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

F. Mattioli1, M. Bettini1, G. Molteni1, A. Piccinini1, F. Valoriani2, S. Gabriele2, L. Presutti1
1 Head and neck Department, University Hospital of Modena, Italy; 2 Nutritionist, University Hospital of Modena, Italy

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 perioperative nutritional status can be helpful to avoid this complication.

KEY WORDS: Laryngectomy • Pharyngocutaneous fistula • Malnutrition

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 Funk1 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. 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. The predisposing factors can be divided into patient-related factors (sex, age, smoking, alcohol consumption, diabetes, heart disease, gastro-oesophageal reflux disease, decreased preoperative haemoglobin, albumin and calcium levels, previous surgical treatment, previous radiotherapy or chemoradiotherapy, tumour recurrence, disease-related factors (stage, lymph nodes and pharynx involvement) and treatment-related factors (marginal status, 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. 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. 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. Prealbumin and their changes during hospitalisation). 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 measurements that reduce patient well-being, tolerate to and prognosis after antineoplastic therapy, decrease immunological responses to tumour cells and resistance to infection, and increase susceptibility to postoperative complications, disability and overall cost of care. 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, particularly squamous cell carcinomas of the oropharyngeal and hypopharyngeal regions. The apparent nutritional depletion in these patients reduces their tolerance to treatment. 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 χ² 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-
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 ≤ 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%) 2-6. 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 29: 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 30 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 obtain by Galli and De Corso 31: systemic diseases, previous radiotherapy, supraglottic origin of tumour and concurrent radical neck dissection were significantly associated with PCF. Cavalot et al. 32 demonstrated that diabetes mellitus influenced the development of PCF. However, using the ‘Cumulative Illness Rating Scale’, Dedivitis et al. 33 found no correlation between systemic disease and development of PCF.

Table I. Patient characteristics (n = 69).

|                        | N (%)     |
|------------------------|-----------|
| **Histology**          |           |
| SCC                    | 65 (94.2%)|
| Basaloid SCC           | 1 (1.4%)  |
| Papillary thyroid tumour| 2 (2.9%)  |
| Undifferentiated       | 1 (1.4%)  |
| **Gender**             |           |
| Male                   | 59 (85.5%)|
| Female                 | 10 (14.5%)|
| **Grading**            |           |
| G1                     | 2.9%      |
| G2                     | 39.1%     |
| G3                     | 49.3%     |
| GX                     | 8.7%      |
| **T Stage**            |           |
| T1                     | 7.2%      |
| T2                     | 8.7%      |
| T3                     | 23.2%     |
| T4                     | 60.9%     |
| **N Stage**            |           |
| N0                     | 58%       |
| N1                     | 15.9%     |
| N2a                    | 0         |
| N2b                    | 13%       |
| N2c                    | 7.3%      |
| N3                     | 5.8%      |
| **AJCC Stage**         |           |
| 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%)   |

SCC: squamous cell carcinoma.
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. 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.

The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines on enteral nutrition recommend the use of nutritional support for 10-14 days before 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

| 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                      |         |
| Vascularopathy | 42.9              | 57.1                      | 0.41    |
| No vascularopathy | 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 | | | |
| Decrease     | 80                     | 20                        |         |
| Increase     | 35.3                   | 64.7                      |         |
| Unchanged    | 50                     | 50                        |         |
| Hb during hospitalisation | | | |
| Decrease     | 34.6                   | 65.4                      | 0.34    |
| Increase     | 44.4                   | 55.6                      |         |

Hb: haemoglobin; RT: radiotherapy.
assess by Herris-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, 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.

References

1. Zhar RIS, Funk GF. Pharyngocutaneous fistula. In: Current therapy in otolaryngology - head and neck surgery. 6th Edition. Mosby, New York; 1998. p. 314-9.
2. Fradis M, Podoshin L, Ben David J. Post-laryngectomy pharyngocutaneous fistula – a still unresolved problem. J Laryngol Otol 1995;109:221-4.
3. Herranz J, Sarandeses A, Fernández MF, et al. Complications after total laryngectomy in nonradiated laryngeal and hypopharyngeal carcinomas. Otolaryngol Head Neck Surg 2000;122:892-8.
4. Hier M, Black MJ, Lafond G. Pharyngo-cutaneous fistulas after total laryngectomy: incidence, etiology and outcome analysis. J Otolaryngol 1993;22:164-6.
5. Ikiz AO, Uca M, Guneri EA, et al. Pharyngocutaneous fistula and total laryngectomy: possible predisposing factors, with emphasis on pharyngeal myotomy. J Laryngol Otol 2000;114:768-71.
6. Papazoglou G, Doundoulakis G, Terzakis G, et al. Pharyngocutaneous fistula after total laryngectomy: incidence, cause, and treatment. Ann Otol Rhinol Laryngol 1994;103:801-5.
7. Parikh SR, Irish JC, Curran AJ, et al. Pharyngocutaneous fistulae in laryngectomy patients: the Toronto Hospital experience. J Otolaryngol 1998;27:136-40.
8. Redaelli de Zinis LO, Ferrari L, Tomenzoli D, et al. Postlaryngectomy pharyngocutaneous fistula: incidence, predisposing factors, and therapy. Head Neck 1999;21:131-8.
9. Seikaly H, Park P. Gastroesophageal reflux prophylaxis decreases the incidence of pharyngocutaneous fistula after total laryngectomy. Laryngoscope 1995;105:1220-2.
10. Tsou YA, Hua CH, Lin MH, et al. Comparison of pharyngocutaneous fistula between patients followed by primary laryngopharyngectomy and salvage laryngopharyngectomy for advanced hypopharyngeal cancer. Head Neck 2001;32:1494-500.
11. Saki N, Nikakhlagh S, Kazemi M. Pharyngocutaneous fistula after laryngectomy: incidence, predisposing factors, and outcome. Arch Iran Med 2008;11:314-7.
12. Lundgren J, Olofsson J. Pharyngocutaneous fistulae following total laryngectomy. Clin Otolaryngol Allied Sci 1979;4:13-23.
13. Krouse JH, Metson RS. Barium swallow is a predictor of salivary fistula following laryngectomy. Otolaryngol Head Neck Surg 1992;106:254-7.
14. Fradis M, Podoshin LF, Ben David J. Fistula analysis after radial forearm free flap reconstruction of hypopharyngeal defects. Laryngoscope 2008;118:1157-63.
15. Saki N, Nikakhlagh S, Kazemi M. Pharyngocutaneous fistula after laryngectomy: incidence, predisposing factors, and outcome. Arch Iran Med 2008;11:314-7.
16. Virtaniemi JA, Kumpulainen EJ, Hirvikoski PP, et al. The incidence and etiology of postlaryngectomy pharyngocutaneous fistulae. Head Neck 1998;20:22-5.
17. Fradis M, Podoshin LF, Ben David J. Fistula analysis after radial forearm free flap reconstruction of hypopharyngeal defects. Laryngoscope 2008;118:1157-63.
18. Van der Schueren MA, van leeuwen PA, Sauerwein HP, et al. Assessment of malnutrition parameters in head and neck cancer patients and their relation to postoperative complications. Head Neck 1997;19:419-25.
19. Jager-Witternaar H, Dijkstra PU, Vissink A, et al. Critical weight loss in head and neck cancer – prevalence and risk factors at diagnosis: an explorative study. Support Care Cancer 2007;15:1045-50.
20. Markou KD, Vlachtsis KC, Nikolaou AC, et al. Incidence and predisposing factors of pharyngocutaneous fistula formation after total laryngectomy. Is there a relationship with tumor recurrence? Eur Arch Otorhinolaringol 2004;261:61-7.
21. Van der Schuueren MA, van Leewuen PA, Sauerwein HP, et al. Assessment of malnutrition parameters in head and neck cancer patients and their relation to postoperative complications. Head Neck 1997;19:419-25.
22. Jager-Witternaar H, Dijkstra PU, Vissink A, et al. Critical weight loss in head and neck cancer – prevalence and risk factors at diagnosis: an explorative study. Support Care Cancer 2007;15:1045-50.
23. Markou KD, Vlachtsis KC, Nikolaou AC, et al. Incidence and predisposing factors of pharyngocutaneous fistula formation after total laryngectomy. Is there a relationship with tumor recurrence? Eur Arch Otorhinolaringol 2004;261:61-7.
24. Van der Schuueren MA, van Leewuen PA, Sauerwein HP, et al. Assessment of malnutrition parameters in head and neck cancer patients and their relation to postoperative complications. Head Neck 1997;19:419-25.
24 Kristina N, Pichard C, Lochs H. Prognostic impact of disease-related malnutrition. Clin Nutr 2008;27:5-15.
25 Chiara B, Ciorba A, Stomeo F, et al. Immunonutrition in head and neck cancer: have a look before surgery! Eur Arch Otorhinolaryngol 2012;269:5-8.
26 Van der Schueren MAEB, von Blomberg A, van der Flier BME, et al. Differences in immune status between well-nourished and malnourished head and neck cancer patients. Clin Nutr 1998;17:107-11.
27 van der Schueren MAEB, van Leeuwen PAM, Kuik DJ, et al. The impact of nutritional status on the prognoses of patients with advanced head and neck cancer. Cancer 1999;86:519-27.
28 Brookes GB. Nutritional status – a prognostic indicator in head and neck cancer. Otolaryngol Head Neck Surg 1985;93:69-74.
29 Erdag MA, Arslanoglu S, Onal K, et al. Pharyngocutaneous fistula following total laryngectomy: multivariate analysis of risk factors. Eur Arch Otorhinolaryngol 2013;270:173-9.
30 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.
31 Galli J, De Corso E. Postlaryngectomy pharyngocutaneous fistula: incidence, predisposing factors, and therapy. Otolaryngol Head Neck Surg. 2005;133:689-94.
32 Cavalot AL, Gervasio CF, Nazionale G et al. Pharyngocutaneous fistula as a complication of total laryngectomy: review of the literature and analysis of case records. Otolaryngol Head Neck Surg 2000;123:587-92.
33 Dedivitis RA, Ribeiro KC, Castro MA, et al. Pharyngocutaneous fistula following total laryngectomy. Acta Otorhinolaryngol Ital 2007;27:2-5.
34 Markou KD, Vlachsis KC, Nikolaou AC, et al. 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.
35 Hanasono MM, Lin D, Wax MK, et al. Closure of laryngectomy defects in the age of chemoradiation therapy. Head Neck 2012;34:580-8.
36 Fung K, Teknos TN, Vandenberg CD, et al. Prevention of wound complications following salvage laryngectomy using free vascularized tissue. Head Neck 2007;29:425-30.
37 Dirven R, Swinson BD, Gao K, et al. 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.
38 Dedivitis RA, Aires FT. Stapler suture of the pharynx after total laryngectomy. Acta Otorhinolaryngol Ital 2014;34:94-8.
39 Morton RP, Fielder CP, Dorman EB. Prediction and prevention of fistulae after major head and neck surgery: a preliminary report. Aust N Z J Surg 1988;58:951-3.
40 Head and Neck Guideline Steering Committee. Evidence based practice guidelines for the nutritional management of patients with head and neck cancer. Sydney: Cancer Council Australia. Available from: http://wiki.cancer.org.au/australia/ COSA:Head and neck cancer nutrition guidelines.
41 Weimann A, Braga M, Harsanyi L, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. 2006;Clin Nutr 25:224-44.

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

Address for correspondence: Margherita Bettini, University Hospital of Modena, Department Head and Neck Surgery, Institute of Otorhinolaryngology, via del Pozzo 71, 41124 Modena, Italy. Tel. +39 059 4222402. Fax +39 059 4222454. E-mail: bettini.margherita@libero.it