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RESEARCH ARTICLE

# Long-term results of suppressing thyroid-stimulating hormone during radiotherapy to prevent primary hypothyroidism in medulloblastoma/PNET and Hodgkin lymphoma: a prospective cohort study

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**Abstract** **Primary hypothyroidism commonly occurs after radiotherapy (RT), and coincides with increased circulating thyroid-stimulating hormone (TSH) levels. We tested therefore the protective effect of suppressing TSH with L-thyroxine during RT for medulloblastoma/PNET and Hodgkin lymphoma (HL) in a prospective cohort study. From 1998 to 2001, a total of 37 euthyroid children with medulloblastoma/PNET plus 14 with HL, scheduled for craniospinal irradiation and mediastinum/neck radiotherapy, respectively, underwent thyroid ultrasound and free triiodothyronine (FT3), free thyroxine (FT4), and TSH evaluation at the beginning and end of craniospinal iiradiation. From 14 days before and up to the end of radiotherapy, patients were administered L-thyroxine checking every 3 days TSH to ensure a value < 0.3 μIU/mL. During follow-up, blood tests and ultrasound were repeated; primary hypothyroidism was considered an increased TSH level greater than normal range. Twenty-two/37 patients with medulloblastoma/PNET and all the 14 patients with HL were alive after a median 231 months from radiotherapy with 7/22 and 8/14 having correctly reached TSH levels < 0.3 μIU/mL and well matched for other variables. Twenty years on, hypothyroidism-free survival rates differed significantly, being 60% ± 15% and 15.6% ± 8.2% in TSH-suppressed vs. not-TSH suppressed patients, respectively ($P = 0.001$). These findings suggest that hypothyroidism could be durably prevented in two populations at risk of late RT sequelae, but it should be confirmed in a larger cohort.**

**Keywords** iatrogenic primary hypothyroidism; late effects of radiotherapy; long-term follow-up; medulloblastoma; Hodgkin lymphoma

## Introduction

Primary hypothyroidism is defined as high serum TSH levels with normal (compensated) or reduced (overt) free thyroxin (FT4) levels. It affects more than one in two patients after radiotherapy (RT) to the neck/mediastinum [1]. Central hypothyroidism is defined instead as low FT4 levels with normal or low basal TSH levels.

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Thyroid-stimulating hormone (TSH) correlates with plasma FT4, and is a marker of hypothyroidism. Thyroid activity relies on hypothalamic thyrotropin-releasing hormone being secreted into the pituitary gland, where it stimulates TSH secretion [1]. The latter results in thyroid cell hypertrophy and hyperplasia, increased iodine trapping, and thyroid hormone synthesis. TSH production is stimulated by lower endogenous thyroid hormone levels, and inhibited by exogenous thyroid hormone or increased endogenous thyroid hormone synthesis [2].

In 1998 we tested a "protective" pharmacological TSH suppression in patients receiving RT to part or all of the thyroid bed. Most of the patients involved had craniospinal

RT for medulloblastoma (MBL) or neck/mediastinum RT for Hodgkin lymphoma (HL). After a mean 7–8 years, our promising results were published [3,4]. Now, with a much extended follow-up, the present report sends a strengthened message to pediatric oncologists and radiotherapists. This paper only concerns primary hypothyroidism as our study goal was to preserve thyroid function in the increasingly common case of children, adolescents, and young adults at risk of hypothyroidism after RT involving the thyroid bed.

## Patients and methods

### Inclusion criteria

Between January 1998 and February 2001 all children in our pediatric unit at Fondazione IRCCS Istituto Nazionale dei Tumori in Milano scheduled for RT if affected by MBL/PNET (classified by the WHO as supratentorial embryonal tumors since 2016 [5]) or by HL if RT would have involved the thyroid bed were proposed to enter this study; consent by parents was obtained.

### Methods

The design followed a prospective cohort study. Patients underwent thyroid ultrasound and FT3, FT4, TSH assay. Simulations with computed tomography, and computer-assisted three-dimensional treatment planning with a dose-volume histogram were used to identify thyroid volumes and corresponding RT isodose distributions. From 14 days beforehand and throughout their RT, patients received L-thyroxine in the morning on an empty stomach (half an hour before breakfast), starting with 1–2 μg/kg, and adjusting the dose every 3 days to ensure TSH $<$ 0.3 μIU/mL (the normal ranges changed for TSH from 1998 to 2011, from 0.6 to 0.3 μIU/mL and from 4.6 to 4.2 μIU/mL for lower and upper level, respectively). The 0.3 μIU/mL threshold was chosen pragmatically as just below normal range but not causing hyperthyroidism (as confirmed in later studies [6]), and defined as "mild" TSH suppression [7]. Based on hormone status, L-thyroxine doses were gradually increased to patients' individual minimum TSH-suppressive dose before starting RT, maintained throughout the treatment, then rapidly tapered off. Patients were followed up for their primary tumor, thyroid function and parenchymal alterations. Blood tests and ultrasound were repeated after 1 year, and at least annually thereafter.

We originally planned to compare our patients with others treated previously without TSH suppression [8] and similar populations reported by the literature [9–11]. At the first assessment after RT, however, a variable adherence to thyroxine treatment enabled us to group our MBL/PNET and HL patients by their TSH levels 0.3 (TSH-suppressed) or $\geqslant$ 0.3 μIU/mL (TSH-not-suppressed) during their RT, obtaining four patient cohorts. Only 2 patients were censored and excluded from further analysis on developing central hypothyroidism.

Differences in hypothyroidism-free survival between patients with and without TSH suppression were analyzed using the Kaplan–Meier method [12] and logrank (Mantel-Cox) test was used to calculate $P$ value. Chi-square tests were used to compare the frequency of patients' characteristics [13]. A $P < 0.05$ was considered statistically significant.

## Results

All the patients object of this paper were maintained in active follow-up consisting of clinical examination, thyroid ultrasound, and blood samples for thyroid function tests that were undertaken at our institution or at a facility closer to the patient's home. Thyroid function testing was repeated every 6 months and thyroid ultrasound examination every other year. Patients were given a brief form documenting clinical history for the radiologist undertaking the ultrasound examination and, whenever possible, subsequent ultrasound examinations were requested at the same facility and with the same operator to limit inter observer variability in sequential assessments.

Twenty-two of the originally 37 treated patients with MBL/PNET [3] and all the 14 with HL [4], alive and in complete remission at the time of writing, had a median post-RT follow-up of 231 (range 213–243) and 232 (range 207–242) months, respectively, and a median 187 months elapsing since their first thyroid function evaluation (range 33–225). Seven of 22 patients with MBL/PNET and 8/14 with HL had received a correct TSH suppression during whole radiotherapy course always maintaining TSH levels 0.3 μIU/mL. Median value for FT3 during radiotherapy was 8.37 pmol/L (range 6.48–10.99 pmol/L), for FT4 it was 26.42 pmol/L (range 12.59–49.15 pmol/L) and for TSH 0.16 μIU/mL (range 0.05–0.28 μIU/mL). Transient asymptomatic hyperthyroidism was recorded in 3/15 TSH-suppressed patients, and in 1/21 TSH-not-suppressed (P n.s.).

Though numerically small, the MBL/PNET and HL cohorts were still — nearly 20 years on — well matched for gender, age at RT, disease stage, chemotherapy courses, use of high-dose chemotherapy, thyroid bed RT dose, and duration of follow-up, as explained in details by Table 1. Fig. 1 shows patients diagram from diagnosis, through study results and last follow-up of their thyroid function. Detailing sex and age for the whole population, females were 15/36 with 7 in the TSH-suppressed group, and mean age at diagnosis was 11.3 years (range 1–21 years, SD 5.11) for the 36 survivors with 14.6 years for the

**Table 1** MBL/PNET and HL cohorts

| Patient code | Sex | Diagnosis | Age at diagnosis (year) | Craniospinal and neck/ mediastinumdoses in Gy | Myeloablative schedule | Adequate TSH suppression | Hypothyroidism | Interval since starting RT (month) | Other endocrine and metabolic problems |
|---|---|---|---|---|---|---|---|---|---|
| 3 | M | MBL-S | 12 | 39 | No | Yes | No | 213 | Growth hormone (GH), vit D deficiency |
| 5 | F | MBL-S | 11 | 39 | No | Yes | No | 215 | GH deficiency, dyslipidemia |
| 11 | M | S-PNET-S | 18 | 39 | No | Yes | No | 239 | No |
| 14 | F | MBL-S | 21 | 39 | Yes | Yes | Yes | 214 | No |
| 17 | M | MBL-S | 21 | 39 | No | Yes | No | 237 | No |
| 19 | M | MBL-S | 13 | 39 | No | Yes | No | 223 | No |
| 22 | M | MBL-S | 15 | 39 | No | Yes | No | 227 | GH deficiency, dyslipidemia |
| 1 | M | MBL-NS | 1 | 20.8 | Yes | No | Yes | 235 | GH deficiency |
| 2 | F | MBL-NS | 6 | 31.2 | Yes | No | Yes | 219 | Dyslipidemia, hyperinsulinism, panhypopituitarism, vit D deficiency, liver steatosis |
| 4 | M | MBL-NS | 8 | 20.8 | No | No | Yes | 243 | Dyslipidemia, vit D deficiency |
| 6 | M | MBL-NS | 6 | 20.8 | No | No | Yes | 240 | No |
| 7 | M | MBL-NS | 7 | 31.2 | No | No | No | 228 | GH deficiency |
| 8 | F | MBL-NS | 16 | 39 | No | No | Yes | 213 | No |
| 9 | M | S-PNET-NS | 2 | 20.8 | Yes | No | No | 219 | Dyslipidemia, hyperinsulinism, liver steatosis, second thyroid tumor |
| 10 | M | MBL-NS | 18 | 39 | No | No | No | 239 | GH deficiency |
| 12 | F | MBL-NS | 7 | 31.2 | No | No | No | 238 | No |
| 13 | F | MBL-NS | 4 | 20.8 | No | No | No | 241 | GH deficiency, vit D deficiency |
| 15 | M | MBL-NS | 3 | 31.2 | Yes | No | No | 232 | GH deficiency |
| 16 | M | MBL-NS | 5 | 20.8 | No | No | Yes | 240 | GH deficiency |
| 18 | M | MBL-NS | 8 | 20.8 | No | No | Yes | 222 | No |

(*Continued*)

| Patient code | Sex | Diagnosis | Age at diagnosis (year) | Craniospinal and neck/ mediastinumdoses in Gy | Myeloablative schedule | Adequate TSH suppression | Hypothyroidism | Interval since starting RT (month) | Other endocrine and metabolic problems |
|---|---|---|---|---|---|---|---|---|---|
| 20 | F | MBL-NS | 10 | 39 | No | No | Yes | 222 | Dyslipidemia, vit D deficiency |
| 21 | M | MBL-NS | 10 | 39 | No | No | Yes | 230 | Dyslipidemia, hyperinsulinism, panhypopituitarism, liver steatosis |
| 23 | M | HL-S | 12 | 30 | No | Yes | No | 212 | No |
| 25 | F | HL-S | 15 | 25 | No | Yes | Yes | 238 | Dyslipidemia |
| 29 | F | HL-S | 16 | 25 | No | Yes | No | 215 | No |
| 30 | M | HL-S | 9 | 25 | No | Yes | Yes | 240 | Second thyroid tumor |
| 31 | F | HL-S | 17 | 25 | No | Yes | No | 207 | No |
| 33 | M | HL-S | 10 | 30 | No | Yes | No | 212 | No |
| 34 | F | HL-S | 12 | 30 | No | Yes | No | 238 | No |
| 36 | F | HL-S | 17 | 30 | No | Yes | No | 227 | No |
| 24 | F | HL-NS | 16 | 25 | No | No | Yes | 222 | No |
| 26 | F | HL-NS | 13 | 26 | No | No | Yes | 238 | No |
| 27 | M | HL-NS | 13 | 20 | No | No | Yes | 209 | Dyslipidemia |
| 28 | M | HL-NS | 10 | 25 | No | No | Yes | 232 | No |
| 32 | F | HL-NS | 10 | 25 | No | No | Yes | 242 | Second thyroid tumor |
| 35 | M | HL-NS | 15 | 25.2 | No | No | Yes | 219 | Second thyroid tumor |

M, male; F, female; MBL/PNET-S, MBL/PNET TSH-suppressed patients; MBL/PNET-NS, MBL/PNET TSH-not-suppressed patients ; HL-S, HL TSH-suppressed patients; HL-NS, HL TSH-not-suppressed patients.

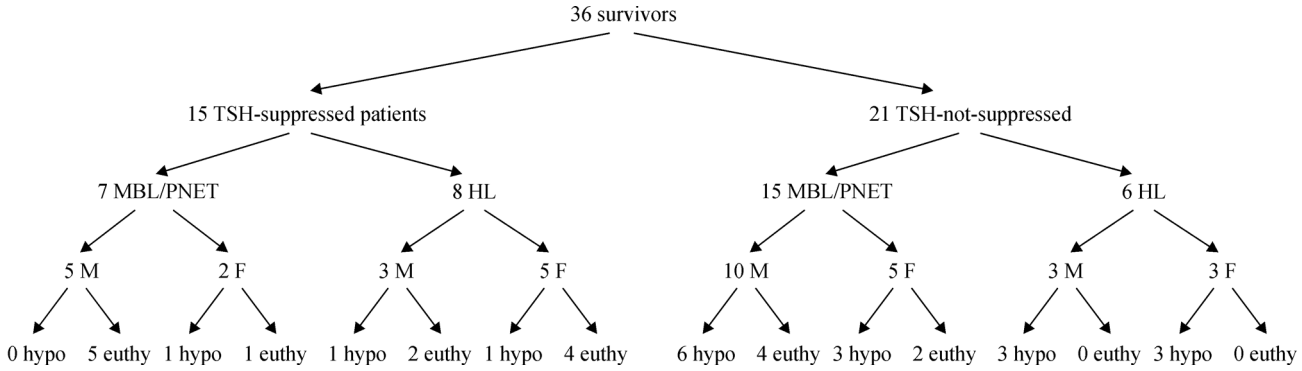


**Fig. 1** MBL/PNET and HL patients diagram from diagnosis to present status. hypo, hypothyroid patients; euthy, euthyroid patients.

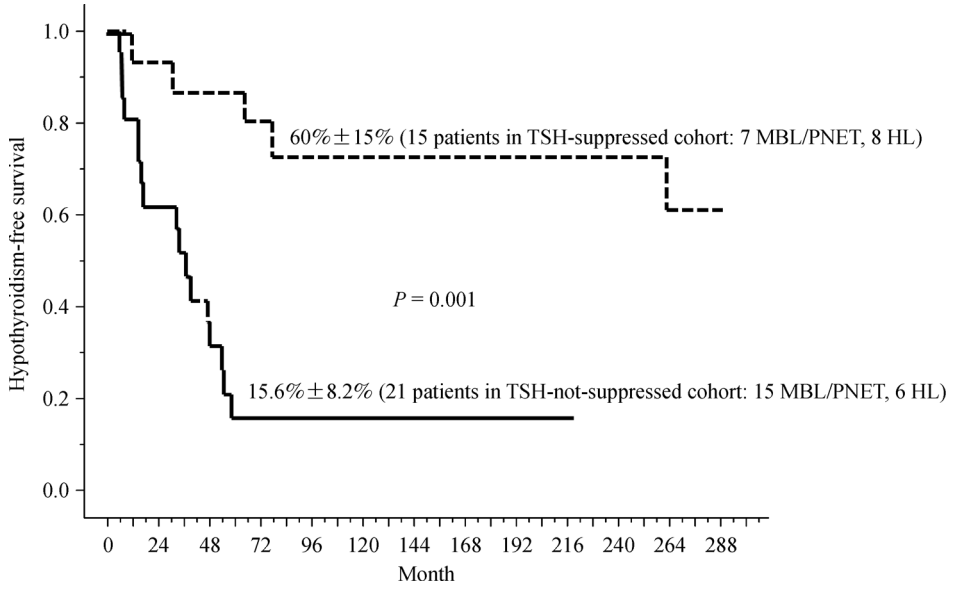


**Fig. 2** Hypothyroidism-free survival rates for TSH-suppressed and TSH-not-suppressed patients.

TSH-suppressed group and 8.9 years for the TSH-not-suppressed group.

Hypothyroidism-free survival rates differed at their latest follow-up: in the MBL/PNET cohort, it was 45.7% ± 22.4% for the 7 TSH-suppressed patients and 22.5% ± 11.3% for the 15 TSH-not-suppressed ($P$ = 0.08); in the HL cohort, it was 75% ± 15.3% for the 8 TSH-suppressed patients and 0% for the 6 controls ($P$ = 0.0009), respectively. Considering the MBL/PNET and HL patients together, the difference was again significant: 60% ± 14.8% for the TSH-suppressed and 15.6% ± 8.2% for the TSH-not-suppressed ($P$ = 0.001) (HR 7.2, range 2.23–23.23) (Fig. 2). In 22/36 patients, primary hypothyroidism developed after a median 33 months (range 6–61). Colloidal cysts and solid nodules occurred in similar proportions in the TSH-suppressed and control patients, with 6 parenchymal alterations (2 cystic and 4 nodular) in 15 TSH-suppressed patients and 11 (1 cystic and 10 nodular) in 21 TSH-not-suppressed. Four patients (3 TSH-not-suppressed) developed secondary thyroid tumors (papillary carcinoma in two, and well differentiated tumors in two) at 34, 72, 110, and 217 months after starting RT. Other endocrine and metabolic alterations did not differ by TSH suppression status or onset of hypothyroidism (Table 1).

## Discussion

Thyroid dysfunction may develop from months to years after RT, even after very small doses only partially involving the gland [8,14,15]. RT almost always causes hypothyroidism, and very rarely leads to hyperthyroidism [8,14–16].

Endocrine disorders negatively affect growth and development in children given lengthy cancer treatments, so modern oncological treatments try to contain the risk of such well-known late sequelae [17]. More than 20 years ago, we tried a cheap and simple approach to protecting our patients against post-RT hypothyroidism involving TSH suppression.

Around the time of our two previous publications [3,4], van Santen *et al*. reported failing to prevent hypothyroidism in an animal model using much the same approach [18]. As van Santen *et al*. themselves suggested, the discrepant results may be largely because TSH was lowered, but not suppressed before RT in their Wistar rats, to avoid causing hyperthyroidism by administering thyroxine and iodine. We had 4 cases of biochemical FT4 elevation during RT too, albeit without any symptoms. In an older paper, Bantle *et al*. also reported no protective effect of thyroxine administered during RT [19]. There were many differences between their study and ours, however, the sample was even smaller than ours; thyroxine medication was begun closer to starting RT; TSH was judged as "suppressed" at higher levels; and the follow-up was less than 3 years. The population of patients with medulloblastoma/PNET considered in our paper did not show indeed a statistical difference in hypothyroidism-free-survival between the two cohorts of patients when updated after 20 years, but this was probably due to the dimension of the sample being reduced from the 36 original patients to the current 22 [3].

As van Santen *et al.* found too (albeit in an animal model) [18], preventing post-RT hypothyroidism did not prevent the occurrence of parenchymal alterations (nodules or colloidal cysts) in our sample.

Radiation-induced thyroid damage varies from one individual to another, with a complex pathogenesis. It evolves very slowly from loss of follicular epithelium function to endothelial changes with cell degeneration and necrosis, thrombosis, acute and chronic inflammation, fibrous organization and partial epithelial regeneration [20]. So far, nobody has succeeded in protecting the thyroid against parenchymal alterations [21,22]. A prolonged TSH suppression after completing RT might be therefore worth trying in a bigger population than the one we treated, also given the absence of significant side effects in our experience.

Harris *et al*. described an invasive procedure involving thyroid transfer to the patient's forearm before administering RT for adult head and neck tumors: at an initial follow-up of one year, the procedure was successful in all 9 patients treated [23]. The feasibility of this procedure in children remains to be seen.

Our study has several limitations because it involved only a few patients and their number diminished along time. The results came moreover after a not-randomized variable thyroxine intake, due to non-compliance of some patients and/or not adequate monitoring of their thyroid function, and not to a treatment arm assignment as in a regular trial designed to show one treatment arm superiority. This of course reduces the power of the findings.

This study suggests, however, that hypothyroidism could be easily, cheaply, and durably prevented in two populations at high risk of late effects of RT. Our results need to be confirmed in larger samples, with a true randomized approach and accurately monitoring patients' TSH levels during a long follow-up.

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## Compliance with ethics guidelines

Maura Massimino, Marta Podda, Lorenza Gandola, Emanuele Pignoli, Ettore Seregni, Carlo Morosi, Filippo Spreafico, Andrea Ferrari, Emilia Pecori, and Monica Terenziani have no conflicts of interest to disclose. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki declaration* of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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