European Archives of Oto-Rhino-Laryngology (2019) 276:143–151
https://doi.org/10.1007/s00405-018-5200-4

LARYNGOLOGY

Pharyngocutaneous fistula after total laryngectomy: multivariate analysis of risk factors and a severity-based classification proposal

Maria Casasayas[1] · Aina Sansa[1] · Jacinto García-Lorenzo[1] · Montserrat López[1] · César Orús[1] · Xavier Peláez[2] · Miquel Quer[1] · Xavier León[1,3]

Received: 28 September 2018 / Accepted: 8 November 2018 / Published online: 13 November 2018

Abstract

Purpose The aim of the study is to determine the predisposing factors for pharyngocutaneous fistula (PCF) in patients undergoing total laryngectomy (TL) or extended TL and, secondarily, to propose a new severity-based classification system.
Methods This is a retrospective study of 400 patients who underwent TL or extended TL. Major fistula was defined as a fistula (1) persisting for ≥ 4 weeks, (2) requiring surgical treatment, or (3) associated with perioperative mortality.
Results PCF formation occurred in 93 patients (23.3%) and major fistula in 72 (18.0%). Extended surgery with partial or total pharyngectomy, previous treatment with radiotherapy, and postoperative hemoglobin levels < 99 g/L were associated with a significantly higher risk of developing major fistula.
Conclusions We propose a new PCF classification system according to clinical severity. Predictors of major fistula were the type of surgery, previous radiotherapy, and low (< 99 g/L) postoperative hemoglobin levels. We consider the use of onlay flaps in irradiated patients who require partial pharyngectomy.

Keywords Total laryngectomy · Pharyngectomy · Pharyngocutaneous fistula · Postoperative complications · Cancer larynx

Introduction

Total laryngectomy (TL) and TL with pharyngectomy are performed to treat advanced laryngeal or hypopharyngeal tumors. These procedures can be performed either for primary treatment or as second-line treatment after organ-preserving options have failed. In some cases, pedicled flaps—mainly the pectoralis major myocutaneous flap (PMMF)—are used to remodel the surgical defect. A potential complication of TL is the development of a pharyngocutaneous fistula (PCF), with an estimated prevalence ranging from 5% [1] to 58% [2]. PCF formation is associated with a longer hospital stay, [3, 4] a delay in adjuvant therapy, and a decrease in quality of life [5].

Numerous variables have been implicated as potential risk factors for PCF formation after TL, including previous radiotherapy [5–14] or chemoradiotherapy [6, 7, 9, 10, 15], neck dissection [6, 13], comorbid illness (e.g., diabetes mellitus) [11], low pre- or postoperative hemoglobin levels [3–7, 11, 14, 16], hypopharyngeal localization of the tumor [4, 5, 12, 13, 17], large tumor size (T3–T4) [5, 12], and extended surgeries [4, 18].

Although numerous potential risk factors have been identified, at present there is a lack of consensus as to which of these factors are the best predictors of PCF. In this context, the aim of the present study was to retrospectively evaluate a large cohort of patients treated with TL at our institution to determine the predisposing factors for PCF development. A secondary aim was to propose a new PCF severity-based risk classification system.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00405-018-5200-4) contains supplementary material, which is available to authorized users.

✉ Maria Casasayas
mcasasayas@santpau.cat

[1] Otorhinolaryngology Department, Hospital de la Santa Creu i Sant Pau, C/ Mas Casanovas, 90, 08041 Barcelona, Spain

[2] Anesthesiology Department, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

[3] Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Madrid, Spain

Materials and methods

Patient description

We retrospectively reviewed all TLs performed consecutively at our center between 2000 and 2017. Inclusion criteria were treatment with simple TL, TL with partial pharyngectomy (TLPP), and TL with total pharyngectomy (TLTP). All cases with a TL associated with esophagectomy or total glossectomy were excluded. All procedures were performed by a team of five surgeons at a tertiary care hospital.

A total of 400 surgeries were performed during the study period. In most cases ($n=390$, 97.5%), surgery was indicated to treat a tumor located in the larynx or pharynx; surgery was the initial treatment in 202 of these 390 cancer patients (50.5%). In 131 cases (32.7%), the surgery was performed as a salvage treatment after partial surgery ($n=3$, 0.8%), radiotherapy ($n=99$, 24.7%), surgery and radiotherapy ($n=4$, 1%), or chemoradiotherapy ($n=25$, 6.3%). In the remaining 57 patients (14.3%), the surgical indication was to resect a second tumor located in the larynx or hypopharynx in patients previously treated with radiotherapy. In the patients without a tumor ($n=10$), the TL was performed to treat chondronecrosis ($n=5$, 1.3%) or severe aspiration episodes in patients with a non-functional larynx ($n=5$, 1.3%); of these ten patients, eight had undergone previous radiotherapy. Overall, 193 of the 400 patients (48.3%) had received radiotherapy prior to surgery.

Surgery description and postoperative care

We performed four different types of surgery: simple TL ($n=272$, 68.0%), TLPP without PMMF ($n=80$, 20%), TLPP with PMMF ($n=26$, 6.5%), and TLTP ($n=22$, 5.5%)—which always included a PMMF. Most patients ($n=361$, 90.3%) underwent neck dissection, which was unilateral in 79 cases (21.9%) and bilateral in 282 cases (78.1%). In 68 patients (18.8%), a radical neck dissection was performed.

In most of the patients ($n=356$) treated with simple TL, an absorbable suture (Dexon or Vicryl) was used for primary closure of the mucosa from the pharynx. Starting in the year 2008, surgeons had the option to perform primary closure using a stapler suture (75-mm Linear Cutter, Ethicon Endo-Surgery LLC) ($n=44$).

In patients requiring TLPP, pharyngeal reconstruction was performed—depending on the extent of the resection—either by directly suturing the mucosa ($n=80$) or by incorporating a PMMF into the suture line ($n=26$).

All TLTP cases ($n=22$) were reconstructed by suturing a full thickness skin graft over the prevertebral plane with a PMMF to recreate the anterior and lateral hypopharyngeal walls in accordance with the technique described by Fabian [19]. A Montgomery salivary bypass tube was inserted in all patients requiring a PMMF for the reconstruction.

Enteral nutrition by nasogastric tube was initiated on the first postoperative day. In the absence of wound complications, the nasogastric tube was generally removed on the 7th postoperative day in non-irradiated patients, and on the 12th postoperative day in patients who had received previous radiotherapy or a PMMF.

Analyses of results

A fistula was defined as any documented clinical suspicion or evidence of salivary leak. All suspected PCFs were confirmed by oral administration of methylene blue dye. In cases with a confirmed PCF, the initial treatment was conservative management involving antibiotic therapy, continuation of enteral nutrition, and daily local wound care. In cases that did not respond adequately to conservative management, a PMMF was considered on a case-by-case basis.

The PCFs were classified as either major or minor fistulas. Major fistula was defined as a fistula (1) persisting for ≥ 4 weeks, (2) requiring surgical treatment, or (3) associated with perioperative mortality. Minor fistula was defined as a fistula that resolved with conservative management within 4 weeks. Perioperative mortality was defined as death for any cause within 30 days of surgery or during hospitalization after the TL surgery.

Patients were classified according to the type of surgery performed, as follows: simple TL, $n=272$ (68.0%); TLPP without PMMF, $n=80$ (20.0%); and TLPP or TLTP with PMMF, $n=48$ (12.0%). The following patient-related variables were assessed: gender, age, alcohol use, smoking habit, diabetes mellitus, and American Society of Anesthesiologists (ASA) physical status classification. Patients were classified into one of three categories according to their use of alcohol and tobacco, as follows: no tobacco or alcohol use; moderate use (<20 cigarettes/day and/or <80 gr alcohol/day); and heavy use (≥ 20 cigarettes/day or ≥ 80 gr alcohol/day).

We also evaluated the following variables: extension and location of the tumor; history of previous radiotherapy; type of surgery; use of stapler suture; neck dissection; placement of voice prosthesis; and preoperative and postoperative hemoglobin levels. Table 1 shows the distribution of patients by variable. Supplementary Table 1 presents descriptive data for the patients grouped according to the type of surgery.

Table 1 Descriptive characteristics of patients

	Total
Sex	
Male	374 (93.5%)
Female	26 (6.5%)
Age (mean/SD) years	65.2/11.1
Tobacco and alcohol use	
None	15 (3.8%)
Moderate	49 (12.2%)
Severe	336 (84.0%)
ASA	
II	118 (29.5%)
III	256 (64.0)
IV	26 (6.5%)
Diabetes	
No	328 (82.1%)
Yes	72 (17.9%)
Subsite location	
Supraglottis	128 (32.0%)
Glottis	201 (50.2%)
Hypopharynx	71 (17.8%)
pT	
0	10 (2.5%)
2	70 (17.5%)
3	138 (34.5%)
4	182 (45.5%)
Previous radiotherapy	
No	207 (51.7%)
Yes	193 (48.3%)
Type of surgery	
Simple TL	272 (68.0%)
TLPP without PMMF	80 (20.0%)
TLPP–TLTP with PMMF	48 (12.0%)
Neck dissection	
No	39 (9.8%)
Unilateral	79 (19.7%)
Bilateral	282 (70.5%)
Voice prosthesis	
No	354 (88.5%)
Yes	46 (11.5%)
Preoperative Hb (mean/SD) g/L	136.9/19.6
Postoperative Hb (mean/SD) g/L	110.0/15.7

SD standard deviation; *ASA* American Society of Anesthesiologists; *TL* total laryngectomy; *TLPP* total laryngectomy with partial pharyngectomy; *TLTP* total laryngectomy with total pharyngectomy; *PMMF* pectoralis major myocutaneous flap; *Hb* hemoglobin

Statistical analyses

We evaluated the association between PCF formation, major fistula, and all assessed variables. We first evaluated the whole sample and then performed subanalyses according to the type of surgery.

The chi-square test or Fisher's exact tests were used, as appropriate, to compare qualitative variables. Student's *t* test was used to compare quantitative variables. Multivariate analyses with logistic regression were carried out using the presence of PCF and major fistula as the dependent variables and all other variables as independent variables. A recursive partitioning analysis (RPA; chi-square automatic interaction detection method) was used to establish the cut-off points to categorize the hemoglobin levels associated with PCF development. The risk of PCF was grouped using RPA (classification and regression tree method).

Results

A total of 93 patients (23.3%) developed a PCF. By type of surgery, the PCF rate was as follows: TL, 14.0%; TLPP without PMMF, 37.5%; and TLPP–TLTP with PMMF, 52.1%.

The mean preoperative hemoglobin values for patients with and without PCF were, respectively, 132.3 g/L [standard deviation (SD), 21.1 g/L] versus 134.8 g/L (SD, 19.5 g/L) ($p=0.314$). The mean postoperative hemoglobin value for the group of patients that developed PCF was 102.6 g/L (SD 15.2 g/L) versus 109.4 g/L (SD 14.9 g/L) for the non-PCF group ($p=0.0001$).

On the RPA, there was no significant association between preoperative hemoglobin levels and PCF formation. By contrast, based on the RPA analysis, patients were classified into three groups according to the association between postoperative hemoglobin values and PCF formation. The PCF rate by postoperative hemoglobin values was as follows: > 115 g/L ($n=118$), 11.9%; 99–115 g/L ($n=161$), 23.0%, and < 99 g/L ($n=121$), 34.7% ($p=0.0001$).

An analysis of postoperative hemoglobin values according to the type of surgery revealed significant between-group differences in postoperative hemoglobin levels only among patients treated with simple TL but not among those treated with extended TL (Supplementary material Table 2).

Table 2 shows the univariate analysis of PCF development for each assessed variable. The PCF rate was significantly higher in patients with hypopharyngeal tumors, large tumors (pT4), extended surgeries, without a primary voice prosthesis, and lower postoperative hemoglobin levels. The absence of a significant association between PCF formation and prior radiotherapy treatment is noteworthy. Supplementary Table 2 shows the univariate analysis for PCF development for each variable according to the type of surgery.

Among the patients treated with simple TL at our institution since the year 2008, in 44 of the 122 cases (36.0%) a stapler suture was used for pharyngeal reconstruction. The PCF incidence rate for patients who underwent reconstruction

Table 2 Percentage of patients with pharyngocutaneous fistula (PCF) and major PCF (M-PCF) for the assessed variables

	% PCF	*p* value	% M-PCF	*p* value
Gender				
Men	23.5	0.616	18.7	0.194
Women	19.2		7.7	
Age				
≤ 65 years	25.3	0.272	20.4	0.172
>65 years	20.7		15.1	
Tobacco and alcohol use				
No	20.0	0.704	13.3	0.875
Moderate	18.4		16.3	
Severe	24.1		18.5	
ASA				
2	16.9	0.128	11.7	0.296
3	26.9		19.2	
4	11.8		11.8	
Diabetes mellitus				
No	23.2	0.969	16.4	0.689
Yes	22.9		18.8	
Subsite location				
Supraglottis	18.8	0.0001	14.8	0.001
Glottis	17.9		14.4	
Hypopharynx	46.5		33.8	
pT				
pT2[a]	16.3	0.034	16.3	0.082
pT3	19.6		13.0	
pT4	29.1		22.5	
Previous radiotherapy				
No	23.7	0.836	16.4	0.396
Yes	22.8		19.7	
Type of surgery				
Simple TL	14.0	0.0001	11.0	0.0001
TLPP without PMMF	37.5		28.8	
TLPP–TLTP with PMMF	52.1		39.6	
Neck dissection				
No	25.6	0.801	12.8	0.612
Unilateral	25.3		20.3	
Bilateral	22.3		18.1	
Voice prosthesis				
No	25.1	0.013	19.5	0.031
Yes	8.7		6.5	
Postoperative hemoglobin				
>115 g/L	11.9	0.0001	8.5	0.001
99–115 g/L	23.0		18.0	
<99 g/L	34.7		27.3	

ASA American Society of Anesthesiologists; *TL* total laryngectomy; *TLPP* total laryngectomy with partial pharyngectomy; *TLTP* total laryngectomy with total pharyngectomy; *PMMF* pectoralis major myocutaneous flap

[a]Includes the ten patients without evidence of cancer

with an absorbable suture was 16.7% versus 11.4% for patients who received a stapler suture ($p=0.428$).

Table 3 shows the results of a multivariate analysis in which PCF was the dependent variable. That analysis showed that extended surgeries (including TLPP without PMMF and TLPP–TLTP with PMMF) and postoperative hemoglobin levels < 99 g/L significantly increased the risk of developing PCF.

We carried out an RPA using the presence of PCF as the dependent variable and all other assessed variables as independent variables (Fig. 1). The first partition yielded a classification tree based on the type of surgery. For patients treated with simple TL, the presence of PCF was correlated with postoperative hemoglobin levels. In patients who underwent TLPP or TLTP, PCF formation was correlated with tumor extension.

The presence of PCF was a significant predictor for longer hospital stay ($p=0.0001$), with a median hospital stay for the non-PCF group of 14.0 days versus 38.0 days for the PCF group. Among the patients who developed PCF, a trend towards longer hospital stays was observed in irradiated patients. In the PCF group, the median hospital stay for non-irradiated patients ($n=49$) was 35.0 days versus 47.0 days for the irradiated subgroup ($n=44$) ($p=0.056$).

Ten patients (2.5%) died during the perioperative period. Of these, eight had a PCF, and the death was directly attributable to local complications of PCF in seven of these patients.

Major fistula

Of the 93 patients with PCF, 72 (77.4%) met the study criteria for major fistula. The distribution of major fistula by surgery type was as follows: simple TL, $n=30$ (11%), TLPP without PMMF, $n=23$ (28.8%), and for TLPP–TLTP with PMMF, $n=19$ (39.6%).

Table 2 shows the univariate analysis for the association between major fistula and the individual variables. The PCF rate was significantly higher in patients with tumors located in the hypopharynx, larger tumors (pT4), in those with extended surgeries, in patients without primary voice prosthesis, and in those with low (< 99 g/L) postoperative hemoglobin levels. Supplementary Table 3 shows the univariate analysis for major fistula for each assessed variable according to the type of surgery.

Table 3 shows the results of a multivariate analysis in which the presence of major PCF was the dependent variable. Patients treated with extended surgeries, previous radiotherapy, or postoperative hemoglobin < 99 g/L had a significantly higher risk of developing a major fistula. Compared to patients not previously treated with radiotherapy, irradiated patients had a 2.9 times higher risk of developing a major fistula (95% CI 1.18–7.09, $p=0.019$).

Table 3 Multivariate analyses

	PCF	*p* value	Major PCF	*p* value
Gender				
Men	1		1	
Women	1.24 (0.37–4.20)	0.722	0.51 (0.09–2.75)	0.436
Age				
≤ 65 years	1		1	
>65 years	1.15 (0.56–2.38)	0.692	0.97 (0.42–2.21)	0.943
Tobacco and alcohol use				
No	1		1	
Moderate	0.70 (0.08–6.08)	0.753	1.01 (0.05–18.83)	0.990
Severe	0.96 (0.13–7.05)	0.962	1.01 (0.06–16.21)	0.992
ASA				
2	1		1	
3	1.57 (0.72–3.45)	0.255	1.66 (0.67–4.14)	0.272
4	0.93 (0.14–4.83)	0.841	1.80 (0.28–11.35)	0.529
Diabetes mellitus				
No	1		1	
Yes	1.75 (0.74–4.18)	0.201	2.48 (0.95–6.51)	0.064
Subsite location				
Supraglottis	1		1	
Glottis	1.71 (0.67–4.35)	0.255	2.25 (0.75–6.77)	0.147
Hypopharynx	1.14 (0.38–3.36)	0.810	0.57 (0.16–1.95)	0.575
pT				
pT2[a]	1		1	
pT3	1.19 (0.39–3.63)	0.748	0.68 (0.20–2.33)	0.545
PT4	2.11 (0.74–6.03)	0.162	1.48 (0.48–4.56)	0.486
Previous radiotherapy				
No	1		1	
Yes	1.57 (0.72–3.42)	0.257	2.90 (1.18–7.09)	0.019
Surgery				
TL	1		1	
TLPP without PMMF	3.77 (1.29–11.01)	0.015	7.61 (2.19–26.42)	0.001
TLPP or TLTP with PMMF	6.04 (1.62–22.14)	0.007	13.13 (2.86–60.17)	0.001
Neck dissection				
No	1		1	
Unilateral	1.55 (0.36–6.70)	0.555	4.97 (0.62–39.43)	0.129
Bilateral	1.51 (0.38–5.93)	0.554	6.24 (0.85–45.57)	0.071
Voice prosthesis				
No	1		1	
Yes	0.92 (0.27–3.15)	0.900	0.92 (0.22–3.79)	0.917
Postoperative hemoglobin				
>115 g/L	1		1	
99–115 g/L	1.50 (0.58–3.88)	0.395	1.25 (0.41–3.75)	0.686
<99 g/L	4.23 (1.62–11.04)	0.003	4.07 (1.34–12.32)	0.013

Hazard ratios (95% confidence interval)

PCF pharyngocutaneous fistula; *M-PCF* major PCF; *ASA* American Society of Anesthesiologists; *TL* total laryngectomy; *TLPP* total laryngectomy with partial pharyngectomy; *TLTP* total laryngectomy with total pharyngectomy; *PMMF* pectoralis major myocutaneous flap

[a]Includes the ten patients without evidence of cancer

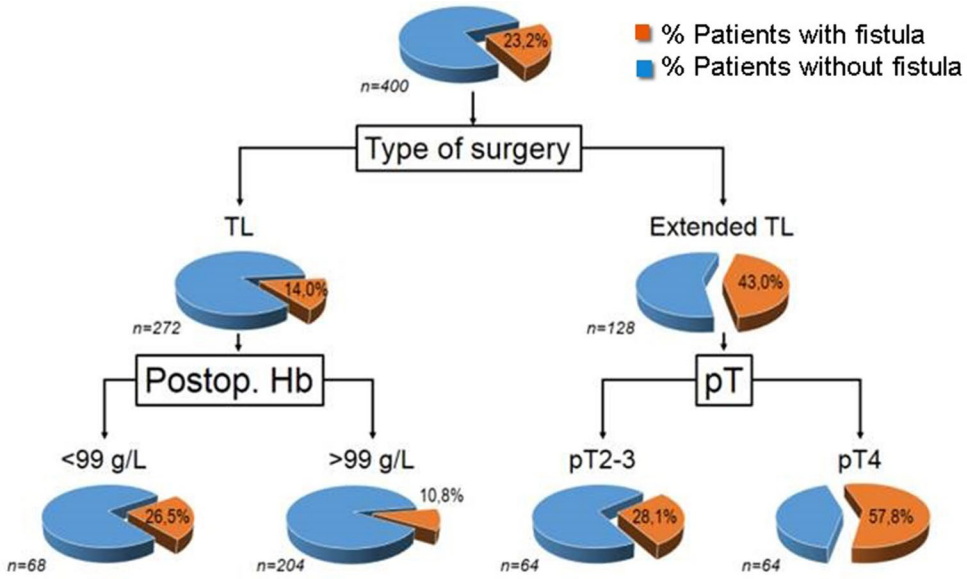

Fig. 1 Classification tree obtained with the recursive partitioning analysis. *TL* total laryngectomy, *Hb* hemoglobin

Discussion

Development of pharyngocutaneous fistula is one of the most common postoperative complications after TL. Although many potential risk factors for PCF formation have been identified, it is still not clear which of these are the most relevant. Therefore, we evaluated these risk factors to determine the variables that were most predictive of PCF formation. On the multivariate analysis, we found that extended surgeries and low (< 99 g/L) postoperative hemoglobin levels were associated with a significantly higher PCF rate.

Tumor- and surgery-related factors

Patients with hypopharyngeal or large tumors (pT4) had higher PCF rates, a finding that is consistent with a recent meta-analysis and some other studies that have found a significant relationship between tumor extension and PCF [4, 5, 12]. The type of resection (i.e., TL or extended TL) is defined by the tumor location and extension, which, in turn, determine the type of reconstruction. In our series, the type of surgery was a significant risk factor for developing PCF. If we consider simple TL as the reference category, patients who underwent TLPP without PMMF had a 3.8 times greater risk of developing PCF while those treated with TLPP or TLTP with PMMF had a sixfold greater risk. Importantly, a TLPP entails a reduction of mucosa available for the pharyngeal reconstruction; consequently, if a primary closure is then performed, the tension within the tissues increases. The use of a PMMF adds another component to the closure, and the interface between the mucosa and the tissues from the PMMF is thought to be the weak point of the suture, especially in the presence of a concomitant neck infection.

In our center, the decision to perform a PMMF is mainly based on the extent of the resection and the lack of free mucosa to create the neopharynx. In patients treated with a TL, there are two techniques for PMMF use: (1) incorporation of the PMMF flap into the suture line and (2) the onlay technique. The first technique, in which the flap is incorporated into the suture line (see "Materials and methods"), is performed to complete the closure of the neopharynx in extended resections. By contrast, the onlay PMMF technique is performed to reinforce the suture by transferring non-irradiated, well-vascularized tissue to the surgical field. The PMMF is then fixed to the parapharyngeal tissue and the prevertebral fascia on each side to separate the neopharynx from the vascular space [20]. However, since these two techniques have different aims, Anschütz et al. [20] have suggested that it is not appropriate to compare them in terms of outcomes. Up to now, our department has never considered the use of an onlay PMMF. A meta-analysis performed by Sayles et al. [21] found that the relative risk of developing PCF with a prophylactic flap versus closure alone in salvage simple TL was 0.56 (95% CI 0.37–0.85, $p = 0.001$). Recently, a systematic review by Guimarães et al. [22] found a 22% decreased risk of PCF in patients treated with the only PMMF technique ($p < 0.001$).

The value of performing neck dissection in these patients is controversial because some authors have found a significant association between neck dissection and the PCF incidence rate [6, 8, 13], whereas others have not [3–5, 7, 9, 14, 16–18, 23, 24]. In our study, we found no differences in PCF rates regardless of whether neck dissection was performed or not.

The multivariate analysis in our study showed that patients with postoperative hemoglobin levels < 99 g/L had a fourfold higher risk of developing PCF compared to patients with levels > 115 g/L. Paydarfar et al. [14] and Benson et al. [3] both found a significant association between postoperative hemoglobin levels and PCF. In our sample, postoperative (not preoperative) hemoglobin levels were significant risk factors, a finding that suggests that blood loss during surgery is the determining factor. Indeed, the need for intraoperative or postoperative transfusion has also been associated with PCF formation [1, 6, 16, 18]. Unfortunately, due to the retrospective design of our study, we are unable to assess transfusion requirements due to lack of data.

The placement of a primary voice prosthesis was a protective factor for PCF on the univariate analyses. In our center, placement of a primary voice prosthesis is indicated in patients who have adequate performance status, few comorbidities, and who show a good predisposition to use the device. This positive selection of prosthesis candidates might explain why the PCF rate was lower in these patients.

In our sample, the use of a stapler suture did not affect the PCF rate. However, Ismi et al. [25] obtained lower PCF rates with stapler suture compared to manual closure. In that study, stapler closure also reduced the operative time and was associated with lower rates of infection at the surgical site [25]. In contrast, Benson et al. [3] found that stapler sutures were associated with higher PCF rates.

Comorbidities and previous therapies

None of the patient-related characteristics—including diabetes—were associated with significant differences in the PCF rate. This finding is worth highlighting given that diabetes is considered a risk factor for PCF [11].

We found no significant correlation between previous radiotherapy and PCF rates, a finding that is consistent with several other reports [3, 15, 18, 24, 26, 27], although it contradicts some other studies which have reported an increased risk of PCF in irradiated patients [5–14, 17]. The effects of radiotherapy on wound healing include obliterative endarteritis, hypoxia, impaired leukocyte migration, fibrosis, delayed wound closure, and an overall decrease in tissue vascularity [8, 11]. Boscolo-Rizzo et al. [11] suggested that technological improvements in radiotherapy, including improved dose delivery through the use of intensity-modulated radiation therapy and modern linear accelerators may have reduced the impact of radiotherapy on PCF formation.

Major fistula

Based on findings presented here, we have developed a new system to classify PCF into major and minor PCF according to severity criteria. We define major PCF as a fistula lasting longer than 1 month, or requiring surgical treatment for repair, or if the PCF leads to death. Horgan and Dedo [28] previously defined major fistula as a fistula lasting ≥ 8 weeks or requiring surgical treatment. However, our clinical experience suggests that fistulas requiring more than 4 weeks to heal are unlikely to heal completely and, therefore, this time point is the optimal moment to consider surgery.

In the multivariate analysis, the following variables were associated with the risk of major fistula: (1) extended surgery (TLPP without PMMF and TLPP-TLTP with PMMF), (2) postoperative hemoglobin level < 99 g/L, and (3) previous radiotherapy. Considering simple TL as the reference category, TLPP without PMMF increased the risk of major fistula by 7.6 times, while TLPP–TLTP with PMMF increased the risk by 13.1 times. Compared to patients who had postoperative hemoglobin levels > 115 g/L, those with levels < 99 g/L had a fourfold greater risk of developing major fistula. Patients who underwent previous radiotherapy had a 2.9 times greater risk of major fistula. Galli et al. [17] suggested that large PCFs, in most cases due to previous radiotherapy, do not close spontaneously with a conservative approach; consequently, those authors proposed waiting a month for the size of the PCF to decrease before planning the reconstruction. Our results are consistent with the findings reported by Virtaniemi et al. [13] who found that fistulas appeared earlier, were larger, and closed later in patients treated previously with radiotherapy; however, it should be noted that their results were not statistically significant. Venegas et al. [27], following the criteria described by Horgan and Dedo [28], found a higher rate of major fistula in radiated versus non-irradiated patients.

Based on the findings of this study and other published studies, which suggest that the PMMF onlay technique can reduce the incidence of major fistulas, our departmental policy will be to consider the use of prophylactic onlay flaps in irradiated patients who require TLPP.

Study strengths and limitations

The main limitation of the present study is the retrospective design, which prevented us from assessing the impact of certain variables—such as nutritional status, thyroid function, and perioperative blood transfusion—that many studies suggest may be related to PCF formation. By contrast, the main strengths are the large sample of patients from a single institution and the inclusion of a wide range of surgical procedures.

Conclusions

The incidence of PCF in our sample was 23.3%, although the rate varied greatly according to the type of surgical procedure, from as low as 14% for simple TL to as high as 52.1%

for patients who underwent TLPP–TLTP with inserted PMMF.

Based on the findings of this study, we have developed a new system to classify PCF as either minor or major according to clinical severity criteria. The proposed criteria for major fistula are (1) duration of 4 weeks or more, (2) requirement for surgical treatment, or (3) fistula-related patient death. The incidence of major fistula in our patients was 18%. The variables significantly associated with major fistula (multivariate analysis) were: extended surgery, previous treatment with radiotherapy, and postoperative hemoglobin < 99 g/L. On that purpose, we suggest considering the use of prophylactic onlay flaps in irradiated patients who require TLPP.

Funding This work was supported by grants from Plan Estatal de I+D+I of the Instituto de Salud Carlos III (FIS PI14/01819). Fondo Europeo de Desarrollo Regional (FEDER), A Way to Build Europe.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Research involving human participants All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional, regional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

References

1. Lebo NL, Caulley L, Alsaffar H, Corsten MJ, Johnson-Obaseki S (2017) Peri-operative factors predisposing to pharyngocutaneous fistula after total laryngectomy: analysis of a large multi- institutional patient cohort. J Otolaryngol Head Neck Surg 23:46–54. https://doi.org/10.1186/s40463-017-0233-z
2. Scotton WJ, Nixon IJ, Pezier TF, Cobb R, Joshi A, Urbano TG, Oakley R, Jeannon JP, Simo RS (2014) Time interval between primary radiotherapy and salvage laryngectomy: a predictor of pharyngocutaneous fistula formation. Eur Arch Otorhinolaryngol 271:2277–2283. https://doi.org/10.1007/s00405-013-2726-3
3. Benson EM, Hirata RM, Thompson CB, Ha PK, Fakhry C, Saunders JR, Califano JA, Arnaoutakis D, Levine M, Tang M, Neuner G, Messing BP, Blanco RGF (2015) Pharyngocutaneous fistula after total laryngectomy: a single-institution experience, 2001–2012. Am J Otolaryngol Head Neck Med Surg 36(1):24–31. https://doi.org/10.1016/j.amjoto.2014.08.017
4. de Zinis LO, Ferrari L, Tomenzoli D, Premoli G, Parrinello G, Nicolai P (1999) Postlaryngectomy pharyngocutaneous fistula: incidence, predisposing factors, and therapy. Head neck 21(2):131–138
5. Liang JW, Li ZD, Li SC, Fang FQ, Zhao YJ, Li YG (2015) Pharyngocutaneous fistula after total laryngectomy: a systematic review and meta-analysis of risk factors. Auris Nasus Larynx 42(5):353–359. https://doi.org/10.1016/j.anl.2015.04.002
6. Dedivitis RA, Aires FT, Cernea CR, Brandão LG (2015) Pharyngocutaneous fistula after total laryngectomy: systematic review of risk factors. Head Neck 37(11):1691–1697. https://doi.org/10.1002/hed.23804
7. Busoni M, Deganello A, Gallo O (2015) Pharyngocutaneous fistula following total laryngectomy: analysis of risk factors, prognosis and treatment modalities. Acta Otorhinolaryngol Ital 35(6):400–405. https://doi.org/10.14639/0392-100X-626
8. White HN, Golden B, Sweeny L, Carroll WR, Magnuson JS, Rosenthal EL (2012) Assessment and incidence of salivary leak following laryngectomy. Laryngoscope 122(8):1796–1799. https://doi.org/10.1002/lary.23443
9. Klozar J, Cada Z, Koslabova E (2012) Complications of total laryngectomy in the era of chemoradiation. Eur Arch Otorhinolaryngol 269(1):289–293. https://doi.org/10.1007/s00405-011-1598-7
10. Dirven R, Swinson BD, Gao K, Clark JR (2009) The assessment of pharyngocutaneous fistula rate in patients treated primarily with definitive radiotherapy followed by salvage surgery of the larynx and hypopharynx. Laryngoscope 119(9):1691–1695. https://doi.org/10.1002/lary.20521
11. Boscolo-Rizzo P, De Cillis G, Marchiori C, Carpenè S, Da Mosto MC (2008) Multivariate analysis of risk factors for pharyngocutaneous fistula after total laryngectomy. Eur Arch Otorhinolaryngol 265:929–936. https://doi.org/10.1007/s00405-007-0562-z
12. Grau C, Johansen LV, Hansen HS, Andersen E, Godballe C, Andersen LJ, Hald J, Møller H, Overgaard M, Bastholt L, Greisen O, Harbo G, Hansen O, Overgaard J (2003) Salvage laryngectomy and pharyngocutaneous fistulae after primary radiotherapy for head and neck cancer: a national survey from Dahanca. Head Neck 25(9):711–716. https://doi.org/10.1002/hed.10237
13. Virtaniemi JA, Kumpulainen EJ, Hirvikoski PP, Johansson RT, Kosma V-M (2001) The incidence and etiology of postlaryngectomy pharyngocutaneous fistulae. Head Neck 23 (1): 29–33. https://doi.org/10.1002/1097-0347(200101)23:1%3C29::AID-HED5%3E3.0.CO;2-P.
14. Paydarfar JA, Birkmeyer NJ (2006) Complications in head and neck surgery: a meta-analysis of postlaryngectomy pharyngocutaneous fistula. Arch Otolaryngol Head Neck Surg 132(1):67–72. https://doi.org/10.1001/archotol.132.1.67
15. Ganly I, Patel S, Matsuo J, Singh B, Kraus D, Boyle J, Wong R, Lee N, Pfister DG, Shaha A, Shah J (2005) Postoperative complications of salvage total laryngectomy. Cancer 103(10):2073–2081. https://doi.org/10.1002/cncr.20974
16. Erdag MA, Arslanoglu S, Onal K, Songu M, Tuylu AO (2013) Pharyngocutaneous fistula following total laryngectomy: multivariate analysis of risk factors. Eur Arch Otorhinolaryngol 270(1):173–179. https://doi.org/10.1007/s00405-012-2111-7
17. Galli J, De Corso E, Volante M, Almadori G, Paludetti G (2005) Postlaryngectomy pharyngocutaneous fistula: incidence, predisposing factors, and therapy. Otolaryngol Head Neck Surg 133(5):689–694. https://doi.org/10.1016/j.otohns.2005.07.025
18. Morton RP, Mehanna H, Hall FT, McIvor NP (2007) Prediction of pharyngocutaneous fistulas after laryngectomy. Otolaryngol Head Neck Surg. https://doi.org/10.1016/j.otohns.2006.11.030
19. Fabian RL (1988) Pectoralis major myocutaneous flap reconstruction of the laryngopharynx and cervicl esophagus. Laryngoscope 98:1227–1231
20. Anschütz L, Nisa L, Elicin O, Bojaxhiu B, Caversaccio M, Giger R (2016) Pectoralis major myofascial interposition flap prevents postoperative pharyngocutaneous fistula in salvage total laryngectomy. Eur Arch Otorhinolaryngol 273(11):3943–3949. https://doi.org/10.1007/s00405-016-4049-7
21. Sayles M, Grant DG (2014) Preventing pharyngo-cutaneous fistula in total laryngectomy: a systematic review and meta-analysis. Laryngoscope 124(5):1150–1163. https://doi.org/10.1002/lary.24448
22. Guimarães AV, Aires FT, Dedivitis RA, Kulcsar MAV, Ramos DM, Cernea CR, Brandão LG (2016) Efficacy of pectoralis major

muscle flap for pharyngocutaneous fistula prevention in salvage total laryngectomy: a systematic review. Head Neck E2317–E2321. https://doi.org/10.1002/hed.24248
23. Patel UA, Moore BA, Wax M, Rosenthal E, Sweeny L, Militsakh ON, Califano JA, Lin AC, Hasney CP, Butcher RB, Flohr J, Arnaoutakis D, Huddle M, Richmon JD (2013) Impact of pharyngeal closure technique on fistula after salvage laryngectomy. JAMA Otolaryngol Head Neck Surg 139(11):1156–1162. https://doi.org/10.1001/jamaoto.2013.2761
24. Markou KD, Vlachtsis KC, Nikolaou AC, Petridis DG, Kouloulas AI, Daniilidis IC (2004) Incidence and predisposing factors of pharyngocutaneous fistula formation after total laryngectomy. Is there a relationship with tumor recurrence? Eur Arch Otorhinolaryngol 261 (2): 61–67
25. Ismi O, Unal M, Vayisoglu Y, Yesilova M, Helvaci I, Gorur K, Ozcan C (2017) Stapler esophageal closure during total laryngectomy. J Craniofacial Surg 28(1):35–40. https://doi.org/10.1097/SCS.0000000000003196
26. Cecatto SB, Monteiro-Soares M, Henriques T, Monteiro E, Moura CIFP (2015) Derivation of a clinical decision rule for predictive factors for the development of pharyngocutaneous fistula postlaryngectomy. Braz J Otorhinolaryngol 81(4):394–401. https://doi.org/10.1016/j.bjorl.2014.09.009
27. Venegas MP, León X, Quer M, Matiño E, Montoro V, Burgués J (1997) Complications of total laryngectomy in relation to the previous radiotherapy. Acta Otorrinolaringol Esp 48(8):639–646
28. Horgan EC, Dedo HH (1979) Prevention of major and minor fistulae after laryngectomy. Laryngoscope 89:250–260