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A prospective longitudinal study on endocrine dysfunction following treatment of laryngeal or hypopharyngeal carcinoma

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SUMMARY

Objectives: The incidences of hypo(para)thyroidism were assessed prospectively in 137 consecutive patients with laryngeal (84.7%) or hypopharyngeal (15.3%) carcinoma who were treated with surgery and/or radiotherapy between 2004 and 2006.

Material and methods: Laboratory studies were performed in patients before primary or salvage treatment of a laryngeal or hypopharyngeal carcinoma and were repeated 6, 12, 18 and 24 months after treatment. All patients were evaluated for the development of hypo(para)thyroidism, and the presence of autoantibodies. The association of hypothyroidism was analyzed against several patient parameters including tumor and treatment characteristics.

Results: The incidence of hypothyroidism following treatment of laryngeal and hypopharyngeal carcinoma was 47.4%: 27.7% subclinical hypothyroidism and 19.7% clinical hypothyroidism. The median time to develop hypothyroidism was 10 months. The incidence of hypoparathyroidism was 7.3%. Univariate analysis showed that patients with laryngectomy, hemithyroidectomy, neck dissection, paratracheal lymph node dissection and radiotherapy had a higher risk of developing hypothyroidism. Multivariate analysis showed laryngectomy, hemithyroidectomy, neck dissection and age to be predictive factors for the development of hypothyroidism. The combination of surgery and radiotherapy increased this risk. Hemithyroidectomy was the most important risk factor.

Conclusion: The incidence rate of hypothyroidism after treatment for laryngeal or hypopharyngeal cancer in this largest prospective study is high (47.4%), especially after combination treatment. Based on the intervals between treatment and the development of hypothyroidism, thyroid testing before treatment, every 3 months during the first year, every 6 months the second year and annually thereafter is recommended as screening procedure.

Introduction

One of the consequences of treatment for laryngeal and hypopharyngeal cancer is that thyroid function may become impaired. 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 than after radiotherapy alone. Since clinical hypothyroidism can develop years after treatment, long-term monitoring of thyroid functions in this patient group is advised.[1–4]

The thyroid gland contains extensive lymphoid and vascular networks through which cancer disseminates quickly throughout the gland once it is invaded.[4] Predisposing factors for thyroid gland involvement are fixation of the hemilarynx by tumor and subglottic extension.[5–7] Therefore, ipsilateral hemithyroidectomy is considered routine surgical practice for patients undergoing total laryngectomy.[2,5,8] 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.[9] Consequently, risk factors for the development of hypothyroidism are laryngectomy and lymph node dissection.[2,3,10,11] Radiation induces damage to

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the endothelial cells of the thyroid capillary network,[1] and may result in thyroid dysfunction several years after radiotherapy because of microvascular and parenchymal damage, leading to loss of functional glandular tissue and fibrosis of the thyroid.[12–14]

Hypothyroidism has been associated with several clinical problems and symptoms such as delayed wound healing, pharyngo-cutaneous fistula, stomal healing problems (e.g. after salvage surgery) and, indirectly, with difficult speech rehabilitation. General signs and symptoms include arrhythmias, hypercholesterolaemia, weight gain, cold intolerance, dry skin, constipation, depression and cognitive impairment.[12,13,15] These consequences have the potential of significantly further impairing quality of life after treatment for laryngeal and hypopharyngeal cancer.

The importance in detecting subclinical hypothyroidism lies in its potential progression into clinical hypothyroidism with its associated complications.[1,14] Since thyroid function is usually tested infrequently, hypothyroidism tends to be diagnosed by the manifestation of clinical symptoms and signs and hence treated late.[11]

There are several retrospective and a few prospective studies demonstrating an association between the development of hypothyroidism surgery (laryngectomy, hemithyroidectomy and/or lymph node dissection), radiotherapy (dose and field) and time post-treatment.[1,2,10] Also, a relation between hypothyroidism and circulating anti-thyroid antibodies has been found.[10,15–17] However, it is not clear if radiation induces development of these antibodies or that patients with circulating anti-thyroid antibodies predispose for development of hypothyroidism after radiotherapy.

Hypoparathyroidism may also occur after treatment for head and neck cancer as a consequence of tumor invasion and (combined) treatment for laryngeal and hypopharyngeal cancer. Although it is predictable after total thyroidectomy, its occurrence after treatments is more variable.

The present study aims to evaluate prospectively the incidence of hypothyroidism in a group of patients treated for laryngeal or hypopharyngeal carcinoma, and to evaluate its association with patient, tumor and treatment characteristics and anti-thyroid antibodies.

Patients and methods

A prospective study was performed on 147 patients treated for laryngeal or hypopharyngeal carcinoma between July 2004 and December 2006. The institutional ethics committee approved this study and informed consent was obtained from each patient. Patients who had preexisting thyroid dysfunction and those that needed total thyroidectomy were not included. Ten patients were excluded because of thyroid dysfunction other than (sub)clinical hypothyroidism. Consequently, 137 patients remained for further analysis.

Patient, tumor and treatment parameters were recorded, including age, gender, tumor site, TNM stage, details of surgery, radiotherapy (dose and timing), chemotherapy and histopathological examination of the removed thyroid glandular tissue (histopathological changes and tumor invasion). Details of surgery included type of laryngectomy (partial or total), and hemithyroidectomy, ligation of thyroid arteries on preserved side, type of neck dissection, and paratracheal lymph node dissection (PLND).

Thyroid functions were classified as euthyroidism (normal TSH (0.3–4.5 mU/L) and normal free T4 (11.0–24.0 pmol/L)), subclinical hypothyroidism (elevated TSH and normal free T4), clinical hypothyroidism (elevated TSH and decreased free T4), subclinical hyperthyroidism (decreased TSH and normal free T4) and clinical hyperthyroidism (decreased TSH and elevated free T4). Parathyroid function was classified as normal when serum calcium (corrected for abnormal albumin) was between 2.20 and 2.60 mmol/L. Hypoparathyroidism was defined as decreased corrected calcium serum levels.

To assess the presence of anti-thyroid peroxidase (TPO) antibodies, Thymune-M™ test (Murex, Biotech Limited, Dartford, Kent, UK) was used. With this passive hemaglutination test, red blood cells are coated with thyroid antigen and mixed with serum of the patient. TPO antibodies will cause agglutination of the red blood cells. A TPO antibody titres exceeding 1:1040 were considered to be positive. Only anti-thyroperoxidase (anti-TPO) was measured because our earlier study[10] showed a higher association of anti-TPO with hypothyroidism than of anti-thyroglobulin (anti-Tg) with hypothyroidism.

In this study patients were followed for a period of 24 months after treatment for their laryngeal or hypopharyngeal carcinoma or until they died of their disease, became unavailable for follow-up or developed (para)thyroid dysfunction. All patients with subclinical hypothyroidism with TSH > 10.0 mU/L or clinical hypothyroidism were referred to the endocrinology service for hormone substitution therapy. Biochemical studies were performed before treatment and were repeated at 6 months intervals until the end of the study, thereafter routine follow-up was continued.

Comparison contingency tables were made with Pearsons χ^2 for nominal data and the trend test for ordinal data. To assess the mutual effects of variables on a dichotomous outcome, stepwise logistic regression analysis was implemented. *P*-values < 0.05 were considered significant. The time to the development of hypothyroidism was analyzed and corrected for survival rate.

Results

Data of 137 (21 female and 116 male) patients were analyzed. Mean age was 63 years (range 42–90). Male to female ratio was 5.5:1. Follow-up time ranged from 6 to 24 months. Twenty-six patients died during the study period. The incidence of hypothyroidism was 47.4%: 27.7% subclinical hypothyroidism and 19.7% clinical hypothyroidism. Mean level of TSH at detection of (sub)clinical hypothyroidism was 15.8 mU/L and of free T4 was 11.4 pmol/L. Patient, tumor and treatment characteristics and the incidences of (subclinical and clinical) hypothyroidism and their association are described in Table 1. The median time to develop hypothyroidism was 10 months (range 6–24; 80% between 6 and 12 months after treatment). Cumulative incidence of the development of hypothyroidism during 24 months after treatment was 47.5% (Fig. 1).

Hypoparathyroidism was found in 7.3% of patients within 24 months after treatment. Mean level of corrected calcium serum level was 2.00 (±0.195) mmol/L (range 1.59–2.19) in patients with hypoparathyroidism.

Surgery

Thirty-seven (27.0%) patients underwent total laryngectomy and 3 (2.2%) patients underwent partial laryngectomy. The type of laryngectomy (total laryngectomy vs. partial laryngectomy) was a significant predictive factor for subsequent hypothyroidism ($p = 0.000$).

All 37 patients treated with total laryngectomy underwent ipsilateral hemithyroidectomy. Of the three patients treated with partial laryngectomy, 1 patient underwent partial thyroidectomy and the other two patients did not undergo thyroidectomy. Of the patients treated by total laryngectomy and hemithyroidectomy, 29 (78.3%) patients developed hypothyroidism. The patient with partial laryngectomy and partial thyroidectomy developed clinical hypothyroidism. Hemithyroidectomy was a significant predictive factor for hypothyroidism ($p = 0.000$).