

## ORIGINAL ARTICLE

# Meta-analysis on the safety and efficacy of early oral feeding after total laryngectomy

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## Summary

**Purpose:** To evaluate the safety and efficacy of early oral feeding ( $\leq 3$  days) and delayed oral feeding ( $\geq 7$  days) following total laryngectomy.

**Methods:** Relevant literatures on early and delayed oral feeding following total laryngectomy published before January, 2019 were searched in PubMed, EMBASE, Web of Science, Cochrane Library, CNKI and Wanfang Database. Two reviewers were responsible for selecting literatures, extracting data and cross-check. The incidence of pharyngocutaneous fistula (PCF) was evaluated by calculating OR and 95%CI. Difference in length of stay (LOS) of patients undergoing early oral feeding or delayed oral feeding was compared using standardized mean difference (SMD) and 95%CI. Sensitivity analysis and publication bias examination were conducted.

**Results:** 14 eligible literatures were enrolled, including 1824 patients who underwent total laryngectomy, with 1250 cases

of early oral feeding and 574 cases of delayed oral feeding. The incidence of PCF was similar in patients receiving early oral feeding or delayed oral feeding following total laryngectomy (OR=1.12, 95%CI=0.81-1.54). LOS was shorter in cases of early oral feeding than those of delayed oral feeding (SMD=-0.77, 95%CI=-1.18-0.36). Reliable conclusions were obtained without obvious publication bias.

**Conclusions:** Early oral feeding following total laryngectomy shortens LOS relative to delayed oral feeding. No significant difference in the incidence of PCF is observed between early oral feeding and delayed oral feeding, suggesting that early oral feeding following total laryngectomy is safe and efficacious.

**Key words:** total laryngectomy; early oral feeding; pharyngocutaneous fistula; length of stay; meta-analysis

## Introduction

Malignant laryngeal tumors are a general term for head and neck malignant tumors originating from the upper and lower glottis and vocal cords. Most of malignant laryngeal tumors are squamous cell carcinoma [1]. Laryngeal cancer mostly affects males, and the high-risk age is about 60 years. In recent years, the onset of laryngeal cancer becomes younger [2]. The major treatments for laryngeal cancer are surgery, adjuvant chemotherapy and radiotherapy [3,4]. With the improvement of economy and living standard, surgery for laryngeal tumors

are required to preserve the basic functions of the larynx (swallowing, vocalization and breathing) as much as possible [5]. However, laryngeal cancer patients in T4 stage, most of T3 cases, recurrent cases and elderly patients with bad situation need to undergo total laryngectomy [6].

PCF is a common complication after total laryngectomy, with the incidence of 3% to 65% in the past [7]. In recent years, the incidence of PCF is reported to be 9% to 25% [8-10]. The occurrence of PCF leads to prolonged LOS and delayed oral feed-

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ing time [11]. Previous researches believed that the incidence of PCF reduces with the postponement of oral feeding. Patients undergoing total laryngectomy are intubated with the nasogastric tube for postoperative feeding through nasal feeding tube. Oral feeding is permitted at 8-10 days after surgery. Long-term intubation and nasal feeding pose a great discomfort and cost a huge economic burden [12]. Current studies have demonstrated that oral fluid diet is safe within 48-72 hours after total laryngectomy without elevating the risk of PCF relative to those with oral feeding at 10 days after surgery [13,14]. Aprigliano et al. [15] identified that the placement of nasogastric tube after total laryngectomy increases the risk of PCF. Early oral feeding should be encouraged following total laryngectomy.

Conclusions on the early oral feeding ( $\leq 3$  days) following total laryngectomy and risk of PCF are controversial. This study analyzed relevant literatures on oral feeding following total laryngectomy by extracting their data. We systematically evaluated the safety and efficacy of early oral feeding ( $\leq 3$  days) and delayed oral feeding ( $\geq 7$  days). Our conclusions provide reliable and convincing evidence of early oral feeding in clinical application.

## Methods

### Searching strategy

Relevant literatures on early and delayed oral feeding following total laryngectomy published before January, 2019 were searched in PubMed, EMBASE, Web of

Science, Cochrane Library, CNKI and Wanfang Database. Key words were as follows: "oral feeding" or "oral intake" and "laryngectomy" or "laryngeal neoplasm". Inclusive criteria were applied: 1) Surgical treatment must be the total laryngectomy; 2) Tumors originating in pharynx and larynx; 3) Study design, experimental methods, statistical analyses and monitoring indexes were similar; and 4) the number of PCF cases and LOS of patients with early oral feeding or delayed oral feeding were provided. Exclusive criteria were applied: 1) Tumors originating in other places except for pharynx and larynx; 2) Surgical treatments were partial laryngectomy and vertical hemilaryngectomy; and 3) repeated studies, low-quality studies and those with incomplete data.

### Data extraction

Data acquisition was independently carried out by two reviewers, and a third reviewer was responsible for re-evaluating disagreements. Baseline data acquisition included: first author, study type, sample size, year of publication, monitoring indexes, etc. Procedures for screening literatures were as follows: 1) Exclude ineligible literatures by reviewing titles and abstracts; 2) Exclude ineligible literatures by reviewing the full-text; and 3) for uncertain literatures, supplementary information were reviewed or contacting the author for in-depth information.

### Outcome evaluation

(1) Safety (incidence of PCF): PCF is a common and serious complication following total laryngectomy. The safety of early and delayed oral feeding was evaluated by analyzing the incidence of PCF (the ratio of PCF cases and total cases). (2) Efficacy (LOS): The average LOS was calculated for evaluating the efficacy of early and delayed oral feeding.

**Table 1.** Main characteristics of studies included in the meta-analysis

Year	Study	Nationality	Study design	Numbers of patients		Study index	Study quality
				Early oral intake	Late oral intake		
2018	Huang	China	RD	18	34	PCF	7 <sup>a</sup>
2016	Suslu	Turkey	RD	582	20	PCF	6 <sup>a</sup>
2015	Serbanescu-Kele	Netherlands	RD	36	30	PCF, LOS	7 <sup>a</sup>
2014	Sousa	Brazil	RCT	44	45	PCF	5 <sup>b</sup>
2014	Timmermans	Netherlands	RD	107	140	PCF	6 <sup>a</sup>
2009	Aswani	South Africa	RD	40	39	PCF, LOS	5 <sup>a</sup>
2006	Prasad	India	RD	40	38	PCF, LOS	6 <sup>a</sup>
2003	Song	China	RD	21	21	PCF, LOS	6 <sup>a</sup>
2003	Seven	Turkey	RCT	32	33	PCF, LOS	4 <sup>b</sup>
2001	Volling	Germany	RCT	21	21	PCF	4 <sup>b</sup>
2001	Medina	American	RD	20	18	PCF, LOS	7 <sup>a</sup>
1998	Soylu	Turkey	RD	252	43	PCF	8 <sup>a</sup>
1995	Rodriguez-Cuevas	Mexico	RCT	18	17	PCF	5 <sup>b</sup>
1989	Boyce	American	RD	19	75	PCF	7 <sup>a</sup>

RD: Retrospective Design; RCT: Randomized Controlled Trials; PCF: Pharyngocutaneous fistula; LOS: Length of stay; a: NOS Scale; b: Jadad Scale

Quality assessment

Randomized controlled trials (RCT) were analyzed using the modified Jadad scale for literature quality evaluation, with 1-3 scores for low quality and 4-7 for high quality. Retrospective studies were analyzed using the Newcastle-Ottawa Scale (NOS) for quality evaluation (>5 score considered as high quality). Only high-quality literatures were enrolled in this study.

Statistical analysis

Statistical analysis was performed using Stata 14 software. The incidence of PCF was evaluated by calculating OR and 95%CI. Difference in LOS of patients undergoing early oral feeding or delayed oral feeding was compared using standardized mean difference (SMD) and 95%CI. The heterogeneity among literatures was tested by Cochran Q test.  $p < 0.05$  considered statistically

significant. Fixed-effect model was used when  $I^2 < 50\%$  and  $p > 0.05$ ; Otherwise, the random-effects model was used. Begg's funnel plots were depicted for evaluating the publication bias.

Results

Studies characteristics

There were 353 relevant literatures searched and 27 were enrolled after reading the titles and abstracts. Based on the inclusive criteria, finally 14 literatures involving 1250 cases of early oral feeding and 574 cases of delayed oral feeding were enrolled [14,16-28]. Baseline characteristics of these literatures were displayed in Table 1. Report searching and selection process were depicted in Figure 1.

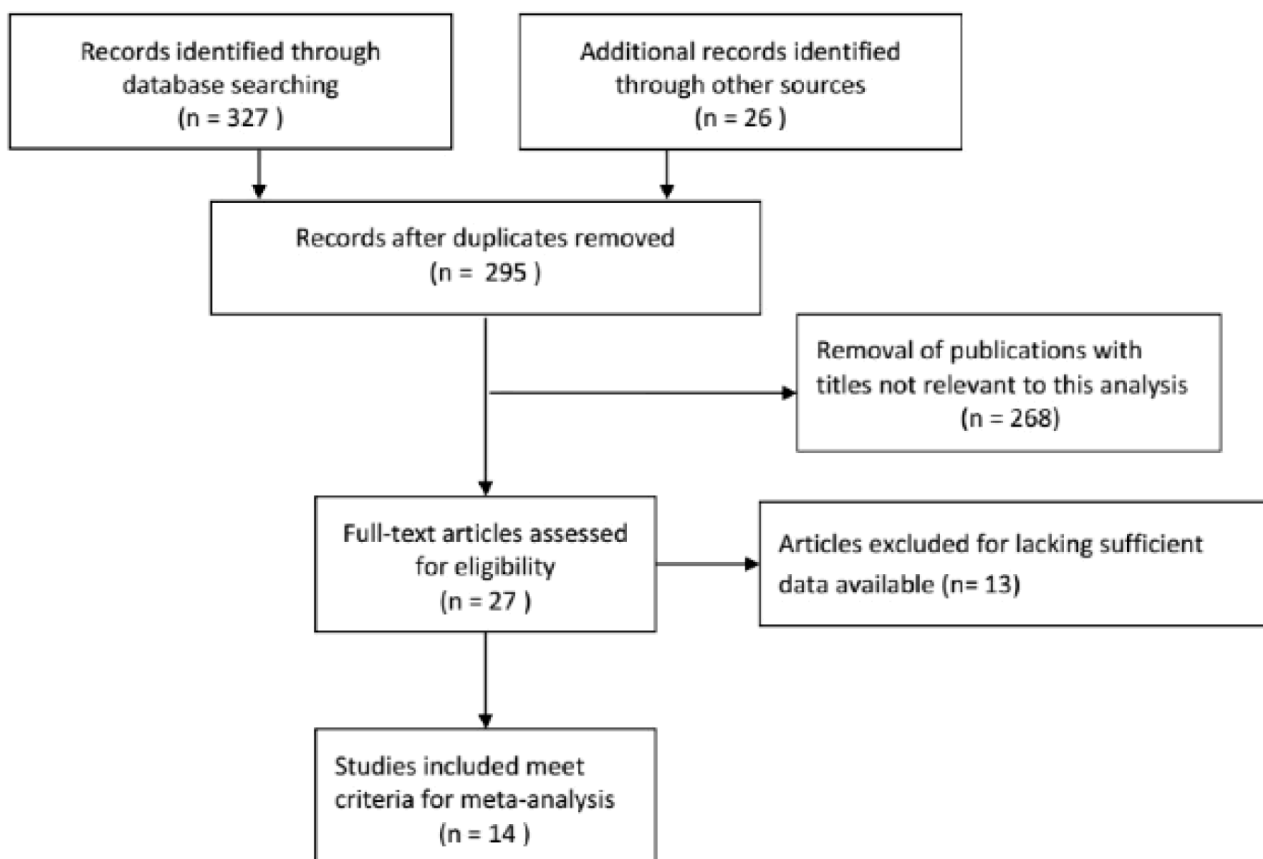


Figure 1. The flowchart of literature search and selection procedure.

Table 2. Meta-analysis for two groups

Study Index	Trials	Heterogeneity		Model	Pooled statistics
		p	I <sup>2</sup> (%)		
PCF	14	0.772	0	Fixed	OR (95% CI)=1.12 (0.81,1.54)
LOS	6	0.003	72	Random	SMD (95% CI) =-0.77 (-1.18,-0.36)

PCF: Pharyngocutaneous fistula; LOS: Length of stay

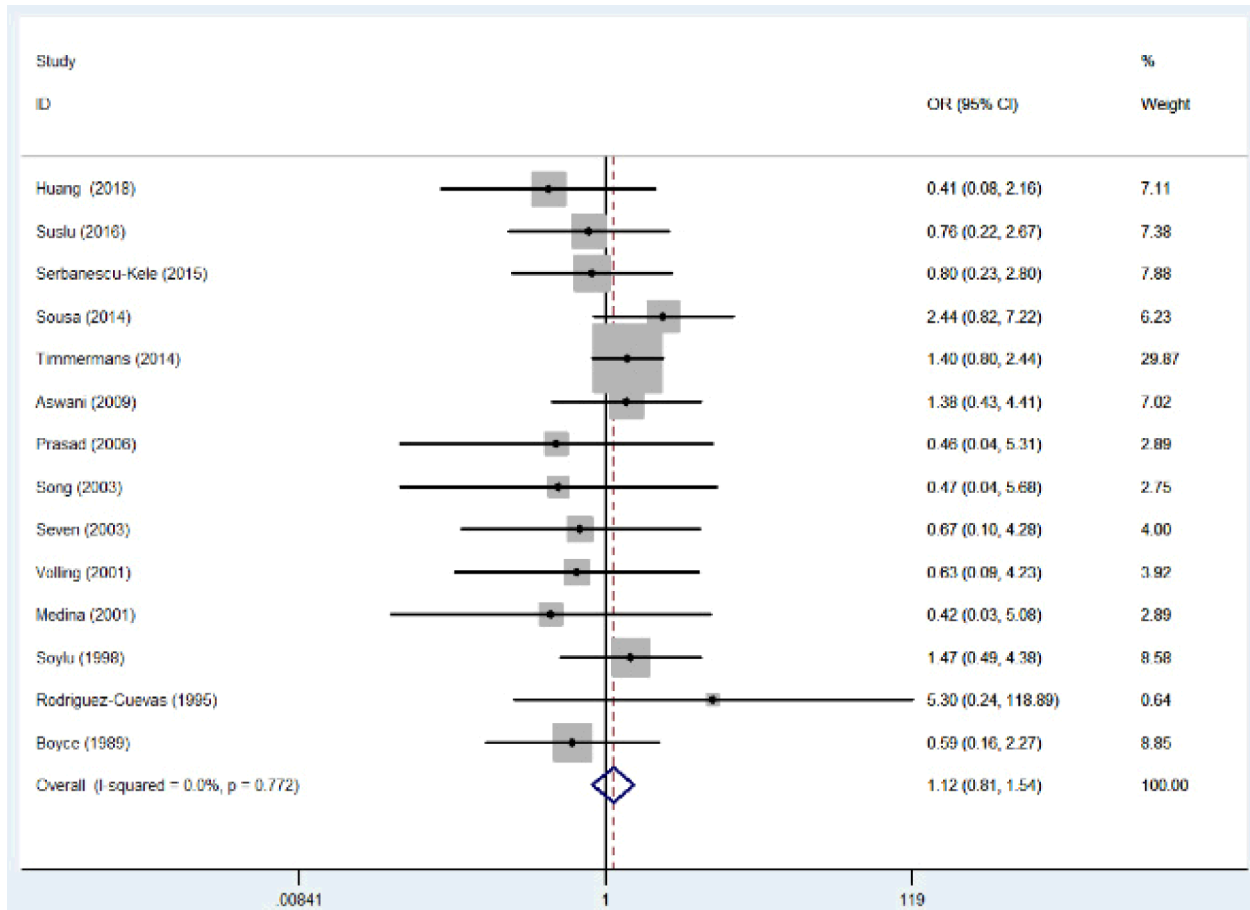


Figure 2. Forest plots of merged analyses of pharyngocutaneous fistula.

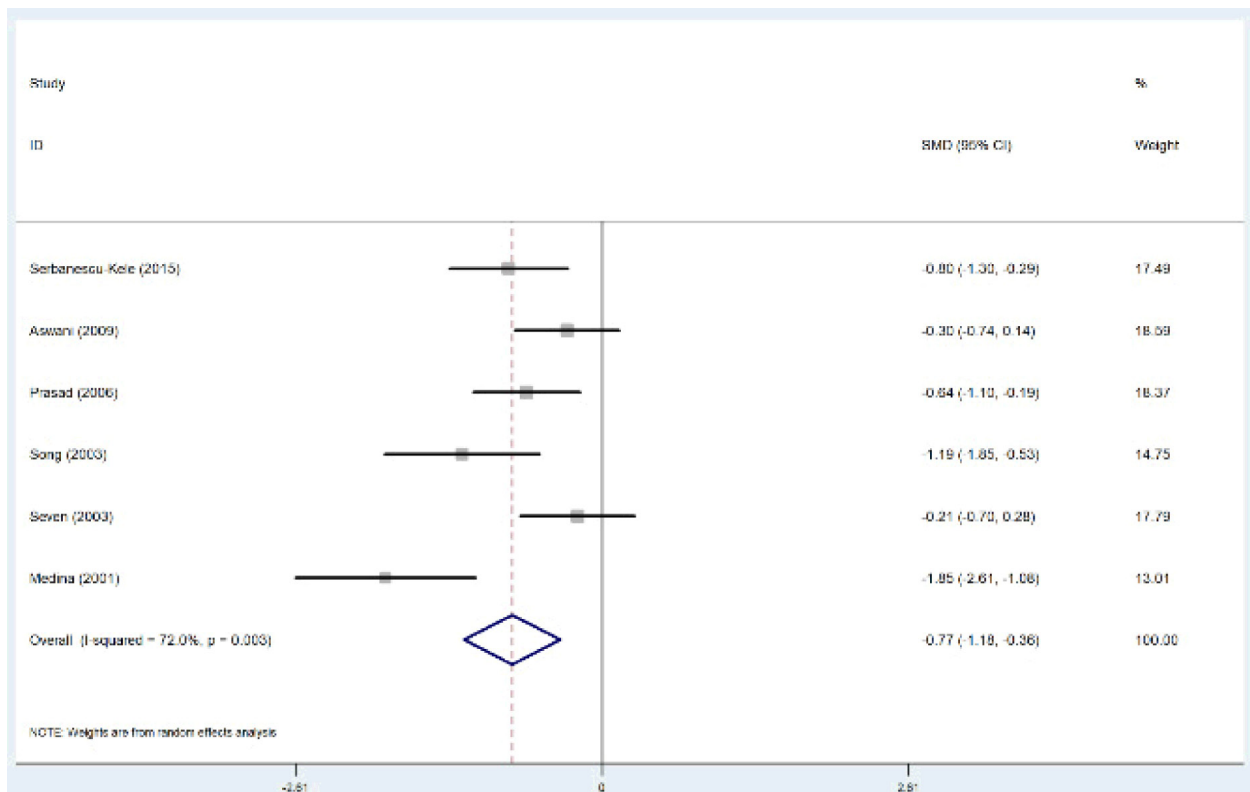


Figure 3. Forest plots of merged analyses of length of stay.

*Safety of early oral feeding and delayed oral feeding following total laryngectomy*

The incidence of PCF was recorded for evaluating the safety of early or delayed oral feeding. No significant difference in the heterogeneity was identified among these studies ( $p=0.772$ ,  $I^2=0\%$ ) (Table 2). Therefore, the fixed-effect model was utilized. The results showed that the pooled OR value was 1.12 (95%CI=0.81-1.54), suggesting that early oral feeding did not increase the risk of PCF relative to delayed oral feeding (Figure 2).

*Efficacy of early oral feeding and delayed oral feeding following total laryngectomy*

LOS was recorded for evaluating the efficacy of early or delayed oral feeding. There were 6 RCTs recoding the LOS, with 189 cases of early oral feeding and 179 cases of delayed oral feeding. A remarkably heterogeneity was identified among these studies ( $p=0.003$ ,  $I^2=72\%$ ). Therefore,

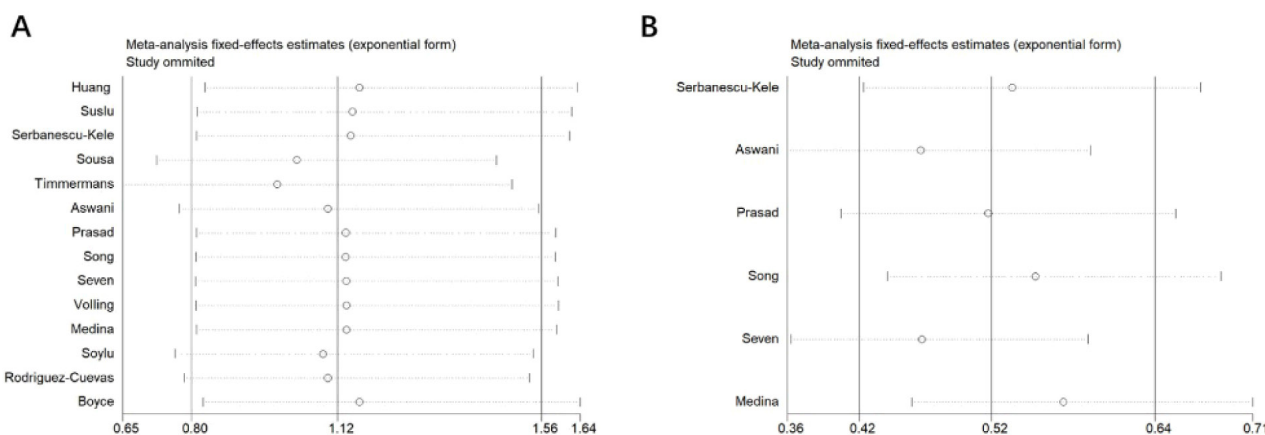
the fixed-effect model was utilized. The results showed that the pooled SMD was -0.77 (95%CI=-1.18-0.36), suggesting a shorter LOS in cases of early oral feeding relative to those of delayed oral feeding (Figure 3).

*Sensitivity analysis*

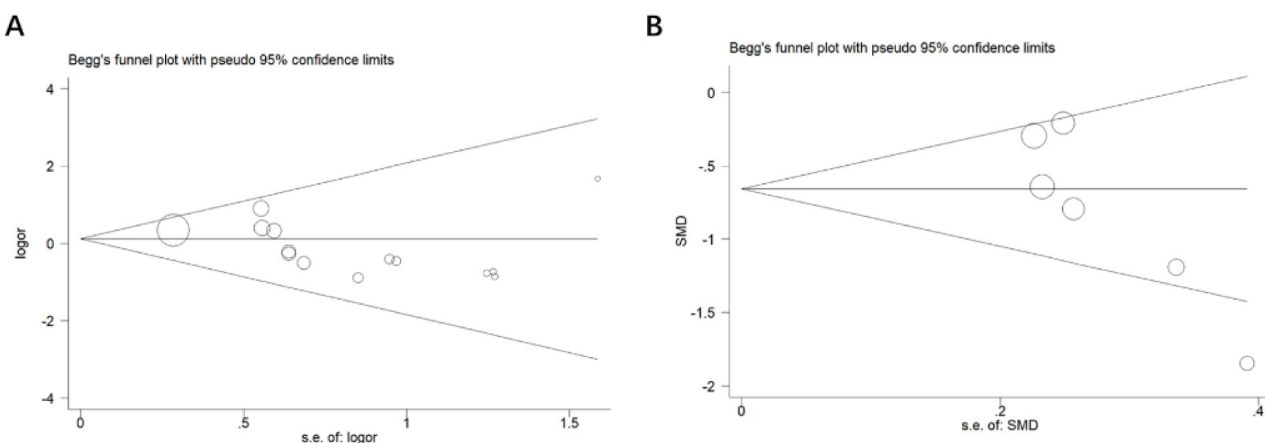
Sensitivity analysis was performed for illustrating the impact of individual literature on the summary estimate. As Figure 4 illustrated, sensitivity analysis indicated the final conclusion was not influenced by an individual literature. We believed that our meta-analysis results were robust and stable.

*Publication bias*

Publication bias in this study was assessed by depicting Begg's funnel plots. The systematic shape of funnel diagram indicated no significant publication bias (Figure 5).



**Figure 4.** (A) Effect of individual studies on the pooled OR for pharyngocutaneous fistula; (B) Effect of individual studies on the pooled SMD for length of stay.



**Figure 5.** Begg's funnel plot of publication bias test for pharyngocutaneous fistula (A) and length of stay (B).

## Discussion

To avoid PCF after laryngeal cancer surgery, postoperative nasogastric tube diet is generally required for about 10 days. The most vulnerable period of the wound is about a week after surgery. Hence, Applebaum et al. [29] proposed that oral feeding should delay to the 10<sup>th</sup> day after surgery. Recently, clinical observations considered that early oral feeding at day 2-3 after surgery does not influence the healing and the incidence of PCF [14,30]. This study summarized and analyzed 14 high-quality literatures involving 1824 cases undergoing total laryngectomy. Our conclusion may provide clinical evidences for the application of early oral feeding.

This study demonstrated no significant difference in the incidence of PCF between cases of early or delayed oral feeding. Hence, early oral feeding was proved to be safe, which decreased psychological burden of affected patients. Meanwhile, early oral feeding shortened LOS, which decreased economical burden. We encouraged early oral feeding in the case of no fistula formation, and it could elevate the bed usage rate and reduce medical expense.

Although Aprigliano et al. [15] suggested no benefit of early oral feeding following total laryngectomy, they believed that the intubation of nasogastric tube is one of the reasons for PCF. Early oral feeding avoids the long-term usage of nasogastric tube. Medina et al. [21] indicated that early oral feeding does not increase the incidence of PCF, and the avoidance of nasogastric tube usage could relieve the fear and discomfort. Patients undergoing early oral feeding could be more cooperated, leading to a better outcome. Akyol et al. [31] analyzed a total of 110 patients undergoing total laryngectomy in 1986-1992. They considered that no application of nasogastric intubation will not elevate the incidence of PCF, and oral feeding could be applied within the 1-2 days after surgery. Soyulu et al. [26] reported that the oral feeding on the third day does not increase the risk of PCF in 295 cases undergoing total laryngectomy. They demonstrated that the third day after total laryngectomy is the most suitable time point for oral feeding. Identifi-

cally, Timmemans et al. [23] also encouraged the early oral feeding. This study proposed the safety of early oral feeding as well.

LOS is a crucial marker for evaluating treatment efficacy. Medina et al. [21] showed the shorter LOS in cases of early oral feeding compared with those of delayed oral feeding (7.05 days vs. 11.87 days). Song et al. [28] revealed that early oral feeding reduces 4.3 days of LOS in patients undergoing total laryngectomy. Our study also pointed out shorter LOS in cases of early oral feeding. However, Seven et al. [17] illustrated that early oral feeding does not shorten the LOS.

Sensitivity analysis is conducted to analyze the data using different statistical methods and models, so as to rule out low-quality studies. In this study, sensitivity analysis indicated the reliable and robust conclusion. Publication bias is evaluated according to the symmetry of funnel plots and the concentration to the midline. Here, the systematic shape of funnel diagram indicated no significant publication bias.

Several limitations in this study should be noteworthy: 1) Sample size was relatively small, and further explorations should be conducted with a large sample size to improve the accuracy; 2) Subgroup analyses on the influence of early oral feeding on the onset time of PCF were lacked; 3) Confounding factors of PCF should be taken into consideration, such as radiotherapy, TNM stage of tumors, albumin level and Hb level; and 4) different physicians with varied surgical experiences could influence the conclusion.

## Conclusions

Early oral feeding following total laryngectomy shortens LOS relative to delayed oral feeding. No significant difference in the incidence of PCF is observed between early oral feeding and delayed oral feeding, suggesting that early oral feeding following total laryngectomy is safe and efficacious.

## Conflict of interests

The authors declare no conflict of interests.

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