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CLINICAL INVESTIGATION **Head and Neck**

HYPOTHYROIDISM AS A CONSEQUENCE OF INTENSITY-MODULATED RADIOTHERAPY WITH CONCURRENT TAXANE-BASED CHEMOTHERAPY FOR LOCALLY ADVANCED HEAD-AND-NECK CANCER

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Purpose: To conduct a retrospective review of 168 consecutively treated locally advanced head-and-neck cancer (LAHNC) patients treated with intensity-modulated radiotherapy (IMRT)/chemotherapy, to determine the rate and risk factors for developing hypothyroidism.

Methods and Materials: Intensity-modulated radiotherapy was delivered in 33 daily fractions to 69.3 Gy to gross disease and 56.1 Gy to clinically normal cervical nodes. Dose–volume histograms (DVHs) of IMRT plans were used to determine radiation dose to thyroid and were compared with DVHs using conventional three-dimensional radiotherapy (3D-RT) in 10 of these same patients randomly selected for replanning and with DVHs of 16 patients in whom the thyroid was intentionally avoided during IMRT. Weekly paclitaxel (30 mg/m^2) and carboplatin area under the curve-1 were given concurrently with IMRT.

Results: Sixty-one of 128 evaluable patients (47.7%) developed hypothyroidism after a median of 1.08 years after IMRT (range, 2.4 months to 3.9 years). Age and volume of irradiated thyroid were associated with hypothyroidism development after IMRT. Compared with 3D-RT, IMRT with no thyroid dose constraints resulted in significantly higher minimum, maximum, and median dose ($p < 0.0001$) and percentage thyroid volume receiving 10, 20, and 60 Gy ($p < 0.05$). Compared with 3D-RT, IMRT with thyroid dose constraints resulted in lower median dose and percentage thyroid volume receiving 30, 40, and 50 Gy ($p < 0.005$) but higher minimum and maximum dose ($p < 0.005$).

Conclusions: If not protected, IMRT for LAHNC can result in higher radiation to the thyroid than with conventional 3D-RT. Techniques to reduce dose and volume of radiation to thyroid tissue with IMRT are achievable and recommended. © 2010 Elsevier Inc.

IMRT, Hypothyroidism, Head-and-neck cancer, Radiation side effects, Concurrent chemoradiation.

INTRODUCTION

The majority of the 40,000 patients diagnosed with head-and-neck cancer annually in the United States (1) receive radiation as a component of treatment. In the 1960s–1980s, the standard treatment consisted of surgery and/or radiotherapy. A paradigm shift occurred in the 1980s: studies showed that chemoradiation can achieve good tumor control with organ preservation, thus chemoradiation became an option for patients with locally advanced and unresectable head-and-neck carcinomas (2). Chronic adverse effects of radiotherapy that could adversely affect the quality of life of locally advanced head-and-neck cancer (LAHNC) survivors include thyroid dysfunction, xerostomia, chronic pain, osteoradionecrosis, trismus, and cervical fibrosis (3, 4). Academic and community centers have adopted intensity-modulated radiotherapy (IMRT) for LAHNC because it conforms the radiation dose around the tumor and reduces high doses to normal tissue. Clinical trials using IMRT have reported excellent tumor control and disease-free survival (3, 5–7), with reduced xerostomia (4, 6, 7). Nonetheless, late toxicities of this new technology are only now beginning to be elucidated (8), especially when it is combined with concurrent chemotherapy (9, 10). Some of the concerns are due to increased integral radiation dose to normal tissues and to

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increased inhomogeneity that can lead to ulceration and necrosis (6, 9, 10).

A well-known side effect of neck irradiation is the development of thyroid disorders, especially hypothyroidism (11–19). Occurrence of hypothyroidism after neck irradiation varies substantially with factors such as addition of chemotherapy (14, 20), surgery (13, 18, 19, 21–26), radiation dose (12, 13, 27, 28), volume of thyroid irradiated (13, 19, 29), and duration of patient follow-up (13, 17, 19, 26). The reported incidence of hypothyroidism after neck irradiation varies between 6% and 48% in prospective and retrospective studies (11, 13, 17–19, 22, 30–33). Latency has been observed as soon as 2 to 3 months (19, 34) and as late as 20 years (14), with the peak occurring at 1.5–3 years after treatment (11, 12, 14, 16–19, 33). The etiology of radiation-induced hypothyroidism remains unclear (15), but it is thought to be related to autoimmune reactions, parenchymal cell damage, and vascular damage (16, 18, 19).

The tolerance dose of the thyroid gland has not been definitively determined (16), and some investigators suggest that the percentage of thyroid volume receiving ≥30 Gy (V30) is a possible predictor of hypothyroidism (35). Others suggest that higher doses of radiation portend a shorter latency period for the development of hypothyroidism (12). To date, all studies of hypothyroidism as a consequence of external-beam radiotherapy have examined patients treated with two-dimensional or three-dimensional (3D) conventional radiotherapy. We conducted a retrospective review of 168 consecutively treated LAHNC patients treated with IMRT/chemotherapy to determine the rate and potential risk factors for developing posttreatment hypothyroidism.

METHODS AND MATERIALS

Patient evaluation

Thyroid function was determined by measuring thyroid-stimulating hormone (TSH). We defined hypothyroidism as a TSH value greater than our institutional upper limit of normal, 5.00 μU/mL. The time to onset of hypothyroidism was defined as the interval between the end of radiotherapy and the first recorded abnormal TSH laboratory value.

From December 2002 to February 2009, 168 sequential patients with biopsy-confirmed LAHNC were treated with IMRT and concurrent platinum/taxane-based chemotherapy for curative intent. Twenty-four patients were excluded from the analysis: 7 had known thyroid disease before treatment, and 17 died before any TSH values were obtained. We had a total of 144 evaluable patients: the first 128 for whom the thyroid was not considered an organ at risk, and 16 more-recent patients for whom the thyroid gland was contoured and dose–volume radiation constraints were used to minimize dose.

Inclusion criteria included Karnofsky performance status ≥60%, normal organ function, and squamous histology. Pretreatment evaluation included history, physical examination, biopsy and endoscopic tumor staging by an otolaryngologist, comprehensive metabolic panel, complete blood count with differential, CT or MRI from the skull base to clavicles, chest X-ray, and dental evaluation. Positron emission tomography was performed whenever possible. When indicated, CT imaging of the chest/abdomen and bone scan were obtained.

Radiation treatment

Patients were immobilized with a thermoplastic head-and-neck mask that included the shoulders to ensure reproducibility of radiotherapy. Computed tomographic simulation was performed in all patients, and the patients were planned using the Eclipse treatment-planning system (Varian Medical Systems, Palo Alto, CA) with 6-MV photons.

To simplify treatment planning, a single IMRT dose-painting technique was developed. Daily fractions of 2.1 Gy were delivered to gross disease (69.3 Gy in 33 fractions, homogeneity −8% to +5%) simultaneously with 1.7 Gy to prophylactic nodal sites down to the clavicles (56.1 Gy) (36). Fifty percent of the volume of sensitive tissue (oral cavity, parotids, back of neck, esophagus, and larynx/trachea) was limited to ≤25 Gy. Intensity-modulated radiotherapy was held for Grade 4 dermatitis or mucositis. Thyroid gland was contoured manually on CT images, and the absolute thyroid volume, dose–volume histograms (DVHs), and percentage of thyroid gland volume absorbing 10, 20, 30, 40, 50, 60, and 70 Gy (V10, V20, V30, V40, V50, V60, and V70, respectively) were determined. The dose to the thyroid was correlated with parameters predicting the development of hypothyroidism.

Treatment plans were available for a retrospective analysis in 113 of 128 of the evaluable IMRT-treated patients. Comparison with DVHs using a 3D conventional radiotherapy plan using a 2-cm-wide midline block on the lower neck field was retrospectively done in 10 randomly selected patients from this group who developed hypothyroidism. Comparison with DVHs of 16 recent patients in whom the thyroid was contoured and protected as an avoidance structure was performed. The dose constraints for the thyroid gland were as follows: 20% volume <20 Gy; 10% volume <30 Gy; 5% volume <40 Gy; and maximum dose 50 Gy.

Chemotherapy treatment

Weekly paclitaxel 30 mg/m^2 and carboplatin area under the curve (AUC)-1 were given concurrently with IMRT to all 168 patients. Seventy-two percent of patients had N2 or N3 disease and also received weekly induction chemotherapy with paclitaxel 60 mg/m^2 and carboplatin AUC-2 for nine cycles. Chemotherapy was held for absolute neutrophil count <1000, platelets <100,000, or Grade 4 mucositis.

Follow-up

Patients were seen and examined every 6–8 weeks for the first year, every 2 to 3 months during the second year, and every 3–6 months thereafter. Thyroid-stimulating hormone was monitored in patients after completion of IMRT at 3–6 months, at 1 year, biannually thereafter, and when clinically indicated.

Statistical methods

Associations between patient characteristics gender, age, stage, site, and thyroid volume and IMRT treatment were tested using Fisher's exact test or the Kruskall-Wallis rank sum test. Associations of the patient characteristics with developing hypothyroidism were tested using Fisher's exact test and the Wilcoxon rank sum test.

Latency of hypothyroidism was estimated using the method described by Gray (37), which appropriately accounts for the competing risk, here death. Area under the DVH curve acted as a summary measure for a patient's DVH curve. A higher-than-average area under the curve indicated that the patient received higher levels of radiation to a greater portion of the thyroid than the average patient. Competing risk regression was used to determine whether area under the DVH curve was associated with time to developing