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Surgical Management of Medullary Thyroid Cancer

I. Koutelidakis, S. Kapoulas, V. Papaziogas, J. Makris

Abstract

Medullary Thyroid cancer is a rare malignancy with aggressive behaviour, which can be either sporadic or hereditary. Diagnosis is based on measuring the serum calcitonin levels of patients with thyroid nodules or on screening for RET gene mutations of the first degree relatives of patients with hereditary MTC. Treatment is surgical and involves total thyroidectomy and central lymph node dissection in all diagnosed cases. Further lateral LN dissection should be performed when indicated and is further analyzed throughout the article. Postoperative observation includes biochemical markers of disease (calcitonin and CEA) as well as imaging studies when indicated. Recurrence rates are high because of early lymphatic metastases. However, the overall 5-year survival rates are also high.

Key words: *Medullary thyroid cancer; lymph node dissection; multiple endocrine neoplasia; surgery*

Introduction

Medullary Thyroid Cancer (MTC) originates from calcitonin (Ct) secreting thyroid C-cells. It is relatively rare, accounting for 5-9% of all thyroid cancers. The disease can be sporadic or inherited. The inherited type is associated with mutations in the RET gene causing Multiple Endocrine Neoplasia syndromes (MEN2A, MEN2B, Familial MTC) [1]. Lymph node (LN) metastases occur during the early stages of MTC, hence surgical treatment involves more or less offensive lymph node dissection in the neck. Due to the aggressive nature of the disease, recurrences are common. However, widespread screening for MTC by measuring serum calcitonin (Ct) has increased the number of cases that are diagnosed early (microcarcinoma <1cm), thereby providing better chances of cure after initial surgical treatment (about 90% for microcarcinoma) [2].

Review of literature

Most recent guidelines concerning the surgical treatment of MTC are those of the American Thyroid Association (ATA) (2009), the British Thyroid Association (BTA) (2014), the European society of Medical Oncology (ESMO) (2010) and the European Thyroid Association guidelines for metastatic MTC (2012). The vast majority of those guidelines among the different associations are in accordance. However, there are a few ambiguous points [3-5].

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Preclinical Disease

Hereditary MTC is considered pre-clinical when the patient has a positive RET gene mutation analysis and the thyroid examination is normal (all thyroid nodules <5mm, serum Ct < 40pg/ml and no pathological LNs diagnosed in neck U/S). The algorithm of treatment according to the ATA 2009 guidelines is shown in Figure 1.

In cases of MEN2B syndrome, the operation of choice is total thyroidectomy (TT) before the age of one. Central LN dissection is not performed unless the patient is older than six months and there is clinical or radiological evidence of LN metastases or thyroid nodules >5mm or basal Ct > 40pg/ml. If the MEN2B patient has exceeded the first year of life at the time of surgery, central LN dissection is proposed, although data are ambiguous.

In general, the matter of LN dissection (central and/or lateral) in asymptomatic preclinical MEN2B patients deserves further discussion because of the aggressiveness of the syndrome.

In cases of MEN2A and FMTC syndrome, the procedure of choice is TT, best performed before the age of five. In patients with MEN2A and less aggressive mutations (ATA-A and ATA-B), treatment can wait until after five years in the setting of annual normal neck U/S, normal Ct values and according to family preference. Central LN dissection is not routinely performed in such cases; it is reserved for patients presenting with suspicious lymph nodes in neck U/S, Ct > 40pg/ml or nodules > 5mm.

Devascularised, normal parathyroid glands during these operations should be autografted (sternocleidomastoid muscle for MEN2B and FMTC, forearm autograft for MEN2A).

In cases of coexistent primary hyperparathyroidism (PHPT), both MTC and hyperparathyroidism are operated on at the same time. Options include resection of only vis-

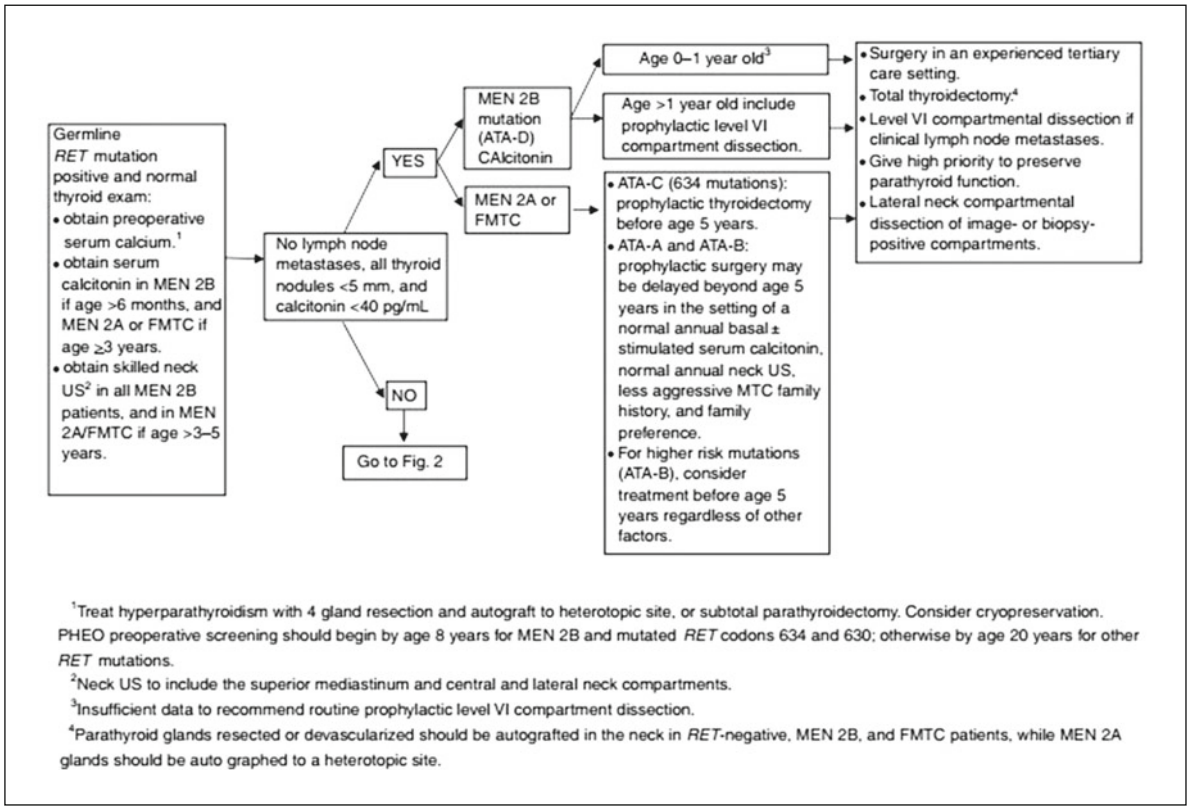

Figure 1. Initial diagnosis and therapy of pre-clinical disease.

ibly enlarged glands, subtotal parathyroidectomy or total parathyroidectomy, accompanied by forearm autografting in all cases because of the high risk of reoperation at the neck. If PHPT is diagnosed after TT, reoperation for the treatment of PHTC is indicated [3-5].

Clinically apparent disease

The algorithm for treating clinically apparent MTC according to the ATA guidelines is shown in Figure 2.

Screening for pheochromocytoma (PHEO) as preoperative workup should begin by the age of eight for MEN2B and mutated codons 634 and 630, and by the age of 20 in other cases of MEN2 syndromes. PHEO should be treated prior to the neck operation.

Preoperative workup for MTC includes basal serum calcitonin, CEA and Ca^{++}. As for imaging, skilled neck ultrasound (U/S) is required. In cases of high elevated serum Ct > 400pg/ml or LN metastases in neck U/S, further staging with neck and chest computerized tomography (CT) is required along with 3-phase liver CT or contrast-enhanced magnetic resonance imaging (MRI) (BTA guidelines 2014 include bone scintigraphy or MRI of the spine in standard systemic staging as well).

In the absence of evidence of LN metastases, treatment includes total thyroidectomy with central LN dissection (compartment VI) in both the sporadic and hereditary type. According to BTA guidelines 2014, standard LN dissection should also include compartment VII, with the innominate artery as the inferior limit of dissection. If U/S imaging is positive for LN metastases in the lateral compartments, the operation is completed with lateral LN dissection of those compartments (IIA, III, IV, V). In situations of locally extended disease or distant metastases, less aggressive surgical treatment is applied to the neck in order to reduce morbidity and preserve speech, swallowing and parathyroid gland functionality while controlling the disease.

The extent of LN dissection in the presence of positive LNs in compartment VI is a matter that requires further investigation. According to BTA guidelines 2014, ipsilateral prophylactic lateral LN dissection is recommended on the basis that the risk of lateral LN involvement is at least 70%. The need for bilateral lateral compartment node dissection is still not clear [3-5].

Postoperative evaluation

Follow-up includes measurements of basal serum Ct and CEA and their doubling times every six months for the first two to three years. Ct is an excellent marker for verify-

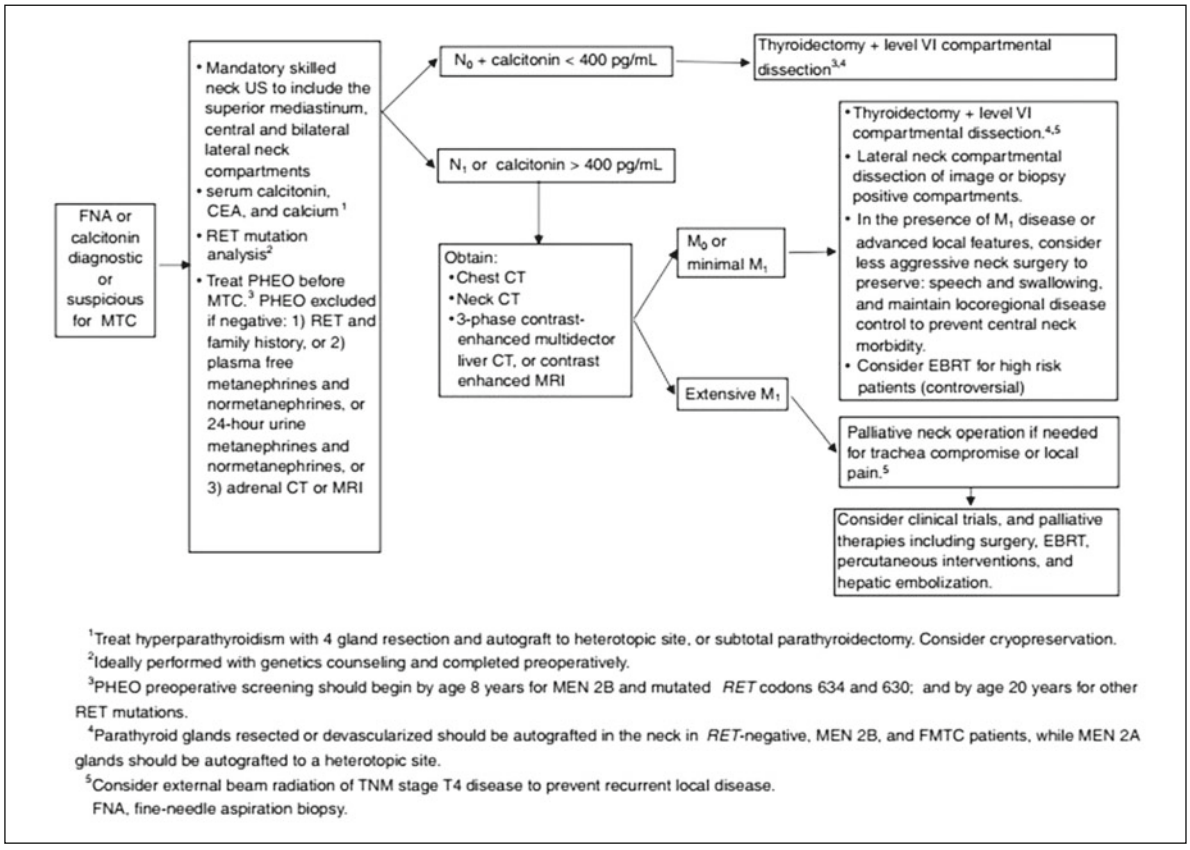

Figure 2. Initial diagnosis and therapy of clinically apparent disease.

ing cure or diagnosing and monitoring recurrent disease. Pentagastrin-stimulated serum Ct measurements are also used if available. Undetectable Ct levels after surgery are achieved in 60-90% of the cases with no LN involvement during the operation while the same rate for those with positive LNs is about 20%. If Ct remains undetectable, long-term surveillance is indicated. Ct levels that are detected postoperatively or become detected in time signify that the patient is not cured. Ct < 150pg/ml possibly reflects neck disease, although in rare cases there can be distant metastases. Neck U/S is indicated. Further control with CT of neck and chest, 3-phase liver CT or MRI, MRI of the spine, positron emission tomography (PET) and bone scintigraphy are indicated, but the chance of positive results is minimal. The same postoperative control is required in cases where Ct exceeds 150 pg/ml.

If the imaging results are all negative, the patient remains under follow-up. If not previously performed, the need for additional central LN dissection in such cases is still undecided.

In locally recurrent disease, compartmental dissection of image or biopsy-positive LN compartments is indicated. Lesions <1cm can be observed as the benefit from quick reoperation has not been proven. In cases of distant metastases or advanced locoregional recurrent disease, the approach to the neck operation is less aggressive so as to reduce morbidity while relieving symptoms [3-5].

MTC as a lucky finding

In the instance of MTC discovery in hemithyroidectomy specimens, further investigation is required. That involves basal serum Ct levels, skilled neck U/S, RET mutations control and family history. If all the results are normal and the histology shows negative surgical margins and monofocal disease without c-cell hyperplasia or metastases, the patient can be observed (although this can be debated with reoperation for TT and central LN dissection). In all other cases, the patient should be reoperated following the clinically apparent disease protocol.

Finally, if MTC is discovered in specimens of TT performed for different reasons, reoperation for LN dissection is indicated in the presence of positive U/S findings and elevated serum Ct levels. In cases of traceable Ct levels without positive imaging, empiric central LN dissection is an ambiguous choice [3].

Surgical treatment of metastases

According to the guidelines of ATA's 2009 and European Thyroid Association 2012, surgery is indicated when metastases are symptomatic.

Isolated or limited brain metastases, spinal cord compression and weight-bearing bone metastases (with fracture or impending fracture) should be considered for surgical treatment. Progressive symptomatic liver metastases causing diarrhoea or pain ought to be treated too (limited lesions to one or two lobes should be considered for surgical resection) [6].

Discussion

Medullary thyroid cancer (MTC) accounts for 5-9% of all thyroid cancers and can be divided into sporadic (75%) and hereditary (25%) disease. The hereditary type is strongly associated with germline mutations of the RET gene and is inherited in an autosomal dominant manner (MEN2A, MEN2B, FMTC syndromes). The tumour originates from the calcitonin-secreting parafollicular thyroid c-cells. It begins with c-cell hyperplasia which is followed by early invasive medullary carcinoma and grossly invasive macroscopic MTC [1].

Lymphatic node (LN) metastases in the neck and upper mediastinum are common and usually occur during the early stages of the disease. Lymph node involvement is already present in 11-31% of patients with microcarcinoma (<1cm). Around 70% of the patients that present with a palpable node already have LN metastases [7]. Their early presence depends on the aggressiveness of the disease which is associated with specific RET gene mutations. Consequently, the tumour's behaviour and malignancy varies.

Diagnosis is based on basal serum calcitonin levels in patients with nodular thyroid disease. Many cases are also diagnosed during the screening of first-degree relatives of patients with MEN2 syndromes. Finally, some cases are diagnosed via FNA biopsy of thyroid nodes or incidentally after thyroidectomy for a different reason.

Genetic RET testing should be offered to all patients presenting MTC and pheochromocytoma. Screening of their relatives ought to be performed as early as possible since prophylactic surgery may be required [7].

Treatment is surgical and involves total thyroidectomy (TT) and central LN dissection (compartment VI) in all cases of diagnosed MTC. Lateral LN dissection (compartments IIA, III, IV, V) should be performed when ultrasound scanning is positive for LN metastases in the lateral neck. We mark that sensitivity of intraoperative palpation for positive lymph nodes is less than 64% [8].

In cases of extensive local disease or distant metastases, palliative treatment is indicated to relieve symptoms and control the disease while minimizing morbidity from complications (hypoparathyroidism, recurrent laryngeal nerve or trachea injuries)

Prognosis depends on the extent of the tumour, the presence of LN disease as well as the age and presence of distant metastases. Metastases are the main cause of death. In general, 10-year survival rates are high (85-95%) [2,9].

As previously mentioned, a few matters remain ambiguous concerning the surgical treatment of MTC, some of which are mentioned below. References are limited.

- The need for TT and central LN dissection in patients with MTC diagnosed accidentally after hemithyroidectomy for benign disease and with all biochemical and imaging studies showing as normal postoperatively
- Possible LN dissection in patients that have been subjected to TT and maintain traceable levels of Ct postoperatively with negative imaging
- The extent of LN dissection in prophylactic total thyroidectomy
- The extent of LN dissection if there are positive LNs at compartment VI
- The addition of lateral LN dissection as a standard technique in MTC.

We have to point out that the possibility of skip metastases with negative central LNs can range from 10-30%, and there is no reliable prognostic factor for the probability and extent of lymph node involvement.

Conclusion

Early diagnosis and adequate LN dissection during the first operation are the cornerstones of successful treatment for MTC patients. Routine serum Ct monitoring for patients with thyroid nodules is necessary for that cause. Central LN dissection should be performed in all diagnosed cases. Extensive LN dissection in advanced local or recurrent disease should be performed by experienced surgeons so as to minimize morbidity.

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