European Review for Medical and Pharmacological Sciences 2022; 26: 257-269

Analysis of surgical treatment strategy and outcome factors in persistent tracheoesophageal fistula: a critical analysis of own cases and review of the literature

M. KOCH, A. VASCONCELOS CRAVEIRO, K. MANTSOPOULOS, M. SIEVERT, A.-O. GOSTIAN, H. IRO

Department of Otorhinolaryngology, Head and Neck Surgery, Friedrich Alexander University of Erlangen–Nuremberg, Erlangen, Germany

Abstract. – OBJECTIVE: Surgical closure of persistent tracheoesophageal fistulas (TEFs) is complex. Most patients present with multiple risk factors, which may negatively impact the outcome and influence the treatment strategies.

PATIENTS AND METHODS: This retrospective study included 22 patients presenting with persistent TEFs. Preoperative RT, comorbidities, tissue conditions of the TEFs and neck skin, and surgical techniques were evaluated regarding a possible impact on success rates and outcome.

RESULTS: 21 patients were operated, 95.45% with final success. However, in 52.39% repeated surgery was needed. Final closure of TEFs was achieved in 91.47% only after more invasive surgery was performed. The surgical technique applied had the most significant impact on success rates and outcome compared to all other risk factors analyzed. Our own data and that of the literature point out that the surgical strategy should be adapted to the patients' individual risk factors.

CONCLUSIONS: According to the literature, surgical closure of persistent TEFs is demanding. Our data suggest that, considering that the majority of patients with persistent TEFs exhibit multiple risk factors, early performance of more invasive surgery seems associated with a better outcome.

Key Words:

Voice prosthesis, Complications, Tracheoesophageal fistula, Treatment, Surgery, Outcome.

Introduction

After total laryngectomy, insertion of voice prostheses (VP) *via* a tracheoesophageal puncture (TEP) is the gold standard[1-4]. Complications may occur with a frequency of up to 19%[5-7], mainly due to enlargement of the TEP with resulting leakage[5,6,8]. After development of a tracheoesophageal fistula (TEFs), its persistence may have serious consequences for the patients affected[7]. Conservative treatment is the first-line therapy, but success rates were not always adequate[1,2,7,9-20]. In addition, modifications of the VP to reduce the peri-prosthetic leakage were described[10-12].

Persisting TEFs requires surgical treatment. In less complicated TEFs, various transtracheal techniques including purse-string suture[13], ligation of the TEFs[14-16] or transplantation of a cartilage graft into the TEFs[17] can be performed with acceptable success rates. Two- or three-layered sutures with or without use of additional materials are more invasive alternative procedures[18-26]. In less favorable conditions, 2-layered sutures of the esophagus and resection of the cranial trachea with cranial transposition of the residual trachea have been reported[27,28]. For TEFs with a higher risk profile, well vascularized tissue provided by the interposition of pedicled local, or regional flaps[29-37] or free flap tissue transfer[38-42] is indicated to close the TEFs.

If surgery had failed, seemed very risky or if patients were inoperable or refused surgery, septal buttons, mostly made of silicon, which may be adapted to the size and shape of smaller TEFs[33,43-46] or individualized custom-made prostheses[47,48] were inserted in recent years to avoid extensive surgery with a high risk of failure.

In one comprehensive publication a classification of TEFs and its possible impact on the management of TEFs were reported[9].

In this study we would like to summarize our experience after surgical treatment of persistent TEFs by including important prognostic factors like size and location of the TEFs, local or regional tissue conditions, previous RT and irradiation

Corresponding Author: Michael Koch, MD; e-mail: michael.koch@uk-erlangen.de

dose, and comorbidities in our analysis. Considering the results reported in the literature, a treatment algorithm is proposed to support a more standardized therapy.

Patients and Methods

The data were collected from the Department of Otorhinolaryngology, Head and Neck Surgery of the Friedrich-Alexander University of Erlangen-Nuremberg (Germany). The Ethics approval was given by the local Institutional Review Board. Informed consent was obtained from all study participants. Patients who developed therapy resistant TEFs after implantation of a VP between January 2004 and December 2020 were included in this retrospective analysis. In all patients, conservative measures failed, and surgical therapy was indicated.

Pre-therapeutic epidemiological, surgical and oncologic data were noted. Age prior to start of surgical treatment was categorized to three categories (50-60, 60-70, >70 years). Comorbidities were noted and categorized according to the presence and number.

The size of the TEFs (3 categories), location of the TEFs (3 categories), the tissue quality within the TEFs tracheal and esophageal layers (2 categories – fair: tissue layers preserved and distinguishable; poor: tissue atrophic, scarred) and of the neck skin (2 categories - fair: trophic preserved, mobilization possible; poor: scarred, "frozen neck") and the final nutrition state (3 categories: oral only; oral+percutaneous gastroenteric tube (PEGT); PEGT only) were all noted and categorized. Time intervals (insertion of the VP - diagnosis of the TEFs; start of conservative measures - first surgeries, between first/second/third surgeries, follow-up time after final surgery) were noted. The surgical approaches were categorized according to their invasiveness into categories for considering technical modifications. Primary endpoints were the rate of successful closure of the TEFs, and the category and number of surgeries needed to achieve closure of TEFs.

Statistical Analysis

Continuous data of all cases are given as mean±SEM, median, range. Only patients treated by surgery were included in the statistical analysis. Differences between the categories were tested by the exact test. The significance level was $p \leq 0.05$. Regression analysis was not conducted due to categorical variables and the small number of cases.

Results

Twenty-three patients presented with TEFs that did not resolve after conservative treatment. In 21 cases, prior therapy was conducted at our institution and two at other institutions (patients 21, 23). One patient died three days after surgical closure of a TEFs due to a heart attack and was not included in the further analysis. 22 patients were included, of whom 86.4% were male. Epidemiologic, oncologic data and data concerning prior therapy and the presence of comorbidities are provided (Table I, Table II). Diagnosis of persistent TEFs was made after a mean of 37.72±6.30 months.

The mean age of our 22 cases at the start of treatment was 63.72±1.84 years (range 52-82). Duration of conservative treatment averaged 3.45±0.81 months (range 1-18 months, Table I).

Seven techniques out of four categories were performed in accordance with the current literature (Table III-IV)[9,13-46,49]

In the 21 patients who had surgery, 38 operations altogether were needed to achieve closure of the TEFs, at least one revision was needed in 11 cases (Table III). If the four separations and relocations of interpolated flaps were included, 43 procedures were performed, but these were not included to evaluate concerning successful closure of TEFs.

First surgery consisted in 11 cases of category 1 surgery (52.54%), in 4.8% of category 2, in 28.6% of category 3 and in 14.3% of category 4. 16.67% of the procedures comprising categories 1-2 and 88.89% of the procedures comprising categories 3-4 were successful. Success rates were significantly different distributed over the surgical categories (category 1 – 9.09%; category 2 – 100%; category 3 – 100%, category 4 – 66.7%; p=0.0001), indicating that more invasive surgery was more successful.

The second surgeries were category 1 and category 3 procedures in 36.4% (n=4) each and category 4 procedures in 27.3% (n=3). The overall success rate was 41.67%. None of the category 1 procedures but 57.14% of categories 3-4 were successful. However, no significant differences were recognizable (Table III), which may be attributed to the low number of cases compared.

The third surgeries were category 3 procedures in 83.33% and category 4 in 16.67%. All of them were successful (Table III).

Finally, in 95.23% of the cases (20/21) surgical closure of the TEFs could be achieved in 90.47%

Table I. Epidemiologic data, oncologic data, data concerning the prior therapy, time frame of conservative measures, data concerning risk factors (comorbidities, tissue conditions of TEFs and neck skin, location of TEFs in 22 patients with persistent TEFs.

Patient (number)	Gender	Primary Tumor Stage	Prior RT (Gy)	Time from laryngectomy to TEFs (months)	Age at diagnosis of TEFs (years)	Time of conservative measures (months)	Comorbidities (n)	Tissue conditions cervical skin	Tissue conditions TEFs	Location of TEFs (distance of the cranial border of the trachea to the caudal border of TEFs - cm)
1	M	T3 N2c	60	43	58	7	0	fair	fair	< 2
2	M	T4a N0	n†	46	82	5	2	fair	poor	2-4
3	M	T4a N2b	66	8	62	1	1	fair	fair	2-4
4	F	T3 N1	10†	6	53	2	0	fair	poor	< 2
5	M	T3 N0	64	6	69	5	0	poor	poor	> 4
6	M	T4 N1	60	46	52	5	2	poor	poor	2-4
7	M	T3 N2a	64	10	58	2	0	fair	poor	2-4
8	F	T3 N0	68	10	59	1	2	poor	poor	> 4
9	M	T4a N1	64	75	54	1	2	fair	poor	< 2
10	M	T4a N0	60	112	69	1	1	fair	poor	< 2
11	M	T4a N1	64	42	64	6	1	fair	poor	< 2
12	M	T4a N2b	64	31	65	18	2	poor	poor	> 4
13	M	T4a N0	60	84	71	1	0	fair	fair	< 2
14	M	T4a N2c	66	81	63	1	3	poor	poor	>4
15	M	T3 cN0	64	21	69	2	2	fair	poor	>4
16	M	T4a N2b	72	30	58	2	1	poor	poor	2-4
17	M	T4a N0	66	29	52	2	3	poor	poor	2-4
18	M	T2 cN0	nd‡	7	76	2	4	fair	fair	2-4
19	M	T2 N0	64	29	55	6	1	fair	poor	2-4
20	M	T4a N2b	40	39	67	1	1	fair	poor	< 2
21	F	T2 N1	56	50	79	4	1	fair	poor	>4
22	M	T4a N2c	70	3	67	1	3	poor	poor	2-4

†Patient 2 refused offered postoperative RCT, patient 4 refused to continue RT after start at 10 Gy. ‡no data available (adjuvant therapy abroad).

Table II. Data concerning the first, second and third procedure (non-surgical/prosthesis, surgical treatment: first, second and third surgery): size of TEF, time interval between procedures, type/category of surgery, success state, post-therapeutic feeding state, follow-up time in 22 cases.

Patient (number)	First operation (n=23)		Second operation (n=12)			Third operation (n=5)			Final success (yes/no)	Feeding state		Follow-up (months)
	Size (cm)	Operation	Time	Size (cm)	Category of surgery	Time	Size (cm)	Category of surgery		Prior occurrence of TEFs	Post-operative	
1	< 1	1b (LA)	0	< 1	1b	-	-	-	no	PEGT	PEGT	3 †
2	1-3	3b (MFPMF) ‡			-	-	-	-	yes	Oral	Oral	16
3	< 1	1b (LA)	0	< 1	3a	-	-	-	yes	Oral	Oral	10
4	< 1	3a	-	-	-	-	-	-	yes	Oral	Oral+PEGT	30
5	1-3	4a (SCF) §	0	> 3	4b (ALT) §	-	-	-	yes	Oral	Oral	11
6	1-3	3a	-	-	-	-	-	-	yes	Oral+PEGT	Oral+PEGT	18
7	< 1	3a	-	-	-	-	-	-	yes	Oral+PEGT	Oral	55
8	< 1	1a	8	1-3	4a (DPF) ¶	1	>3	4b (RFF) ¶	yes	Oral	Oral	16
9	< 1	1b (LA)	4	< 1	1b	2	1-3	3a	yes	Oral	Oral	86
10	1-3	3a	-	-	-	-	-	-	yes	Oral	Oral	13
11	< 1	1b	0	< 1	1a (MF)	2	< 1	3b (MSCM/IHMF) ‡	yes	Oral	Oral	93
12	1-3	Prosthesis	-	-	-	-	-	-	yes	Oral+PEGT	Oral+PEGT	12
13	< 1	1b	-	-	-	-	-	-	yes	Oral	Oral	108
14	<1	1b	7	1-3	4a (DPF) ¶	-	-	-	yes	Oral	Oral+PEGT	58
15	1-3	4a (DPF) ¶	-	-	-	-	-	-	yes	Oral	Oral	27
16	< 1	1a	5	< 1	3a	2	< 1	3a	yes	Oral	Oral	41
17	1-3	4a (DPF) #	-	-	-	-	-	-	yes	Oral	Oral	27
18	< 1	2b	-	-	-	-	-	-	yes	Oral	Oral	14
19	< 1	1a	4	< 1	3a	-	1-3	3b (MFPMF) ‡	yes	Oral	Oral	13
20	< 1	3a	-	-	-	-	-	-	yes	PEGT	PEGT	44
21	< 1	1a	1	< 1	3a	-	-	-	yes	PEGT	PEGT	24
22	< 1	1a	0	< 1	1a	0	1-3	4a (PMF) ¶	yes	Oral	Oral	11

† due to development of distant metastases no further attempts. ‡ myofascial flap as interpolation between esophagus and trachea. § replacement of pharyngeal/esophageal and/or tracheal defect. ¶ replacement of posterior trachea. # replacement of cervical skin. Legend: LA, local anesthesia; MF, mucosa flap; MSCM, musculo-sternocleidomastoid flap; IHMF, infrahyoid muscle flap DPF, deltopectoral flap; PMF, pectoralis major flap; MFPMF, myofascial pectoralis major flap; SCF, suprascapular flap; RFF, radial forearm flap; ALT, anterolateral thigh flap.

Table III. Classification of the operative treatment according to invasiveness and complexity (including own experiences and in consideration of literature results).

1. Debridement of and/or around the TEFs without separation of the esophageal and tracheal walls with or without local mucosal flaps:
   a) suture with single stitches
   b) pursuit/sling sutures
2. Debridement of and/or around the TEFs with separation of the esophageal and tracheal walls:
   a) Ligation of fistula with debridement of the fistula without resection of the TEFs ± local flaps and ± additional grafts;
   b) Extended debridement with separation of the esophageal and tracheal walls, resection of the fistula and closure with 2 or 3-layered sutures, ± local flaps, ± additional grafts
3. Extended debridement with separation of the esophageal and tracheal walls, resection of the TEFs, ± resection of the cranial trachea and transposition/ascension of the caudal trachea:
   a) resection of the cranial trachea and transposition/ascension of the caudal trachea without flap ± additional grafts;
   b) any surgery with regional/pedicled flap for interpolation of tissue between the trachea and esophagus
4. Extended surgery with separation of the esophageal and tracheal walls, resection of TEFs and closure of tracheal and/or esophageal defects with and/or replacement of the cranial trachea:
   a) pedicled flap (replacement of cranial trachea and/or cervical skin)
   b) pedicled flap and/or free flap (defect covering of trachea and/or esophagus)

after application of more invasive techniques (category 3 – 57.1%; category 4 – 28.6%), while it could be achieved by category 1 and 2 in only 4.8% each (Table III).

In one case surgical therapy was not successful. This patient presented with distant metastases; only category 1b surgery was attempted twice unsuccessfully before the patient died of the disease (patient 1, Table III). A custom-made prosthesis was implanted in one patient with unfavorable risk factors who needed extensive surgery (category 4 a/b). Finally, the patient decided to have closure of the TEFs by a custom-made prosthesis (patient 12, Table III).

The size of the TEFs at first surgery was ≤1 cm (category 1) in 71.4% and 1-3 cm in 28.6% (category 2). No large TEFs (≥ 3 cm, category 3) was present primarily. With smaller-sized TEFs, less invasive first surgeries were performed significantly more often compared to larger TEFs (80 *vs.* 0%; p=0.001). Notably, there was a strong trend for the success rates to be lower after surgery of smaller compared to larger TEFs (33.33% *vs.* 83.33%; p=0.063). Larger TEFs tended to be associated with worse neck skin conditions. The TEFs size increased in 27.27% before the second and in 33.33% before the third surgery was performed. Also, at the second surgery more invasive surgery was conducted significantly less often in small TEFs compared to the larger-sized TEFs of categories 2 and 3 (50% *vs.* 100%; p=0.006). Finally, independent of the TEFs size, more invasive surgery was needed in > 90% of the cases to achieve successful closure.

The caudal border of the TEFs was at a depth of ≤ 2 cm (category 1) in 33.3%, at 2-4 cm (category 2) in 42.90%, and at > 4 cm (category 3) in 23.8%. No patients with worse cervical tissue conditions of the neck skin presented with a cranially located TEFs (category 1). All patients with unfavorable tissue conditions in the neck region presented with more deeply located TEF, compared to only 46.14% of those who presented with fair tissue conditions. To achieve final success, a strong tendency for higher surgical categories in deeper TEFs was noted: category 1 - 16.67%, category 2 - 88.89%, category 3 – 100% (p=0.022). In TEFs of > 4 cm depth (n=5; 23.8%), final success was achieved only by surgery of categories 3-4, and in 80% more than one surgical procedure was performed (Tables I, III).

Tissue condition within the TEFs was poor in 81.0% of all, in 73.33% of the smaller, and in all of the larger TEFs at first surgery (Table I). A trend towards an association with a higher number of comorbidities, worse tissue conditions of the neck skin, and increasing size after failure was observed. TEFs tissue conditions were not distributed significantly differently over the categories of first or revision surgeries, nor were the success rates significantly influenced. However, if final success is considered, all TEFs with a poor tissue category were associated significantly more often with more invasive surgical techniques compared to TEFs with fair tissue conditions (100% *vs.* 66.67%; p=0.016).

Tissue condition of the cervical skin was poor in 38.1% (Table I). All more deeply located TEFs (categories 2-3) were present in cases with poor tissue condition (see above; p=0.031). No further significant differences were observed. A tendency towards an association with a larger TEFs size, worse

TEFs tissue conditions, and the number of comorbidities (see below) was observed. More invasive surgery was finally needed to achieve success in 100% of the patients with poor neck skin conditions and in 83.33% of those with fair conditions.

RT was performed preoperatively in 95.20% (dose > 60 Gy in 76.2%, Table I). The patient who had no RT had successful first surgery (category 1). In another patient who had successful category 2 surgery, no dose could be evaluated (treatment elsewhere). 90.90% of patients who had category 1 surgery, 50% who had category 3 surgery and 100% of those who had category 4 surgery were irradiated with a dose of > 60 Gy (p=0.056). No significant association with any parameter evaluated was observed.

Comorbidities were noted in 76.2% of the surgical patients (mean 1.43±0.25/patient, range 0-4, Tables I, IV). Neither the presence nor the number of comorbidities were significantly distributed over the success rates of first or second surgeries. However, the surgery category showed a significantly different distribution over the number of comorbidities (p=0.037): patients after category 1 surgery presented with comorbidities in 81.81% (45.45% had one, 18.18% each two and three). The patient after category 2 surgery had four comorbidities. Patients after category 3 surgeries had comorbidities in 66.67% (33.3% of them each had one and two). Patients after category 4 surgeries had comorbidities in 66.67% (33.3% of them each had two and three). The number of comorbidities were significantly higher in patients with worse compared to those with fair skin conditions (87.5% *vs.* 69.23%; p=0.048). The age categories of the patients did not show any significant differences after their distribution was tested against any parameter. The documented postoperative follow-up averaged 34.19±6.51 months (range 3–108 months, Table III).

Out of the surgical cases, 71.4% were fed orally (category 1), 14.3% by mixed oral feeding and PEGT (category 2) and 14.3% by PEGT alone (category 3). In 9.52% a deterioration was noted, and in 4.2% an improvement (Table III), the pre- and postoperative nutritional state was unchanged in 85.71% (p=0.001). No significantly different distribution or tendency was found after testing the nutrition state against any categorized parameter.

Discussion

Treatment of TEFs is tricky because it is located in a sensitive and functionally important region and most patients present with multiple risk factors. Surgical closure of TEFs is difficult. This is documented by the diversity of surgical methods published, ranging from less invasive to maximally invasive procedures[9,13-46,49]. In only one publication was a classification of TEFs and its possible impact on the management of TEFs reported[9]. All four types of TEFs described were also considered in our publication, which focused on complications of the TEFs after implantation of a VP. A detailed analysis of individual risk factors and their possible impact on the success rates and the surgical strategies has not been performed up to now. Out of the parameters investigated in the present study, the surgical technique was of most importance. Surgical techniques out of seven of eight (sub)-categories, which were used in the literature for closure of TEFs[9,13-46,49], were also used in our patients (Tables III-IV). Successful closure was achieved in 95.45% of all, and in 100% of cured cases. However, in 52.38% of the patients, revision surgery had to be performed (Table III). While most publications addressed only one surgical method[13-46,49], several techniques were addressed in one publication[9]. In only 9.6% (2/21) cases, success was achieved after using less invasive techniques (categories 1-2, Tables III-IV). Looking at the literature, transtracheal suture techniques in various modifications were performed with success rates of 50%-80%[13,16,17]. Better results were reported for transtracheal category 2 techniques when layered sutures were used, with success rates in the literature ranging from 50-100%, sometimes in combination with interpolation of grafts[18,19 15,20-26] Less invasive procedures were performed in all reports in small-sized TEFs (0.5-1 cm) located cranially with fair tissue conditions. Category 1 or 2 techniques were performed successful in only 4.76% of each of our cases. Consistently better results were reported after more invasive techniques were performed (categories.3-4, Tables III-IV). For 2-layered sutures of the esophagus with resection and cranial transposition of the trachea, success rates of at least 80% were reported in the literatur[24,27,28] and in the present study, which revealed a success rate of 76.92%. Using this technique, extensive surgery in a wide surgical field, which is already potentially damaged by prior surgery and irradiation, can be avoided. It was performed successfully in 44.45% of our patients, also in TEFs with unfavorable conditions without any bulking effect. Additional grafts/materials or interpolated flaps may be used to increase safety, which

Table IV. Presence and number of comorbidities in 22 patients with TEFs persistent to conservative treatment.

Comorbidities								
Patient	Hypertension	Heart disease	Renal insufficiency	Peripheral artery disease	Diabetes mellitus	COPD	Autoimmune disease	Total
1								0
2	x					x		2
3						x		1
4								0
5								0
6					x	x		2
7								0
8			x			x	x	3
9						x		1
10		x						1
11	x							1
12	x				x			2
13								0
14	x	x				x		3
15	x				x			2
16	x							1
17	x	x						2
18	x			x	x	x		4
19						x		1
20						x		1
21						x		1
22	x	x				x		3

was done successfully in all 3 cases involved (13.63% of all cases). 85-100% success rates were reported after interpolation of various modifications of sternocleidomastoid muscle flaps[30,32,35,36] or deltopectoral flaps[31,34,37] in combination with other techniques. However, compromised vascularization and tissue bulking may lead to a worse (functional) outcome in such cases. Pedicled and/or interpolated flaps are also a valuable option to replace defects in worse tissue conditions of the cervical skin and/or the cranial trachea. We used this technique with various flaps in 6 cases with a success rate of 66.67% (Table III, Figures 1-5). One of the failures occurred after using a supraclavicular flap, which does not seem suitable for this purpose, as its vascularization is potentially compromised by prior surgery and RT. As in those cases more complex TEFs have to be treated, free flaps in particular are a valuable alternative. The RFF was successfully used in various modifications[38-40,42]. Fasciocutaneous ALT may also be suitable. One case each was successfully operated using RFF and ALT. Bi-paddled flaps may be of special interest if a simultaneous pharyngeal stenosis has to be treated.

The fact that 90.47% of all successful surgeries were of higher categories points to the fact that more invasive surgery may be more prom-

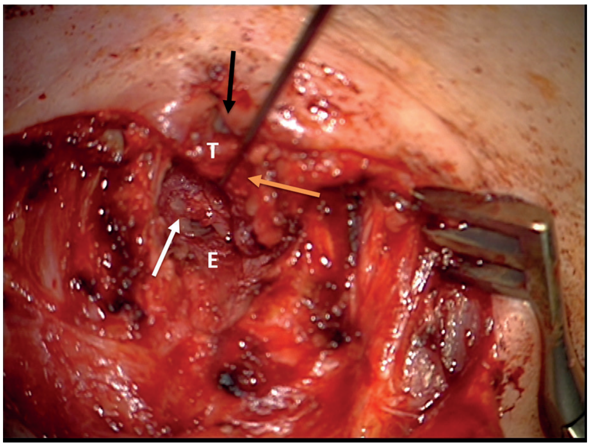

Figure 1. Situation after preparation of the cervical skin, which has to be resected due to bad tissue conditions (for overview, see also Figure 3). Trachea (T) is separated from the esophagus (E) down to the level of the TEFs (white arrow). Note the fixation of the trachea to the anterior wall (black arrow), only an estimated 70% of the circumference of the trachea is mobilized (posterior wall indicated by the orange arrow).

ising in achieving surgical closure of TEFs. In our cases it was evident that success rates were significantly differently distributed over the surgical categories, indicating that more invasive surgery was more successful (p=0.0001). Second surgeries were more invasive in 63.63% with no transtracheal technique (categories 1-2) and only category 3-4 techniques were successful with no significant differences observed. The failure rates after less invasive techniques contributed to inadequate success rates after the first (45.5%) and second surgeries (36.4%). Third surgeries were all of categories 3 or 4 with a success rate of 100% (Table III). Importantly, the pre- and postoperative nutrition state was unchanged in 85.71% (p=0.001). It was noted that neither the surgical method nor any other factor investigated had any influence.

Although the surgical technique applied seems to be of most importance, the presence of other systemic and local factors defines the risk profile of the individual patient and may contribute to the indication for more complex surgical techniques and influence the success rates. Age did not have any significant influence, and prior surgery was performed in all patients and RT in > 90%. Prior RT with a dose of > 60 Gy, poor tissue conditions within the TEFs and comorbidities were present in 70-80% of patients. Prior RT is known to be associated with worse tissue conditions, disturbed wound healing or an unfavorable outcome after surgery[50-52]. The high frequency of prior RT may be the reason why no significant impact on any parameter was recognizable. But it may explain at least in part, why first surgeries of category 1 had low success rates of only 16.67%, why over 50% of all cases needed revision surgeries and why category 3-4 surgery was needed in 90% to achieve definitive closure of the TEFs. Interestingly, the only successful case after category 1 surgery had not received RT.

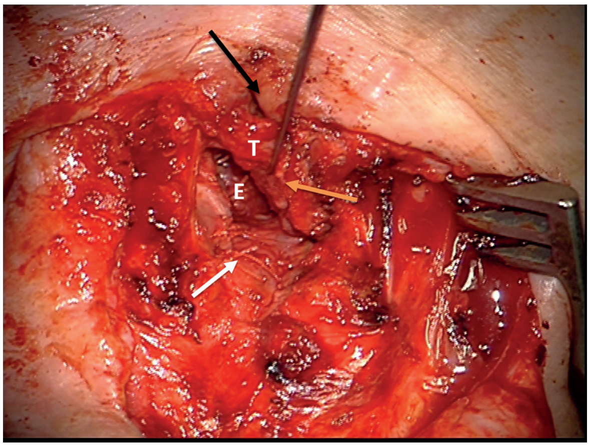

Figure 2. Situation after two-layered closure of the esophagus (E, white arrow). The trachea (T) is fixed anteriorly (black arrow) and the posterior wall is pulled anteriorly (orange arrow).

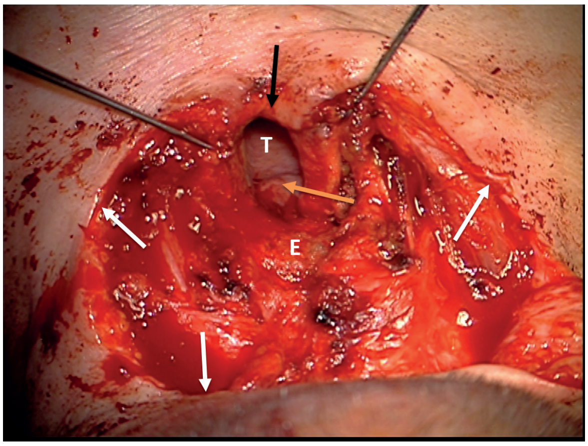

Figure 3. Size of the skin defect (8x8 cm, area indicated by white arrows) after resection of the cervical skin and after resection of the cranial part of the posterior 70% of the trachea (T, upper border of the trachea indicated by the orange arrow) with the anterior part fixed at the skin superior to the manubrium (black arrow). The skin defect had to be covered with a flap. A deltopectoral flap was chosen to achieve a defect closure as less invasive and risky as possible.

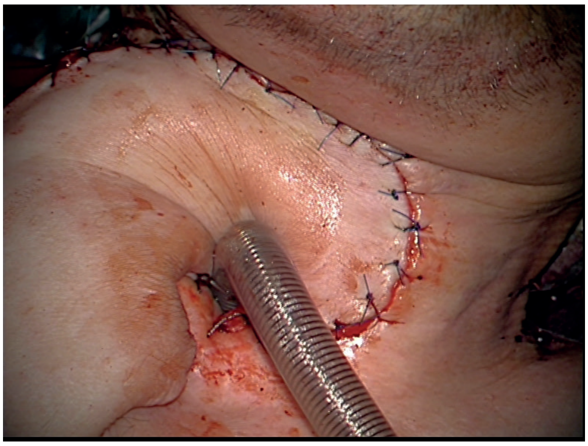

Figure 4. Situation after closure of the anterior cervical and supra-tracheal skin with an interpolated deltopectoral flap

The fact that the presence and higher number of comorbidities were noted significantly more often in patients who were treated by less invasive surgery (p=0.037), may be another indication of the need to perform more invasive surgery early, in particular if the high failure rate after the first surgery is considered.

Unfavorable tissue conditions of the neck skin and larger-sized TEFs were present in nearly 40% of all patients. The presence of an immobile neck skin ("frozen neck") means that replacement of the neck skin by a pedicled or free flap should be taken into account (Figures 1-6). More deeply located TEFs were present in two thirds of the cases. The deeper location of TEFs (categories 2-3) was significantly more frequent in patients with unfavorable neck skin tissue compared to cases with fair tissue conditions (100% *vs.* 46.1%; p=0.031). In all patients with poor tissue conditions of the neck skin, TEFs with poor tissue conditions were also diagnosed and the tendency for a higher number of comorbidities was observed. This, and the fact that in deeply located TEFs (23.8%) surgery of higher complexity was always needed to achieve successful closure, underscores the importance that more invasive surgery should be considered in more deeply located TEFs, as parts of the trachea may be involved and/or have to be replaced. As in the case of unfavorable neck skin, more extensive surgery results in better success rates in deeply located TEFs.

In smaller-sized TEFs less invasive techniques were applied in the first surgeries significantly more often than in larger TEFs (80 *vs.* 0%, p=0.001), and simultaneously there was a trend for the success rates to be lower after surgery of smaller compared to larger TEFs (33.33% *vs.* 83.33%; p=0.063). The size of TEFs increased in 30% prior to revision surgery, which may explain why at the second surgery in 50% of cases less invasive surgery was nevertheless conducted in small TEFs compared to the larger-sized TEFs of categories 2 and 3 (0%; p=0.006), again with inadequate success rates. Finally, independent of the TEFs size, more invasive surgery (categories 3-4) was needed to achieve successful TEFs closure in all failures.

Tissue conditions within the TEFs were poor in over 80%. The fact that in the first and second procedures less invasive techniques were used in 57.14% and in 36.4%, may explain why failure rates were not significantly different distributed between poor and fair tissue conditions. However, final successful closure was achieved using more invasive surgery in significantly more cases when poor tissue conditions were present compared to cases presenting with fair tissue conditions (100% *vs.* 66.67%; p=0.016).

Out of all investigated parameters the surgical technique was the most significant factor compared to all others. Nevertheless, a careful evaluation of risk factors is important as these have a high prevalence. The presence of a single risk factor may not have a major impact. But if a cluster of risk factors is present, the choice of the surgical technique should be based on the number and severity of the risk factors. As the majority of our patients presented with a cluster of risk factors, more invasive surgery should be considered early if TEFs closure is planned. Less

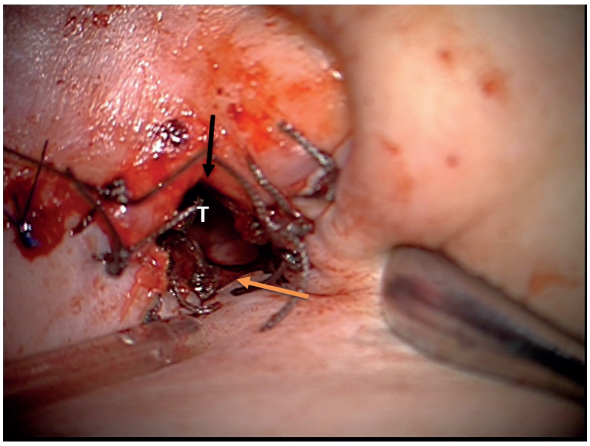

Figure 5. View to the residual peri-tracheostomal neck skin (black arrow) after suturing the skin of the deltopectoral flap to the upper tracheal border (brown arrow) and reestablishing the tracheal lumen (T).

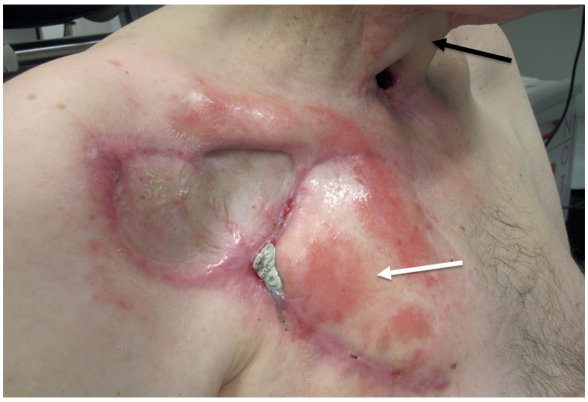

Figure 6. State after separation of the deltopectoral flap, which was performed 6 weeks later. The deltopectoral flap (black arrow) healed correctly and replaces the anterior cervical skin. The TEFs was closed. The proximal part of the flap was repositioned (white arrow).

invasive techniques (categories 1-2) should be reserved for small TEFs with good to fair tissue conditions and located cranially in patients with limited individual risk factors. Larger TEFs, poor tissue conditions within the TEFs and the neck skin, diagnosed in patients with several individual risk factors, demand more invasive techniques. Surgery of categories 3a, 3b, 4a provides excellent exposure, but avoids extensive surgery and wide wound opening. In very large TEFs, which mostly show poor tissue conditions and an extension to the caudal trachea, free tissue transfer (category 4b) may be necessary. After successful placement of Montgomery® salivary stents as prophylactic measure to prevent postoperative fistula after pharyngolaryngectomy to prevent pharyngocutaneous fistulas described[53], in recent studies Montgomery® bypass tubes were used successful in the treatment of patients with TEFs or pharyngoesophageal stenosis[50,54]. Although further studies are needed to evaluate this, stents or tubes may represent an interesting measure to support surgical efforts and may contribute to the successful management of TEFs, in particular in complex cases. Extended surgery carries the risk of disturbed wound healing with possibly severe or fatal consequences. If surgery is refused or the

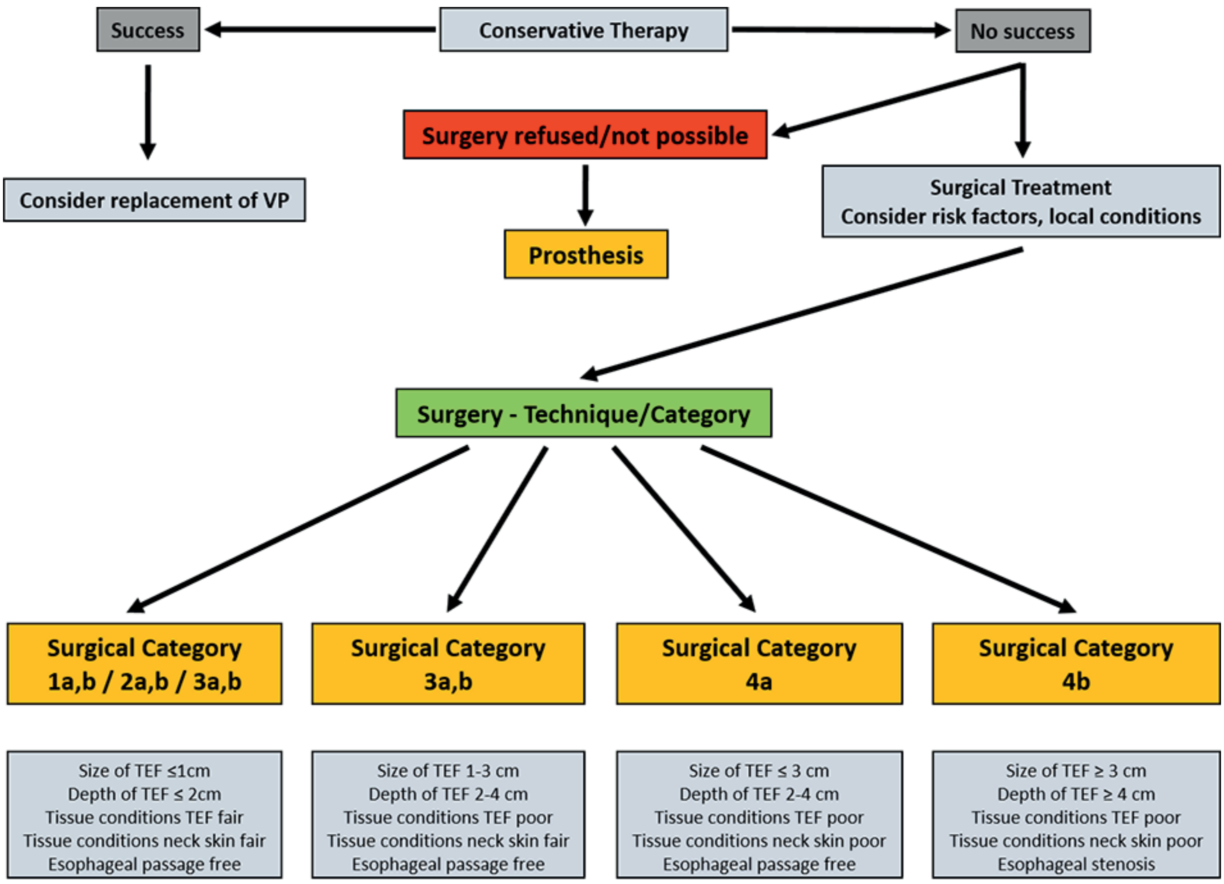

Figure 7. Flow chart for surgical treatment of TEFs in consideration of possible relevant prognostic factors.

patient's condition does not allow any (extensive) surgery, non-surgical closure can be offered. Septal button or silicon buttons[33,43-46] and in particular custom-made tracheal prostheses[47,48] have been introduced recently for this purpose. A treatment algorithm based on our own data and that in the literature was elaborated (Figure 7).

We are aware of the limitations of our study, which were mainly its retrospective design, the limited number of patients and the categorization of the parameters for statistics analysis.

Conclusions

Treatment of resistant TEFs is complex and demanding, as relevant risk factors are present in nearly all patients. The surgical technique was the parameter with the most significant impact on success rates. Final closure of TEFs was achieved in 90.90% of the cases using more invasive surgery. In contrast to the individual risk factors, which are difficult to influence, the surgical technique can be chosen in consideration of local risk factors. In high-risk TEFs (large size, deep location, poor tissue conditions, presence of a pharyngeal/esophageal stenosis), extensive but risky surgery or implantation of a prosthesis can be reasonable alternatives.

ORCID ID
Michael Koch: https://orcid.org/0000-0001-7838-6490.

Conflicts of Interest
The authors declare no conflicts of interest.

References

1) Brown DH, Hilgers FJ, Irish JC, Balm AJ. Postlaryngectomy voice rehabilitation: state of the art at the millennium. World J Surg 2003; 27: 824-831.
2) Pawar PV, Sayed SI, Kazi R, Jagade MV. Current status and future prospects in prosthetic voice rehabilitation following laryngectomy. J Cancer Res Ther 2008; 4: 186-191.
3) Tang CG, Sinclair CF. Voice restoration after total laryngectomy. Otolaryngol Clin North Am 2015; 48: 687-702.
4) Zenga J, Goldsmith T, Bunting G, Deschler DG. State of the art: Rehabilitation of speech and swallowing after total laryngectomy. Oral Oncol 2018; 86: 38-47.
5) Issing WJ, Fuchshuber S, Wehner M. Incidence of tracheo-oesophageal fistulas after primary voice rehabilitation with the Provox or the Eska-Herrmann voice prosthesis. Eur Arch Otorhinolaryngol 2001; 258: 240-242.
6) Imre A, Pınar E, Callı C, Sakarya EU, Oztürkcan S, Oncel S, Katılmış H. Complications of tracheoesophageal puncture and speech valves: retrospective analysis of 47 patients. Kulak Burun Bogaz Ihtis Derg 2013; 23: 15-20.
7) Tong JY, Pasick LJ, Benito DA, Sataloff RT. Complications associated with tracheoesophageal voice prostheses from 2010 to 2020: A MAUDE study. Am J Otolaryngol 2020; 41: 102652.
8) Hutcheson KA, Lewin JS, Sturgis EM, Kapadia A, Risser J. Enlarged tracheoesophageal puncture after total laryngectomy: a systematic review and meta-analysis. Head Neck 2011; 33: 20-30.
9) Gehrking E, Raap M, Sommer KD. Classification and management of tracheoesophageal and tracheopharyngeal fistulas after laryngectomy. Laryngoscope 2007; 117: 1943-1951.
10) Hilgers FJ, Soolsma J, Ackerstaff AH, Balm FJ, Tan IB, van den Brekel MW. A thin tracheal silicone washer to solve periprosthetic leakage in laryngectomies: direct results and long-term clinical effects. Laryngoscope 2008; 118: 640-645.
11) Lewin JS, Hutcheson KA, Barringer DA, Croegaert LE, Lisec A, Chambers MS. Customization of the voice prosthesis to prevent leakage from the enlarged tracheoesophageal puncture: results of a prospective trial. Laryngoscope 2012; 122: 1767-1772.
12) Erdim I, Sirin AA, Baykal B, Oghan F, Guvey A, Kayhan FT. Treatment of large persistent tracheoesophageal peristomal fistulas using silicon rings. Braz J Otorhinolaryngol 2017; 83: 536-540.
13) Jacobs K, Delaere PR, Vander Poorten VL. Submucosal purse-string suture as a treatment of leakage around the indwelling voice prosthesis. Head Neck 2008; 30: 485-491.
14) Geyer M, Tan N, Ismail-Koch H, Puxeddu R. A simple closure technique for reversal of tracheoesophageal puncture. Am J Otolaryngol 2011; 32: 627-630.
15) Mobashir MK, Basha WM, Mohamed AE, Anany AM. Management of persistent tracheoesophageal puncture. Eur Arch Otorhinolaryngol 2014; 271: 379-383.
16) Riva G, Dagna F, Ricci E, Cavalot AL. Closure of tracheoesophageal puncture after total laryngectomy. Otolaryngol Head Neck Surg 2019; 161: 368-370.
17) Yenigun A, Ozturan O, Kulaksiz Y, Aksoy F, Tugrul S. Tracheoesophageal puncture site closure with butterfly cartilage graft. J Craniofac Surg 2019; 30: e257-e259.
18) Annyas AA, Escajadillo JR. Closure of tracheoesophageal fistulas after removal of the voice prosthesis. Laryngoscope 1984; 94: 1244-1245.
19) Rosen A, Scher N, Panje WR. Surgical closure of persisting failed tracheoesophageal voice fistula. Ann Otol Rhinol Laryngol 1997; 106: 775-778.

20) Hosal SA, Myers EN. How I do it: closure of tracheoesophageal puncture site. Head Neck 2001; 23: 214-216.
21) Moerman M, Vermeersch H, Heylbroeck P. A simple surgical technique for tracheoesophageal fistula closure. Eur Arch Otorhinolaryngol 2004; 261: 381-385.
22) Cavalot AL, De Sanctis A, Palonta F, Preti G, Piumetto E, Albera R. Closure of tracheo-oesophageal fistula following removal of voice prosthesis; a new surgical technique. Acta Otorhinolaryngol Ital 2004; 24: 75-77.
23) Unal M. Three-layer closure of a tracheoesophageal puncture site: a technical note. Adv Ther 2006; 23: 733-738.
24) Hu A, Merati A, Meyer TK. Closure of tracheoesophageal fistula with two-layer tracheal-esophagoplasty and tracheal advancement. Laryngoscope 2013; 123: 446-450.
25) Dwivedi RC, Sattar R, Tsiropulous G, Repanos C. Fascia lata graft closure of an enlarged tracheoesophageal puncture (TEP) after laryngectomy/laryngopharyngectomy. Eur Arch Otorhinolaryngol 2019; 276: 2355-2359.
26) Neves JF, Nobre AR, Portugal E, Branquinho F. Surgical Closure of Tracheoesophageal Puncture Without a Flap Interposition. Otolaryngol Head Neck Surg 2020; 163: 618-620.
27) Bessede JP, Bories F, Enaux M, Orsel S, Sauvage JP. [Closure of esotracheal fistula after phonation implants. Technique and results of tracheal ascension]. Ann Otolaryngol Chir Cervicofac 1995; 112: 353-355.
28) Koch M, Zenk J, Birk S, Alexiou C, Iro H. Surgical closure of persistent tracheoesophageal fistulas by esophageal suturing and cranial transposition of the trachea. Otolaryngol Head Neck Surg 2010; 143: 843-844.
29) Siu KF, Wei WI, Lam KH, Wong J. Use of the pectoralis major muscle flap for repair of a tracheoesophageal fistula. Am J Surg 1985; 150: 617-619.
30) Lee LM, Razi A. Three-layer technique to close a persistent tracheo-oesophageal fistula. Asian J Surg 2004; 27: 336-338.
31) McMurtrie A, Georgeu GA, Kok K, Carlin WV, Davison PM. Novel method of closing a tracheo-oesophageal fistula using a de-epithelialized deltopectoral flap. J Laryngol Otol 2005; 119: 129-131.
32) Judd O, Bridger M. Failed voice restoration: closure of the tracheo-oesophageal fistula. Clin Otolaryngol 2008; 33: 261-264.
33) Schmitz S, Van Damme JP, Hamoir M. A simple technique for closure of persistent tracheoesophageal fistula after total laryngectomy. Otolaryngol Head Neck Surg 2009; 140: 601-603.
34) Balasubramanian D, Iyer S, Thankappan K. Tracheoesophageal puncture site closure with single perforator-based deltopectoral flap. Head Neck 2013; 35: E60-63.
35) Jaiswal D, Yadav P, Shankhdhar VK, Gujjalanavar RS, Puranik P. Tracheoesophageal puncture site closure with sternocleidomastoid musculocutaneous transposition flap. Indian J Plast Surg 2015; 48: 278-282.
36) Wasano K, Suzuki N, Kawasaki T, Yamamoto S, Minami S, Yamashita T, Ogawa K. Closure of tracheoesophageal puncture with pedicled fascia flap of the sternocleidomastoid muscle. Auris Nasus Larynx 2015; 42: 318-321.
37) Murono S, Ishikawa E, Nakanishi Y, Endo K, Kondo S, Wakisaka N, Yoshizaki T. Closure of tracheoesophageal fistula with prefabricated deltopectoral flap. Asian J Surg 2016; 39: 243-246.
38) Delaere PR, Delsupehe KG. Closure of persistent tracheoesophageal fistulas after removal of the voice prosthesis. Laryngoscope 1994; 104: 494-496.
39) Wreesmann VB, Smeele LE, Hilgers FJ, Lohuis PJ. Closure of tracheoesophageal fistula with prefabricated revascularized bilaminar radial forearm free flap. Head Neck 2009; 31: 838-842.
40) Dewey EH, Castro JR, Mojica J, Lazarus CL, Su HK, Alpert EH, Dos Reis LL, Urken ML. Reconstruction of expanding tracheoesophageal fistulae in post-radiation therapy patients who undergo total laryngectomy with a bipaddled radial forearm free flap: Report of 8 cases. Head Neck 2016; 38 Suppl 1: E172-178.
41) Machado RA, Moubayed SP, Urken ML. Repair of pharyngoesophageal stenosis and a tracheoesophageal fistula using a dual-paddled radial forearm free flap: flap design and surgical technique. Laryngoscope 2017; 127: 2081-2084.
42) Spaulding SL, Yue LE, O'Malley QF, Sims JR, Urken ML. A novel radial forearm free flap design to treat pharyngoesophageal stenosis in combination with the posterior wall of the trachea. J Surg Oncol 2019; 120: 1446-1449.
43) Mirza S, Head M, Robson AK. Silicone septal button in the management of a large tracheo-oesophageal fistula following primary puncture in a laryngectomee. ORL J Otorhinolaryngol Relat Spec 2003; 65: 129-130.
44) Wong BY, Kurian M, Chidambaram A. Alternative management of leaking tracheoesophageal fistula after laryngectomy using nasal septal button. Clin Otolaryngol 2011; 36: 97-99.
45) Unsal O, Akpinar M, Turk B, Rifki D, Uslu Coskun B. Total closure of enlarged tracheoesophageal puncture with septal button: long-term results. ORL J Otorhinolaryngol Relat Spec 2015; 77: 268-272.
46) Mutlu A, Dasli S, Ozturk M, Topdag M. A simple closure technic for tracheoesophageal puncture failures. J Craniofac Surg 2016; 27: 2149-2150.
47) Mueller SA, Dehnbostel S, Dehnbostel F, Giger R. Treatment of tracheoesophageal fistula after laryngectomy by a customized tracheal prosthesis. Laryngoscope 2018; 128: 1858-1861.
48) Herzog M, Lorenz KJ, Glien A, Greiner I, Plontke S, Plossl S. Treatment of tracheopharyngeal and tracheo-oesophageal fistulas following laryngectomy and fistula classification based on individual silicone casts. Eur Arch Otorhinolaryngol 2015; 272: 2961-2968.
49) Yu P. One-stage reconstruction of complex pharyngoesophageal, tracheal, and anterior neck defects. Plast Reconstr Surg 2005; 116: 949-956.
50) Minni A, Ralli M, Di Cianni S, Cialente F, Candelori F, Colizza A, Cambria F, de Vincentiis M. Montgomery salivary bypass tube in head and neck cancer: the experience of our otolaryngology clinic. Ear Nose Throat J 2020: 145561320961754. doi: 10.1177/0145561320961754. Epub ahead of print.

51) Scherl C, Kauffels J, Schützenberger A, Döllinger M, Bohr C, Dürr S, Fietkau R, Haderlein M, Koch M, Traxdorf M, Mantsopoulos K, Müller S, Iro H. Secondary tracheoesophageal puncture after laryngectomy increases complications with shunt and voice prosthesis. Laryngoscope 2020; 130: E865-E873.
52) Clancy K, Sozansky Lujan J, Xia T, Zender C, Maronian N. Outcomes of tracheoesophageal puncture in twice-radiated patients. Am J Otolaryngol 2019; 40: 102272.
53) Bondi S, Giordano L, Limardo P, Bussi M. Role of Montgomery salivary stent placement during pharyngolaryngectomy, to prevent pharyngocutaneous fistula in high-risk patients. J Laryngol Otol 2013; 127: 54-57.
54) Gilardi A, Colizza A, Minni A, de Vincentiis M. A new montgomery(r) salivary bypass tube placement technique: report of procedures performed on patients with tracheoesophageal fistula or pharyngoesophageal stenosis. Ear Nose Throat J 2021: 1455613211006002.