4

Thyroid Neoplasm

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1. Introduction

Thyroid gland comprises 2 types of cells: Follicular cells (or thyrocytes) which produce and secrete thyreoglobulin and thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3) and Parafollicular cells (or C cells), secrete calcitonin. Papillary Thyroid Carcinoma (PTC) and Follicular Thyroid Carcinoma (FTC) are tumors originating by thyrocytes and are referred as Differentiated Thyroid Carcinomas (DTCs). Anaplastic Thyroid Carcinoma (ATC) is the undifferentiate tumor which may arises from DTCs or may be undifferentiated to origin. Medullary Thyroid Carcinoma (MTC), is the tumor arising to C cell. Rare tumors of non-epithelial thyroid origin are lymphoma, fibrosarcoma, squamous cell carcinoma, malignant teratoma and metastasis of other tumors.

2. Differentiated thyroid carcinomas (DTCs)

2.1 Epidemiology

Thyroid tumor represent about 1% of all human malignancy and about 90% of all endocrine tumor. PTC represents about 90% and FTC the 10% of DTCs. The annual incidence of thyroid cancer has been reported to range between 1.2 and 2.6 cases per 100.000 in men and 2.0-3.8 cases per 100.000 in women. Recently epidemiological studies have shown an increased incidence of DTCs in worldwide (Kosary, 2007; Kilfoy et al., 2009). PTC and microPTC (size < 1cm) represents the cancer prevalently increased. Reasons of increased incidence are not completely understood and controversies exist whether this increase is real or only apparent due to an increase in diagnostic activity. Probably the increased incidence may reflect the increased detection of small tumors through the use of imaging, particularly ultrasonografy (US), and increased use of fine needle aspiration citology (FNAC). Mortality records in the SEER database from 1997-2006 show relatively stable or slightly improved mortality rates for thyroid cancer (Edwards et al, 2010). However, over the same period, SEER mortality rates measured in terms of relative survival show reduced mortality rates in women respect to in men (Kosary, 2007).

2.2 Risk factors

2.2.1 Ionizing radiation

Ionizing radiations interacting with DNA produce mutations. thyroid was a tissue sensitive to ionizing radiation as demonstrate by the increased incidence in thyroid cancer after

Chernobyl accident. Children and young people were affected by DTCs and PTC was the histotype prevalently. Moreover, WHO has reported that newborn and children below 5 years old have high risk to develop thyroid cancer respect to adolescent and adults (Papadopoulou et al., 2009; Williams, 2008).

2.2.2 Iodine intake

Iodine is essential for T_4 and T_3 production. iodine deficient or inadequate intake induces low t4 levels and TSh increase and chronic tsh stimuli promotes growth goiter and nodules. thyroid nodules represent a clinical condition to develop thyroid cancer and especially FTC histotype. Studies have show a reduction of PTC/FTC ratio in iodine deficient area (Farahati et al., 2004; Lind et al., 1998).

2.3 Familial thyroid cancer syndromes

Non Medullary Familial Thyroid Cancer represents a rare disease where thyroid cancer is the only manifestation or thyroid cancer may represent a component of a complex syndrome.

Familial thyroid cancer PTC may have familial factors in 3.2 and 6.2%of cases. in fact, has been reported an increased incidence in relatives of patients with PTC of 4-10 fold (Pal et all, 2001). Some studies have found an association between altered telomere length (TL) and cancer phenotype (Capezzone et al, 2011). In these cases, the tumors are PTC with onset at an earlier age, with reversed gender distribution and with a more aggressive phenotype (Hemminki et al., 2005) with anticipation of neoplasia.

2.4 Familial tumour syndromes with thyroid cancer

1. Polyposis coli and Gardner's syndrome: Familial Adenomatous Polyposis (FAP) and Gardner's syndrome are inherited diseases characterized by colonic polyposis the former, and osteomas, lipomas and fibromas plus colonic polyposis the latter. Both syndromes show 5–10-fold increase in the incidence of PTC and tumor is multicentric. Germline mutations of tumor suppressor gene APC (Adenomatosis Polyposis Coli) are described in both syndromes. PTC in familial polyposis syndromes often harbours RET/PTC rearrangements (see below) in addition to the APC deletion (Cetta et al., 1998).
2. Cowden's disease: Patients with Cowden's disease have breast carcinoma and hamartomas. Cowden's disease is caused by germ-line mutations in the phosphatase and tensin homologue (PTEN) tumour suppressor gene inheritance in autosomal dominant pattern. Cowden's disease increases the incidence of follicular tumours of the thyroid, but the incidence is hard to estimate (Hemmings, 2003). Papillary cancer is also found with increased frequency.
3. Carney complex: The Carney complex consists of spotty skin pigmentation, myxomas, schwannomas, pigmented nodular adrenal hyperplasia, pituitary and testicular tumors and an increased incidence of follicular adenoma and FC. It is due to a mutation in the type 1 alpha regulatory subunit of the protein kinase A (PRKAR1A) which leads to constitutively activated protein kinase A (PKA) (Boikos & Stratakis, 2006) PRKAR1A mutations have been found in sporadic thyroid tumors and are more common in FC than follicular adenoma.

2.5 Somatic genetic alterations

DTCs frequently have somatic mutations that constitutively activated the mitogen-activated protein kinase (MAPK) pathway and PI3K-AKT pathway. These pathways include cell surface receptors such as RET and NTK, and intracellular signal transduceds , RAS gene and kinases RAF. Ultimately, this leads to increased nuclear translocation of phosphorylated MAPK and altered transcriptional regulation of target genes. Although the characteristic genetic alterations in PTC are all capable of activating the MAPK pathway, the histological phenotype and the expression profile are not identical between the different genetic alterations suggesting that other pathways such as the phosphoinositide-3-kinase (PI3K), protein kinase C and Wnt signalling pathways may be variously involved (figure 1).

2.5.1 Thyrosine kinase receptors

Tyrosine kinase receptors function as receptors for many growth factors and carry growth signals into the cell through tyrosine autophosphorylation and the initiation of kinase cascades. Tyrosine kinase receptors implicated on thyroid oncogenesis include RET and TRK:

1. RET: RET proto-oncogene is a 21-exons gene located on the proximal long arm of chromosome 10 that encodes a tyrosine kinase receptor. It is involved in the regulation of growth, survival, differentiation, and migration of cells of neural crest origin. It is not normally expressed in the follicular cell. The interaction extracellular ligand-binding domain and RET receptor leads the activation of a serine/threonine kinase pathway including RAS, BRAF and MAPK. This ultimately leads to a proliferative signal as well as inhibiting apoptosis and increasing genetic instability.

RET/PTC rearrangement: Rearrangements of RET gene in papillary thyroid carcinoma (PTC) are known as RET/PTC. Low-level expression may be seen in non-malignant follicular cells especially in Hashimoto's thyroiditis (Nikiforov, 2006). Although more than 10 rearrangements have been described, RET/PTC1 (60–70%), RET/PTC2 (20–30%), and RET/PTC3 (10%) account for most of the rearrangements found in PTC. Other RET/PTC rearrangements are rare (Santoro et al., 2006). In each of these rearrangements, the upstream (5´) component of a “housekeeping” (or ubiquitously expressed) gene drives the expression of the tyrosine kinase domain of RET. Two of the most common rearrangement types are RET/PTC1 and RET/PTC3. Both type of rearrangement paracentric intrachromosomal inversions, as all fusion partners reside on the long arm of chromosome 10. By contrast, RET/PTC2 and nine more RET/PTC rearrangements are all intrachromosomal rearrangements formed by RET fusion to genes located on different chromosomes. In the adult population, the RET rearrangements have been found in 2.6% to 34% of PTC. This variation is due to true differences in the prevalence of this alteration in PTC in specific age group in individuals exposed to ionizing radiation. Other causes might be represented by heterogeneous distribution of this rearrangements within the cancer and the various sensibilities of the detention methods used. In the pediatric population RET/PTC1 and RET/PTC3 have been found in up to 80% of the cases. These mutations are found in children exposed to radiation after the Chernobyl nuclear accident or to external irradiation for treatment of benign diseases of the head and neck. There are evidences that RET/PTC

rearrangements represent an early genetic changes leading to the development of PTC (Nikiforov, 2002; Xing, 2005).

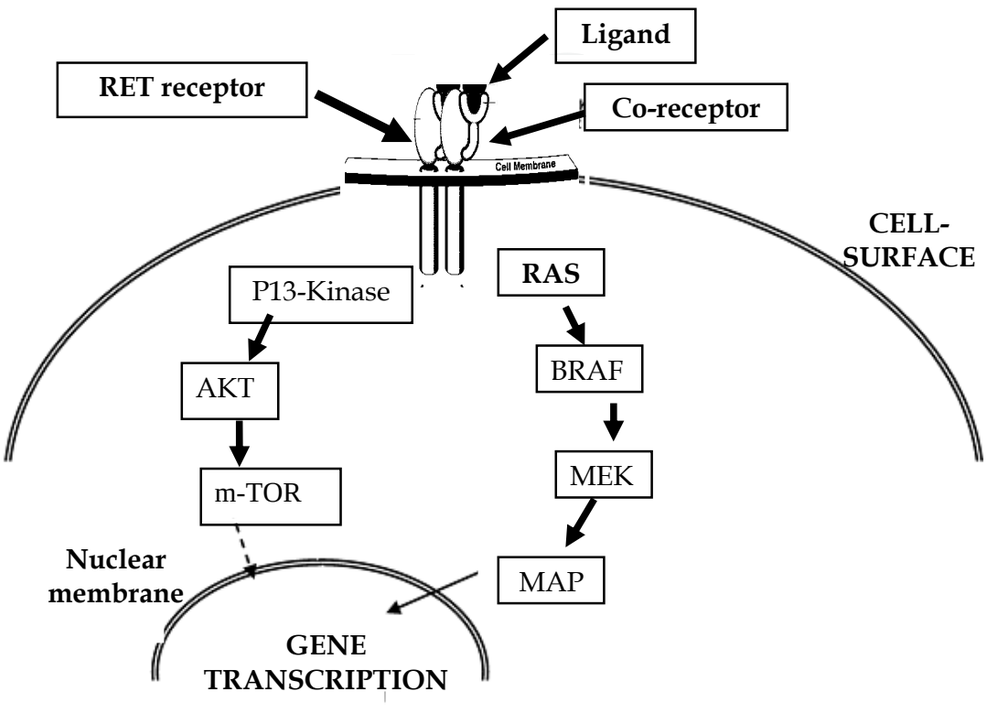

Fig. 1. RET receptor with MAP-Kinase and PI3-Kinase-AKT pathways in thyroid cell.

2. Trk: Trk proto-oncogene is located on chromosome 1q22 and encodes a tyrosine kinase receptor for nerve growth factor (27). It is expressed in the neurons in both peripheral and central nervous system, and is involved in the regulation of growth, differentiation and survival of these cells.

Trk rearrangements: occur in DTCs with lower prevalence than RET/PTC rearrangements. In thyroid follicular cells, the gene is activated through chromosomal rearrangement, with juxtaposes the intracellular thyrosine kinase domain of NTRK1 to the 5′ terminal sequence of different genes. Various genes combine with TRK gene forming chimeric genes. The main ones are tropomyosin gene (TPM3) gene and the translocated gene promoter (TPR). Trk rearrangements have been identified in 2-5% of PTC. (Musholt et al., 2000).

2.5.2 BRAF mutations

The RAF proteins are serine/threonine kinases involved in intracellular signalling via the MAPK pathway (Davies et al., 2002). Point mutations in BRAF leading to mutant proteins that mimic the conformation of the phosphorylated form and are therefore constitutively activated are involved in several of human malignancies including melanoma, ovarian and colorectal cancers. Mutations in the BRAF gene are the most common genetic alteration seen

in PTC. BRAF mutations occur in 30–60% of PTC and are 100% specific. BRAF point mutations are rarely associated with radiation-induced PTC. A paracentric inversion involving BRAF (AKAP9-BRAF) was found in 11% of post Chernobyl tumors BRAF and RET/PTC are mutually exclusive, not occurring in the same tumor. The presence of BRAF mutations appears to be associated with poor prognosis, reduced iodine uptake and failure of radioiodine ablation. Poorly differentiated and ATC harbour BRAF mutations, but not RET/PTC rearrangements, suggesting that BRAF mutations may predispose PTC to de-differentiation (Xing et al., 2005a; Nikiforova et al., 2003).

2.5.3 RAS mutations

Three RAS genes, H-RAS, K-RAS, and N-RAS, synthesize a family of 21-kDa proteins that play an important role in tumorigenesis. Their function is to convey signals originating from tyrosine kinase membrane receptors to a cascade of mitogen-activated protein kinases (MAPK). This activates the transcription of target genes involved in cell proliferation, survival, and apoptosis. The RAS proteins exist in two different forms: an inactive form that is bound to guanosine diphosphate (GDP) and an active form that exhibits guanosine triphosphatase (GTPase) activity. Oncogenic RAS activation results from point mutations, affecting the GTP-binding domain (codons 12 or 13) in exon 1 or the GTPase domain (codon 61) in exon 2, which fix the protein in the activated state and thus resulting in chronic stimulation of downstream targets, genomic instability, additional mutations, and malignant transformation. Mutations in all three cellular RAS genes have been identified in benign and malignant thyroid tumors. They seem to be common in follicular carcinoma (50%) (Di Cristofaro et al., 2006), PDTC, and ATC and occur less frequently in PTC (<10%) (Meinkoth, 2004). Some studies have shown a similar prevalence of RAS mutations in benign and malignant thyroid neoplasms, suggesting that RAS activation may represent an early event. Other studies have shown that RAS mutations, specifically mutations at codon 61 of N-RAS, are involved with tumor progression and aggressive clinical behavior. The presence of RAS mutations predicted a poor outcome for WDTC independent of tumor stage. Furthermore, they found that PDTC and ATC often harbor multiple RAS mutations. These mutations probably represent an intermediate event in the progression of thyroid carcinoma.

2.5.4 PAX8-PPARγ

The PAX8 gene encodes a transcription factor essential for the genesis of thyroid follicular cell lineages and regulation of thyroid specific gene expression. The Peroxisome Proliferator-Activated Receptor **γ** (PPAR**γ**) is a member of the nuclear hormone receptor superfamily that includes thyroid hormone, retinoic acid, and androgen and estrogen receptors. The PAX8-PPAR**γ** rearrangement leads to in-frame fusion of exon 7, 8, or 9 of PAX8 on 2q13 with exon 1 of PPARγ on 3p25. It appears as though the PAX8-PPARγ chimeric protein inactivates the wild-type PPARγ, which is a putative tumor suppressor (Ying et al., 2003) As with RAS mutations, PAX8-PPARγ rearrangement has also been shown to be involved in the development of FTC. The PAX8-PPARγ rearrangement is found in FTC (26–63%) and in the follicular variant of PTC, where it occurs in approximately 33% of all tumors (Castro et al., 2006) The role of this rearrangement in the progression

and dedifferentiation of follicular thyroid cancer to PDTC and ATC has not been well defined.

2.5.5 PI3K/AKT mutations

The PI3K/Akt pathway is a key regulator of cell proliferation and inhibitor of apoptosis. This pathway can be activated by the upstream stimulatory molecules (i.e. RAS), through the loss of function of PTEN protein that normally inhibits PI3K signaling, or as a results of activating mutations or amplification of gene coding for the effectors of this pathway. Inactivating mutations in PTEN are seen in Cowden's disease, a familial tumour syndrome associated with FC. In sporadic FC, the incidence of PTEN mutations is low (7%). Activating mutations of the catalytic subunit of PI3K have been found in small numbers of FC and FA (Wang et al., 2007; Hou et al., 2007).

2.6 Clinical features

The thyroid carcinoma manifesting as thyroid nodule. Palpable thyroid nodules are present in approximately 4-7% while high-resolution ultrasonography thyroid nodules are described in 19-67% of the general population. Most thyroid nodules are benign and only 5-10% are malignant. Thyroid nodule of large or small size have the same risk of malignancy. Solitary nodules in patients older more than 60 years and in young patients of less 30 years old are more frequently malignant. Male subjects have more risk of thyroid cancer than women. Rapid growth of a nodule may suggest malignancy.

2.6.1 Papillary carcinoma

Women develop PTC 3 times more frequently than men do, and the mean age at presentation is 34-40 years.

1. *Pathology:* Macroscopically the PTC are whitish nodules, without capsule and with ill-defined margins compared to the surrounding thyroid tissue. Microscopically the tumor cells of PTC typically grow with papillae and are characterized by ground-glass nuclei with pseudoinclusios, rare mitosis, and psammoma bodies (in 50% of papillary carcinomas). Beyond this classic PTC other variants of PTC may be present as Oxyphilic, Tall Cell, Columnar cell invade the thyroid capsule and surrounding extrathyroidal structures such as trachea, laryngeal, Follicular variant and diffuse sclerosing
2. *Local invasion* → Cancer can nerves, and airways. In these cases the patient may present with hemoptysis, hoarse voice and dysphagia.
3. *Regional and metastatic disease* → PTC spreads to the cervical lymph nodes. Clinically evident lymph node metastases are present in approximately one third of patients at presentation. Microscopic metastases are present in one half. The most common site of lymph node involvement is central compartment (level 6). The jugular lymph node chains (levels 2-4) are the next most common sites of cervical node involvement. Lymph nodes in the posterior triangle of the neck (level 5) may also develop metastases. This finding has important implications on the treatment algorithm for patients in this situation (Figure 2). Approximately 5-10% of patients develop distant metastases. Distant spread of PTC typically affects the lungs and bone

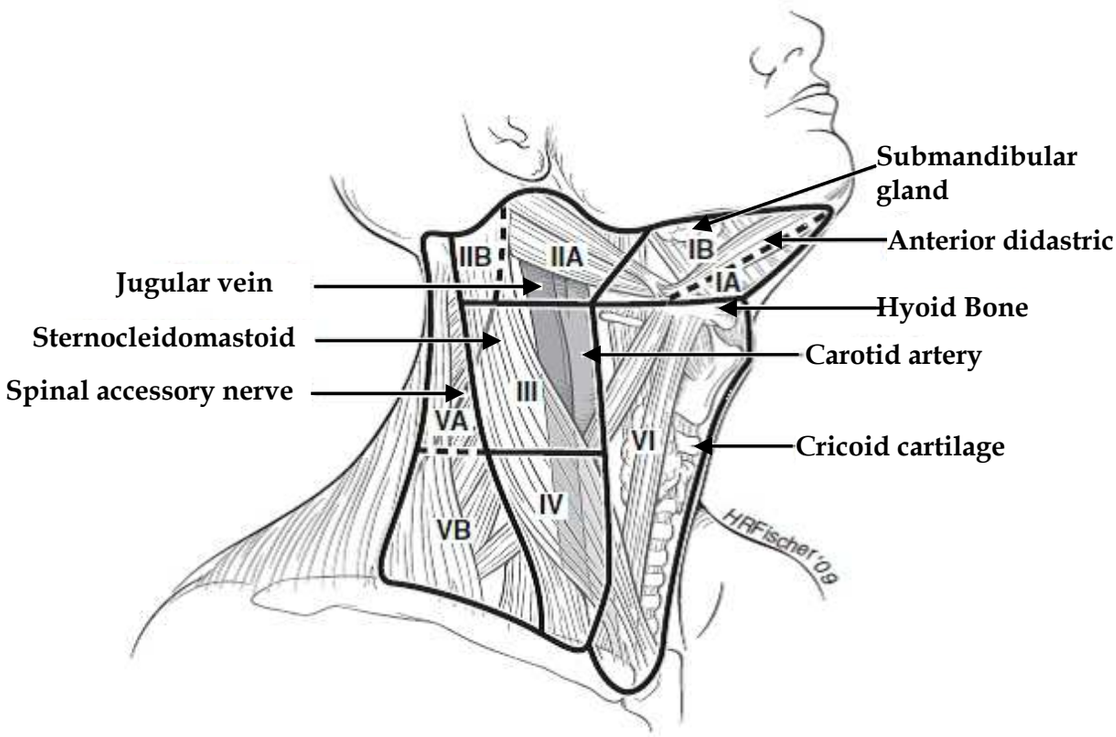

Fig. 2. Shows the lymph nodes in 6 neck clustered in compartments.

2.6.2 Follicular carcinoma

FTC represents thyroid cancers in area with insufficient iodine intake. As PTC, FTC occurs 3 times more frequently in women than in men. The mean age range at diagnosis is late in the fifth to sixth decades.

1. *Pathology*. Macroscopically, FTC appears as encapsulated nodule. Microscopically, tumor cells may show an increase solid, trabecular or follicular, which may invade the tumor capsule or the surrounding vascular structures. The tumors are divided into minimally invasive and widely invasive lesions depending on the histologic evidence of capsule and vascular invasion.
2. *Local invasion*. Local invasion can occur as PTC (see Local invasion for Papillary Carcinoma, above).
3. *Cervical and distant metastases*. Cervical metastases might be present at diagnosis. However, the rate of distant metastasis is significantly increased (approximately 20%) respect to PTC. Lung and bone are the most common sites.

2.7 Diagnosis

Clinical presentation of thyroid cancer is a thyroid nodule. Suspicious criteria of malignancy are: 1) Age: <20 or> 60 years 2) Sex: male> female; 3) Irradiation of head and/or neck; 4) Family history of papillary carcinoma 5) Rapid growth of the nodule 6) Growth during suppressive therapy with LT4 (L-thyroxine); 7)Fixed, hard consistency 8) Lymphadenopathy

2.7.1 Laboratory and thyroid scintigraphy

TSh evaluation allows to identify hyperfunction nodule. The TSH determination should be performed in nodule with large size > 2.5-3 cm. Tc^{99} thyroid scintiscan allows to confirm the uptake of large nodule. Hyperfunctioning nodules rarely are malignant, therefore no other diagnostic procedure should be performed.

2.7.2 Thyroid ultrasound (US)

US is a widespread technique that is used as a first-line diagnostic procedure for detecting and characterizing nodular thyroid disease. US permit to distinguish solid, cystic or mixed nodule, to evaluate ultrasound characteristic as hyperechogenicity , hypoechogenicity or isoechogenicity. the presence of some US aspects in the same thyroid nodule might have a higher likelihood of malignancy. These include: hypoechogenicity, irregular margins, microcalcifications, an absent halo, increased intranodular vascularity (Moon et al., 2008).

Elastography is an emerging and promising sonographic technique that requires additional validation with prospective studies (Machens et al., 2005; Rago et al., 2007).

2.7.3 Fine-needle aspiration cytology (FNAC)

Fine-needle aspiration cytology (FNAC) is the most accurate and cost-effective method for evaluating thyroid nodules. FNAC is not recommended in all nodules. The presence in the same nodule of 2 or more US characteristics above reported, recommended FNAC.

Cytology results should be included in the following diagnostic categories **(**Fadda et al., 2010**):** THYR 1: non diagnostic; THYR 2: negative for malignant cells; THYR 3: inconclusive /indeterminate (follicular proliferation); THYR 4: suspicion of malignancy; THYR 5: positive for malignant cells

THYR 1:.The "non diagnostic" can be classified as inadequate and/or non representative, depending on technical factor. *Operative suggestion.* FNAC repetition after at least one month from the previous one, according to the clinician's opinion.

THYR 2.This category accounts for 60-75% of all cytologic samples. Operative suggestion. FNAC repetition to reduce the false negative results, .if nodule growing during L-T4 treatment or modified US aspects

THYR 3.This category encompasses all follicular-patterned lesions: About 80% of the TIR 3 diagnoses are benign lesions whereas only 20% of them result as malignant tumors after surgery and histologic examination. Some immunohistochemical markers such as Galectin-3, HBME-1, Cytokeratin 19 may improve the accuracy of the cytologic diagnosis. Operative suggestion. Surgical excision of the lesion and histological examination. The surgical option should be evaluated in the clinical and imaging setting.

THYR 4.It represents an heterogeneous group of lesions. Are included in this category samples without a sufficient amount of malignant cells or without cytological atypias sufficient for a diagnosis of cancer. Operative suggestion. Surgery

THYR 5.All cases with a diagnosis of malignant neoplasm (papillary, medullary and anaplastic carcinomas, lymphomas and metastasis) are included in this category Operative suggestion. Surgery for differentiated carcinomas. The results of FNAC are very sensitive for the differential diagnosis of benign and malignant nodules although there are limitations: inadequate samples and follicular neoplasia. In these cases the definitive diagnosis can be made only by histological examination

2.8 Treatment

2.8.1 Neartotal or total thyroidectomy

Near-total or total thyroidectomy is recommended if the primary thyroid carcinoma is >1 cm, multinodular goiter, regional or distant metastases at diagnosis, patient with personal history of radiation therapy to the head and neck, or patient with family history of DTCs. Older age (>45 years) may also be a criterion for recommending near-total or total thyroidectomy even with tumors <1–1.5 cm, because of higher recurrence rates in this age group. Increased extent of primary surgery may improve survival for high-risk patients and low-risk patients (Bilimoria et al., 2007)

2.8.2 Lymph node dissection

Regional lymph node metastases are frequently at diagnosis ranging from 20 to 90%. Although lymph node metastases in PTC patients are reported no clinically relevance on outcome in low risk patients, recently SEER registry study concluded that cervical lymph node metastases are a poor prognostic factor on survival in patients with FTC and in patients with PTC over 45 years (Zaydfudim et al., 2008). In experienced hands, therapeutic or prophylactic central compartment dissection can be achieved with low morbidity. In addition, selective unilateral paratracheal central compartment node dissection increases the proportion of patients who appear disease free.

2.8.3 Risk staging

Postoperative staging for thyroid cancer is used: 1) to permit prognostication for an individual patient with DTC; 2) to tailor decisions regarding postoperative adjunctive therapy, including RAI therapy and TSH suppression, to assess the patient's risk for disease recurrence and mortality; 3) to make decisions regarding the frequency and intensity of follow-up, directing more intensive follow-up towards patients at highest risk; and 4) to enable accurate communication regarding a patient among health care professionals. Varius risk definition for thyroid carcinoma have been evaluated. The American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification has been used in clinical practice for DTC. This classification has also been evaluated to determine its utility in discriminating patients who have distinct outcomes. The fifth edition AJCC/UICC TNM classification (1997) was revised as the sixth edition in 2002 (Table 1).

In 2009, ATA has developed classes of risk in DTCs patients, to predict risk for recurrence, not death (ATA Surgery Working Group, 2009):

1. Low-risk patients have the following characteristics: 1) no local or distant metastases; 2) all macroscopic tumor has been resected; 3) there is no tumor invasion of locoregional tissues or structures; 4) the tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma) or vascular invasion; 5) and, if 131I is given, there is no 131I uptake outside the thyroid bed on the first post-treatment whole-body RAI scan (RxWBS)
2. Intermediate-risk patients have any of the following:1) microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery; 2) cervical lymph node metastases or 131I uptake outside the thyroid bed on the RxWBS done after thyroid remnant ablation or 3) tumor with aggressive histology or vascular invasion
3. High-risk patients have:1) macroscopic tumor invasion, 2) incomplete tumor resection, 3) distant metastases, and possibly 4) thyroglobulin out of proportion to what is seen on the post-treatment scan

T0	Failure to evidence of primary tumor
T1	Tumor diameter ≤ 2 cm, limited to the thyroid
T2	Tumor diameter > 2 cm but < 4 cm, limited to the thyroid
T3	Tumor diameter > 4 cm, limited to the thyroid
	Any tumor size with minimal extrathyroidal extention (soft perithyroid tissue or sternocleidomastoid muscle)
T4a	Any tumor size with extension beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
Nx	Regional lymph nodes can not be assessed
N0	Absence of lymph nodes metastases
N1	Metastasis to regional lymph nodes
N1a	Metastasis to level IV (pretracheal, paratracheal and prelaryngeal lymph nodes)
N1b	Ipsilateral, controlateral or bilateral cervical lymph nodes metastases or superior mediastinal lymph nodes metastases
Mx	Distant metastasis can not be assessed
M0	No distant metastasis
M1	Presence of distant metastasis

Table 1. TMN 6th edition (IUCC 2002)

The TNM classification allows to stratify patients into four classes according to risk of death at 10 years (Table 2).

	Age < 45 years			Age ≥ 45 years		
Stage	**T**	**N**	**M**	**T**	**N**	**M**
I	Any T	Any N	M0	T1	N0	M0
II	Anny T	Any N	M1	T2	N0	M0
III				T3	N0	M0
				T1 - T3	N1a	M0
IVA				T4a	N0	M0
				T4a	N1a	M0
				T1 - T4a	N1b	M0
IVB				T4b	Any N	M0
IVC				Any T	Any N	M1

Table 2. TMN classification

Tuttle (Tuttle et al., 2008a) stratified risk of death into four categories: very low risk, low risk, intermediate risk and high risk (table 3).

	Very low	**Low**	**Intermediate**	**High**
Age at diagnosis	< 45 years	< 45 years	< 45 years Classic PTC > 4 cm or vascular invasion, or extrathyroidal extention, or worrisome histology of any size	> 45 years
Primary tomor size	<1 cm	1-4 cm	>45 years Classic PTC > 4cm or extrathyroidal extention, or worrisome histology < 1-2 cm confined to the thyroid	> 4 cm classic PTC
Histology	Classic PTC, confined to the thyroid gland	Classic PTC, confined to the thyroid gland	Histology in conjunction with age as above	Worrisome histology > 1-2 cm
Completennes of resection	Complete resection	Complete resection	Complete resection	Incomplete tumor resection
Lymph node involvement	None apparent	Present or absent	Present or absent	Present or absent
Distant metastasis	None apparent	None apparent	None apparent	Present

Table 3. Risk of death.

In accordance with this system, a European Consensus Report (ETA) defined three categories of risk to establish the indication for radioiodine ablation therapy (Pacini et al., 2006):

1. very low-risk: unifocal T1 (<1 cm) N0 M0, no extension beyond the thyroid capsule, favourable histology], no indication for radioiodine ablation,
2. low-risk : T1 (>1 cm) or T2 N0 M0 or multifocal T1 N0 M0, or unfavourable histology, probable indication
3. high-risk: any T3 and T4 or any T, N1, or any M1, definite indication

Recently, has been proposed an 'ongoing risk stratification' which takes into account the response to therapy (Tuttle et al., 2008). Patients can be classified as having an excellent, acceptable or incomplete response to therapy:

1. Excellent response (undetectable basal and stimulated Tg, negative AbTg and negative neck US) patients should have a very low risk of recurrence and their long-term follow-up will be based on yearly physical examination and suppressed Tg value.
2. Acceptable response (undetectable basal Tg, stimulated Tg <10 ng/ml, trend of Tg in decline, AbTg absent or declining, substantially negative neck US) patients require a closer follow-up reserving additional treatment in the case of evidence of disease progression.
3. Incomplete response (detectable basal and stimulated Tg, trend of Tg stable or rising, structural disease present, persistent or recurrent RAI-avid disease present) patients require continued intensive follow-up with neck ultrasound, cross-sectional imaging, RAI imaging and FDG-PET imaging. The majority of these patients will require additional therapy such as surgical resection, RAI therapy, external beam irradiation and systemic therapies.

2.8.4 Radioiodine ablation

Surgery is usually followed by the administration of ^{131}I activities aimed at ablating any remnant thyroid tissue and potential microscopic residual tumour. This procedure decreases the risk of locoregional recurrence and facilitates long-term surveillance based on serum Tg measurement and diagnostic radioiodine whole body scan (WBS). In addition the high activity of ^{131}I allows obtaining a highly sensitive post-therapeutic WBS. Radioiodine ablation is recommended for all patients except those at very low risk. FTC and Hurthle cell cancer are generally regarded as higher risk tumors. On the contrary, "minimally invasive FTC", characterized only by capsular invasion, has an excellent prognosis with surgery alone and RAI ablation may not be required. Effective thyroid ablation requires adequate stimulation by TSH. The method of choice for preparation to perform radioiodine ablation is based on:

1. Endogenous TSH elevation: can be achieved by thyroid hormone withdrawal, increasing serum TSH levels >30mU=L in more than 90% of patients. Patients affected by chronic kidney failure, heart failure, panhypopituitarism, ecc...might worse their clinical status with thyroid hormone withdrawal
2. Administration of recombinant human TSH (rhTSH) rhTSH is helpful in patients with chronic diseases, able to increase tSH levels after L-T4 withdrawal, or intollerant hypothyroidism (Tuttle et al., 2008b).

Recent studies demonstrated ablation with lower doses than 100 mCi of I131. In fact the same ablation rate might be performed with 50 (Chianelli et al., 2009) and 30 mCi (Maenpaa et al., 2008) with rhTSh stimuli. These low doses reduce the radiation exposure to the whole body. Body weight or surface area should be evaluated for ablation in pediatric patients (Franzius et al., 2007).

2.8.5 Levo-thyroxine (L-T4) therapy

Thyroid hormone suppression therapy has an important role during follow-up blocking the recurrence and metastasis progression. Several reports have shown that L-T4 suppressive treatment has usefull in patients with high-risk decreasing progression, recurrence rates, and cancer-related mortality (Mc Griff et al., 2002; Hovens et al., 2007). On the other hand, in patients with low-risk no significant improvement has been obtained by L-T4 suppressive therapy. The duration of suppression therapy is currently being debated. According to the current guidelines, low-risk patients free at the first follow-up might have replacement L-T4 therapy, with the goal of maintaining serum TSH level within the normal range. On the contrary, high risk patients even free at the follow-up should continue with suppressive L-T4 doses for the high risk of relapse (Jonklaas et al., 2006; Cooper et al., 2009)

2.9 Prognosis

2.9.1 Tumour factors

1. Histology Histological characteristics have critical role of patient outcomes. The variants of PTC include the following:
   - Encapsulated tumor: About 10% of PTC are completely surrounded by a dense fibrous capsule. The prognosis for this subtype is better than unencapsulated PTC.
   - Diffuse sclerosing variant: Occurs in PTC of younger age, the diffuse sclerosing variant constitutes 2% of PTC. Prognosis for this subtype is less favorable than typical PTC.
   - Oxyphilic (Hürthle) cell type: The oxyphilic (Hürthle) cell type may be more aggressive than usual PTC.
   - Follicular variant: The follicular variant is less favorable than typical PTC.
   - Tall-cell carcinoma: Tall-cell carcinoma is a more aggressive form of thyroid carcinoma that differs from the usual form by showing tall columnar cells.
   - Columnar cell carcinoma: Columnar cell carcinoma is a distinctly more aggressive form of PTC that occurs more often in older men and is associated with a poor prognosis.

FTC is encapsulated, and invasion of the capsule and vessels is the key feature distinguishing follicular carcinomas from follicular adenomas. The subtypes are: 1) minimally invasive: good prognosis is a cancer with very low aggressiveness; widely invasive: cancer with poor prognosis for quick spreading of metastasis; 3) Hurthle-cell (oxyphilic follicular or oncocytic) carcinoma is a cytological variant of FTC with poor outcome

2. Tumour size: Tumor size correlates with outcome in patients with PTC; larger tumours are more likely to present with locoregional and/or distant metastases. However, the risk of recurrent disease and cancer-specific mortality increases linearly with tumour size.
3. Lymph node metastases: Cervical lymph nodes are involved in 20–50% of DTC, particularly PTC, and may be the first presentation. The frequency of micrometastases may approach 90%. Preoperative US identifies suspicious cervical adenopathy in 20–31% of cases, (Stulak et al., 2006). Confirmation of malignancy in lymph nodes with a suspicious sonographic appearance is achieved by US-guided FNA aspiration for cytology. Malignant lymph nodes are much more likely to occur in levels III, IV, and VI than in level II (Figure 2). Controversy exists over the clinical importance of lymph node metastases. Several studies have found no difference in survival between patients with and without lymph node metastases. Other studies have found that their presence leads to an increased risk of recurrence and reduced survival (Lee et al., 2009). The presence of lymph node metastases in patients <45 years has no effect on survival. On the contrary lymph nodes metastasis in patient ≥45 years are associated an increased risk of death.
4. Extrathyroidal extension: The extension of cancer outside the thyroid into the surrounding tissues may be found in about 30% of patients with PTC (Mazzaferri, 2007). The massive extension out thyroid into the surrounding musculature, oesophagus or trachea is associated with a high-risk of locoregional disease recurrence. It requires massive surgical debulking and may benefit from external beam radiotherapy. Microscopic extension beyond the thyroid capsule is associated with a higher risk of recurrent disease, greater likelihood of lymph node metastases and a higher mortality rate than in patients without such extracapsular spread (Lee et al., 2009).
5. Distant metastases The main cause of death from DTC is distant metastases; fortunately, only 5–10% of patients have distant metastases at initial presentation. Over 50% have lung involvement alone, 25% have bone involvement alone, 20% have both lung and bone involvement, and about 5% develop distant metastases in other sites (Lee & Soh, 2010). Mortality is high with distant disease, with 50% survival at 3.5 years. Less frequently are liver metastasis.
6. Oncogenes The study of oncogenes and their ability to predict the clinical behaviour of thyroid cancers has been an exciting and intensely investigated field. Moreover, these researches have resulted in the creation of several new therapeutic agents to target these genetic aberrations.
    - BRAF: The presence of a *BRAF* mutation is associated with extrathyroidal invasion, multicentricity, presence of nodal metastases, higher-stage disease, older age at initial presentation, and higher likelihood of recurrent or persistent disease. (Elisei et al., 2008). Further study is needed to clarify this complex issue.
    - RAS: Numerous studies have show that ras mutations define a subset of thyroid carcinoma characterized by aggressive behavior. This is indicated by the close relationship between oncogenic ras and the loss of those histologic features that characterize well-differentiated thyroid tumor phenotypes. Remarkably, oncogenic K-ras correlates with the loss of tumor differentiation, presence of distant

metastases, and is associated with poor prognosis among DTC independently tumor stage (Garcia-Rostan et al., 2003).

- RET/PTC: Ret/PTC1 is the most frequent (60–70%), while ret/PTC3 (20–30%) and ret/PTC2 are the least common (10%). RET/PTC rearrangements are associated with PTC that lacks evidence of progression to PDTC or ATC demonstrating a low potential for de-differentiation.

2.9.2 Patient variables

1. Age: Age at diagnosis and therapy is a critical predictor of patient outcome; patients aged >45 years have increased recurrence rates and reduced mortality. Children and adolescents (age <20 years) tend to present with higher-stage disease and greater likelihood of locoregional and distant metastases. Despite late-stage presentation of tumors, children generally have excellent survival rates. The exception to this rule is when the disease presents in children aged ≤10 years; in this age group, the disease is notably more aggressive. Mortality is high in this group (Fugazzola et al., 2004).
2. Gender: As discussed above, mortality rates are higher among men than women even DTCs are more frequent in woman. Recurrence rates are also higher in men.

2.10 Follow-up

The aim of the follow-up is the early discovery of persistent disease. Local recurrences develop in the first 5 years mainly, and only in a minority of cases local or distant recurrences develop 20 years after the initial treatment. Thyroid hormone FT3, FT4, TSH, should be evaluated 2-3 months after initial treatment to check the adequacy of LT4 suppressive therapy. At 6–12 months the first follow-up is aimed to ascertain whether the patient is free of disease.

Disease-free status comprises all of the following:

1. no clinical evidence of tumor,
2. no imaging evidence of tumor (no uptake outside the thyroid bed on the initial posttreatment WBS, or, if uptake outside the thyroid bed had been present, no imaging evidence of tumor on a recent diagnostic scan and neck US), and
3. undetectable serum Tg levels during TSH suppression and stimulation in the absence of interfering antibodies.

In the absence of Tg antibody the measurement of serum Tg levels is an important modality to monitor patients for residual or recurrent disease. Serum Tg has a high degree of sensitivity and specificity to detect thyroid cancer recurrences during thyroid hormone withdrawal or stimulation using rhTSH. Serum Tg measurements obtained during L-T4suppression therapy may fail to identify patients with relatively small amounts of residual tumor (Hovens et al., 2007). Nevertheless, a single rhTSH-stimulated serumTg<0.5 ng/mL in the absence of anti-Tg antibody has an approximately 98–99.5% likelihood of identifying patients completely free of tumor on follow-up (67). On the contrary, diagnostic-therapeutic procedures should be performed in patients with basal or after rhTSH stimuli Tg detectable values (value>2ng/ml). Diagnostic procedures comprise neck US, diagnostic I131 Whole Body Scan, Computer Tomography. Negative

radiological imagines require a therapeutic dose of I131 to identified recurrences and the subsequent follow-up will be evaluated on post dose scintiscan. PET- TC 18 FDG sholud be performed in all patients with detectable Tg values and negative post therapeutic I 131 dose scintiscan. The identification of PET-TC positive lesions implies the de-differentation of metastasis.

The long-term follow-up differs on class of risk of recurrence. Very low-risk patients should be followed through physical examination, basal serum Tg measurement on substitutive LT4 therapy and neck US yearly if Tg values was undetectable at first follow-up. Low risk, Intermediate Risk and High-risk require Tg evaluation after rhTSH stimuli, neck US. Radiological techniques imagines if Tg increased up the cut-off, as above described. However, the recent introduction of an ultrasensitive Tg assay might reduce the need to perform Tg measurements after rhTSH-stimuli (Robert et al., 2007). About 25% of DTCs shows anti-Tg antibodies that could falsely lower serum Tg in immunometric assays (Cooper et al., 2009). Serial serum anti-Tg antibody quantification using the same methodology may serve as an imprecise surrogate marker of residual normal thyroid tissue or tumor. Patients with anti Tg antibodies should perform follow-up with I 131 Whole Body Scan. Suppressive doses of L-T4 with TSH levels under 0.1 mU/l reduce recurrence or progression of disease only in patients with high risk. Therefore, TSH levels <0.1 mU/l should be maintained until first follow-up and in high risk patients. Patients disease free and very low risk should take replacement doses.

3. Poor differentiate thyroid carcinoma (PDTC)

PDTC includes tumors of follicular origin that retain sufficient differentiation to produce Tg, histologically show scattered small follicular structures, but generally lack the usual morphologic characteristic of PTC or FTC. PDTC could be considered as an intermediate form of thyroid cancer with a prognosis that falls between DTCs and ATC (Sobrinho-Simoes et al., 2002). It is noteworthy that in the north half of Italy about 15% of thyroid cancer are PDTC whereas in North America the PDTC comprise only 2-3% of thyroid malignancy. These observations demonstrate that environmental factors may play a significant role in the genesis of these lesions, including iodine deficiency. PDTC may occur in a recurrence of a previously treated DTCs or at the time of diagnosis PDTC parts of tumor may show characteristics histological characteristics of PTC more rarely FTC. Clinically PDTC can produce Tg but do not respond to radioactive iodine. Therefore, therapy of PDTC can be inefficient by radioiodine. PDTC with extracapsular extension, massive lymph nodes involvement and no radioiodine up-take benefits of external radiotherapy (RT) after surgery, but no advantage to adjuvant RT to the neck in PDTC with diffuse metastasis. PDTC has poor sensitive to chemotherapy using different drugs as methotrexate, adriamycin, bleomycin and vinblastin. Response ranging from 55 to 70% when chemotherapy is associated to RT.

4. Anaplastic thyroid carcinoma (ATC)

Anaplastic thyroid carcinoma (ATC) is the most aggressive and lethal form of thyroid cancer with a median survival of 4 to 12 months from the time of diagnosis.

4.1 Epidemiology

ATC accounts for less than 2% of all thyroid malignancies, it is responsible for 14%-39% of deaths related to malignant thyroid tumors. The female/male ratio is 5 to 1 and the peak of incidence is in the sixth and seventh decades of life. The age at diagnosis of ATC is over 70 years. The incidence of ATC is estimated at 1 to 2 cases per million population per year, and the trend has been decreasing even though the incidence of well-differentiated subtypes (e.g., papillary and follicular) of thyroid cancer has been increasing.

4.2 Risk factors

Patients with ATC show goiter in 25% of cases, in 10% a family history of goiter. Therefore, ATC is more common in places with endemic goiter and iodine supplementation has decrease the incidence of ATC in these countries (Besic N, 2010).

4.3 Genetic alteration

ATC may derive from DTCs, including PTC, FTC or Hurthle cell or may be "de novo". Several mutations are identified in ATC, some occurring in PTC and FTC (e.g., RAS and BRAF). Late mutations include p53, catenin (cadherin-associated protein), beta 1, and PIK3CA, suggesting that one or more of these mutations contribute to the extremely aggressive behavior of ATC. By contrast, the RET/PTC rearrangements found in childhood and radiation-induced PTCs, and the PAX8/PPARG fusion protein detected in follicular carcinoma, are not observed in poorly differentiated and ATCs. RAS and BRAF are the same described in DTCs. p53 is a tumor suppressor gene located in chromosome 17p that increases the cyclin kinase inhibitor, p21, promoting cell cycle arrest at G1/S. Mutations impair p53 transcriptional activity, and occur in 55% of ATC. Polymorphism in codon 72, identify only in ATC, but in no benign nodules or differentiated thyroid cancers, could be considered as a risk factor (Boltze C, 2002). Other gene as Wnt, a catenin beta 1 gene is involved in signaling and cell–cell adhesion, was detected in ATC and PDTC but not in PTC and FTC.

4.4 Clinical presentation

Clinical manifestation of ATC is a nodule with a rapidly growth, enlarging anterior neck mass, accompanying dysphagia (40%), voice change or hoarseness (40%), and stridor (24%). Regional symptoms included a noticeable lymph node mass (54%) and neck pain (26%). Systemic symptoms include anorexia, weight loss, and shortness of breath with pulmonary metastases. ATC is usually advanced at diagnosis and frequently surgically unresectable. Around 20%-50% of patients present with distant metastases, most often pulmonary, and another 25% develop new metastasis during the rapid course of the disease, lungs (80%), bone (6–16%), and brain (5–13%) were the most common sites of metastasis.

4.5 Prognosis

The median survival rate from 4 to 12 months. On multivariate analysis, distant or metastatic disease, tumor size greater than 7 centimeters, and treatment with surgery with or without radiotherapy were statistically significant prognostic markers(Chen et al.,

2008). Age, sex, size of the tumor, resectability, and the extent of disease has been shown to affect the course of the disease. Age less than 60 years, female sex, tumor size less than 7 centimeters, were the most favourable prognostic markers (Kim et al., 2007). A recent study from France based on 26 patients with ATC, univariate analysis showed that age above 75, capsular invasion, lymph nodes metastasis, tumor residue after surgery, and lack of multimodal treatment (particularly radiotherapy in patients without tumor residue) are poor prognosistic factors. Multivariate analysis in the same cohort showed age above 75, followed by node invasion, capsular invasion, and female sex to be poor prognosticators (Roche B, 2010).

4.6 Therapeutic approach

Patients with ATC even in the absence of metastatic disease are considered to have systemic disease at the time of diagnosis. ATC is considered stage IV by the International Union Against Cancer (UICC)—TNM staging and American Joint Commission on Cancer (AJCC) system. Multimodality treatment consisting of surgery when feasible combined with radiation and chemotherapy is generally recommended.

4.6.1 Surgery

The aim of surgery in ATC, whether it is removal of all gross disease or palliation, remains controversial. Complete resection has been identified as a prognostic factor in several clinical trials. When feasible, surgery must aim at a radical intent. The categories of patients that may be most suitable for this approach are young patients (< 65 years old) with small lesions (< 6 cm) and no distant metastasis. However, surgery also plays an important role for palliation. Partial resection of the tumor followed by radiotherapy and chemotherapy may delay or avoid airway obstruction, although it can improve survival only by a few months (Miccoli et al., 2007). It is theoretically possible that, in selected patients, even in the setting of metastatic disease, surgery may result in an improved quality of life and prevent death from suffocation (Yau et al., 2008). Since surgery alone is not able to control the disease even in patients with small intra-thyroidal masses, adjuvant therapy is always required, and can be administered either with radiotherapy (RT) or chemoradiotherapy.

4.6.2 Systemic treatment

Chemotherapy: ATC cannot be regarded as a very chemo-sensitive tumor. Doxorubicin is not able to achieve more than a 20% response rate. A study (Shimaoka et al., 1985) has observed that combination chemotherapy based on doxorubicin (60 mg/m2) and cisplatin (40 mg/m2) was more effective than doxorubicin alone and provided a higher complete response rate. More recently, single drug docetaxel was tested as first-line chemotherapy in patients with advanced ATC. In a prospective phase II clinical trial of paclitaxel, showed a remarkable response rate of 53% (Schoenberger et al., 2004). In a preclinical experiment only paclitaxel, gemcitabine and vinorelbine appeared to be active in ATC (Bauer et al., 2003) and the combinations of vinorelbine/gemcitabine and paclitaxel/gemcitabine seemed to act synergistically. These results should receive confirmation in clinical trials.

4.6.3 Radiation

Achieving local control is important since death from ATC is usually a consequence of uncontrolled local disease. The indication for RadioTherapy (RT) range from providing palliation to improving survival. RT is used alone or in combined with surgery and chemotherapy. Intensity-modulated radiation therapy (IMRT) based on computerized treatment planning and delivery is able to generate a dose distribution that delivers radiation accurately with sparing of the surrounding normal tissue (Lee et al., 2007). Higher doses of radiation can be given over a shorter time with less toxicity by employing hyperfractionation techniques. Toxicity can be a limiting factor with radiation. Kim and Leeper reported complications particularly, pharyngoesophagitis and tracheitis in their series. Wong also noted skin changes, esophageal toxicity, and radiation myelopathy (Wong et al., 2001). Daily doses of greater than 3 Gy should be cautiously used as it can increase the incidence of myelopathy.

5. New treatments

PDTC and ATC are poor sensitive to radioiodione, chemotherapy and RT alone or associate. The knowledges on genetic transformation and the intracellular pathway involved in thyroid cancer transformation has permitted to develop target drugs. Therefore, interest arose in the therapeutic potential of target-specific kinase inhibitors for these diseases. Angiogenesis plays a critical role to support tumor cell growth and metastasis, supplying nutrients and oxygen, removing waste products, and facilitating distant metastasis.

5.1 Targeting signaling kinases

RET and VEGFR kinases have considerable similarity structural and multitargeted kinase inhibitors are capable of affecting both kinases. A wide variety of kinase inhibitors have entered clinical trials for patients with advanced thyroid cancers, PDTC or ATC. Because of the targeting similarities of many of these agents, common toxicities exist among these agents, including hypertension, diarrhea, skin rashes, and fatigue.

1. Motesanib (AMG706): is an oral, tyrosine kinase inhibitor targeting the VEGF receptors 1, 2, and 3.
2. Sorafenib (BAY 43-9006): is an oral, small molecule tyrosin-kinase inhibitor (TKI) and targeting VEGF receptors 2 and 3, RET and BRAF. Like other agents that inhibit BRAF, sorafenib also has been associated with development of cutaneous squamous cell carcinomas in up to 5% of treated patients, and a similar frequency of keratoacanthomas and other premalignant actinic lesions (Dubauskas et al., 2009). In a recent retrospective series, sorafenib therapy was associated with prolongation of median progression-free survival by at least 1 year, compared with patients' rate of disease progression prior to initiation of therapy (Cabanillas et al., 2010). A randomized, placebo-controlled phase III study of sorafenib as first-line therapy for progressive metastatic DTC has been initiated. Although not specifically approved for thyroid carcinomas, sorafenib is being used in selected patients with PDTC and medullary thyroid carcinoma for whom clinical trials are not appropriate

(Waguespack et al., 2009). Compared with patients' rate of disease progression prior to initiation of therapy, sorafenib may prolong progression-free survival in DTC by at least 1 year (Cabanillas et al., 2010). The drug may also be appropriate in selected pediatric cases; in 1 report, treatment with sorafenib yielded a marked response in a child whose lung metastases from PTC were progressing despite radioiodine therapy (Waguespack et al., 2009).

3. Sunitinib (SU11248): is an oral, small molecule TKI of all 3 VEGF receptors, RET, and RET/PTC subtypes 1 and 3 (Pasqualetti et al., 2011)
4. Axitinib (AG-013736): is an oral inhibitor that effectively blocks VEGF-1, -2 and -3. Partial response was seen in patients refractory radioiodine. Currently ongoing is a multicenter, open-label phase II study to determine the efficacy of axitinib in patients with metastatic DTC refractory to doxorubicin, or for whom doxorubicin therapy is contraindicated.
5. Pazopanib: is a potent small molecule inhibitor of all VEGFR subtypes as well as PDGFR. Like axitinib, it has insignificant inhibitory activity against the oncogenic kinases RET, RET/PTC, or BRAF, and therefore its actions are expected to be primarily anti-angiogenic in thyroid carcinoma.
6. Gefitinib (ZD1839): is an oral, small molecule inhibitor of the EGF receptor, was initially introduced for treatment of non-small cell lung carcinoma. Because many PDTC and ATC display activated EGFR signaling, and inhibitors have had demonstrated efficacy in preclinical models, an open-label phase II study was initiated, examining the effectiveness of gefitinib in a mixed cohort of thyroid cancer patients (Mrozek et al., 2006).

5.2 Other drugs

Beyond direct inhibitors of angiogenic kinases such as VEGFR, other drugs are capable of either inhibiting angiogenesis or disrupt existing tumor vasculature. Two of these agents, thalidomide and fosbretabulin (combretastatin A4 phosphate), have been of particular interest following reported responses in individual patients with ATC .

1. **Thalidomide and lenalidomide** Thalidomide was found to be an angiogenesis inhibitor decades after it achieved notoriety as a teratogenic cause of neonatal dysmelia. Eligibility was limited to PDTC patients whose measured tumor volumes had increased by at least 30% in the past year.
2. **Combretastatin** A4 phosphate (CA4P): is a tubulin-binding vascular disrupting agent that inhibits tumor blood flow. In a phase Ⅰ trial, one patient with ATC showed a progression-free survival of 30 mo, however, the drug was found to be associated with significant cardiovascular side effects at the escalating doses employed.
3. **Romidepsin** The cyclic peptide romidepsin (previously known as depsipeptide) selectively inhibits four isotypes of histone deacetylases. Toxicities were primarily hematologic, nausea, and vomiting. A phase II trial was initiated in patients with radioiodine-unresponsive, PDTC. Romidepsin induces stable disease and in few subjects exhibited restoration of uptake permitting therapeutic radioiodine administration.
4. **Vorinostat and valproic acid (VPA)** The orally available histone deacetylase (HDAC) inhibitor vorinostat, derived from hydroxamic acid, inhibits all known classes of HDAC

enzymes. An ongoing phase II trial is evaluating the effect of monotherapy with VPA on tumor size and radioiodine uptake in patients with radioiodine-refractory PDTC. One PTC patient had prolonged stable disease beyond 1 year, but no objective responses were identified in any tumor type.

5. **Azacytidine and decitabine** → A broad array of tumor suppressor genes is hypermethylated in PTC and FTC leading to their decreased expression, including *PTEN*, tissue inhibitor of metalloproteinase-3, and death-associated protein kinase . A phase II trial of 5-azacytidine monotherapy to restore radioiodine uptake was initiated, but results were never reported. Given the greater potency and tolerance of the azacytidine derivative decitabine, a phase II trial of this latter agent has been underway, evaluating the ability to restore radioiodine uptake in radioiodine-non-avid metastases; results of this multicenter trial are expected shortly.

6. Medullary thyroid carcinoma (MTC)

6.1 Epidemiology

MTC arises from C cells o parafollicular cells which produce and secrete Calcitonin (Ct) . MTC represents about 5-10% of all thyroid cancers and 13.4% of all thyroid-related deaths. Survival rates for MTC are impacted by age of diagnosis and stage of disease

6.2 Secretory products

Several biochemical features typical of normal C cells (production of Ct) are retained by neoplastic C cells and represent specific and sensitive diagnostic markers. Ct is a small peptide (32 amino acids) coded by a gene located on the short arm of chromosome 11, the gene codes a second peptide called CT-gene-related peptide (CGRP). Carcinoembryonic antigen (CEA) is produced by neoplastic C cells. There is no close relationship between serum concentrations of CEA and CT. Serum CEA concentration is normal in patients with preclinical MTC and does not increase after pentagastrin stimulation. Measurement of serum CEA concentration is useful during follow-up because high concentrations or rapidly increasing concentrations indicate disease progression.

6.3 Clinical presentation

MTC is mainly in sporadic form, but an hereditary pattern is present in 20–30% of cases, transmitted as an autosomal-dominant trait (Schlumberger & Pacini, 2006).The hereditary form is also referred to as 'multiple endocrine neoplasia type 2' (MEN 2), characterized by MTC in combination with pheochromocytoma and hyperparathyroidism (MEN 2A), or MTC in combination with pheochromocytoma, multiple mucosal neuromas and marfanoid habitus (MEN 2B). The occurrence of familial MTC (FMTC) in the absence of other neoplasias is also possible.

6.3.1 Sporadic MTC

Patients with sporadic MTC usually present with a palpable thyroid nodule indistinguishable from any other thyroid nodule. Clinical neck lymph node metastases are detected in at least 50% of patients and may reveal the disease. Metastases outside the neck, in liver, lungs or

bones, are initially present in 10–20% of cases. Flushing and diarrhea might occur in the presence of liver metastasis. FNAC has made it possible to diagnose MTC prior to surgery. However, cytology may be misleading and, in case of doubt, positive immunocytochemical staining for Ct, Ct measurement in the washout fluid of FNAC or both (Kudo et al., 2007) will confirm the diagnosis. Patients with clinical MTC have elevated basal circulating Ct concentrations. Whenever MTC is suspected, staging and careful clinical screening for pheochromocytoma and hyperparathyroidism should be carried out before surgery.

6.3.2 Hereditary MTC

1. **Multiple Endocrine Neoplasia Type 2A (MEN2A):** MEN 2A is a syndrome characterized by MTC, pheochromocytoma and hyperparathyroidism. Clinically MTC develops in about 100% of patients affected by this syndrome. Pheochromocytoma occurs in about 50% of *MEN 2A* patients depending on the type of gene mutation. Hyperparathyroidism occurs in 10–25% of known *MEN 2A* gene carriers with a mutation in codon 634, usually after the third decade of life (Leboulleux et al., 2002). Clinical MTC is rarely observed under 10 years of age; prevalence increases with age, and is 25% at 13 years and about 70% at 70 years. The pentagastrin stimulation test is positive in about 20% of gene carriers at 10 years of age; this increases with age to 50% at 13 years, 65% at 20 years and 95% at 30 years. At present, genetic testing is carried out before 5 years of age in all subjects at risk to establish which individuals are gene carriers. Pheochromocytomas are located in an adrenal gland, and very few cases have been observed in the retroperitoneal region. It is bilateral in 50% of cases, but often after an interval of several years. Pheochromocytoma is almost always benign. Hyperparathyroidism consists of parathyroid hyperplasia, with one or more adenomas in older patients, develops slowly and is usually mild. Clinical and biochemical features do not differ from those seen in sporadic hyperparathyroidism.Cutaneous lichen amyloidosis is a pruritic and hyperpigmented lesion of the skin on the upper portion of the back has been observed in some families with MEN 2A. This lesion may occur early in life and often precedes C-cell disease. Hirschsprung's disease has been observed in a few families with MEN 2A. Patient with multiple endocrine neoplasia type 2A with lichen cutaneous amyloidosis over the interscapular area. The patient reported intense pruritus in this area since 3 years of age.
2. **Multiple Endocrine Neoplasia Type 2B (MEN2B):** MEN2B is a syndrome with MTC, pheochromocytoma, ganglioneuromatosis, marfanoid features and skeletal abnormalities. MTC associated with MEN 2B is the most aggressive form of MTC and occurs early in life, usually before the age of 5 years. It is frequently associated with extension beyond the thyroid capsule, with lymph node and distant metastases at the time of diagnosis. Pheochromocytomas are identified in about one-half of the individuals presenting with the syndrome. Mucosal neuromas are a typical feature of MEN 2B. They occur on the distal portion of the tongue, on the lips, throughout the intestinal tract and eventually in the urinary tract. These patients also have chronic constipation and colonic cramping due to the presence of megacolon disorder. Hypertrophy of corneal nerves is frequent and is evaluated by slit lamp ophthalmic examination. Marfanoid features include long, thin extremities, an altered upper-to-lower body ratio and ligament hyperlaxity. Skeletal abnormalities are frequent, including slipped femoral epiphysis and pectus excavatum.

3. **Familial Medullary Thyroid Carcinoma (FMTC):** FMTC have only hereditary MTC. Clinical presentation of MTC at a later age, 60-70 years old, and a relatively more favourable prognosis respect the others hereditary forms. It is still debated whether FMTC represents a separate syndrome or a variant of MEN 2A in which the genetic component is modified to delay the onset of the array of manifestations typifying the MEN 2A syndrome.

6.4 Genetic alterations

6.4.1 Germline mutations

The predisposing gene for inherited MTC was the RET proto-oncogene localized to centromeric chromosome 10 , identified by genetic linkage analysis in 1987, and germline mutations of were demonstrated in 1993 in MEN 2A, FMTC and MEN 2B. The RET gene is a 21-exon gene that encodes a tyrosine kinase receptor. This membrane-associated receptor is characterised by a cadherin-like region in the extracellular domain, a cysteine-rich region immediately external to the membrane, and an intracellular tyrosine kinase domain. Hereditary MTC is caused by germline autosomal-dominant gain-of-function mutations in the RET proto-oncogene. About 98% of patients with MEN 2 have germline mutations in exons 5, 8, 10, 11, 13, 14, 15 or 16 of the RET gene. Mutations causing MEN 2A affect the cysteine-rich extracellular domain with substitution of a cysteine to another amino acid in exon 10 and, and more commonly (80%), in exon 11. In about 95% of patients with MEN 2B, a single mutation converting methionine to threonine in codon 918 of exon 16 has been identified. It is frequently (>50%) a de-novo mutation in the allele inherited from the patient's father. Other rare intracellular mutations associated with MEN 2B involve exon 15. Rare patients with MEN 2B phenotype have double *RET* mutations. Germline mutations induce different tirosin-kinasi activity. Strong activation of the *RET* proto-oncogene is associated with a more aggressive form of MTC, and mutations providing weaker *RET* activation result in a less aggressive and late-onset form of the disease. On the basis of these findings, the American Thyroid Association (ATA) has recently developed an MTC risk stratification based on genotype (Kloos et al., 2009) (Table 4.)

1. Level D mutations carry the highest risk for MTC. These mutations include codons 883 and 918, and are associated with the youngest age of onset and highest risk of metastases and disease-specific mortality.
2. Level C mutations carry a lower, yet still high, risk of aggressive MTC, and include mutations in codon 634.
3. Level B mutations carry a lower risk for aggressive MTC mutations, and include mutations at *RET* codons 609, 611, 618, 620 and 630.
4. Level A mutations carry the 'least high' risk, and include *RET* gene mutations in codons 768, 790, 791, 804 and 891. This system may be used to individualise the aggressiveness of treatment.

6.4.2 Somatic mutations

Somatic mutations in codon 918 of the *RET* proto-oncogene have been identified in 25–33% of sporadic MTC, and may be associated with a poor outcome compared with sporadic tumours without *RET* mutation (Elisei et al., 2008). Mutations in codons 618, 634, 768, 804 and 883 and partial deletion of the *RET* gene have been identified in a few tumours

Exon	Mutation	Phenotype	ATA risk level*
5	G321R	FMTC/MEN 2A	A
8	C515S	FMTC/MEN 2A	A
	G533C	FMTC/MEN 2A	A
	532 duplication	FMTC	A
	531/9 base pair duplication	FMTC/MEN 2A	A
10	R600Q	FMTC/MEN 2A	A
	K603E	FMTC/MEN 2A	A
	Y606C	FMTC	A
	C609F/R/G/S/Y	FMTC/MEN 2A	B
	C611R/G/F/S/W/Y	FMTC/MEN 2A	B
	C618R/G/F/S/Y	FMTC/MEN 2A	B
	C620R/G/F/S/W/Y	FMTC/MEN 2A	B
11	C630R/F/S/Y	FMTC/MEN 2A	B
	D631Y	FMTC	B
	633/9 base pair duplication	FMTC/MEN 2A	B
	634/12 base pair duplication	FMTC/MEN 2A	B
	C634R	FMTC/MEN 2A	C
	C634G/F/S/W/Y	FMTC/MEN 2A	C
	635/insertion ELCR; T636P	FMTC/MEN 2A	A
	S649L	FMTC/MEN 2A	A
	K666E	FMTC/MEN 2A	A
13	E768D	FMTC/MEN 2A	A
	N776S	FMTC/MEN 2A	A
	L790F	FMTC/MEN 2A	A
	Y791F	FMTC/MEN 2A	A
14	V804L	FMTC/MEN 2A	A
	V804M	FMTC/MEN 2A	A
	V804M+E805K	MEN 2B	D
	V804M+Y806C	MEN 2B	D
	G819K	FMTC	A
	R833C	FMTC	A
	R844Q	FMTC	A
15	R866W	FMTC/MEN 2A	A
	A883F	MEN 2B	D
	S891A	FMTC/MEN 2A	A
16	R912P	FMTC/MEN 2A	A
	M918T	MEN 2B	D
13/14	V804M+V778I	FMTC/MEN 2A	B
14/15	V804M+S904C	MEN 2B/MEN 2A	D

Table 4. MTC risk stratification based on genotype by American Thyroid Association (ATA)

6.5 Therapeutic approach

6.5.1 Initial treatment

Before surgery, all patients with suspicious MTC should undergo a staging work-up. The goal of pre-operative evaluation is to define the extent of disease and to identify the comorbid conditions of hyperparathyroidism, pheochromocytoma or both in the case of hereditary forms. The pre-operative biochemical evaluation should include basal serum Ct, CEA, calcium and 24-h urine collection for metanephrines and normetanephrines determination. Pre-operative imaging, including neck US, should be carried out in all patients; pre-operative chest and neck computed tomography. The primary treatment of both hereditary and sporadic forms of MTC is total thyroidectomy and removal of all neoplastic tissue present in the neck. Several studies have shown that survival in patients with MTC is dependent upon the adequacy of the initial surgical procedure. Multicentric and bilateral MTC is observed in 30% of sporadic cases and in nearly 100% of hereditary cases. The therapeutic option for lymph node surgery should be dictated by the results of presurgical evaluation. Patients with no clinical or imaging evidence of lymph node metastases should undergo prophylactic central compartment (level VI) neck dissection. This strategy will probably include about 30–40% of patients with MTC. In the remaining patients lymph node involvement are documented before surgery. Lymph node metastases may occur in 20–30% of cases with tumours <1 cm in diameter, in 50% of patients with a tumour 1–4 cm in diameter, and in up to 90% in patients with a tumour >4 cm or with a T4 tumour.

6.5.2 Postoperative management

After total thyroidectomy, replacement thyroxine treatment is given to maintain the serum TSH value into the normal range. Measurement of the serum marker Ct and CEA is of paramount importance in the postsurgical follow-up of patients with MTC because this reflects the presence of persistent or recurrent disease. The half-life of serum Ct is reported to be about 30 h. An undetectable basal serum Ct level after surgery is a strong predictor of complete remission. Complete remission may be further confirmed if the serum Ct level remains undetectable after a provocative (pentagastrin or calcium) test. In this situation, no other diagnostic test is indicated. Serum Ct should be repeated every 6 months for the first 2–3 years and annually thereafter. Patients with biochemical remission after initial treatment have only a 3% chance of recurrence during long-term follow-up. On the contrary, if basal serum Ct is detectable or becomes detectable after stimulation, the patient is not cured. Radiological imagines comprise neck US, because frequently recurrence are in locoregional lymph nodes, FNAC with Ct measurement in the washout fluid should typically be carried out to confirm the diagnosis when US demonstrates suspicious lymph nodes enlargement. Chest CT, abdominal MRI, bone scintigraphy, 18 Fluorodeoxyglucose (FDG) positron emission tomography (PET) and 18-F-dihydroxyphenylalanine (DOPA) PET when there is suspicious of diffuse metastasis. These imaging techniques will be positive when Ct levels are high >150 pg/ml. In patients with serum CT <150 pg/ml, clinical evaluation of disease should be limited to neck US and a careful every 6 months follow up with Ct and CEA determinations (Laure Giraudet et al., 2008). Patients with detectable basal serum Ct and no evidence of disease, long-term surveillance is indicated. Pain by bone metastases rapidly improvements with local RT

and it can also be useful for brain metastases. In patients with predominant liver involvement, embolisation or chemo-embolisation proved to be efficient for some symptomatic benefit and for partial reduction in tumour mass (Fromigué et al., 2006).

6.5.3 Novel chemotherapy

Traditional chemotherapy is inefficient in metastatic MTC. New strategies to treat metastates of MTC are being evaluated and include radio-immunotherapy and vaccine-based therapies (Kraeber-Bodere et al., 2009). Improved understanding of MTC molecular oncogenesis has resulted in identification of novel molecular targets for treatment, and there has been recent focus on the use of compounds inhibiting receptors of intracellular kinases. These new therapies primarily target RET oncogene and angiogenesis and have entered clinical trials for metastatic MTC. Partial response rates of up to 30% have been reported in single-agent studies, but prolonged disease stabilization is seen more commonly. The most successful agents target the vascular endothelial growth factor receptors (VEGFRs), with focus on tyrosine kinase inhibitors; these compounds include motesanib diphosphate, vandetanib, sorafenib, and sunitinib (Sherman et al., 2009). In a phase I trial, (Kurzrock et al., 2010) treated patients with metastatic MTC with XL184, an oral inhibitor of MET, VEGFR2, and RET that exhibits anti-angiogenic, antiproliferative, and anti-invasive effects. A phase III trial, comparing XL184 with placebo, is now underway. Wells et al. (Wells et al., 2010) describe an open-label, phase III study that assessed the efficacy of vandetanib, a selective inhibitor of RET, VEGFR, and epidermal growth factor receptor. A total of 30 patients with unresectable locally advanced or metastatic hereditary MTC were enrolled. By response evaluation criteria in solid tumors (RECIST), 20% of patients experienced a confirmed partial response and an additional 53% of patients experienced stable disease at 24 weeks; this yielded a disease control rate of 73%. In addition, vandetanib had a tolerable adverse event profile, as well as significant progression-free survival prolongation when compared to placebo.

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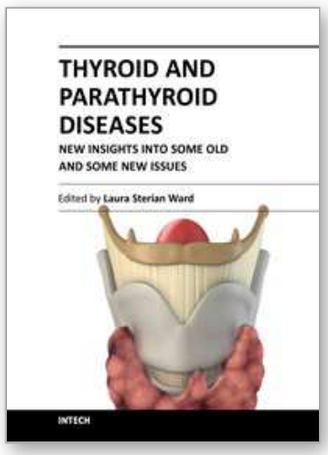

Thyroid and Parathyroid Diseases - New Insights into Some Old and Some New Issues

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