Association Between Development of Hypothyroidism and Improved Survival in Patients With Head and Neck Cancer

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Objective: To determine if the development of hypothyroidism has an effect on the outcome of advanced-stage head and neck squamous cell carcinoma.

Design: Retrospective database analysis.

Setting: Tertiary care center.

Patients: The study population comprised 155 patients with advanced-stage head and neck squamous cell carcinoma.

Interventions: Patients underwent radiation therapy alone or in combination with chemotherapy and surgery when indicated.

Main Outcome Measures: Kaplan-Meier analysis was used to assess survival, not adjusting for timing of the detection of hypothyroidism. The following 2 analyses were then performed to adjust for the timing of detection: (1) hypothyroidism was assessed as a time-varying covariate in a Cox proportional hazards model and (2) a landmark analysis was conducted at 9, 12, 15, 18, 21, and 24 months using the Kaplan-Meier method.

Results: Of the 155 patients, 59 developed hypothyroidism, defined as a thyrotropin level greater than 5.5 mIU/L (institutional value). An unadjusted Kaplan-Meier analysis indicated that patients who develop hypothyroidism have significantly better survival than patients who do not ($P < .001$, log-rank test). After adjusting for the timing of hypothyroidism, a Cox proportional hazards analysis indicated that survival was better, but not statistically significant, for patients who developed hypothyroidism (hazard ratio, 0.62; $P = .12$); results from a landmark analysis supported this finding ($P$ values ranged from .11 to .19).

Conclusions: Development of hypothyroidism may be associated with improved survival and increased recurrence-free survival. Larger, prospective studies appear warranted to test the beneficial effect of hypothyroidism.

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General population studies have shown a decreased incidence of nonthyroidal cancer and also an overall reduced mortality from many types of cancer in hypothyroid patients. Anecdotal reports have described complete spontaneous remission of malignant inoperable disease following the development of an iatrogenic hypothyroid state. In a study of 34 patients with advanced neoplasms of various types treated with interleukin (IL)-2 and lymphokine-activated killer (LAK) cells, of the 7 patients who developed hypothyroidism after treatment, 5 (71%) had evidence of tumor regression compared with only 5 (19%) of 27 euthyroid patients. A report of 13 patients with advanced malignancy treated with interferon alfa-2a and IL-2 showed that of the 6 patients who developed hypothyroidism, only 1 died of progressive disease, while all 7 euthyroid patients died of progressive disease. Weijl et
al" found a significant correlation between the development of hypothyroidism and a favorable response to treatment with IL-2 in renal cell cancer. Of 15 patients, 7 became hypothyroid, of whom 5 had a complete or partial response. None of the 8 euthyroid patients had a favorable response. In a retrospective study of 127 patients with metastatic renal cell cancer, 9 patients became hypothyroid after treatment with cytokine-based therapy. The median survival of these patients was 27 months, while in euthyroid patients, the median survival was 7 months. Prolonged survival has also been demonstrated in patients with advanced breast cancer who became secondarily hypothyroid.

Animal studies have been conducted to further investigate the role of the thyroid hormones in neoplasia. Mishkin et al noted that survival of hepatoma-bearing rodents was significantly prolonged by the induction of hypothyroidism, while this beneficial effect was significantly reduced, though not neutralized, by the administration of T3 supplement. Earlier induction of hypothyroidism resulted in lower tumor weight and smaller number and size of pulmonary metastases than later induction, although there was benefit in both cases. Similarly, Kumar et al studied a murine model of transplanted sarcoma. One group treated with T4 had significantly increased tumor weight and metastatic rate compared with controls, while a second group with induced hypothyroidism showed the opposite effect. Shoemaker et al found that mice with implanted mammary tumors that were made hypothyroid for the first 21 days after implantation showed diminished tumor growth and significantly improved survival.

We hypothesized that hypothyroidism may have a role in head and neck cancer. Our purpose was to identify a group of patients in whom a significant cohort developed hypothyroidism at some point after diagnosis and initiation of treatment to address the question of whether hypothyroidism correlated with outcome.

## METHODS

### PATIENTS

A retrospective analysis was performed on a database of 155 patients with advanced HNSCC diagnosed between November 1989 and June 1997 at the Cleveland Clinic Foundation, Cleveland, Ohio. The original study was designed to compare different treatment protocols. The patients were initially randomized to receive radiation alone or in combination with a chemotherapeutic regimen; however, after the first 100 patients, a significantly better response was seen in the combined treatment group, and randomization was discontinued for the next 53 patients.

Chemotherapy comprised intravenous fluorouracil (1000 mg/m^2 per day) and cisplatin (20 mg/m^2 per day) given during the first and fourth week of radiation therapy. Radiotherapy was given in fractionated doses of 1.8 to 2.0 Gy. After 50 to 55 Gy were administered, clinical response was evaluated. Those with an obvious response continued with radiotherapy to a total dose of 66 to 72 Gy. Patients with no obvious response were referred for surgery.

Surgery was performed in the following cases: (1) patients who completed a full course of radiotherapy but had persistent biopsy-proven primary site tumor underwent primary site resection; (2) patients with a less than complete neck response to the previous protocol underwent neck dissection 6 to 8 weeks after radiotherapy; (3) patients with stage N2 tumor or higher at diagnosis underwent neck dissection 6 to 8 weeks after radiotherapy regardless of the response; and (4) patients underwent salvage surgery when appropriate for locoregional recurrence.

Hypothyroidism was defined by a thyrotropin level greater than 5.5 mIU/L (institutional value). Following the original study protocol, thyrotropin level was checked when treatment was completed, then every 3 to 6 months thereafter. Follow-up data also included date of recurrence, if any, and date of last follow-up or date of death.

### STATISTICAL ANALYSES

Patient characteristics were compared between patients who developed hypothyroidism and those who did not, using either the chi-square test or t test.

In the initial analysis, outcomes were assessed for the 2 groups without adjusting for the timing until detection of hypothyroidism. Time until the specific outcome event was calculated from the date of onset of radiotherapy. Event curves were constructed using the Kaplan-Meier method and compared between patients who developed hypothyroidism and those who did not, using the log-rank test. Cox proportional hazards analysis was also used to estimate the effect of hypothyroidism; results are summarized as the hazard ratio (HR), 95% confidence interval for the HR, and corresponding P value. An HR less than unity indicates that hypothyroidism has a protective effect on the outcome, thus it results in an improved outcome.

In the “unadjusted” analyses, the timing of hypothyroidism is not considered, which may bias results because patients had to live long enough to develop hypothyroidism. Two additional analyses were conducted to adjust for these biases. First, hypothyroidism was assessed as a time-varying covariate in a Cox proportional hazards analysis. As a supplemental analysis, and as a way to graphically present the data, a landmark analysis was conducted at 9, 12, 15, 18, 21, and 24 months following treatment. Outcomes at each of the 6 landmark time points were then estimated using the Kaplan-Meier method and compared between patients who became hypothyroid and those who did not, using the log-rank test. To illustrate this concept, patients were classified into 2 groups using a 9-month landmark time point: those who became hypothyroid within the first 9 months following treatment initiation and those who did not. Time to specific events were then recalculated relative to the landmark time point for each of the 2 groups, and hypothyroidism was assessed using standard methods, such as Kaplan-Meier or Cox analysis. Patients who died or were lost to follow-up before the landmark time were excluded from the landmark analysis. The adjusted Cox analysis was the primary analysis because it used data from all 155 patients. The landmark analysis was supplemental and was performed primarily to provide a graphical representation of the outcome data. It should be noted that as the landmark time increased, the landmark analysis was based on smaller subsets of the 155 patients.

All analyses were conducted using SAS software, version 6.12 (SAS Institute Inc., Cary, NC). All statistical tests were 2-sided. P < .05 indicated statistical significance and P < .20 indicated trends.

A descriptive analysis of the patient data set is provided in Table 1. Of the 155 patients undergoing treatment, 59 (38.1%) developed new-onset hypothyroidism after...
initiation of treatment. The mean time until hypothyroidism was detected was 22.8 months after initiation of treatment (range, 3.8-86.4 months). The absolute measure of initial thyrotropin level was available in 57 of the 59 patients, with a mean of 22.8 mIU/L (range, 5.6-122.4 mIU/L). Quantitative thyrotropin level at initial detection did not correlate with increased survival. Of all outcomes, again without accounting for the timing until detection of hypothyroidism, Kaplan-Meier plots indicated that patients who developed hypothyroidism in the post-treatment period had less recurrence (P = .02), improved survival (P < .001), and longer recurrence-free survival (P < .001) compared with patients who did not.

Cox proportional hazards analysis was performed using hypothyroidism as a time-varying covariate (Table 2). Although all HRs were less than unity, trends toward significance were noted for survival, recurrence, and survival without recurrence (P = .12; recurrence-free survival (P = .06); recurrence was not significant (P = .77). To account for the effect of race on the results, the adjusted analysis was repeated in the white-only population. Again, the results are not statistically significant, but HRs remained less than unity (P values ranged from .11 to .76).

As a supplemental analysis, landmark analyses were performed between the 2 groups with respect to overall survival and survival without recurrence. Landmark graphs of overall survival were plotted for each 3-month interval in the first 2 years after treatment, beginning at 9 months (graphs are included for 9, 18, and 24 months after treatment in Figures 2, 3, and 4). Similar trends were found with recurrence-free survival (not displayed). As shown in the Figures, patients who developed hypothyroidism had better survival than patients who did not, although this finding did not achieve statistical significance (P values ranged from .11 to .19). The results of the landmark analysis are

The first analysis involved a comparison of the 2 groups (those patients who eventually became hypothyroid vs those who never developed hypothyroidism) and did not take the timing into account until the detection of hypothyroidism. Kaplan-Meier curves were constructed for survival, recurrence, and survival without recurrence (a plot of recurrence-free survival is shown in Figure 1). When no adjustment is made for the timing until detection of hypothyroidism, Kaplan-Meier plots indicated that those patients who developed hypothyroidism in the post-treatment period had less recurrence (P = .02), improved survival (P < .001), and longer recurrence-free survival (P < .001) compared with patients who did not.

The second portion of the analysis was done by adjusting for the timing until detection of hypothyroidism. First, for the primary analysis, Cox proportional hazards analysis was performed using hypothyroidism as a time-varying covariate (Table 2). Although all HRs were less than unity, trends toward significance were noted only for survival (P = .12) and recurrence-free survival (P = .06); recurrence was not significant (P = .77). To account for the effect of race on the results, the adjusted analysis was repeated in the white-only population. Again, the results are not statistically significant, but HRs remained less than unity (P values ranged from .11 to .76).

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therefore consistent with the findings from the Cox proportional hazards analysis treating hypothyroidism as a time-varying covariate.

COMMENT

Hypothyroidism has been linked to decreased tumorigenicity and increased survival in many animal and human cancers. A review of the literature revealed that this effect has not been reported in HNSCC. Our retrospective review indicates that patients who develop secondary hypothyroidism after treatment have increased overall survival and increased recurrence-free survival compared with patients who did not become hypothyroid. However, in patients who are cured with chemotherapy therapy, it may be expected that a certain percentage of patients would eventually develop secondary hypothyroidism. To address this question, we performed a Cox proportional hazards analysis as well as a landmark study to account for the covariate of time until detection of hypothyroidism. When factoring in the interval until detection of hypothyroidism and its relationship to survival and recurrence, statistical significance was not obtained, although the general trend of increased survival and increased recurrence-free survival in hypothyroid patients was preserved. We do not have a plausible explanation for the fact that of the small number of African American patients in this study, none developed hypothyroidism. It has been shown for many types of cancer that survival is poorer in the African American population than in the white population, even when initial stage and treatment are similar. The reason for this finding remains unsettled. In our study, outcomes for this subset of patients were less favorable than the overall patient population (ie, more recurrence and worse survival relative to white patients). When the adjusted time-varying analysis is repeated in the white-only population, the results do not reach statistical significance, but again, the trend of increased survival and increased recurrence-free survival in hypothyroid patients continues.

Various mechanisms have been proposed for the role of thyroid hormones in cancer. It is widely believed that proliferation of cancer results in part from uncontrolled ligand activation of autocrine/paracrine loops involving growth factors. In normal epithelial cells, epidermal growth factor (EGF) interaction with its receptor (EGF-R) is an effective inducer of proliferation in vitro.\(^{13,14}\) In several in vitro cancer cell systems, T3 exposure led to significant EGF-R production, while T3 deprivation was associated with EGF-R down-regulation and decreased proliferation.\(^{4,15}\) In addition to EGF-R, insulinlike growth factor (IGF)-1 and IGF-1R are overexpressed in many solid tumors, and each may play a role in blocking apoptosis.\(^{9}\)

Thyroid hormone is believed to play a role in controlling the cell cycle, in both normal and neoplastic cells. The addition of T3 to the human breast cancer cell line MCF-7 has been shown to stimulate proliferation.\(^{11}\) In a separate study, incubation with T3 led to a dose-dependent increase in the growth rate of GC cells, a growth hormone–producing pituitary tumor.\(^{16}\) These cells were found to have a decreased G1 phase in the cell cycle. The effects of T3 are mediated by interaction with thyroid hormone nuclear receptors. In normal cells, tumor suppressor p53 physically interacts with the \(\beta_2\) subunit of the thyroid hormone nuclear receptor, inhibiting the thyroid hormone nuclear receptor from interacting with the promoter sequence of T3 responsive genes. In their study of this effect, Bhat et al\(^{17}\) demonstrated that cells with mutated p53 lost this negative regulator, and there

Table 2. Unadjusted and Adjusted Cox Models

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Abbreviations: CI, confidence interval; HR, hazard ratio.
was a shortening of the duration of the G1 phase. If T3 was depleted, there was little transcriptional activity, but if T3 was given in higher amounts, there was greater transcriptional activity.\textsuperscript{17} The tumor suppressor p21 is a key mediator of G1 growth arrest induced by p53 in response to DNA damage.\textsuperscript{18} Toms et al\textsuperscript{19} demonstrated how T3 depletion inhibited the proliferation of a glioblastoma cell line possessing a mutant p53. In cells placed in T3-depleted serum, p53-independent induction of p21 began within 5 hours, resulting in G1 arrest of cells. In a report by Cheng et al,\textsuperscript{20} the authors were able to isolate and characterize T3-specific binding proteins in the nuclear envelope and endoplasmic reticulum in human squamous cell carcinoma cell lines (A431).

Thyroid hormone may also play a role in apoptosis. In a study of cerebellar cells in newborn rats, T3 promoted Bcl-2 expression in a dose-dependent manner, while low T3 concentrations were associated with loss of Bcl-2 expression and significant apoptosis.\textsuperscript{21} Triiodothyronine has also been shown to play an important role in the membrane potential of the inner mitochondrial membrane, where Bcl-2 is located.

It is likely that a combination of these effects is involved, leading to a modulating effect on proliferation while impeding apoptosis. Therefore, a shift in local factors secondary to thyroid deprivation, albeit temporary or of limited magnitude, may disrupt the proliferation/apoptosis balance within the tumor mass and may allow some patients to escape progression of disease.

Recently, a prospective trial was initiated to examine the efficacy of induced hypothyroidism on outcome in patients with high-grade recurrent glioma.\textsuperscript{22} In this study, 34 patients were treated with propylthiouracil and Lugol solution, and 28 of the 34 patients also received tamoxifen in combination. Eighteen patients developed biochemical hypothyroidism, while only 1 patient developed symptoms of hypothyroidism. Positive response by magnetic resonance imaging criteria was seen in 5 (28\%) of the 18 hypothyroid patients vs 0 in the euthyroid group (n = 16) (P < .04). Preliminary results indicated that the median survival for the hypothyroid group was 10.6 months vs 3.1 months for the euthyroid group (P < .002). In addition, IGF levels were significantly reduced in the hypothyroid group. Insulinlike growth factor is mitogenic and anti-apoptotic in glioma cell cultures and also inhibits tamoxifen-induced cytotoxic effects. Such an effect may also exist with squamous cell carcinoma. The development of an appropriate animal model to further study this effect would be useful.

The inherent difficulty in determining the actual onset and duration of clinically relevant hypothyroidism in a retrospective fashion made interpretation of the results more challenging. Thyrotropin was measured every 3 to 6 months; thus, the actual duration of hypothyroidism can only be approximated.

Patients who were determined to be hypothyroid were treated with T4 supplementation, but follow-up data on the efficacy of this treatment were not available. However, studies in rodents have demonstrated that T4 supplementation alone in the treatment of hypothyroidism does not necessarily restore euthyroidism because peripheral conversion of T4 to T3, the more biologically active form, is incomplete in many tissues.\textsuperscript{23} Plasma T3 concentrations and thyrotropin indexes in patients receiving T4 therapy are approximately 80\% of those in healthy individuals.

The optimal duration of hypothyroidism to produce an improved outcome is not well documented in the literature. In several of the studies previously mentioned, the duration of hypothyroidism was as little as 2 months, at which time the patient was given thyroid supplementation or the disease was self-limited. However, these patients had hypothyroidism that was detected sooner than in our patient population. Thus, either the timing of onset or the duration of hypothyroidism may play a role in the outcome.

CONCLUSIONS

In this retrospective review, we have shown that HNSCC patients who were hypothyroid at any point after treatment had improved survival, lower recurrence rates, and increased recurrence-free survival from the initiation of treatment. When the timing until detection of hypothyroidism was taken into account, the trend toward improved survival and recurrence-free survival continued, yet did not reach statistical significance. Although the time-adjusted analyses do not achieve statistical signifi-
cance, it must be taken into account that patients were started on thyroid supplementation as soon as the elevated thyrotropin level was detected. It is possible to speculate that an increased duration of hypothyroidism may have led to an improved outcome, but it is difficult to demonstrate in this data set because of the limitations already noted. Theoretically, maintaining patients at a clinically tolerable level of hypothyroidism may have a beneficial effect in regard to their neoplastic disease. Larger, prospective studies would be necessary to test this hypothesis.

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Correspondence: Dr Nelson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Nelson, Herbergs, and Strome. Analysis and interpretation of data: Nelson, Herbergs, and Rybicki. Drafting of the manuscript: Nelson, Rybicki, and Strome. Critical revision of the manuscript for important intellectual content: Herbergs, Rybicki, and Strome. Statistical analysis: Rybicki. Administrative, technical, and material support: Strome. Study supervision: Herbergs and Strome.

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