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WILEY
How Reliably Can Computed Tomography Predict Thyroid Invasion Prior to Laryngectomy?

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**Objectives/Hypothesis:** There is little evidence to support the removal of thyroid tissue during total laryngectomy. Although oncological control of the tumor is the priority, thyroidectomy can lead to hypothyroidism and hypoparathyroidism. This study aimed to test the usefulness of preoperative computed tomography in predicting histological invasion of the thyroid.

**Study Design:** Ambispective cohort study.

**Methods:** All patients undergoing total laryngectomy for squamous cell carcinoma at one center from 2006 to 2016 were included. Data were recorded prospectively as part of the patients' standard care, but were collated retrospectively, giving this study an ambispective design. The histology report for thyroid invasion was taken as the gold standard. The computed tomography report was categorized by invasion of tumor into intralaryngeal, laryngeal cartilage involvement, and extralaryngeal tissues.

**Results:** Seventy-nine patients were included. Nine patients had thyroid involvement on histology, translating to an incidence of 11.29% in this population. The positive predictive value for cartilage involvement on computed tomography for thyroid invasion was 52.9% (95% confidence interval [CI]: 28.5%-76.1%) and the negative predictive value was 100% (95% CI: 92.7%-100%). The positive predictive value for extralaryngeal spread on computed tomography for thyroid involvement was 100% (95% CI: 62.9%-100%), and the negative predictive value was also 100% (95% CI: 93.5%-100%).

**Conclusions:** This study has shown that preoperative computed tomography is an effective method of ruling out thyroid gland invasion. The absence of extralaryngeal spread on computed tomography has been shown to be the most useful finding, with a high negative predictive value and a narrow 95% CI.

**Key Words:** Laryngectomy, thyroidectomy, thyroid gland, squamous cell carcinoma, computed tomography scan, computerized axial tomography scan.

**Level of Evidence:** 4.

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INTRODUCTION

Total laryngectomy remains a vital part of many patients' treatment for squamous cell carcinoma. As part of a total laryngectomy the thyroid gland is divided and may be removed, either as a hemithyroidectomy or a total thyroidectomy. The evidence base for this decision is scanty; traditionally at least the thyroid lobe, ipsilateral to the tumor, would be excised, but in recent years there has been a drive to establish if this is truly necessary.¹²

Although oncological control of the tumor with adequate margins is the overriding priority, the removal of thyroid tissue may have significant consequences. Evidence shows that high levels of hypothyroidism are seen even if one thyroid lobe is preserved, and this may be exacerbated by radiotherapy.³ Furthermore, the parathyroid glands are closely aligned to the thyroid poles on their end-arteriole supply. Studies examining thyroidectomy have shown that early, transient, or permanent hypoparathyroidism occurs even following hemithyroidectomy only, and this incidence increases markedly if both thyroid lobes are removed.³ Postoperative hypocalcemia can be difficult to treat, resulting in critical care admission, delayed discharge, serial blood tests, and life-long medication. Therefore, removal of thyroid tissue unnecessarily results in increased healthcare costs, in addition to the increased morbidity to the patient. It can be argued that a total laryngectomy is morbid enough, and any incremental improvement should be sought, providing it does not jeopardize oncological outcome.

Several recent articles have sought to improve the evidence behind the decision to remove the thyroid during laryngectomy. The main route of spread of malignancy from the larynx to the thyroid appears to be direct invasion through the cartilage or adjoining membranes, rather than hematogenous or lymphatic.¹² It has been shown that involvement of the subglottis carries a significantly higher risk of thyroid invasion.²⁴⁻⁶⁻⁸ It has also been suggested that poorly differentiated cancers may have a propensity for thyroid invasion, although currently the evidence to support this is low.⁹

This study aimed to test the usefulness of preoperative computed tomography (CT) in predicting histological...
involvement of the thyroid. The alternative hypothesis was, therefore, that preoperative CT has a high positive and negative predictive value for thyroid involvement prior to total laryngectomy.

MATERIALS AND METHODS

Data Source

To ensure all patients were included they were identified using clinical coding, surgeons’ operative logbooks and the local head and neck multidisciplinary team (MDT) database. Data were then obtained from electronic records, including pathology, radiology, letters, and operation notes. Data were recorded in the electronic records prospectively as part of the patients’ standard care, but were collated retrospectively, giving this study an ambispective design.

Inclusion Criteria

All patients undergoing total laryngectomy for treatment of squamous cell carcinoma at the Royal Gwent Hospital from January 1, 2006 to January 1, 2016 were included. This included patients undergoing primary or salvage laryngectomy. Patients undergoing laryngectomy for aspiration or for other forms of malignancy were excluded.

Data Collection and Analysis

Data were collated in Microsoft Excel (Microsoft, Redmond, WA), and were anonymized at entry and kept in an encrypted file. Data were analyzed in SPSS version 20.0 (IBM Corp., Armonk, NY). Patient specific variables included age at diagnosis and gender. Other variables included initial TNM staging, previous neck radiotherapy, date of laryngectomy, and degree of thyroid excision. Follow-up records were analyzed for disease recurrence.

The histopathologist’s report of the main specimen for thyroid invasion was taken as the gold standard. Malignant cells abutting, but not invading, the capsule was taken as negative. Any invasion through the capsule was taken as positive for thyroid gland invasion.

The CT report was analyzed for laryngeal cartilage invasion by the primary tumor and extralaryngeal spread (defined independently as an individual CT may exhibit both features). These characteristics were chosen as they are consistently reported as part of the standard care of these patients to allow staging of the primary tumor. This was taken as a dichotomous value, with any degree of laryngeal cartilage invasion taken as positive. Extralaryngeal spread was defined as any invasion of tumor reported as extending beyond the larynx (for example, into the tongue base, strap muscles, trachea, or thyroid gland).

The CT was reported in all cases by consultant radiologists, as part of the standard workup of these patients. The radiologists were all experienced in head and neck radiology and were working as part of the head and neck MDT. If a report was updated or corrected, the result was taken as the most up to date at the time of laryngectomy.

Ethical Approval

In accordance with the institutions ethical research policy, and the NHS Health Research Authority guidelines, ethical approval was not required for this project. This was because all researchers were part of the team caring for these patients. All data were collected as part of the patients’ standard care, and data were collated anonymously.

RESULTS

Seventy-nine patients fulfilled the inclusion criteria during the study period. Two patients were excluded who were undergoing laryngectomy for aspiration following oncologically successful radiotherapy and one patient for a locally aggressive follicular thyroid cancer. The average age of the included patients was 64 years (range, 43–87 years), and 82.2% were male. Overall, 32.90% of patients were undergoing a salvage laryngectomy for recurrent disease, having previously undergone primary radiotherapy, 53.20% of patients underwent postoperative radiotherapy, and 13.90% of patients were treated without radiotherapy.

CT scans were conducted on average 24 days preoperatively (range, 2–46 days). The CT reporting was consistent and dichotomous, allowing cartilage invasion and extralaryngeal spread to be defined without extrapolation or deliberation by the authors. Cartilage invasion was seen in 17 patients (21.5%), and extralaryngeal spread was seen in nine patients (11.4%). A total thyroidectomy was performed in six patients (7.6%), 64 patients (81%) underwent a hemithyroidectomy (including the thyroid isthmus), and the thyroid was divided but left in situ in nine patients (11.4%). Of those in whom all thyroid tissue was left in situ, histology showed the tumor was confined to the larynx and none were found to have local recurrence by the time of data collection (average follow-up 5 years [range, 1–9 years]). These were therefore included in the “thyroid not involved” group. The justification for the decision to remove or leave thyroid tissue was not consistently recorded, and therefore this information could not be collected with any degree of certainty.

Nine patients had thyroid gland involvement on histology, translating to an incidence of 11.29% in this population. Table I details patient demographics, comparing the patients with thyroid invasion on histology to those without.

Table II describes the results of cartilage invasion on CT compared to histology. The positive predictive value for cartilage involvement on CT for thyroid invasion was 52.9% (95% confidence interval [CI]: 28.5%–76.1%; margin
for thyroid invasion between a preoperative CT and invasion as an outcome. Lin et al. showed a statistically significant correlation between CT findings and thyroid invasion, but focused on either cricoid cartilage invasion or thyroid invasion as an outcome. Lin et al. also explored the reliability of magnetic resonance imaging in predicting thyroid invasion in a sample of 41 laryngectomy patients and described a high negative predictive value; however, only three patients had thyroid invasion, and there were no statistical tests of significance (such as CIs) reported. Kinshuck et al. also looked at magnetic resonance imaging in this setting; however, 113 of 194 patients were excluded from their analysis, and only one case of histological thyroid invasion was discovered; this makes it difficult to draw firm conclusions from their study. Furthermore, although magnetic resonance imaging is now readily available, all patients in our sample underwent CT as part of their standard staging. The usefulness of additional imaging in answering this question, such as magnetic resonance imaging or ultrasonography, is an area for further analysis.

In this sample, 88.6% of patients underwent a hemi- or total thyroidectomy, despite a prevalence of 11.29% thyroid invasion on histology. The drive to take more tissue, ensuring clear margins and a thorough excision is understandable. However, if thyroid involvement can be reliably excluded preoperatively, this decision can be based on objective evidence, and many patients may be spared a thyroidectomy and any resulting morbidity. This information is available at the time of consenting, and patients can therefore be further counseled and prepared.

No evidence was found exploring the extent of the thyroidectomy needed in laryngectomy with a high risk of thyroid invasion. The thyroid gland is known to have a rigorous cross-gland lymphatic system, and the usefulness of a hemithyroidectomy may be questionable. Certainly, thyroid gland invasion on histology has been shown to be associated with a poor prognosis, although this may be a reflection on the type of disease that undergoes thyroid invasion, rather than the thyroid involvement itself.

Another area that requires further investigation is the hormonal benefit from leaving thyroid tissue in situ. In studies following patients after hemithyroidectomy alone (without laryngectomy), there is a proven risk of hypothyroidism and hypoparathyroidism, which increases markedly if the entire thyroid is removed. In laryngectomy, the disruption to the thyroid and parathyroid glands, even if they are left in situ, may be significantly greater, and many of these patients will undergo radiotherapy, if they have not already. There are some cohort studies that suggest that retaining as much thyroid tissue as possible results in improved thyroid function following radiotherapy, but the power of these studies are low. The benefit in terms of thyroid function of retaining both lobes of the thyroid gland during laryngectomy is therefore unknown at this time.

**TABLE II.**

| Cartilage Invasion on CT Compared to Thyroid Invasion on Histology. |
|---------------------------------|------------------|------------------|
| Thyroid Invasion                | No Thyroid Invasion | Total            |
| Cartilage invasion on CT        | 9 (true positive) | 8 (false positive) | 17 |
| No cartilage invasion on CT     | 0 (false negative) | 62 (true negative) | 62 |
| Total                           | 9                 | 70               | 79 |

*CT = computed tomography.*

**DISCUSSION**

This ambispective review of 10 years of consecutive patients treated for squamous cell carcinoma with total laryngectomy at a single center has shown that preoperative CT is an effective method of ruling out thyroid gland invasion. The 11.29% incidence for thyroid invasion described in this study is similar to that reported in larger series; Kumar et al.’s large meta-analysis reported 10.7% (95% CI: 7.6%-14.2%).

Cartilage invasion has not been shown to be predictive of thyroid invasion, as described in other studies. However, extralaryngeal spread on CT has been shown to have a high negative predictive value and specificity, with narrow 95% CIs. This means that if the CT is reported as having no extralaryngeal spread, the surgeon can be confident that the thyroid gland is not involved. The margins for error for both positive predictive values are large; therefore, a positive CT finding cannot be taken as indicative of thyroid involvement. Combined with the results for the negative predictive value, this means that if cartilage involvement is reported with no extra laryngeal spread, there is still a low chance of thyroid invasion.

This is the first article to explore this specific question. Gorphe et al. showed a statistically significant correlation for thyroid invasion between a preoperative CT and histology, but did not evaluate CT as a test as in this article. Gaillardin et al. also showed a statistically significant correlation between CT findings and thyroid invasion, but focused on either cricoid cartilage invasion or thyroid invasion as an outcome. Lin et al. explored the reliability of magnetic resonance imaging in predicting thyroid invasion in a sample of 41 laryngectomy patients and described for error, 23.8%), and the negative predictive value was 100% (95% CI: 92.7%-100%; margin for error, 3.7%). The sensitivity of cartilage invasion on CT for thyroid invasion was 100% (95% CI: 66.4%-100%), the specificity was 88.6% (95% CI: 78.7%-94.9%), and the accuracy was 89.9%.

Table III describes extralaryngeal spread on CT compared to histology. The positive predictive value for extralaryngeal spread on CT for thyroid involvement was 100% (95% CI: 62.9%-100%; margin for error, 18.6%), and the negative predictive value was also 100% (95% CI: 93.5%-100%; margin for error, 3.3%). The sensitivity of extralaryngeal spread on CT for thyroid invasion was 100% (95% CI: 66.4%-100%), the specificity was 100% (95% CI: 94.9%-100%), and the accuracy was 100%.

**TABLE III.**

| Extralaryngeal Spread on CT Compared to Thyroid Invasion on Histology. |
|---------------------------------|------------------|------------------|
| Thyroid Invasion                | No Thyroid Invasion | Total            |
| Extralaryngeal spread on CT     | 9 (true positive) | 0 (false positive) | 9 |
| No extralaryngeal spread on CT  | 0 (false negative) | 70 (true negative) | 70 |
| Total                           | 9                 | 70               | 79 |

*CT = computed tomography.*
There are areas of limitation in this study. The retrospective design means the study has been reliant on the data recorded at the time. Additional characteristics consistently reported on the CT report would have allowed further analysis. In particular, thyroid invasion itself was inconsistently reported on the CT; some reports described extensive invasion beyond the larynx into the pretracheal soft tissue but did not specifically mention the thyroid, whereas many do not mention negative thyroid gland invasion. CT is also a subjective test due to the requirement of interpretation by a human radiologist, and there is likely to be a difference between interpretations. A prospective study design might allow for this by ensuring all CTs are reported by the same radiologist, or by several to check for uniformity. This is not seen as an important source of bias in this study, however, as it reflects the situation in clinical practice. All CTs in this study were reported by a consultant radiologist with an interest in head and neck, routinely working as part of the head and neck MDT. This therefore reflects the quality of the information available to inform decisions prior to laryngectomy at this center. Another possible source of bias is the time delay between CT and laryngectomy, with a range of 2 to 46 days. Although this again reflects the reality in many centers, ideally the interval would be more homogenous.

Although this study describes 10 years of consecutive patients, the numbers are still relatively small. An attempt has been made statistically to allow for this, using 95% CIs, and as described above useful conclusions can be drawn. A larger prospective study would allow additional features to be examined with increased confidence, and may also utilize different imaging modalities such as ultrasound or magnetic resonance imaging.

CONCLUSION
Despite the traditional aggressive approach of removing at least a single lobe of the thyroid as part of a total laryngectomy, there is a growing body of evidence that this is unnecessary and increases the morbidity of the procedure. It is unlikely that a single test will give enough confidence to leave thyroid tissue behind. However, this study suggests that taken in context with other risk factors, such as the absence of subglottic disease, the number of thyroidectomies as part of laryngectomy can be greatly reduced by noting the lack of extralaryngeal spread on the preoperative CT.

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BIBLIOGRAPHY