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Does thyroid-sparing total laryngectomy decrease the risk of hypothyroidism?

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Abstract

Background. Thyroid lobectomy is recommended with total laryngectomy for laryngeal cancer in the National Comprehensive Cancer Network ('NCCN') guidelines. However, it is associated with a 32–89 per cent risk of hypothyroidism, with or without adjuvant radiotherapy.
Objective. The study aimed to determine whether preserving the whole thyroid, compared to a single lobe, does indeed significantly lower the incidence of hypothyroidism in the setting of total laryngectomy.
Method. A retrospective study was conducted at Groote Schuur Hospital in Cape Town, South Africa.
Results. Eighty-four patients met the inclusion criteria. The overall incidence of hypothyroidism was 45.2 per cent. The incidence of hypothyroidism was significantly reduced in patients who underwent thyroid-sparing total laryngectomy compared to hemithyroidectomy ($p = 0.037$). Adjuvant radiotherapy was associated with a higher incidence of hypothyroidism ($p = 0.001$).
Conclusion. Thyroid-preserving laryngectomy should be advocated in carefully selected patients with advanced laryngeal carcinoma, as it reduces the incidence of hypothyroidism.

Introduction

The National Comprehensive Cancer Network ('NCCN') guidelines recommend routine thyroid lobectomy on the side of a laryngeal cancer for advanced laryngeal cancer requiring total laryngectomy, and this is common practice.[1–3] Yet, thyroid gland invasion by laryngeal cancer is uncommon, with an overall pooled incidence of 10.7 per cent.[4] In addition, hemithyroidectomy with total laryngectomy is associated with a 32–89 per cent risk of hypothyroidism, with a relative risk of 2.1–3.6.[2,5–10]

Rendering a patient as hypothyroid may be problematic if follow up is unreliable, or if the ability to monitor and treat hypothyroidism is unavailable, as it is in much of the developing world.[11] Therefore, thyroid-sparing laryngectomy has been advocated to reduce the need for thyroid hormone replacement, with ipsilateral lobectomy or total thyroidectomy reserved for: intra-operative suspicion of thyroid involvement, cancers with more than 10 mm of subglottic extension, subglottic cancers, tumour (T) stage T_4 cancers extending through thyroid cartilage, and T_4 pyriform sinus cancers.[12] By employing this policy, thyroid-sparing laryngectomy surgery may be performed without adversely affecting oncological control when carried out in selected patients with advanced laryngeal and hypopharyngeal carcinoma.[13]

Aims

The study aimed to determine whether preserving the whole thyroid, compared to a single lobe, does indeed significantly lower the incidence of hypothyroidism in the setting of total laryngectomy with or without adjuvant radiotherapy.

Materials and methods

We conducted a retrospective, cross-sectional study of all patients who underwent total laryngectomy or laryngopharyngectomy for laryngeal and hypopharyngeal squamous cell carcinoma from 2009 to 2019 at Groote Schuur Hospital in Cape Town, South Africa. Institutional ethics approval was obtained. Patients were excluded on the following grounds: undocumented intra-operative status of the thyroid gland; patient outcome unavailable; patients who did not complete at least six months' follow up; or patients who were lost to follow up.

Patients were divided into either an euthyroid group or a hypothyroid group. The euthyroid group consisted of patients with normal thyroid-stimulating hormone (TSH) and normal free thyroxine (FT4) levels. The hypothyroid group included patients with subclinical hypothyroidism (increased TSH and normal FT4) and overt hypothyroidism (increased TSH and decreased FT4). The normal range of TSH was regarded as 0.27–4.20 mIU/l and the normal range of FT4 as 12.0–22.0 pmol/l. Patients already commenced on thyroid replacement therapy were included in the hypothyroid group.

Main Article

Dr G Viljoen takes responsibility for the integrity of the content of the paper

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The two groups were compared in terms of age, gender, cancer stage, whether the thyroid gland was spared or sacrificed during surgery, and whether they received post-operative radiotherapy.

The radiotherapy technique at our institution evolved over the time of the study. Before 2012, patients were treated using three-dimensional techniques, and the stoma was not routinely irradiated. Since 2012, three-dimensional conformal radiotherapy and intensity modulated radiotherapy have been employed. The current protocol advocates stomal irradiation in patients with positive surgical margins, subglottic extension, or positive level 4, 5 or 6 nodal metastases.

The Fisher's exact test was used to determine whether there was an association between two categorical variables. A p-value of less than 0.05 was taken as the level for significance.

Results

Eighty-four patients met the inclusion criteria for the study. The median age at surgery was 57 years (interquartile range, 51–65 years). The male to female ratio was 4.6:1. A summary of patients' characteristics is presented in Table 1.

Forty-six patients (54.8 per cent) were euthyroid and 38 (45.2 per cent) were hypothyroid. Age and local tumour extension (T stage) were not significant risk factors for developing hypothyroidism. Of patients who underwent thyroid-sparing total laryngectomy, 36.4 per cent (20 out of 55) were hypothyroid, compared to 62.1 per cent (18 out of 29) of patients who underwent hemithyroidectomy ($p = 0.037$).

Adjuvant radiotherapy was a significant risk factor for developing hypothyroidism: 58.9 per cent of patients (33 out of 56) who underwent adjuvant radiotherapy became hypothyroid, compared to 17.9 per cent (5 out of 28) who received no adjuvant radiotherapy ($p = 0.001$).

In patients who underwent thyroid-sparing total laryngectomy without adjuvant radiotherapy, 9.1 per cent (2 out of 22) had hypothyroidism, compared to 50 per cent (3 out of 6) who underwent hemithyroidectomy and no adjuvant radiotherapy ($p = 0.05$).

In the thyroid-sparing with adjuvant radiotherapy group, 54.5 per cent of patients (18 out of 33) were hypothyroid; in the hemithyroidectomy with adjuvant radiotherapy group, 65.2 per cent (15 out of 23) were hypothyroid ($p = 0.582$).

Discussion

The principal reasons for performing thyroid lobectomy as part of a total laryngectomy are to obtain clear surgical resection margins should there be direct tumour extension to the thyroid gland, and to clear occult paratracheal cervical metastases with subglottic and hypopharyngeal carcinomas.[14–16] The potential oncological benefits of thyroid lobectomy should, however, be weighed against the morbidity of iatrogenic hypothyroidism.

Thyroid preservation is appropriate when intra-operative inspection of the larynx shows no extralaryngeal extension or when paratracheal nodal metastases are not a concern. It may be performed without adversely affecting oncological control when carried out in selected patients with advanced laryngeal and hypopharyngeal carcinoma.[13] Intra-operative suspicion of thyroid involvement, cancers with more than 10 mm of subglottic extension, subglottic cancers, T_4 cancers extending through thyroid cartilage, and T_4 pyriform sinus cancers warrant ipsilateral lobectomy or total thyroidectomy.[12]

Medical therapy for hypothyroidism is relatively inexpensive and is readily available in developed countries (a year's worth of generic levothyroxine costs the equivalent of USD $8.00). However, many patients in developing countries cannot afford or access treatment or monitoring of thyroid function. Current management of thyroid disease in the developing world is comparable to that received by a patient in North America or Western Europe 50 years ago.[11] Hypothyroidism goes undetected unless patients are frequently screened for two years after surgery, and untreated hypothyroidism may contribute to poor wound healing and cause depression.[8,12,17,18] It would therefore be beneficial to spare the thyroid gland to prevent this morbidity and to decrease the burden of disease on the already strained healthcare systems in developing countries.

Age and gender

The incidence of hypothyroidism in the normal population is 0.4 per cent per year in women and 0.06 per cent per year in men; the expected prevalence of clinical hypothyroidism is 1–2 per cent.[19,20]

Several epidemiological studies confirm the occurrence of changes in thyroid hormone levels with ageing. Thyroid-stimulating hormone does not vary with age among males, but increases markedly among females after the age of 45 years.[21] The prevalence of thyroid deficiency in an unselected population of elderly subjects older than 60 years is 4.4 per cent.[22]

A correlation was found for mean age peak between those who developed hypothyroidism (60 years) versus euthyroid patients (50 years) following hemithyroidectomy with total laryngectomy.[23] An increased incidence of hypothyroidism with advanced age following hemithyroidectomy for primary thyroid pathology has also been reported.[24] Despite this, there was no significant difference between the age groups in our cohort ($p = 0.229$).

A single TSH measurement that is just below or above the reference limits may be a transient deviation in approximately 50 per cent of older patients. Therefore, treatment decisions should wait, if clinically possible, until repeat determinations are made over time.[25]

According to some studies on head and neck carcinoma patients, hypothyroidism appears more frequently in women.[26–28] This is possibly related to the increased prevalence of thyroid disorders in females. Other studies did not establish a similar link.[29,30] Our cohort showed no difference in thyroid function between males and females ($p = 0.778$).

Surgery

The pooled risk of hypothyroidism after a hemithyroidectomy for primary thyroid pathology is 22 per cent.[31] In patients with laryngeal cancer who undergo hemithyroidectomy with total laryngectomy, this rises to 32 per cent, and 89 per cent with adjunctive post-operative radiotherapy.[2,7–10]

There was a significant difference in hypothyroidism rates in our cohort of patients who received thyroid-sparing surgery compared to those who had a hemithyroidectomy ($p = 0.037$). The incidence of hypothyroidism was 36.4 per cent among patients who had thyroid-sparing total laryngectomy, compared to 62.1 per cent in patients who had a hemithyroidectomy.

Similarly, in the cohort of patients who did not receive adjuvant radiotherapy, the incidence of hypothyroidism was significantly lower in the thyroid-sparing group (9.1 per cent) compared to the hemithyroidectomy group (50 per cent). Our results are supported by the findings of a study by Léon *et al.*[5]

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Table 1. Demographics of euthyroid and hypothyroid groups

Characteristic	Total patients (*n*)	Euthyroid (*n* (%))	Hypothyroid (*n* (%))	*P*-value
Gender				0.778
– Male	69	37 (53.6)	32 (46.4)	
– Female	15	9 (60)	6 (40)	
Age at surgery (years)				0.229
– <60	50	24 (48)	26 (52)	
– 60–70	25	15 (60)	10 (40)	
– >70	9	7 (77.8)	2 (22.2)	
Local extension (pathologically confirmed tumour (T) stage)				0.125
– T_2	7	4 (57.1)	3 (42.9)	
– T_3	32	23 (67.7)	11 (32.3)	
– T_4	43	19 (44.2)	24 (55.8)	
Thyroid status				0.037
– Thyroid preserved	55	35 (63.6)	20 (36.4)	
– Hemithyroidectomy	29	11 (37.9)	18 (62.1)	
Radiotherapy?				0.001
– Yes	56	23 (41.4)	33 (58.9)	
– No	28	23 (82.1)	5 (17.9)	
Surgery & no adjuvant radiotherapy				0.050
– Thyroid-sparing	22	20 (90.9)	2 (9.1)	
– Hemithyroidectomy	6	3 (50)	3 (50)	
Surgery & adjuvant radiotherapy				0.582
– Thyroid-sparing	33	15 (45.5)	18 (54.5)	
– Hemithyroidectomy	23	8 (34.8)	15 (65.2)	

Radiotherapy

The effects of radiotherapy on the thyroid gland have been studied extensively. The most notable study comprised a large series of patients treated for Hodgkin's lymphoma with radiotherapy that included the thyroid gland. The incidence of hypothyroidism was 30.6 per cent.[32]

Primary radiotherapy in the absence of thyroid surgery for head and neck cancers may result in a 23–53 per cent prevalence of subclinical hypothyroidism and an 11–33 per cent prevalence of clinical hypothyroidism.[33–38]

The incidence of hypothyroidism following adjuvant radiotherapy in our study was 58.9 per cent, which is comparable to reports in the literature.[5] In the cohort of patients who received adjuvant radiotherapy, 54.5 per cent of patients who had thyroid-sparing surgery developed hypothyroidism, compared to 65.2 per cent of patients who had a hemithyroidectomy. These results showed no significant difference ($p = 0.582$).

Possible aetiological factors to explain the correlation between radiotherapy and hypothyroidism include injury to the endothelium of nutrient vessels and damage to the vasculature. These changes result in secondary degeneration of the follicular epithelium and decreased thyroid function.[39]

Preservation of as much of the thyroid gland as possible during a total laryngectomy is important to prevent radiotherapy-induced hypothyroidism.[40] The possibility of injury to thyroid feeding vessels during neck dissection should also be considered and avoided, as this incurs a high risk for hypothyroidism following radiotherapy for head and neck cancer. Other risk factors include a high radiation dose, elapsed time since therapy and not shielding the midline.[41]

Cancer stage

Advanced stages of laryngopharyngeal cancer may be associated with an increased risk for hypothyroidism. This may be a result of the increased likelihood of these patients undergoing thyroid-sacrificing total laryngectomy because of direct extension of the tumour to the thyroid gland or the necessity to resect level 6 nodes. These patients are also more likely to require adjuvant radiotherapy because of close surgical margins, nodal metastases or perineural invasion. In our study, 32.3 per cent of patients with pathologically staged T_3 cancer developed hypothyroidism, compared to 55.8 per cent of patients with pathologically staged T_4 cancer. This difference was, however, not significant ($p = 0.125$).

- Thyroid lobectomy is recommended with total laryngectomy for laryngeal cancer, but is associated with a 32–89 per cent risk of hypothyroidism
- Many patients in developing countries cannot afford or access treatment or monitoring of thyroid function
- Sparing the thyroid gland does not need to compromise oncological control
- There was a significant difference in hypothyroidism rates for thyroid-sparing surgery versus hemithyroidectomy patients
- The incidence of hypothyroidism following adjuvant radiotherapy was 58.9 per cent, comparable to the literature
- Thyroid-sparing laryngectomy reduces the risk of hypothyroidism and should be considered in selected patients

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Limitations

Most of the patients did not have baseline TSH assessments prior to surgery and radiation. Furthermore, the time schedule during follow up for thyroid function tests was not consistent, and the tests were not taken at specific, pre-determined time points.

Conclusion

This study, with a level of evidence of 4, found that thyroid-sparing laryngectomy reduces the risk of hypothyroidism. It should therefore be considered in selected patients without extralaryngeal cancer extension or when paratracheal nodal metastases are not a significant concern.

Competing interests. None declared

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