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Incidence and predictors of thyroid gland invasion by laryngeal carcinoma: a 7-year experience review

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Abstract

Background: Study the incidence of thyroid gland invasion by laryngeal carcinoma and the risk factors that may predispose to this condition. Aiding surgeons develop an evidence-based plan for the management of the thyroid gland during total laryngectomy.

Results: Retrospective analysis of the available medical records for patients who had total laryngectomy together with total thyroidectomy or hemithyroidectomy in the same procedure. Associated pathological features were also investigated. Patients who had laryngeal carcinoma managed by total laryngectomy with total thyroidectomy or hemithyroidectomy between January 1, 2011, and December 31, 2017.
Three hundred seventy-seven records were retrieved. The incidence of thyroid gland invasion by the laryngeal carcinoma was 24 (6.4%). Three patients showed microscopic extension (3/356; 0.8%). Six patients had malignant pathology other than squamous cell carcinoma (SCC). Two over six had invasion of the thyroid gland; OR (95% CI): 7.9 (1.4-45.4). Patients who had primary tumor stage of T4a were 244. 23/244 had thyroid gland invasion, 13.7 (1.8-102.9). Poorly differentiated tumors had significant incidence of thyroid gland invasion (4/15), 6.2 (1.8-21.3). Patients who had subglottic extension by the primary tumor were 177 with 20 patients having thyroid gland invasion (20/177), 6.2 (2.1-18.6).

Conclusion: Several risk factors are associated with higher incidence of invasion of the thyroid gland by laryngeal carcinoma. Identification of these factors can help surgeons develop a surgical strategy for the management of the thyroid gland during total laryngectomy.

Keywords: Thyroid gland, Laryngeal carcinoma, Invasion, Thyroidectomy, Laryngectomy

Background

Primary and salvage total laryngectomy (TL) are commonly performed for the management of laryngeal carcinoma (LC) [1]. The management of a clinically negative thyroid gland during TL remains to be an issue of controversy [2, 3]. Most surgeons prefer to perform hemithyroidectomy (HT) on the ipsilateral side of the tumor. Others prefer to perform total thyroidectomy (TT) if the tumor is crossing the midline [1, 4, 5]. TT can be complicated with temporary or permanent hypocalcemia, while permanent hypothyroidism is an inevitable consequence [6–8]. Hemithyroidectomy is not associated with the risk of hypocalcemia; however, the incidence of hypothyroidism remains to be a significant risk. Factors that may contribute to hypothyroidism after HT includes radiotherapy (either primary or adjuvant), revision neck or thyroid surgery, associated thyroid gland pathology, and/or devascularization of the contralateral lobe during TL [9, 10]. The condition can be frequently missed because of the false sense of security of preservation of the thyroid lobe during surgery. If untreated, it can lead to delayed wound healing and

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recovery, increased risk of fistula formation and major cardiovascular complications that can lead to mortality [11, 12]. Treatment requires lifelong thyroid stimulation hormone (TSH) monitoring and thyroid hormone replacement therapy [13–15]. On the other hand, postoperative hypocalcemia, can be very agonizing to both the patient and the surgeon with the inconvenience of replacement therapy which includes multiple pills and doses throughout the day with the associated symptoms and morbidity that can be temporary or permanent [8, 16].

The aim of this study is to aid surgeons to develop an evidence-based plan for the management of a clinically negative thyroid gland during TL.

Methods

This is a retrospective study, which was conducted at a tertiary care practice of the Otolaryngology Department, Faculty of Medicine, Cairo University, between January 1, 2011, and December 31, 2017. Available final pathology reports were obtained using the search word "laryngectomy". The study included patients who had concurrent TL with HT or TT—for the management of LC. All patients gave their informed consent prior to treatment. Records for patients who did not have HT or TT with TL, partial laryngectomy, or TL for afunctional larynx were excluded. Patients with distant metastasis were not candidates for TL. The incidence of thyroid gland invasion by LC was determined. Pathology reports indicating absence of evidence of gross invasion of the thyroid gland were considered to have preoperative clinically negative thyroid gland status. Associated features were also examined which included gender, age, histological type of the LC, performance of neck dissection, primary tumor pathological (pT) stage, nodal (pN) stage, degree of differentiation, epicenter for the primary tumor, subunit invasion (glottic, supraglottic, and/or subglottic), thyroid cartilage invasion, margin invasion, hostile pathological features (vascular invasion, perineural invasion, and/or extracapsular spread) and the presence of a second primary malignancy in the thyroid gland. Informed consent is always obtained as a routine step in the proceedings before commencing to treatment of all patients at our institution.

Statistical analysis

Pre-coded data was entered on the computer using the "Microsoft Office Excel Software" program (2010) for windows. Data was then transferred to the Statistical Package of Social Science Software program, version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) to be statistically analyzed. Data was presented using frequency and percentage.

Comparison between groups was performed using chi-square and Fisher's exact test for qualitative variables.

P values less than 0.05 were considered statistically significant.

Results

The total number of final pathology reports retrieved from our hospital system for patients who met the inclusion criteria within the specified time frame was 377. Table 1 describes the rates of the associated study variables. The thyroid gland was found to be invaded by LC in 24 patients (6.4%). Three patients (3/24) had only microscopic metastasis while 21 patients showed gross extension. Four pathological features were found to have statistically significant association with the incidence of thyroid gland invasion by LC. Findings are reported using the odds ratio (OR) and 95% confidence interval (CI). Patients with primary tumor pathological stage T4a were 244/377, with 23 patients showing thyroid gland invasion, 13.7 (1.8-102.9). One hundred seventy-seven patients had subglottic invasion by the LC, with 20 patients showing thyroid gland invasion, 6.2 (2.1-18.6). Poorly differentiated carcinoma incidence was 15, with 4 patients showing thyroid gland infiltration, 6.2 (1.8-21.3). Pathology other than SCC was found in 6 patients, with two patients having thyroid gland invasion, 7.9 (1.4-45.4). Detailed analysis of the correlation of all variables and the incidence of thyroid gland invasion by the LC are described in Table 2.

Discussion

The thyroid gland is specifically vulnerable to invasion by LC due to its proximity to the cricothyroid membrane which represents a weak barrier between the primary tumor and the gland [17–19]. Prelaryngeal lymph nodes which overlie the cricothyroid membrane can harbor metastatic tumor foci and hence represents an additional risk of the invasion of the thyroid gland by LC [3]. The thyroid gland is located in the lymphatic drainage pathway of the larynx which adds to the risk of lymphatic invasion of the gland by malignant laryngeal tumors. For these reasons, it has been routinely practiced performing HT or TT together with TL for the management of LC [1–5].

Despite being oncologically sound, HT or TT comes at costs of transient or permanent hypocalcemia and/or permanent hypothyroidism [8, 16]. The incidence of such complications is variable according to different reports [19, 20]. Arslanoglu and his colleagues reported that laryngeal tumors with thyroid cartilage invasion, anterior commissure extension, and subglottic extension were indicative of thyroid gland invasion and required thyroidectomy [19]. Mourad et al. concluded that laryngeal carcinoma with thyroid cartilage involvement and subglottic extension, particularly through the posterior

Table 1 Description of all variables

	Description (%) $n = 377$
Gender	
Male	353 (93.6)
Female	24 (6.4)
Age	
< 50	44 (11.7)
50-59	131 (34.7)
60-69	176 (46.7)
70+	26 (6.9)
Histological type	
Sq. CC	371 (98.4)
Others	6 (1.6)
Neck dissection	343 (91)
T staging	
T2	35 (9.3)
T3	98 (26)
T4a	244 (64.7)
N staging	
No	234 (62.1)
N1	56 (14.9)
N2a	2 (0.5)
N2b	40 (10.6)
N2c	38 (10.1)
N3	7 (1.9)
Degree of differentiation	
Well differentiation	33 (8.8)
Moderate	329 (87.3)
Poor	15 (4)
Site of the primary tumor	
Supraglottic	27 (7.2)
Glottic	13 (3.4)
Subglottic	1 (0.3)
Glottic supraglottic	160 (42.4)
Glottic subglottic	82 (21.8)
Glottic, supra, sub	94 (24.9)
Subglottic invasion	177 (46.9)
Thyroid cartilage invasion	
Microscopic	32 (8.5)
Gross	209 (55.4)
Nodal metastasis	143 (37.9)
Margin invasion	25 (6.6)
Margin invasion	
Upper	5 (1.3)
Right	3 (0.8)
Left	8 (2.1)
Combined	9 (2.4)
Thyroid gland invasion	24 (6.4)
Gross	21 (5.6)
Microscopic	3 (0.8)
Hostile pathological features	12 (3.2)
Hostile pathological features	
Vascular invasion	1 (0.3)
Peri-neural spread	2 (0.5)
Extracapsular spread	9 (2.4)

and lateral cricothyroid space have been considered risk factors for likely thyroid gland involvement [20].

The risk of developing such morbidities is particularly higher with salvage surgery, reoperative neck surgery, associated thyroid gland pathology, and devascularization of the preserved contralateral thyroid lobe during TL [9, 10].

Several other reports in the literature described risk factors that are associated with higher incidence of thyroid gland invasion [6, 14, 21].

Leon et al. reported a fifty-two percent of patients treated with total laryngectomy developed either clinical or subclinical hypothyroidism. The triad of HT, TL, and radiotherapy was a risk factor for the development of hypothyroidism [21]. In their report, Ho et al. indicated that for patients who were treated with TL and irradiation for laryngeal carcinoma, 19.9% of patients developed hypothyroidism at 3 years, 38.6% at 6 years, and at 10-year follow-up, 93.3% of them had hypothyroidism [6]. Sinard and his team found that up to 20% of patients treated for advanced-stage head and neck cancer with surgery and radiotherapy will develop hypothyroidism. It is estimated that 60% of those who received total laryngectomy, thyroid lobectomy, and radiotherapy will develop hypothyroidism [14]. As per our report, it was found that the primary tumor pathological stage of T4a, subglottic involvement by the tumor, and poorly differentiated carcinoma were all associated with a significantly higher risk of thyroid gland invasion by LC.

Hypothyroidism represents a common postoperative morbidity that can be easily missed after HT with the false sense of security of having a preserved contralateral lobe [9, 11, 22]. After TT, the problem is inevitable. Managing this disease carries the financial burden of the need for frequent monitoring of the TSH blood levels and the lifelong need for thyroid hormone replacement [13, 23, 24]. More problematic after TT is the management of temporary or permanent hypocalcemia. Patients manifest with clinically bothering frequent symptoms of tingling, numbness, and painful cramps. Treatment requires multiple pills and doses throughout the day which

Table 2 Analysis of the correlation of all variables and the incidence of thyroid gland invasion by the LC

	Thyroid gland invasion		*P* value*	OR (95% CI)
	Yes (*n* = 24)	No (*n* = 353)		
Gender				
Male	23 (95.8)	330 (93.5)	0.648	1.6 (0.2-12.4)
Female	1 (4.2)	23 (6.5)		Ref.
Age				
< 50	2 (8.3)	42 (11.9)	0.888	Ref.
50-59	9 (37.5)	122 (34.6)		1.5 (0.3-7.5)
60-69	12 (50)	164 (46.5)		1.5 (0.3-7.1)
70+	1 (4.2)	25 (7.1)		0.8 (0.1-9.7)
Histological type				
SCC	22 (91.7)	349 (98.9)	**0.049**	Ref.
Others	2 (8.3)	4 (1.1)		7.9 (1.4-45.4)
Neck dissection				
Yes	21 (87.5)	322 (91.2)	0.466	0.7 (0.2-2.4)
No	3 (12.5)	31 (8.8)		Ref.
T staging				
T2	1 (4.2)	34 (9.6)	**0.004**	Ref.
T3	0 (0)	98 (27.8)		0.1 (0.001-2.9)
T4a	23 (95.8)	221 (62.6)		3.5 (0.5-27.1)
T staging				
T2 + T3	1 (4.2)	132 (37.4)	**0.001**	Ref.
T4a	23 (95.8)	221 (62.6)		13.7 (1.8-102.9)
N staging				
No	15 (62.5)	219 (62)	0.204	Ref.
N1	2 (8.3)	54 (15.3)		0.5 (0.1-2.4)
N2a	0 (0)	2 (0.6)		2.8 (0.1-61.6)
N2b	6 (25)	34 (9.6)		2.6 (0.9-7.1)
N2c	1 (4.2)	37 (10.5)		0.4 (0.1-3.1)
N3	0 (0)	7 (2)		0.9 (0.1-17.3)
Degree of differentiation				
Well differentiation	2 (8.3)	31 (8.8)	**0.004**	Ref.
Moderate	18 (75)	311 (88.1)		0.9 (0.2-4.0)
Poor	4 (16.7)	11 (3.1)		5.6 (0.9-35.0)
Degree of differentiation				
Well + moderate	20 (83.3)	342 (96.9)	**0.004**	Ref.
Poor	4 (16.7)	11 (3.1)		6.2 (1.8-21.3)
Site of the primary tumor				
Supraglottic	0 (0)	27 (7.6)	**< 0.001**	
Glottic	0 (0)	13 (3.7)		
Subglottic	1 (4.2)	0 (0)		
Glottic supraglottic	4 (16.7)	156 (44.2)		
Glottic subglottic	4 (16.7)	78 (22.1)		
Glottic, supra, sub	15 (62.5)	79 (22.4)		
Glottic invasion				

Table 2 Analysis of the correlation of all variables and the incidence of thyroid gland invasion by the LC *(Continued)*

	Thyroid gland invasion		*P* value*	OR (95% CI)
	Yes (*n* = 24)	No (*n* = 353)		
Yes	23 (95.8)	326 (92.4)	0.529	1.9 (0.2-14.7)
No	1 (4.2)	27 (7.6)		Ref.
Supraglottic invasion				
Yes	19 (79.2)	262 (74.2)	0.590	1.3 (0.5-3.6)
No	5 (20.8)	91 (25.8)		Ref.
Subglottic invasion				
Yes	20 (83.3)	157 (44.5)	**< 0.001**	6.2 (2.1-18.6)
No	4 (16.7)	196 (55.5)		Ref.
Thyroid cartilage invasion				
Yes	18 (75)	223 (63.2)	0.243	1.7 (0.7-4.5)
No	6 (25)	130 (36.8)		Ref.
Thyroid cartilage invasion				
No	6 (25)	130 (36.8)	0.090	Ref.
Microscopic	0 (0)	32 (9.1)		0.3 (0.02-5.6)
Gross	18 (75)	191 (54.1)		2.0 (0.8-5.3)
Nodal metastasis				
Yes	9 (37.5)	134 (38)	0.964	0.98 (0.4-2.3)
No	15 (62.5)	219 (62)		Ref.
Margin invasion				
Yes	4 (16.7)	21 (5.9)	0.065	3.2 (0.99-10.1)
No	20 (83.3)	332 (94.1)		Ref.
Hostile pathological features				
Yes	2 (8.3)	10 (2.8)	0.174	3.1 (0.6-15.1)
No	22 (91.7)	343 (97.2)		Ref.

is always inconvenient to both patients and surgeons. Each effort should be exercised to prevent the development of such complications [3, 8, 16].

The management of clinically negative thyroid gland in non-thyroid head and neck cancer has been a subject of ongoing debate. Because our study is based on the final pathology reports for data collection, reports which indicated absence of evidence of gross invasion of the thyroid gland by the LC were considered to have preoperative clinically negative thyroid gland (356). In a total of 24 patients with pathological evidence of thyroid gland invasion, 21 patients had evidence of gross invasion of the thyroid gland by the LC. In other means, our study reported 356 patients without evidence of gross invasion of the thyroid gland; of them, only three patients (3/356; 0.8%) were found to have microscopic extension of the LC into the thyroid gland. Li et al. used the term extension by metastasis to describe microscopic metastasis to the thyroid gland by LC. They reported a cohort of 196 patients with 10 patients showing extension of the tumor to the thyroid gland. In their report, only one patient had extension by metastasis. Their low rates run in accordance with our reported low rates of thyroid gland affection [25].

Strengths of this study included the long study period (7 years) which allowed the research team to recruit a large cohort of patients (377). By reviewing the final pathology reports, we were able to meticulously identify definitive pathological features that were associated with higher risk of thyroid gland invasion. These factors can be identified during preoperative planning and hence can guide surgeons to develop an oncologically sound plan regarding the controversial management of the thyroid gland. Multiple surgeons were involved in the surgical treatment of our study population, and this added to the versatility of our study. Another advantage is that the use of the final pathology reports to determine the preoperative status of the thyroid gland—despite being impractical—provided the most accurate way to confirm the thyroid gland status.

This study is not free of drawbacks. Our research lacks follow up of patients who actually had HT to exactly

determine our incidence of postoperative hypothyroidism with a preserved thyroid lobe. Some clinical details were unavailable to the research team while conducting the study, most importantly the differentiation of patients who had TL as a primary treatment versus those who had salvage surgery. The latter group remains to be at a particular risk of developing postoperative hypothyroidism even with HT [4]. Lack of preoperative clinical and radiological data forced the authors into assuming an impractical way of determining the preoperative status of the thyroid gland based on the final pathology report. Another nonexistent important clinical factor was the postoperative calcium level whenever TT was performed. Patients may develop parathyroid glands stunning after TT even with surgery for benign pathology and hence they require calcium taper regimen over 3 weeks [26]. The unavailability of this information made it impossible for the research team to identify the true incidence of postoperative hypocalcemia after TT either temporary or permanent. This incidence is reported to be common according to various reports [8, 26]. In their review, Paduraru et al. reported a variable incidence of postoperative hypocalcemia ranging from 1.2 up to 40% [8].

Another pitfall is the presence of 35 patients (9.3%) of our study population with primary tumor pathological stage T2. Surgeons can argue the need for TL in such tumor stage. Our data is mainly stemmed from the final pathology reports. Due to the lack of complete clinical information about our patients before surgery, the research team was only able to postulate theories about the need for such an aggressive treatment with an early stage disease. The first explanation was that these patients might have been operated on due to primary radiation failure. The second explanation was that some patients may prefer TL rather than partial surgery or radiotherapy aiming for better chances of cure and avoiding daily commitment of therapy and short follow-up intervals as they had to travel long distances from where they live to the nearest tertiary care facility. Another possibility was that most patients with LC are chronic heavy smokers with poor pulmonary reserve making partial surgery unfeasible for them. Finally, some patients can be upstaged based on clinical and radiological findings then eventually become downstaged with the final pathology report.

Our findings showed that malignant pathology other than SCC (e.g., adenoid cystic carcinoma) showed significantly higher risk of invasion of the thyroid gland by LC 2/6; OR 7.9, 95% CI (1.4-45.4). The research team was skeptical about this finding. The incidence of non-SCC LC is exceedingly rare. We were only able to identify 6 patients with non-SCC laryngeal malignancy. Such tumors tend to be aggressive from the start and usually require—as radical as possible—surgery. Drawing conclusion from such small cohort makes the interpretation subject to both criticism and unreliability. For these reasons, we recommend that this variable to be studied separately with larger and dedicated studies.

Conclusion

Revisiting the practice of routine concurrent HT or TT with TL in this study showed that the incidence of thyroid gland invasion by LC is low (24/377; 6.4%). Patients, with presumably preoperative clinically negative thyroid glands, showed less than 1% incidence of harboring microscopic foci of the LC (3/356; 0.8%). Certain pathological features showed significantly higher risk of association with thyroid gland invasion by LC which was primary tumor pathological stage T4a, poorly differentiated carcinoma, and invasion of the subglottis by the tumor. These three factors can be determined before commencing to definitive TL and hence can provide an evidence-based strategy to aid surgeons develop their plan for the management of thyroid gland during TL; thus, minimizing morbidity and optimizing outcome. Malignant laryngeal pathology other than SCC showed significant correlation with thyroid gland invasion; however, the research team is skeptical about this finding owing to the small proportion of this subgroup and we recommend further dedicated studies with larger sample sizes to further analyze this factor.

Abbreviations

LC: Laryngeal carcinoma; TL: Total laryngectomy; TT: Total thyroidectomy; HT: Hemithyroidectomy; SCC: Squamous cell carcinoma; TSH: Thyroid stimulating hormone

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None

Authors' contributions

A M. Elt: drafting the work. A A. N: contributions to the conception of the work, acquisition, interpretation of data. A M. Elb: revising the work. S G. I: revising the work critically for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All procedures performed in the study were in accordance with the ethical standards of the practice at which the study was conducted (Otolaryngology Department of Cairo University, ethical committee; permit number: 7-5-2017). Consent to participate is inapplicable for this retrospective study.

Consent for publication

Does not apply for this study. Our manuscript does not contain any personal data.

Competing interests
None to declare.

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