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## Research Article

# Outcomes following total Laryngectomy for Squamous Cell Carcinoma at a Singapore Tertiary Referral Centre

### Abstract

**Objectives:** To evaluate the clinical outcomes and complications following total laryngectomy in a South-East Asian Population.

**Design:** 10-year retrospective review of cases of total laryngectomy or laryngo-pharyngectomy.

**Main outcome measures:** 5-year overall survival (OS) and disease-free survival (DFS).

**Results:** 61 patients of which 55 (90%) had laryngeal SCC while 6 (10%) had hypopharyngeal SCC. Overall median survival was 85 months. 5-year OS and DFS for laryngeal SCC were 65% and 47% respectively while 5-year OS and DFS for hypopharyngeal SCC were both 33%. Most common cause of death was due to advanced cancer secondary to disease recurrence.

**Conclusion:** Although there is increasing tendency towards laryngeal preservation, surgery remains a safe treatment option for selected patients with laryngeal and hypopharyngeal SCC. In our local population, patients often present late with advanced cancer, as demonstrated by the high rate of emergency preoperative tracheostomy. However, there is no evidence that this affects survival.

## Introduction

Squamous cell carcinomas (SCC) of the larynx is the one of the most common cancers of the head and neck region, accounting for 2.4% of new malignancies and 0.7% of all cancer deaths worldwide every year [1]. Hypopharyngeal SCCs, although less common, carry a poor overall prognosis. Worldwide estimation of 5-year overall survival (OS) of laryngeal and hypopharyngeal cancers ranges from 32 to 70% and 7 to 35% respectively [2,3].

In Singapore, there has been an overall decline in incidence rates among males from 6.8 per 100,000 in 1968-1972 to 3.7 per 100,000 in 2003-2007. Laryngeal cancer constituted only 1.2% of all male cancer deaths in 2003-2007. As consistent with the global pattern, laryngeal cancer exhibits a marked male predominance. In 2003-2007, the male:female ratio was 10.7:1. The rates are significantly lower in Malay and Indian males compared to those with Chinese ethnicity [4].

Despite advances in chemoradiation, surgery continues to play an important role in the management of laryngeal and hypopharyngeal cancers. Laryngeal preservation techniques such as transoral resection with or without laser have been gaining in popularity but total laryngectomy (TL) remains the gold standard for advanced disease in selected patients.

In this context, the aims of our study was to evaluate our local patient population and report our clinical outcomes and complications following TL in a head and neck cancer unit of a tertiary hospital in Singapore.

## Methods

### Patients

The Department of Otolaryngology, Head and Neck Surgery at Tan Tock Seng Hospital is part of the National Healthcare Group, a regional health system for the central part of Singapore, serving a population of 1.5 million. A retrospective review of the departmental electronic database and clinical notes was undertaken between January 2000 and December 2010. The cases were reviewed for epidemiological data, tumour stage, and extent of surgery, complications and survival outcomes.

Patients who underwent TL for squamous cell carcinoma (SCC) of the larynx and hypopharynx were included, as well as those who had salvage TL for recurrence following primary radiotherapy (RT), chemoradiation (CRT) or transoral resection. Recurrence was defined as histological evidence of malignancy at least 12 months after completion of the primary treatment. Patients who had TL as part of tumour resection for cancers of other sites in the head and neck region such as thyroid, tongue base were excluded. The departmental database and patient clinical case notes were reviewed for epidemiological data, tumour stage, extent of surgery, complications and survival outcomes.

All patients were staged according to the American Joint Commission on Cancer (AJCC) staging system. If patients presented with acute airway distress, either preoperative tracheostomy or endoscopic tumour debulking would be performed. Preoperative staging of tumour was performed by endoscopy and radiological

imaging (CT neck and chest). The management of all patients were discussed at the weekly head and neck multi-disciplinary team (MDT) meeting. Patients were counselled regarding possible treatment options including methods of voice restoration and informed consent for surgery was obtained. Therapeutic and selective neck dissections were performed at the time of laryngectomy in patients with or without cervical node involvement respectively. Adjuvant RT or CRT were given to the primary site and neck based on clinicopathological risk factors including status of resection margins, perineural invasion, lymph node involvement and the presence of extra capsular nodal spread.

Patients were regularly followed up in the head and neck cancer clinics. The standard follow-up regime in our institution is monthly review in the 1<sup>st</sup> year, 2-monthly in the 2<sup>nd</sup> year, 4-monthly in the 3<sup>rd</sup> year, 6-monthly in the 4<sup>th</sup> year and yearly onwards from the 5<sup>th</sup> year onwards.

### Ethical considerations

NHG Domain Specific Review Board (DSRB) approval was granted for this retrospective review.

### Statistical analysis

Statistical analysis of the data was performed with Stata. All survival probabilities were estimated by using the Kaplan-Meier method from the day of surgery. Log-rank tests (Cox Mantel) were performed to compare differences between the estimates. Results were regarded as statistically significant if  $P \leq 0.05$ .

The 2 main survival end-points considered in our analysis were the cumulative 5-year overall survival (OS) and disease-free survival (DFS). Time was calculated from the date of diagnosis to the event of interest, which was death (due to any cause) or date last known alive for OS, and first treatment failure, defined as either disease or death, for DFS. Mean survival period, together with standard error (SE) and 95% confidence interval (95% CI) were also calculated.

## Results

### Patient population

The review period spanned 10 years. 61 patients (60 males, 1 female) fulfilled the inclusion criteria for this study. The median age of the patients was 66 years (range 37-88 years). Eighty-seven percent of the patients were Chinese, followed by Malays at 7%, Indians 5% and Eurasians 1%. Seventy-seven percent of the patients had a positive history of smoking while 18% had a positive history of alcohol consumption. Twenty-five patients (41%) had a preoperative tracheostomy before definitive surgery while only 1 patient had endoscopic tumour debulking, thus avoiding tracheostomy.

The median post-operative follow-up period was 25 months (range 1-132). Patients stayed in hospital for a median of 19 days (range 9-120 days).

Fifty-five (90%) patients were diagnosed with laryngeal SCC, out of which 23 (42%) had glottic tumours, followed by 21 (38%) supraglottic tumours, 3 (5%) subglottic tumours and 8 (15%) transglottic tumours. Only 6 patients (10%) had hypopharyngeal SCC.

**Table 1** represents the stage of disease at presentation. Overall, 52 patients (85%) presented with either T3 or T4 SCC. The remaining 9 patients (15%) had T2 tumours at presentation, of which 7 out of 9 patients had previously undergone RT, CRT or transoral resection.

### Treatment

Of the 42 patients (69%) who had surgery as the primary treatment modality, 38 had TL including 1 patient who had a total glossectomy while 4 had total laryngo-pharyngectomy. Thirty-two patients subsequently had adjuvant RT while 4 had adjuvant CRT.

The remaining 19 patients (31%) had salvage surgery of which 8 had previously been treated with CRT and 11 with RT which also include 2 patients with prior transoral resection. Of these, 16 had TL, 2 had horizontal partial laryngectomies (1 supracricoid laryngectomy, 1 supraglottic laryngectomy) with completion laryngectomies at a later date, and 1 had total laryngo-pharyngectomy.

Out of the cohort, 5 patients had flap reconstruction (3 pectoralis major flaps, 1 anterolateral thigh flap, and 1 deltopectoral flap and jejunal free flap). 59 patients (97%) had neck dissections at the time of laryngeal resection.

### Post-operative complications

Overall, there were low rates of post-operative complications amongst the cohort.

Pharyngocutaneous fistula (PCF) was the most common post-operative complication, occurring in 8 patients (13%). Five cases were from the salvage surgery group who all did not have prior flap mucosal reconstruction, and 3 cases from the primary surgery group of which only 1 had a prior flap mucosal reconstruction. **Table 2** shows the fistula rates for primary versus salvage surgery groups while **Table 3** shows the fistula rates for primary mucosal closures and flap mucosal closures.

**Table 1:** Clinical stages of laryngeal and hypopharyngeal cancers at presentation.

Larynx (n=55)	Untreated				Previously treated			
	T2	T3	T4	Total	T2	T3	T4	Total
N0	0	2	12	14	5	3	5	13
N1	0	2	3	5	1	1	0	2
N2	1	2	15	18	1	0	2	3
<b>Total</b>	<b>1</b>	<b>6</b>	<b>30</b>	<b>37</b>	<b>7</b>	<b>4</b>	<b>7</b>	<b>18</b>
Hypopharynx (n=6)	Untreated				Previously treated			
	T2	T3	T4	Total	T2	T3	T4	Total
N0	0	0	2	2	0	0	1	1
N1	0	0	1	1	0	0	0	0
N2	1	0	1	2	0	0	0	0
<b>Total</b>	<b>1</b>	<b>0</b>	<b>4</b>	<b>5</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>1</b>

**Table 2:** Fistula rates for primary versus salvage surgery groups.

Group	Number of cases of pharyngocutaneous fistula	Primary mucosal closure	Flap mucosal closure	Fistula rate (%)
Primary	3	2	1	7 (3 out of 42)
Salvage	5	5	0	26 (5 out of 19)

Four patients subsequently required flap repair for closure which included 1 patient who had 3 flap procedures due to recurrent wound breakdown. The other 4 cases resolved with conservative management.

The details of the rest of the post-operative complications are shown in [Table 4](#).

### Voice rehabilitation

Twenty-eight (46%) patients opted for the Tracheoesophageal Voice Prosthesis (TEP) whereby the puncture was performed secondarily in all but 1 case. Four patients (7%) had the electrolarynx while 29 patients (47%) did not have any final voice rehabilitation.

### Overall survival outcomes

The overall median survival period following TL was 85 months.

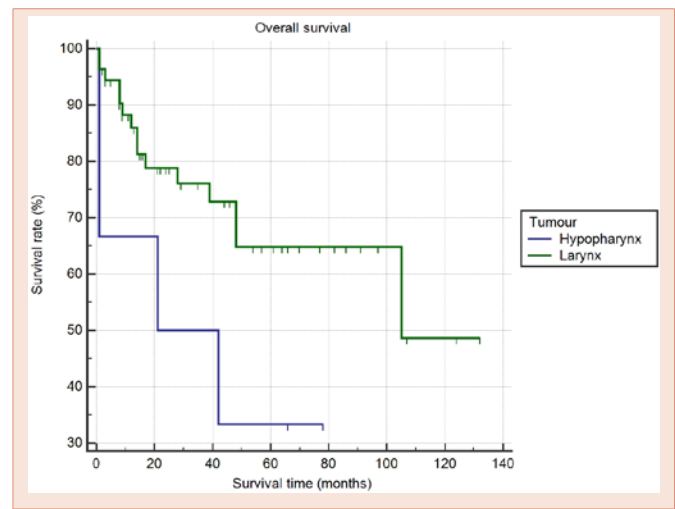
The 5-year OS and DFS for laryngeal SCC were 65% and 47% respectively while the 5-year OS and DFS for hypopharyngeal SCC were both 33%. ([Figures 1,2](#))

The 5-year OS for the primary and salvage TL groups were 59% and 63% respectively while the 5-year DFS for the primary and salvage TL groups were both 45%. There was no statistical difference ([Figures 3,4](#)).

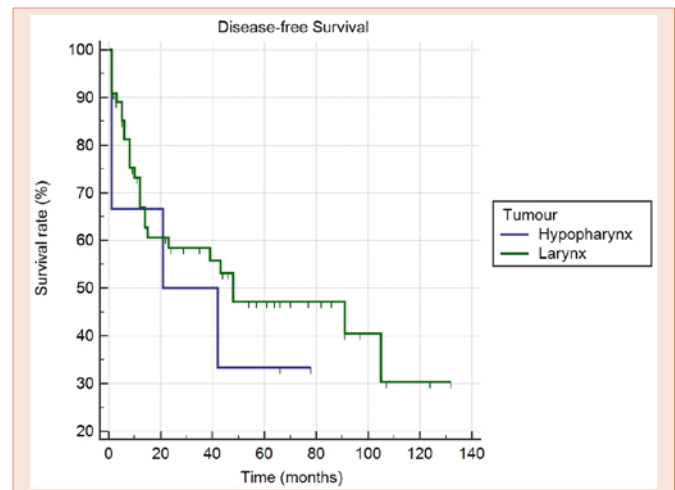
In terms of laryngeal subsites, the 5-year OS for glottic and supraglottic tumours were 73% and 56% respectively while the 5-year DFS for glottic and supraglottic tumours were 58% and 37% respectively. There was no statistical difference. No comparison could be made for transglottic and subglottic tumours due to small numbers.

### Disease recurrence

Nineteen patients (31%) had recurrent disease after surgery, of which 8 (13%), 3 (5%) and 14 (23%) patients developed local, regional and distant recurrence respectively. All were cases of laryngeal SCC. 3



**Figure 1:** Overall survival for laryngeal and hypopharyngeal cancers.



**Figure 2:** Disease-free survival for laryngeal and hypopharyngeal cancers.

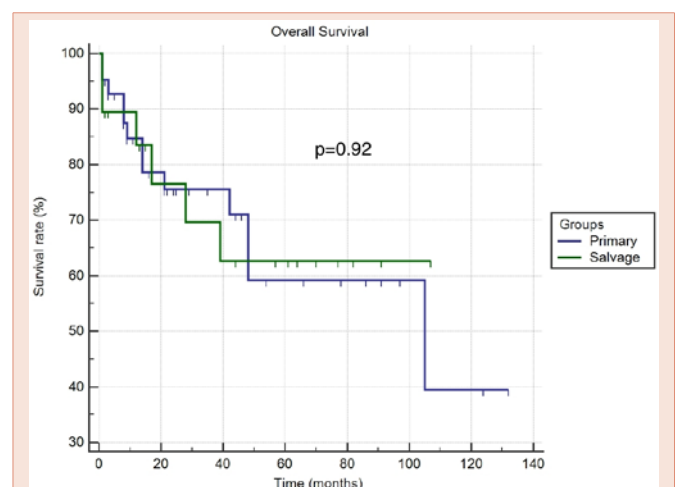
**Table 3:** Fistula rates for primary and flap mucosal closures.

Method of mucosal closure	Numbers	Fistula rate (%)
Primary mucosal closure	56	13 (7 out of 56)
Flap mucosal closure	5	20 (1 out of 5)

**Table 4:** Incidence of post-operative complications and management.

Complication	Primary	Salvage	Total (%)	Management
Pharyngocutaneous fistula	3	5	8 (13)	4: flap closure 4: conservative
Chyle leak	3	2	5 (8)	All conservative
Tracheo-stomal stenosis	5 (4 had adjuvant RT)	0	5 (8)	4: stomaplasty
Carotid/Internal jugular vein blowout	0	3	3 (5)	2: ligated 1 carotid blowout: fatal
Neopharyngeal & oesophageal strictures	2 (primary mucosal closure with adjuvant RT)	0	2 (3)	Endoscopic dilatation

RT: radiotherapy.



**Figure 3:** Overall survival for primary and salvage laryngectomy groups.

patients developed recurrence at all sites. The median times for local, regional and distant recurrence were 7, 8 and 12 months respectively.

For local recurrences, there were 5 glottic tumours and 3 transglottic tumours. Interestingly, out of the 8 patients who developed local recurrence, there were 4 patients each from the primary and salvage surgery groups. In addition, there were 4 cases each for peristomal and pharyngeal/base of tongue recurrences. Out of the 4 patients with peristomal recurrences, 2 (50%) had a preoperative tracheostomy.

For regional recurrences, there were 2 transglottic tumours and 1 glottic tumour.

For distant recurrences, there were 7 supraglottic tumours, 5 glottic tumours and 2 transglottic tumours.

### Causes of death

The most common cause of death was due to advanced cancer secondary to disease recurrence (Table 5).

### Discussion

#### Survival outcomes

In this review, over a 10-year period, 60 males and 1 female were treated for laryngeal and hypopharyngeal SCC. The overall mean survival period following surgery was 85 months. Nineteen patients (31%) died during the follow-up period, of which the majority (47%) was due to advanced cancer.

The 5-year OS and DFS for laryngeal SCC were 65% and 47% respectively which are comparable or better as compared to other studies in the literature (Table 6). This could be attributed to close clinical follow-up, lifestyle changes (smoking and alcohol withdrawal) and early treatment for disease recurrence. The small number of hypopharyngeal SCC who underwent TL in this study was a reflection of the practice that most cases underwent organ preservation therapy with CRT rather than primary surgery as first-line treatment.

Similarly, our survival outcomes for cases of salvage TL were comparable with other studies in the literature (Table 7).

In terms of laryngeal subsites, there were no statistically significant differences in survival although the 5-year OS for glottic tumours (73%) appeared to be better as compared to supraglottic tumours (56%). This finding was also observed in the study by Papsdas et al. [5]. This could be explained by the fact that patients with glottis tumours generally present earlier with hoarseness with lower incidence of nodal metastases as compared to patients with supraglottic tumours who generally remain symptom-free till disease is more advanced with higher incidence of nodal metastases.

#### Preoperative tracheostomy (POT) and local/peristomal recurrence

There has been a move away from POT towards trans-oral debulking in recent years which has been driven by earlier studies which showed that POT was associated with a higher risk of peristomal recurrences [15,16]. However, tracheostomy is often the easiest way to secure a critical airway. Trans-oral debulking can be limited in its

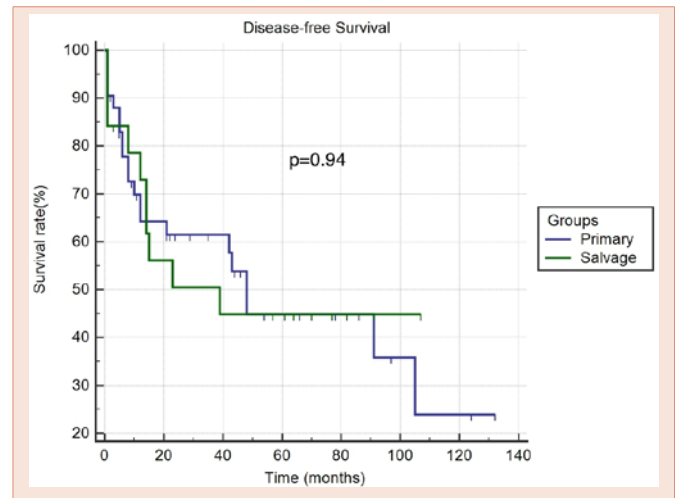


Figure 4: Disease-free survival for primary and salvage laryngectomy groups.

Table 5: Causes of death.

Cause of death	Number of deaths (%)
Advanced cancer	9 (47)
Pneumonia	5 (26)
Carotid blowout	2 (11)
Sepsis	2 (11)
Stroke	1 (5)
<b>Total</b>	<b>19 (100)</b>

Table 6: Comparison of survival outcomes for laryngeal and hypopharyngeal cancers.

Series	Cancer	Numbers	5-year OS (%)	5-year DFS (%)
Papadas et al. 2010 <sup>5</sup>	Larynx	133	45	53
	Larynx	90	67	-
Hall et al. 2003 <sup>6</sup>	Hypopharynx	57	37	-
Varghese et al. 2009 <sup>7</sup>	Larynx	99	35	-
	Hypopharynx	63	19	-
Ampil et al. 2004 <sup>8</sup>	Larynx	28	43 (7-year)	30 (7-year)
Francis et al. 2014 <sup>9</sup>	Larynx	30	60	60
Leong et al. 2012 <sup>10</sup>	Larynx & Hypopharynx	71	-	54
Pezier et al. 2013 <sup>11</sup>	Larynx	60	36	-
	Larynx	55	65	47
Our series	Hypopharynx	6	33	33

Table 7: Comparison of survival outcomes for salvage laryngectomy.

Series	Initial treatment	Numbers	5-year OS (%)	5-year DFS (%)
Fowler et al. 2006 <sup>12</sup>	RT/CS/RT+CS	61	65	-
Putten et al. 2011 <sup>13</sup>	RT/CRT	120	50	57
Weber et al. 2003 <sup>14</sup>	RT/CRT/IC+RT	129	72 (2-year)	-
Our series	RT+/-TOR /CRT	19	63	45

CRT: chemoradiation, CS: conservation surgery, IC: induction chemotherapy, RT: radiotherapy, TOR: transoral resection.



application as it requires specialist equipment and experience, both in surgical and anesthetic fields. In addition, it has the potential disadvantage of post-operative oedema and rapid tumour regrowth necessitating repeat debulking [17].

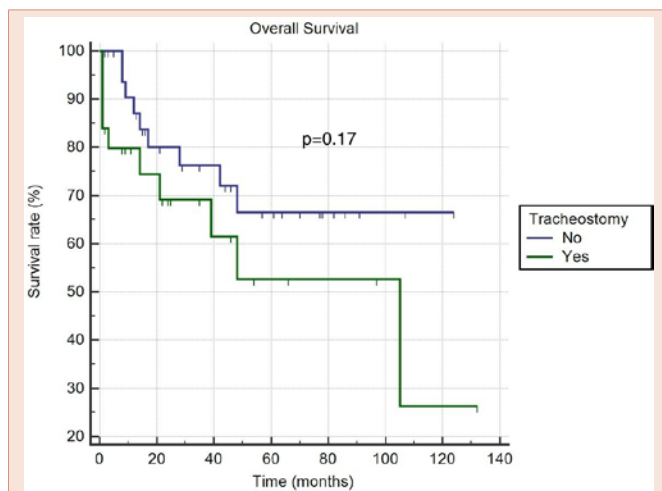
Peristomal recurrence following total laryngectomy occurs in approximately 2-15% of cases and has been defined as “a diffuse infiltration of neoplastic tissue at the junction of the trachea and skin” [18]. However, the exact understanding of how peristomal recurrence occurs has been difficult to establish and it is difficult to distinguish from spread from local paratracheal lymph nodes and the thyroid gland [19].

In our study, 25 patients (40%) presented with acute airway distress requiring POT before TL. The relatively high rate of emergency POT is attributed to the nature of our local population where patients often present late with advanced laryngeal and hypopharyngeal cancer. Out of these 25 patients, 4 patients (16%) developed local recurrences which included 2 (8%) peristomal recurrences. Of the 36 patients that did not require POT, 4 (11%) developed local recurrences which included 2 (6%) peristomal recurrences. There is no statistical difference in survival outcomes between both groups (Table 8, Figures 5,6). However, it is important to note that the stage of disease at presentation is a confounding factor.

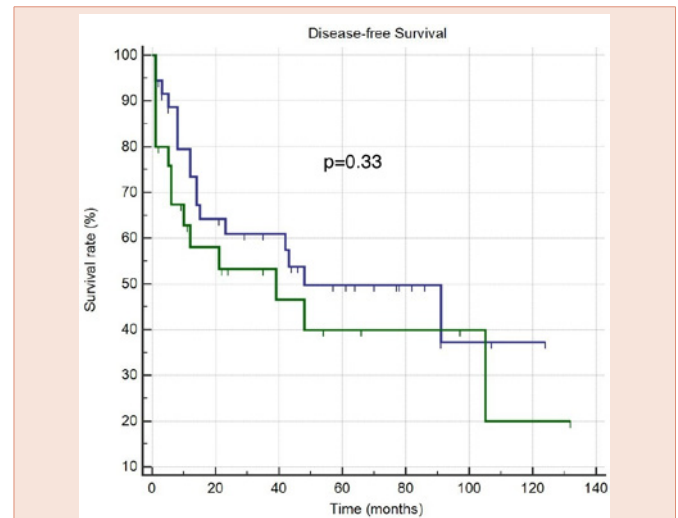
This issue remains controversial as more recent studies have suggested that POT may not lead to poor oncological outcomes<sup>20</sup>. In a recent study by Pezier et al., of 60 patients undergoing primary TL for laryngeal SCC, there were no statistical difference in the 5-year OS and local recurrence-free survival of the patients undergoing POT and those who did not [21].

**Table 8:** Comparison of survival outcomes for cases with and without pre-operative tracheostomy.

Pre-operative tracheostomy)	5-year OS (%)	5-year DFS (%)
Yes	53	40
No	67	50



**Figure 5:** Overall survival for cases with and without preoperative tracheostomy.



**Figure 6:** Disease-free survival for cases with and without preoperative tracheostomy.

### Pharyngocutaneous fistula (PCF)

The most common major wound complication following TL is the development of a PCF. A meta-analysis by Paydarfar et al., identified prior radiotherapy, prior tracheostomy, and postoperative serum haemoglobin level <12.5g/dL as the only independent risk factors for PCF [22]. The increased incidence of PCF is increased in salvage TL is due to the impaired healing characteristics of irradiated tissues. The addition of chemotherapy further exacerbates the obliterative endarteritis and fibrosis induced by RT. Development of a PCF is associated with delay in adjuvant treatment, prolonged hospital stay, requirement for reoperation in a highly comorbid patient group, and mortality from carotid blowout or aspiration pneumonia [23].

In our study, out of the 8 patients with PCF, 5 patients were from the salvage surgery group, of which 3 had prior RT and 2 had prior CRT, giving a fistula rate of 26% as compared to 7% for the primary surgery group. This group also included one patient who subsequently had a carotid artery blowout and another case with an internal jugular vein blowout which were both successfully ligated. All did not require a flap for pharyngeal mucosal closure at the time of surgery.

Several observational studies have investigated the role of prophylactic vascularized flaps to aid pharyngeal closure following STL, with variable results [24-26]. In a recent systemic review by Sayles et al, they showed that the PCF incidences following primary TL, salvage TL and salvage TL with flap-reinforced closure are 14.3%, 27.6% and 10.3% respectively. CRT is associated with a higher PCF incidence of 34.1%, compared to 22.8% for RT alone. Hence, they concluded that prophylactic flaps should be offered in salvage cases, especially for patients who have failed CRT [27].

### Conclusion

The results of this study represent the clinical outcomes of a cohort of patients from a tertiary general hospital in Singapore. This is the first study of a cohort of patients in a South-east Asian population.

We have demonstrated similar or better survival rates in comparison to other published studies. It is also clear that emergency preoperative tracheostomy has no effect on survival or local disease recurrence in our population.

While there is an increasing tendency towards laryngeal preservation with CRT, total laryngectomy remains the gold standard in patients with advanced disease. The data presented improves our ability to counsel patients regarding important therapeutic decisions and end-of-life issues.

## Summary

- Worldwide estimation of 5-year overall survival (OS) of laryngeal and hypopharyngeal cancers ranges from 32 to 70% and 7 to 35% respectively.
- Despite advances in chemoradiation, surgery continues to play an important role in the management of laryngeal and hypopharyngeal cancers.
- Emergency preoperative tracheostomy has no effect on survival or local disease recurrence.
- While there is an increasing tendency towards laryngeal preservation with chemoradiation, total laryngectomy remains the gold standard in patients with advanced disease.

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