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CLINICAL INVESTIGATION **Brain**

THYROID-STIMULATING HORMONE SUPPRESSION FOR PROTECTION AGAINST HYPOTHYROIDISM DUE TO CRANIOSPINAL IRRADIATION FOR CHILDHOOD MEDULLOBLASTOMA/PRIMITIVE NEUROECTODERMAL TUMOR

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Purpose: Hypothyroidism is one of the earliest endocrine effects of craniospinal irradiation (CSI). The effects of radiation also depend on circulating thyroid-stimulating hormone (TSH), which acts as an indicator of thyrocyte function and is the most sensitive marker of thyroid damage. Hence, our study was launched in 1998 to evaluate the protective effect of TSH suppression during CSI for medulloblastoma/primitive neuroectodermal tumor.

Patients and Methods: From Jan 1998 to Feb 2001, a total of 37 euthyroid children scheduled for CSI for medulloblastoma/primitive neuroectodermal tumor underwent thyroid ultrasound and free triiodothyronine (FT3), free thyroxine (FT4), and TSH evaluation at the beginning and end of CSI. From 14 days before and up to the end of CSI, patients were administered L-thyroxine at suppressive doses; every 3 days, TSH suppression was checked to ensure a value <0.3 μM/ml. During follow-up, blood tests and ultrasound were repeated after 1 year; primary hypothyroidism was considered an increased TSH level greater than normal range. CSI was done using a hyperfractionated accelerated technique with total doses ranging from 20.8–39 Gy; models were used to evaluate doses received by the thyroid bed.

Results: Of 37 patients, 25 were alive a median 7 years after CSI. They were well matched for all clinical features, except that eight children underwent adequate TSH suppression during CSI, whereas 17 did not. Hypothyroidism-free survival rates were 70% for the "adequately TSH-suppressed" group and 20% for the "inadequately TSH-suppressed" group ($p = 0.02$).

Conclusions: Thyroid-stimulating hormone suppression with L-thyroxine had a protective effect on thyroid function at long-term follow-up. This is the first demonstration that transient endocrine suppression of thyroid activity may protect against radiation-induced functional damage. © **2007 Elsevier Inc.**

Craniospinal irradiation, Iatrogenic hypothyroidism, Thyroid protection, Childhood brain tumors.

INTRODUCTION

Hypothyroidism is one of the earliest late side effects of craniospinal irradiation (CSI) for medulloblastoma/primitive neuroectodermal tumor (PNET) (1). The thyroid parenchyma's particular susceptibility to irradiation is well known. Irrespective of the total doses and CSI technique adopted, subsequent hypothyroidism-related morbidity is ~40–80% (2). Thyroid-stimulating hormone (TSH) is a glycoprotein produced and secreted by the anterior pituitary. It is the main thyroid-function regulator and also has a fundamental role in the control of differentiated thyroid carcinomas and their metastases (3–5).

Thyroid activity relies on thyrotropin-releasing hormone, which is produced in the hypothalamus and secreted into the pituitary, where it stimulates TSH secretion. An increase in TSH results in thyroid cell hypertrophy and hyperplasia and increased iodine trapping and thyroid hormone synthesis. Together with thyroid irradiation, chronic TSH stimulation is believed to be related to the progression of thyroid nodules. TSH production is inhibited by exogenous thyroid hormone or an increase in thyroid hormone synthesis. Thyroid hormone is frequently used to suppress TSH secretion to control the growth of differentiated thyroid cancers and their metastases (4, 5).

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By blocking the metabolic activity of thyroid cells, TSH suppression might also make these cells less vulnerable to radiation damage after they are in a metabolically quiescent condition. Based on this rationale and the chance to reduce the morbidity related to iatrogenic hypothyroidism and the risk of secondary thyroid nodules, we elected to study the thyroid parenchyma and endocrine function in all children scheduled for irradiation of the thyroid bed before delivery of any antineoplastic therapy and administer a TSH-suppressive doses of L-thyroxine to all patients during radiotherapy with a view to obtaining metabolic ''quiescence'' during their potentially cytotoxic and mutagenic exposure.

We planned to compare the results obtained in these patients against those achieved in previous patients and those reported in the literature for similar populations.

We report here the results obtained in 37 children with medulloblastoma/PNET who were treated with L-thyroxine (at different doses, achieving different levels of TSH suppression for reasons unrelated to study methods) in concomitance with their specific radiation therapy in 1998–2001.

PATIENTS AND METHODS

All children with medulloblastoma/PNET were evaluated by using neck ultrasound and serum free triiodothyronine (FT3), free thyroxine (FT4), TSH, and thyroglobulin assay after surgical removal of their primitive tumor and before oncologic treatment, then after primary chemotherapy and before and after radiotherapy.

Before receiving radiotherapy, all children underwent a computed tomography–based simulation and computer-assisted three-dimensional treatment planning with a dose–volume histogram (DVH) to precisely identify thyroid volume and relative radiation isodose distributions (Fig. 1).

During irradiation, all children were to be treated with TSH-suppressive doses of L-thyroxine beginning 2 weeks before radiotherapy started. TSH suppression was considered adequate when the value was $\leq$0.3 μM/ml (normal values, 0.6–4.6 μM/ml) and was generally obtained with L-thyroxine doses of 1–2 μg/kg/d, taken in the morning on an empty stomach half an hour before breakfast. After 3 days, hormone status was checked to guide the administration of progressively increasing L-thyroxine doses to reach the individual's minimum suppressive dose before starting radiotherapy and maintain it throughout treatment. At the end of the course of radiotherapy, L-thyroxine dose was rapidly tapered off.

Follow-up evaluation involved ultrasound and fT3, fT4, TSH, and thyroglobulin measurements 1 year after completing radiotherapy. Thereafter, patients underwent repeated serum fT3, fT4, TSH, and thyroglobulin measurements every 6 months and thyroid ultrasound every 2 years. Primary hypothyroidism is defined as increased serum TSH level greater than normal range (>4.6 μM/ml), with normal (compensated) or decreased (overt) FT4 levels. Central hypothyroidism is defined as decreased FT4 levels with normal or decreased basal TSH levels. From this point onward, we use hypothyroidism to mean primary hypothyroidism because our goal is to preserve thyroid function. However, central hypothyroidism was

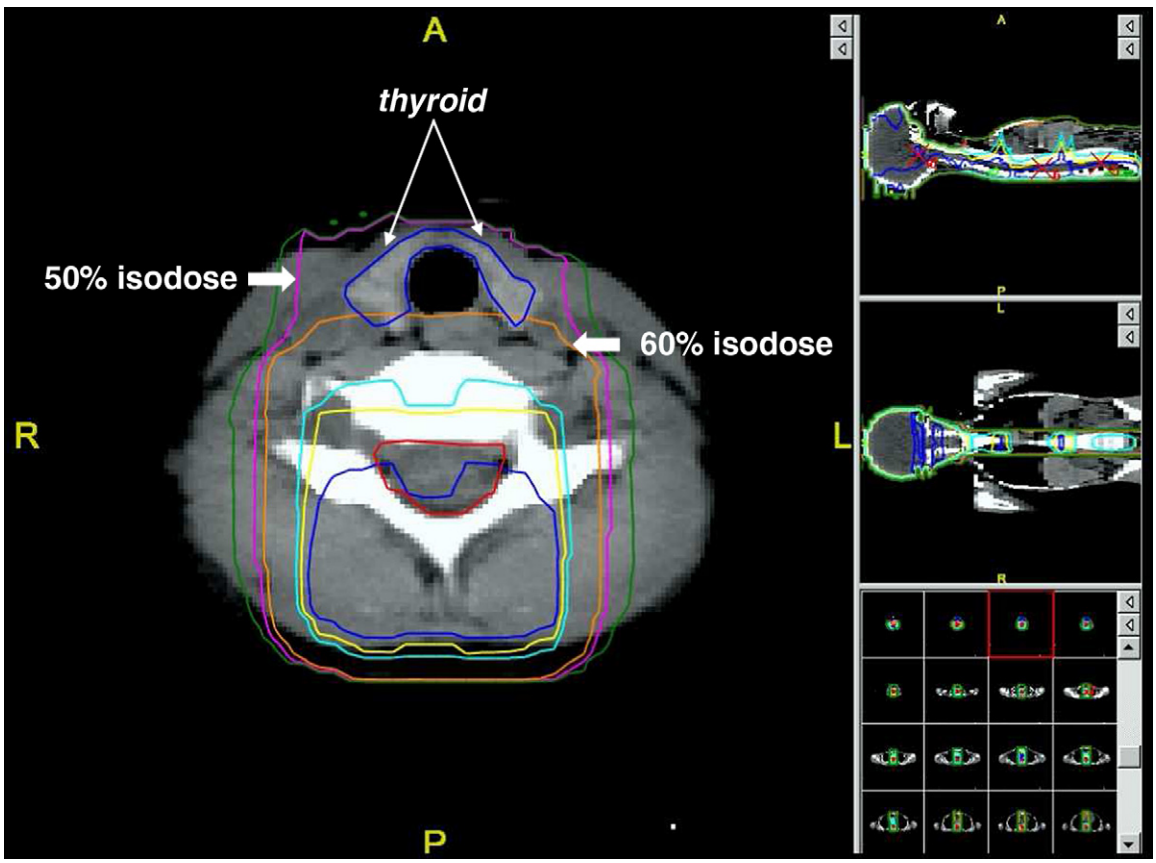

Fig. 1. Radiation dose distribution related to thyroid parenchyma.