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Title: A matched pair analysis of outcomes after stapler-assisted pharyngeal closure following laryngectomy

Short Title: Stapler-assisted pharyngeal closure following laryngectomy

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Abstract

Objective

To compare perioperative and oncological outcomes between stapler and manual closure in patients undergoing total laryngectomy for advanced endolaryngeal squamous cell carcinoma.

Methods

Patients with advanced endolaryngeal tumours operated between 2017 till 2023 were retrospectively dichotomised into stapler closure(SC) and manual closure(MS) cohorts and compared.

Results:

Seventy-one patients with a median age of 57 years were included in our study. The median surgical duration was 270 minutes for the MS cohort and 245 minutes for the SC cohort. The PCF rate was 6% less in the SC cohort. The estimated mean survival was not significantly different (54.5 months (95% CI 46.3-62.71) in the MS cohort vs 28.12 months (95% CI 23.6-32.63) in the SC cohort, p=0.79).

Conclusion:

Stapler closure can be used in endolaryngeal tumours, and it reduces operating time, thus facilitating efficient utilization of operation time with non-inferior oncological outcomes as compared to traditional manual closure.

Keywords: Laryngectomy, Laryngeal Cancer, Surgical Staplers, Squamous Cell Carcinoma of Head and Neck, Treatment Outcome.

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INTRODUCTION

Surgical treatment in the form of total laryngectomy is the treatment of choice for advanced laryngeal malignancies and in failed organ preservation strategies(1). Common complications following laryngectomy includes pharyngo-cutaneous salivary fistula (PCF), surgical site infections (SSI), cricopharyngeal spasm and atony and stoma associated complications including stomal stenosis and dehiscence. PCF, the most common complication, not only depends on the pharyngeal closure technique but is also influenced by the mucosal viability, prior chemoradiation history and nutritional status of the patient(2–4). Recent literature has shown a gradual decrease in the incidences of PCF from as high as 60-70% to 5-10%(5). Our prior data suggest an overall incidence of PCF in 16% of cases undergoing total laryngectomy and manual closure pharyngoplasty(6). Stapler-assisted closure, in both closed and semi-closed techniques, achieves a water-tight closures without contamination of pharyngeal secretion, with minimal trauma to remnant mucosa and thus reducing the incidence of PCF and SSI(7–9). Stapler assisted closure requires a prior margin assessment to establish a purely endolaryngeal extent since margin adequacy is crucial while engaging the stapler device(5,10).

Multiple studies in the literature have looked at functional aspects of stapler-assisted closure but bereft of an oncological safety profile(7,11–14). This study was designed to look at both the functional and oncological safety profiles of stapler-assisted pharyngeal closure compared with traditional manual closure as a matched pair analysis.

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Materials and methods

This retrospective matched-pair cohort study was conducted with prior institutional review board clearance (IRB Minute No 15485 (RETRO) dated 28.06.2023) and recruited all eligible patients with diagnosed advanced endo-laryngeal squamous cell carcinoma without pharyngeal mucosal extension between July 2017 and July 2023. The study included patients who underwent total laryngectomy in a primary or salvage setting in the Department of Head and Neck Surgery (Figure 1). All patients underwent clinico-radiological evaluation, multi-disciplinary team discussion and preoperative endoscopic disease assessment as a routine. Patients were staged as per American Joint Committee on Cancer (AJCC) 8th edition. An on-table endoscopic reassessment or direct laryngoscopy was performed under general anaesthesia prior to laryngectomy for reaffirming the disease extent. Following total laryngectomy traditional repair of the neopharynx was done using continuous Connell's stitch with 3-0 absorbable polyglactin suture material or 3-0 braided polyester suture material. Since March 2020, closed stapler closure technique was used when feasible and manual suture technique was used when oncological clearance is in doubt. Tracheoesophageal puncture (TEP) with voice prosthesis insertion was done as per the decision of the patient following voice rehabilitation counselling. Cricopharyngeal myotomy was done in all patients. Linear stapler 60mm TX60 with 4mm by 4.8mm reload (®Ethicon Endosurgery, Johnson & Johnson) was used in cases undergoing stapler closure.

Electronic medical reports of outpatient visits and inpatient records were scrutinised and those with endolaryngeal tumours were recruited to the study. Collected data parameters include

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patient general characteristics, laboratory investigations, surgery details, histopathological findings, adjuvant therapy details, post-operative details and followup of patient.

Operation time was defined as the duration between incision time and wound closure. PCF was suspected in the presence of progressive neck oedema or neck wound dehiscence with associated mucoid or mucopurulent discharge.

All cases were discussed in Multi-Disciplinary Tumor Board at each treatment decision phase starting preoperatively, prior to adjuvant therapy and at diagnosis of a suspected disease failure. Overall survival was defined as the period between the date of biopsy to the last follow up.

The patients were dichotomised based on the type of closure into two cohorts, namely stapler-assisted closure and manual closure. Both cohorts were matched in a 3:1 ratio for age, co-morbidities, salvage surgery and tumour stage, as these variables predominantly influence the outcomes in question. Data was collected on SPSS [IBM SPSS Version 20]. Continuous variables were compared with an independent sample t-test, and categorical variables were compared by a non-parametric independent sample median test. Statistical Analysis was done in SPSS and R [Version 4.3.1]. A two-sided p-value of < 0.05 was considered significant.

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RESULTS

Seventy-one patients were included in our study, with 53 undergoing manual suturing for pharyngeal closure and 18 patients undergoing stapler-assisted closure. The median age of the study population was 57 years. The mean age of patients in the stapler group was 58± 7 years, and that in the manual closure group was 57± 9 years (p: 0.98), Table 1. There was only one female patient in the study population who underwent manual closure. The majority of patients were in an advanced stage in the stapler group (III-39%, IVA-39%, IVB- 11%) as well as in the manual closure group (III- 31%, IVA- 50%, IVB- 6%).

Both the groups were matched in terms of age (p=0.45), gender (p=0.56), comorbidities (p=0.089), prior history of substance abuse and irradiation (p=0.08), laboratory and histopathological parameters. The majority of the patients (57% Vs 23%) who underwent manual closure had a prior history of radiotherapy, though it did not meet statistical significance. In the stapler closure group, it was noted 67% had thyroid cartilage involvement and 22% had cricoid cartilage invasion, but none of the patients had pre-epiglottic space invasion.

There were no stapler device-related technical failures in any patients who underwent stapler-assisted pharyngeal closure. None of the patients underwent change in the pharyngeal closure method following intraoperative assessment. Median operation duration was 270 minutes (IQR: 225-310 min) in manual suturing group compared to 245 minutes (IQR: 220-320 min) in stapler assisted closure (*p*: 0.50). The surgery costs incurred in stapler closure was 1.002 as that in manual closure. No cases of early-onset pharyngeal leaks were noted in either group within the first five days from surgery. The PCF rates were slightly higher in the manual suturing group

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as compared to stapler closure, although this difference was not of statistical significance (17% v/s 11% respectively, p: 0.55). There was no difference between the two cohorts in terms of duration of hospital stay, time taken for initiation of oral feeds, time taken for initiation of adjuvant therapy, operating time, cost of surgery, blood loss, (Table 2) Primary TEP with voice prosthesis insertion was done in three patients in the stapler group and none had TEP failures. One patient in the manual closure group required multiple sitting of oesophageal dilatation for swallowing difficulty. None of the patients in the stapler group had swallowing difficulty.

All patients in the stapler closure group had a clear margin on histopathological examination (n=18, 100%). Three (6%) patients had a positive margin in the manual closure group. Sixteen patients (30.2%) in the manual closure group underwent overlay flap reconstruction. Majority of them were sternocleidomastoid muscle (SCM) overlay flap (n=11, 21%) followed by four patients with pectoralis major pedicled flap and supraclavicular artery island flap (SCAIF) in one patient. Six patients (33.3%) in the stapler closure group underwent overlay flap, of these, three patients (17%) underwent SCAIF overlay, two underwent SCM flap, and one underwent a pectoralis major pedicled flap overlay. Twelve (67%) of the patients were closed without a flap cover.

With a median follow-up of 22.28 months in the study population, 19.7% of the patients developed disease recurrence. The estimated mean overall survival was 28.12 months (95% CI 23.6-32.63) for the stapler-assisted closure cohort and 54.5 months (95% CI 46.3-62.71) for manual closure cohort (p 0.79), with a comparable oncological outcomes and tumour control rates (Table 3).

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Eighty-three percentage (n=15) of the stapler closure patients and 76% (n=34) of the patients in manual closure group were disease free. One patient had a regional nodal recurrence and two patients had distant metastasis to lung in the stapler group compared to three (7%) local recurrences, five (11%) regional recurrence and two (4%) distant metastases in the manual closure group(Figure 2).

DISCUSSION

Mechanical stapling was initially used in abdominal surgeries. The earliest mention of the use of a stapler for laryngeal defect closure was in 1971(15). Mechanical stapling of pharyngeal defect can be either done by a closed or semi-closed technique. In the closed technique, the tracheal cut is made, and the laryngectomy specimen is completely skeletonised, separating it from the posterior pharyngeal/oesophageal wall, keeping only the mucosa intact. Vallecula mucosa is thinned and the epiglottis is lifted up with the help of a Babcock forceps or folded inside using a cricoid hook passed through the tracheal stump, before the stapler is engaged. While the closed method is technically easier, it is rather a blind procedure in terms of margin assessment, and care should be taken so that the nasogastric tube, if placed, or epiglottis should not come in the engagement line of the linear stapler(9). The semi-closed technique gives the advantage of real-time surgical margin assessment with the help of an endoscope and preventing entrapment of the epiglottis in the engagement line of the stapler. In this method, before engaging the stapler device, a small pocket is created in the mucosa of the vallecula, ideally in the midline, and an endoscope is introduced to assess the margins. The tip of the epiglottis is

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everted and the stapler device can be engaged achieving safe margins(7). We prefer doing a closed technique, having a safety margin assessment done using a direct laryngoscopy examination before the start of the procedure. This will avoid mucosal breach and help attain all the benefits of using a stapler closure. Thus, endolaryngeal tumours with or without minimal thyroid cartilage invasion are ideal candidates for stapler-assisted laryngectomy(16).

Stapler closure techniques have shown to improve PCF rates, decrease hospital stay and also achieve earlier initiation of oral feeds(17–19). Aires et al., in a systematic review of four studies noted the incidence of PCF among those undergoing stapler closure to be 8.7% compared to 22.9% in those undergoing manual closure(18). A similar incidence rate was noted for stapler closure in a recent meta-analysis by Chiesa-Estomba et al. (Stapler closure 9.5% v/s Manual closure 23.4%)(17). Similar results were found in our study where PCF was noted in nine (16.98%) of the 53 patients who underwent manual suturing and two (11.1%) among the 18 patients with stapler closure. Various techniques have been adopted to decrease the incidence of PCF such as tension-free manual closure techniques namely T-shaped closure or vertical closure and overlaying of a pedicled or a free flap.

In our study population, an overlay flap was used to secure the pharyngoplasty closure line as an added protection in 32.4% of patients. The SCM myogenous augmentation of the pharyngoplasty is advantageous in terms of shorter operation time as it belongs to the same field of surgery and is less bulky thus avoiding a tractional force on the suture line. However, this flap closure may be unreliable in salvage settings and on the side where neck dissection is performed. SCM flap was used for augmentation in 11 of the manual closure cases, of which one case had a PCF and in two patients of stapler closure. We also prefer de-epithelialized SCAIF as an overlay

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flap, as it is less bulky and reliable. Pectoralis major pedicled myogenous flap overlay is used in patients undergoing salvage laryngectomy with significant post-radiotherapy-related changes in the neck.

The stapling techniques attempt to eliminate the surgeon factor in pharyngeal closure and achieve a water-tight closure line. In addition, stapler closure prevents unduly manipulation of neopharyngeal mucosa thereby reducing mucosal trauma and vascular insufficiency and prevents contamination of the surgical site with pharyngeal secretions.

Moreover, stapler closure decreases surgery duration. The mean operating time saved in stapler closure was noted to be 40.67 minutes in a randomised control trial of 60 patients(11). Similarly, there was an 80 minutes operation duration advantage noted in the systematic review by Aires et al(18). We noted the median operating time was 25 minutes lesser in the stapler closure group compared to the manual closure group but it did not meet statistical significance (p: 0.5). Since stapler closure step is a one-step short procedure, in practice, the total procedure time is more meaningful than assessing only the time for pharyngeal closure. On considering the costs incurred, we have noted that the overall surgical costs were comparable. This could be due to the increased time taken for surgery, anaesthesia, and procedural charges in the manual closure group. In a prospective randomised control study by Ahmed et al., the costs incurred for stapler closure were 1.78 times that of manual closure technique(11). The same was not noticed in our study. This might be because the cost incurred by the device might be overcome by reduced surgical duration related and anaesthesia costs.

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Oncological safety is of paramount importance in malignancy resections. Most of the prior studies have not studied oncological margin safety and survival analysis for those undergoing stapler closure. Galli J et al. noted 4.3% of margins to be involved in their retrospective cohort of 46 patients undergoing stapler-assisted closure compared to 17.6% involved margin rate in those undergoing manual closure(12). Similarly, Babu S et al. in a retrospective study of 30 patients, noted 6.7% of the patients with involved margins(20). The present study noted three (5.7%) patients to have a positive margin in the manual closure group and none in the stapler closure group (*p*: 0.3). Mean lateral margins achieved were 13.11 ± 8.6 mm in the stapler closure group versus 10.0 ±7.87 mm in the manual closure group on the ipsilateral side of the tumour subsite (*p*: 0.16) and 18.61 ±7.52mm versus 16.64 ± 9.94 mm respectively on the contralateral lateral margin (p: 0.45). We also noted that neither thyroid cartilage (67%) nor cricoid cartilage (22%) involvement precluded from performing a stapler closure. However, stapler closure is avoided in cases of pre-epiglottic space involvement. The other reason for avoiding a stapler is the obvious involvement of the hypopharynx and extension of the tumour to the transitional zone of the larynx. Though we preferred to consider stapler closure in the salvage setting, only 22% had prior irradiation history compared to 45% in the manual closure group. This might have been due to the extra caution taken in this subgroup.

Although the present study was not able to find significant advantages for stapler closure over manual closure for oncological safety, we have noted stapler closure not to be inferior to manual closure in terms of margin safety, two-year mean survival(Figure 2) and surgical costs incurred. A long-term follow-up can give further insights into this aspect. There are a few specific considerations while performing stapler-assisted closure of neopharynx: (1) cricopharyngeal myotomy should be performed and the same can be made easy by stretching the

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pharynx over the indwelling nasogastric tube; (2) TEP and primary voice prosthesis insertion can be performed in primary setting using puncture set; (3) Inferior constrictor muscles are sutured over the neopharynx closure site, as second layer.

The present study has its own limitations. To begin with, the study is of a retrospective nature and more strict and phased time measurements may derive significant operation time differences between the two types of closure. Objective criteria for diagnosis of PCF were not available and hence some cases with minimal pharyngeal breach otherwise undiagnosed may have missed leading to underestimation of PCF rates. Since stapler closure was adopted recently in our unit, the follow up period is of lesser duration. Larger prospective and multicentre trials will be able to provide meaningful oncological outcome data for the safety of stapler closure post-laryngectomy.

CONCLUSION

Stapler-assisted neopharyngeal closure during laryngectomy appears to be oncologically safe comparable to manual suturing technique. Careful selection of patients with endolaryngeal disease with no extension to hypopharynx or pre-epiglottic space is mandatory for a good outcome following stapler assisted closure. There appears to be a reduction in duration of the surgery enabling better efficient utilisation of the operation theatre. PCF rates in the stapler closure group appear lower.

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Legends

Figure 1: Study flow chart.

Figure 2: Kaplan-Meier plots comparing stapler closure and manual closure groups.

Table 1: Comparison of Demographic details and tumour characteristics between stapler closure and manual closure groups.

Table 2: Comparison of Surgery parameters and functional outcomes between stapler closure and manual closure groups.

Table 3: Comparison of oncological outcomes between stapler closure and manual closure groups.

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Table 1: Comparison of Demographic details and tumour characteristics between stapler closure and manual closure groups.

Parameter	Stapler Closure Group (N=18)	Manual Closure Group (N=53)	*p*-value
Age, mean in years (SD)	58 (7)	57 (9)	
<55 years	6 (33%)	23 (43%)	0.45
>55 years	12 (67%)	30 (57%)	
Gender			
Male	18 (100%)	52 (98%)	0.56
Female	0 (0%)	1 (2%)	
Comorbidities			
No	12 (67%)	23 (43%)	0.088
Yes	6 (33%)	30 (57%)	
Prior Irradiation			
No	14 (78%)	29 (55%)	0.084
Yes	4 (22%)	24 (45%)	

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Substance Use History			
Former Smoker	10 (56%)	40 (75%)	0.19
Former Alcohol user	4 (22%)	13 (25%)	0.84
Smokeless Tobacco	6 (33%)	11 (21%)	0.28
Mean Haemoglobin in g/dL, (SD)	11.54 (1.55) g/dL	11.33 (1.37) g/dL	0.60
Mean serum Albumin in g/dL	3.79 (0.50)	3.87 (0.62)	0.68
Mean serum Creatinine in mg/dL	0.95 (0.23)	0.86 (0.17)	0.072
T-stage			0.94
T0	0 (0%)	1 (2%)	
T2	2(11%)	6 (12%)	
T3	8 (44%)	21 (40%)	
T4a	8 (44%)	24 (46%)	
N-stage			0.67

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N0	14 (78%)	35 (71%)	
N1	0 (0%)	1 (2%)	
N2a	0 (0%)	2 (4%)	
N2b	0 (0%)	4 (8%)	
N2c	2 (11%)	4 (8%)	
N3b	2 (11%)	3 (6%)	
Stage			0.83
0	0 (0%)	1 (2%)	
II	2 (11%)	6 (12%)	
III	7 (39%)	16 (31%)	
IVA	7 (39%)	26 (50%)	
IVB	2 (11%)	3 (6%)	
Grade of Differentiation			0.49
WDSCC	1 (6%)	6 (11.3%)	
MDSCC	15 (83%)	43 (81.1%)	
PDSCC	2 (12%)	4 (7.6%)	

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Lymphovascular Emboli (LVE)			
No	15 (83%)	44 (86%)	0.76
Yes	3 (17%)	7 (14%)	
Perineural Invasion (PNI)			
No	13 (72%)	34 (67%)	0.66
Yes	5 (28%)	17 (33%)	
Paraglottic Space Involvement			
No	3 (17%)	12 (24%)	0.54
Yes	15 (83%)	39 (76%)	
Pre-epiglottic Space Involvement			
No	18 (100%)	44 (86%)	0.097
Yes	0 (0%)	7 (14%)	
Thyroid Cartilage Involvement			
No	6 (33%)	29 (56%)	0.10

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Yes	12 (67%)	23 (44%)	
Cricoid Cartilage Involvement			
No	14 (78%)	36 (69%)	0.49
Yes	4 (22%)	16 (31%)	
Thyroid Gland Involvement			
No	17 (100%)	34 (83%)	0.069
Yes	0 (0%)	7 (17%)	

Abbreviations: SD-standard deviation,

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Table 2: Comparison of Surgery parameters and functional outcomes between stapler closure and manual closure groups.

Parameter	Stapler Closure Group (N=18)	Manual Closure Group (N=53)	*p*-value
Operating time, minutes (IQR)	245 (220-320)	270 (225,310)	0.5
Blood loss, mL (IQR)	300 (250-700)	400 (275-500)	0.89
Blood Transfusion			
No	17 (94%)	48 (91%)	0.80
Yes	1 (6%)	5 (9%)	
Flap Reconstruction			
None	12 (67%)	36 (68%)	0.18
Yes (as overlay)	6 (33%)	17 (32%)	
TEP-VP insertion			
No	15 (83%)	13 (25%)	<0.001
Yes	3 (17%)*	40 (75%)	
TEP Failure			
No	3 (100%)	36 (90%)	0.57

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Yes	0 (0%)	4 (10%)	
Hospital Stay (d)	5 (4,7)	5 (4,6)	0.27
Time to initiate oral feeds (d)	13 (8,18)	13 (11,15)	0.97
PCF			
No	16 (89%)	44 (83%)	0.55
Yes	2 (11%)	9 (17%)	

Abbreviation: IQR-inter quartile range, TEP-VP: Tracheoesophageal puncture with voice prosthesis, PCF: pharyngocutaneous fistula, d: day, *primary TEP

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Table 3: Comparison of oncological outcomes between stapler closure and manual closure groups.

Parameter	Stapler Closure Group (N=18)	Manual Closure Group (N=53)	*p*-value
Margin			
Negative	18 (100%)	50 (94%)	0.30
Positive	0 (0%)	3 (6%)	
Mean Lateral Margin			
Ipsilateral	13.11 ±8.60mm	10.0 ±7.87mm	0.16
Contralateral	18.61 ±7.52mm	16.64 ±9.94mm	0.45
Disease Status			
Disease free	15 (83%)	34 (64.5%)	0.56
Local Recurrence	0 (0%)	3 (5.7%)	
Regional Recurrence	1 (6%)	5 (9.4%)	
Distant Metastasis	2 (11%)	2 (3.6%)	
Second Primary	0 (0%)	1 (1.8%)	
Status Unknown	0 (0%)	8 (15%)	
Survival Status			

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Alive	14 (82%)	31 (69%)	0.29
Dead	3 (18%)	14 (31%)	
Death unrelated to disease	2 (66.7%)	3 (21%)	
Mean Follow up			
Overall Survival (months)	51 (95% CI: 43.25-58.84)	29 (95% CI: 24.16 – 33.18)	

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Summary:

What is already known:

- The technique would reduce operating time, minimise post-operative morbidity and help in early recovery.

What this paper adds to our understanding:

- Stapler-closure of laryngectomy defects is oncologically safe for endolaryngeal tumors.
- The technique is avoided when preepiglottic space is involved, while the involvement of paraglottic space, cricoid, or thyroid cartilage is not the contraindication for this technique.
- The post-operative surgical margin on histopathology specimens in stapler closure was statistically comparable to the manual closure technique. There was no difference in survival between the two groups.
- Primary tracheoesophageal puncture with voice prosthesis insertion is possible in stapler-assisted pharyngeal closure.

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Figure 1. Study FlowchartLarynx

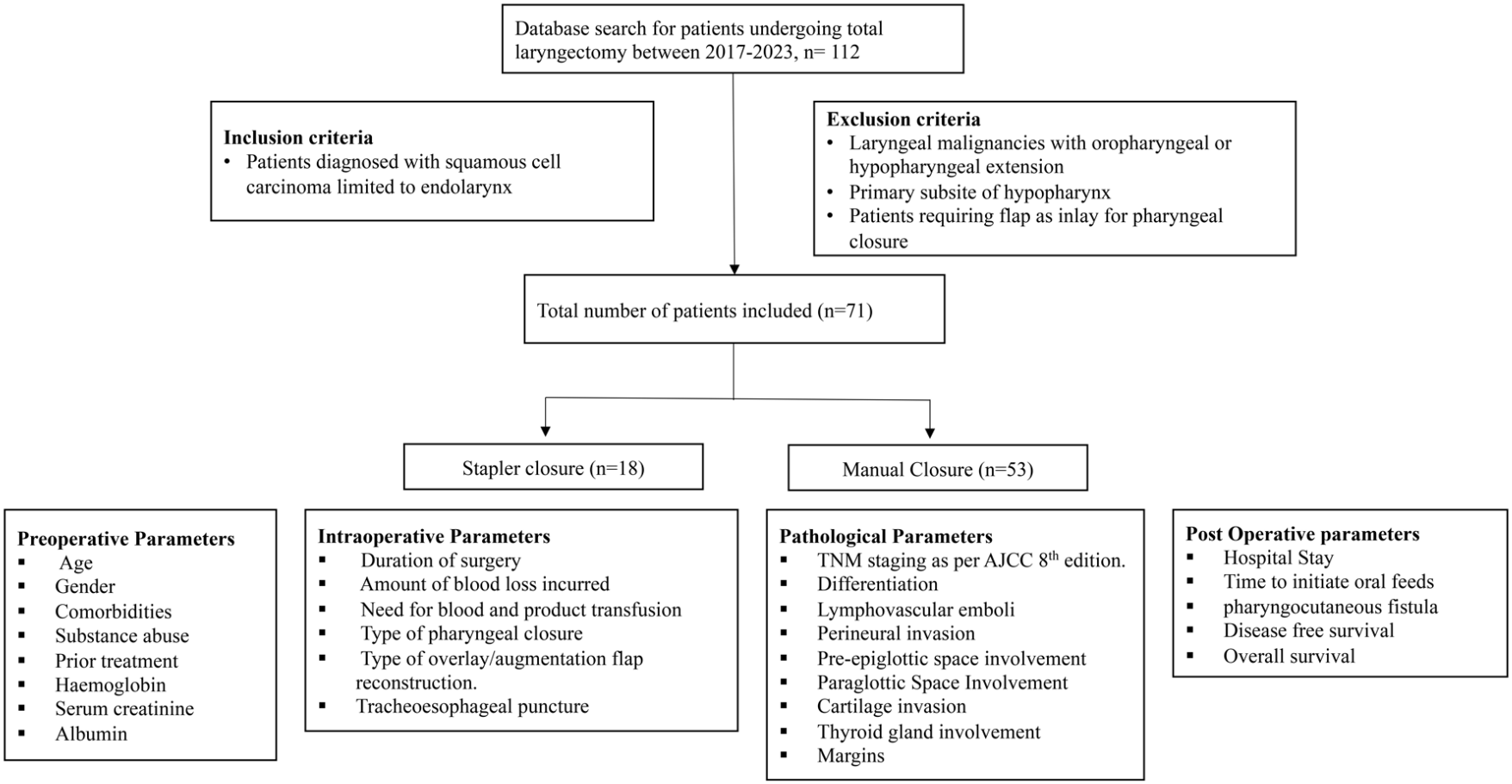

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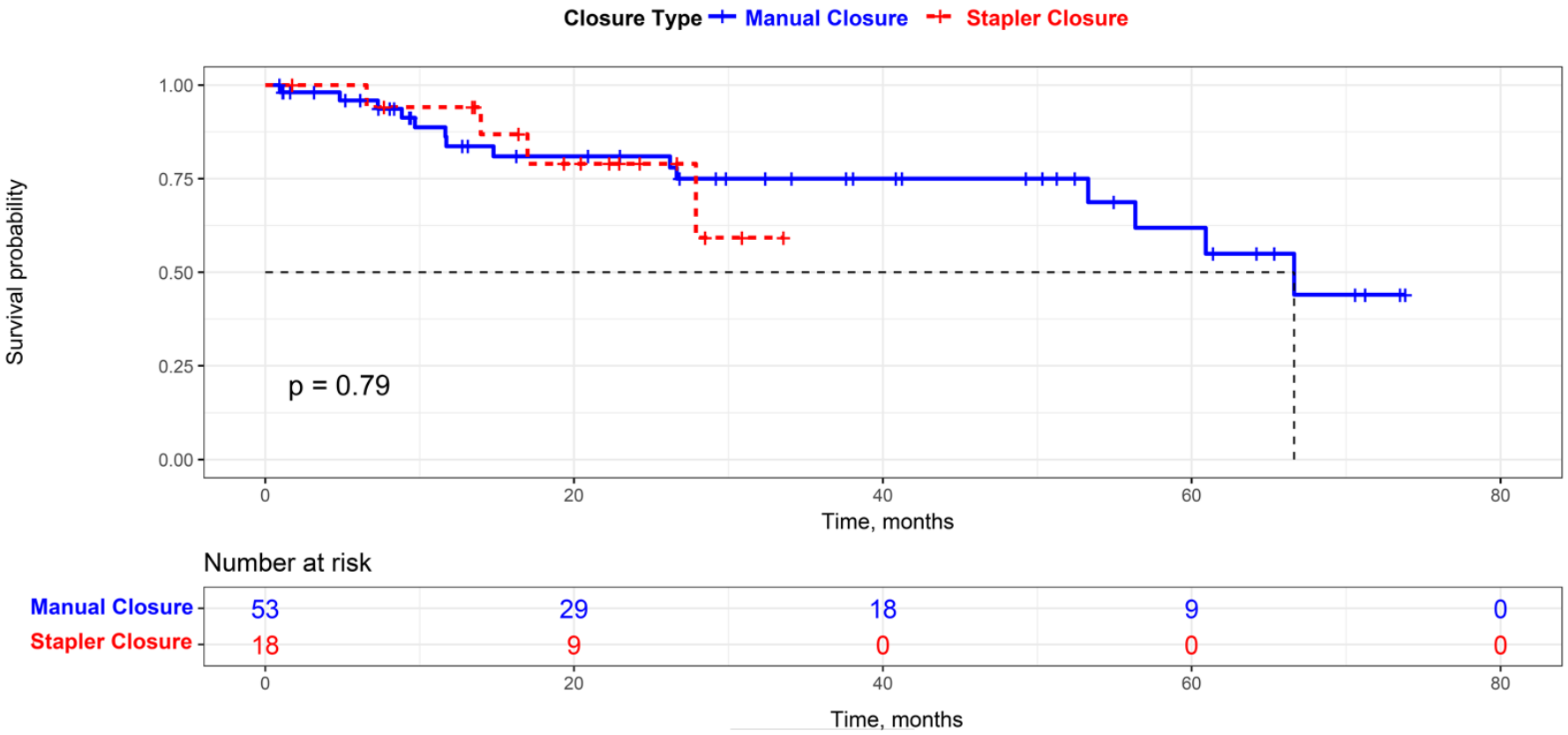
Figure 2 Kaplan-Meier plots for the study group



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