Suspected Malignancy and Malignant Thyroid Tumors

4

Nunzia Cinzia Paladino, David Taïeb, and Frédéric Sebag

4.1 Introduction

Thyroid cancer (TC) is the most common endocrine tumor, with an annual incidence of 3.4% of all cancers [1]. Recent years have seen an increase in the incidence of TC, which has been shown to be three times higher in women than in men, according to the 2012 European network of cancer registries. Data are variable from country to country with higher incidence rates in Lithuania (15.5 cases per 100,000 person-years), Italy (13.5) Croatia (11.4) and Luxembourg (11.1). However, mortality remains low: 0.7 and 0.5 cases per 100,000 person-years for women and men, respectively [2, 3]. The increase in incidence would appear to be related to improved diagnostic techniques in recent years that allow diagnosis of even small and subclinical cancers [2]. There was also found to be a smaller but consistent increase in thyroid cancers of larger size. Autopsy studies have demonstrated a high incidence of subclinical thyroid cancer, particularly small papillary thyroid cancers [4].

The challenge for physicians is to identify patients with advanced or high-risk disease and those with lower risk in such a way as to perform appropriate treatment for each case.

The surgical strategy must take into account that the clinical behavior of thyroid cancers varies from indolent tumors with low mortality to very aggressive malignancies [5].

N. C. Paladino (✉) · F. Sebag
Department of General Endocrine and Metabolic Surgery,
Conception University Hospital, Aix-Marseille University, Marseille, France
e-mail: nunzia.paladino@ap-hm.fr; frederic.sebag@ap-hm.fr

D. Taïeb
Department of Nuclear Medicine, La Timone University Hospital, Aix-Marseille University,
Marseille, France
e-mail: david.taieb@ap-hm.fr

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Differentiated thyroid cancer has a good prognosis and long-term survival [5]. However, follicular thyroid cancer, Hürthle cell thyroid cancer, and poorly differentiated thyroid cancers are high-risk with a tendency for hematogenous spread to distant sites, in particular to lung and bones [5].

The last decade has seen many advances in understanding the molecular basis of thyroid cancer [6].

Most thyroid cancers have mutations along the mitogen-activated protein kinase (MAPK) cellular signaling pathway that plays a central role in the regulation of cellular proliferation [5]. An accurate diagnostic strategy and referral to specialized centers are critical for the proper management of thyroid malignancies.

4.2 Suspected Malignancy

Thyroid nodules are common in clinical practice, so it is important to distinguish benign nodules from nodules suspicious for malignancy.

The first step is the clinical examination, which will distinguish a parenchymatous nodule from a firm one. If cancer is suspected, the patient must undergo a diagnostic-imaging workup.

The first-level imaging examination to be performed is ultrasonography. Ultrasonographic scoring systems are helpful in differentiating between benign and malignant thyroid nodules by offering a risk stratification model. Depending on the number of suspicious ultrasound features, a fine-needle biopsy is recommended [7, 8].

Over the years different classifications have been proposed.

Thyroid nodule risk stratification systems – called Thyroid Imaging Reporting and Data Systems (TIRADS), the first of which was proposed in 2009 by Horvath [9] – have been developed with the aim of:

- establishing a standard lexicon for nodule description and providing a standardized report;
- defining the suspicious characteristics;
- placing the nodule in a risk category;
- identifying nodules for which a fine-needle aspiration biopsy (FNAB) is indicated, also taking into account their size [10];
- helping define the surgical strategy.

In 2017 the executive committee of the European Thyroid Association set up a working group to create a standardized risk stratification system, called the EU-TIRADS score, now commonly used in expert centers. This system has five evaluation categories: from no thyroid nodules to benign, low risk, intermediate risk, and high risk. The nodule is thus assigned a number from 1 to 5 that reflects an increasing risk of malignancy [11].

In this context, EU-TIRADS 5 is considered a high-risk category with an incidence of malignancy of 26–87% [10, 11] and FNAB is indicated for nodules >10 mm in size. FNAB is also indicated in the presence of EU-TIRADS 5 nodules <10 mm but in progression, depending on risk context (case of irradiation, familiarity for cancer, or hypermetabolic nodule on PET scan), and in the search for a primary thyroid cancer.

With regard to risk classification in cytology, several classifications have been drafted to arrive at an evidence-based approach. The most widely used international classification is the Bethesda system that was originally developed in October 2007 in Bethesda, Maryland [12].

Knowledge of the Bethesda system is essential for clinical practice because cytology, besides giving a stratification of the risk of malignancy, defines the surgical indication and the extension of the surgery. The Bethesda system provides six different categories, with a precise definition of cytologic appearance and a malignancy risk range for each category.

Since its first publication in 2009, the Bethesda classification has been updated in 2010 and 2017. Major changes include the definition of NIFTP (noninvasive follicular thyroid neoplasm with papillary-like nuclear features) and recalculation of the expected risk of malignancy based on the exclusion of NIFTP from the diagnosis of malignancy, followed by the introduction of molecular biology as an aid to diagnosis and treatment decision [12].

According to the Bethesda system, Bethesda 6 is an at-risk category with a cancer incidence of 97–99%. This category includes all criteria for malignancy. The type of tumor should be mentioned: papillary, medullary, poorly differentiated, anaplastic, lymphoma, or metastasis.

Another category with suspected malignancy is Bethesda 5 with a cancer risk of 45–60% (after NIFTP).

It is important not to underestimate doubtful cytology, which includes Bethesda 3 and 4 categories.

Bethesda 4 designated as “follicular neoplasm and follicular oncocytic cell neoplasm” has a calculated risk of malignancy between 25% and 40% (10–40% post-NIFTP). In this category we can also find vesicular carcinoma (whose cytological diagnosis is impossible).

Finally, the Bethesda 3 category, known as “atypia of undetermined significance or follicular lesion of undetermined significance”, presents a cancer risk of 10–30% in the latest 2017 Bethesda classification (recalculated to 6–18% post-NIFTP). This is a controversial category because the cytologic abnormalities present cannot assure benignity but are insufficient to lead to surgical excision [13].

An ultrasound scan performed by an experienced radiologist, with nodule characterization according to the EU-TIRADS classification is essential to distinguish suspicious nodules to be referred for FNAB from benign nodules to be monitored.

Ultrasonography will also confirm the presence of suspected lymphadenopathy and the affected cervical compartments, thereby directing the surgical strategy.

4.3 Malignant Thyroid Tumors

Malignant tumors of the thyroid gland are divided into three main histological types (Table 4.1):

- differentiated thyroid cancer;
- undifferentiated: poorly differentiated and anaplastic thyroid cancer;
- medullary thyroid cancer.

Differentiated thyroid cancer is the most common cancer. It accounts for 90% of thyroid malignancies and includes:

– papillary thyroid cancer;
– follicular thyroid cancer;
Hürthle cell thyroid cancer [1, 5].

Undifferentiated cancers are rare and include:

– poorly differentiated thyroid cancer (incidence of 5% median survival time of 5 years);
– anaplastic thyroid cancer (1% of incidence and survival of 6 months).

Medullary thyroid cancer accounts for 5% [1].

Table 4.1 Classification of malignant thyroid tumors

Differentiated thyroid cancer	Papillary thyroid cancer	• Classic • Follicular • Diffuse sclerosing • Tall cell • Columnar • Solid variant • Hobnail	
	NIFTP[a]		
	Follicular thyroid cancer	• Minimally invasive • Encapsulated angioinvasive • Widely invasive	
	Hürtle cell thyroid cancer	• Microfollicular • Solid • Trabecular	• Minimally invasive • Encapsulated angioinvasive • Widely invasive
Undifferentiated thyroid cancer	Poorly differentiated thyroid cancer	• Solid • Trabecular • Insular	
	Anaplastic thyroid cancer		
Medullary thyroid cancer			

[a] *NIFTP* Noninvasive follicular thyroid neoplasm with papillary-like nuclear features [1]

The molecular pathogenesis of most TC involves dysregulation of MAPK and PI3K/AKT (phosphatidylinositol-3 kinase). MAPK activation is crucial for the onset of papillary thyroid cancer through point mutations of the *BRAF* and *RAS* genes. *TERT* promoter mutations have been described in all histological TC types with a significant prevalence in aggressive and undifferentiated cancers. *RET* mutations occur in most medullary thyroid cancers. *H-*, *K-*, and *N-RAS* mutations are responsible for a minority of sporadic medullary thyroid cancers [1].

The most frequent form of TC is papillary thyroid cancer.

4.4 Papillary Thyroid Cancer

Papillary thyroid cancer (PTC) is the most common and indolent TC with the best overall prognosis (90% of survival) in its classical and follicular variants [5, 14]. Metastases most commonly involve cervical lymph nodes and, less commonly, the lungs [5].

PTC has a relatively stable genome and that would explain the indolent trend of this cancer.

However, recurrent disease occurs in 25–35% of patients. In this rare case, the tumors are aggressive but nevertheless maintain some degree of functional differentiation (e.g., thyroglobulin production) [2]. Hence the importance of the early identification of patients in need of aggressive treatment [1].

The subtypes that occur as more aggressive variants include the following: diffuse sclerosing variant, tall cell variant, columnar cell variant, solid variant, and hobnail variant [2, 14, 15].

Several mutations have been associated with PTC malignancy. *RET* rearrangements or point mutations of *RAS* or *BRAF* proto-oncogenes have been described in 70% of patients. Based on a *BRAFV600E-RAS* gene expression score, PTC can be divided into *BRAFV600E*-like and *RAS*-like PTC [1]. A propensity for clinically aggressive PTC has been found in tumors bearing a *BRAF* mutation. However, despite about 50–70% of PTC having a *BRAF* mutation, most of these tumors remain indolent. This finding suggests that other events are involved in the development of more aggressive behavior. *TERT* mutation has been detected in more aggressive PTC [5].

Among the variants of PTC, NIFTP represents a novel entity with a genomic profile more similar to follicular thyroid cancer than PTC [1]. The estimated risk of recurrence of NIFTP is <1% [16].

According to a recent study by Brandler et al. [17], 67% of NIFTP had *RAS* mutations alone or in tandem with other mutations and *BRAF* mutation was not described; 22% of NIFTP had *PAX8/PPARG* and *THADA/IGF2BP3* gene fusion mutations. As a result, this overlap makes it difficult to identify NIFTP with FNAB.

4.5 Follicular Thyroid Cancer

In 2017, follicular thyroid cancer (FTC) was reclassified into the following subtypes:

– minimally invasive (miFTC)
– encapsulated angioinvasive (eaFTC)
– widely invasive (wiFTC).

The progression from miFTC to wiFTC is still not clear [1]. The most common mutation involves the *RAS* family genes and a recent study found no negative effect on prognosis [18]. The fusion gene *PAX8-PPARγ* was identified in 12–53% of cancers. *TERT* promoter mutations have been found in 15% of FTC. The presence of all mutations has a worse prognostic effect [1].

4.6 Hürthle Cell Thyroid Cancer

Hürthle-cell cancer (HCC) are noninvasive, encapsulated tumors composed of Hürthle cells with microfollicular or solid to trabecular architecture. HCC have overlapping but distinct clinical features from FTC [19, 20].

They are rare and demonstrate either capsular or vascular invasion. Prognosis is worse in patients with angioinvasion than in those with capsular invasion. According to the College of American Pathologists, HCC is divided into minimally invasive, encapsulated angioinvasive and widely invasive. Like FTC, HCC has high rates of distant metastasis due to its hematogenous spread. HCC exhibits *RAS* mutations in only 10–15% of cases and does not show *PAX8-PPARγ* rearrangements and *BRAFV600E* mutation [19].

4.7 Poorly Differentiated Thyroid Cancer

Poorly differentiated thyroid cancer (PDTC) is a more aggressive follicular-derived thyroid cancer than differentiated thyroid cancer [5]. Two main classifications of PDTC exist, depending on the histological features: the Turin criteria and the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria.

The Turin criteria include a solid, trabecular or insular growth pattern in the absence of the conventional nuclear features of PTC and at least one of the following:

- convoluted nuclei;
- high mitotic rate;
- tumor necrosis.

The MSKCC criteria include a high mitotic rate and necrosis independently from the growth pattern.

BRAF mutations are described in 19–33% and *H-*, *K-*, and *N-RAS* mutations in 5–28% of PDTC.

BRAF and *RAS* are correlated with a different clinical behavior.

PDTC with *BRAF* mutation are associated with a higher rate of lymph node metastases compared with *RAS*-mutated PDTC, which have a higher rate of distant metastases. There is also a lowered expression of thyroid-specific genes related to radioiodine avidity in *BRAF*-mutated PDTC compared to *RAS*-mutated PDTC. These mutations can be associated with that of the *TERT* promoter that affects 33–40% of cases and is associated with a risk of distant metastasis and mortality. Another important difference with PTC is the chromosome number variation [21]. Identification of these mutations is decisive for choosing the type of treatment.

4.8 Anaplastic Thyroid Cancer

Anaplastic thyroid cancer (ATC) is a rare cancer with an incidence <1% that presents clinically as a rapidly evolving cervical mass [5]. In order to determine the therapeutic strategy, rapid patient care and biopsy of the neoplastic mass are indicated.

Distant metastases most commonly involve the lung followed by bones and brain. ATC originates from a differentiated tumor but can also occur ex novo [5]. The median survival is about 5 months and the 1-year overall survival is 20%; because of this, all patients with ATC are classified as stage IV according to the TNM system. Radiological tumor staging with computed tomography (CT) of the neck, chest, abdomen and pelvis, fluorodeoxyglucose positron emission tomography (FDG-PET)/CT, cerebral CT or magnetic resonance imaging (MRI) are necessary in order to establish patient care. It is important to assess the presence of vocal cord paralysis. Goals of care may be therapeutic and/or palliative depending on the stage and prognosis [22]. Each case should be analyzed and discussed in a specialized team.

In ATC the incidence of *BRAF* and *H-*, *K-* and *N-RAS* mutations is 19–45% and 9.5–27%, respectively. The two most frequent mutations are: *TERT* promoter mutation (43–73%) and *TP53* mutation (48–73%) [1, 21]. *PT53* is highly frequent and is considered pathognomonic for this aggressive cancer. *PTEN*, *PI3KCA* mutations and mutations in genes involved in cell-cycle regulation and in the chromatin remodeling complex were also found [21]. Identification of such mutations is critical for the development of chemotherapy treatment.

4.9 Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) accounts for 1–2% of all thyroid cancers and it originates from parafollicular cells (C-cells) that produce calcitonin. Sometimes neck lymphadenopathy is the first manifestation and 70% of patients that present palpable MTC have cervical node metastases at surgery [5, 23].

The markers commonly used for the diagnosis are calcitonin and carcinoembryonic antigen that are also used for the follow-up. Before surgery it is essential to perform detailed neck ultrasound on lymph node stations, and genetic screening [5]. In the presence of very high markers (calcitonin >146 pmol/L) [5], a total body exploration with CT, MRI of the pelvis, spine, and liver and ^{18}F-DOPA PET/CT is recommended [23, 24].

MTC can be sporadic (75–80%) and familial (20–25%) linked to a rearrangement *RET* mutation [23, 25]. However, the proto-oncogene *RET* has a crucial role in both cases. All familial cases have a germline *RET* mutation (>98%) [25]. *RET* mutations can occur sporadically as somatic events or as inherited germline events that exhibit autosomal dominant inheritance. Because 1–7% of patients with sporadic MTC had a *RET* germline mutation, genetic screening should be recommended to all patients with a diagnosis of MTC [5]. In sporadic MTC, *RET* mutation is the most common genetic variant and occurs in 44% of cases, followed by *RAS* mutations (13% of cases) [26]. Recent studies showed that patients with *RET* mutations have a lower survival than those with *RAS* mutations [1, 27].

Germline mutations in *RET* can predispose patients to the early development of MTC as in multiple endocrine neoplasia type 2A and 2B syndromes (MEN 2A and MEN2B). Prophylactic thyroidectomy is often indicated. In cases of MEN, associated endocrinopathies will need to be investigated [5].

Surgery is the only curative treatment in MTC and it should be complete since recurrence reflects the likely incompleteness of the initial surgery. The surgical strategy should always take into account that preoperative imaging often does not identify central compartment micrometastases [23].

According to a recent study [24], an important role in this context is played by ^{18}F-DOPA PET/CT whose sensitivity in identifying locoregional and distant metastases was shown to be 75.6%; the authors emphasize that ^{18}F-DOPA PET/CT is sensitive in the early diagnosis of a significant number of patients with distant metastases although its sensitivity in the detection of residual disease was limited.

Total thyroidectomy with central neck dissection is therefore recommended for patients with MTC, and incomplete interventions, such as removing only grossly involved nodes at initial surgery, should be avoided [5, 23]. Lymphadenectomy of the lateral compartments should be discussed depending on calcitonin rates and preoperative imaging from case to case.

Follow-up is lifelong and consists of surveillance of tumor markers and rapid identification of recurrences. Calcitonin and carcinoembryonic antigen doubling times are useful measures, as they are predictive of aggressive tumor behavior [5].

4.10 Treatment

Treatment decisions rely on a preoperative risk assessment that includes clinical, imaging and cytological data. The therapeutic choice depends on location and extension of the cancer. According to the American Thyroid Association 2015 guidelines, the therapeutic approach is more conservative than in the past.

Surgery is only curative treatment for resectable cancer and for MTC. After surgery, risk can be defined based on histological examination, and it can be determined whether to perform radioiodine ablation or TSH suppression, or both. This assessment is conventionally based on the TNM staging system which, however, was conceived to predict mortality and is less effective for estimating the probability of persistent or recurrent disease [5]. The need to estimate the risk of recurrence led to the introduction, in 2009, of a new system for risk stratification into high, intermediate and low [28].

The revised system of the American Thyroid Association 2015 guidelines provides more accurate information about the risk of recurrence [13].

Radioactive iodine treatment after total thyroidectomy is often performed with the aim of eliminating residual thyroid tissue and it can also be used in metastatic disease.

TSH-suppressive doses of thyroid hormone therapy are commonly used after surgery to reduce the risk of recurrence. Patients with differentiated thyroid cancer require follow-up including serum thyroglobulin assay. This follow-up is important since 77% of patients have a recurrence within 5 years after the first surgery.

Systemic treatment is reserved for cases of differentiated cancer with radioactive iodine-refractory disease. Metastasectomy can be taken into consideration for low-volume metastatic disease if it will delay or prevent morbidity.

Two kinase inhibitors have been approved for use in advanced-stage differentiated thyroid cancer: sorafenib and lenvatinib. These are multikinase inhibitors with antiangiogenic properties.

Treatment of anaplastic cancer should be prompt and provided by an experienced center.

The surgeon should determine whether the tumor is resectable. Biopsy is often indicated in order to define the histological profile of the tumor and to institute chemotherapy treatment.

External beam radiation is recommended soon after resection, preferably with radiosensitizing drugs. Palliative chemoradiation is reserved for patients with unresectable tumors [5, 13].

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