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REVIEW

Pharyngeal Reconstruction Methods to Reduce the Risk of Pharyngocutaneous Fistula After Primary Total Laryngectomy: A Scoping Review

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ABSTRACT

Introduction: The most common early postoperative complication after total laryngectomy (TL) is pharyngocutaneous fistula (PCF). Rates of PCF are higher in patients who undergo salvage TL compared with primary TL. Published meta-analyses include heterogeneous studies making the conclusions difficult to interpret. The objectives of this scoping review were to explore the reconstructive techniques potentially available for primary TL and to clarify which could be the best technique for each clinical scenario.

Methods: A list of available reconstructive techniques for primary TL was built and the

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potential comparisons between techniques were identified. A PubMed literature search was performed from inception to August 2022. Only case–control, comparative cohort, or randomized controlled trial (RCT) studies were included.

Results: A meta-analysis of seven original studies showed a PCF risk difference (RD) of 14% (95% CI 8–20%) favoring stapler closure over manual suture. In a meta-analysis of 12 studies, we could not find statistically significant differences in PCF risk between primary vertical suture and T-shaped suture. Evidence for other pharyngeal closure alternatives is scarce.

Conclusion: We could not identify differences in the rate of PCF between continuous and T-shape suture configuration. Stapler closure seems to be followed by a lower rate of PCF than manual suture in those patients that are good candidates for this technique.

Keywords: Laryngectomy; Reconstruction; Systematic review; Meta-analysis; Suture

Key Summary Points

The most common early postoperative complication after total laryngectomy (TL) is pharyngocutaneous fistula (PCF), which increases length of stay and costs, impacts quality of life, and delays beginning of adjuvant treatment.

We explored the reconstructive techniques potentially available after primary TL, and critically appraised published systematic reviews to clarify which could be the best reconstruction technique for each clinical scenario.

A meta-analysis showed a risk difference of 14% (95% CI 8–20%) in PCF favoring stapler closure, without statistical heterogeneity (I^2 = 0%).

In a meta-analysis we could not find statistically significant differences between both vertical suture vs. T-shaped after primary total laryngectomy.

There is an important deficit of information to evaluate the effectiveness of other reconstructive options such as regional pedicled flap vs. free flap after primary laryngectomy.

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INTRODUCTION

The larynx is the second most common site for head and neck squamous cell carcinoma (HNSCC). Currently, upfront primary total laryngectomy (TL) is reserved only for advanced T4a cases [1], while primary treatment for T3 laryngeal cancer consists of chemoradiotherapy (CRT) or induction chemotherapy followed by radiotherapy combined with salvage TL in cases of incomplete response. TL, partial laryngectomy, or transoral laser microsurgery is indicated in selected cases [2–4].

Since Theodor Billroth performed the first TL in 1873, the most feared complication has been

pharyngocutaneous fistula (PCF) [5]. For more than a century, surgeons have been designing surgical techniques aiming to decrease the frequency of PCF, but even in the best hands, the rate for TL remains close to 10% [6]. PCF is the most common early postoperative complication after TL, especially as a salvage procedure after failure of CRT [7], and increases length of stay and costs, impacts quality of life, and delays beginning of adjuvant treatment. The indication for TL (primary or salvage) is one of the most relevant predictive factors. Rates of PCF are higher in patients who undergo salvage TL compared with primary TL and several surgical techniques focused on avoiding PCF have been designed [8]. The current literature reports a number of studies exploring the effectiveness of these techniques, but most of them are case series and case reports without comparisons with standard treatments. Moreover, published meta-analyses have tried to evaluate these interventions by combining case series and comparative studies, primary and salvage TL, which are methodological factors that increase clinical and statistical heterogeneity and introduce a high risk of bias [9, 10]. All these reasons make the conclusions of systematic reviews difficult to interpret and limit their application in real-world practice. Specifically, for the case of primary TL, the available information is limited, and heterogeneous [11, 12].

The objectives of this scoping review were to explore the reconstructive techniques potentially available after primary TL and to critically appraise published systematic reviews to clarify which could be the best reconstruction technique for each clinical scenario.

METHODS

The aim of this study was to answer the following research question: Which are the best reconstructive methods to reduce the risk of PCF after primary TL? We designed a scoping review, using the recommendations of the Joanna Briggs Institute (JBI) (www.https://jbi.global/). Of note, scoping reviews are useful for examining available evidence when a robust systematic review cannot be done [13]. Maneuvers aimed at preventing PCF in patients with exclusive salvage laryngectomy will not be discussed in this manuscript.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Definition of Available Reconstructive Alternatives After Primary Total Laryngectomy

We first built an inventory of all available reconstructive techniques for this setting. In the first round, the authors generated a list of alternatives for primary closure after primary TL. In the second round, these options were organized in a diagram to identify the potential comparisons between techniques (e.g., for primary closure including both manual suturing and stapler closure) that helped to make a focused search for studies.

Literature Search

The search was performed in the PubMed/MEDLINE database using related terms ("larynx"[MeSH Terms] OR ("larynx"[MeSH Terms] OR "larynx"[All Fields] OR "larynxes"[All Fields]) OR "laryngectomy"[MeSH Terms] OR ("laryngectomy"[MeSH Terms] OR "laryngectomy"[All Fields] OR "laryngectomies"[All Fields])) AND ("surgical flaps"[MeSH Terms] OR ("surgical flaps"[MeSH Terms] OR ("surgical"[All Fields] AND "flaps"[All Fields]) OR "surgical flaps"[All Fields] OR "flap"[All Fields]) OR ("pectoral"[All Fields] OR "pectorals"[All Fields]) OR ("anterolateral"[All Fields] OR "anterolaterally"[All Fields]) OR ("jejunum"[MeSH Terms] OR "jejunum"[All Fields] OR "jejunums"[All Fields]) OR ("radial artery"[MeSH Terms] OR ("radial"[All Fields] AND "artery"[All Fields]) OR "radial artery"[All Fields] OR "radial"[All Fields] OR "radially"[All Fields] OR "radials"[All Fields]) OR ("closure"[All Fields] OR "closure s"[All Fields] OR "closures"[All Fields] OR ("suturability"[All Fields] OR "suturable"[All Fields] OR "sutural"[All Fields] OR "suturation"[All Fields] OR "suture s"[All Fields] OR "sutured"[All Fields]

OR "sutures"[MeSH Terms] OR "sutures"[All Fields] OR "suture"[All Fields] OR "suturing"[All Fields])) OR "fistul*"[All Fields]). A "snowball" search was also done with references of identified studies. The last search was done in August 30, 2022 by two reviewers (MPO and AS).

In the first step, we searched only for studies that mentioned that a systematic review or meta-analysis was performed (in the title, abstract, or methods section). In the second step, we performed a specific search in the reference section of these systematic reviews. In the third step, we selected all primary references to find studies comparing alternatives and complemented them with the primary database search. We did not consider exclusion based on the year of publication or language.

All articles were screened for title and abstract. Two investigators (MPO and AS) reviewed the full texts of selected studies. Divergences in selection were solved by consensus. The flowchart of the study search is shown in Fig. 1. The primary search identified 49 studies. After inclusion and exclusion criteria were applied, 24 remained to be appraised.

In this review we only considered studies that included adult patients (over 18 years old) with carcinoma of the larynx who required primary TL, compared two or more techniques, and reported outcomes related to PCF. Therefore, only case–control, comparative cohort, or randomized controlled trials (RCT) were included. Data of the studies were collected in an Excel spreadsheet (Microsoft Corp., USA). Institutional review board approval was not necessary as a result of the study design.

Analysis

If three or more primary studies were identified and the authors considered them suitable to be pooled, we performed a meta-analysis using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, 2020). We selected a random effects analysis because of the expected heterogeneity and used a risk difference (RD) outcome with 95% confidence interval (CI).

RESULTS

First, we identified a list of potential alternatives for pharyngeal reconstruction: manual suture (continuous vertical or horizontal suture or T-shape configuration; single or more than one layer); stapler closure; primary closure with regional pedicled flap reinforcement (pectoral or other regional flaps; in-lay or on-lay); and free flaps (radial forearm free flap [RFFF], anterolateral thigh [ALT] with different techniques such as U-shape or tube-shape, or jejunum). In the second round, potential comparisons for reconstruction after primary TL were identified (Fig. 2). A list of potential comparisons was obtained from this diagram.

Comparison 1: Primary Closure vs. Primary Closure with Flap Reinforcement After Primary Total Laryngectomy

We could not find any meta-analyses about this comparison or any of its modifications (on-lay vs. in-lay).

Comparison 2: Manual Primary Closure vs. Stapler Closure

There are three systematic reviews comparing manual and stapler closure [14–16]. Aires et al. included four studies [16], Lee et al. [15] included seven studies, and Chiesa et al. [14] included eight. A fourth meta-analysis focused on the evaluation of risk factors for fistula after TL found that suturing with staplers decreased the risk of PCF [17].

Most primary studies included in these meta-analyses were non-randomized retrospective cohorts and only two were RCTs [18, 19]. Although Galletti et al. [19] report their study as an RCT, it is noteworthy that it includes an unbalanced number of patients between groups and the lack of description of common methodological conditions for this design.

All these systematic reviews concluded that stapler closure was superior to manual closure. Aires et al. [16] performed a subgroup analysis exploring the differential rate between studies that included only primary TL and those that

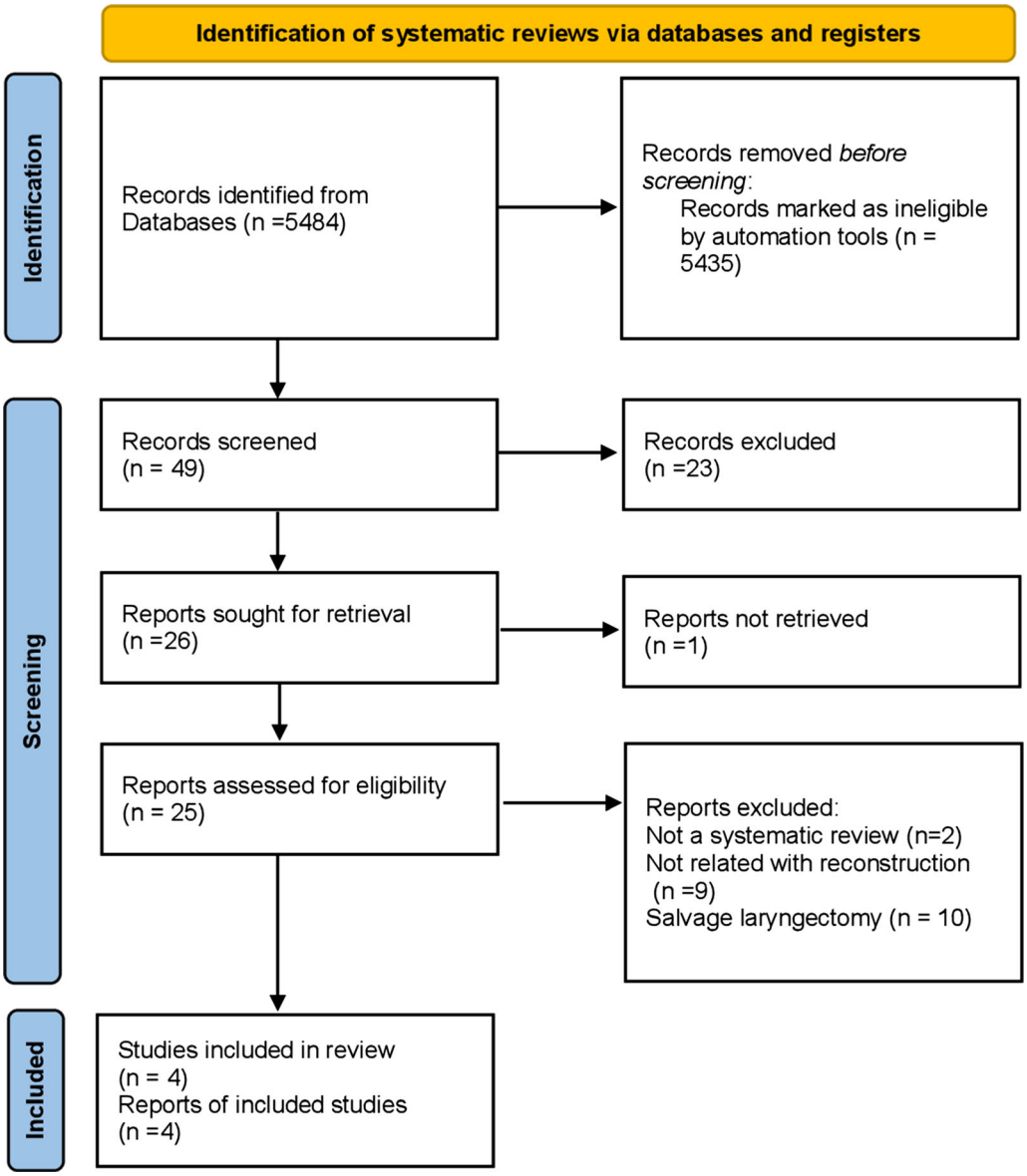

Fig. 1 PRISMA literature search flowchart

mixed primary and salvage TL, and did not find statistically significant differences (Table 1).

(a) Studies that included primary total laryngectomy exclusively: Seven studies [18, 20–25] exclusively included patients with primary TL. Three new studies, not included in previous systematic reviews, were identified and included in the present analysis [23–25]. Santaolalla et al. [21] added a third group with the open technique of mechanical suture (i.e., the mechanical closure is done after resecting the larynx, aligning the mucosal edges of the resultant vertical defect), which was not considered in the analysis. Sansa-Perna et al. [23] discriminated patients for primary and salvage TL, and data were used independently. Asher et al. [25] combined information of T classification and tumor location making it impossible to get specific information. Two of these seven studies found a decrease in the rate of PCF [20, 21].

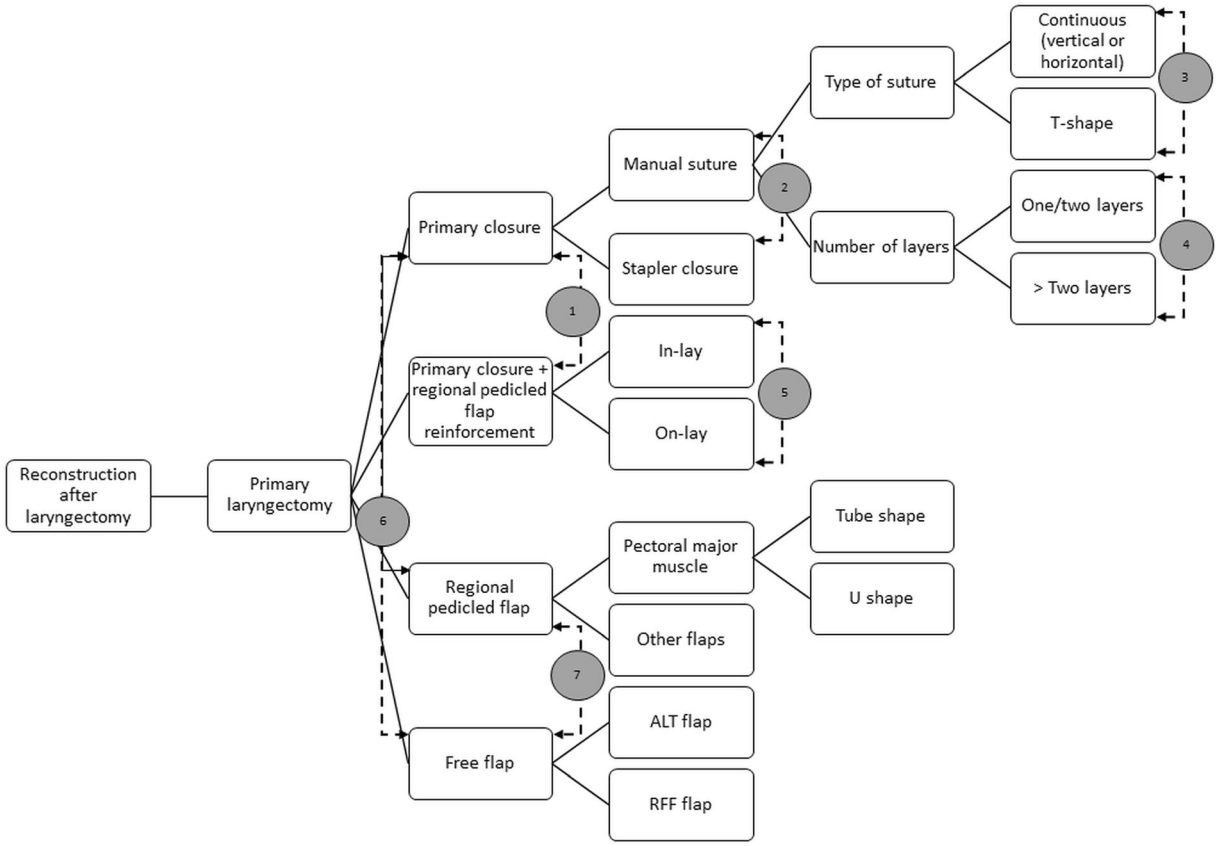

Fig. 2 Diagram of available reconstruction methods and potential comparisons. *ALT* anterolateral thigh, *RFF* radial forearm free flap

A meta-analysis of them showed an RD of 14% (95% CI 8–20%) in PCF favoring stapler closure, without statistical heterogeneity (I^2 = 0%) (Fig. 3).

(b) Studies that mixed primary and salvage total laryngectomy: Five studies included patients with primary/salvage TL [19, 26–29]. Two studies [27, 28] found a decrease in the PCF rate while the others did not find statistically significant differences. A meta-analysis could not find differences (RD − 11%, 95% CI − 26% to 4%) in the rate of PCF and showed moderate statistical heterogeneity (I^2 = 60%). Because these studies mixed data from primary and salvage TL, the results may be influenced by selection bias (Fig. 3).

Comparison 3: Manual Primary Vertical Suture vs. T-Shaped After Primary Total Laryngectomy

We only found one systematic review assessing the results based on the shape of the suture after TL [30]. However, this review pooled results from comparative and descriptive studies and did not discriminate between primary or salvage TL.

Twelve studies were identified comparing the shape of manual suture, which included primary [25, 31–33] and mixed primary/salvage TL [34–41] (Table 2). Bril et al. [42] did not report specific rates of PCF and the study was thus excluded. El-Marakby et al. [37] used other types of reconstruction, but only data related to suture configuration were used. In a meta-

Table 1 Studies comparing manual versus stapler closure

	Author	Year	Number of studies	Type of studies (observational/RCT)	Number of patients in suture group	Number of patients in stapler closure group	Number of patients with salvage laryngectomy suture group	Number of patients with salvage laryngectomy stapler closure group	PCF in manual suture group (%)	PCF in stapler group (%)	T3/4
Systematic reviews	Aires et al.	2013	4	4/0	275	149	ND		63 (22.9%)	13 (8.7%)	
	Lee et al.	2021	7	4/2	331	204	26	35	90 (27.2%)	28 (13.7%)	
	Chiesa et al.	2022	8	7/1	380	242	29	25	89 (24%)	28 (9.5%)	
Primary total laryngectomy	Santaolalla et al.	2002			50	38	0	0	14	2	
	Calli et al.	2011			116	60	0	0	24	3	182
	Sannikorn et al.	2013			26	26	0	0	3	2	50
	Öztürk et al.	2019			21	20	0	0	7	3	ND
	Galli et al.	2020			26	11	0	0	2	1	ND
	Sansa et al.	2020			41	20	0	0	8	1	ND
	Asher et al.	2016			180	3	0	0	35	2	ND

Table 1 continued

	Author	Year	Number of studies	Type of studies (observational/RCT)	Number of patients in suture group	Number of patients in stapler closure group	Number of patients with salvage laryngectomy suture group	Number of patients with salvage laryngectomy stapler closure group	PCF in manual suture group (%)	PCF in stapler group (%)	T3/4
Mixed primary and salvage total laryngectomy	Gonçalves et al.	2009			30	30	7	21	11	2	60
	Miles et al.	2013			26	16	6	4	ND	ND	35
	Dedivitis et al.	2012			67	20	15	15	14	6	80
	Ismi et al.	2017			40	30	7	6	10	1	70
	Galletti et al.	2018			27	15	ND	ND	21	11	43

ND not determined, *RCT* randomized controlled trial, *PCF* pharyngocutaneous fistula

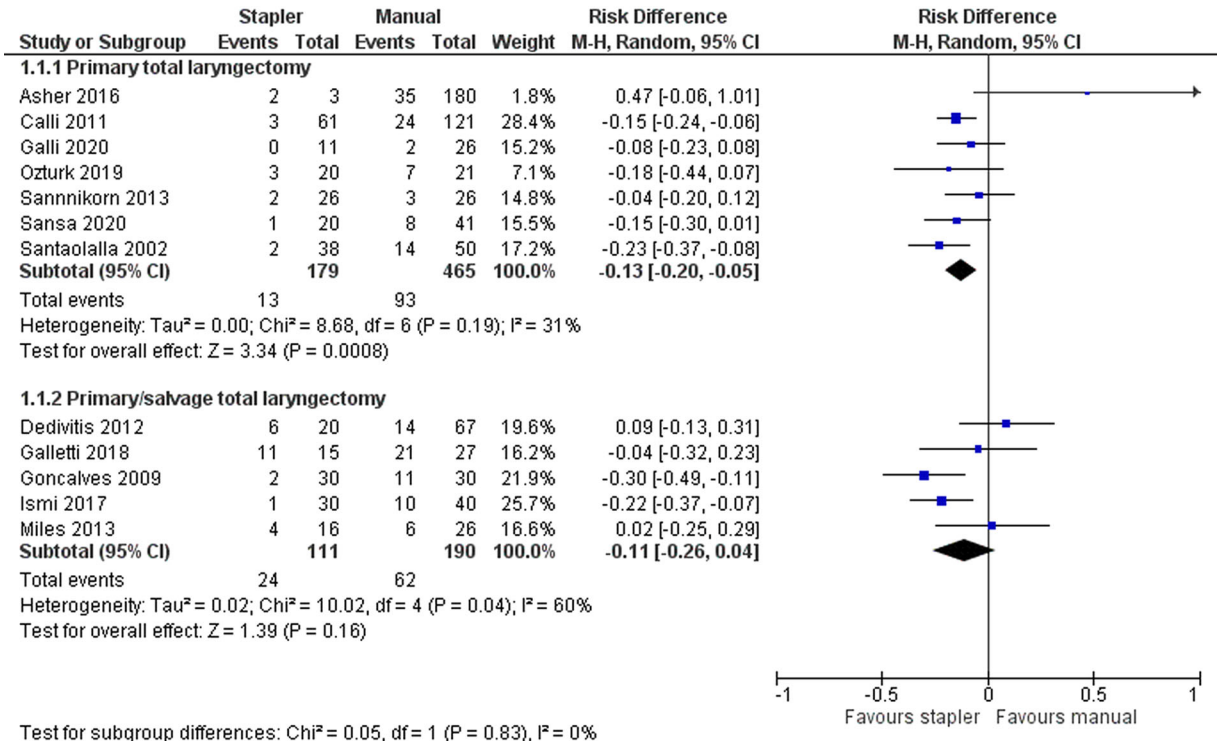

Fig. 3 Meta-analysis of studies assessing stapler versus manual closure. *CI* confidence interval

analysis we could not find statistically significant differences between both techniques, neither for the primary TL (RD 1%, 95% CI − 16% to 19%) nor for the group that mixed primary/salvage TL (RD 3%, 95% CI − 15% to 21%), but both comparisons had high statistical heterogeneity (Fig. 4).

Comparison 4: Manual Primary Suture in One Layer vs. Two Layers vs. More Than Two Layers After Primary Total Laryngectomy

Other technical modifications have been proposed for primary manual suture. Avci et al. [43] compared continuous versus interrupted suture using a vertical approach and found a statistically significant difference between PCF rates favoring continuous suture (16% vs. 39%). Shukla et al. [44] compared a single vs. a double-layer suture using the T-shape technique and found a statistically significant difference favoring two-layer suture (PCF rate 12.5% vs. 33.3%). Wang et al. [45] and Saha et al. [46] compared the two-layer suture with a modified technique using the remnant of constrictor muscles as suture reinforcement and found a statistically significant difference favoring the two-layer technique without muscle reinforcement (PCF rate 3% vs. 10% and 0% vs. 27%, respectively).

Comparison 5: Regional Pedicled Flap Inlay vs. On-lay After Primary Total Laryngectomy with Partial/Circumferential Pharyngectomy

We could not find any meta-analyses or primary studies about this comparison. All studies found were focused on patients treated by salvage TL.

Comparison 6: Manual Primary Suture vs. Regional Pedicled Flap/Free Flap After Primary Laryngectomy with Partial/Circumferential Pharyngectomy

We could not find any meta-analyses about this comparison. Kim et al. [47], in an analysis of

Table 2 Studies comparing continuos (vertical or horizontal) suture versus T-shape suture

	Authors	Year	Number of patients in continuous suture group	Number of patients in T-shape suture group	PCF in continuous suture group (%)	PCF in T-shape group (%)	T3/4
Primary total laryngectomy	Davis et al.	1982	12	15	3	2	ND
	Nitassi et al.	2016	36	52	11	18	88
	Deniz et al.	2015	13	7	0	4	20
	Asher et al.	2016	129	19	32	3	ND
	Walton et al.	2017	96	40	14	1	ND
Mixed primary and salvage total laryngectomy	Lundgren et al.	1979	23	31	0	8	28
	Soylu et al.	1998	272	23	35	2	175
	El-Marakby et al.	2009	39	56	13	10	90
	Suslu et al.	2015	146	5	17	3	ND
	Kilic et al.	2015	44	33	12	20	ND
	Van der Kamp et al.	2017	39	27	14	23	
	Govindasamy et al.	2019	9	17	11	47	ND

ND not determined, *PCF* pharyngocutaneous fistula

676 patients (213 patients in the flap group and 463 in the non-flap group) from the NSQIP database, found statistically significant differences between the group with flap (pedicled regional or free flap) vs. no flap regarding wound disruption (1.7% vs. 3.8%) and organ/space infection (0.4% vs. 2.3%) favoring no flap closure, but this difference disappeared in the multivariate analysis. As this study was based on administrative data, they did not discriminate between the indication for TL, so it is possible that some cases of hypopharyngeal tumors were included. In addition, they could not isolate the rates of PCF and used wound disruption and organ/space infection as a proxy for PCF. Besides, it is possible that a selection bias favoring non-flap closure exists, because patients that need a flap probably have more extensive tumors and thus require reconstruction of larger mucosal defects. Furthermore, they could not define if the flap was used as a reinforcement of the primary suture (on-lay technique) or as a part of the pharyngeal wall (in-lay technique).

Comparison 7: Regional Pedicled Flap vs. Free Flap After Primary Laryngectomy with Partial/Circumferential Pharyngectomy

We could not find any meta-analyses about this comparison. Haidar et al. [48], in a subgroup analysis of the National Cancer Database, found that free flap reconstruction has similar rates of PCF compared with regional pedicled flaps in patients who underwent primary TL. Kim et al. [47], in a subgroup analysis of data from the NSQIP, did not find differences between the

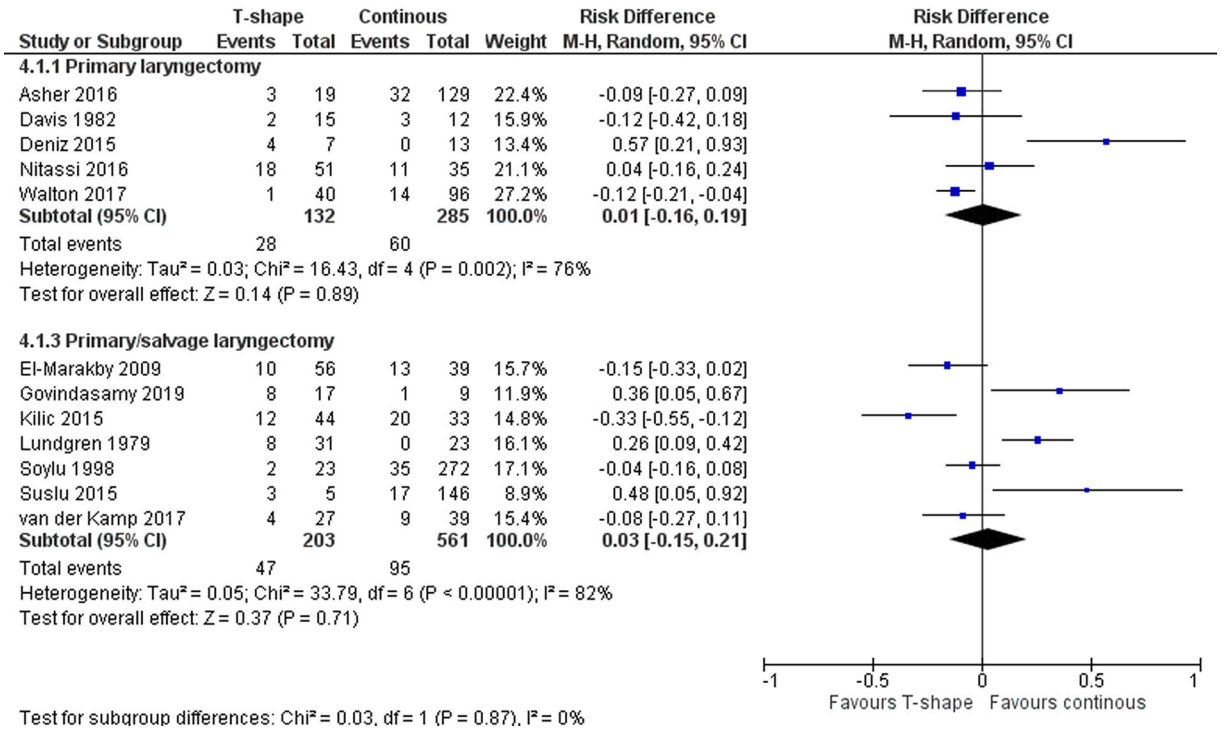

Fig. 4 Meta-analysis of studies assessing continuous (vertical or horizontal) versus T-shape suture. *CI* confidence interval

groups of reconstruction flap (pedicled or free flap) regarding wound disruption and organ space infection. These studies did not discriminate on the basis of the indication for TL. In multivariate analysis, the type of flap was not independently associated with the rate of PCF.

DISCUSSION

Several techniques and modifications have been described to reduce the incidence of PCF, but there is still significant controversy about the best strategy. A simple MEDLINE search with the terms "laryngectomy" and "reconstruction" reported more than 600 studies about this subject, describing an important number of different surgical approaches. Although there are a vast number of studies reporting methods for pharyngeal closure after TL, most of them are case series, the number of comparative studies is low, and there is scarce information about the effectiveness of the different techniques designed.

Therefore, the first aims of this review were to describe the surgical techniques of pharyngeal closure and to identify the potential comparisons needed to determine the best options.

The first step allowed the design of a framework of alternatives for pharyngeal closure in primary TL and the potential comparisons needed to solve uncertainty. The simplest approach is the primary suture of the pharynx using manual suture, and it can become as complex as a case when a free flap is needed. In each of these levels of complexity, there are common surgical questions about technical details such as the number of layers to be sutured, the type of suture to be used, the need for using mechanical devices through to the selection of the most appropriate flap. This effort to organize available literature helps us to design a search to solve these common questions, but also serves as a map to design future trials to fill the knowledge gaps still existing on this specific subject. This exercise identified seven potential comparisons to be evaluated, but this number can be higher depending on the specificity of the research question.

However, it is unlikely that a flap would be needed for reconstruction after primary TL. Therefore, flap reconstructions due to insufficient mucosa for direct closure in laryngeal tumors are sporadic and some alternatives are not used as was evident in comparisons 1 and 5.

The most basic question was how to suture the pharynx. It could be done primarily by a manual suture, and this suture could be with a continuous or interrupted suture. We only identified one comparative study specifically evaluating this question, showing that a continuous suture decreases the rate of PCF. Avci et al. [43] found a difference of almost 20% lower rate of PCF with a two-layer suture and, although this is an observational non-RCT, the magnitude of the difference is so high that it should be accepted as conclusive [44]. Regarding the number of layers the situation was similar: two layers were more effective than a single one [44]. However, when the question was if it was worthwhile adding a third layer using the constrictor muscles, the answer was not so clear. Only two studies [45, 46] evaluated this strategy and, although the incidence of PCF was higher in the three-layer group, the magnitude was not so high, and the results of the studies were very heterogeneous. In this case, a specific trial could help to clarify this issue. Pending this discussion, the decision to use a third layer will depend on the individual conditions of the case and the surgeon's preference.

The second question addressed the best configuration to manually suture the pharynx, if in a continuous suture, be it vertical or horizontal, or using a T-shape configuration. It is a common belief that T-shape suture could have a higher rate of PCF owing to its greater length and the risk of mucosal necrosis at the intersection of suture lines [49]. However, T-shape closure builds a wider neopharynx that could improve postoperative swallowing [50]. This study, which included 12 trials in patients with primary TL and mixed primary and salvage TL [25, 31–41], could not find statistically significant differences between both techniques. However, although this represents the best available evidence, these conclusions could be affected by selection bias due to the observational design and the high heterogeneity found. The final decision will depend on other factors such as surgeon experience, the size of the defect, and intraoperative findings such as suture tension.

The next question was whether using a mechanical device with a standard distance between staplers and avoiding field contamination with saliva would decrease the risk of PCF. Confirming the findings of three systematic reviews [14–16], a meta-analysis of 12 trials [18–29] with patients who underwent primary TL showed that stapler suture significantly decreases the rate of PCF by about 13%, with minimal statistical heterogeneity. However, this conclusion was not reproduced in the trials that combined primary/salvage TL. According to these findings, the use of stapler should be encouraged, but the selection of patients (endolaryngeal tumors without risk of hypopharyngeal extension), the surgical technique (wide liberation of the tracheoesophageal groove and retraction of the epiglottis), and surgeon experience in the procedure are critical factors to get the maximal benefit. However, many surgeons no longer use staples on a regular basis.

For cases in which a larger mucosal resection is needed, an alternative could be the use of a regional flap to reinforce the suture. Unfortunately, we could not find studies evaluating these options. This makes it necessary to design trials focused on the subgroup of primary TL to make a more robust clinical recommendation.

All previous scenarios were focused on patients with endolaryngeal tumors without any involvement of the hypopharynx. However, in patients with tumors invading the hypopharynx or the oropharynx it is necessary to include resection of extralaryngeal mucosa to obtain free margins. In these cases, a primary suture will not be feasible because of the high risk of neopharyngeal stenosis and/or fistula, and technical modification will be necessary. Some authors [47, 48, 51] have suggested the use of regional pedicled or free flaps. Although we did not find literature evidence supporting the use of regional or free flaps for patients with significant mucosal defects, results are prone to selection biases, and expert opinion generally favors use of regional or free tissue flaps when there is significant mucosal deficit. The final decision in these cases will depend on the

advantages and disadvantages of each flap (operative time, lack of donor vessels in the neck, functional and cosmetic consequences, availability of a microsurgical team, associated comorbidities, and surgeon's preference).

It is necessary to highlight the limitations of this study. First, most meta-analyses included trials with a retrospective observational design and are therefore prone to selection biases. In most cases, the comparisons were not adjusted for by other factors such as clinical tumor stage and subsite, extent of surgery, and comorbidities. The data were difficult to analyze because the publications did not discuss the amount of pharyngeal tissue resected or the status of the mucosa (edematous, fragile, etc.). Besides, some studies mixed data from primary and salvage TL, which are populations with very different risks of PCF. To resolve this difficulty, we performed a subgroup analysis that allowed us to use the data and assess the effect that the combination of the two groups might have on the results.

CONCLUSIONS

This scoping review evaluates the different options for mucosal reconstruction after TL and found that a continuous double-layer suture offers a lower rate of PCF. We could not identify differences in the rate of PCF between continuous and T-shape suture configuration. Stapler closure seems to be followed by a lower rate of PCF than manual suture in patients that are good candidates for this technique, but there is an important deficit of information to evaluate the effectiveness of other reconstructive options. A framework that identifies knowledge gaps was designed and it can serve as a tool for future clinical trials addressing specific issues that are still unclear.

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Disclosures. Alvaro Sanabria, María Paula Olivera, Carlos Chiesa, Marc Hamoir, Luiz P Kowalski, Fernando López, Antti Mäkitie, K. Thomas Robbins, Juan Pablo Rodrigo, Cesare Piazza, Ashok Shaha, Elizabeth Sjögren, Carlos Suarez, Mark Zafereo and Alfio Ferlito declare that they have no competing interests.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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