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# Diagnosis and Differential Diagnosis of Medullary Thyroid Cancer

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## 1. Introduction

Medullary thyroid cancer (MTC) occurs in less than 1% of thyroid nodules and accounts for 5-10% of thyroid malignancies. It is a well-differentiated neuroendocrine carcinoma arising from parafollicular calcitonin-producing cells (C-cells) of the thyroid gland and is associated with elevated serum calcitonin levels. Among well-differentiated thyroid carcinomas, MTC is the most aggressive, with survival rates of 40-50% at 10 years (American Thyroid Association [ATA] Guidelines Task Force et al., 2009; Leboulleux et al., 2004). In about 20-25% of cases, MTC can be part of an autosomal dominant inherited cancer syndrome called Multiple Endocrine Neoplasia type 2 (MEN2), caused by activating germline mutations of the *RET* proto-oncogene, where this tumor is isolated (Familial MTC - FMTC) or is associated to other tumors (parathyroid adenoma, pheochromocytoma and cutaneous lichen amyloidosis in MEN2A; pheochromocytoma, mucosal and intestinal ganglioneuromatosis, marfanoid habitus in MEN2B). In the remaining 75-80% of cases MTC is sporadic (ATA Guidelines Task Force et al., 2009; Brandi et al., 2001; Leboulleux et al., 2004). Depending on the type of the genetic syndrome, clinical features, therapeutic approaches and prognosis of MTC are very different (Brandi et al., 2001).

Calcitonin is a small peptide secreted by C-cells. It is the most specific and sensitive marker of MTC in patients with one or more thyroid nodules, useful in the diagnosis and follow-up of this tumor (ATA Guidelines Task Force et al., 2009; Leboulleux et al., 2004). High serum calcitonin levels are physiological in neonates, followed by an age-related decline from birth to about 1 year of age (Leboulleux et al., 2004). Elevated basal serum calcitonin levels are found in subjects with C-cells hyperplasia (CCH) or MTC. Anyway, in some cases it is possible to observe false positive or false negative for serum calcitonin levels in adult individuals.

After excluding conditions that may cause falsely positive high levels of calcitonin, it is necessary to exclude tumors associated to ectopic production of calcitonin, which may represent up to 15% of cases (Pacini et al., 2010; Toledo et al., 2009).

Another tumor marker used in the follow-up of MTC is carcino-embryonic antigen (CEA), a cytosolic enzyme which is not a specific biomarker for MTC being generally expressed by many endocrine and non-endocrine tumors. In MTC, CEA is considered to have lower diagnostic accuracy than calcitonin (Meijer et al., 2010). There is no close relationship

between serum levels of CEA, that are normal in patients with early stage MTC, and calcitonin.

Pentagastrin stimulation test for calcitonin is the most widely used test for calcitonin secretion, useful to distinguish normal C-cells from pathological C-cells (Leboulleux et al., 2004; Milone et al., 2010; Pacini et al., 2010).

CCH and early-stage MTC are often difficult to distinguish on routine biochemical and histological examination. This differentiation is very important for therapy and for prognosis.

If the diagnosis of MTC needs to be always confirmed by histology, by a clinical and biochemical point of view, pentagastrin stimulation test, immunocytochemistry for calcitonin and calcitonin measurement in wash-out fluid from fine-needle aspiration of suspicious thyroid nodules may reliably indicate this diagnosis.

Primary treatment of both hereditary and sporadic MTC is total thyroidectomy with lymph node dissection, with the intention of remove all neoplastic tissue present in the neck (Leboulleux et al., 2004).

The postoperative follow-up of patients with MTC should be performed to early identify recovery or persistence/relapse of MTC in patients with elevated concentrations of biochemical markers after surgery.

### **1.1 Embryogenesis of C-cells and pathogenesis of MTC**

Parafollicular calcitonin-producing cells (C-cells) arise from the neural crest and have a common origin with the adrenal medullary chromaffin cells, enterochromaffin cells, pituitary corticotrophs and melanotrophs, and islet cells. This entire series of cells was included under the descriptive term APUD cells by Pearse (Hazard, 1977). During the embryonic life C-cells migrate forward into the thyroid gland. The thyroid should be looked upon as a double gland with two separate types of peptide-producing cells. C-cells account less than 1% of thyroid cells, are located inside the thyroid follicles and are most numerous at the junction of the upper third and the lower two-thirds of the thyroid lobes (Leboulleux et al., 2004).

Thyroid C-cells differ from solid cell nests (SCN) of the thyroid gland. They are two thyroid specific cell type with a common embryological origin in the ultimobranchial body but with different physiological roles. SCN are found in about 5-60% of human thyroid gland and comprise compact spindle or polygonal cells with a strong and diffuse immunostaining for cytokeratin, galectin-3 (GAL-3) and CEA and rarely for calcitonin. In contrast, normal and hyperplastic C-cells express both calcitonin and CEA but not GAL-3 while malignant C-cells forming MTC are positive for calcitonin, CEA and GAL-3 immunostaining. SCN are often found in both normal and pathological thyroid tissue and they are not related to the presence of thyroid disorder (Faggiano et al., 2003).

GAL-3 is a  $\beta$ -galactoside-binding protein, localized predominantly in the cytoplasm, that plays a role in various processes such as cell adhesion, growth and neoplastic transformation. In epithelial thyroid tumors, GAL-3 immunostaining is positive in malignant tumors but negative in benign lesions. GAL-3 immunostaining is also a reliable marker of malignancy in patients with C-cells disease and its use may have clinically relevant prognostic and therapeutic implications (Faggiano et al., 2002) (Figure 1).

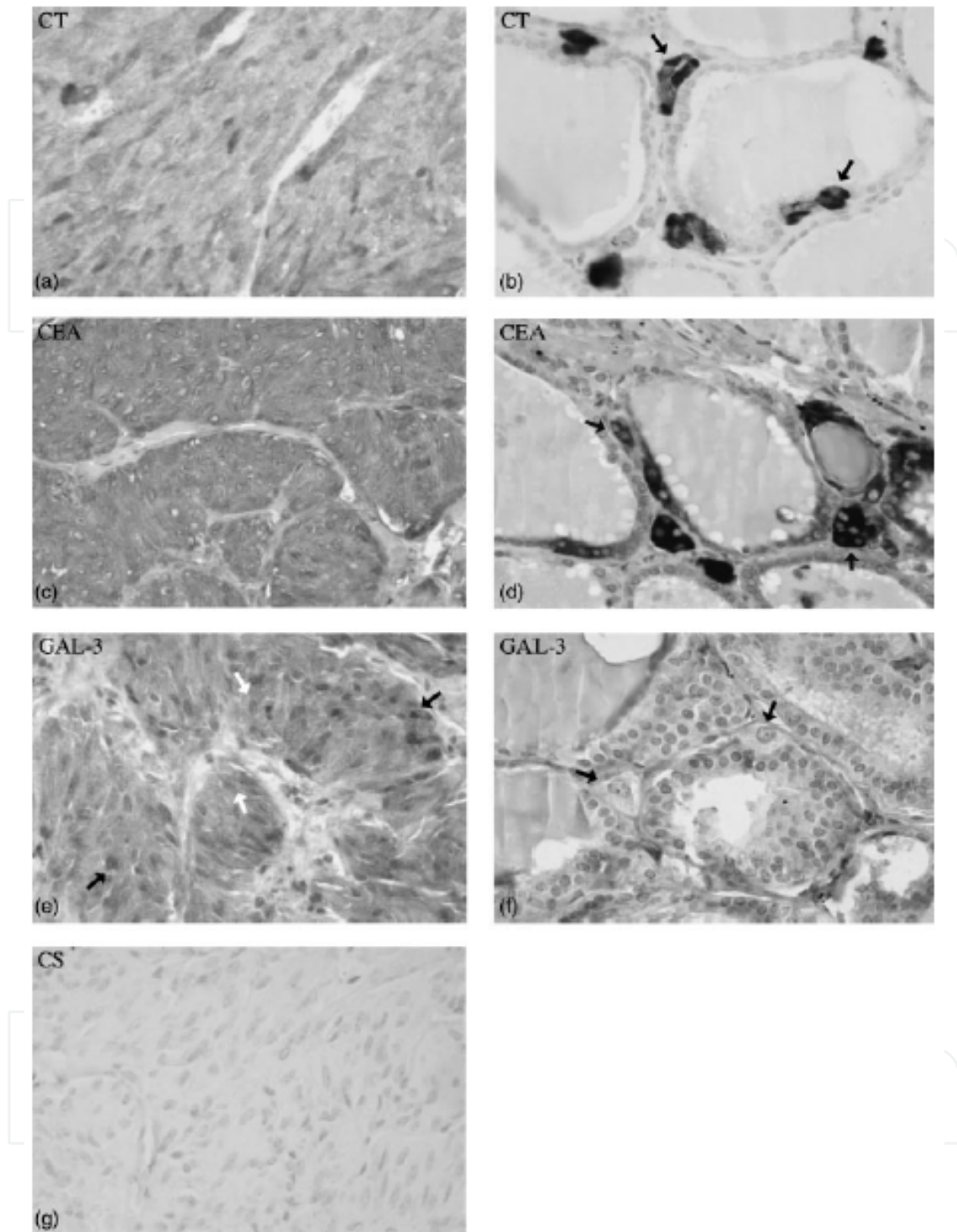


Fig. 1. Expression of calcitonin (CT), CEA and GAL-3 in medullary thyroid cancer (MTC) and C-cells hyperplasia (CCH). Photos a, c, e, g represent a MTC case: CT, CEA and GAL-3 are diffusely expressed in tumor tissue at the cytoplasmatic level. Some tumor cells also display GAL-3 positivity at the nuclear level (black arrows). The specificity of anti-GAL-3 antibodies is demonstrated by negativity in control sections (CS) of the same tumor. Photos b, d, f represent a CCH case: CT and CEA are strongly positive and GAL-3 is negative in large C-cells (from Faggiano et al., 2002).

CCH is defined as the presence of at least three fields containing more than or equal 50 C-cells in a single low-power field (magnification of  $\times 100$ ) (Santesano et al., 1997). The prototypic histologic features of MTC are sheets, packets or irregular islands of polygonal or plump spindly cells traversed by small fibrovascular septa (Hazard, 1997). MTC is defined by the presence of fibrous and/or amyloid stroma between C-cells, infiltration of interstitial tissue by C-cells and coalescence of hyperplastic C-cells nodules (Faggiano et al., 2002; Faggiano et al., 2003).

MTC cells typically produce an early biochemical signal that consists of hypersecretion of calcitonin. Calcitonin and CEA are expressed in hyperplastic and malignant C-cells (Leboulleux et al., 2004).

In all CCH and MTC there is a positive immunohistochemical staining for calcitonin and CEA. Mixed MTC are uncommon and are characterized by the combination of C-cells and follicular features (Leboulleux et al., 2004).

Sporadic C-cells hyperplasia differs from C-cells hyperplasia associated to hereditary MTC syndromes. While the first one, in fact, is usually benign and associated with much less, if any, malignant potential, the latter is generally considered a precancerous condition in the familial MTC where there is a progression from normal C-cells to CCH, micro-MTC and clinical MTC (Leboulleux et al., 2004; Milone et al., 2010; Perry et al., 1996). Sporadic MTC is usually unifocal and represented by a unique tumor nodule while familial MTC appears bilateral and multicentric, often with multifocal disease in a background of CCH. In fact, all patients with hereditary MTC virtually presented CCH (Leboulleux et al., 2004).

There are two different types of CCH: physiologic or reactive, where the number of follicles with one or more C-cells is increased, associated with inflammatory and metabolic disorders and classically with a chronic lymphocytic thyroiditis, and nodular or neoplastic, characterized by an increased number of C-cells aggregates, frequent in tumors. Physiologic CCH cannot be recognized with certainty on routine histological sections and has to be diagnosed with the help of immunostains. On the other hand, nodular or neoplastic CCH can be identified with conventional histological sections because the C-cells are large, mildly to moderately atypical and cytologically indistinguishable from those of invasive MTC, resulting in a partial or complete replacement of the follicle (Albores-Saavedra & Krueger, 2001; Perry et al., 1996).

### 1.1.1 Hereditary MTC syndrome

Hereditary MTC syndrome (MEN2 - multiple endocrine neoplasia type 2 or Sipple's syndrome) is an autosomal disorder characterized by activating germline mutations of the *RET* proto-oncogene, with a prevalence of 1:30,000 subjects (Brandi et al., 2001). It is divided in three clinical variants: a) MEN2A (medullary thyroid cancer, mono- or bilateral pheochromocytoma, primary hyperparathyroidism and cutaneous lichen amyloidosis); b) familial medullary thyroid cancer (FMTC); c) MEN2B (medullary thyroid cancer, mono- or bilateral pheochromocytoma, mucosal and intestinal ganglioneuromatosis, marfanoid habitus) (Brandi et al., 2001; Raue & Frank-Raue, 2007). Although these variants have MTC as a common denominator, they differ for the aggressiveness of this cancer, in a decreasing order MEN2B>MEN2A>FMTC (Raue & Frank-Raue, 2007).

In patients with FMTC, MTC is the only clinical manifestation. According to the "International *RET* Mutation Consortium", to make the diagnosis of FMTC is required the onset of MTC in at least four family members (Mulligan et al., 1995).

Patients affected with hereditary MTC syndrome initially develop CCH that then progresses to early invasive medullary microcarcinoma, and eventually develop invasive macroscopic MTC (ATA Guidelines Task Force et al., 2009).

MEN2 has a genotype-phenotype correlation. In fact, an association between specific mutations of the *RET* gene and the age at onset, the aggressiveness of MTC and the presence of other endocrine disorders is well documented. The *RET* mutation screening allows to stratify the risk in three levels, depending on the mutated codon. The specifically mutated *RET* codons correlate with the MEN2 variant, with the age at onset and the aggressiveness of thyroid cancer. MTC generally occurs in the first year of age in subjects with MEN2B, between 5 and 25 years in subjects with MEN2A and later in subjects with FMTC. In patients with MEN2, the therapeutic approach is correlated to the clinical subtype and to the mutation, according to the risk levels (Brandi et al., 2001) (Table 1).

Risk level	Domain	Codons	MEN2 variant
1 (Low)	Extracellular	609	MEN2A
	Intracellular	768, 790, 791, 804	FMTC
	Intracellular	891	MEN2A
2 (High)	Extracellular	611, 618, 620, 630, 634	MEN2A
3 (Very high)	Intracellular	883, 918, 922	MEN2B

Table 1. Risk levels in MEN2 syndrome.

Subjects with the highest risk level (3) have the most aggressive MTC and should have thyroidectomy with a central node dissection within the first six months of life and preferably within the first month of life. In subjects classified as risk 2 level, thyroidectomy with removal of the posterior capsule should be performed before the age of five years. For subjects with the lowest risk level (1) at this moment there are differing opinions on when thyroidectomy should be performed. According to some authors, in fact, total thyroidectomy with lymph node dissection of the central compartment should be practiced within the fifth year of life, according to others such intervention should be performed later, but within the tenth year of life. Other authors finally suggest to periodically perform the pentagastrin stimulation test for calcitonin and to perform the surgery at the first positive test. In all cases, if a pheochromocytoma is present, total thyroidectomy should be performed after surrenectomy to avoid a catecholaminergic crisis during the surgery (Brandi et al., 2001).

### 1.2 Diagnosis of MTC in patients with the suspicion of MTC

Thyroid tumors are the most common endocrine neoplasms. Most of thyroid nodules are benign but in the 5-10% of cases they are carcinomas. MTC occurs in less than 1% of thyroid nodules and accounts for 5-10% of thyroid malignancies (Schlumberger et al., 2003).

Sporadic MTC can arise clinically at any age but its incidence peaks during the fourth and sixth decades of life (Leboulleux et al., 2004).

The suspicion of MTC arises in a patient with one or more thyroid nodules associated with elevated basal calcitonin levels ( $> 10$  pg/ml), with or without a familial history of MTC.

In the presence of a thyroid nodule, several clinical features may prompt to suspect a MTC: its location in the upper third of the thyroid lobe, pain during the thyroid palpation, a diarrhoeal syndrome and flushing that are more frequent in patients with a large tumor burden. At the ultrasonography, MTC usually appears as a hypoechogenic solid nodule with frequent microcalcifications, with or without lymph node abnormalities (Leboulleux et al., 2004).

High serum calcitonin levels are physiological in neonates, followed by an age-related decline from birth to about 1 year of age (Leboulleux et al., 2004). Elevated basal serum calcitonin levels are found in subjects with CCH or MTC. Anyway, in some cases it is possible to observe false positive for high serum calcitonin levels in adult individuals. Conditions related to high calcitonin levels are: severe chronic renal failure and dialysis, chronic hypercalcemia, therapies with proton-pump inhibitors or other drugs, chronic hypergastrinemia, pernicious anemia, hepatic cirrhosis, auto-immune thyroid disorders or follicular tumor, hyperthyroidism, hyperparathyroidism and pseudohypoparathyroidism, systemic inflammatory state, pregnancy and lactation. Furthermore, calcitonin assays can be falsely positive because of interference with circulating heterophilic antibodies binding (Leboulleux et al., 2004; Pacini et al., 2010). Calcitonin levels are also correlated with age and BMI (especially in men) and cigarette smoking can increase the plasma concentration of calcitonin (van Veelen et al., 2009) (Table 2). False negative for calcitonin serum concentrations are also possible and are related to the "hook effect" (Leboeuf et al., 2006).

Non-thyroid diseases	Thyroid diseases	Drugs	Physiological conditions
Hypergastrinemia	Auto-immune thyroiditis	Proton-pump inhibitors	Age
Hyperparathyroidism	Hyperthyroidism	Glucocorticoids	BMI
Pseudohypoparathyroidism	Thyroid carcinoma	Beta-blockers	Sex
Chronic renal failure		Glucagon	Physical activity
Pernicious anemia			Pregnancy
Hepatic cirrhosis		Smoking	Lactation
Inflammatory state			
Neuroendocrine tumors			
Pheochromocytoma			
Paraganglioma			
Breast cancer			
Enteropancreatic tumors			
Small cell lung carcinoma			

Table 2. Conditions associated to high serum calcitonin levels independently of medullary thyroid carcinoma.

MTC may also express a number of genes usually not expressed or expressed at low levels in the normal C-cells. The protein products of these genes include somatostatin, pro-opiomelanocortin, vasointestinal active peptide, serotonin, prostaglandins and others and they can produce clinical syndromes including Cushing's disease, flushing or diarrhoea. Chromogranin-A levels may also be elevated in the presence of large metastases (Leboulleux et al., 2004).

Diagnosis of MTC is based on typical histological characteristics (tumor cells arranged in trabecular, insular or sheet-like patterns with or without stromal amyloid deposits) and immunohistochemical findings (positive staining for calcitonin, CEA and chromogranin and negative staining for thyroglobulin) (Costante et al., 2007). Anyway, pentagastrin stimulation test, immunocytochemistry for calcitonin and calcitonin measurement in wash-out fluid from fine-needle aspiration of thyroid nodules are suggestive.

The primary treatment of both hereditary and sporadic MTC is total thyroidectomy with lymph node dissection, with the intention of remove all neoplastic tissue present in the neck. Surgery should be performed after careful exclusion of pheochromocytoma (Leboulleux et al., 2004). Classification of MTC is based on the pathological tumor node metastases (TNM) system (Table 3).

<b>T</b> (primary tumor)	<p><b>Tx:</b> Primay tumor cannot be assessed</p> <p><b>T0:</b> No evidence of primary tumor</p> <p><b>T1:</b> Tumor size <math>\leq 2</math> cm and no growth out of the thyroid</p> <p><b>T1a:</b> Tumor size <math>&lt; 1</math> cm and no growth out of the thyroid</p> <p><b>T1b:</b> Tumor size between 1 and 2 cm and no growth out of the thyroid</p> <p><b>T2:</b> Tumor size between 2 and 4 cm and no growth out of the thyroid</p> <p><b>T3:</b> Tumor size <math>\geq 4</math> cm or small growth out of the thyroid</p> <p><b>T4a:</b> Tumor of any size with extensive growth beyond the thyroid gland into nearby tissues of the neck (Moderately advanced disease)</p> <p><b>T4b:</b> Tumor of any size with either back toward the spine or into nearby large blood vessels (Very advanced disease)</p>
<b>N</b> (regional lymph node metastases)	<p><b>Nx:</b> Regional lymph nodes cannot be assessed</p> <p><b>N0:</b> No evidence of regional lymph nodes</p> <p><b>N1:</b> The cancer has spread to nearby lymph nodes</p> <p><b>N1a:</b> The cancer has spread to lymph nodes around the thyroid</p> <p><b>N1b:</b> The cancer has spread to other lymph nodes in the neck or behind the throat or in the upper chest</p>
<b>M</b> (distant metastases)	<p><b>Mx:</b> Distant metastases cannot be assessed</p> <p><b>M0:</b> No evidence of distant metastases</p> <p><b>M1:</b> Evidence of distant metastases</p>

Table 3. TNM system for medullary thyroid cancer (MTC).



A diagnosis of MTC in an early and therefore potentially surgically eradicable and higher curable stage of disease is essential to improve the prognosis of this tumor (Pacini et al., 1994).

In patients with non-metastatic MTC, survival rates amount about 78-100% at 5-year and 75% at 10-year, respectively. Survival rates strongly decrease in case of metastatic disease and amount about 24% at 5-year and 10% at 10-year respectively (Kapiteijn et al., 2011).

### **1.3 Usefulness of pentagastrin stimulation test for diagnosis of MTC and differential diagnosis between subjects affected by C-cells proliferation and normal subjects and between CCH and MTC**

Pentagastrin stimulation test for calcitonin is the most widely used test for calcitonin secretion, useful to distinguish normal C-cells from pathological C-cells (Leboulleux et al., 2004; Milone et al., 2010; Pacini et al., 2010). This test is performed in case of borderline serum calcitonin levels or in case of high serum calcitonin levels but less than 100 pg/ml. After overnight fasting, basal serum calcitonin is measured and then the patient receives a slow intravenous injection of 0.5 µg pentagastrin per Kg body weight and calcitonin is measured again 3 and 5 minutes after the injection.

Serum calcitonin concentrations are helpful in the early detection of C-cells disease but it is still unclear whether they can be used also for the preoperative differential diagnosis between CCH and MTC on the basis of the calcitonin peak after pentagastrin stimulation test. Few studies have been performed to preoperatively discriminate between CCH and MTC but they show high variability in the calcitonin cut-offs after pentagastrin test to discriminate between CCH and MTC. A calcitonin cut-off after pentagastrin stimulation test corresponding to about 300 pg/ml seems to be highly predictive in preoperatively distinguishing CCH from MTC (Figure 2). In the clinical practice, this finding may need to perform surgery in patients with calcitonin levels higher than these after pentagastrin stimulation test and to submit a periodical re-evaluation with the stimulation test and neck ultrasonography in those patients with calcitonin levels between about 100 and 300 pg/ml (Milone et al., 2010).

The pentagastrin stimulation test is contraindicated during pregnancy and in patients with asthma, coronary disease, severe hypertension or duodenal ulcer. Side-effects include dizziness, tachycardia/bradycardia, nausea and substernal tightness (Leboulleux et al., 2004; Pacini et al., 2010).

### **1.4 Differential diagnosis between CCH/MTC and ectopic calcitonin secretion**

In about 15% of cases high levels of calcitonin are associated to ectopic production by tumors. Neuroendocrine tumors arising from gastro-entero-pancreatic tract (gastrinoma, VIPoma, insulinoma, etc.), respiratory tract (lung, bronchus), breast, medulla of adrenal gland and paraganglia may be associated with elevated serum calcitonin levels, even in cases where there is a negative immunohistochemistry reaction for calcitonin (Pacini et al., 2010; Toledo et al., 2009) (Table 2).

Considering false positive causes of increased serum calcitonin levels and the above mentioned tumors associated with ectopic secretion of this marker, it is not surprising that hypercalcitoninemia could result sometimes in erroneous recommendations of total thyroidectomy. Therefore, in order to avoid misdiagnosis and unnecessary thyroid surgery, it is mandatory to conduct correct investigations in cases with elevated basal serum calcitonin levels in order to rule out possible diagnosis different from MTC (Toledo et al., 2009).

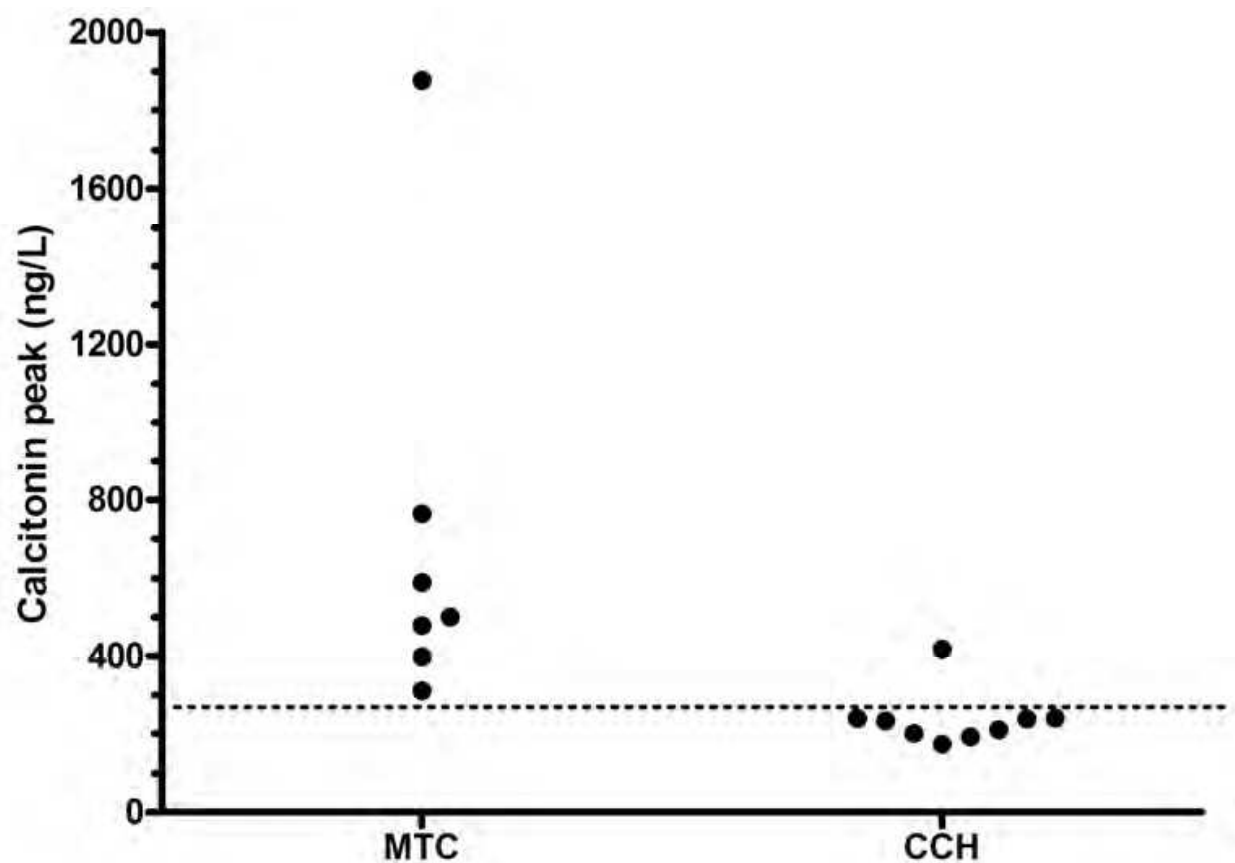


Fig. 2. Calcitonin peak after pentagastrin stimulation test performed before surgery to preoperatively distinguish C cell hyperplasia (CCH) and medullary thyroid cancer (MTC) (from Milone et al., 2010).

### 1.5 Usefulness of fine-needle cytology (FNC) to preoperatively recognize a MTC

Fine-needle aspiration cytology (FNC) represents the main tool in the diagnostic evaluation of thyroid nodules, but it is not frequently proposed as a routine procedure in patients with high serum calcitonin levels, due to its low specificity and sensitivity (Boi et al., 2007).

Routine measurement of calcitonin in nodular thyroid disease is a specific and sensitive method to improve the early preoperative diagnosis of unsuspected sporadic MTC with better accuracy than routine FNC. Serum calcitonin is also more sensitive than FNC in the pre-operative diagnosis of MTC (Elisei et al., 2004). Serum calcitonin is the most sensitive and accurate diagnostic tool for MTC, but it is not helpful to localize primary tumor in the thyroid and its neck recurrence or metastases in patients submitted to thyroidectomy (Boi et al., 2007). Immunohistochemistry with anti-calcitonin antibodies improves the diagnostic sensitivity of FNC. Anyway, this procedure is only performed when there is a strong suspicion of MTC and not on routine basis. On this basis, serum calcitonin should be measured routinely in the clinical work-up of thyroid nodules, followed by a pentagastrin stimulation test in all cases of detectable basal calcitonin levels (Elisei et al., 2004). Increasing the diagnostic accuracy could help the surgeon to perform more radical treatment of MTC, thus achieving frequent normalization of postoperative serum calcitonin levels. Anyway, whether this results indicates definitive cure remains to be established on the basis of longer follow-up (Pacini et al., 1994).

Assaying calcitonin in the wash-out fluid and immunohistochemistry for calcitonin from FNC under ultrasonographic guidance could be useful in the preoperative diagnosis of MTC.

There are several studies that aimed to evaluate the usefulness of calcitonin assay in the wash-out from FNC, alone or combined with cytology in the pre-surgical evaluation of MTC patients with thyroid nodules. Anyway, although elevated serum calcitonin levels, basal and after pentagastrin stimulation test, strongly suggest the presence of MTC, no study showed a statistical correlation between serum calcitonin levels and calcitonin levels in the wash-out fluid from FNC.

Calcitonin assay in the wash-out from FNC seems to be a highly reliable diagnostic procedure to identify primary tumor and recurrent or metastatic MTC (Boi et al., 2007).

### **1.6 Diagnosis of MTC persistence/relapse after surgery**

The definitive cure of MTC is strongly dependent on the completeness of the first surgical treatment. If tumor tissue is not totally removed, the subsequent surgeries are not as effective as a complete primary surgery in achieving the disease remission. Anyway, the clinical, biochemical and radiological criteria to establish how extended has to be the surgical act to completely abrogate the risk of relapse are not clear.

For node-positive thyroid cancers, compartment-oriented microdissection is the gold standard of care, whereas the concept of prophylactic lymph-node dissection continues to arouse controversy. Most studies agree that routine lymph-node dissection is unnecessary for low-risk well-differentiated thyroid cancer. Because occult lymph-node metastases are frequent in high-risk MTC, compartment-oriented microdissection helps prevent reoperations for recurrences arising from residual nodes, sparing patients the excess morbidity from reoperations in the neck (Dralle & Machens, 2008).

Total thyroidectomy and central neck dissection is recommended for all patients with MTC, but the indication for lateral neck dissection is still controversial and there is not a standard approach to neck surgery. The total number of lymph node metastases is predictive for biological remission after surgery. Because of the same frequency in the ipsilateral, contralateral and central compartments involvement in either sporadic or hereditary MTC, Scollo et al. suggested performing a central and bilateral neck dissection in all patients with MTC. A bilateral neck dissection may be avoided in patients with unilateral tumor involvement of the thyroid only when no involvement of the ipsilateral and central neck compartment is found (Scollo et al., 2003).

Intraoperative calcitonin monitoring seems to be a predictor of the final outcome after surgery in patients with MTC. A calcitonin decrease greater than 50% 30 minutes after surgery is associated with a complete tumor removal while a decrease of calcitonin less than 50% 30 minutes after surgery indicates an incomplete tumor removal and suggests to extend the surgery on other lymph node compartments (Faggiano et al., 2010) (Figure 3).

In comparison to the differentiated thyroid carcinoma, MTC is more difficult to treat and has higher rates of recurrence and mortality. Unlike differentiated carcinoma, there is no known effective systemic therapy since MTC cells do not concentrate radioactive iodine and MTC does not respond well to external radiotherapy or conventional chemotherapy (Czepczyński et al., 2007).

Prognostic factors (relevant) to predict outcome in MTC include: age at diagnosis, gender, initial extent of the disease, such as lymph node and distant metastases, tumor size, extra-

thyroid invasion, vascular invasion, calcitonin immunoreactivity, amyloid staining and Ki-67 score in tumor tissue, postoperative gross residual disease, and postoperative plasma calcitonin levels (Schlumberger et al., 2003) (Table 4).

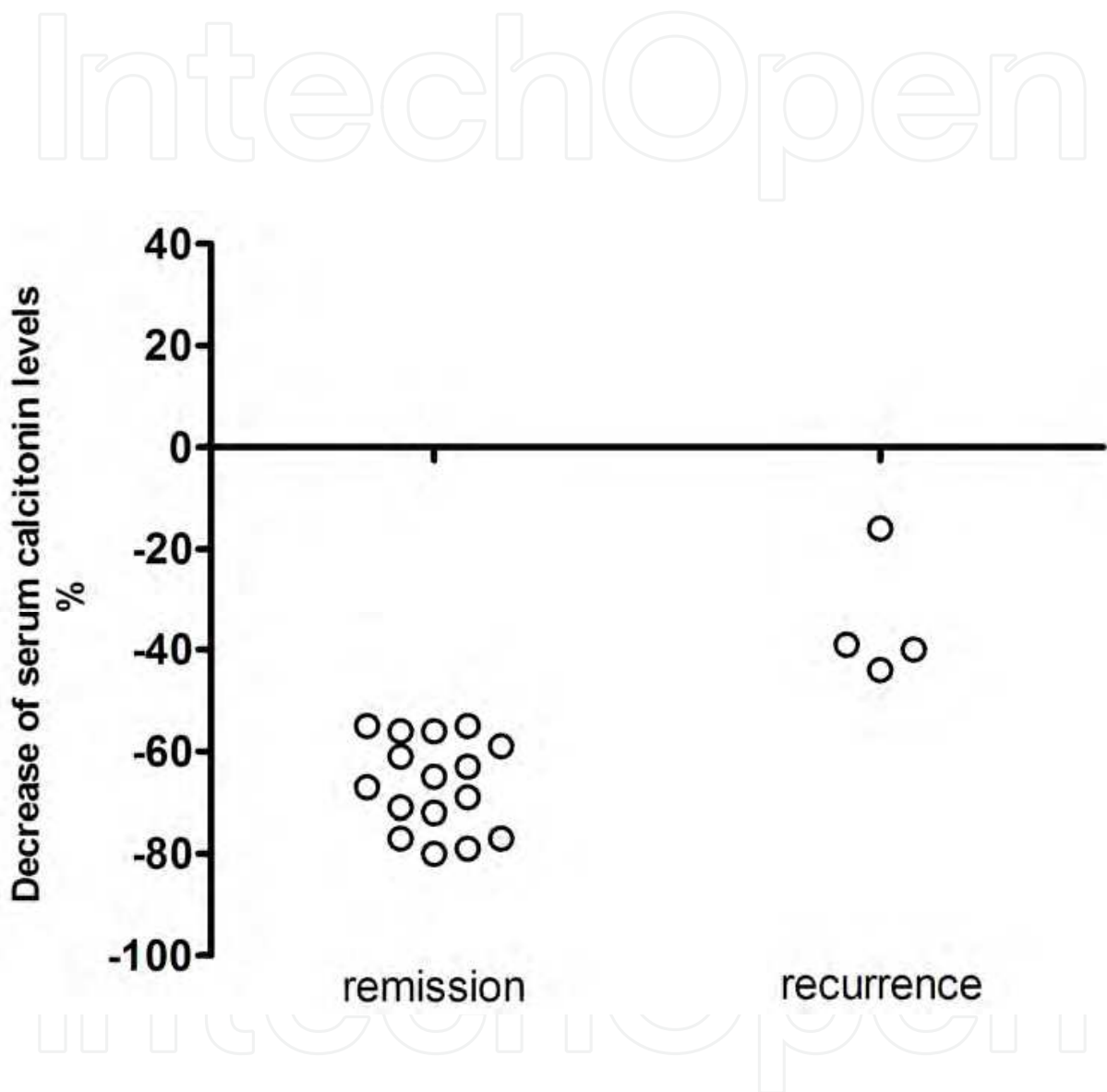


Fig. 3. Correlation between percentage calcitonin decrease 30 minutes after surgery and post-surgical outcome in patients undergone surgery for medullary thyroid cancer (from Faggiano et al., 2010).

Age	Patients aged over 50-60 years fare worse
Sex	The male sex has been associated with a worse prognosis
Stage of MTC	This is the most important prognostic factor. The presence of lymph node and distant metastases at presentation is associated with a worse prognosis with poor survival
Genetics	In a decreasing order, the aggressiveness of hereditary medullary thyroid cancer is MEN2B>MEN2A>FMTC. MTC of the MEN2A variety is associated with a better prognosis than the sporadic variety
Size	Small tumors <1 cm are associated with a better prognosis
Biochemical cure	It predicts a good survival
Histological features	High mitotic count (> 1 per 25 high-power field), high Ki-67%, small-cell variant, necrosis, absence of amyloid are associated with a worse prognosis

Table 4. Prognostic factors to predict outcome in patients with medullary thyroid carcinoma (MTC).

In patients with MTC a long-term biochemical monitoring including serum calcitonin and CEA measurements is mandatory (ATA Guidelines Task Force et al., 2009).

Postoperative unsuppressed calcitonin and CEA concentrations may persist elevated during 2-3 months after surgery due to their long half-life in the blood, while increasing calcitonin and CEA serum levels after this time indicate disease persistence and progression (Leboulleux et al., 2004; Pacini et al., 2010; Faggiano et al., 2009). Undetectable basal serum calcitonin levels, further confirmed after a pentagastrin stimulation test, are a strong predictor of complete remission (Pacini et al., 2010).

In patients with postoperative persistent calcitonin levels the use of imaging techniques is mandatory for diagnostic purposes and therapy decision. Anyway, the detection of tumor foci is often not achieved with conventional imaging techniques (neck ultrasonography, CT-scan, MRI, bone scintigraphy). Postoperative calcitonin concentrations less than 500 pg/ml usually indicate a small residual disease in the neck or mediastinal lymph nodes, not easily detectable. The evaluation of the clinico-biological and immunohistochemical tumor profile may be used in order to select the best imaging technique to be performed in patients with postoperative persistent or relapsing MTC. In particular, FDG-PET seems to correlate to tumor proliferation index Ki-67% and to be able to detect metastases in patients with postoperative persistent MTC when conventional imaging techniques are negative (Faggiano et al., 2009) (Figure 4).

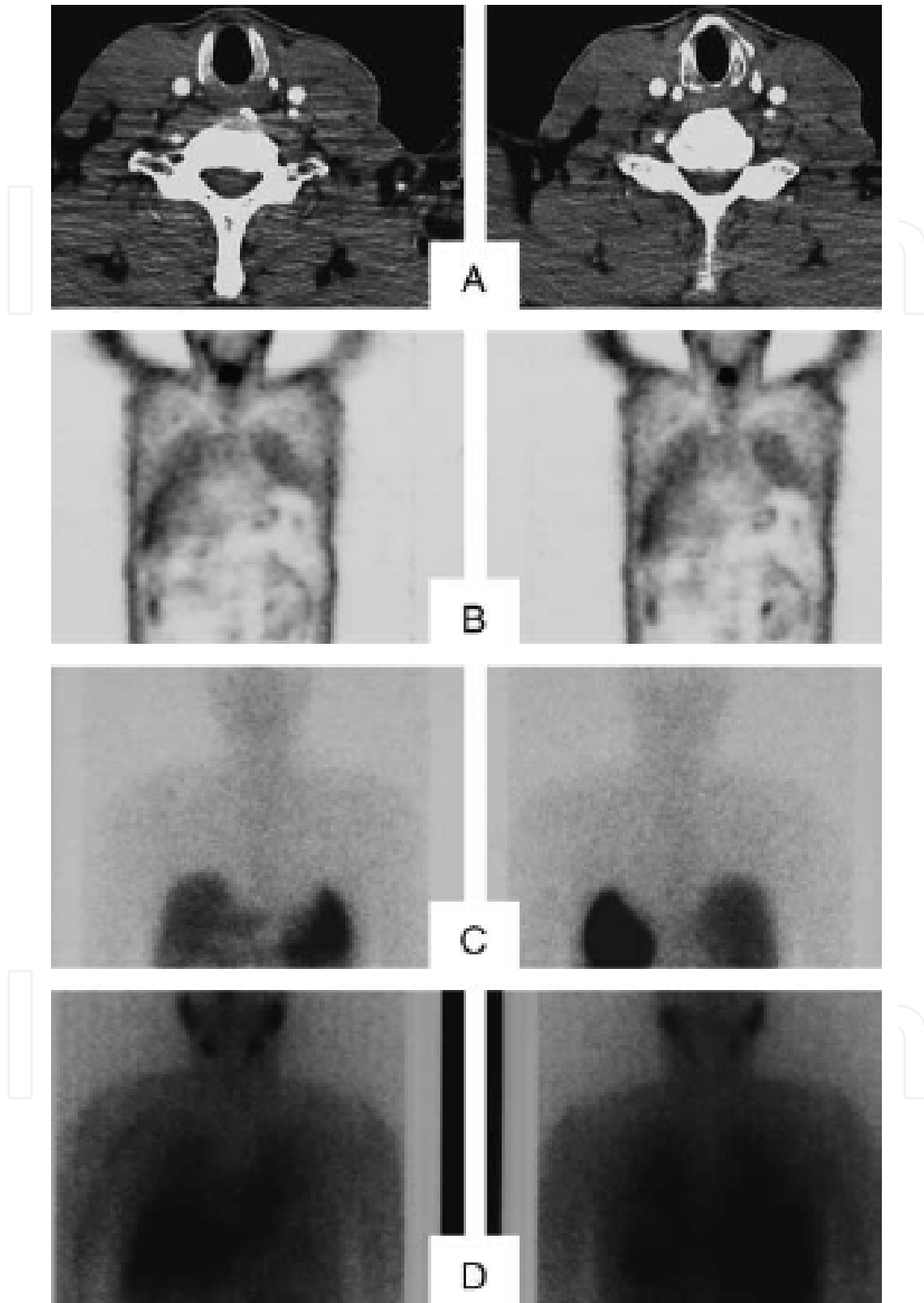


Fig. 4. Lymph node metastases in a patient with postoperative persistence of medullary thyroid carcinoma (MTC) positive at FDG-PET (B) and negative at conventional imaging techniques (CT-scan [A], Octreoscan [C] and MIBG-scintigraphy [D]) (from Faggiano et al., 2009).

For advanced MTC, conventional oncological therapies (radiotherapy and systemic chemotherapy) have scarce effectiveness. For patients with MTC unresponsive to conventional treatments, novel therapies are needed to improve disease outcomes. As a result of the increasing knowledge on the biological basis of MTC, therapeutic agents that target specific molecular pathways have been developed (Kapiteijn et al., 2011). Multiple novel therapies primarily targeting angiogenesis have entered clinical trials for metastatic thyroid carcinoma (including MTC). Partial response rates up to 30% have been reported, but prolonged disease stabilization is more commonly observed. The most successful agents are those targeting the vascular endothelial growth factor receptors (VEGFRs) (Sherman, 2011). Monotarget kinase inhibitors and multikinase inhibitors could represent the best therapeutic option to manage patients with advanced MTC (Kapiteijn et al., 2011).

## 2. Conclusions

Medullary thyroid carcinoma is a secretive neuroendocrine tumor originating from thyroid C-cells. This tumor is, after the anaplastic carcinoma, the most aggressive thyroid malignancy with high morbidity and mortality. The prognosis of MTC strongly depends on early diagnosis and the completeness of the first surgical treatment. In case of lymph node involvement at the time of the diagnosis, the outcome is poorer because of a very high rate of disease persistence or relapse after surgery.

Treatment for patients with metastatic or advanced MTC has to taken in account novel agents targeting specific molecular pathways and resulting in arrest of tumor growth. Future efforts should be directed to develop diagnostic and therapeutic algorithms to obtain as early as possible the identification of tumor onset and to differentiate MTC from CCH, ensuring high rates of cure and long-time disease free survival. Further studies are required to improve knowledge of CCH and MTC, to detect new hereditary MTC-causing mutations and develop new diagnostic procedures and therapeutic strategies.

Finally, to optimize the management of patients with MTC, a multidisciplinary team of all the different specialists involved in MTC diagnosis and therapy is highly recommended.

## 3. Acknowledgments

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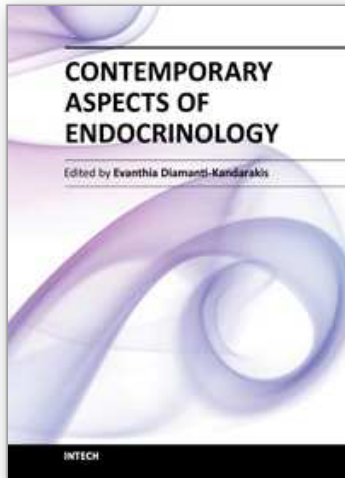
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This book aims to provide readers with a general as well as an advanced overview of the key trends in endocrine disorders. While covering a variety of topics ranging from thyroid carcinogenesis and pituitary adenomas to adrenal tumors and metabolic bone disease, this book also focuses on more specific issues not yet fully elucidated (e.g. the molecular pathways involved in thyrotropin beta gene regulation or monogenic phosphate balance disorders). Readers of different fields and background will have the opportunity to update their knowledge and more importantly to clarify areas of uncertainty and controversies in several topics of endocrine disorders.

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