

LARYNGOLOGY

# Pharyngocutaneous fistula following total laryngectomy: analysis of risk factors, prognosis and treatment modalities

*Fistola faringocutanea dopo laringectomia totale: analisi dei fattori di rischio, della prognosi e delle modalità di trattamento.*

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## SUMMARY

The aim of this study was to establish the incidence, risk factors, and the management of pharyngocutaneous fistula (PCF) after primary and salvage total laryngectomy. A retrospective, match-paired analysis of 86 patients who developed fistula after total laryngectomy was carried out and compared with a control group of 86 patients without fistula, randomly selected from a pool of 352 total laryngectomies, performed between January 1999 to October 2014. The overall incidence of PCF in the series was 24.4%; we recorded rates of 19.0%, 28.6% and 30.3% following primary total laryngectomy (PTL), salvage laryngectomy post-radiotherapy (RT-STL) and salvage laryngectomy post-chemoradiotherapy (CRT-STL), respectively. Multivariate analysis revealed that the relative risk of fistula was respectively 2.47, 3.09 and 7.69 for hypoalbuminaemia  $\leq 3.5$  g/dL, RT-STL and CRT-STL. An early onset of PCF within 10 postoperative days was recorded in case of salvage total laryngectomy. The management of PCF significantly differed between PTL, RT-STL and CRT-STL, with exclusive conservative treatment for PTL (93.55%), while in the CRT-STL group surgical closure with regional flaps (58.82%) prevailed. Conservative management, adjuvant hyperbaric oxygen therapy and surgical closure were equally distributed in the RT-STL group. Thorough knowledge of patient-related risk factors and its prognostic value, allows the surgeon to better evaluate preventive strategies with the aim of minimising fistula formation, hospitalisation times and related costs.

KEY WORDS: Pharyngocutaneous fistula • Salvage total laryngectomy • Risk factors • Chemoradiotherapy

## RIASSUNTO

*In questo studio sono state valutate l'incidenza, i fattori di rischio e le modalità di trattamento in pazienti con fistola faringocutanea dopo laringectomia totale primaria e di salvataggio. Nel periodo compreso tra gennaio 1999 e ottobre 2014, 352 pazienti affetti da carcinoma squamocellulare della laringe sono stati sottoposti a laringectomia totale. Il decorso postoperatorio di 86 pazienti è stato complicato dall'insorgenza di fistola faringocutanea. Questi sono stati comparati in uno studio caso-controllo con 86 pazienti selezionati tramite software, fra quelli che non avevano sviluppato la fistola salivare. L'incidenza globale di fistola dopo laringectomia totale è stata del 24,4%, rispettivamente abbiamo registrato incidenze del 19,0%, del 28,6% e del 30,3% dopo laringectomia totale primaria, dopo radioterapia e dopo radiochemioterapia. L'analisi multivariata ha rivelato che per ipoalbuminemia  $\leq 3,5$  g/dL, per pregressa radioterapia e radiochemioterapia il rischio relativo di sviluppo di fistola è stato rispettivamente 2,47, 3,09 e 7,69. In caso di laringectomia totale di salvataggio abbiamo registrato una comparsa precoce della fistola entro i primi 10 giorni postoperatori. Le modalità di trattamento della fistola faringocutanea sono risultate essere significativamente differenti in caso di laringectomia totale primaria, dopo radioterapia e dopo radiochemioterapia. Infatti, mentre nel primo caso è stato sufficiente un trattamento di tipo conservativo (93,55%), dopo chemioradioterapia ha prevalso il ricorso a tecniche chirurgiche ricostruttive con lembi regionali (58,82%). Nel caso dei pazienti radiotrattati, le opzioni terapeutiche della fistola sono risultate essere equamente distribuite tra quella medica, eventualmente con l'aggiunta dell'ossigenoterapia iperbarica, e quella chirurgica ricostruttiva. La conoscenza dei fattori di rischio soggettivi e il loro valore prognostico, permettono al chirurgo di pianificare le strategie preventive al fine di ridurre il rischio di formazione della complicanza e, conseguentemente, dei tempi di degenza e dei relativi costi.*

PAROLE CHIAVE: *Fistola faringocutanea • Laringectomia totale di salvataggio • Fattori di rischio • Radiochemioterapia*

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## Introduction

The development of a pharyngocutaneous fistula represents a complication of total laryngectomy that is usually self-limiting. Its management is thus mainly based on careful conservative treatment; however, at times, this complication can carry potentially devastating sequelae, and further surgery is required.

The incidence of pharyngocutaneous fistula has been reported to be 14.3% (95% CI 11-17.0) after primary total laryngectomy, increasing significantly to 22.8% (95% CI 18.3-27.4) and 34.1% (95% CI 22.6-45.6) in case of previous radiotherapy or previous chemoradiotherapy<sup>1</sup>.

Numerous risk factors, such as pre-existing comorbidities, smoke and alcohol abuse, pre- and postoperative haemoglobin and albumin values, tumour site and stage, concurrent neck dissection etc., have been implicated in fistula formation<sup>2-13</sup>, although, the actual impact of these remains debatable.

In this retrospective study, we analysed potential risk factors for the development of postoperative pharyngocutaneous fistula after total laryngectomy and describe our systematic approach in the management of this complication.

## Materials and methods

Between January 1999 and October 2014, 352 consecutive total laryngectomies for laryngeal squamous cell carcinoma were performed at the Otolaryngology Clinic of the Department of Surgery and Translational Medicine of the University of Florence. The search was restricted to laryngeal SCC and to total laryngectomies without flap reconstruction.

One hundred and sixty-three patients (46.3%) underwent primary total laryngectomy (PTL), 133 (37.8%) underwent salvage total laryngectomy after radiotherapy (RT-STL), and 56 (15.9%) received salvage total laryngectomy after chemoradiotherapy (CRT-STL). In 31 patients, the procedure was extended to the pharynx (piriform sinus and/or base of tongue), and in PTL we also included salvage procedures after previous transoral laser or previous partial laryngectomy.

Institutional Review Board permission was obtained by the local committee.

Pretreatment staging was corrected using the (UICC) TNM 7th edition based on the clinical charts<sup>14</sup>.

The postoperative course of 86 patients was complicated by the onset of a pharyngocutaneous fistula; this group was matched and compared with a control cohort group of 86 patients without PCF, randomly selected within our series. Groups were homogeneous for age and gender.

Between groups we matched and compared risk factors for PCF, including smoke and alcohol habits, comorbidities, previous radiotherapy and chemoradiotherapy, pre-

and postoperative haemoglobin ( $\leq 12.5$  mg/dL) and albumin ( $\leq 3.5$  g/dL), tumour site and T stage (T1-3 vs. T4a), N stage (N0 vs. N+), uni- or bilateral neck dissection and type of neck dissection [selective neck dissection (SND), modified radical neck dissection (mRND), radical neck dissection (RND)], neck level VI dissection.

The surgical technique was standardised among all surgeons. Laryngectomy included standard removal of the hyoid bone and infrahyoid muscles, pharyngeal closure was always performed in a single layer, with a "T" shaped suture line, using Vicryl (polyglactin 910) 3/4-0 sutures. Two suction drains were applied and generally removed when producing less than 15 cc in 24 hours. Antibiotic therapy with amoxicillin/clavulanate was generally started one day before surgery and continued for the following seven days. Skin sutures were removed on postoperative day 9. Enteral feeding through the nasogastric tube was started on the third postoperative day, and oral feeding was started on postoperative day 14 if contrast radiographic study showed no signs of fistula.

### Statistical analysis

Randomisation was carried out with the Intel® Digital Random Number Generator. A chi-square test was used to compare discrete variables. A p value  $< 0.05$  was considered statistically significant. Analysis was conducted using Graph Pad software (Graph Pad, San Diego, CA). A logistic regression model was used on the significant risk factors to estimate the relative impact of fistula formation. McNemar's test was used to assess time interval significance between variables within a cut-off time (10 days after intervention). Data regarding fistula treatment were also collected and an ANOVA test was employed to compare different treatment modalities in the three patient groups (PTL, RT-STL, and CRT-STL). These tests were all conducted using STATA (Stata Corporation, College Station, TX).

## Results

In this series, the incidence of PCF was 19% among patients receiving primary total laryngectomy, while it increased to 28.6% and 30.3% for patients receiving salvage total laryngectomy after radiotherapy and chemoradiotherapy.

The match-paired analysis for factors predisposing to PCF formation showed a statistical significant difference regarding comorbidities, salvage laryngectomy and postoperative albumin values in the two groups (Tab. I).

Furthermore, pre- and postoperative haemoglobin values below 12.5 mg/dL and bilateral neck dissection with inclusion of level VI showed a trend towards statistical significance.

The assessment of the relative impact of independent variables was established using logistic regression analysis on the most relevant risk factors: odds ratios for PCF development were 2.478 for postoperative albumin val-

**Table I.** Patient, disease, treatment and pathology specimen-related factors predisposing to PCF formation.

Variables	Fistula Group (n = 86)	Control Group (n = 86)	p value
<b>Smoke</b>			
No	18	27	p = ns
Yes	68	59	p = ns
<b>Alcohol</b>			
No	50	47	p = ns
Yes	36	39	p = ns
<b>Alcohol+Smoke</b>	34	29	p = ns
<b>Comorbidities</b>	<b>42</b>	<b>28</b>	<b>p = 0.0433</b>
<b>Previous RT</b>	<b>38</b>	<b>22</b>	<b>p = 0.0161</b>
<b>Previous CRT</b>	<b>17</b>	<b>4</b>	<b>p = 0.0042</b>
<b>Pharyngolaryngectomy</b>	4	3	p = ns
<b>Neck dissection (type)</b>	46	43	p = ns
RND	7	4	p = ns
mRND	18	15	p = ns
SND	21	24	p = ns
<b>Neck dissection (side)</b>			
Monolateral	29	31	p = ns
Bilateral	17	12	p = ns
<b>Neck dissection+ VI level</b>			
Monolateral	10	8	p = ns
Bilateral	7	1	p = 0.0640
<b>Preoperative haemoglobin ≤12.5 mg/dL</b>	34	22	p = 0.0730
<b>Postoperative haemoglobin ≤12.5 mg/dL</b>	58	46	p = 0.0859
<b>Preoperative albumin ≤3.5 g/dL</b>	21	25	p = ns
<b>Postoperative albumin ≤3.5 g/dL</b>	<b>28</b>	<b>14</b>	<b>p = 0.0204</b>
<b>T Stage II,III</b>	55	48	p = ns
<b>T Stage IV</b>	31	38	p = ns
<b>N Stage</b>			
NO	42	37	p = ns
N+	44	49	p = ns
<b>T site</b>			
Supraglottic	30	26	p = ns
Pharyngolarynx	4	6	p = ns
Glottic	44	51	p = ns
Transglottic	3	2	p = ns
Subglottic	5	1	p = ns

ns; not significant.

ues below 3.5g/dL (p=0.023), 3.072 for salvage TL after radiotherapy (p=0.002) and 7.694 for salvage TL after chemoradiotherapy (p=0.001) (Tab. II).

Mean hospitalisation time for fistula group and control group was respectively 51.6 (19-250) and 19.8 (15-22) days, (p=0.0034). The mean time interval between total

laryngectomy and fistula formation was 18.33 (3-180) days; patients submitted to primary total laryngectomy showed a mean time of PCF formation of 21.43 days, while for those who developed PCF after salvage procedures was 15.19 days. Risk factors that showed significance at multivariate analysis were analysed with a McNemar test for early PCF formation, with a cut-off time of 10 days after surgery, radiotherapy and chemoradiotherapy tested positive for early fistula formation (Tab. III). Fifty-four fistula patients (62.8%) were treated conservatively (neck dressing, antibiotic therapy, PPI etc.), 15 patients (27.7%) received hyperbaric oxygen therapy and 32 patients (37.2%) needed further surgery: of these, in 17 cases (53%) surgical revision and primary closure was sufficient, while in the remaining 15 patients (47%) surgical repair was performed using pectoralis major myofascial or myocutaneous flap transposition. Figure 1 displays our flowchart in the management of PCF.

Conservative treatment for PCF was the most frequent option for patients after PTL, CRT-STL patients were mostly treated with pectoralis major flap transposition, RT-STL patients were equally treated either with conservative treatment or conservative treatment plus hyperbaric oxygen therapy and surgical revision.

### Discussion

With the evolution of non-surgical organ preservation protocols for treatment of laryngeal and hypopharyngeal squamous cell carcinomas, total laryngectomy is increasingly performed as salvage procedure. Wound complications and pharyngocutaneous fistula have become an increasing concern. Wound healing complications can have a multi-factorial origin including previous chemoradiotherapy, hypoalbuminaemia, hypohemoglobinaemia, neck dissection, tumour stage and site <sup>2-13</sup>.

Our study showed that postoperative albumin level below 3.5 g/dL, previous radiotherapy and chemoradiotherapy were significantly correlated with PCF formation. Because of the retrospective setting, we were unable to assess the impact of nutritional status in multivariate analysis. In fact, the albumin level in itself is an insufficient parameter, and the prognostic nutritional index, which is a combination of biochemical factors (serum albumin, transferrin), immune competence (total lymphocyte count, hypersensitivity skin tests) and anthropometric measurements (BMI, arm muscle circumference, and skin fold thickness), would be more

**Table II.** Multivariate analysis of PCF risk factors.

Risk factors	p value	Odds ratio (95% CI)
Comorbidities	0.191	1.584 (0.794-3.158)
Postoperative albumin ≤3.5 g/dL	0.023	2.478 (1.131-5.428)
Previous RT	0.002	3.072 (1.485-6.353)
Previous CRT	0.001	7.694 (2.338-25.323)

**Table III.** McNemar test for the risk factors related time interval impact on PCF formation.

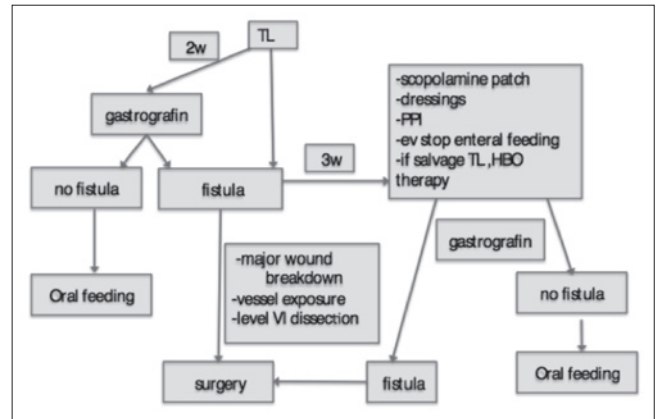
Risk factors	Exact McNemar significance probability	Odds ratio	95% CI
Postoperative albumin $\leq 3.5$ g/dL	0.7283	0.8333	0.3909-1.7509
Radiotherapy	0.0008	3.0909	1.5292-6.7626
Radiochemotherapy	0.00004	9.8	3.9260-31.5173

appropriate. Moreover, in head and neck carcinoma, nutritional status deteriorates during chemoradiotherapy or hyperfractionated RT<sup>15</sup> and this has been shown to have a negative effect on morbidity, mortality and survival<sup>16,17</sup>. It is likely that the increased morbidity of surgery in patients receiving CRT-STL compared with patients of comparable T classification receiving PTL is due to impaired nutritional status as well as the direct toxic effects of chemoradiation on tissue healing.

The role of radiotherapy in the genesis of pharyngocutaneous fistula has been extensively described, and some authors report that there is no significant associations<sup>18-22</sup>. In a recent meta-analysis, Paydarfar et al.<sup>23</sup> showed that, although preoperative radiotherapy represented a significant relative risk (RR) of PCF formation, there was also heterogeneity of effects among studies; in fact, other radiotherapy-associated variables such as radiotherapy dose and time frame between the end of radiation and surgery, did not demonstrate an increased RR. At multivariate analysis, the odds ratio for PCF formation after radiation was 3.072 ( $p=0.002$ ), and fistula seemed to occur early (OR=3.0909; within 10 days).

Similar results have been reported by a small number of authors<sup>19,24</sup>. Chemoradiotherapy showed an odds ratio of 7.694 for fistula formation ( $p=0.001$ ) with a high OR=9.8 for early onset.

Assessment of fistula formation was proven by X-ray swallow study, after two weeks postoperatively (Fig. 1). Some authors advocate the scintigraphic analysis as an objective and non-invasive tool to precisely identify the presence of pharyngocutaneous fistula and location of its internal orifice and to monitor its spontaneous closure<sup>25</sup>. Our study is in agreement with the findings from the meta-analysis of Sayles et al., where chemoradiotherapy seems to increase the risk of major wound complications more than radiotherapy alone. Furthermore, concurrent chemoradiotherapy protocols offers superior locoregional control at the expense of more frequent wound complications in the event of salvage surgery than induction chemotherapy followed by radiotherapy<sup>1</sup>. Newman reported similar rates of PCF between patients receiving RT alone or more intensive therapy with either sequential or concomitant chemoradiotherapy<sup>26</sup>. Aires et al. found no significant differences between PTL and CRT-STL in terms of PCF development<sup>27</sup>. Regarding PCF treatment, the results from our observational study pointed out that in PTL patients conservative therapy is almost exclusive, while pectoralis major flap transposition prevails in CRT-STL patients who develop fistula. In our se-

**Fig. 1.** Fistula treatment flow-chart.

ries, the management of PCF in RT-STL was equally distributed among conservative treatment +/- hyperbaric oxygen therapy and revision surgery (Tab. IV). Hyperbaric oxygen therapy improves wound healing, although the data do not suggest that it promotes short-term growth of cancer<sup>28</sup>, and thus its use remains controversial. We believe that for salvage patients who cannot receive further adjuvant radiotherapy its use is well justified and highly effective since in all cases it eventually promotes complete healing.

Early revision surgery with pectoralis major flap transposition was employed in case of major wound breakdown with vessel exposure and in case of evidence of fistula progression in CRT-STL patients, otherwise surgical revision with or without flap transposition was undertaken after persistence of the fistula despite 3 weeks of conservative therapy. The pectoralis major flap can be harvested as a myofascial or myocutaneous flap<sup>29,30</sup>. In general, at re-exploration, the pharyngeal mucosa is oedematous and fragile so that

**Table IV.** ANOVA for fistula treatments in PTL, RT-STL and CRT-STL groups. Fisher's exact= 0.000.

	Med	Med+HbO	Surgical revision	PM flap	Total
PTL	29	1	1	0	31
%	93.55	3.23	3.23	0.00	100.00
STL-RT	7	14	12	5	38
%	18.42	36.84	31.58	13.16	100.00
STL-CTRT	2	1	4	10	17
%	11.76	5.88	23.53	58.82	100.00
Total	38	16	17	15	86
%	44.19	18.60	19.77	17.44	100.00

MED = medication, HbO = Hyperbaric Oxygen, PM = pectoralis major



primary closure is feasible and wise only when the defect is minimal and direct suture will not produce excessive tension. In all other cases, the myofascial transposition of the flap is the preferred method, and the muscle is sutured inlay around the defect ensuring a tight closure. The myocutaneous transposition is used only in rare cases of large pharyngeal breakdown with major tissue loss/necrosis of the pharyngeal mucosa. In these cases, the skin paddle, sutured inlay, will prevent pharyngeal stenosis that could occur more easily with a large myofascial inlay placement. If the necrosis also involves the central portion of the skin of the neck, we recommend to address the pharyngeal closure as described above and to provide outer skin reconstruction using a split thickness skin graft over the pectoralis major muscle that will be sutured inlay to the outer skin defect. In our opinion, pectoralis major flap transposition is the most efficient option since it is easy and quick to harvest and rotate, and has been demonstrated to be reliable even in hostile recipient sites<sup>31,32</sup>. Furthermore, it does not require postoperative monitoring<sup>33</sup> and is cost effective<sup>29</sup>.

One minor disadvantage is the morbidity associated with loss of the pectoralis major muscle function especially in case of concomitant shoulder dysfunction following neck dissection<sup>30,34-36</sup>.

Based on our retrospective analysis, the incidence of PCF after previous RT or CRT was 29.1% (55 of 189), and the incidence of salvage laryngectomies requiring a flap transposition was 7.9% (15 of 189). We do not suggest to routinely harvest flaps in case of salvage total laryngectomies, although this seems reasonable after previous chemoradiation in patients with comorbidities and low preoperative albumin values. In these cases, we would recommend a myofascial transposition of the pectoralis major flap overlay that is placed over the suture line of the primary pharyngeal closure to protect the suture and overlying skin of the neck. Some authors recently described the use of the myofascial infrahyoid flap for defects following total laryngectomy<sup>37</sup>, despite our enthusiastic experience with this reconstructive method<sup>38-42</sup>, we always remove the infrahyoid muscles during total laryngectomy for oncologic reasons. Furthermore, we do not believe that this flap can represent a valid solution in the standard management of PCF because of the relative contraindication represented by previous radiotherapy, and because this flap always needs to be harvested during ablative surgery and not when PCF appears in the postoperative course.

Unfortunately, there is no evidence that mechanical stapler pharyngeal closure might reduce fistula formation in high risk cases<sup>43</sup>.

We currently continue to assess serum albumin, transferrin, total lymphocyte count and BMI and we are testing other anthropometric parameters to better establish the time for surgery and identify easy-to-obtain parameters during follow-up consultations. We are also trying to improve the preoperative nutritional status by integrating with Oral Impact® (Nestlé, Vevey, Switzerland) 1000 ml

(1000 kcal) per day plus usual diet for 5-7 days prior to surgery, as suggested by our nutritionists. However, we have data in this regard at the time of writing.

The limitations of this study are mainly represented by its retrospective setting. Even if the cohort of patients with PCF is relatively small (86 cases), this represents a single institution experience over the last 15 years. Using software, we tried to avoid other biases by random assignment of patients to the control group.

## Conclusions

This study confirms that postoperative albumin values below 3.5 g/dL, previous radiotherapy and chemoradiotherapy are significant predictors of PCF. Conservative treatment is advisable for PCF developing in non-(chemo) radiated patients, hyperbaric oxygen therapy is effective as adjuvant treatment after previous radiotherapy, and most PCF developing in chemoradiated patients tend to progress and need flap coverage to avoid devastating outcomes.

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