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# Role of RET codonic mutations in the surgical management of medullary thyroid carcinoma in pediatric age multiple endocrine neoplasm type 2 syndromes

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**Abstract**

**Purpose:** Hereditary medullary thyroid carcinoma (MTC) therapy is surgical resection. Because the genetic screening was available, the early diagnosis of the disease has been possible. The purpose of this study was to evaluate the role of the genetic test in the management of these children and to draw some information about the surgical timing.

**Methods:** Thirteen patients underwent total thyroidectomy at our institute between 1995 and 2007. Seven patients underwent a curative thyroidectomy, and 6 patients underwent a prophylactic thyroidectomy. Two patients were operated with a minimally invasive video-assisted technique. We studied the following parameters: age, risk level associated to the RET gene mutations, aim of surgery (curative or prophylactic), tumor histopathologic features, lymph node involvement, and distal metastases.

**Results:** We found a statistical association between cancer maximum diameter and some parameters analyzed: age of patients, aim of surgery, single or multifocal MTC, and number of organs involved by distal metastases. Cancer diameter at the moment of diagnosis seems to increase according to the aggressiveness of RET gene mutation found.

**Conclusions:** The best strategy to cure MTC is to prevent it. Genetic screening could be a fundamental tool in the management of multiple endocrine neoplasm type 2 children. An improvement of scientific knowledge regarding RET gene alterations and an early and appropriate use of genetic tests could allow a better understanding of the correct surgical timing and a wider use of less aggressive surgical procedures.


## 1. Background

Medullary thyroid carcinoma (MTC) is a rare thyroid tumor, counting for 3% to 10% of all thyroid malignancies. Medullary thyroid carcinoma may be sporadic, mostly in

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adult patients, or may be a manifestation of the hereditary multiple endocrine neoplasm type 2 (MEN2) syndromes, mostly in pediatric patients. Multiple endocrine neoplasm type 2 syndromes include MEN 2A (65% of cases), characterized by MTC, pheochromocytoma, and hyperparathyroidism; MEN 2B (25% of cases), characterized by MTC, pheochromocytoma, mucosal ganglioneuromatosis, and a distinct marfanoid habitus; and familial medullary thyroid carcinoma (FMTC) (10% of cases), characterized by just MTC [1].

Almost always, MTC is the first tumor to develop in these syndromes, and the disease outcome is much more aggressive in the patients who are affected by MEN2B; in fact, cancer cells are found in very small children's thyroids, sometimes in their first months of life; multiple foci of MTC and an important metastatic lymph node engagement are often found at the moment of the diagnosis; distal metastases could be precociously identified, mainly at the liver, lungs, and bones, with a bad prognosis.

The gold therapeutic standard for MTC is total thyroidectomy. Until recent years, MTC has essentially been identified by basal calcitonin test and pentagastrin-stimulated calcitonin. However, with these procedures, even if effective, often allow the diagnosed of MTC at an advanced stage.

In 1993, characteristic germline mutations of the "REarranged during Transfection" (RET) proto-oncogene on chromosome 10 are responsible for the inherited forms of MTC. RET gene encodes a plasma membrane-bound tyrosine kinase enzyme. MEN2 are caused by point mutations leading to a constitutive activation of this enzyme and then to a function gain of the molecule. Specific mutations are associated to every form of MEN2.

Now, the screening of all the members of MEN2 families is possible with a simple peripheral blood sampling, even immediately after their birth. The carriers of RET mutations have a probability near 100% to develop, sooner or later, an MTC. To avoid the tumor, the suitable treatment is to prevent it through thyroidectomy.

In our study, we present 13 MTC patients: 7 patients treated with curative surgery and 6 with prophylactic surgery. All of them underwent a genetic test to identify RET gene mutations.

Therefore, the purpose of our study was to value prophylactic surgery to prevent MTC in MEN2 children and to draw some information about the surgical timing.

## 2. Methods

Between 1995 and 2007, 13 patients, 9 girls (69%) and 4 boys (31%), aged 17 years or less (average age, 13.8 years), underwent a surgical operation for MTC within MEN2 syndromes, at the General Surgery Department of the University of Pisa (Italy). At the moment of diagnosis, the youngest patient was 8 years old and the oldest one 17.

MEN 2A was diagnosed in 7 patients (54%), FMTC in 4 patients (31%), and MEN 2B in 2 patients (15%). The average age was 13 years for MEN2 patients, 16 for FMTC patients and 12.5 for MEN2B patients. Each patient underwent physical examination, laboratory tests, and instrumental examinations. A family tree of 1 or 2 generations was made for each patient.

Preoperative laboratory tests required were basal calcitonin test and pentagastrin-stimulated calcitonin test, indexes of thyroid function (Free-Thyroxine, Free-Triiodothyronine, thyroid-stimulating hormone), antithyroglobulin and antithyroperoxidase antibodies, parathyroid hormone, phosphate and calcium, and plasma and urinary cathecolamines.

Each patient underwent a genetic test for the identification of RET proto-oncogene mutations. DNA was taken from peripheral blood, amplified through polymerase chain reaction, and sequenced according to the procedures previously described [1-3].

According to the RET gene mutations, we stratified our patients in 3 different risk levels, as described in the 2001 guidelines for diagnosis and therapy for MEN type 2 [4].

Preoperative instrumental examinations included cervical ultrasonography (US), fine-needle agobiopsy for cytological test in case of thyroid nodules, laryngoscopy, thoracic radiography, cervical and thoracic computed tomography, abdominal US, abdominal computerized tomography (CT), 123I-meta-iodobenzylguanidine scintigraphy, double contrast barium enema, and colonoscopy with biopsy in case of MEN2B.

Surgical indications were thyroid nodulation, inheritance for MTC, altered basal calcitonin test (>100 pg/mL) or pentagastrin-stimulated calcitonin test (>250 pg/mL), and positive genetic test in 5 patients with MEN2A; characteristic phenotype (marfanoid habitus, mucosal neurinoma) in 2 girls with MEN2B; and inheritance for MTC and a positive genetic test (RET gene point mutation) in the last 6 patients, 2 MEN2A, and 4 FMTC. According to us, prophylactic thyroidectomy indicates a total thyroidectomy performed on a patient with genetic diagnosis of MEN2, clinically asymptomatic, with basal calcitonin values lower than 100 pg/mL and with pentagastrin-stimulated calcitonin test lower than 250 pg/mL [5,6].

In each case, the surgical treatment required was a total thyroidectomy associated with lymph node dissection of the central compartment. In patients with metastases to the lateral-cervical lymph nodes, we associated a bilateral lateral-cervical lymphadenectomy.

In patients with primary hyperparathyroidism, a parathyroidectomy was carried out.

In 2 cases, instead of an open surgery, we performed a minimally invasive video-assisted thyroidectomy.

Postoperative serum calcium measurement and a postoperative laryngoscopy were also performed.

TNM staging system was used for preoperative and postoperative staging, according to the American Joint Committee on Cancer [7].