

## HEAD AND NECK

# Analysis of risk factors for pharyngocutaneous fistula after total laryngectomy with particular focus on nutritional status

## *Fistola faringocutanea dopo laringectomia totale: analisi dei fattori di rischio con particolare attenzione allo stato nutrizionale*

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## SUMMARY

Pharyngocutaneous fistula (PCF) is the most common complication following total laryngectomy and the most difficult to manage. It often causes increased morbidity, delays starting adjuvant therapy, prolongs hospitalisation, increases treatment costs and reduces the quality of life (QoL). The objective of this study is to analyse the predisposing factors and the most important nutritional parameters related to the development of PCF in patients undergoing total laryngectomy and to suggest medical alternatives that might improve results. We performed a retrospective study of 69 patients who underwent either primary or salvage total laryngectomy in our department between January 2008 and January 2012. Risk factors for fistula formation were analysed including tumour characteristics (histology, grading, AJCC stage), treatment (primary or salvage surgery, extent of resection, flap reconstruction, preoperative radiotherapy), comorbidity and nutritional status (preoperative haemoglobin, albumin and prealbumin levels and their changes during hospitalisation). Twenty-four patients developed a PCF (overall incidence 34.8%). Fistula formation was significantly higher in patients with diabetes, preoperative malnutrition (identified from low preoperative albumin and prealbumin levels). After specific nutritional evaluation and support, no patient developed a PCF. Risk factors for PCF formation are extensively treated in the literature but identification of high-risk patients is still controversial. Our study demonstrates that nutritional status of the patient, assessed by preoperative albumin, is also an important risk factor for PCF formation in addition to classical factors. Maintenance of a normal preoperative nutritional status can be helpful to avoid this complication.

KEY WORDS: Laryngectomy • Pharyngocutaneous fistula • Malnutrition

## RIASSUNTO

*La formazione di fistole faringocutanee è una delle complicanze più frequenti dopo laringectomia totale e la più difficile da gestire. La comparsa di una fistola faringocutanea determina spesso aumento della morbilità, ritardo nell'inizio delle terapie adiuvanti, prolungata ospedalizzazione, aumento dei costi di trattamento e riduzione della qualità di vita. L'obiettivo di questo studio è analizzare i principali fattori di rischio e i parametri nutrizionali correlati allo sviluppo di fistole faringocutanee nei pazienti sottoposti a laringectomia totale e valutare i possibili interventi terapeutici finalizzati a ridurre l'incidenza di tale complicanza. Abbiamo effettuato uno studio retrospettivo su 69 pazienti sottoposti presso il nostro istituto a laringectomia totale, come trattamento primitivo o di salvataggio, fra gennaio 2008 e gennaio 2012. I fattori di rischio per la formazione di fistole faringocutanee analizzati sono stati: caratteristiche del tumore (istologia, grading, stadio, ecc.), trattamento (chirurgia primitiva o di salvataggio, estensione della resezione, ricostruzione con lembo, radioterapia preoperatoria, ecc.), comorbilità e stato nutrizionale (valori e trend di emoglobina preoperatoria, albumina e prealbumina). Dopo valutazione e supporto nutrizionale mirato nessun paziente ha sviluppato fistole faringocutanee. L'identificazione dei pazienti ad alto rischio di fistola faringocutanea dopo laringectomia totale è argomento ancora dibattuto in letteratura. Il nostro studio ha dimostrato che lo stato nutrizionale del paziente, valutato attraverso i valori di albumina preoperatoria, è anch'esso un fattore di rischio per lo sviluppo di fistole faringocutanee. Quindi il mantenimento di un stato nutrizionale adeguato può essere utile per evitare tale complicanza.*

PAROLE CHIAVE: *Laringectomia • Fistola faringocutanea • Malnutrizione*

Acta Otorhinolaryngol Ital 2015;35:243-248

## Introduction

Pharyngocutaneous fistula (PCF) consists of a communication between the digestive tract and the cervical skin that causes the appearance of saliva on the skin surface after swallowing. PCF are classified by Zbar and Funk<sup>1</sup>

as either a pharyngocutaneous fistula (an anomalous path connecting the pharynx and the skin) or a pharyngostoma (a direct opening of the pharynx to the skin, often accompanied by skin loss).

PCF is the most common complication after total laryngectomy and the most difficult to manage. The rate for

development of a PCF varies from 8% to 22% of patients undergoing total laryngectomy<sup>2-6</sup>. It is the major cause of increased morbidity, delays starting of adjuvant therapy, prolongs hospitalisation, increases treatment costs and reduces the quality of life (QoL). In 1998, Parikh et al. estimated a cost of \$400,000 per annum to treat fistulae after laryngectomy at their reference care centre in Toronto<sup>7</sup>.

The predisposing factors can be divided into patient-related factors (sex, age, smoking, alcohol consumption, diabetes, heart disease<sup>8</sup>, gastro-oesophageal reflux disease<sup>9</sup>, decreased preoperative haemoglobin<sup>8</sup>, albumin<sup>10</sup> and calcium levels, previous surgical treatment, previous radiotherapy<sup>11-13</sup> or chemoradiotherapy, tumour recurrence<sup>14</sup>), disease-related factors (stage<sup>13-15</sup>, lymph nodes and pharynx involvement<sup>16-17</sup>) and treatment-related factors (marginal status<sup>11-12-18</sup>, type and technique of closure, experience of the surgeon, preoperative tracheostomy and wound infection).

Risk factors are extensively investigated in the literature, but how to identify high-risk patients is still controversial<sup>11-18</sup>. Regarding patient-related factors, it is well known that patients with head and neck cancer are at particular risk for malnutrition for several reasons. Poor dietary habits together with excessive smoking and alcohol consumption are frequently observed among these patients and predispose them to malnutrition<sup>19</sup>.

Moreover, the location and stage of the tumour can lead to dysphagia, odynophagia, dysgeusia, or trismus, and result in reduced energy levels and protein intake<sup>20-21</sup>. Regardless of the underlying mechanisms, cancer-related weight loss and cancer-related malnutrition are multi-dimensional manifestations that reduce patient well-being<sup>22</sup>, tolerance to and prognosis after antineoplastic therapy<sup>23-24</sup>, decrease immunological responses to tumour cells<sup>24-25</sup> and resistance to infection<sup>24-26</sup>, and increase susceptibility to postoperative complications<sup>24-27</sup>, disability and overall cost of care<sup>24</sup>. For these reasons, malnutrition can contribute to the development of PCF.

Malnutrition has been reported in 30% to 50% of patients with head and neck malignancies<sup>20-21-28</sup>, particularly squamous cell carcinomas of the oropharyngeal and hypopharyngeal regions. The apparent nutritional depletion in these patients reduces their tolerance to treatment<sup>24-28</sup>.

In 70 to 80% of cases, the fistulae close spontaneously with local care and tube or parenteral feeding, and further intervention is required in only a minority of cases: the most widely reported technique in use is pectoralis major myofascial flap reinforcement.

In this study, we analyse the predisposing factors and most important nutritional parameters related to the development of PCF in patients undergoing either primary or salvage laryngectomy and suggest medical options to improve the outcomes.

## Materials and methods

A retrospective analysis of patients who underwent total laryngectomy at the ENT Department of University Hospital of Modena between January 2008 and January 2012 was carried out. Patients who underwent either primary or salvage total laryngectomy were included.

### *Surgery*

Surgery was performed with curative intent consisting of total laryngectomy as a single procedure or combined with dissection of the neck, thyroidectomy and reconstruction with pectoralis major flap.

Surgical technique and postoperative care were generally standardised.

Pharyngeal reconstruction was performed in three layers: mucosal, fascia and muscular. In all patients, nasogastric feeding was initiated on the first postoperative day and oral feeding was started after a swallowing study on day 7-10.

### *Risk factors*

The primary endpoint was to identify risk factors predisposing patients to fistula formation. A retrospective chart review was conducted. A database was built including data with regard to tumour characteristics (histology, grading, T stage, N stage, AJCC stage), treatment (eventual flap reconstruction, presence of preoperative tracheostomy, primary or salvage surgery, preoperative radiotherapy), comorbidities (history of diabetes or vascular disease), blood values assessing nutritional status (preoperative serum haemoglobin, albumin and prealbumin and their changes during hospitalisation). In fact, preoperative serum albumin was not available for all patients. Since albumin is a blood protein with a lifespan of about 30 days, the value of the first postoperative serum albumin (measured 1 week after surgical intervention) can be considered to be equal to the preoperative value.

### *Statistical analysis*

Pearson's  $\chi^2$  test was used to evaluate the correlation between the incidence of fistula formation and potential predisposing factors. A p value < 0.05 was considered statistically significant.

## Results

Sixty-nine patients were included in the study. Patient and tumour characteristics are detailed in Table I. Median age was 71 years (range 37-88 years). Fistula formation was noted in 24 patients (34.8%). The time of fistula formation is summarised in Table II. Laryngectomy was performed as primary treatment in 51 patients (73.9%). Ten patients underwent pretreatment radiotherapy (14.5%). Preopera-

**Table I.** Patient characteristics (n = 69).

	N (%)
<b>Histology</b>	
SCC	65 (94.2%)
Basaloid SCC	1 (1.4%)
Papillary thyroid tumour	2 (2.9%)
Undifferentiated	1 (1.4%)
<b>Gender</b>	
Male	59 (85.5%)
Female	10 (14.5%)
<b>Grading</b>	
G1	2.9%
G2	39.1%
G3	49.3%
GX	8.7%
<b>T Stage</b>	
T1	7.2%
T2	8.7%
T3	23.2%
T4	60.9%
<b>N Stage</b>	
N0	58%
N1	15.9%
N2a	0
N2b	13%
N2c	7.3%
N3	5.8%
<b>AJCC Stage</b>	
I	4 (5.8%)
II	5 (7.2%)
III	17 (23.2%)
IVa	40 (58%)
IVb	1 (1.4%)
IVc	2 (2.9%)

SCC: squamous cell carcinoma.

**Table II.** Time of fistula formation.

Postoperative day	N (%)
0-11	14 (20.3%)
12-23	7 (10.1%)
24-33	2 (2.9%)
> 33	1 (1.4%)

tive tracheostomy was performed in 15 patients (22.1%). Lateral neck dissection was performed bilaterally in 29 patients (42%) and unilaterally in 22 (31.9%). In the majority of cases, histology was squamous cell carcinoma (94.2%) with different grades of differentiation. Two patients were affected by papillary thyroid carcinoma with larynx extension, and two patients by an undifferentiated carcinoma.

Table III summarises the results of univariate analysis on the impact of the potential predisposing factors on fistula formation. From the analysis, p values  $\leq 0.05$  were present for the correlation of fistula formation with diabetes (p = 0.004), and low preoperative albumin and prealbumin levels (p = 0.005).

## Discussion

From January 2008 to January 2012, our data show an incidence of PCF that is higher than that reported in other studies (34.8% vs 8-22%)<sup>2-6</sup>. The retrospective analysis of our results and review of the literature were used to identify the most important risk factors of PCF and to improve perioperative management to avoid this complication. The most comprehensive study on PCF risk factors is a multivariate analysis study by Onal and colleagues<sup>29</sup>: a significant relationship was found between development of PCF and previous radiotherapy, positive ipsilateral and contralateral lymph nodes, accompanying systemic disease, pre- and postoperative haemoglobin < 12.2 g/dl and postoperative albumin level < 3.5 g/dl.

In their meta-analysis of postlaryngectomy PCF, Paydarfar and Birkmeyer<sup>30</sup> considered 10 separate variables and established that preoperative radiotherapy, postoperative haemoglobin < 12.5 g/dl, prior tracheotomy and concurrent neck dissection were all significant risk factors for formation of PCF. Similar results were obtained by Galli and De Corso<sup>31</sup>: systemic diseases, previous radiotherapy, supraglottic origin of tumour and concurrent radical neck dissection were significantly associated with PCF.

Cavalot et al.<sup>32</sup> demonstrated that diabetes mellitus influenced the development of PCF. However, using the 'Cumulative Illness Rating Scale', Dedivitis et al.<sup>33</sup> found no correlation between systemic disease and development of PCF.

Preoperative radiotherapy, lymph node involvement, positive surgical margins and low pre- and postoperative haemoglobin have been considered relevant risk factors in other studies<sup>11 12 29 34-36</sup>. In particular, radiotherapy can increase the incidence of PCF because of the decreased healing capacity secondary to fibrosis and hypovascularisation.

In a recent study, Dirven et al.<sup>37</sup> demonstrated a correlation between risk of PCF and interval between radiotherapy and surgery: patients undergoing salvage surgery within 12 months after radiotherapy had a higher risk of developing PCF compared to those undergoing salvage surgery more than 12 months after radiotherapy (p = 0.014).

In our analysis, a significant correlation was detected between diabetes and the development of PCF, whereas other risk factors such as preoperative radiotherapy and haemoglobin levels were not.

All our patients underwent total laryngectomy with manual closure of the pharynx. Many surgeons prefer to close the pharynx using a stapler. In a prospective study, Dedivitis<sup>38</sup> found no significant difference in the incidence of PCF between the mechanical closure group and the manual suture group. Morton et al.<sup>39</sup> showed that preoperative low serum albumin levels were significantly associated with development of PCF. Our results also showed how poor nutritional status in terms of albumin levels plays a

**Table III.** Univariate analysis of the impact of predisposing factors on fistula formation.

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	
<b>Co-morbidity</b>			
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	
<b>Albumin during hospitalisation</b>			0.4
Decrease	80	20	
Increase	35.3	64.7	
Unchanged	50	50	
<b>Hb during hospitalisation</b>			0.34
Decrease	34.6	65.4	
Increase	44.4	55.6	

Hb: haemoglobin; RT: radiotherapy.

crucial role in PCF development. In fact, low preoperative albumin is an important index of malnutrition.

Only few studies have been carried out on the relationship between nutritional parameters and the incidence of major postoperative complications<sup>19 21 23 24</sup>. Unintentional weight loss, and a lesser degree albumin, were predictive for postoperative complications. Weight loss seems to be the most important parameter for predicting major postoperative complications; patients with > 10% weight loss during the 6 months before surgery are at greater risk for the occurrence of major postoperative complications<sup>19 40</sup>.

The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines on enteral nutrition<sup>41</sup> recommend the use of nutritional support for 10-14 days be-

fore major surgery in patients with severe nutritional risk (weight loss > 10–15% within 6 months before surgery, BMI < 18.5%, serum albumin < 3 g/dl).

We are presently carrying out a prospective multicentre study to evaluate if the correction of malnutrition can reduce the incidence of PCF in patients with head and neck cancer.

The nutritional status of these patients was defined preoperatively. Thus, in the presence of malnutrition nutritional support is offered before surgery. If there is good preoperative nutritional status, the onset of postoperative malnutrition is thus avoided. Tube feeding for patients starts within 24-48 h after surgery and takes from 2 to 3 days to reach nutritional targets. Energy requirement will be



assess by Herrer-Benedict equation and each patient will receive 1.2-1.4 g/kg/day of proteins.

We have initiated a standardised enteral nutritional plan tailored on patients requirements in according with current recommendations for enteral feeding.

This prospective study is still on-going. Fifteen patients underwent total laryngectomies in the last year in our hospital. Two patients had preoperative prealbumin < 20 mg/dl and preoperative albumin < 3.5 g/dl, and can be considered malnourished. No patient developed a PCF.

The present study tried to emphasise that nutritional evaluation should always be performed preoperatively. Malnutrition has to be corrected to avoid a complication such as PCF. Our prospective analysis confirms this, although a small case series bias can be present. Moreover, good nutritional status is known to increase the rates of therapy completion, oncologic survival and post-treatment QoL during all types of therapy for head and neck cancer.

## Conclusions

It is important to identify the risk factors associated with formation of PCF to improve perioperative management and avoid this complication. In addition to the classical risk factors for PCF highlighted in many studies<sup>29 30 34</sup>, we must also consider the poor nutritional status of the patient as a risk factor, as assessed by preoperative albumin. Preoperative and periodic postoperative evaluations are mandatory in patients with head and neck cancer. Moreover, for the maintenance of normal haematologic values, frequent biochemical analyses and adequate nutritional support are necessary to prevent PCF following total laryngectomy. A multicentre prospective study is ongoing with the aim of evaluating if the correction of malnutrition can reduce the incidence of PCF in patients with head and neck cancer.

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Received: January 10, 2015 - Accepted: April 30, 2015

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