THYROID DISORDERS IN PATIENTS TREATED WITH RADIOTHERAPY FOR HEAD-AND-NECK CANCER: A RETROSPECTIVE ANALYSIS OF SEVENTY-THREE PATIENTS

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Purpose: To evaluate the incidence of thyroid disorders and dose distribution to the thyroid in patients treated with radiotherapy for head-and-neck carcinomas.

Methods and Materials: A retrospective evaluation of data from 73 patients treated for head-and-neck cancers in our department was performed. Thyroid function was evaluated mainly by the measurement of thyrotropin (thyroid stimulating hormone [TSH]). A retrospective analysis of treatment plans was performed for 57 patients. Percentages of thyroid glandular volume absorbing 10, 30, and 50 Gy (V10, V30, and V50 respectively) were considered for statistical analysis.

Results: A majority of patients (61%) had a normal thyroid function whereas 19 patients (26%) had hypothyroidism. Mean thyroid volume was 30.39 cc. Point 3 (located at isthmus) absorbed lower doses compared with other points (p < 0.0001). Median values of V10, V30, and V50 were 92% (range, 57–100%), 75% (range, 28.5–100%), and 35% (range, 3–83%) respectively. Gender was associated with toxicity (presence of any kind of thyroid disorders) (p < 0.05), with females displaying higher levels of TSHr (relative TSH = patient’s value/maximum value of the laboratory range) (p = 0.0005) and smaller thyroid volume (p = 0.0012) compared with male population. TSHr values were associated with thyroid volume, and the presence of midline shielding block in the anterior field was associated with relative free thyroxine (FT4r = patient’s value/maximum value of the laboratory range) values.

Conclusions: Gender and thyroid volume seem to play an important role in the occurrence of thyroid toxicity, but further studies on dose–effect relationship for radiotherapy-induced thyroid toxicity are needed. © 2007 Elsevier Inc.

INTRODUCTION

Despite technical advances, exposure of nontarget organs (thyroid gland, salivary glands, mandibular bone, spinal cord, and others) during radiation therapy of patients with squamous cell carcinoma of head and neck still remains unavoidable. Among different radiation-induced late effects, thyroid disorders are probably underestimated, even though hypothyroidisms and hyperthyroidisms, Hashimoto thyroiditis, Graves’ disease, benign adenoma, and thyroid cancers have been reported in the literature (1). Among them, primary hypothyroidism seems to be the most frequent late effect with an incidence of 20% to 30%.

Different studies have attempted to correlate incidence of thyroid disorders to patient, tumor, and treatment characteristics, but results are quite controversial and, to date, the tolerance dose of the thyroid gland has not been definitively established (1). The minimal thyroid tolerance dose (TD) defined as TD5/5 (the dose of radiation that could cause no more than 5% severe complication rates within 5 years after treatment) is considered 20 Gy when all or part of the gland is irradiated with conventional fractionation (2). This value is accepted for individuals with a normal baseline organ function (excluding children and elderly) and an absence of previous surgery or chemotherapy. In a review paper, Emami et al. reported different tolerance values of 8/5, 13/5,
and 35/5 (incidence of clinical hypothyroidism in 8%, 13%, and 35% of patients at 5 years) at the level of 45, 60, and 70 Gy, respectively (3). A few other studies tried to correlate the dose–response curves to thyroid disorders with nonhomogeneous results (4–6).

In this study, we performed a retrospective analysis on 73 consecutive head-and-neck patients treated with radiotherapy in which thyroid hormone levels and evaluation of thyroid dose distribution were performed. Associations between clinical data, thyroid hormone levels, and physical parameters were then assessed.

METHODS AND MATERIALS

The study includes a retrospective analysis of 73 consecutive head-and-neck cancer patients treated with radiotherapy at the European Institute of Oncology between July 1995 and May 2003.

Evaluations of thyroid function at the last follow-up

Thyroid function at the last follow-up was evaluated by thyrotropin (thyroid stimulating hormone [TSH]) level in all patients and by free tri-iodothyronine (FT3) and free thyroxine (FT4) levels in 72 patients. Because of differences in laboratory ranges, the relative values calculated as “patient’s value/maximum value of the laboratory range” were used (TSHr, FT3r, FT4r). These “relative” values were used only for statistical analysis to obtain more comparable data. The time of onset of thyroid abnormalities was defined as the interval between the end of radiotherapy and the first abnormal thyroid hormone value. Additional thyroglobulin level was measured in 25 patients and thyroid antibodies level (antithyroglobulin antibodies, antimicrosomal, and antiperoxidase) in 25, 25, 8, and 17 patients, respectively.

Based on thyroid hormone values at the last follow-up, patients were then grouped in four categories: (1) normal thyroid function (normal levels of thyroid hormones and normal levels of thyroid antibodies); (2) hypothyroidism (high level of TSH and/or low level of FT3 and/or FT4); (3) hyperthyroidism (low level of TSH and/or high level of FT3 and/or FT4); (4) thyroiditis and normal thyroid function (normal level of TSH, FT3, and FT4 and altered levels of thyroid antibodies).

Both hypothyroidism and hyperthyroidism could be associated with altered values of thyroid antibodies (thyroiditis). Information on previous thyroid disorders was recorded for 4 patients and TSH dosage before radiation on 14 patients.

Dosimetric analysis

Treatment plans were available for a retrospective analysis in 57 cases. Thyroid gland was contoured manually on computed tomography scan, followed by an assessment of the following: point doses at the superior and inferior portion of left and right thyroid glandular lobes (points 1, 2, 4, and 5, respectively) and at the isthmus (point 3) (Fig. 1), absolute thyroid volume, dose–volume histograms (DVHs), and percentage of thyroid gland volume absorbing 10, 30, and 50 Gy (V10, V30, and V50, respectively).

Statistical methods

Associations between some thyroid parameters (toxicity was considered as any kind of thyroid disorders, FT3r and FT4r values) with relevant clinical information (age, sex, tumor site, clinical stage, chemotherapy, surgery, or follow-up time) or physical data (presence of a midline shielding block in the anterior field, fractionation schedule, point 3 dose value, total glandular volume, V10, V30, and V50) were tested by Fisher exact test (7) which was also used to assess association between thyroid volume and age, chemotherapy, and surgery. Continuous variables were dichotomized at their median values.

For each couple of points, the absorbed doses were compared by means of the Wilcoxon signed rank test. Pretreatment TSH, FT4, and FT3 values, available for 14 patients, were compared with the corresponding values obtained after treatment by Wilcoxon test. Cumulative incidence actuarial curve of toxicity was calculated using the Kaplan-Meier method and plotted (8). The log–rank test (8) was used to assess statistical differences of cumulative incidence of toxicity between subgroups determined by binary variables such as sex, surgery, chemotherapy, and by dichotomized continuous variables such as age, radiotherapy course, thyroid total volume, V10, V30, V50, P1, P2, P3, P4, P5. For all statistical tests, the significance level was set to 0.05 (two-sided).

To allow a visual assessment of data dispersion, minimum, maximum, mean, and median values, lower and upper quartiles of the DVH curves were obtained by calculating the minimum, maximum, mean, median values, and quartiles, respectively of the percentages of the irradiated volume at each dose level. SPlus 2000 and Mathematica 4 (9) software systems were used.

RESULTS

Clinical, tumor, and treatment characteristics of the 73 patients are summarized in Table 1. Median follow-up was 24.19 months (range, 1.91–49.48 months).

Analysis of thyroid function at the last follow-up

Thyroid hormone levels were performed on 73 patients. Most patients (61%) had a normal thyroid function, 19 (26%) hypothyroidism, 7 (10%) hyperthyroidism, and 2 (3%) thyroiditis with normal thyroid function. In 7 patients (10%), hypothyroidism or hyperthyroidism was also associated with autoimmune thyroiditis (altered antibodies dosage). There were no cases of hypothyroidism or hyperthyroidism...
related to pituitary gland dysfunction (low level of TSH associated with low levels of FT3 and/or FT4 or high level of TSH associated with high levels of FT3 and/or FT4, respectively) nor of radiation-induced tumor of the thyroid gland.

Four patients (5%) experienced thyroid disorders before radiotherapy: 1 patient had a diagnosis of hyperthyroidism, 2 thyroiditis, and 1 nodular goiter. At the last follow-up, the first 3 patients had hyperthyroidism, whereas the last one showed a normal thyroid function. Baseline TSH dosage, obtained before radiation therapy in 14 patients, showed reduced values in 2 and normal values in the other 12 patients.

Physical analysis

A retrospective analysis of radiotherapy treatment plans of 57 patients (78%) indicated that three-dimensional treatment planning with two opposite equally weighted lateral fields plus one anterior field was used. Irradiation was performed using 6-MV photons from a linear accelerator for all patients. In all cases, for the lateral fields a twice a day fractionated schedule (1.2 Gy each, with an interfraction interval of at least 6 h, 5 days a week) was employed, whereas the anterior field was treated with a single fraction schedule (1.8–2 Gy/day). Median total dose for lateral fields was 74.4 Gy (range, 50.4–76.4 Gy) prescribed at the International Commission on Radiation Units and Measurements reference point. The lower cervical and supraclavicular lymph nodes were treated with an anterior photon beam up to 50 Gy. A midline shielding block was used for anterior field when spinal cord dosage exceeded 40–42 Gy.

When contoured on computed tomography scan, the thyroid gland was found to be localized within anterior field in 37 patients (65%), within the lateral fields in 2 (3.5%), and both in anterior and lateral fields in 18 (31.5%). In 43 patients (75%) a midline shielding block was used in the anterior field from the beginning of treatment whereas in 7 patients it was added only for the last fractions to obtain a maximum total dose of 40–42 Gy to the spinal cord. Median thyroid volume was 27.66 cc (range, 7.93–89.24 cc).

Point doses were calculated and the boxplots of the 5 points absorbed doses are shown in Fig. 2. DVHs were also calculated (Fig. 3). The percentages of thyroid volume absorbing 10, 30, and 50 Gy (V10, V30, and V50 respectively) were calculated.

Statistical associations

Statistically significant associations are presented in Table 2 where the female sex is associated with both higher number of toxicity ($p < 0.05$) and higher TSHr values ($p = 0.013$). Females also have a smaller thyroid volume compared with males ($p = 0.0019$). TSHr values are associated with thyroid volume and among physical parameters, only midline shielding block is associated with FT4r values ($p = 0.03$). In Table 3, we report the toxicity data and the median and interquartile ranges of the main continuous variables for both men and women.

When comparing pretreatment TSH, FT3, and FT4 values in 14 patients with the same values obtained after radiation therapy, only a slight statistically significant trend ($p = 0.0494$, paired Wilcoxon test) was observed for TSH values, with no variation between FT3 and FT4 values before and after treatment ($p = 0.8077$ and $p = 0.5$, respectively, paired Wilcoxon test).

Point number 3 (located at isthmus) was the point with the lowest absorbed dose compared with points 1, 2, 4, and 5 (Wilcoxon tests with $p < 0.05$ in all cases).

Kaplan-Meier estimated cumulative incidence of thyroid disorders showed presence of thyroid disorders at 1, 3, and

![Fig. 2. Boxplot of the absorbed doses at points 1, 2, 3, 4, and 5. Isthmus absorbed lowest dose when compared with lateral lobes.](image-url)
5 years of 8%, 21%, and 48% respectively (Fig. 4). The estimated higher incidence of thyroid disorders in female compared with male population \( (p = 0.02, \text{log–rank test}) \) is shown in Fig. 5.

DISCUSSION

Hypothyroidism represents the most frequent thyroid-related effect in patients treated with radiotherapy for head-
and-neck cancers (20–30%). Nevertheless, the dose to the thyroid gland and the level of thyroid hormones before and after radiation therapy are not yet assessed in clinical practice. In our retrospective analysis, incidence of hypothyroidism (26%) evaluated after radiation therapy confirmed literature data (20–30%) (1). Major limitations of our study are the lack, in most patients, of the baseline hormone values assessed before radiation therapy and the lack of a comparative group.

Few studies have been performed in an attempt to evaluate the correlation between thyroid absorbed dose and hormone values and patient, tumor, and treatment characteristics. To our knowledge, ours is the first study in which all these parameters have been analyzed together in the same group of patients (head-and-neck cancer patients treated with radiotherapy).

Table 2. Statistically significant associations between patients, tumor and treatment characteristics and thyroid hormone values and physical parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.01</td>
</tr>
<tr>
<td>Toxicity</td>
<td>0.013</td>
</tr>
<tr>
<td>Dichotomized TSHr</td>
<td>0.0019</td>
</tr>
<tr>
<td>Dichotomized thyroid volume</td>
<td>0.0009</td>
</tr>
<tr>
<td>Dichotomized TSHr</td>
<td>0.0009</td>
</tr>
<tr>
<td>Dichotomized FT4r</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Abbreviations: TSHr = relative thyroid stimulating hormone (patient’s value/maximum value of the laboratory range); FT4r = relative free thyroxine (patient’s value/maximum value of the laboratory range).

Table 3. Values of the variables for men and women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td>12/49 (24.5%)</td>
<td>12/20 (60%)</td>
</tr>
<tr>
<td>Thyroid volume</td>
<td>30.37 (20.17, 37.34)</td>
<td>17.71 (13.80, 20.95)</td>
</tr>
<tr>
<td>TSHr</td>
<td>0.30 (0.22, 0.47)</td>
<td>0.88 (0.45, 2.84)</td>
</tr>
<tr>
<td>T3r</td>
<td>0.71 (0.61, 0.80)</td>
<td>0.66 (0.60, 0.81)</td>
</tr>
<tr>
<td>T4r</td>
<td>0.55 (0.47, 0.65)</td>
<td>0.55 (0.46, 0.71)</td>
</tr>
<tr>
<td>RT at P1</td>
<td>50.30 (47.52, 52.4)</td>
<td>47.74 (43.04, 50.61)</td>
</tr>
<tr>
<td>RT at P2</td>
<td>48.83 (40.08, 51.59)</td>
<td>35.61 (30.08, 47.64)</td>
</tr>
<tr>
<td>RT at P3</td>
<td>6.27 (5.47, 10.12)</td>
<td>5.56 (5.13, 27.31)</td>
</tr>
<tr>
<td>RT at P4</td>
<td>50.04 (44.95, 52.24)</td>
<td>49.61 (45.82, 51.08)</td>
</tr>
<tr>
<td>RT at P5</td>
<td>48.00 (41.65, 51.53)</td>
<td>46.20 (40.61, 49.10)</td>
</tr>
</tbody>
</table>

Abbreviations: TSHr = relative thyroid stimulating hormone (patient’s value/maximum value of the laboratory range); T3r = relative T3 = patient’s value/maximum value of the laboratory; T4r = relative T4 = patient’s value/maximum value of the laboratory; RT = radiotherapy.

For the binary variable toxicity, we indicated the number of patients experiencing toxicity relative to the total number of men/women, and the corresponding percentage. For the continuous variables, the median value and the interquartile range were indicated.

Different factors have been found to be associated with higher risk of postirradiation hypothyroidism (6, 10–19). We analyzed different risk factors such as age, sex, treatment (surgery and chemotherapy) and follow-up duration. Our results showed that only the female sex was associated with a higher incidence of thyroid toxicity. Moreover, females seem also to have a smaller thyroid volume compared with males. On the contrary, many other factors, such as tumor-related variables (primary disease, tumor site, and size, stage, nodal status, initial diagnosis) and follow-up duration were not found to be associated with higher risk of hypothyroidism by several authors (11, 20–24). Only Collevas et al. (21) found a trend toward decreased rating of hypothyroidism in patients with clinical stage T1 or N3 and for tumor located in the oral cavity. Results of our analysis produced no correlation between tumor-related variables and follow-up duration and incidence of thyroid disorders.
The importance of total dose and fractionation schedule in determining the incidence of late effect on the thyroid gland has not yet been definitively demonstrated (13, 15, 21, 22, 25–31). Two studies showed that the risk of hypothyroidism was 40% for patients receiving 30–45 Gy and 12–27% for those receiving less (32, 33) in patients treated for Hodgkin's disease. In our retrospective analysis, total dose was similar for all patients. Thus, the correlations between this parameter and thyroid dysfunction could not be assessed. Colevas et al. (21) found that twice-daily fractions were associated with a lower incidence of hypothyroidism, but this difference did not persist when correction for the length of follow-up was performed. A reduction of hypothyroidism incidence was also found when a hyperfractionated schedule was used instead of a conventional schedule in pediatric patients treated with craniospinal irradiation (29). In our analysis, we did not find any correlation between patients treated with conventional fractionation or with a hyperfractionated schedule, but we have to point out that for many patients (31%) thyroid gland was irradiated partially with a conventional schedule and partially with a hyperfractionated schedule. This is due to the fact that, for these patients, thyroid volume lay within both the anterior and lateral fields.

Some authors have also evaluated the correlation between irradiated thyroid volume and toxicity. Irradiated volume was often calculated with indirect parameters such as dimension of the irradiation fields. Using this method, Kumpulainen et al. found that only 9% of patients with radiation field height lower than 7 cm had hypothyroidism, compared with 36% of patients with field height 7 cm or more (15). To our knowledge, only Yoden et al. used DVHs to evaluate the correlation between percentage of gland volume absorbing a defined dose and thyroid function (20). They found that percentage volume of thyroid gland receiving radiation doses between 10 and 60 Gy (V10–60) seemed to be a possible risk factor for hypothyroidism. Moreover, V30 (thyroid volume receiving over 30 Gy) appeared to be correlated with TSH values. In our analysis, DVHs were calculated and no associations were found between V10, V30, and V50 and both toxicity and thyroid hormone values. This is probably due to relatively uniform DVH in our cohort of patients. Point doses were never used before to evaluate thyroid absorbed dose. In our analysis, the absorbed dose was calculated in 5 representative points (4 points located at the upper and lower portion of the right and left lobe, respectively and 1 point located at the isthmus) and results yielded no association between the absorbed dose in these points and both toxicity or thyroid hormone values. A limitation of these analyses remains the small number of patients.

It has already shown that midline block placed to the posterior neck field and used to spare spinal cord reduces the radiation doses to the central portion of thyroid gland (isthmus) in patients treated for Hodgkin’s disease (5). When possible, a midline block to the anterior field was also used if prophylactic irradiation of lower cervical nodes was necessary. In our analysis, most patients (approximately 75%) had a midline block during the entire treatment course. For this reason, isthmus absorbed lower dose when compared with lateral lobes. No association was found between the point 3 values (absorbed dose at isthmus) and both clinical parameters and hormone values, but the presence of midline block was found to be associated with FT4r values.

CONCLUSIONS

Thyroid disorders after radiation therapy for head-and-neck cancer still represent a clinically underestimated problem. Recent advances in radiotherapy treatment planning (such as intensity-modulated radiation therapy) allow one to better spare normal tissues (spinal cord or parotid glands). To date, thyroid sparing is not yet performed routinely, probably owing to lack of literature data related to the association between physical and clinical data. Our results demonstrated that sex and thyroid volume seem to play an important role in determining the incidence of thyroid toxicity. Among physical parameters, only the presence of midline shielding block used in the anterior field was found to be associated with FT4r values. Further prospective well-designed studies on dose–effect relationship for radiotherapy-induced thyroid toxicity are therefore needed, and thyroid should be considered as an organ at risk in all patients treated for head-and-neck tumors.

REFERENCES


