Thyroid and Parathyroid Dysfunction after Total Laryngectomy


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Abstract

Background: The proximity of the thyroid and parathyroid glands to the larynx puts them at risk in treatment of squamous cell carcinoma of this region. Hypothyroidism and hypoparathyroidism are of the complications that follow treatment of various head and neck cancers.

Aim of Work: To assess the incidence of hypothyroidism and hypoparathyroidism after total laryngectomy.

Patients and Methods: Parathyroid and thyroid gland functions were evaluated in 40 patients who were diagnosed as T3, T4 cancer larynx who were treated with total laryngectomy with or without postoperative radiotherapy. It is a prospective analytic study. Serum T3, T4 TSH and total calcium levels were performed in those patients before and after total laryngectomy and were repeated one month later. The association of hypothyroidism and hypoparathyroidism were analyzed against several patient parameters including tumor and treatment characteristics.

Results: Study included 40 patients who were treated with total laryngectomy with thyroidectomy with or without postoperative radiotherapy. Twenty five patients (62.5%) had hypoparathyroidism proved by hypocalcemia 1 week postoperative. While 4 patients (10%) had hypothyroidism 1 week postoperative and 3 patients (7.5%) had only high TSH. After 1 month 6 patients (15%) continued to have hypoparathyroidism, and 8 patients (20%) had hypothyroidism.

Conclusion: Thyroid and parathyroid dysfunction are common complications after total laryngectomy specially if combined with radiotherapy. They should be anticipated and treated promptly.

Key Words: Parathyroid – Thyroid gland functions – Cancer larynx.

Introduction

The thyroid gland contains extensive lymphoid and vascular networks through which cancer disseminates quickly throughout the gland once it is invaded. Factors predisposing for thyroid gland involvement are vocal cord fixation and subglottic extension [2].

Therefore, ipsilateral hemithyroidectomy is recommended in routine surgical practice for patients undergoing total laryngectomy [3].

Resection of part of the thyroid gland for oncological reasons may injure the vascular supply of the remaining gland. Also local or proximal lymph node dissection may contribute to the devascularization of the gland. Consequently, risk factors for the development of hypothyroidism are laryngectomy and lymph node dissection [4].

Radiation induces damage to the endothelial cells of the thyroid capillary network, and may result in thyroid dysfunction after radiotherapy because of microvascular and parenchymal damage, leading to loss of functional glandular tissue and fibrosis of the thyroid [5].

Ipsilateral hemithyroidectomy during total laryngectomy for carcinoma of the larynx has been the accepted form of treatment [6].

In addition the blood supply of the preserved thyroid and parathyroid glands may be disturbed by mobilization or ligation of the superior and inferior thyroid vessels. In most cases hypothyroidism can be minimized by the preservation of both thyroid lobes at total laryngectomy but total thyroideectomy is still indicated in the surgery of subglottic and postcricoid carcinomas [7].

Hypothyroidism following laryngectomy with or without radiotherapy for squamous cell carcinoma of the larynx is well known. The incidence following
surgery and radiotherapy for laryngopharyngeal cancer is reported to vary from 54 to 81% [8].

Patients and Methods

We conducted this study on 40 patients with laryngeal carcinoma stage T3, T4 who presented to otorhinolaryngology Head and Neck Surgery Department, Kasr El-Aini Hospital, Cairo University during the period from October 2012 to August 2014. All patients were candidate for total laryngectomy.

Clinical staging of the primary tumor as well as neck nodes was based on physical examination, endoscopic assessment and radiological findings according to the American Joint Committee on Cancer Staging 2002 classification TNM staging.

All the patients in the study were subjected to full history taking, examination of the neck, external examination of the larynx, thyroid gland and cervical lymph nodes, and endoscopic laryngeal assessment, C.T. scan of the Neck with contrast (coronal and axial cuts, soft tissue and bone windows), MRI (T 1, T2 and T 1 with contrast) in some cases, and direct laryngoscopy to take biopsy.

Inclusion criteria were:

Patients with laryngeal carcinoma stage T3, and laryngeal carcinoma stage T4 who are candidate for total laryngectomy with or without post-operative radiotherapy.

Exclusion criteria were:

Laryngeal carcinoma stage T1, laryngeal carcinoma stage T2, laryngeal carcinoma stage T4B, cases with previous thyroidectomy, history of primary thyroid cancer, patients candidate for conservative laryngectomy, distant metastasis, comorbidities precluding major surgical intervention.

Total laryngectomy with or without partial pharyngectomy was carried out with variable types of thyroidectomies according to tumor extent and staging with preservation of at least one parathyroid gland.

Patients were followed-up by full history taking, complete general examination, external neck examinations, and postoperative CT in suspicious cases every month for the first 6 months then every 3 months to assess nodal or stomal or thyroid gland recurrence and to assess the need of thyroid and parathyroid replacement. Thyroid and parathyroid functions were monitored immediate and late postoperative and the need of hormonal replacement was assessed.

Thyroid function tests were done through thyroid stimulating hormone, T4, and thyroxin to assess thyroid gland function. Parathyroid gland function was assessed through using serum calcium.

Data of the patients were collected and tabulated and descriptive statistics for all parameters were submitted and analyzed.

Results

This study included 40 patients presented with Laryngeal carcinoma T3 or T4. There were 37 males (92.5%), and 3 females (7.5%). So, results were not studied separately for men and women. Their age ranged from 45 to 80 years old with the mean 61.1 years with slandered deviation (SD) 9.3.

There were 16 patients (40%) with associated medical comorbidity. 14 patients (35%) with single medical co-morbidity, and 2 patients (5%) had more than one co-morbidity. And 24 patients (60%) had no associated chronic medical disease. Comorbidities included: Bronchial asthma, hypertension, diabetes mellitus, liver cirrhosis, HCV, arrhythmias, IHD and heart failure.

There were 15 glottic tumor (37.5%), 13 transglottic tumors (32.5%), 7 supraglottic tumors (17.5), and 5 subglottic tumors (12.5%).

Eight patients had previous radiotherapy treatment, 2 patients (5%) received only radiotherapy, 4 patients (10%) received combined chemoradiotherapy, and 2 cases (5%) had LASER excision and radiotherapy. 10 cases (25%) had preoperative tracheostomy.

Thirty three patients (82.5%) had unilateral fixed vocal cord. 5 patients (12.5%) had fixed both vocal cords. 2 Patients (5%) had freely mobile vocal cords. Anterior comissure was invaded by the carcinoma in 35 cases (87.5). Arytenoid cartilages were in infiltrated in 25 cases (62.5%).

Subglottic area was assessed preoperatively by endoscopy and CT scan. 28 cases (70%) had subglottic extension >1cm, 25 cases had unilateral subglottic extension (62.5%), and 3 cases bilateral extension (7.5%). Thyroid cartilage invasion was found (by CT scan) in 22 patients (55%).

TNM staging based on clinical, radiological and histopathological tests found that, 18 cases T3 (45%), "10 cases (25%) T3a, 8 cases (20%) T3b and 22 cases were T4a (55%). There were 8 cases (20%) N1 (Deep cervical lymph node"s" <3cm), 2 cases (5%) N2 (Deep cervical lymph node"s" >3cm and <6cm), 2 cases (5%) N3 (Deep cervical
lymph node’s >6cm), and 28 cases (70%) N0 (no palpable lymph nodes).

Thyroid gland findings in CT scan (Table 3) Fig. (8) were as followed: 36 cases (90%) had free thyroid gland, 2 cases (5%) had nodular lesions, and 2 cases (5%) were found to be infiltrated by the laryngeal carcinoma.

33 cases (82.5%) had been subjected to hemithyroidectomy, 4 cases (10%) had subtotal thyroidectomy, 3 cases (7.5%) had total thyroidectomy. 19 patients received postoperative radiotherapy (47.5%).

There was no thyroid cartilage infiltration by pathological examination in 11 cases (27.5%). Meanwhile 4 cases (10%) had infiltration of inner cortex of the cartilage without invasion. 12 cases (30%) had invasion of the cartilage only without strap muscles invasion. 13 cases (32.5%) had prelaryngeal muscle invasion as well.

There were 33 cases (82.5%) with thyroid gland free of any pathology. 2 Cases (5%) with colloid nodules. 1 Cases (2.5%) with follicular adenoma. 4 Cases (10%) with thyroid gland invasion by laryngeal carcinoma. There were 2 cases (5%) of laryngeal adenoidcystic carcinoma, 2 cases (5%) of mucoepidermoid carcinoma, and 36 cases of squamous cell carcinoma; 4 cases (10%) had grade I well differentiation, 24 cases (60%) had grade II differentiation, 6 cases (15%) had grade III differentiation, and 3 cases (7.5%) with basiloid degeneration.

The overall complication percentage was 45% (2 8 cases), 4 cases (10%) had more than one complication and 4 cases (35%) had one complication. The most common complications were pharyngocutaneous fistula and wound infection. While the most serious was recurrent carotid blow out which was well managed.

Tumor recurrence occurred in 8 cases (20%); 5 cases (10%) had nodal recurrence, 1 case (2.5%) had stomal recurrence, 2 cases (5%) had both nodal and stomal recurrence.

25 patients (62.5%) had hypoparathyroiism proved by hypocalcemia 1 week postoperative. While 4 patients (10%) had hypothyroidism 1 week postoperative and 3 patients (7.5%) had only high TSH. After 1 month 6 patients (15%) continued to have hypoparathyroidism, and 8 patients (20%) had hypothyroidism (Table 1).

Among the 8 cases that had hypothyroidism after one month; there were three cases subglottic carcinoma & three cases with transglottic carcinoma. Also three cases received preoperative radiotherapy. Six of them were stage T4. Three of them had total thyroidectomy, three had subtotal thyroidectomy, and two had hemithyroidectomy. Three cases were poorly differentiated SCC, three were moderate differentiated SCC, and one case was adenoid cystic carcinoma of the larynx. None of them had invaded thyroid gland. Four cases 50% developed postoperative complications. Six cases need lifelong hormonal replacement.

We founded that 2 cases (50%) with TGI developed hypocalcemia 2ry to hypoparathyroidism. There were no hypocalcemia after 1 month. There were no hypothyroidism either 1 week, or 1 month postoperatively Table (2).

| Table (1): Postoperative thyroid and parathyroid functions in the study group. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Serum calcium level after (1 week) | Serum calcium level after (1 month) | Thyroid function tests after (1 week) | Thyroid function tests after (1 month) |
| Normal                         | 15 (37.5%)       | 34 (85%)        | 33 (82.5%)      | 23 (80%)        |
| Low                            | 25 (62.5%)       | 6 (15%)         | 4 (10%)         | 8 (20%)         |
| High TSH level                 |                 |                 | 3 (7.5%)        |                 |
| Total                          | 40 (100%)        | 40 (100%)       | 40 (100%)       | 40 (100%)       |

| Table (2): Thyroid and parathyroid functions in TGI cases in the study group. |
|-----------------|-----------------|-----------------|-----------------|
| Case in the study | Total | Invaded | Free | p-value |
| Calcium after 1 week: |
| Low              | 25    | 2     | 23   | 0.622   |
| Normal           | 15    | 2     | 13   |         |
| Calcium after 1 month: |
| Low              | 6     | 0     | 6    | 1.000   |
| Normal           | 34    | 4     | 30   |         |
| Thyroid functions after 1 week: |
| Low              | 4     | 0     | 4    | 0.624   |
| Normal           | 33    | 4     | 29   |         |
| High TSH only    | 3     | 0     | 3    |         |
| Thyroid functions after 1 month: |
| Low              | 8     | 0     | 8    | 0.566   |
| Normal           | 32    | 4     | 28   |         |
Discussion

The occurrence of hypothyroidism after a combination of treatments involving the laryngothyroid region is not surprising. The involvement of thyroid glands in laryngeal cancer, especially in advanced stages, is common. Such involvement may be due to either direct invasion or metastasis via loco regional lymphatics [2].

Radiotherapy to the laryngeal region alone may itself lead to fibrosis within the thyroid capsule and may also compromise the thyroid vascularity through a similar mechanism, which may result in decreased thyroid function [9].

Symptomatic hypothyroidism occurs in about 15% of patients treated for laryngeal carcinoma. This may result in delayed wound healing, salivary fistula, difficult speech rehabilitation, cardiac morbidity, and depression [10].

Asymptomatic or subclinical hypothyroidism, on the other hand, is probably underestimated in both the true incidence and its clinical impact. The importance of subclinical hypothyroidism lies in its potential progression into clinical hypothyroidism and the related complications [11].

The incidence of hypothyroidism after treatment for laryngeal or hypopharyngeal carcinoma is high and dependent on the treatment modalities employed. Hypothyroidism occurs more often after radiotherapy combined with surgery.

Since clinical hypothyroidism can develop years after treatment, long-term monitoring of thyroid functions in this patient group is advised [12].

In our study, during the 1st postoperative week, 25 patients (62.5%) developed hypoparathyroism, 4 patients (10%) developed hypothyroidism and 3 patients (7.5%) had only high TSH. Six cases (15%) continued to have hypoparathyroidism after 1 month, and 8 patients (20%) had hypothyroidism. Seven of them (17.5%) needed lifelong hormonal and calcium replacement.

Some authors noted 15% hypothyroidism after radiation therapy alone, 33% after laryngectomy followed by irradiation, and 63% after laryngectomy with hemithyroidectomy followed by irradiation [4]. Similarly, others found the incidence of hypothyroidism to be 48% after laryngectomy followed by irradiation and 61% after laryngectomy with hemithyroidectomy. Similar results were found in other studies [11,13,14].

While, Dequanter et al., [15] found a higher incidence of hypothyroidism (91%) following total laryngectomy.

Others reported thyroid dysfunction in 40% of patients with advanced laryngeal cancer after radiotherapy only and in 65% of patients treated with both radiotherapy and surgery for subglottic carcinoma [16].

Hypoparathyroidism may also occur after treatment for head and neck cancer as a consequence of tumor invasion and treatment for laryngeal cancer although it is predictable after total thyroidectomy. Its occurrence after treatments is more variable. The reported incidence of hypoparathyroidism following thyroidectomy varies from 2-21% but depends upon the extent and the indications of the surgery [17].

In the study of Garcia-Serra et al., [14] the incidence of hypoparathyroidism after radiotherapy was 40% whereas this was 77% after radiotherapy and laryngectomy.

Others reported that the rate of thyroid dysfunction was 74% for patients treated with radiotherapy, laryngectomy and hemithyroidectomy [13].

Regarding the risk factors of developing thyroid and parathyroid gland dysfunction after cancer larynx treatment with total laryngectomy and total laryngectomy with radiotherapy, Ipsilateral hemithyroidectomy when performing a total laryngectomy for squamous carcinoma of the larynx, has long been the accepted form of treatment [13].

Also, other variables such as sex, age, neck dissection, or timing of radiotherapy were not significant risk factors. Some studies in patients with head and neck carcinoma demonstrated that hypothyroidism was more common in women [10].

Also the results of this study highlight the importance of regular evaluation of hypothyroidism and hypoparathyroidism.

To prevent hypoparathyroidism, the surgeon must look for the parathyroids during procedures to the thyroid or extended neck surgery. Autotransplantation of parathyroid tissue should be taken into consideration in those patients if they were exposed to accidentally removal for the parathyroid gland during the laryngectomy.

After reviewing the literature and the data of previous published about the thyroid and parathyroid
gland dysfunction after different treatment modalities of the cancer larynx, we found that our results are matched and supported by the published data which is the relevant incidence of thyroid and parathyroid gland dysfunction after total laryngectomy and after total laryngectomy with post-operative radiotherapy. Thyroid replacement therapy should be administered in the presence of hypothyroidism and Calcium with Vitamin D in the presence of hypoparathyroidism.

**Conclusion:**

Hemithyroidectomy and advanced stages of cancer larynx were risk factors in the development of hypothyroidism in treating cancer larynx patients. We need high clinical suspicion and periodic evaluation of thyroid function to diagnose post treatment hypothyroidism. Thyroid function should be periodically evaluated in total laryngectomy patients. Hypoparathyroidism is common in laryngopharyngeal carcinoma patients treated with radiotherapy alone or with radiotherapy and surgery.

**References**

الملخص العربي

شملت هذه الدراسة 40 مريضا تم علاجهم من سرطان الحنجرة بواسطة الاستئصال الكلي للحُنجرة، وكانت المتابعة لفترة طويلة ما بين عام 2010 إلى 2014 في قسم جراحة الأذن والأنف والحُنجرة وجراحات الرأس الدراسية بمستشفى قصر العيني، جامعة القاهرة.

أجريت اختبارات وظائف الغدة الدرقية والجار الدرقي بواسطة قياس كل من الهرمون المنشط للغدة الدرقية وهرمونات الغدة الدرقية، والثالث والرابع وذلك بالكالسيوم بالدم بعد أسبوع وبعد شهر من العلاج لجميع المرضى.

النتائج، تم جمعها وإحصائها وكشفت عن وجود خمسة وعشرين مريضا (52٪) لديهم قصور بوظائف الغدة الدرقية أثناء اسمنتة الكالسيوم بالدم بعد أسبوع واحد من العملية الجراحية. بينما كان أربع مرضى (10٪) لديهم قصور في وظائف الغدة الدرقية بعد أسبوع واحد من الجراحة. بينما واصل 6 مرضى (15٪) بعد شهر واحد قصور الغدة جار درقية، وواصل 8 من المرضى (20٪) بقصر الغدة الدرقية. بعد الحصول على هذه النتائج ومحاولة لم تنشرة في المجلات العلمية بشكل متزامن. هذا الموضوع، كشف تقييم جميع جراحات الرأس وال وجراحات بالدواء المتنافسة في التشريح حول الغدة الدرقية أثناء الاستئصال التصفيج للغدة الدرقية أثناء استئصال الحنجرة، وأيضاً التقييم المنتظم لوظائف الغدة الدرقية والكالسيوم بالدم بعد الانتهاء التام من العلاج خلال فترة المتابعة في ما بعد العلاج، ويبقى أيضاً بزرع الغدد الجار درقية إذا لم تصلبوا عن طريق الخطأ أثناء الجراحة.