The Laryngoscope

Management of the Thyroid Gland During Total Laryngectomy in Patients With Laryngeal Squamous Cell Carcinoma

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Objectives/Hypothesis: The goal of the study was to determine the role of routine total thyroidectomy and hemithyroidectomy in patients undergoing total laryngectomy for laryngeal squamous cell carcinoma.

Study Design: The study group consisted of 343 patients who underwent total laryngectomy (98 treated with surgery alone, 136 treated following radiation failure, and 109 following chemoradiation failure). Total thyroidectomy was performed in all obstructing and bilateral lesions or if there was suspicion of contralateral lobe involvement. Hemithyroidectomy was performed in all lateralized lesions. Retrospective histopathologic analysis of thyroid specimens was subsequently performed.

Results: In all, 262 patients underwent total thyroidectomy during total laryngectomy, six of which demonstrated squamous cell carcinoma evident within the thyroid gland (4 from transglottic lesions, 2 from subglottic lesions). Hemithyroidectomy was performed in 81 patients, with only one patient demonstrating evidence of squamous cell carcinoma within the thyroid gland. Hypothyroidism was observed in 88% (n = 61) of patients who underwent thyroid lobectomy alone, requiring hormone supplementation.

Conclusion: Routine surgical management of the thyroid gland should not be performed, except in cases of subglottic primary lesions, lesions with significant subglottic extension, or transglottic lesions. Despite efforts to preserve the contralateral thyroid lobe in cases of selective lobectomy, these patients often have a high rate of hypothyroidism, and a total thyroidectomy should be considered when involvement of the thyroid gland is suspected.

Key Words: Total laryngectomy, thyroidectomy, hemithyroidectomy, subglottic lesions, glottic cancer.

Level of Evidence: N/A.

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INTRODUCTION

In 1955, Ogura characterized the pathologic spread of advanced staged laryngeal cancer. Within his series, he described 10% (6/59) lesions that demonstrated thyroid gland invasion and recommended for the first time en bloc resection of the ipsilateral thyroid lobe and isthmus during total laryngectomy.[1] In 1973, Harrison et al. further echoed the recommendations by Ogura, as well as adding that frozen section analysis of the contralateral thyroid lobe should be performed.[2] The decision to surgically address the ipsilateral thyroid remains controversial. Harrison et al. recommend elective removal of the thyroid lobe in all cases.[2] Other authors recommend a more selective approach to removal of the thyroid lobe. Most recently, a meta-analysis by Mendelson et al. recommended elective ipsilateral thyroid lobectomy and isthmusectomy for all tumors with subglottic extension greater than 10 mm, as well as all transglottic tumors.[3] Other recommendations include further surgical management of the thyroid gland in all cases of large T3 and T4 tumors that involve the anterior commissure.[4]

Currently, there is no consensus on the guidelines directing management of the ipsilateral thyroid lobe during total laryngectomy for laryngeal squamous cell carcinoma. To the best of our knowledge, we provide the largest review of laryngeal and thyroid specimens following total laryngectomy for laryngeal squamous cell carcinoma to date.

MATERIALS AND METHODS

We reviewed 343 consecutive patients undergoing total laryngectomy for squamous cell carcinoma at our institution between September 1997 and September 2011. Nonfunctional laryngectomies as well as rare laryngeal tumors were excluded from the study design. The study involved assessment of laryngeal squamous cell carcinoma in 261 males and 82 females, with ages ranging from 22 to 88 (mean 64.3). Management protocol involved unilateral thyroidectomy in all lateralized cancers. All patients with bilateral lesions or with palpable or suspicious disease on exam underwent total thyroidectomy. Suspicious disease was defined as the presence of a firm contralateral nodule, clinically evident calcification, or the presence of a clinically apparent node. Histopathological analysis of all specimens were performed and reviewed retrospectively.

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TABLE I.
Cohort Description of 343 Patients Undergoing Total Laryngectomy in the Primary and Salvage Surgical Setting.

Total Laryngectomy (n = 343)	
Primary laryngectomy (n = 98)	
EBRT	67
EBRT + chemotherapy	23
No additional intervention	8
Salvage laryngectomy (n = 245)	
Radiation failure	136
Radiation and chemotherapy failure	109

EBRT = external beam radiation therapy.

RESULTS

Overall, 343 total laryngectomy specimens were evaluated (Table I). In all, 28% (98/343) of the patients underwent primary surgery for obstructing lesions or thyroid cartilage involvement. All patients were subsequently recommended to proceed with postoperative radiation therapy. However, only 68% (67/98) went on to receive external beam radiation therapy alone, with 23% (23/98) receiving concurrent chemotherapy. In the remainder of the patients, 40% (136/343) had radiation failure, and 32% (109/343) failed chemoradiation.

In all, total thyroidectomy was performed in 76% (262/343) of the patients, and hemithyroidectomy in 24% (81/343) (Table II). Within the total thyroidectomy group, 34% (90/262) of cases were performed in the primary surgical setting, while 66% (172/262) were performed in the salvage setting. In the hemithyroidectomy group, 10% (8/81) were performed in the primary surgical setting, while 92% (90/98) were performed in the salvage setting.

On review of the pathological specimens in the total thyroidectomy population, six patients had direct extension into the thyroid gland by squamous cell carcinoma. All 2% (6/262) patients had obstructing lesions in otherwise nontreated patients, two with subglottic primaries and four with transglottic lesions. No patients with glottic or supraglottic obstructing lesions had direct extension into the thyroid gland. In the hemithyroidectomy population, 1% (1/81) had squamous cell carcinoma involving the thyroid lobe, extending from a transglottic lesion (Table III). Interestingly, two had incidental papillary carcinoma that underwent subsequent completion thyroidectomies.

Subsequent postoperative hypothyroidism was analyzed in the hemithyroidectomy group. Follow-up at 1 year revealed that of the 81 patients having undergone hemithyroidectomy, 85% (69/81) were alive and free of disease. Review of pathologic specimens revealed no evidence of recurrent malignancy in the remnant thyroid lobe in the 12 patients who had succumbed to death in the 12 months following surgery. Within the group of 69 patients who were alive and free of disease, 88% (61/69) had developed hypothyroidism requiring thyroid hormone replacement therapy. Patients had undergone previous radiation therapy in 90% (55/69) of this group, whereas only 10% (6/61) developed hypothyroidism without previous radiation exposure. The average time to development of hypothyroidism in the radiation exposed group was 42 days as compared to 110 days in the nonradiated group (Table IV).

Analysis of patients requiring calcium supplementation secondary to prolonged hypocalcemia was performed. It was determined that of the 343 patients having undergone total laryngectomy, no patients required calcium supplementation beyond 2 months postoperatively.

TABLE II.
Comparison of Surgical Settings for All Patients Undergoing Total Thyroidectomy Compared to Hemithyroidectomy.

Total Thyroidectomy (n = 262)	
Primary laryngectomy	90
Salvage laryngectomy	172
Hemithyroidectomy (n = 81)	
Primary laryngectomy	8
Salvage laryngectomy	73

TABLE III.
Pathologic Analysis of Thyroid Lobe Specimens Found to Have Squamous Cell Carcinoma Correlated With Primary Sites of Tumor.

Total thyroidectomy (n = 6)	
Subglottic	2
Transglottic	4
Hemithyroidectomy (n = 1)	
Transglottic	1

DISCUSSION

Ogura first described thyroid gland involvement as a metastatic feature of laryngeal cancer in 1955, recommending its routine removal.[1] Thyroid gland involvement is thought to occur by direct extension due to specific anatomical considerations. In our study, we found that 100% of patients in both total thyroidectomy (6/6) and hemithyroidectomy (1/1) populations with squamous cell carcinoma of the thyroid occurred through direct extension. In Brennan et al. review of the literature, the majority of squamous cell carcinoma (78%) invasion was through direct extension, with only 10% (11/107) of cases with documented involvement via lymphatic spread.[4] Laryngeal regions most susceptible to spread are at the anterior angle of the thyroid cartilage and the cricothyroid membrane.[5,6]

TABLE IV.
Analysis of Patients Alive and Disease-Free 12 Months Postoperatively Having Undergone Selective Hemithyroidectomy (n = 81) and Resultant Hypothyroidism Requiring Hormone Replacement.

	Number of Patients	Mean Time (days)
Previous radiation therapy	55	42
No previous radiation therapy	6	110

Histopathologic studies have shown that cancer spread seems to occur along collagen bundles where the connective tissue membranes attach to the cartilage. As the cancer expands, it causes expansion of the collagen bundles, resulting in a direct pathway for the spread of cancer through the perichondrium.[6] This subsequently makes the cricothyroid membrane and anterior commissure ligament more susceptible to direct extension of tumor. Furthermore, a defect exists in the inner perichondrium, at the anterior angle of the thyroid cartilage, where it is pierced by Broyles's ligament, further providing a route for tumor spread.[2,6,7] Typically, perichondrium provides an excellent protective barrier to the spread of carcinoma. However, once the carcinoma has spread beyond the perichondrium, it may spread in a subperichondrial plane throughout the cartilage, further predisposing to extralaryngeal spread.[8] Therefore, extra laryngeal spread to the thyroid gland should be suspected in cases of anterior commissure or cricothyroid membrane involvement, or in cases with evidence of perichondrial compromise.

Primary subglottic lesions, as well as the presence of subglottic extension beyond 10 mm, has been a predictor for likely extralaryngeal and thyroid gland involvement.[4,9–11] Sparano et al. determined that 100% (7/7) of cases with thyroid gland involvement had subglottic extension beyond 15 mm.[10] Brennan et al. further found that 8% (2/26) of tumors with greater than 5-mm subglottic extension had extralaryngeal spread to the thyroid.[4] In the series by Biel and Maisel, they found that 70% of all glottic cancers with thyroid gland involvement had subglottic extension more than 1.5 cm.[12] In a series by Yuen et al., 16% of tumors with subglottic extension demonstrated thyroid gland involvement.[13] Subglottic extension further predisposes to paratracheal lymph node metastases and also is a predictor of surgical treatment failure.[2,14] Within our study, of the six patients who underwent total thyroidectomy for direct involvement, 33% (2/6) of the tumors were subglottic primary tumors.

Strome et al. postulated a model for the spread of lesions, with significant subglottic extension based on the susceptibility of the fibroelastic barriers within the subglottis to spread.[9] Pathologic analysis revealed that chondroid tissue had very little carcinomatous involvement and little erosive changes. The bulk of invasive carcinoma was found to penetrate through gaps between tracheal rings, respecting the boundaries of the cartilaginous framework. The majority of spread was found to be through the paraglottic space into the region bounded medially by the conus elasticus and laterally by the laryngeal cartilages.[9]

Predisposition of subglottic tumors to thyroid gland involvement may also be due to patterns of lymphatic spread.[11] Drainage of the anterior subglottis is by lymphatic penetration of the cricothyroid membrane to pretracheal and prelaryngeal nodes. Posterolaterally, lymphatic drainage occurs through the cricotracheal membrane to the paratracheal nodes. The pretracheal, prelaryngeal, and paratracheal nodes all are within close proximity to the thyroid gland.[11,15] Therefore, the thyroid gland should be addressed in tumors of primary subglottic origin or with significant subglottic extension.

It should be noted that no patients with obstructing supraglottic or glottic lesions had involvement of the thyroid gland. Extralaryngeal spread of supraglottic tumors is thought to be impeded by the circumferential covering provided by the thyrohyoid membrane and the resilient protective barrier of the hyoepiglottic ligament.[5,16] Extralaryngeal spread from supraglottic lesions is thought to occur by means of direct extension through the thyroid cartilage.[5]

Transglottic lesions as well as paraglottic space involvement has been further predictive of extralaryngeal spread. Within our study, we found that of the seven patients with extension into the thyroid gland, 71% (5/7) were transglottic lesions. Tucker and Smith first defined the paraglottic space as being bounded by the conus elasticus inferior medially, the quadrangular membrane superior medially, the thyroid cartilage anterolaterally, and the pyriform sinus posteriorly.[17]

Studies have indicated that subglottic tumors frequently involve the paraglottic space, increasing likelihood of extra laryngeal spread.[4,9,18,19] Brennan et. al found the paraglottic space to be the most important space to be predictive of thyroid gland involvement.[4] They reported that 100% (8/8) of patients with thyroid gland involvement had transglottic lesions, with subsequent laryngeal cartilage invasion in the lower third of the thyroid cartilage and upper portion of the cricoid.[4] Lam et al. found that of 54% (19/35) of tumors with anterior extralaryngeal spread involved the paraglottic space.[5] Harrison showed an incidence of 25% involvement of thyroid gland in a series evaluating the tumor spread of transglottic and subglottic tumors.[15]

Transglottic lesions, as well as lesions within the paraglottic space, likely spread inferiorly due to the lack of a fibroelastic or cartilaginous impedance. As the tumor advances through the paraglottic space, it maintains the medial boundary provided by the conus elasticus, subsequently spreading outward laterally through the cricothyroid membrane.[20] An intricate relationship exists between the subglottis and paraglottic space, which facilitates extralaryngeal spread of transglottic lesions to the thyroid. Therefore, surgical management of the thyroid gland should be directed appropriately in cases of transglottic lesions.

Thyroid cartilage involvement has also been considered a risk factor for likely thyroid gland involvement and an indication for thyroid lobectomy, despite having never been verified as an independent risk factor.[3,10,11] In Buckley et al.'s histopathologic study of laryngeal cancer spread, they found that 65% (19/29) of cancers with invasion of the laryngeal framework occurred through the thyroid cartilage.[18] This was found to be correlated almost entirely with subglottic extension, particularly through the posterior and lateral cricothyroid space.[18] Brennan et al. further found that thyroid cartilage involvement was always invariably associated with transglottic tumor extension.[4] Furthermore, Biel et al. found that 100% (11/11) of cases with thyroid gland involvement involved the thyroid cartilage. However, it

is important to recognize that it is rare to find isolated thyroid cartilage involvement without transglottic or subglottic extension, making validation of thyroid cartilage involvement as an independent risk factor difficult.[3]

Thyroid cartilage invasion is considered to occur in areas in which cartilage has undergone ossification.[21] In a study by Olszewski, laryngectomy blood vessels were injected with silicone rubber, and the behavior of the vessels was mapped.[22] It was determined that cancer had most commonly spread through neo-ossified cartilage, with little to no involvement of nonossified avascular cartilage.[22] Therefore, in the aging larynx that has undergone ossification changes, these centers provide potential routes for direct extension of laryngeal tumors.

We found that, despite attempts to preserve the contralateral lobe in cases of selective ipsilateral thyroid lobectomy, hypothyroidism requiring hormone replacement was seen in 88% of cases (61/69) at 1-year postoperatively. The incidence of hypothyroidism following total laryngectomy in combination with ipsilateral thyroidectomy ranges from 44% to 89%.[23–26] It is thought that hypothyroidism may be a consequence of disruption of the vasculature to the intact contralateral lobe either due to adjuvant radiation therapy or during surgical manipulation of the neck during neck dissection.[23,25] Other authors have further postulated an immune-mediated mechanism to thyroid dysfunction caused by radiation, as indicated by increased levels of detected postoperative antithyroglobulin antibodies.[24] Within our study, the majority of patients who developed hypothyroidism were in the group having undergone previous radiation therapy (55/61) as compared to those without previous radiation exposure (6/61). Time to development of hypothyroidism was also determined to be sooner (42 days) in the previously radiated group as opposed to the nonradiated group (110 days). Therefore, due to the high rates of hypothyroidism in cases of selective lobectomy in the previously radiated patient, it can be recommended that total thyroidectomy routinely be performed, providing superior oncologic benefit.

Disruption of the vasculature may also compromise parathyroid gland activity. Within our study, we observed four patients who required calcium supplementation due to persistent hypocalcemia in the immediate postoperative setting. However, beyond 2 months postoperatively, calcium supplementation was not required in any patients.

CONCLUSION

Close anatomic relationships exist between the subglottis, paraglottic space, cricothyroid space, thyroid cartilage, and cricothyroid membrane. These anatomical relationships and the predictive migration pattern of cancer along the laryngeal fibroelastic framework allows for better understanding of thyroid gland management in advanced stage laryngeal tumors. Surgical management of the thyroid lobe should be addressed in tumors with significant cartilaginous involvement, anterior commissure involvement, and increased subglottic extension; and in cases of transglottic tumors. Despite efforts to preserve the contralateral thyroid lobe in cases of selective lobectomy in the previously radiated patient, these patients often have a high rate of hypothyroidism, and a total thyroidectomy should be considered as standard protocol when the thyroid gland is to be surgically addressed.

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