

## Surgical treatment of sporadic medullary thyroid carcinoma: strategy and outcome

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**SUMMARY:** Surgical treatment of sporadic medullary thyroid carcinoma: strategy and outcome.

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**Background.** Medullary Thyroid Carcinoma (MTC) originates from the thyroid C cells and accounts for approximately 5-9% of all thyroid cancers. Aim of this study was to retrospectively evaluate the outcomes of 41 patients with MTC who underwent treatment at our institution.

**Patients and methods.** We reviewed the records of 41 patients who underwent surgery between 1995 and 2004. The patients were divided into two groups: A) patients (n 30) without any previous surgery; B) patients (n 11) previously thyroidectomized and high calcitonin levels with or without radiological evidence of local regional or distant metastases.

We performed total thyroidectomy with central compartment lymphadenectomy and ipsilateral modified radical neck dissection in group A patients. Group B patients underwent re-excision of the central neck compartment and bilateral modified radical neck dissection if it had not been previously performed.

**Results.** Most patients had major reduction in postoperative calcitonin levels. Compartmental dissection of the cervical node significantly improved the results of primary surgery and calcitonin returned to normal levels in approximately 60% of the patients in group A, but only the 30% of the patients in group B.

**Conclusions.** The extent of the primary surgical resection and the evidence of local or distant metastases significantly influence the outcome of MTC patients. An extensive lymphadenectomy performed early in the treatment and re-operative cervical lymphadenectomy in patients with persistently high calcitonin levels after thyroidectomy significantly improved the outcome, although re-operation rarely results in normalized calcitonin levels and is associated with a higher incidence of complications.

**RIASSUNTO:** Trattamento chirurgico del carcinoma midollare della tiroide: strategia e risultati.

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**Introduzione.** Il carcinoma midollare della tiroide (CMT) origina dalle cellule C della tiroide e rappresenta circa il 5-9% di tutti i carcinomi tiroidei. Lo scopo di questo lavoro è stato valutare retrospettivamente i risultati di 41 pazienti con diagnosi di CMT trattati presso il nostro Istituto.

**Pazienti e metodi.** Abbiamo rivalutato i dati di 41 pazienti operati presso il nostro Istituto tra il 1995 e il 2004. I pazienti sono stati divisi in due gruppi: gruppo A, pazienti (n 30) senza alcun precedente intervento chirurgico; gruppo B, pazienti (n 11) precedentemente operati di tiroidectomia con alti livelli di calcitonina, con o senza evidenza radiologica di recidiva locoregionale o metastasi a distanza.

Abbiamo praticato una tiroidectomia totale con linfadenectomia del compartimento centrale e dissezione radicale modificata del compartimento omolaterale alla lesione nei pazienti del gruppo A. I pazienti del gruppo B sono stati sottoposti a revisione del compartimento centrale e linfadenectomia radicale modificata bilaterale, se non era stata precedentemente praticata.

**Risultati.** La maggior parte dei pazienti ha avuto una riduzione significativa nei livelli di calcitonina postoperatoria. La dissezione del compartimento centrale migliora in modo significativo i risultati della prima chirurgia e i livelli di calcitonina ritornano a valori normali nel 60% dei pazienti del gruppo A, e solo nel 30% dei pazienti del gruppo B.

**Conclusioni.** L'estensione della chirurgia iniziale e l'evidenza di metastasi locoregionali o a distanza influenzano significativamente la prognosi dei pazienti con diagnosi di CMT. Un'estesa linfadenectomia praticata precocemente come primo intervento chirurgico e una linfadenectomia cervicale come reintervento, in pazienti con persistenti alti livelli di calcitonina dopo tiroidectomia, migliorano significativamente la prognosi, sebbene un reintervento chirurgico raramente porti ad una normalizzazione dei livelli di calcitonina e sia associato ad un'alta percentuale di complicanze.

**KEY WORDS:** Medullary thyroid carcinoma - Calcitonin - Thyroidectomy.  
Carcinoma midollare della tiroide - Calcitonina - Tiroidectomia.

## Introduction

Medullary Thyroid Carcinoma (MTC) arises from parafollicular cells and secretes different hormones, in

particular calcitonin. It is a rare tumour accounting for 3% to 10% of all thyroid cancers, with sporadic and familial forms. Sporadic MTC (SMTC) occurs in 75% of patients (1). MTC is characterized by early spread to regional lymph nodes. Prognosis is less favourable than differentiated thyroid cancer, accounting for up to 14% of all thyroid cancer-related deaths (2). Its outcome, similarly to the differentiated forms of thyroid carcinoma, depends on the extent of the disease, the tumour biology, and the overall efficacy of primary surgical resection. Surgery is the most effective therapy. The worldwide accepted guidelines recommend primary total thyroidectomy and central compartment lymphadenectomy with modified ipsilateral radical neck dissection for tumors larger than 1 cm or for patients with central compartment lymph node involvement (3, 4). High calcitonin serum levels represent a strong marker of residual tumour disease and a postoperative normalization predicts a survival rate of 97.7% at 10 years (5, 6). The microscopic residual disease, local-regional lymph node infiltration or metastases to distant organs can be suspected in presence of elevated serum levels of calcitonin and CEA even in the absence of clinical or radiographic evidence of disease (5-7). After inadequate surgery or tardive diagnosis, MTC may be fatal or remain stable for decades. In the latter case the persistence of high serum calcitonin levels is frequent and associated with higher rates of local and distant recurrence and mortality (8).

The aim of this study was to evaluate the outcome of patients with diagnosis of SCMT who underwent treatment in our institution.

## Patient and methods

Between 1986 and 2005 a total of 4668 patients underwent thyroid surgery. In this period 41 patients with SMTC (30 women and 11 men; median age at diagnosis 41 years, range 20-72), were operated in our institution.

Only patients with complete follow up were included in the study. All patients were screened for pheochromocytoma through a 24-hour urine collection for metanephrine vanillylmandelic acid and free catecholamines. Preoperative serum calcitonin levels were assessed in our clinical laboratory by radioimmunoassay after 1995; 11 patients previously operated had been tested with another calcitonin assay. Patients with normal or undetectable calcitonin values underwent pentagastrin test. Preoperative cervical ultrasonography and fine-needle aspiration biopsy were performed in patients who presented a palpable thyroid nodule or lymph node in the neck at presentation.

Patients were divided into two groups: group A included 30 patients without previous surgery; group B included 11 patients previously thyroidectomized and with recurrent or persistent elevation of plasma calcitonin levels.

Group A included 24 patients with high basal serum calcitonin levels and palpable nodule in the thyroid at presentation and

6 patients with diagnosis of multinodular goitre and hypercalcitoninemia. These patients underwent total thyroidectomy with central compartment lymphadenectomy. If the tumor size was >1 cm, an ipsilateral modified radical neck dissection was also performed. Six patients from group A, operated before 1995, underwent total thyroidectomy with central neck compartment and bilateral modified radical neck dissection.

Group B included 11 patients who had been referred after surgery in other centers and who presented with elevated basal calcitonin plasma levels. Four out of eleven patients previously totally thyroidectomized without lymphadenectomy were considered as patients with incomplete surgical resection and underwent re-excision of the central neck compartment and bilateral modified radical neck dissection. Three out of eleven patients with total thyroidectomy, dissection of the central lymph node compartment and lateral modified radical neck dissection showed metastatic lymph nodes detected with radiological investigation and consequently underwent additional neck dissection. Four out of eleven patients showed high calcitonin levels without any clinical or morphological evidence of local regional or distant metastases. These patients underwent cervical ultrasonography, CT scan chest, CT or magnetic resonance imaging (MRI) of the liver, radionuclide bone scanning, and FDG-PET. These patients were not surgically treated. Laparoscopic examination of the liver was performed in 3 patients of group B.

Three months after surgery, calcitonin plasma levels were measured in all patients. The post-operative calcitonin levels were routinely measured during the first month of follow up. Patients with normal or undetectable calcitonin levels were re-assessed by pentagastrin stimulation.

Adjuvant therapy, including external beam irradiation and chemotherapy, was performed in 3 patients (1 patient from group A, 2 patients from group B) with rapidly increasing calcitonin levels, indicating a highly aggressive and rapidly progressive metastatic disease.

## Results

We retrospectively analyzed a cohort of 37 patients out of 41 with high calcitonin levels operated in our Institution. Thirty patients were diagnosed with MTC and classified as group A, while 7 were included in group B since they had been previously surgically treated for MTC. Preoperative median plasma calcitonin was 600 pg/ml (range 80-2060 pg/ml) in group A and 400 pg/ml in group B (range 150-2500 pg/ml). The pathologic features (Tab. 1) and the surgical procedures performed (Tab. 2) are reported for all patients.

The pathologic features showed a tumor size ranging between 1.5 and 5 cm (mean 3 cm). In 30 patients the tumours were unilateral; 30 patients (25 of group A and 5 of group B) presented a tumor confined entirely within the thyroid gland without any sign of extra-capsular invasion and 11 patients (9 of group A and 2 of group B) presented tumours with extension beyond the thyroid gland directly into the surrounding adipose and connective tissues.

During surgery, 21 patients (17 from group A, 4 from group B) showed no histological evidences of lymph node metastases. Ten patients (8 from group A,

TABLE 1 - PATHOLOGIC FEATURES.

Patient characteristics	Group A	Group B
Total patients (n)	30	11
Mean size of primary tumour (cm)	1.5	1.9
Tumour within the thyroid gland (n)	25	5
Extrathyroidal tumor extension (n)	9	2
No lymph node metastases (n)	17	4
Ipsilateral positive central lymph nodes (n)	13	5
Bilateral positive central lymph nodes (n)	–	2
Extranodal tumor extension (n)	5	4

TABLE 2 - SURGICAL PROCEDURES.

Procedure	Group A	Group B
Total operated patients (n)	30	7
TT+CND	10	–
TT+CND+unilateral MRND	14	–
TT+CND+bilateral MRND	6	–
Unilateral MRND+CND	–	5
Bilateral MRND	1	2
Re-excision CND	–	2
Re-excision lateral neck dissection	1	2

TT: Total thyroidectomy; CND: Central Neck Dissection; MRND: Modified Radical Neck Dissection.

2 from group B) with tumor size < 1cm as maximum diameter were observed. Lymph node metastases in the central neck and ipsilateral jugular chain were found in 18 patients (13 of group A and 5 of group B). Furthermore 2 patients from group B presented contralateral cervical lymph node metastases.

Postoperative complications included 10 cases of transient hypocalcemia, 1 case of permanent hypoparathyroidism (one patient from group B) and 3 cases of permanent unilateral recurrent laryngeal nerve paralysis. Of these, two patients showed a paralysis due to nerve traumatism, one of which had the inferior laryngeal nerve included within the tumour mass. One patient presented postoperative palsy of the 11<sup>th</sup> cranial nerve.

After a mean follow up period of 52 months, outcome analysis showed that 20 patients from group A (66.6%) and 4 patients from group B (36%) presented normal basal and stimulated calcitonin levels while 10 patients from group A and 7 patients from group B had still high calcitonin plasma levels even though they showed an overall decrease of >50% when compared to the pre-operative levels. During the follow up, local recurrence and distant metastases were documented in 6 patients from group A and 3 patients from group B.

Four patients from group A and 4 patients from group B, with persistent hypercalcitoninemia without

radiological evidence of local regional or distant metastases, showed gradually increasing calcitonin levels in the follow up period. Diagnostic laparoscopy of the abdomen performed in three of these patients revealed multiple microscopic metastases, while one patient presented liver and peritoneal disease. FDG-PET detected no residual tissue in these patients.

Systemic chemotherapy and local regional radiotherapy were ineffective in our treated patients (1 from group A, 2 from group B) with aggressive disease as demonstrated by the rapidly increasing plasma calcitonin levels and the clinical evidence of recurrent disease. Three patients died from metastatic disease and represent those patients who underwent incomplete surgery and that presented with a more advanced tumor stage.

## Discussion

In the management of SMTC the serum levels of calcitonin represent a highly sensitive marker of persistent or recurrent disease (5). Clinical and biochemical treatment could be easily monitored by calcitonin plasma levels. The persistence of high serum calcitonin levels after surgery is associated with higher rates of local and distant metastatic recurrence (9). Several studies have demonstrated that delayed diagnosis, incomplete primary surgical resection, the presence of tumour invasion of the thyroid capsule, and distant metastases negatively affect the prognosis (10). Early diagnosis is important in improving remission rates (11). Therefore, we usually perform routine measurements of serum calcitonin in the clinical management of nodular goitre.

Surgery is the most effective therapy that can result in the treatment or reduction in tumour burden. After primary surgical treatment calcitonin levels still remain high in over 50% of the patients with palpable tumour and in 50-70% of the cases it indicates the presence of metastatic disease at the time of primary surgery (12). In our experience, only four out of eleven patients (36%) could not normalize calcitonin

plasma levels, indicating that the extent of surgical resection is an important predictor of outcome.

MTC is commonly associated with regional lymphatic spread. Most treatment guidelines to date recommend performing a more extensive lymphadenectomy at the time of initial thyroidectomy and to consider re-operative cervical lymphadenectomy in patients with persistently high calcitonin levels after thyroidectomy (7, 13, 14). It has been clearly demonstrated that compartment-oriented systematic lymphadenectomy decreases the local regional recurrence rates and may improve length of survival in patients with SMTC. A more aggressive surgical approach is therefore recommended in SMTC patients. Several studies reported increased complication rates after lymph node dissection; a standard central neck dissection often involves the removal of inferior parathyroid glands, with an increased incidence of permanent hypoparathyroidism (15,16). However, total thyroidectomy and central-lateral neck dissection are safe surgical procedures and show low morbidity as described in many surgical series in MTC patients who have not had previous cervical surgery, when the architecture of the neck is most clearly defined to afford the greatest

chance of treatment (12). General surgeons without specific experience in endocrine surgery should be very careful in treating a rare and complex pathologic entity such as MTC.

In our experience, surgical-related complications essentially occurred in patients from group B, indicating that a more radical primary approach is usually recommended. In our series, failure to achieve a normal stimulated calcitonin levels occurred in patients over 40 years old, with tumour size larger than 2 cm, and lymph nodes and distant metastases and in patients with a long time interval from the initial surgery.

## Conclusions

Based on our result and according to previous literature it is well recognized that incomplete primary surgical resection and advanced tumour stages in the treatment of patients with SMTC negatively affect the outcomes. Accordingly, additional or secondary neck dissection rarely brings calcitonin levels back to normal and is associated with a high incidence of persistent hypercalcitoninemia and higher morbidity after surgery.

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