Hypothyroidism After Treatment for Nonthyroid Head and Neck Cancer

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Objectives: To determine the incidence of posttreatment hypothyroidism in patients treated with surgery with or without radiotherapy for advanced-stage nonthyroid head and neck cancer and to make recommendations for its detection.

Design: A prospective study to assess the incidence and time frame of occurrence of hypothyroidism in patients by primary tumor site and treatment modality. Thyroid function tests were performed preoperatively, at the first postoperative visit, and then approximately every 6 months. Patients were followed up for up to 3 years.

Setting: Arthur G. James Cancer Hospital and Research Institute, Columbus, Ohio.

Patients: A total of 251 patients with nonthyroid head and neck cancer were originally enrolled; 198 patients with evaluable data were studied to determine the incidence of posttreatment hypothyroidism. Approximately 80% of the patients had advanced stage (III or IV) or recurrent cancer.

Results: The overall incidence of posttreatment hypothyroidism was 15% in 198 patients followed up for a mean of approximately 12 months. Hypothyroidism developed in 12% of patients treated with nonlaryngeal surgery and radiotherapy. The group undergoing total laryngectomy (with thyroid lobectomy) and radiotherapy had a 61% incidence of hypothyroidism. The average time to detection of hypothyroidism was 8.2 months.

Conclusions: Approximately 15% of patients treated for advanced head and neck cancer with surgery and radiotherapy will develop hypothyroidism. Those treated with total laryngectomy and radiotherapy are at greatest risk.


HYPOTHYROIDISM CAN be a complication after treatment of head and neck cancers. The effects of radiotherapy on the thyroid gland have been extensively studied, most notably in a series of 1677 patients treated for Hodgkin disease with radiotherapy that included the thyroid gland.\(^1\)

The incidence of hypothyroidism, including both clinical (elevated thyrotropin level, decreased thyroxine [T\(_4\)] level) and subclinical (elevated thyrotropin level, normal T\(_4\) level) disease, was 30.6% with a median follow-up of 10 years. Other studies\(^2\-\(^6\) support a 30% to 40% incidence of elevated thyrotropin levels at variable times after external beam radiotherapy.

Several retrospective\(^7\-\(^13\) and a few small prospective\(^14\,\(^15\) studies have examined the incidence of hypothyroidism after multimodality treatment for head and neck cancer that included combinations of surgery, radiotherapy, and chemotherapy. Leining et al\(^6\) found elevated thyrotropin levels in 6% of patients treated with radiation alone, in 28% of those treated with neck surgery and radiotherapy, and in 65% of patients treated with neck surgery, radiotherapy, and hemithyroidectomy. Tami et al\(^7\) found a 45% incidence of thyroid dysfunction among 62 patients tested at varying intervals from completion of combined therapy. Cannon\(^15\) prospectively studied 62 patients at 4- to 6-month intervals after treatment for head and neck cancer and found an overall 15% incidence of serum thyroid hormone abnormalities. Turner et al\(^14\) found a 55% incidence of increased thyrotropin level among 20 patients tested after undergoing total laryngectomy, hemithyroidectomy, and postoperative radiotherapy. Others have performed similar measurements of thyroid function. However, few studies include pretreatment baseline thyroid function tests, and most have measured thyroid function at varying intervals after completion of therapy, giving little information on the
PATIENTS AND METHODS

From December 1, 1992, through June 30, 1995, 251 patients from the Department of Otolaryngology–Head and Neck Surgery at the Arthur G. James Cancer Hospital and Research Institute at The Ohio State University, Columbus, were treated for nonthyroid head and neck malignant neoplasms. These patients were prospectively studied to monitor the development of hypothyroidism during the course of their treatment. This study was approved by the Biomedical Sciences Review Committee for research involving human subjects at The Ohio State University. Fifty-three patients were deemed to have ungradable data because of lack of follow-up or because of the diagnosis of pretreatment hypothyroidism (see the “Results” section), leaving 198 patients with evaluatable data. Approximately 80% of the patients had stage III or IV or recurrent cancer.

Patients were followed up for a maximum of 3 years or until they (1) became hypothyroid, (2) died, or (3) became unavailable for follow-up.

PATIENT ELIGIBILITY

All patients with nonthyroid head and neck malignant neoplasms treated with surgery or combined therapy were eligible to be included. Excluded from the study group were patients with primary thyroid malignant neoplasms, patients requiring surgery that included total thyroidectomy, and patients previously treated for hyperthyroid or hypothyroid conditions. The concomitant use of chemotherapy was noted and evaluated.

STUDY DESIGN

Patients were placed into one of 6 groups on the basis of the type of treatment they received for their head and neck malignant neoplasm. These 6 groups consisted of patients treated with (1) nonlaryngopharyngeal resections without radiotherapy, (2) nonlaryngopharyngeal resections with radiotherapy, (3) partial laryngectomy or partial laryngopharyngectomy without radiotherapy, (4) partial laryngectomy or partial laryngopharyngectomy with radiotherapy, (5) total laryngectomy with thyroid lobectomy without radiotherapy, and (6) total laryngectomy with thyroid lobectomy with radiotherapy. Treatment was with and without neck dissection and the use of chemotherapy were also evaluated as separate variables.

Thyrotropin level, total T4 level, free T4 index, triiodothyronine (T3) resin uptake, T3 radioimmunoassay, and antimicrosomal antibody levels were determined in patients before treatment began. These laboratory studies were repeated regularly after treatment. An attempt was made to evaluate laboratory test results 1 month postoperatively before initiation of radiotherapy and then every 6 months after completion of radiotherapy. Difficulties with patient noncompliance altered this schema in some cases. Hypothyroidism was defined as a thyrotropin level of 10 mU/L or more, with the reference range being 0.5 to 5 mU/L. Patients found to have a thyrotropin level of 10 mU/L or more began receiving thyroid hormone replacement.

STATISTICAL ANALYSIS

Statistical comparisons of data from patients who became hypothyroid and those who remained euthyroid within each treatment group were performed by Fisher exact test. Multivariate analysis was also performed with a logistic regression for binary outcomes. Time to development of hypothyroidism was analyzed.

RESULTS

PATIENTS

Of the original 251 patients enrolled in the study, 25 patients were unavailable for follow-up, 16 died before any posttreatment laboratory values were obtained, and 12 patients were found to be hypothyroid on their initial screening thyroid function tests. Therefore, 198 patients were studied.

PRETREATMENT HYPOTHYROIDISM

Of the original 251 patients enrolled in the study, 12 (5%) were found to be hypothyroid before the initiation of treatment for their head and neck cancer. Two of these patients had recurrent cancers and had previously undergone radiotherapy to the neck. One patient had previously undergone a total thyroidectomy and was receiving insufficient thyroid replacement. The remaining 9 patients had no history or risk factors for hypothyroidism.

INCIDENCE OF HYPOTHYROIDISM

In the group of 198 patients who were euthyroid before the initiation of treatment, 29 became hypothyroid during the course of therapy. The incidence of hypothyroidism was 14.6%.

Hypothyroidism After Nonlaryngeal Surgery

Fourteen (11%) of the 130 patients treated with nonlaryngeal resections (with and without neck dissection) became hypothyroid (Table). Twelve percent (11/89) of those treated with nonlaryngeal resections and radio-
therapy became hypothyroid. Seven percent (3/41) of those treated with nonlaryngeal resections and no radiotherapy became hypothyroid. There was no statistically significant difference ($P = .78$) between patients undergoing nonlaryngeal surgery with or without radiotherapy. The average time to detection for this group was 8.9 months.

### Hypothyroidism After Partial Laryngectomy

Of the 39 patients treated with partial laryngectomy (including hemiglottic and/or supraglottic laryngectomies), 1 (3%) became hypothyroid (Table). Five percent (1/19) of those treated with partial laryngectomy and radiotherapy became hypothyroid. None of the patients treated with partial laryngectomy and no radiotherapy became hypothyroid. There was no statistically significant difference ($P = .49$) between those undergoing partial laryngectomy with or without radiotherapy.

### Hypothyroidism After Total Laryngectomy and Thyroid Lobectomy

Of the 29 patients treated with total laryngectomy and thyroid lobectomy, 14 (48%) became hypothyroid (Table). Sixty-one percent (14/23) of those treated with total laryngectomy and radiotherapy became hypothyroid. None of the 6 patients treated with total laryngectomy without radiotherapy became hypothyroid. The incidence of hypothyroidism after total laryngectomy with radiotherapy was significantly higher than the incidence for the overall group of 198 patients ($P < .001$).

### Surgery vs Surgery and Radiotherapy

Of 62 patients treated with surgery only, 3 (5%) developed hypothyroidism. Of the 136 patients treated with surgery and radiotherapy, 26 (19%) developed hypothyroidism (Table). Multivariate analysis indicated that this difference was not statistically significant ($P = .17$).

The group of patients who underwent total laryngectomy was also analyzed to see if radiotherapy was an independent risk factor for the development of hypothyroidism within this subgroup. Of the 6 patients who underwent total laryngectomy and thyroid lobectomy without postoperative radiotherapy, none developed hypothyroidism (Table). Given the small size, this was not statistically significant.

### Neck Dissection

There were 155 patients who had a neck dissection as part of their treatment, of which 139 were comprehensive and 16 were selective neck dissections. Forty-three patients did not undergo a neck dissection as part of their treatment. Nineteen (14%) of the 139 patients treated with a comprehensive neck dissection became hypothyroid. Of the 16 treated with a selective neck dissection, 1 (6%) became hypothyroid. Twenty-one percent (9/43) of those treated without a neck dissection became hypothyroid (Table). The incidences of hypothyroidism between the groups were not significantly different ($P = .41$).

### Chemotherapy

Sixty-six patients received chemotherapy (cisplatin and/or paclitaxel) as part of their treatment. Seventeen percent (11/66) of the patients who received chemotherapy became hypothyroid. Fourteen percent (18/132) of the patients who did not receive chemotherapy became hypothyroid. The difference was not statistically significant ($P = .45$).

### PATIENT FOLLOW-UP AND TIMING OF DETECTION OF HYPOTHYROIDISM

The average length of follow-up for the 198 patients with evaluable data was 12.1 months. The average time to detection of hypothyroidism was 8.2 months (range, 1-21 months) after completion of treatment. Approximately 83% (24/29) of the cases of hypothyroidism were detected within 12 months. The average time to detection in patients treated with total laryngectomy with thyroid lobectomy and radiotherapy was 7.4 months.

Forty-seven of the 251 original patients died during the course of the study. Sixteen of these patients died before any thyroid function tests could be measured after their treatment, which made their data unevaluable.

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### Incidence of Hypothyroidism by Treatment Modality

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>No. of Patients</th>
<th>No. Who Became Hypothyroid</th>
<th>Incidence, %</th>
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</thead>
<tbody>
<tr>
<td>Nonlaryngeal surgery*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All</td>
<td>130</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>With radiotherapy</td>
<td>89</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Without radiotherapy</td>
<td>41</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Partial laryngectomy†</td>
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<td></td>
</tr>
<tr>
<td>All</td>
<td>39</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>With radiotherapy</td>
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<td>0</td>
<td>0</td>
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<tr>
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</tr>
<tr>
<td>All</td>
<td>29</td>
<td>14</td>
<td>48</td>
</tr>
<tr>
<td>With radiotherapy</td>
<td>23</td>
<td>14</td>
<td>61*</td>
</tr>
<tr>
<td>Without radiotherapy</td>
<td>6</td>
<td>0</td>
<td>0§</td>
</tr>
<tr>
<td>Surgery vs surgery with radiotherapy</td>
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<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>62</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>With radiotherapy</td>
<td>136</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Primary resection with or without neck dissection¶</td>
<td>139</td>
<td>19</td>
<td>14</td>
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<tr>
<td>With comprehensive neck dissection</td>
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<tr>
<td>With selective neck dissection</td>
<td>16</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>No neck dissection</td>
<td>43</td>
<td>9</td>
<td>21</td>
</tr>
</tbody>
</table>

* $P = .78$.  † $P = .49$.  ‡ $P < .001$.  § $P = .02$.  †† $P = .17$.  †¶ $P = .41$.  

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Forty-one patients (20%) had follow-up ranging from 1 to 6 months. This group consisted of patients who died within 6 months, were noncompliant with follow-up, or were followed up elsewhere after their initial treatment.

**ANALYSIS OF THYROID FUNCTION TEST RESULTS**

A thyrotropin level of 10 mU/L or more was used to identify hypothyroidism. No patients were identified with low free T<sub>4</sub> index or total T<sub>4</sub> level and a normal thyrotropin level. Of the 29 patients who became hypothyroid after treatment, 7 had a low free T<sub>4</sub> index or total T<sub>4</sub> level. These patients had thyrotropin levels ranging from 16 to greater than 150 mU/L.

Antimicrosomal antibodies were found to be present in 21 patients. Twelve of these patients were euthyroid and 9 became hypothyroid. Five patients with elevated antimicrosomal antibody titers while euthyroid later became hypothyroid as determined by elevated thyrotropin level. The identification of a positive antimicrosomal antibody titer was noted to be sporadic in individual patients across time (ie, positive on one date and negative at a later date).

Twenty-seven patients (14%) were found to have thyrotropin levels greater than 5 mU/L and less than 10 mU/L (reference range, 0.2-5.0 mU/L) that continued to remain less than 10 mU/L. These patients were clinically euthyroid. The significance of this is not clear.

Of the 29 patients who were hypothyroid after treatment, 12 (41%) were noted to have had a thyrotropin level greater than 5 mU/L and less than 10 mU/L before eventually developing a thyrotropin level of 10 mU/L or more.

**COMMENT**

The importance of recognizing hypothyroidism cannot be understated. Known manifestations of hypothyroidism include slowed mentation, depression, skin dryness, pleural and pericardial effusions, decreased gastrointestinal tract motility, weight gain, and cold intolerance. Potential posttreatment complications include decreased wound healing, impaired development of tracheoesophageal speech, congestive heart failure, acceleration of atherosclerosis, hypercholesterolemia, and an increased chance of developing thyroid cancer.16,17

Primary hypothyroidism can be divided into clinical and occult states. Clinical hypothyroidism in the setting of this study is characterized by an elevated thyrotropin level with a decreased T<sub>4</sub> level, whether or not the patient actually has clinical manifestations of decreased thyroid function. Patients with occult hypothyroidism have an elevated thyrotropin level with normal T<sub>4</sub> levels. Although there is evidence that occult hypothyroidism can lead to hypercholesterolemia, there is no consensus regarding the actual thyrotropin level at which to begin treatment. Rosenthal et al<sup>18</sup> found that, among a population of healthy adults, all subjects who had a thyrotropin level above 20 mU/L developed clinical hypothyroidism within 4 years. A thyrotropin level of 10 mU/L was chosen as a threshold to treat in this study after we observed that the first few patients whose thyrotropin levels rose to or above 10 mU/L ultimately had levels above 20 mU/L. Furthermore, problems with reliability of patient follow-up in the head and neck cancer population has encouraged us to take a more aggressive approach.

The previously cited literature supports an overall incidence of 10% to 40% for posttreatment hypothyroidism among patients with head and neck cancer. This wide variation results from the inclusion of varying numbers of different subpopulations of patients, the measurement of serum levels at different intervals after completion of therapy, and the lack of pretreatment serum tests that may have discovered hypothyroidism as a preexisting condition.

The use of chemotherapy in some patients and not others may further confound the data. Although chemotherapy alone is not thought to independently affect thyroid function, its use concomitantly with radiotherapy has not been widely studied.2 This study included patients treated with various chemotherapeutic regimens, making a statistically meaningful study of the effects of specific chemotherapeutic agents infeasible.

The current assay for thyrotropin is recommended as the first-line serum test to measure thyroid function. The total T<sub>4</sub> level is a measure of total output by the thyroid, although the free fraction (free T<sub>4</sub>) is the "active" substrate that is converted peripherally to T<sub>3</sub>. To estimate the free T<sub>4</sub> level, T<sub>3</sub> resin uptake values were measured to calculate the free T<sub>4</sub> index. However, free T<sub>4</sub> assays are now available and are a more convenient, single test for measuring total thyroid function. Serum T<sub>4</sub> levels were measured but did not add substantially to the other thyroid data or change our patient treatment. Thyroid antimicrosomal antibodies, the most sensitive marker for underlying autoimmune thyroid disease, were measured to investigate whether radiotherapy produced a measurable autoimmune reaction that preceded the development of hypothyroidism. An association between positive antimicrosomal antibody titers and hypothyroidism was noted. Interestingly, positive antimicrosomal antibody titers were noted to precede the development of hypothyroidism in 5 of the 29 patients who were hypothyroid after treatment. The significance of this is unclear.

The overall incidence of hypothyroidism in our series was lower than that reported in similar studies of patients who received treatment for cancers of the head and neck. There are several probable explanations. About 6% of study patients were found to be hypothyroid before beginning therapy and were eliminated from the study. In addition, our follow-up period averaged 12.1 months, which is shorter than in some other studies. However, in this prospective study, 19% of patients died of disease during follow-up, many of whom might have developed hypothyroidism had they survived their disease. Only 23 (12%) of 198 patients in this study underwent total laryngectomy with hemithyroidectomy and radiotherapy, a combination that has been demonstrated to result in a high incidence of hypothyroidism (61% in this series). Clearly, the primary issue is not
the overall percentage of patients developing hypothyroidism but an understanding of the risk factors and the time course of its development.

From the data in this study, it is apparent that hemithyroidectomy and postoperative radiation to the remaining thyroid lobe are the 2 most important factors leading to hypothyroidism in the patient with head and neck cancer. Of the 29 patients who underwent total laryngectomy with hemithyroidectomy, 14 (48%) became hypothyroid. Twenty-three of these 29 also received radiotherapy, and 14 (61%) of this population became hypothyroid. Radiotherapy is thought to damage the thyroid through direct effects on parenchymal cells and indirectly through vascular injury. The results of this study suggest that direct parenchymal injury is the major mode of damage, since 83% of all patients became hypothyroid within 12 months of treatment, whereas the vascular effects of radiotherapy are generally believed to occur over a more protracted period. Hemithyroidectomy appears to reduce the critical mass of functioning thyroid to a level where the effects of radiotherapy become rapidly apparent. Interestingly, of the 6 patients who underwent total laryngectomy without postoperative radiotherapy, none became hypothyroid. This indicates that it is the combination of hemithyroidectomy and radiotherapy to the remaining lobe that is most predictive of the development of posttreatment hypothyroidism. Whether total laryngectomy with thyroid lobectomy without postoperative radiotherapy is an independent risk factor for the development of hypothyroidism is not clear from this study because this group was too small to yield statistically significant conclusions.

Neck dissection and chemotherapy do not independently increase the incidence of posttreatment hypothyroidism. The slightly higher rates of hypothyroidism in patients who received chemotherapy or were treated with comprehensive neck dissections are more likely related to the fact that most of these same patients also received radiotherapy.

Consideration should be given to treating all patients who undergo total laryngectomy, hemithyroidectomy, and radiotherapy with thyroid supplementation because of the high prevalence of hypothyroidism in this group. Our rate of 61% compares favorably with those in other studies, whose incidence ranges from 44% to 66%. Longer follow-up may disclose an even higher incidence.

All patients with head and neck cancer should undergo thyroid function studies before beginning treatment. Twelve (6%) of 210 patients entering this study were discovered to be hypothyroid on routine testing before initiation of treatment.

The measurement of thyroid function tests within 3 months after completion of therapy and then at 6-month intervals is a reasonable approach for detecting hypothyroidism. The majority of cases will be discovered within the first 2 years, as the latest discovery of hypothyroidism in this series was at 21 months. A normal thyrotropin value alone will establish euthyroidism. If the thyrotropin level is elevated but less than 10 mU/L, free T4 level should be measured to confirm occult hypothyroidism or establish clinical hypothyroidism. These patients may be at increased risk to develop hypothyroidism later, as it was observed in this study that 12 (41%) of the 29 patients who were hypothyroid after treatment had thyrotropin levels between 5 and 10 mU/L before eventually developing a thyrotropin level of 10 mU/L or more. It should be noted, however, that others have shown transient elevations of thyrotropin level after radiotherapy that eventually returned to normal. A thyrotropin level at or above 10 mU/L should be treated as clinical hypothyroidism, regardless of the free T4 level, as these patients are highly likely to develop further increases in thyrotropin level over time and ultimately a decreased T4 level.

CONCLUSIONS

Up to 20% of patients treated for advanced-stage head and neck cancer with surgery and radiotherapy will develop hypothyroidism. Approximately 60% of those treated with total laryngectomy, thyroid lobectomy, and radiotherapy will become hypothyroid. Most patients will develop abnormal thyroid function test results within the first year. It is recommended that thyrotropin levels be measured within 3 months of completion of therapy and then every 6 months in patients treated for head and neck cancer. These patients should be followed up for at least 2 years. Consideration should be given to empirically initiating thyroid replacement for patients treated with total laryngectomy with thyroid lobectomy and radiotherapy, assuming there are no contraindications to levothyroxine sodium administration, such as coronary artery disease. The algorithm shown in the Figure is suggested.

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