, a thorough control of ganglionic areas was achieved through radical or functional dissection on various areas.

The pharyngeal sutures were two-plane; a Lembert-type muscle plane (serosubmucous) covered by the second perichondromuscular plane.

In cases where ganglionic areas were dissected, large blood vessels were covered by muscle. Four patients underwent total pharyngolaryngectomy from which three patients had reconstructive surgery using the pectoralis major flap and the other patient underwent reconstructive surgery using a radial flap. A nasogastric tube was used for all patients that underwent surgery for 7 to 8 days postoperatively.

Results and Discussions:

In the majority of cases, (88,98%) good postoperative evolution, was noted. The patients were able to be discharged 9 to 12 days postoperatively. In the majority of cases, delayed trachea anchoring suture thread removal was performed, which led to prolonged hospitalization from 7 days (incision suture thread removal moment) up to 10 to12 days.

In 15 (12,71%) patients initial treatment consisted of radiotherapy followed by laryngectomy.

Of the 118 patients, PCF developed in only 13 (11,02%) patients. The PCF developed within an average of nine days, however, the time frame for fistula development ranged from 5 to 12 days.

Of the 13 post-operative fistulas, 10 closed in 12 to 30 days while in three other cases, surgical intervention was necessary for fistula closure. Patients that had small fistuals where surgical intervention was not necessary in order to be closed, the nasogastric tube placed post-operatively was maintained until the fistula fully closed.

To ensure inactivity of the upper digestive system in patients with high flow PCF, a gastrostoma was performed and kept in place until the fistula closed properly.

Other encountered complications were: hematomas in 29 cases (24,58%), secondary hemorrhage in 4 cases (3,39%) and fever above 38 °C in 18 patients (15,25%).

The analysis of PCF factors shows the following:

1. **Patient related factors**:

Patient sex – Of the 118 patients that underwent laryngectomy, 6 were women. All the women operated never developed fistulas post-operatively. Since the number of women was statistically insignificant, a protective value based on sex cannot be taken into consideration.

Smoking – From the men that underwent laryngectomy, all were smokers and of the women operated, 4 were smokers. Even though smoking has been taken into account in separate [2,6,7,13] or multicentric studies [19], significant influence in PCF development has not be noted. The multicenter study [19] included 846 studies of which only 39 studies were selected for review and had statistical significance showing that smoking is not a risk factor.

The prevalence of patients that smoked was high (Table I) and it was observed that PCF development was greater in smokers than non-smokers (OR=4.4615; CI 95%: 0,3781-52.6409; AP=0,7758). In conclusion, the statistical analysis of the data included in our study shows that smoking is a risk factor in PCF development.

Table I: Patient related PCF risk factors, blood constants and associated disease

Patient, blood constants, associated disease	PCF No. (%)	Total Patients (%)
Smoking	13 (11.20%)	116 (100%)
Nutritional deficiency	10 (47.62%)	21 (17.80%)
Low hemoglobin	10 (23.26%)	43 (36.44%)
Leukocytosis + Thrombocytosis	13 (14.77%)	88 (74.58%)
Arterial hypertension (HTA)	1	22 (18.64%)
Hepatic disease	1	13 (11.02%)
Diabetes	3	13 (11.02%)

Alcohol ingestion – In the lot of studied patients, 86 male patients (76,79%) were considered chronic alcoholics, from which 9 (7,63%) patients developed PCF (OR=1,1944; CI 95%: 0,3437-4,1515; AP=0,1627).

The results from the statistical analysis, incriminates alcohol consumption as a PCF risk factor.

Nutritional deficiencies –Although according to some authors, deficiencies in which 10% of body mass was lost were regarded as risk factors in PCF development [20,21], others in accord with American Society of Anesthesiologists did not find any significant associated between nutritional deficiencies and PCF development [6,17,22].

Regarding our study, of the 118 operated patients, 21 (17,80%) had nutritional deficiencies of which 10 (47,62%) had PCF (OR=0,0962; CI 95%: 0,0271 – 0,3422).

2. **Blood constants:**

Decreased **hemoglobin**, **leucocytosis** and **thrombocytosis** are considered as significant risk factors in PCF development[4, 21].

Based on a lot of 3,420 cases, authors like Schwartz et al[21], Tsou et al[13], Cavalot et al [23] and Esteban et al[24] consider that low hemoglobin values are a risk factor for PCF while other authors like Qureshi et al[2], Redaelli de Zinis et al [17], Palomar-Asenjo et al [7], Wakisaka et al [25] and Morton et al[26] do not.

For our patients, a lower than 12,5% haemoglobin was established for 43 (36,44%) patients from which 10 (23,26%) developed PCF (OR=0.2293; CI 95%: 0,0678-0,7758).

Leucocytosis and thrombocytosis was found in 88 (74,58%) patients, 13 (14,77%) patients had developed PCF (OR=0.2256; CI 95%: 0.0283 – 1.7985).

3. Asociated disease:

Hypothyroidism has been incriminated as a wound complication determining factor in head and neck cancer patients [14]. In our study, no hypothyroidism was found in any of the patients.

Myocardial infarction is mentioned as an enhancing factor in PCF development [13]. Our patients were carefully observed after surgery in order to prevent a possible cardiac event but none occurred.

Chronic obstructive pulmonary disease has been considered by Boscolo-Rizzo et al [27] and Wulff et al[18] as a significant risk factor.– In a 501 patient analysis, Pinnar et al [28] and Radaelli de Zinis et al[17] have not found enough evidence to sustain the assumption that these diseases are a risk factors. In our study two of the patients with fistulas had pulmonary complications.

Hepatic cirrhosis and other hepatic diseases have been previously associated with fistula in studies of a total 671 patients [13,23,27]. In our study we have encountered hepatic disease with modified hepatic laboratory tests in 13 (11,02%) patients out of which 1 developed PCF.

Diabetes is considered as a major risk factor for PCF by Scwartz [21], Cavalot [23] and Boscolo-Rizzo [27] of a total of 2,500 patients- studied. Other studies that included a lot of a total 845 patients did not consider it a significant factor [17,25,28,30]. Among the patients included in our study, 13 (11,02%) had diabetes, of which 3 devoloped PCF; of these patients 2 were insulin dependent and 1 patient was not dependent on insulin (OR=0.4127; CI 95%: 0.1004-1.6956).

Arterial hypertension has been associated with fistulisation by Makitie [1], Pinar [28] and Radaelli de Zinis [17] in studies which totaled 769 patients. Among studied patients, 22(18,64%) had high blood pressure and only one patient developed PCF.

Fever that developed after surgery has been considered as a PCF forming factor [1,27,30]. In our opinion, patients that develop local infections have a fever of 38^0 to 39^0 C starting with the second post-operative day. This symptom foreshadowed fistula formation. Of the patients operated, two patients that developed PCF had fever.

4. Tumor related factors:

Regarding the relationship between tumor staging and PCF, the majority of authors [2,3,6,13,23-26, 29,31-33] that studied 3,036 patients in total, did not find that advanced tumors (T4) represent a significant risk factor for PCF formation. Not all the studies had the same considerations and presented results showing that an advanced tumoral stage was an enhancing factor for PCF formation [34-36].

Aires et al [37] considered that PCF prevalence is significantly higher for tumors in the T4 stage in comparison to patients with tumors in stage T2 or T3. In this particular study, a total of 94 patients underwent total laryngectomy, of which 20 patients (22.27%) had developed PCF (OR=0.3034; CI 95%: 0.0977-0.9417).

In our study, 27 patients had T4 stage tumors and (tab. II), 6 (22,22%) of them developed fistulas. Statistical analysis shows that T4 stage tumors are a risk factor for PCF development.

Out of 89 **T2-T3 tumor stage** patients, just 7 (7,87%) developed PCF; the prevalence for this type of complication being 7,89% in this subgroup (Tab. II).

Table II. Primary tumor stage related to PCF development enhancing factors

Tumor stage	Number PCF(%)	Patients
T4	6 (22.22%)	27

T2-T3	7 (7.87%)	89

As far as **ganglionic invasion** is concerned, there are no concurring opinions. Some authors have established a link between fistula development and advanced stage ganglionic invasion [23,26] and others does not consider ganglionic invasion as a risk factor [29].

Differences in opinion about tumor histology exist between those who consider that a well-differentiated tumor enhances fistula development [30] and the majority of authors [17,31,33,35] believe there is no correlation.

5. **Treatment related factors:**

Choosing the best therapeutic algorithm is a major concern for oncologists. Thus, tumor treatment may benefit form 3 therapeutic approaches: surgery, radiotherapy and chemotherapy.

Choosing the first line of therapy is done by taking into account the patient's status, tumoral characteristics, local availabilities and patient informed consent (it is unlikely that an experienced medical professional would consider surgery as the first line of treatment).

In 54% of the studies analyzed, the decision to use **radiotherapy** as the first line of treatment in the case of PCF, shows a strong correlation between preoperative radiotherapy and PCF [19]. Studies have shown a stronger correlation between PCF and pre-operative radiotherapy due to studying a greater number of patients.

In a review Cecatto et al had published in 2013, included 846 other studies, out of which 83 were selected and later only 39 studies were considered for analysis (they were evaluated by 2 investigators and divergences were solved after consensus) [19]. The meta-analysis reiterated the significant role of radiotherapy in PCF development.

Hilliary [38] has found a significant correlation between PCF and laryngectomy predating irradiation therapy and no correlation between intervention chemotherapy prior to surgery and PCF

In our therapeutic algorithm, **surgery** usually represents the first therapeutic gesture and in rare cases radiotherapy is performed before surgery. Out of the patients studied, just 15 (12.72%) patients were irradiated before surgery, out of which 6 developed PCF (OR=5.8857; CI 95%: 1.7419-19.8876; AP=0.8301, p=0.00689). Irradiation is a statistical significant factor in PCF development.

As far as pre-operative radiotherapy in association with chemotherapy is concered, Wakisaka et al [25], Klozar et al [35] and Dirven et al [39] suggest that there is a positive correlation between pre-operative radiotherapy and post-operative fistula development.

Radical neck dissection is not considered a risk factor for PCF development and it is debated by many authors. The majority of authors [13,15,17,26-28,31,35,36,40] found no correlation that was statistically significant between fistula formation and radical neck dissection, after analyzing 10 studies and 2,200 total patients.

Other authors [5,6,33,41], have established that radical neck dissection enhances PCF development, after analyzing 4 studies and 840 cases.

Out of the patients in this study, 32 (27.12%) patients underwent radical neck dissections, of which, 6 (18.75%) patients developed PCF. The data in Table III reveals that 32 (27.12%) patients underwent radical neck dissection and of these patients was 6 (18,75%) patients developed PCF (OR=0.5365; CI 95%: 0.1862-1.5460).

Table III. Surgical treatment related to PCF development risk factors

Surgical treatment	PCF number (%)	Total cases (%)
Radical neck dissection	6 (18.75%)	32 (27.12%)
Pre-operative tracheotomy	9 (23.68%)	38 (32.20%)
No tracheotomy	4 (5.13%)	78 (66.10%)
Pharynx tumor	11 (21.57%)	51 (43.22%)
Larynx tumor	2 (2.98%)	67 (56.78%)

The **tumoral infiltration of surgical resection margins** is considered [25,3,15] as an enhancing factor in PCF development in 965 cases while in 645 total studies [2,23,17] there is no statistically significant correlation between these factors.

Among our patients just 1 had positive resection margins.

Tracheotomy before the intervention: From a prognostic and evolutive point of view, tracheotomy performed prior to surgical treatment is not just a risk factor for fistula formation but also laryngeal neoplasm.

If only PCF is concerned, the majority of authors did not acknowledge a positive correlation between pre-operative tracheotomy and PCF development [3,10,15,17,20,21,23,24,28,31,36].

Other authors [31,42,43,44] consider that pre-operative tracheotomy is a risk factor for PCF development, after analyzing 384 patients.

As for patients in our study, because of multiple other negative influences that tracheotomy would pose (local infection, unachievable tumor related safety limit), we proposed whenever it is possible to perform both tracheotomy and extemporaneous biopsy at the same time with the total laringectomy. This protocol was applied to 78 (66.10%) of our patients and each time, an extemporaneous biopsy—of the surgically removed specimen was later anatomopathologically examined, confirming the diagnosis. Out of the patients included, only 4 (5.13%) patients developed PCF; out of 38 (32.00%) patients who underwent tracheotomy before surgery, 9 (23,68%) developed PCF. Statistical data analysis (OR=2.131; CI95%: 0.8464-5.3656; AP=0.5307) showed that tracheotomy is a risk factor for PCF development.

Pharyngeal tumor extension is a debated factor in literature. Some authors recognize it as a risk factor [7,17,35,38,45]. On the other hand, Schwartz [21], in a multicenter study of 2,063 patients did not find a statistically significant correlation between pharyngeal tumoral extension and PCF.

Regarding the 118 patients in our study, the tumor extended into the pharynx in 51 patients (43.22%) and among these patients, 11 (21.57%) developed PCF. Statistical analysis results (OR=2.768; CI 95%: 1.2942-5.9200; AP=0.6387; p=0.0052) show that pharyngeal tumor extension is a statistically significant risk factor in PCF development.

From among 67 patients (56.78%), without pharyngeal tumor extension, only 2 patients (2.98%) developed PCF.

Other local complications like hematomas and local infection are considered significant risk factors for PCF development [15,28,46].

In our studied cases, infection had determined PCF in 1 patient that was discharged after 8 days of hospitalization with tracheal anchoring sutures and returned 22 days later with an infection located at the site of the tracheal sutures. Two days after tracheal suture removal, 24th post-operative day, the patient had developed PCF. Another two patients developed a local infection on the 3rd post-operative day and developed PCF on the 6th post-operative day (OR=0.4936; CI95%: 0.1225-1.9881). Another patient with a hematoma developed a PCF on the 8th pot-

operative day that spontaneously closed after 7 days.

PCF prevalence in our study was 11.02% and according to medical literature, this range is between 5% and 65%; however, these values have decreased in the last decade, reaching a prevalence of 9% to 25%.

The diseases and risk factors that increase the possibility for PCF development, based on statistical data, are as shown in Table IV.

Table IV Risk factors for PCF development after total laryngectomy

Patient related factors	Smoking
	Alcohol
Tumor related factors	Advanced tumor (T4)
Treatment related factors	Pre-operative radiotherapy
	Pharynx tumor extension
	Local Complications

In order to decrease the number of patients that develop PCF after total laryngectomy it is important to consider the following aspects:

- careful patient examination with a thorough comorbidity analysis;
- laryngeal examination with highlighting optics and CT or MRI;
- DST conducted antibiotherapy started at the moment of surgery ;
- thorough and carefully conducted dissection during the surgical procedure with a two-plane suture of the pharyngeal mucous;
- adequate materials for pharyngeal mucous suture and a meticulous approach to knot execution;
- daily follow-up of local development and quick intervention in case of PCF;
- pharyngeal rest by using gastrostomy in case of PCF;

In conclusion, a pharyngocutaneous fistula has a declining prevalence as an occurring complication regarding laryngeal surgical procedures; however, morbidity, hospitalization time and high health care costs are significant. We consider highly important studying the PCF developing risk factors, multicenter studies being absolutely necessary. It is important to study PCF and the risk factors that influence its post-operative development, thus making multicenter studies necessary in Romania as well.

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