

Clinicodemographic and Computed Tomography Scan Findings Associated with Thyroid Gland Invasion among Patients with Laryngeal Squamous Cell Carcinoma

Anna Kristina M. Hernandez, MD, MMPM,^{1,2*} Cindy Pearl J. Sotalbo, MD,^{3,4*}
Antonio Marlo P. Nievera, MD³ and Ryner Jose C. Carrillo, MD, MSc^{1,4}

¹Department of Otolaryngology - Head and Neck Surgery, Philippine General Hospital, University of the Philippines Manila

²Smell and Taste Clinic, Department of Otorhinolaryngology, Technische Universität Dresden

³Department of Radiology, Philippine General Hospital, University of the Philippines Manila

⁴Department of Anatomy, College of Medicine, University of the Philippines Manila

ABSTRACT

Objective. We aim to determine the association between preoperative CT scan findings of thyroid cartilage invasion, cricoid cartilage invasion, and paraglottic space involvement with tumor extension to the thyroid gland on final histopathology among patients with laryngeal squamous cell carcinoma (SCC) in a tertiary hospital in the Philippines.

Methods. Patients with histopathologically-confirmed laryngeal SCC who underwent total laryngectomy with thyroidectomy while admitted at the public ward of the Department of Otorhinolaryngology, Philippine General Hospital, from January 2013 to December 2019 were included. CT scans were reviewed by 2 blinded independent radiologists. CT scan data including subsite/s involved, thyroid cartilage/cricoid cartilage erosion, paraglottic space involvement, thyroid gland involvement, and thyroid gland involvement on final histopathology were gathered. Clinicopathologic data such as age, T Stage, early tracheostomy, and time between CT scan and surgery were also collected and analyzed. Fisher's exact test was computed for both clinicopathologic and CT scan data with a significant value having $p < 0.05$. Cramer's V and phi coefficient were computed for nondichotomous and dichotomous variables, respectively. Odds ratio was also computed for dichotomous variables with $p < 0.05$ on Fisher's exact test.

Results. Fifty-nine (59) men and 4 women were included, aged 43 to 81 years old. Most patients were classified as T3 (n=18) and T4 (n=41) (total=93.7%), with most having transglottic primary tumors (n=29, 46%), and only 8 (12.7%) patients having subglottic tumor involvement on final histopathology. Thyroid cartilage erosion or invasion were noted in 63.4% (n=40) of patients' CT scans and 58.7% (n=37) of patients' final histopathology reports. Cricoid cartilage and paraglottic space involvement were often not reported on final histopathology results. Thyroid gland involvement was only noted in the final histopathology reports of 5 patients (7.9%). Significant association between cricoid cartilage findings ($p=0.032$, Cramer's V=0.318) or thyroid gland involvement on CT scan ($p=0.018$, Phi=0.384; OR 13 95% CI 1.797, 94.035) with thyroid gland involvement on final histopathology was noted. The rest of the variables had no significant association with thyroid gland involvement on final histopathology.

Conclusion. Cricoid cartilage involvement (erosion or invasion) and thyroid gland involvement on CT scan are associated with thyroid gland involvement on final histopathology in patients with laryngeal SCC. Patients with these CT scan findings may stand to benefit more from thyroidectomy to ensure good margins of resection.

Keywords: cancer of larynx, thyroidectomy, carcinoma, squamous cell

*Dr. Hernandez and Dr. Sotalbo share primary authorship for this manuscript.

Corresponding author: Anna Kristina M. Hernandez, MD, MMPM
Department of Otorhinolaryngology
Philippine General Hospital, University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: akmhernandezmd@gmail.com

INTRODUCTION

In the Philippines, laryngeal cancer is the 17th most common cancer over-all, and remains as the 4th most common head and neck cancer after thyroid, oral cavity and nasopharyngeal. An incidence of 2.2 per 100,000 cases was reported in 2012.^{1,2} Institutional and foreign guidelines^{3,4} recommend total laryngectomy with thyroidectomy for advanced T3 and T4 laryngeal cancers to achieve adequate margins of resection.

In recent years, there has been an increased reliance on Computed Tomography (CT) Scans as a diagnostic tool for tumor mapping and surgical planning. Thyroid cartilage erosion or invasion on CT scan may distinguish between a T3 and a T4 tumor and also determine the likelihood of extra-laryngeal spread of tumor to the thyroid gland.⁴ The role of routine thyroidectomy for laryngeal cancer remains controversial, due to the low incidence of thyroid involvement and the potential post-operative morbidities that may arise from this procedure. A study by Li et al.⁵ reports of overdiagnosis of thyroid cartilage involvement on CT scan, leading to overtreatment of patients that should have had options for potentially organ saving treatment or more conservative surgical management. Moreover, a study by Holgado et al. in 2015 found that only 11% of patients who underwent total laryngectomy with thyroidectomy for laryngeal cancer were found to have thyroid gland involvement on final histopathologic examination.²

Laryngeal tumors can involve the thyroid gland through direct extension or lymphovascular spread.^{2,6,7} Several studies have cited subglottic involvement and direct extension via extra-laryngeal spread as the more common routes. Weak points such as the cricothyroid membrane and paramedian cricothyroid space have also been identified as potential routes for extra-laryngeal spread.^{2,6} Subglottic extension of greater than or equal to 10 mm for laryngeal cancers and cricoid cartilage destruction on CT scan for all laryngopharyngeal cancers were statistically correlated with histological thyroid gland invasion. When laryngeal cartilages are intact on CT scan, the thyroid gland can be preserved while ensuring good local control.⁷

The paraglottic space has also been identified as an important predictor of extra-laryngeal spread, as it is composed only of loose soft tissues that provide little resistance to neoplastic dissemination and is contiguous inferiorly with the extra-laryngeal compartment via the cricothyroid space.⁶

Thyroid gland invasion by laryngeal squamous cell carcinoma (SCC) has been found to be indicative of poor prognosis.^{6,7}

There may be a tendency for invasion of the thyroid lobe ipsilateral to the primary tumor bulk in laryngeal SCC, with extra-laryngeal spread, tracheostomal involvement, and tracheal extension as factors strongly-associated with tumor extension to the thyroid gland.²

When done in conjunction with a total laryngectomy, thyroidectomy often results in hypothyroidism requiring lifetime thyroid hormone replacement. Hemithyroidectomy has been found to cause hypothyroidism in 63% of patients, with the incidence rising to 89% if combined with radiotherapy – which is often the case in many patients.⁸ Despite preservation of residual gland, the rate of post-operative hypothyroidism remained high (22 to 88%) after total laryngectomy with hemithyroidectomy.²

Total thyroidectomy or lobectomy and isthmusectomy are performed unnecessarily in more than 85% of cases, an unacceptable figure in view of the potential endocrine complications associated with this procedure. Some studies advocate that the thyroid gland need not be removed routinely in all laryngectomies, unless there is advanced disease with thyroid cartilage erosion and gross thyroid gland involvement or disease with significant subglottic or esophageal involvement.⁸

This study intends to determine if CT scan findings of thyroid cartilage erosion/invasion, cricoid cartilage erosion/invasion, and paraglottic space involvement are associated with the presence of tumor extension to the thyroid gland among patients with laryngeal cancer. Secondly, we aim to determine if there is a significant difference between CT scans and final histopathologic findings of thyroid/cricoid cartilage and paraglottic space involvement. Lastly, we aim to explore clinicodemographic factors (i.e., age, sex, T Stage, early tracheostomy, primary tumor location on CT scan) that may be associated with thyroid gland involvement in laryngeal SCC.

MATERIALS AND METHODS

With institutional review board approval, this cross-sectional study included records of patients admitted at the Philippine General Hospital Department of Otorhinolaryngology public ward from January 1, 2013 – December 31, 2019 who were diagnosed with histopathologically-confirmed laryngeal SCC. Records of patients diagnosed with other cancers of the larynx and those with incomplete records, unavailable CT scans and/or histopathology results were excluded.

Participants and variables

One hundred thirty-three (133) patients were identified. Seventy (70) patients were excluded for the following reasons: incomplete patient records (n=53), no laryngectomy done (n=2), no thyroidectomy done (n=7), prior radiotherapy (n=1), and non-SCC on final histopathology report (n=7). The following predictors will be considered in this study: 1) clinicodemographic: age, sex, T Stage, early tracheostomy; 2) radiologic: CT scan findings of primary tumor location (supraglottic, glottic, subglottic, transglottic, glottic-supraglottic, glottic-subglottic), thyroid cartilage erosion/invasion, cricoid cartilage erosion/invasion, paraglottic space

involvement, thyroid gland tumor invasion, and time between imaging and surgery; and 3) histopathologic: findings of thyroid cartilage erosion/invasion, cricoid cartilage erosion/invasion, paraglottic space involvement and thyroid gland involvement.

Definition of terms

Supraglottis is the region from the tip of the epiglottis to the superior edge of the true vocal cords, including the epiglottis, aryepiglottic folds, arytenoids, false vocal cords, and ventricles. Glottis is the region comprised of the true vocal cords up to 1cm below the true vocal cords, including the anterior and posterior commissures. Subglottis is the region extending from 1cm below the true vocal cords up to the lower border of the cricoid cartilage.³ Transglottic tumors represent tumors that involve all three subsites.⁶

Cartilage erosion is defined as involvement of the inner cortex only, punch out lesions, or focal lytic defects within sclerotic bone marrow comparable to osteolysis. Cartilage invasion is defined as major cartilage destruction involving both inner and outer cortices of the cartilage, or presence of tumor on both inner and outer aspects of the cartilage.⁹

Paraglottic space is bounded by the thyroid cartilage anterolaterally, conus elasticus inferomedially, ventricle and quadrangular membrane medially, and the pyriform sinus mucosa posteriorly.¹⁰

The researchers reviewed the patient database of the Department of Otorhinolaryngology to determine eligible patients for this study. Patient records were assigned codes and anonymized. The principal investigator reviewed online database and patients' records to obtain the clinico-demographic data and final histopathologic findings. Interpretation of the CT scans was done using anonymized DICOM format loaded onto a standard reader (Radiant DICOM viewer 64bit, ver 5.0.1) and medical grade screens. Both soft tissue and bone windows were included in the interpretation, with the latter used specifically for cartilage evaluation. All the images were interpreted twice, first

by a junior Radiologist (fellow-in-training) then later on confirmed by a senior Radiologist (Consultant). Findings were finalized by both as a team. Findings were assumed to be normal (no tumor) for relevant histopathologic data that were unavailable in the final report.

Fisher's exact test of association was done to determine the association between presumed predictors (age, sex, T stage, early tracheostomy), primary tumor location (supraglottic, glottic, subglottic, transglottic, glottic-supraglottic, glottic-subglottic), thyroid cartilage erosion/invasion, cricoid cartilage erosion/invasion, paraglottic space involvement, thyroid gland tumor invasion, and time between imaging and surgery, and the outcome (thyroid gland involvement on final histopathologic report). SPSS ver. 28.0.0.0(190) was used for statistical analysis, with a p value of <0.05 considered significant. Strength of association was initially planned to be determined by logistic regression. However, due to the small sample size, the researchers opted to determine strength of association using Cramer's V for nondichotomous variables, Phi coefficient and odds ratio for dichotomous variables.¹¹

RESULTS

Logistic regression was initially planned but not done for the significant variables due to the low sample size. An estimated sample size of 150 was computed to be necessary to make this analysis possible with adequate power.

A total of 59 men and 4 women (total n=63) were included, with ages ranging from 43 to 81 years old and a mean age of 62. Fifty six percent (56%, n=35) of patients were over 60 years old. Most patients were classified as T3 (n=18) and T4 (n=41) (total=93.7%). There were no T1 patients who underwent total laryngectomy due to present clinical guidelines that provide alternative voice-conservation therapies for such tumors. (Table 1)

A summary of CT scan and histopathology data is listed on Table 2. Most tumors were classified as transglottic on CT scan (n=24, 38.1%) and on final histopathology

Table 1. Clinicodemographic Data

Variable	Frequency (%)	With Thyroid Involvement	Without Thyroid Involvement	Mean (SD)	P-value
Age					
≤60 years	28 (44.4%)	2 (40%)	26 (44.8%)	62 (8.3)	1.000
>60 years	35 (55.6%)	3 (60%)	32 (55.2%)		
Sex					
Men	59 (93.7%)	5 (100%)	54 (93.1%)		1.000
Women	4 (6.3%)	0 (0%)	4 (6.9%)		
T Stage					
T1	0 (0%)	0 (0%)	0 (0%)		1.000
T2	4 (6.3%)	0 (0%)	4 (6.9%)		
T3	18 (28.6%)	1 (20%)	17 (29.3%)		
T4	41 (65.1%)	4 (80%)	37 (63.8%)		
Early Tracheostomy					
Yes	50 (79.4%)	5 (100%)	45 (77.6%)		0.574
No	13 (20.6%)	0 (0%)	13 (22.4%)		

Table 2. CT Scan and Final Histopathology Data

Variable	CT Scan			P-value	Strength of Association	Histopathology			P-value	Mean (SD)
	Frequency (%)	With Thyroid Gland Involvement on Final Histopathology	Without Thyroid Gland Involvement on Final Histopathology			Frequency (%)	With Thyroid Involvement	Without Thyroid Involvement		
Primary Site				0.259					0.409	
Supraglottic	1 (1.6%)	0 (0%)	1 (1.7%)			2 (3.2%)	0 (0%)	2 (3.4%)		
Glottic	15 (23.8%)	0 (0%)	15 (25.9%)			17 (27%)	0 (0%)	17 (29.3%)		
Subglottic	0 (0%)	0 (0%)	0 (0%)			2 (3.2%)	0 (0%)	2 (3.4%)		
Transglottic	24 (38.1%)	4 (80%)	20 (34.5%)			29 (46%)	5 (100%)	24 (41.4%)		
Glottic Supraglottic	12 (19%)	0 (0%)	12 (20.7%)			7 (11.1%)	0 (0%)	7 (12.1%)		
Glottic Subglottic	11 (17.5%)	1 (20%)	10 (17.2%)			6 (9.5%)	0 (0%)	6 (10.3%)		
Thyroid Cartilage				0.181					0.117	
No tumor	23 (36.5%)	0 (0%)	23 (39.7%)			26 (41.3%)	0 (0%)	26 (44.8%)		
Erosion	20 (31.7%)	3 (60%)	17 (29.3%)			9 (14.3%)	1 (20%)	8 (13.8%)		
Invasion	20 (31.7%)	2 (40%)	18 (31%)			28 (44.4%)	4 (80%)	24 (41.4%)		
Cricoid Cartilage				0.032*	0.318 _a				1.000	
No tumor	41 (65.1%)	1 (20%)	40 (69%)			61 (96.8%)	5 (100%)	56 (96.6%)		
Erosion	15 (23.8%)	2 (40%)	13 (22.4%)			1 (1.6%)	0 (0%)	1 (1.7%)		
Invasion	7 (11.1%)	2 (40%)	5 (8.6%)			1 (1.6%)	0 (0%)	1 (1.7%)		
Paraglottic Space				1.000					0.457	
No tumor	3 (4.8%)	0 (0%)	3 (5.2%)			56 (88.9%)	4 (80%)	52 (89.7%)		
Involved	60 (95.2%)	5 (100%)	55 (94.8%)			7 (11.1%)	1 (20%)	6 (10.3%)		
Thyroid Gland				0.018*	0.384 _b					
No tumor	54 (85.7%)	2 (40%)	52 (89.7%)			13 (1.797, 94.035) _c	58 (92.1%)			
Involved	9 (14.3%)	3 (60%)	6 (10.3%)				5 (7.9%)			
Time between CT scan and Surgery				1.000						25.21 (24.45)
≤14 days	27 (42.9%)	2 (40%)	25 (43.1%)							
>14 days	36 (57.1%)	3 (60%)	33 (56.9%)							

Notes: * significant, ^a Cramer's V; ^b Phi Coefficient; ^c Odds Ratio

(n=29, 46%). Only 8 (12.7%) patients had subglottic tumor involvement on final histopathology.

No patient had an isolated subglottic tumor, indicating that involvement of the subglottis is usually by tumor extension from another subsite. Thyroid cartilage erosion and invasion were noted in 67.8% of patients' CT scans and 62.7% of patients' histopathology. Cricoid cartilage invasion and paraglottic space involvement were often not reported on final histopathology results and have been likewise tagged as "no tumor." Thyroid gland involvement was only noted in the final histopathology reports of five patients. Over fifty percent of surgeries (n=34, 54%) were done within 16 days from the time of the CT scan which is relatively comparable to the ideal of two weeks.⁵

Only cricoid cartilage involvement (p=0.032, Cramer's V=0.318, fair) and thyroid gland involvement on CT scan (p=0.018, Phi=0.384, fair; OR 13 95% CI 1.797, 94.035) had a significant association with moderate effect size and strong association, respectively, with thyroid gland involvement on final histopathology. The researchers also checked for association between CT scan and final histopathology findings of paraglottic space, thyroid and cricoid cartilage. Significant association was noted only for CT scan and

final histopathology findings of thyroid cartilage (p=0.002, Cramer's V=0.364, fair). No significant association was noted for cricoid cartilage (p=1.000) or paraglottic space (p=1.000).

DISCUSSION

Only five patients had thyroid gland involvement on final histopathology. Although all five had subglottic involvement, no significant association was observed between laryngeal subsite (p=0.259) or subglottic extension (p=0.06) on CT scan and thyroid gland involvement on final histopathology. Thyroid gland invasion is also indicative of poor prognosis.^{6,7} Perhaps a combination of both advanced tumor stage and subglottic involvement may be crucial to tumor extension to the thyroid gland, given that all five patients were staged as IVA and transglottic in terms of extension.

Thyroid cartilage, cricothyroid membrane¹² and paraglottic space involvement⁶ have been identified as predictors of extra-laryngeal spread. Thyroid cartilage involvement and paraglottic space involvement may not have been significant due to the limited variability in the population, where 95.2% of patients (n=53) had involved paraglottic space on CT scan and patients were roughly equally divided among those who

had no tumor, erosion, and invasion of the thyroid cartilage on CT scan. However, among the five patients identified with thyroid gland involvement, all had thyroid cartilage erosion (n=3) or invasion (n=2) on preoperative CT scan.

As expected, thyroid gland involvement on CT scan is significantly associated with thyroid gland involvement on final histopathology ($p=0.018$). This reaffirms that CT scans are useful in determining tumor extension for operative planning.

The significant association between CT scan and final histopathology findings of thyroid cartilage may be indicative of the frequency of reporting of this structure. Cricoid cartilage and paraglottic space involvement were often not reported on final histopathology results and have been likewise tagged as “no tumor” but this may grossly underestimate the true incidence in our population.

Worth noting is that only two patients had cricoid cartilage findings on final histopathology and 22 on CT scan, while 60 patients had paraglottic space involvement on CT scan and only 7 on final histopathology. These results could also be reflective of the greater variability between the interpretation of involvement on imaging and the reporting of these findings on final histopathology results. The lack of association of thyroid cartilage findings on CT scan to thyroid gland involvement on final histopathology may be reflective of a true non-association or it may be due to the low number of observable outcomes (n=5), which is lower than the 11% noted in literature.²

The researchers theorized a potential effect of early tracheostomy, usually done in a separate surgery prior to definitive treatment with laryngectomy, as a potential route of tumor spread. However, this was also found to be not significant ($p=0.574$).

Several limitations to this study include: the non-standardized CT scan cuts and use of different machines, possible differences in CT scan protocols, and non-standardized final histopathology reports. It would have been ideal that all CT scans be done in one center only, however this situation is actually reflective of what happens in clinical practice and may provide a more accurate insight to challenges experienced in the process of surgical planning. A unified and standardized format for reporting both CT scan and histopathology findings in patients with laryngeal cancer would likely entail dialogue between otorhinolaryngologist-surgeons, radiologists and pathologists. MRI may be more sensitive in detecting cartilage involvement compared to CT scans.^{13,14} Future studies may also investigate the MRI as a more sensitive modality for determining cartilage involvement.

The small population limited the kind of analysis possible for the data gathered. Fisher’s exact test can only determine presence of association but not the strength of association or the effect of a combination of variables and the like. Cramer’s V was used for the effect size of the cricoid cartilage, while odds ratio was computed for the thyroid gland

involvement on CT. Analysis using logistic regression with a larger sample size may be worth exploring in future research.

CONCLUSION

The presence of cricoid cartilage erosion or invasion and thyroid gland involvement on CT scan is associated with thyroid gland involvement on final histopathology in patients with laryngeal SCC. Association between CT scan and final histopathology findings on the thyroid cartilage was noted. A standardized criteria for reporting of CT scan findings and final histopathologic findings may be developed for the benefit of future patients with laryngeal SCC.

The authors were unable to confirm that thyroid cartilage involvement on CT scan was significantly associated with thyroid gland involvement on final histopathology reports and thus, this study is unable to recommend preservation of the thyroid gland in the setting of an intact thyroid cartilage, as is seen in literature. Laryngeal SCC patients with advanced tumor stage, transglottic extension, and involvement of the cricoid cartilage and thyroid gland on CT scan may stand to benefit from thyroidectomy to ensure good margins of resection.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising of manuscript, and final approval of version to be published.

Author Disclosure

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