Introduction

Squamous cell carcinomas (SCC) of the larynx is 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, and 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 1st year, 2-monthly in the 2nd year, 4-monthly in the 3rd year, 6-monthly in the 4th year and yearly onwards from the 5th 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 ≤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 included 2 patients with prior transoral resection. Of these, 16 had TL, of which only 1 had a prior flap mucosal reconstruction. 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.

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

| Larynx (n=55) | Untreated | Previously treated |
|---------------|-----------|-------------------|
| T2 (1) | T3 (2) | T4 (13) | Total (16) | T2 (4) | T3 (5) | T4 (18) | Total (37) |
| N0 (1) | 0 | 2 | 12 | 14 | 5 | 3 | 5 | 13 |
| N1 (1) | 0 | 2 | 3 | 5 | 1 | 1 | 0 | 2 |
| N2 (1) | 1 | 2 | 15 | 18 | 1 | 0 | 2 | 3 |
| Total (1) | 1 | 6 | 30 | 37 | 7 | 4 | 7 | 18 |

| Hypopharynx (n=6) | Untreated | Previously treated |
|-------------------|-----------|-------------------|
| T2 (1) | T3 (1) | T4 (5) | Total (7) | T2 (1) | T3 (3) | T4 (5) | Total (9) |
| N0 (1) | 0 | 0 | 2 | 2 | 0 | 0 | 1 | 1 |
| N1 (1) | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| N2 (1) | 1 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |
| Total (1) | 1 | 0 | 4 | 5 | 0 | 0 | 1 | 1 |

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) |

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.

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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.

| 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)  |

| Complication                          | Primary | Salvage | Total (%) | Management                        |
|---------------------------------------|---------|---------|-----------|-----------------------------------|
| Phonaryngocutaneous 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.
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 Papadas 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
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[20]. 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            |

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].

**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 obliteratorative 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].

**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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