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ORIGINAL ARTICLE

Associations between hypopharyngeal defect closure and quality of life in long-term total laryngectomy survivors

Anthony M. Tonsbeek MD[1] | **Caroline A. Hundepool MD, PhD**[1] | **Aprilia L. Molier BSc**[1] | **Eveline Corten MD, PhD**[1] | **Bianca Rijken MD, PhD**[2] | **Aniel Sewnaik MD, PhD**[3] | **Marc A. M. Mureau MD, PhD**[1]

[1]Department of Plastic & Reconstructive Surgery, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

[2]Department of Plastic & Reconstructive Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

[3]Department of Otorhinolaryngology – Head and Neck Surgery, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

Correspondence
Anthony M. Tonsbeek, Department of Plastic & Reconstructive Surgery, Erasmus MC Cancer Institute, University Medical Center Rotterdam, P.O. Box 2040, NL-3000 CA, Rotterdam, The Netherlands.
Email: a.tonsbeek@erasmusmc.nl

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Abstract

Background: Few studies have examined health-related quality of life (HRQOL) outcomes in long-term total laryngectomy survivors in relation to the type of hypopharyngeal defect.

Methods: A cross-sectional study was performed in long-term total laryngectomy survivors, treated between 2000 and 2020. The primary outcome was HRQOL, assessed using the FACE-Q Head and Neck Cancer Module, in relation to the type of hypopharyngeal closure (primary closure, partial or circumferential reconstruction).

Results: Seventy-nine survivors were included with a median follow-up of 92.1 months (IQR 75.6–140.2 months). Patients requiring partial hypopharyngeal reconstruction ($n = 18$) scored significantly worse than patients with primary closure ($n = 51$) on 4 of 13 FACE-Q domains: functional domains of eating ($p = 0.03$), speech ($p = 0.05$), and swallowing ($p = 0.03$), and the psychological domain of speaking-related distress ($p = 0.02$). No statistically significant differences were found between the circumferential hypopharyngeal defect reconstruction group ($n = 10$). Stricture occurrence was the only clinical factor associated with worse eating, speaking, swallowing, eating-related distress, and cancer worry in multivariable analyses.

Conclusion: Several functional and psychological domains were significantly worse following partial hypopharyngeal reconstruction than in patients who received primary closure. Efforts to reduce stricture rates to enhance reconstructive outcomes following total laryngectomy merit further research.

KEYWORDS

head and neck cancer, quality of life, reconstruction, survivorship, total laryngectomy

1 | INTRODUCTION

The management of laryngeal and hypopharyngeal cancer by total laryngectomy (TLE) results in substantial functional and psychosocial consequences, which affect short- and long-term health-related quality of life (HRQOL). In addition to the risk of major complications (e.g., fistulas and strictures), patients regularly face impairment in speech, oral intake, salivation, social life, and mental health.[1,2] The frequent use of radiotherapy for locoregional control causes an increased risk of complications and long-term toxicity of irradiated tissues, the effects of which are amplified by concurrent chemotherapy.[3,4] In recognition of the treatment consequences that patients with head and neck cancer face during follow-up, both the American and European Head and Neck Society have underscored the significance of survivorship care with management guidelines.[5,6] Over the past decades, achieving a favorable quality of life has become an important consideration in the choice of treatment and reconstruction, in conjunction with the aim of improving oncological outcomes.

Despite the shift towards laryngeal preservation in the early 1990s,[7] TLE remains indicated in select cases with a locally advanced primary tumor, tumor recurrence, or dysfunctional larynx. The majority of studies on HRQOL following TLE include patients with less than 1 year postoperative follow-up, and generally focus on comparisons of HRQOL in laryngeal preservation with (chemo)radiation.[8] However, long-term survivors may have inherently different characteristics than patients who do not live beyond the first years of follow-up when recurrence is most prevalent.[9,10] With 5-year survival in advanced-stage disease ranging from 42% to 67% in laryngeal cancer and 19% to 42% in hypopharyngeal cancer, respectively, a select group of TLE patients outlive these first years.[11] Therefore, it is crucial to elucidate which domains of HRQOL are most impaired in these long-term survivors, which can be used to improve and individualize their long-term care.

With the increase in TLEs being performed as salvage treatment, reconstructions are required more frequently. Common reconstructions in salvage TLEs include onlay flaps to reinforce the suture line after primary closure, limiting the rate of pharyngocutaneous fistulas.[12,13] Primary closure can be performed when a mucosal strip of approximately >3 cm remains following resection. Alternatively, an inlay or tubed flap for a partial or circumferential hypopharyngeal defect, respectively, may be necessary if insufficient viable tissue for primary closure remains following (partial) pharyngectomy. The chosen type of reconstruction is crucial for the prevention of complications, but also for enhancing functional outcomes in the long term.[14–16] Nonetheless, the existing literature on long-term HRQOL fails to account for the inherent dissimilarities between survivors who required a reconstruction and those who received primary hypopharyngeal defect closure. Considering the lack of studies on HRQOL following hypopharyngeal reconstruction, it is essential to determine the challenges these survivors face in the long term.

Therefore, the aim of this cross-sectional study was to assess associations between clinical variables and long-term HRQOL (>3 years) in survivors of laryngeal and hypopharyngeal cancer following TLE, in relation to the type of hypopharyngeal defect closure (either primary closure, partial or circumferential (free) flap reconstruction). We hypothesized that the type of hypopharyngeal defect closure would be mainly associated with functional domains of HRQOL at long-term follow-up. In addition, the present study aimed to determine which patient-specific factors are associated with positive or negative HRQOL outcomes.

2 | METHODS

2.1 | Study design

A cross-sectional single-center study was performed at the largest tertiary referral hospital for head and neck surgery in The Netherlands, including all patients who had previously undergone a TLE with or without a pharyngectomy. Patients treated between 2000 and 2020 were identified based on retrospective chart reviews. In this period, 717 TLEs were performed. Patients who were still alive were eligible for inclusion if they: (i) had undergone curative TLE for laryngeal or hypopharyngeal cancer for primary or recurrent disease, (ii) were at least 18 years old during treatment, (iii) had no metastases and were not in a palliative setting during follow-up, and (iv) were at least 3 years after TLE, because only long-term survivors were included. Patients were excluded if they were legally incompetent or unable to understand the Dutch language. The medical ethics committee approved the study prior to the start of the data collection (MEC-2018-1336).

2.2 | Outcomes

For assessment of HRQOL, the FACE-Q Head and Neck Cancer Module (hereafter: FACE-Q) was used.[17] As previously described in other studies, this psychometrically validated patient-reported outcome measure (PROM) attempts to address some of the shortcomings of

alternative PROMs in terms of their methodological and content issues.[17–20] The FACE-Q has been developed and validated using patient input from a broad selection of HNC patients including TLE patients, although it was not developed for TLE patients in specific. The questionnaire contains 14 independent domains, which cover functional and psychological aspects. In this study, the "experience of care" domain was not used, due to a high possibility of recall bias in patients with a long follow-up. An invitation to participate was distributed to all qualifying patients by email or per post, based on patient preference. The number of items of each FACE-Q domain ranges from 5 to 10, with 3 to 5 response options depending on the domain, with questions on HRQOL regarding the patient's past week. The included 13 domain scores were converted to a 0–100 score according to Rasch analysis principles.[21] Higher FACE-Q domain scores indicate better HRQOL outcomes, except for the domain of "cancer worry," where higher scores inversely refer to a worse outcome.

Two relevant questions for TLE patients were previously added by our research group, prior to the functional domains of "eating" and "speaking": (1) "Are you able to eat and drink or are you dependent on tube feeding?" (Yes, I am able to eat and drink; No, I have a feeding tube). (2) "Are you able to talk or is this impossible due to your treatment?" (Yes, I am able to talk; No, I am not able to talk due to my treatment).[20] To mitigate bias arising from not-randomly missing data, a Rasch score of 0 was assigned to patients dependent on tube feeding for "eating" and "eating-related distress" domains and for those experiencing speech inability for "speaking" and "speaking-related distress" domains.[20]

The primary outcomes of the study were 13 independent FACE-Q domain scores. Secondary outcomes were the rate of fistulas, anastomotic leakage, strictures, and flap failure, in the immediate postoperative period. Secondary outcomes also included self-reported rates of feeding tube dependence and ability to talk, as discussed in the previous paragraph. Additionally, we collected data on type of speech at the latest moment of follow-up. All clinical data were retrospectively collected from the electronic medical records. Speech and oral intake were self-reported by patients, as described in the previous paragraph. At our institute, patients who received primary hypopharyngeal closure generally underwent primary tracheoesophageal puncture (TEP) placement, whereas patients who required a reconstruction were offered secondary TEP placement after 3–4 months following TLE.

Fistulas were defined as any abnormal connection between skin or trachea and the reconstructed hypopharyngeal segment requiring surgical revision. In contrast, in anastomotic leakage, the connection between skin or trachea spontaneously resolved following prolonged tube feeding, antibiotic therapy, and/or scopolamine therapy.[16] A stricture was defined as any abnormal narrowing of the neohypopharynx, identified using videofluoroscopy, which required either (outpatient) dilation or surgical revision. Patients were classified by type of hypopharyngeal closure: primary closure, and partial and circumferential hypopharyngeal reconstruction. Reconstructions were only performed if the remainder of mucosal tissue following resection was insufficient to be closed primarily. Partial defect reconstructions were performed if a viable strip of less than 3 cm of stretched mucosal tissue was left and amenable for a patch (free) flap reconstruction. If case of complete circumferential resection, or in case of a remnant strip of poorly perfused mucosa, a tube reconstruction was performed.

2.3 | Statistical analysis

Differences across the three defect groups in age were analyzed using one-way ANOVA tests, differences in months since TLE were analyzed using Kruskal–Wallis tests, and differences in other categorically coded demographic and clinical variables were assessed using Fisher–Freeman–Halton exact tests. For the primary outcomes, differences across the defect groups in FACE-Q domains were examined using Kruskal–Wallis tests and Dunn–Bonferroni post hoc tests. We chose to include strict post hoc tests in which correction for multiple testing was performed. Post hoc tests were only performed for significant results of the initial analyses, consisting of Bonferroni-adjusted χ^2 or Fisher's exact tests, Tukey's tests (one-way ANOVA test), and Dunn–Bonferroni tests (Kruskal–Wallis test). As we chose conservative post hoc tests, no further adjustments for multiple testing were made for critical p-values. Additionally, the effects of various predetermined factors on FACE-Q domain scores were evaluated using multivariable regression analysis: age at surgery (years), sex (female/male), AJCC stage (low/high stage), follow-up time after TLE (months), need for reconstruction (yes/no), postoperative radiotherapy (PORT; yes/no), stricture occurrence (yes/no), and fistula/anastomotic leakage occurrence (yes for either complication/no for both). Separate multivariable models were examined for each FACE-Q domain. Significant variables were presented as parameter estimates (β) and 95% confidence intervals (CI). The models were assessed using Q–Q plots, independence of residuals, analysis of residuals against fitted values, variance inflation factor, the Akaike information criterion, and multiple R^2 values. To prevent overfitting of the models, one variable in approximately 10 patients could be included.

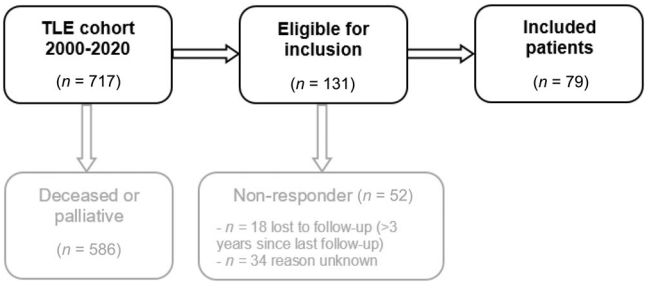

FIGURE 1 Flowchart of the inclusion process.

Multivariable regression analyses were performed using R version 4.3.2. Group differences in the secondary outcomes involving complications, self-reported feeding tube dependence, and self-reported ability to talk were reported descriptively. Two-sided p-values <0.05 were considered statistically significant.

3 | RESULTS

In total, 131 long-term TLE survivors were eligible for inclusion, from the original cohort of 717 TLE procedures performed between 2020 and 2023 (Figure 1). Of these patients, 79 patients were included (response rate: 60%), with a median follow-up duration of 92.1 months (IQR 75.6–140.2 months) following TLE. In this cohort, 51 patients (65%) underwent primary closure of the hypopharyngeal defect, 18 patients (23%) required a partial reconstruction, and 10 patients (13%) a circumferential reconstruction. Patient characteristics by the type of defect are shown in Table 1.

The majority of patients with a partial defect underwent a pectoralis myocutaneous flap reconstruction ($n = 14$, 78%), three patients (17%) received a fasciocutaneous free flap and one patient (6%) a supraclavicular artery island flap. Circumferential defects were reconstructed with a jejunal free flap ($n = 5$, 50%), a tubed fasciocutaneous free flap ($n = 3$, 30%), or gastric pull-up ($n = 2$, 20%). Three patients (6%) in the primary closure group received an onlay pectoralis major myofascial flap.

To evaluate potential participation bias, we performed a non-responder analysis (Table S1, Supporting Information), comparing the 79 participants with the 52 non-responders (eligible patients who did not respond) on selected demographic and clinical variables. Of the 52 non-responders, 18 patients (35%) were lost to follow-up with their last medical record entry being more than 3 years prior to data collection. Non-responders were significantly younger than participating patients and had significantly higher fistula rates (15% vs. 4%), respectively. Also, the rate of strictures was higher in non-responders (39% vs. 27%), although not statistically significant. Due to these differences, underestimation of adverse long-term HRQOL consequences in this cohort is plausible.

3.1 | Long-term HRQOL outcomes

Among the three types of hypopharyngeal defect closure, significant group differences were observed in 5 of 13 FACE-Q domains: the functional domains of eating ($p = 0.01$), speech ($p = 0.01$), and swallowing ($p = 0.03$), and the psychological domains of eating-related ($p = 0.01$) and speaking-related distress ($p = 0.006$; Table 2). In contrast, few differences were observed for functional domains of appearance, smiling, oral competence, and the psychological domains of appearance-, drooling-, and smiling-related distress. Post hoc tests were performed to examine which underlying groups were significantly different. Results indicated that the partial defect reconstruction group reported significantly greater problems than the primary closure group on the functional domains of eating, speech, and swallowing, and the psychological domain of speaking. The circumferential defect reconstruction group did not differ significantly from the other two groups on any of the FACE-Q scores. However, as the Dunn–Bonferroni post hoc test was very conservative for the post hoc α-value in Table 2, we also compared patients with primary closure to those who required a reconstruction (partial and circumferential defects combined; Table S2) using Mann–Whitney U tests. Similar differences were observed as shown in Table 2, with the exception of one domain. Oral competence was found to be significantly worse ($p = 0.02$) in the reconstruction group (median 87.0, IQR 66.0–100.0) compared to the primary closure group (median 100.0, IQR 87.0–100.0).

Using multivariable analyses, we examined associations of several long-term FACE-Q outcomes with several predetermined clinical variables (i.e., age at surgery, sex, AJCC stage, follow-up time after TLE, need for reconstruction, PORT, stricture occurrence, and fistula/anastomotic leakage occurrence). We selected the following three functional domains (eating, speaking, and swallowing) and two psychological domains (eating-related distress, and cancer worry). The remaining eight domains were omitted because these domains showed low variability between patients. The data were highly skewed and not amenable to standard transformation methods. The observed ceiling-effect precluded further analyses for associated factors.

Stricture occurrence was the only factor significantly associated with functional domains of eating ($\beta = -22.5$,

TABLE 1 Patient characteristics.

	Primary closure ($n = 51$)	Partial defect closure ($n = 18$)	Circumferential defect closure ($n = 10$)	p-value
Age at survey, years				
Mean (SD)	72.9 ± 8.9	67.9 ± 8.4	75.7 ± 7.4	0.046[a,b]
Sex, *n* (%)				0.79[c]
Female	11 (22)	4 (22)	3 (30)	
ACE-27 total comorbidity score, *n* (%)				0.29[c]
None/mild	21 (41)	4 (22)	2 (20)	
Moderate/severe	30 (59)	14 (78)	8 (80)	
Indication for TLE, *n* (%)				0.01[a,c]
Primary tumor	21 (41)	7 (39)	2 (20)	
Recurrence/second primary	27 (53)	5 (28)	8 (80)	
Dysfunctional larynx	3 (6)	6 (33)	0 (0)	
Lymph node dissection, *n* (%)	26 (51)	10 (56)	6 (60)	0.84[c]
Tumor stage (AJCC 8th edition), *n* (%)				0.22[c]
Low stage (stage 0, I, or II)	14 (28)	9 (50)	3 (30)	
High stage (stage III, IVA, or IVB)	37 (73)	9 (50)	7 (70)	
Prior radiotherapy, *n* (%)	28 (55)	11 (61)	8 (80)	0.37[c]
Prior chemoradiotherapy, *n* (%)	4 (8)	3 (17)	2 (20)	
Postoperative radiotherapy, *n* (%)	22 (43)	7 (39)	2 (20)	0.43[c]
Follow-up after TLE, months				0.40[d]
Median [IQR]	96.5 [78.9–140.2]	77.9 [70.9–124.9]	113 [75.9–153.1]	

[a]Denotes statistical significance ($p < 0.05$).
[b]One-way ANOVA (post hoc Tukey's test nonsignificant).
[c]Fisher–Freeman–Halton test (Bonferroni-adjusted post hoc testing for "indication for TLE" showed the results were significantly different due to the higher rate of a dysfunctional larynx in the partial defect group, compared to the primary closure group; $p < 0.001$).
[d]Kruskal–Wallis test.

95% CI −35.2 to −9.8, $p = 0.001$), swallowing ($\beta = -18.4$, 95% CI −30.5 to −6.4, $p = 0.003$), speaking ($\beta = -18.9$, 95% CI −35.3 to −2.4, $p = 0.03$) and the psychological domains of eating distress ($\beta = -34.74$, 95% CI −49.17 to −20.31, $p < 0.001$) and cancer worry ($\beta = 10.92$, 95% CI 0.3–21.5, $p = 0.04$). Age, sex, follow-up time, PORT, AJCC stage category, need for reconstruction, and fistula/anastomotic leakage occurence were not significantly associated with the analyzed long-term FACE-Q domain scores.

3.2 | Postoperative outcomes

In the primary closure, partial defect, and circumferential defect reconstruction groups, respectively, the postoperative complication rates were: fistula formation (0% | 0% | 30%), anastomotic leakage (14% | 56% | 20%), and stricture occurrence (16% | 44% | 50%). Flap failures only occurred in the circumferential defect group ($n = 2$, 20%). Self-reported (naso)gastric tube dependency was only reported by four patients: two patients in the primary closure group (4%) and two in the circumferential defect group (20%).

TEP speech was achieved in 51 patients (100%) who received primary closure, in 18 patients (100%) of the partial defect group, and 8 patients (80%) of the circumferential defect group. Primary TEP was performed in 50 out of 51 patients (98%) in the primary defect group, followed by 9 out of 18 (50%) patients in the partial defect group and 1 out of 10 patients (10%) in the circumferential defect group. At long-term follow-up, there was a

TABLE 2 Median FACE-Q group scores by type of hypopharyngeal closure.

Median FACE-Q subscale scores [IQR][a]	Primary closure ($n = 51$)	Partial defect closure ($n = 18$)	Circumferential defect closure ($n = 10$)	p-value[b]	Post hoc test[c] (adjusted p-value)
Function scales					
Appearance	100.0 [X]	100.0 [X]	100.0 [X]	0.86	-
Eating	78.0 [62.0–100.0]	57.0 [47.3–73.5]	57 [28.5–80.3]	0.01[d]	Primary > partial (0.03)[d]
Oral competence	100.0 [87.0–100.0]	87.0 [66.0–100.0]	81.0 [63.8–100.0]	0.05	-
Salivation	78.0 [62.0–100.0]	69.0 [46.0–90.3]	82.5 [56.0–100.0]	0.27	-
Smile	100.0 [X]	100.0 [78.0–100.0]	100.0 [94.5–100.0]	0.74	-
Speech	63.0 [43.0–75.0]	40.0 [23.3–63.0]	18.5 [0.0–75.0]	0.01[d]	Primary > partial (0.05)[d]
Swallowing	73.0 [58.0–88.0]	53.0 [45.0–70.0]	63.0 [48.0–88.0]	0.03[d]	Primary > partial (0.03)[d]
Distress					
Appearance	100.0 [88.3–100.0]	100.0 [66.0–100.0]	95.0 [9.0–100.0]	0.24	-
Drooling	100.0 [X]	100.0 [90.0–100.0]	100.0 [87.8–100.0]	0.60	-
Eating	94.5 [79.3–100.0]	74.0 [50.0–91.8]	81.0 [22.0–85.0]	0.01[d]	Not significant
Smile	100.0 [X]	100.0 [X]	100.0 [X]	0.86	-
Speaking	77.0 [61.0–100.0]	49.0 [42.0–73.0]	56.0 [0.0–82.8]	0.006[d]	Primary > partial (0.02)[d]
Modifiers					
Cancer worry	16.0 [4.5–34.0]	29.0 [20.0–43.5]	24.0 [0.0–32.3]	0.18	-

Note: [X] denotes that the IQR minimum and maximum value are identical to the maximum median value of 100.
Abbreviation: IQR, interquartile range.
[a]Higher scores indicate more favorable outcomes, except for the cancer worry domain.
[b]Kruskal–Wallis test.
[c]Dunn–Bonferroni test (all significant differences were due to significantly better scores in the primary closure group compared to the partial hypopharyngeal defect group; there were no significant differences between partial and circumferential defect groups). Unadjusted p-values for significant domains without post hoc Bonferroni correction did show significant differences between the primary and circumferential groups for domains of eating ($p = 0.04$), speaking ($p = 0.03$), eating distress ($p = 0.02$), and speaking distress ($p = 0.03$).
[d]Denotes statistical significance ($p < 0.05$).

significant difference between the self-reported speaking inability rates of the circumferential defect group (40%), partial defect group (17%), and primary closure group (8%).

Type of voice used at the latest follow-up moment was significantly different between the groups ($p = 0.007$). TEP speech was predominantly used by 48 out of 51 (94%) patients in the primary closure group, followed by 16 out of 18 (89%) and 6 out of 10 (60%) patients in the partial and circumferential defect group, respectively. Synthesized speech using an electrolarynx was used by 2 out of 51 (4%), 1 out of 18 (6%), and 4 out of 10 (40%) patients of these groups, respectively. One patient (2%) in the primary closure group utilized pseudo-whispered speech, while another patient (6%) in the partial defect group declined TEP replacement and expressed no interest in using an electrolarynx.

4 | DISCUSSION

This study is the first to compare long-term HRQOL by type of hypopharyngeal defect and closure in a select cohort of long-term TLE survivors, using the FACE-Q Head and Neck Cancer Module. The outcomes of the study underline that long-term HRQOL impairments were more pronounced in patients who received a partial hypopharyngeal reconstruction than those who received primary closure. Both functional domains (eating, speech, oral competence, and swallowing) and one psychological domain (speaking distress) were worse in the former group. No significant differences between the groups were observed in 9 out of 13 FACE-Q domains. Patients who received a primary defect closure reported similar functional and psychological HRQOL issues, commonly related to dysphagia and speaking. No

statistically significant differences were found in post hoc tests between the circumferential defect reconstruction group and the other two closure groups. The occurrence of a stricture was the only clinical variable that was negatively associated with several FACE-Q HRQOL domains.

Various types of hypopharyngeal defects can arise following TLE, which may subsequently necessitate reconstruction if primary closure is not feasible. In the current study, we observed significant differences in functional and psychological outcomes between the primary closure and partial hypopharyngeal defect reconstruction groups in 4 of 13 FACE-Q domains. Remarkably, in a recent systematic review by Wulff et al. on HRQOL after TLE, merely one of 51 included studies compared HRQOL outcomes between different types of hypopharyngeal defects, nor were the different types acknowledged as criteria for in- or exclusion in the majority of the study designs.[8] The majority of available studies on HRQOL following TLE included patients with short-term follow-up, less than 1 year postoperatively.[8] However, these studies did not adequately address the issues of long-term survivorship, which may lead to misrepresentation of HRQOL outcomes due to heterogeneity and time-dependent confounding. In addition, incidence rates of complications (e.g., stricture) are seldom reported in relation to HRQOL, but complications may inherently have a large influence on functional outcomes. Neglecting the dissimilarities between types of hypopharyngeal defects might introduce a major source of bias when presenting HRQOL outcomes for TLE patients collectively.

Long-term TLE survivors frequently report functional problems related to dysphagia and speech, as shown in prior non-randomized studies. Commonly, these studies compared HRQOL with patients who were treated with laryngeal preservation. Boscolo-Rizzo et al. found that TLE patients, at a mean follow-up time of 30 months, experienced significantly more speech difficulties, sleep disturbance, dyspnea, pain, and issues with social contact and senses, than patients who underwent chemoradiation as primary therapy.[2] Wulff et al. reported that TLE patients scored worse than a normative reference population on nearly all HRQOL domains, at a median follow-up of 6.3 years after TLE. The most common issues were dysphagia (46%), voice problems (57%), and mental health issues (depression 16%, anxiety 20%).[22]

In contrast to lasting functional deficits, various studies have reported that psychological HRQOL outcomes in head and neck cancer patients generally show large improvements and return towards baseline during follow-up.[23,24] Although this is often attributed to coping mechanisms and decreasing uncertainty about survival,[20,24,25] the current cohort of survivors still experienced substantial eating-related and speaking-related distress. In addition, the psychological distress in the daily lives of patients may also affect their concerns regarding cancer recurrence, as was reflected by the cancer worry domain, which highlights the additional long-term psychological burden these patients face.

Few studies have specifically reported HRQOL following reconstruction of partial and circumferential hypopharyngeal defects using PROMs. The results of this cohort of long-term survivors are in line with prior non-randomized studies. We found significantly worse HRQOL for eating and speaking-related functional and psychological domains in patients who required a hypopharyngeal defect reconstruction, compared to patients who received primary closure (Table S2). Similarly, in terms of speech outcomes, Graville et al. identified significantly worse voice-related quality of life in patients who required a radial forearm free flap for a partial hypopharyngeal defect reconstruction compared to primary closure at a median follow-up of 69 months.[26] Deschler et al. found an inferior subjective voice quality and voice-related HRQOL in patients who required a reconstruction, but no difference in general and disease-specific HRQOL.[27] However, the authors did not specify the duration of follow-up. For swallowing outcomes, Harris et al. reported superior oral intake rates following primary closure and significantly longer pharyngeal transit times for patients who required a hypopharyngeal defect reconstruction (1.9 vs. 3.5–4.7 s, respectively) in a videofluoroscopic swallow study at 1 year follow-up.[28] However, no difference in self-reported dysphagia was observed between the groups.[28] Remarkably, a study with 18 patients by Cleere et al. reported that free flap reconstruction of a hypopharyngeal defect following salvage TLE yielded significantly better results on dysphagia-specific HRQOL compared to patients who underwent primary closure with or without an onlay pectoralis flap, with follow-up ranging from 12 to 78 months.[29] However, these findings should be interpreted with caution, considering the small sample size and limited analyses that could be performed.

Identification of effect modifiers is important to predict HRQOL outcomes following TLE, in an effort to improve patient-tailored interventions and guidance. Wulff et al. reported that younger age, greater comorbidities, voice problems, dysphagia, and mental health issues were negatively associated with HRQOL.[22] In our cohort, only the occurrence of a stricture was significantly associated with poorer HRQOL scores in all five analyzed FACE-Q domains: eating, speaking, swallowing, eating-related distress, and cancer worry. Considering the significant impact of dysphagia on HRQOL, it is crucial to reduce stricture rates. Therapeutic swallowing exercises can be implemented to improve swallowing and

communication, as was shown in a multicenter randomized controlled trial in TLE patients.[30] Moreover, minimization of complications following surgery by optimizing reconstructive outcomes is a key factor in improving HRQOL outcomes. Stricture prevention requires a reduction of fistula rates, as the latter was reported to be significantly associated with an elevated risk of subsequent stricture formation in a study by Schuman et al.[31] Moreover, technical modifications can be implemented, including the use of a spatulated anastomosis and Z-plasty at cranial and distal anastomotic sites, among others.[14,32]

Nonetheless, there is considerable heterogeneity in reconstructive techniques used between institutions, with large differences in complication rates between flap types. For partial defect reconstructions, there is debate in the current literature regarding the use of regional flaps (e.g., pectoralis major myocutaneous or myofascial flap, supraclavicular artery island flap) versus fasciocutaneous free flaps.[15,33,34] Similarly, there is debate regarding circumferential defect reconstructions between the use of free fasciocutaneous flaps versus jejunal free flaps.[14,16,35] Formulation of international guidelines on hypopharyngeal defect reconstruction may reduce undesired practice variation, which could potentially reduce complication rates and ultimately optimize HRQOL.

The current study had some limitations. First, due to the observational design, no causal inferences could be made. Second, the reconstructive groups were disparate in size, which is inevitably related to the less frequent incidence of patients who require a reconstruction following TLE. Alternatively, the group size differences might be explained by a difference in overall survival following surgery, as patients who required a reconstruction may have an unfavorable tumor stage or tumor site from baseline. Third, only 5 of 13 FACE-Q domains could be analyzed using multivariable analyses of clinical and demographic data due to skewed FACE-Q data. The observed rates of secondary outcomes were low, which limited the statistical analyses between the groups. Fourth, the FACE-Q was not developed for TLE patients in specific, but for a broader surgical HNC patient population. Development of novel TLE-specific PROMs could potentially allow for accurate assessment of aspects of HRQOL specific for TLE patients in future studies, which are not assessed by more general HNC PROMs. The LARY-Q is an example of such a potential PROM, although it has yet to be validated.[36] Additionally, we did not include an objective measurement tool for swallowing, e.g. using instrumental swallowing assessment, but the association of objective parameters with reported HRQOL is important to investigate. Finally, it is important to note the exploratory nature of the associations between patient-specific factors and HRQOL in this study. With the current sample size, heterogeneity of the included patients, and limited power, the analyses require replication in a larger cohort of survivors following TLE in future (multicenter) studies.

4.1 | Future recommendations

In future applications of the FACE-Q, it is important to account for non-random missing data in patients who are unable to eat, drink, or speak. In the current study we therefore added questions on (naso)gastric tube dependence and speaking inability. Furthermore, the addition of composite FACE-Q scores for functional and psychosocial domains, respectively, would potentially facilitate analyses of predictive clinical factors by prevention of multiple testing (type I error). The composite score should be complementary to the full questionnaire and should be used for research purposes. It should not replace the full questionnaire, as this could obscure relevant domains and hinder clinical interpretability.

Future studies should preferably examine long-term HRQOL scores in TLE patients in a longitudinal multicenter design and account for types of hypopharyngeal defect closure and occurrence of complications. Ultimately, there is a need for international consensus and reconstructive guidelines to reduce institutional variation in reconstructions, which could potentially optimize surgical outcomes and HRQOL.

5 | CONCLUSION

Few studies have assessed long-term survivorship HRQOL challenges following TLE using PROMs. HRQOL outcomes of patients who require hypopharyngeal defect reconstruction have been mostly neglected. In a unique cohort of only long-term TLE survivors, late negative consequences were common and were significantly associated with various functional and psychological HRQOL domains. The type of hypopharyngeal defect reconstruction was significantly related to several long-term HRQOL outcomes. Stricture occurrence was the only negatively associated factor for HRQOL scores. Efforts to reduce stricture rates to enhance reconstructive outcomes following total laryngectomy merit further research.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Anthony M. Tonsbeek https://orcid.org/0000-0002-9430-4878
Marc A. M. Mureau https://orcid.org/0000-0001-6941-7734

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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