SUMMARY

Background: RET genotype analysis allows identification of asymptomatic carriers at risk of developing medullary thyroid carcinoma (MTC). However, there is still controversy regarding the ideal timing & extent of prophylactic thyroidectomy (Tx) due to the wide spectrum of clinical presentation. Surveillance of a large number of young patients is crucial to advance our understanding of the natural course of the disease. This study aimed to describe the clinical presentation, oncological features, and treatment outcome of children and young adults harboring RET mutations followed from 1997 to 2007.

Method: Forty-one individuals aged ≤25 years from 17 independent multiple endocrine neoplasia (MEN) type 2A kindred were studied. Twenty-one individuals presented with thyroid nodules at diagnosis, and 20 were disease free at physical examination.

Results: Preoperative basal calcitonin (CT) levels were elevated in 85.7% of patients with clinical disease and in 54.5% of asymptomatic carriers. Thyroid ultrasonography (US) showed one or more nodules in 69.0% of the patients. A positive correlation between age at surgery and tumor-node-metastasis (TNM) stages was observed (p<0.001). None of the patients under 15 years of age presented lymph node or distant metastasis. After a follow-up of 4.4±1.4 years, all asymptomatic patients were disease free based on physical examination, cervical US, and undetectable serum CT levels. In the group of patients with clinical disease, 47.6% have persistent disease (follow-up of 12.0 ±5.9 years). Indeed, palpable thyroid nodule at diagnosis was significantly associated with persistent disease (p<0.001, odds ratio [OR] 1.9, 95% confidence interval [CI 95%] 1.27–2.87). Of note, none of the patients who presented lymph node metastasis at diagnosis were cured by surgical intervention (p<0.001, OR 5.0, CI 95% 1.45–17.0).

Conclusion: The data show a time-dependent MTC progression. Presence of palpable thyroid nodule and lymph node metastasis at diagnosis was associated with persistent or recurrent disease after surgical procedure.

COMMENT

This is a nice clinical study carried out by Ana Luiza Maia and her colleagues in Southern Brazil, dealing with long term evaluation and follow-up of young subjects with multiple endocrine neoplasia (MEN) type 2A, and particularly with medullary thyroid carcinoma (MTC). Thanks to DNA-based RET genotyping, the identification of asymptomatic carriers of a mutated gene who are, therefore, at high risk of developing hereditary MTC has allowed to perform prophylactic thyroidectomy (Tx) at a very early age (<5 years). Because of the poor prognosis of MTC once it has spread beyond the thyroid bed, early Tx offers the only chance to cure such patients before MTC develops or at
least when the disease is still confined within the gland.

Present study included 41 patients. Nineteen patients had been diagnosed before 1997 (i.e., before molecular RET mutation diagnosis was available in the center), on the basis of serum CT levels, clinical findings, family history, or associated neoplasia. In patients with molecular RET diagnosis, the following mutations were identified: C634Y (27), C634R (6), C634W (5), & C618R (3). Thus, the most prevalent mutation in the RET proto-oncogene was observed at codon 634 (92% of patients). Of notice, there were 4 cases with associated pheochromocytoma and 5 with hyperparathyroidism in the present series.

Tx was performed between 5 & 29 years (mean: 16 years). In the group of patients with clinical MTC disease (N = 21), TNM stages 1+2 accounted for 66% of the cases, while stages 3+4 for the remaining 34%. By contrast, 18 of the 20 asymptomatic subjects who underwent prophylactic Tx were classified as TNM stage 1. It is also important to note that lymph node metastases were rarely found before 15 years of age.

With regard to the long term follow-up, 74% of patients were considered disease-free (after a mean period of 9 years). Also, there was a clear-cut correlation between a palpable nodule at the time of diagnosis and persistent or recurrent disease after Tx, indicating that the presence of nodule constitutes a valid predictor of therapy outcome in these young patients.

In summary, the data show a time-dependent progression of MTC, emphasizing the need to determine for each case the right moment (early!) to perform thyroid surgery.

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See Figure below

![Figure 1](image-url)

**FIG. 1.** Correlation between age at surgery and TNM stage of patients who underwent therapeutic or prophylactic total thyroidectomy. Horizontal lines represent mean of age at each stage. CCH, C-cell hyperplasia.