



# Frequency of Thyroid Gland Invasion by Laryngeal Squamous Cell Carcinoma: The Role of Subglottic Extension

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## Abstract

**Introduction** Management of the thyroid gland during laryngectomy has been controversial. The primary tumor may invade the thyroid gland by direct invasion or lymphovascular spread. Hypothyroidism and hypoparathyroidism are potential risks when lobectomy or total thyroidectomy are performed simultaneously.

**Objective** To report the frequency of thyroid gland involvement by primary laryngeal squamous cell carcinoma in patients undergoing laryngectomy and to identify possible risk factors for thyroid gland involvement so that judicious excision of thyroid gland can be attained.

**Methods** We performed a retrospective review of 9 years. Data was collected from medical records of patients dated from December 2009 to October 2018. All patients with laryngeal cancer who underwent laryngectomy with lobectomy or total thyroidectomy were included in the present study.

**Results** We reviewed 151 laryngectomy records. A total of 130 surgeries included the thyroid gland with the excised specimen and were available for analysis. There were 124 males and 6 females. The mean age was 59.4 years old. The glottis was the most common subsite involved, in 70 patients, followed by 38 transglottic, 16 supraglottic and 03 subglottic tumors. On histology, 12 out of 130 excised thyroid glands were involved by squamous cell carcinoma. Only subglottic involvement ( $p = 0.01$ ) was significantly associated with thyroid gland invasion (TGI). Type of laryngectomy, subsite of the primary tumor, thyroid cartilage involvement, neck nodal metastases, and perineural and lymphatic invasion by the primary tumor were not associated with TGI.

**Conclusion** Only subglottic involvement is associated with TGI; therefore, preoperative and intraoperative assessment is necessary prior to considering excision of the thyroid gland.

## Keywords

- ▶ larynx carcinoma
- ▶ laryngectomy
- ▶ thyroid lobectomy

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## Introduction

Laryngectomy is the treatment of choice for advanced laryngeal cancer amenable to surgical resection. Laryngeal carcinoma is staged as T4 when it involves the thyroid cartilage, according to the AJCC TNM classification (8<sup>th</sup> edition). The primary tumor may then invade the thyroid gland by direct invasion or by lymphovascular spread.<sup>1,2</sup> The management of the thyroid gland during laryngectomy has been controversial because the incidence of thyroid gland involvement by laryngeal carcinomas varies in the literature from 1 to 30%.<sup>3–10</sup> In a recent systematic review, Kumar et al. concluded that only cases with a subglottic extension of the tumor have a significant risk of thyroid gland involvement, and surgeons should reconsider routine thyroidectomies.<sup>11</sup> Lobectomy or total thyroidectomy impose a risk of hypothyroidism and hypoparathyroidism.<sup>12,13</sup> Adjuvant radiation after laryngectomy increases this risk to up to between 70 and 90%.<sup>14</sup> Hypothyroidism can also result from adjuvant treatments like chemoradiation.

Currently, there are no guidelines regarding the management of the thyroid gland during laryngectomies. Preservation of the thyroid gland can prevent hypothyroidism and hypocalcemia, reduce overall costs, and improve quality of life. However, it is imperative to achieve this without compromising oncological clearance.

Our study aims to report the frequency of thyroid gland involvement by primary laryngeal squamous cell carcinoma in patients undergoing laryngectomy with ipsilateral or total thyroidectomy. We aim to identify possible risk factors for thyroid gland involvement to attain judicious excision of the thyroid gland.

## Methods

We performed a retrospective review of 9 years in the Department of Otolaryngology & Head and Neck Surgery at a tertiary care center. After exemption from the Ethical review committee (2019–1765–5022), data were collected from medical records of patients dated from December 2009 to October 2018 on a predesigned proforma. All patients with laryngeal cancer who underwent laryngectomy with lobectomy or total thyroidectomy were included in the present study. Patient records with missing data, patients without simultaneous thyroidectomy, and pathologies other than squamous cell carcinoma were excluded.

We recorded patient age and gender, primary versus salvage laryngectomy, subsite of the primary tumor, extension into an adjacent subsite, thyroid cartilage invasion, lymphatic and perineural invasion, and involvement of the thyroid gland from 130 eligible patients.

Qualitative variables were reported using frequencies, while mean and standard deviations (SDs) were used for quantitative data. Statistical analysis was performed with IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). A *p*-value  $\leq 0.05$  was considered statistically significant. Associations between variables and thyroid

gland invasion (TGI) were tested using the chi-squared test and the Fisher exact test.

## Results

We reviewed 151 laryngectomy records. A total of 130 surgeries included the thyroid gland with the excised specimen and were available for analysis – all being squamous cell carcinoma on histology. There were 124 (95.4%) males and 6 (4.6%) female patients. The mean age was  $59.4 \pm 12$  years old. The glottis was the most common subsite, involved in 70 (53.8%) patients, followed by 38 (29.2%) transglottic, 16 (12.3%) supraglottic, and 03 (2.3%) subglottic tumors (► **Table 1**). A total of 106 (81.5%) patients underwent definitive primary laryngectomy, while 24 (18.5%) patients needed a salvage laryngectomy after inadequate response to chemoradiation. Ipsilateral lobectomy was performed in 118 patients (91%), while the remaining 12 underwent total thyroidectomy.

On histology, 12 out of 130 (9.2%) excised thyroid glands were involved by squamous cell carcinoma. Ten males and 2 females made up this group. Seven out of these 12 patients (58.3%) had subglottic involvement – 3 being primarily in the subglottis and 4 from transglottic cancers. The thyroid cartilage was involved in 9 out of the 12 cases (75%). Eleven out of these 12 laryngectomies were primary definitive surgeries, while only 1 salvage laryngectomy specimen had the tumor involving the thyroid gland. Characteristics of these 12 patients are shown in ► **Table 2**. None of the thyroid glands showed gross invasion during the surgical procedure.

Out of the 12 patients who underwent total thyroidectomy with laryngectomy, 3 developed transient hypocalcemia that needed calcium supplementation for 3 to 6 months. Only one patient had permanent hypocalcemia and needed long-term calcium replacement. None of the patients who underwent lobectomy suffered hypoparathyroidism.

Only subglottic involvement (*p* = 0.01) was significantly associated with TGI. Type of laryngectomy, subsite of

**Table 1** Patient demographics

Patient demographics		Frequency
Gender	Male	124 (95.4%)
	Female	6 (4.6%)
Subsite	Supraglottis	16 (12.3%)
	Glottis	70 (53.8%)
	Subglottis	03 (2.3%)
	Transglottis	38 (29.2%)
	More than one subsite	03 (2.3%)
Laryngectomy	Primary	106 (81.5%)
	Salvage	24 (18.5%)
Thyroidectomy	Ipsilateral thyroid lobectomy	118 (91%)
	No	12 (9%)

**Table 2** Characteristics of patients with involved thyroid glands

Gender	Age (years old)	Site	Thyroid Cartilage erosion	Surgery
Male	40	Transglottis	Yes	Total laryngectomy
Female	40	Transglottis	Yes	Total laryngectomy
Male	45	Glottis	Yes	Total laryngectomy
Male	49	Glottis	Yes	Total laryngectomy
Male	50	Glottis	Yes	Total laryngectomy
Male	52	Supraglottis	Yes	Total laryngectomy
Male	52	Transglottis	No	Total laryngectomy
Male	59	Transglottis	Yes	Total laryngectomy
Male	60	Subglottis	No	Total laryngectomy
Male	60	Glottis	No	Total laryngectomy
Male	62	Transglottis	Yes	Salvage laryngectomy
Female	70	Transglottis	Yes	Total laryngectomy

the primary tumor, thyroid cartilage involvement, neck nodal metastases, and perineural and lymphatic invasion by primary tumor were not associated with TGI. (→ **Table 3**).

**Table 3** Factors affecting thyroid gland invasion

		Thyroid gland invasion	
		Yes	No
Gender	Male	10	114
	Female	2	4
Subsite	Supraglottis	1	15
	Glottis	4	66
	Subglottis	1	2
	Transglottis	6	32
	More than one subsite	0	3
Involved subglottis*	Yes	7	34
	No	0	89
Thyroid cartilage invasion	Yes	9	83
	No	3	32
Lymph node metastases	Yes	6	46
	No	5	69
Laryngectomy	Primary	11	95
	Salvage	1	23
Perineural invasion	Yes	4	20
	No	3	54
Lymphatic invasion	Yes	3	20
	No	8	92

\* $p < 0.05$ 

## Discussion

We found that 12 (9%) of the laryngeal squamous cell carcinomas in the study invaded the thyroid gland. Our study also found that only subglottic extension of the tumor was associated with TGI (7 out of 12 had subglottic tumors). The remaining five tumors had direct erosion of the thyroid cartilage to involve the thyroid gland. Males were found to have a higher incidence of TGI compared with females. However, this could be because only 6 out of the 130 patients were females.

Studies report varying frequencies of thyroid gland involvement, ranging from 1 to 30%.<sup>3-5,15</sup> In 2013, Kumar pooled 1,287 patients in his systematic review, reporting 10.7% (95% confidence interval [CI]: 7.6–14.2) thyroid glands positive for carcinoma. They also found subglottic involvement – primary subglottic tumors or tumors extending to the subglottis – to be a risk factor for TGI.

Different mechanisms potentially explain this: direct extension through the cricothyroid membrane, gaps between tracheal rings, eroding the tracheal cartilage, and by draining pretracheal or paratracheal lymphatics of the subglottis. Direct extension from tumors at the anterior commissure is unlikely because the isthmus is located inferior to the lamina of the thyroid cartilage, which is the level of the vocal cords – unless a pyramidal lobe is present. Tumors from the subglottis could extend to involve the thyroid lobes more readily because of their proximity to the tracheal cartilages. A few other authors have also suggested the involvement of the thyroid gland when tumors spread to the subglottis.<sup>9,16-18</sup> Al Hakami et al. found only 2 out of 47 (4.3%) thyroid glands positive for carcinoma. Both had subglottic involvement by the primary tumor, suggesting that TGI was by direct extension of the cancer.<sup>6</sup> A multicenter study from Malaysia reported 3 out of 72 (4.2%) patients to have thyroid gland infiltration on histology. All three patients had subglottic or transglottic disease with evident thyroidal invasion

preoperatively.<sup>7</sup> In one study, the authors found 24% of T4 laryngeal cancers to have TGI. However, they mentioned that all these cases were very advanced, with preoperative contrast-enhanced computed tomographies (CTs) showing gland involvement.<sup>19</sup>

Many authors consider thyroid cartilage involvement a risk factor for the invasion of the thyroid gland.<sup>1,8,20</sup> Thyroid cartilage involvement (on histology) was not associated with TGI in our study. Thyroid or cricoid cartilage involvement, anterior commissure invasion, and transglottic extent have been associated with TGI in other studies.<sup>11,21,22</sup> A Turkish study found 4 (5.3%) TGIs among 75 patients.<sup>8</sup> Li et al. found that 8% of the thyroid glands were involved by cancer, and thyroid cartilage involvement had a positive predictive value of only 26%.<sup>23</sup>

Similar to our findings, Mangussi-Gomes found no association of TGI with lymph node staging, angiolymphatic or perineural invasion. Less differentiated tumors were also unrelated to TGI, reinforcing the contiguous spread theory. They documented a frequency of 19.1% among laryngeal cancers, and the most robust odds ratio was seen for cricoid cartilage involvement followed by subglottic and anterior commissure extension.<sup>24</sup> The cricothyroid membrane was suggested as the possible route for the direct extension of the tumor to the thyroid gland.

Thyroidectomy during laryngectomy should be judicial to avoid unnecessary hypothyroid and hypoparathyroid complications. Isolated total laryngectomy causes hypothyroidism in 20 to 63% of the patients.<sup>25</sup> The morbidity is worse in patients undergoing adjuvant radiation to the neck.<sup>14</sup> Preoperative radiation with salvage laryngectomy results in a greater risk of hypothyroidism than laryngectomy, followed by postoperative radiation.<sup>26</sup> Identifying risk factors for possible involvement of the thyroid gland is prudent to minimize morbidity while ensuring oncological clearance. Some authors have also suggested the use of the thyroid gland to augment the neopharynx.<sup>27</sup> Panda et al. reported an incidence of 8.8% of TGI in 125 patients with carcinoma of the larynx or of the hypopharynx. They also documented 48% hypothyroidism and 12.8% hypoparathyroidism in their cohort. However, TGI did not affect the prognosis, locoregional control, or overall survival. The authors suggested that thyroidectomy be tailored for patients with extra laryngeal spread seen radiologically or intraoperatively.<sup>28</sup> Baghel et al. recommended thyroidectomy only in gross radiological or intraoperative thyroid gland involvement and subglottic extension.<sup>25</sup> In another study, 88% of the patients who had lobectomies during laryngectomy needed thyroid supplementation later in life.<sup>29</sup>

Few studies debate thyroid gland involvement as a poor prognostic factor and risk for local or stomal recurrences.<sup>16,30</sup> Gorphe et al. reported thyroid cartilage invasion, cricothyroid membrane invasion, and prelaryngeal soft tissue extension associated with TGI. Thyroid gland invasion portends worse disease-free survival and peristomal control.<sup>31</sup> Other studies show that TGI did not affect locoregional recurrence or survival.<sup>28,32</sup>

Small sample sizes limit most studies to draw confident associations between factors and thyroid gland involvement.

Our study is the second-largest single-center data after Gorphe et al.<sup>31</sup> to address these factors. However, we did not have a follow-up. Thus, we are limited by our data to speculate long-term outcomes both in terms of oncological control and endocrine abnormalities. Further studies, including a more significant number of cases, are needed to confirm risk factors for TGI.

## Conclusion

Few laryngeal cancers justify routine thyroidectomy. Only subglottic involvement – either primary subsite or transglottic tumors – is associated with TGI. Careful preoperative and intraoperative assessment can help avoid unnecessary complications of thyroidectomy.

### Disclosure

None.

### Conflict of Interests

The authors have no conflict of interests to declare.

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