

The Incidence of Thyroid Gland Invasion in Patients with Carcinoma of the Larynx who Underwent Total Laryngectomy

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ABSTRACT

Introduction: Total thyroidectomy or at least hemithyroidectomy is routinely performed alongside total laryngectomy in patients with advanced carcinoma of the larynx. Life-threatening hypocalcaemia and hypothyroidism are common sequelae especially with adjuvant radiation. The study aims to determine the incidence of microscopic thyroid gland invasion and challenge the idea of routine thyroidectomy in advanced carcinoma of the larynx. **Materials and Methods:** This study was a retrospective observational study. It was done in two tertiary centres in Malaysia between 2003 and 2013 for a total duration of 11 years. A total of 72 patients were included in this study. Data from medical records, operative notes, and histopathological reports were collected and analysed. **Results:** Three patients (4.2%) had the presence of microscopic thyroid gland invasion. There were no significant associations between microscopic thyroid gland invasion and tumour subsites, histological types of a tumour nor T staging ($p>0.05$) **Conclusion:** The incidence of microscopic thyroid gland invasion in advanced carcinoma of the larynx is low, disavowing routine thyroidectomy. **Limitations:** Some factors such as cartilage invasion on CT imaging and central lymph node treatment were not considered due to limitations in case documentation.

KEYWORDS: Thyroidectomy, Cancer of the Larynx, Laryngectomy.

INTRODUCTION

Total laryngectomy has stood the test of time as an oncologically safe surgery in the treatment of advanced carcinoma of the larynx since it was introduced by Billroth in the year 1880. The surgical management of the lymphatic and non lymph-bearing structures, however, is a matter of debate. Our centre practices routine selective neck dissections (Level 11a, 11b and 1V) and at least hemithyroidectomy alongside total laryngectomy for patients with advanced carcinoma of the larynx.

Thyroid gland being an adjacent organ to the larynx, can be contiguously or non-contiguously invaded by

the malignant tumour which occurs via lymphatic or vascular metastasis.² Many studies have analysed various factors that could influence the invasion of thyroid gland in laryngeal cancer. Recent meta-analysis by Mendelson et al has concluded that thyroidectomy may only be required during total laryngectomy for transglottic tumours, subglottic tumours and tumour with subglottic extension of more than 10mm.³

Total laryngectomy with total thyroidectomy often results in hypothyroidism and hypoparathyroidism requiring life-long thyroid hormone replacement and calcium replacement.⁴ Even if total laryngectomy and hemithyroidectomy is performed, a 23-percent risk of hypothyroidism still exists.⁵ If radiotherapy is to be given to these patients, a substantial increase of the incidence of hypothyroidism will be found at around 59-89 percent.^{4,6,7}

The need for daily thyroid hormone replacement will be very troublesome in some patients especially elderly patients who tend to forget to take their

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medication. As a result, life-threatening hypothyroidism may happen leading to heart failure and arrhythmias. Additionally, they require long term physician follow up and cost of care will increase.

Objective

The main objective of this study was to determine the incidence of thyroid gland invasion and challenge the idea of routine thyroidectomy in advanced carcinoma of the larynx. This study will study its association with various factors including anatomical subsite, clinical or radiological thyroid invasion, T staging and tumour differentiation.

Design

This was a retrospective observational study conducted in two tertiary centres in Malaysia. Hospital Pulau Pinang is a tertiary hospital receiving referrals from east and west coast of Malaysia while Universiti Kebangsaan Malaysia receives referrals from central and southern parts of Malaysia.

Settings

The incidence of thyroid gland invasion in advanced carcinoma of the larynx was evaluated in a retrospective observational study conducted at Department of ORL-HNS, Universiti Kebangsaan Malaysia Medical Centre and Hospital Pulau Pinang from January 2003 until December 2013 (11 years). This study was approved by the institutional and National Ethical Review Board along with its financial support on the 6th of June 2013.

Patients

Patients who satisfy inclusion and exclusion criteria (Table 1) were recruited for the study. Demographic data including patients’ age, gender and race were obtained from their medical records. Information regarding the clinical and radiological staging, primary subsite of the tumour, operative finding and extent of surgical resection was obtained. The histopathologic reports were also traced and information regarding microscopic thyroid gland invasion, histological type of tumour, degree of differentiation and pathologic staging was collected. The radiological and histopathological reports were traced from patients’ medical records.

Table 1: Inclusion and exclusion criterias

Inclusion criteria	All patients that underwent total laryngectomy in Hospital Pulau Pinang and Universiti Kebangsaan Malaysia Medical Centre from 2003-2013
Exclusion criteria	Patient who underwent total laryngectomy for other indications besides malignancy (eg. benign tumour, intractable aspiration). Patient with primary thyroid gland malignancy. Thyroid gland was not surgically removed Unavailable medical records

Cancer staging was based on either radiological reports or final pathological report following surgical resection (latter takes precedence when available). Tumour was staged based on American Joint Committee for Cancer 2007.

All data were analyzed using Statistical Products and Service Solution (SPSS) software version 22.0. For demographic data, descriptive analysis like percentage was used. Age was presented as median with minimum and maximum range. Categorical data were analyzed using Chi-square test.

Main Outcome Measures

The main outcome measure in this study was presence of microscopic thyroid gland invasion in the histopathological specimens of dissected thyroid glands that were concurrently removed during total laryngectomy. Other outcome measures analysed include tumour anatomical subsite, presence of clinical or radiological thyroid gland invasion, T staging and tumour differentiation.

RESULTS

Demographic characteristics

A total of 88 total laryngectomies were done for laryngeal malignancy in the study period at these 2 centres. 72 cases were included in this study. 10 of the cases were excluded due to preservation of both thyroid lobes in the surgery. Another 6 cases were excluded as we were unable to trace the histopathological reports and medical records.

The age of the patients ranged from 45 to 89 years (average mean age 65.2 years), with a male predominance (male 95.8% vs female 4.2%) preponderance. As for ethnicity; 43 (59.7%) were Chinese, 22 (30.6%) were Malay, 3 (4.2%) were Indian, 1(1.4%) was Punjabi and 3 (4.2%) were Indonesians. Table 2 summarizes the demographic characteristics of our study population.

Table 2: Demographic characteristics of study population

Demographic characteristics	n	%
Age	72	100
41-50 years	5	7.0
51-60 years	15	20.8
61-70 years	33	45.8
71 years and above	19	26.4
Gender	72	100
Male	69	95.8
Female	3	4.2
Race	72	100
Chinese	43	59.7
Malay	22	30.6
Indian	3	4.2
Punjabi	3	4.2

Pathological tumour characteristics

36 patients were at T4 stage of the tumour, 33 patients at T3 stage and 3 were at T2 stage. All of the T2 cases were patients who had salvaged laryngectomy after radiation had failed.

Tumour subsite distribution was as follows: supraglottis 6.9% (5 patients), glottis 12.5% (9 patients), subglottis 5.6% (4 patients) and transglottis 75% (54 patients). Total thyroidectomy was performed in 46 patients (63.9%) and hemithyroidectomy in 26 patients (36.1%).

Of all the laryngeal carcinoma, 68 cases (94.4%) of the carcinoma were squamous cell carcinoma. Among them, 59.7% was well differentiated carcinoma, 30.6% was moderately differentiated carcinoma and 4.2% was poorly differentiated carcinoma. The other 4 cases (5.6%) were malignant spindle cell tumour, basaloid squamous cell carcinoma, adenocystic carcinoma and adenosquamous carcinoma.

Microscopic thyroid gland invasion

69 patients (95.8%) who had their thyroid gland removed by means of either hemithyroidectomy or

total thyroidectomy did not have thyroid gland invasion (TGI) from laryngeal carcinoma. Interestingly, among the 69 patients, 3 patients were found with synchronous papillary carcinoma of the thyroid in their thyroid specimen. In all these 3 cases, the preoperative radiological imaging showed presence of a suspicious thyroid nodule.

Microscopic thyroid gland invasion (TGI) was present in 3 patients (4.2%). The first patient was a 74-year old Chinese man who presented with hoarseness and swelling over the anterior neck. He was diagnosed to have T4 transglottic tumour in which the cricoid cartilage was infiltrated with the tumour. He later had stomal recurrence 6 months post total laryngectomy which was managed with wide local excision and pectoralis major myocutaneous flap reconstruction.

The second patient was a 52-year old Indian lady who presented with reduced effort tolerance for 1 year duration. There was a subglottic mass seen 2.5cm from the vocal cord and histopathological examination showed adenoid cystic carcinoma. She underwent total laryngectomy alongside total thyroidectomy. She then defaulted follow up soon after total laryngectomy hence we were unable to determine the outcome.

The third case was a 64-year old Indonesian gentleman who complained of hoarseness associated with stridor for 8 months duration. Emergency tracheostomy was performed in Indonesia 2 months prior to his presentation. On examination, there was a fungating mass from the anterior neck above the tracheostomy. Total laryngectomy and total thyroidectomy were performed and histopathological report showed transglottic well differentiated carcinoma. He was subsequently lost to follow up after he returned back to Indonesia.

Factors associated with microscopic thyroid gland invasion

Of the 3 patients identified with TGI, 2 had transglottic tumour and 1 had subglottic tumour. Table 3 summarizes the incidence of TGI according to tumour subsite, histology and T staging. Due to very limited patients with microscopic TGI, it is difficult to proceed with statistical analysis of factors that may predict presence of TGI. No significant associations were found between T

staging, primary tumour subsite and histological results with presence of TGI. We attributed this to the low number of patients with microscopic TGI. Table 3

Table 3: Factors affecting thyroid gland invasion

Factors affecting TGI	TGI		x ²	P-value
	No (n,(%))	Yes (n,(%))		
Tumour subsite	69 (95.8%)	3 (4.2%)	4.99	0.17
•Supraglottic	5 (7.2%)	0 (0%)		
•Glottic	9 (13%)	0 (0%)		
•Subglottic	3 (4.3%)	1 (33.3%)		
•Transglottic	52 (75.4%)	2 (66.7%)		
Tumour histology	69 (95.8%)	3 (4.2%)	4.85	0.18
• Well differentiated SCC	42 (60.9%)	1 (33.3%)		
• Moderately differentiated SCC	21 (30.4%)	1 (33.3%)		
• Poorly differentiated SCC	3 (4.3%)	0 (0%)		
• Others	3(4.3%)	1 (33.3%)		
T staging	69 (95.8%)	3 (4.2%)	3.13	0.21
T2	3 (4.3%)	0 (0%)		
T3	33 (47.8%)	0 (0%)		
T4a	33 (47.8%)	3 (100%)		

DISCUSSION

Total laryngectomy is the mainstay of treatment in advanced and radio recurrent carcinoma of the larynx. It affects predominantly male patients, with a male to female ratio of 23:1 in this study. This was comparable to the previous published local study by Sani et al in 1992 (7.6:1).¹

This study was carried out in two tertiary centres in multi-ethnic Malaysia. The ethnic distribution of our study population was mainly Chinese (50.7%), followed by Malay (30.6%) and Indian (4.2%). This was comparable to previous published data, in which majority of the patients with advanced carcinoma of the larynx are Chinese.¹

Hypothyroidism is common after total laryngectomy even after hemithyroidectomy and isthmusectomy due to vascular compromise of the remaining thyroid lobe.⁸ The long term incidence of post radiation hypothyroidism during 5 and 10 year follow-up for patients with head and neck cancer who did not undergo surgical resection has been reported as 20% and 27% respectively.⁹ Patients who had previous surgery in addition to the radiation therapy has significantly higher risk of

hypothyroidism.⁹ Seventy percent of patients post laryngectomy and hemithyroidectomy followed by radiation therapy will suffer from permanent hypothyroidism.⁵ Although simple to treat, postoperative hypothyroidism can be difficult to treat in some cases and often exists undetected without routine screening for up to 2 years postoperatively.¹⁰ The sequelae of hypothyroidism are poor wound healing, cardiac morbidity, and mental depression. One potential way of reducing the incidence of post treatment hypothyroid is to reduce unnecessary thyroidectomy.

Another common morbidity after laryngectomy is hypoparathyroidism. Mortimore et al in 1998 determined the calcium levels and parathyroid hormones pre and post operatively and post radiotherapy in 30 patients with squamous cell carcinoma of the laryngopharynx who were treated with total laryngectomy, hemithyroidectomy and radiotherapy. They concluded that 57% of the patients had postoperative hypoparathyroidism.¹¹ Thorp et al in 1999 showed that hypocalcaemic hypoparathyroidism occurred in 63- 89% of the patients 5 years following treatment of squamous cell carcinoma of the larynx and hypopharynx.⁴ A potential way of reducing the incidence of post treatment hypoparathyroidism is to reduce unnecessary dissection of the thyroid and the adjacent parathyroid glands.

Table 4: Reported incidence for invasion of the thyroid gland with laryngeal carcinoma

Author	Laryngeal carcinoma	Total number of patients
Ceylan et al	0%	129
Harrison et al	25%	25
Biel et al	5%	261
Yuen et al	19%	16
Fagan et al	2%	102
Croce et al	30%	23
Brennan et al	8%	247

The incidence of TGI in laryngeal carcinoma varies between authors. Table 4 summarises the reported incidence for invasion of the thyroid gland with laryngeal carcinoma by various authors. Ceylan et al in 2004 showed that the incidence of TGI is 0% for laryngeal and hypopharyngeal carcinoma.¹² Harrison in 1971 showed a 25% incidence of thyroid gland invasion in 25 transglottic and subglottic cancer

patients and advocated radical surgery with resection of thyroid lobe.¹³ Biel and Maisel in 1985 reported a 5% incidence of thyroid gland involvement in 261 laryngectomies, 70% of which had subglottic extension of more than 1.5 cm, and advocated ipsilateral and total thyroidectomy for selected cases such as palpably suspicious thyroid glands seen intraoperatively, subglottic tumours, glottic tumours with a more than 1cm subglottic extension, T4 endolaryngeal tumours with transcartilaginous invasion, and T4 pyriform sinus tumours.⁵ Yuen et al in 1995 reported a 4% incidence of thyroid gland invasion in 226 total laryngectomies, with 16% incidence in patients with subglottic extension.¹⁴ Fagan and Kaye in 1997 observed a 2% incidence of thyroid gland invasion in their series of 102 cases of T3 laryngeal cancers.¹⁰ 25 of their patients showed subglottic extension.¹⁰ Croce et al in 1991 reported a high incidence of TGI which is 30% in a very small sample size of 23 patients.¹⁵ Brennan et al in 1991 investigated 247 cases with T3 and T4 transglottic tumours and found that the incidence of thyroid gland invasion was low at 8% in their series. They recommended indications of thyroidectomy which includes involvement of the anterior commissure, subglottic space, and transglottic extension of a T3 or T4 tumour.¹⁶

In our study, the incidence of TGI was 4.2% (3/72). Two patients had transglottic tumours and the other one has tumour over the subglottic region. All 3 patients were at stage T4. One might expect that thyroid gland invasion would be more commonly seen in patients with biologically aggressive, poorly differentiated carcinomas. In our study, 2 had squamous cell carcinoma (1 well differentiated and 1 moderately differentiated) and 1 had adenoid cystic carcinoma. Using chi-square test, no significant association was seen between the presence of TGI and T staging of the tumour, subsite of disease and histopathological grading of tumour.

TGI in laryngeal cancer occurs either by direct or indirect extension via lymphatic or vascular structures.¹⁷ The thyroid isthmus normally overlies the second, third, and fourth tracheal rings. The anterior commissure of the vocal cords is, however, located approximately at the junction of the upper and lower halves of the thyroid cartilage at the midline. Tumours invading the anterior commissure

and the thyroid cartilage are therefore unlikely to extend to the thyroid isthmus unless the isthmus is located at a higher level or has an attached pyramidal lobe. The thyroid lobes, however, are often positioned close to the thyroid laminae, the cricothyroid membrane, and the upper tracheal cartilages, affording a greater likelihood of direct invasion by glottic tumours with subglottic extension or paraglottic space invasion. In addition, the lymphatics system of the subglottis drain anteriorly to the prelaryngeal and pretracheal lymph tissue and posterolaterally to the paratracheal lymph tissue, all of which lay close to the lobes of the thyroid gland.^{17,18}

Preoperative imaging and intraoperative assessment may be useful in determining whether a thyroidectomy needs to be performed. Chang et al in a study of 49 patients with hypopharyngeal carcinoma found that preoperative CT imaging was the only statistically significant predictive factor for TGI ($p=0.034$).¹⁹ Intraoperative assessment of the thyroid gland by palpation is also useful in detecting synchronous lesions involving the thyroid gland.²⁰ In our series, incidental presence of papillary thyroid carcinoma was found in 3 thyroid specimens. We propose that the presence of a suspicious thyroid nodule on preoperative imaging or intraoperative palpation warrants a hemithyroidectomy. On the other hand, gross radiological direct extension on preoperative imaging and macroscopic direct extension to the thyroid gland intraoperatively indicates the need to perform thyroidectomy, depending on the tumour extension.

Presence of TGI is associated with poor prognosis and local recurrence.^{2,5} Gallegos-Hernández et al in 2005 reported on the higher incidence of stomal recurrence in patients with thyroid gland invasion (27%) compared with patients without thyroid gland invasion (17%).²¹ This was supported by Vermund et al in 2004, who also found a higher recurrence rate in patients with thyroid gland invasion.²² In our patients with TGI, one developed stoma recurrence 6 month post operatively and another two was lost to follow up.

CONCLUSION

In conclusion, the incidence of TGI was low at 4.2% in patients with advanced carcinoma of the larynx disavowing routine thyroidectomy. A more informed

and selective approach should be undertaken when addressing decision for thyroidectomy so as to limit unnecessary iatrogenic hypothyroidism.

Limitation

This study has limitations in that it was retrospective and involved a relatively small cohort of 72 patients. Moreover, CT imaging, cartilage invasion and central lymph node treatment was not considered. The authors had difficulties retrieving these data due to poor documentation.

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