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Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Pacini[1], M. G. Castagna[1], L. Brilli[1] & G. Pentheroudakis[2], on behalf of the ESMO Guidelines Working Group*

[1]*Department of Internal Medicine, Endocrinology and Metabolism and Biochemistry, Section of Endocrinology and Metabolism, University of Siena, Sienna, Italy;*
[2]*Department of Medical Oncology, Medical School, University of Ioannina, Ioannina, Greece*

incidence and epidemiology

Thyroid cancer is the most common of the endocrine malignancies and it represents <1% of all human tumors. The annual incidence of thyroid cancer varies considerably by geographic area, age and sex.

A recent review reported an overall incidence of all types of thyroid cancer in the USA of 7.7 per 100 000 person-years, with rates of 11.3 per 100 000 woman-years and 4.1 per 100 000 man-years [1]. The incidence of papillary thyroid cancer is 5.7 per 100 000 person-years, with rates of 8.8 per 100 000 woman-years and 2.7 per 100 000 man-years [1]. Among women, papillary thyroid cancer incidence rates are higher among Asians (10.96 per 100 000 woman-years) and lower among blacks (4.9 per 100 000 woman-years). Among men, papillary thyroid cancer incidence rates are higher among whites (3.58 per 100 000 woman-years) and lower among blacks (1.56 per 100 000 woman-years) [1]. The incidence of follicular thyroid cancer in the USA is 0.82 per 100 000 person-years, with rates of 1.06 per 100 000 woman-years and 0.59 per 100 000 man-years. The incidence of follicular cancer does not vary substantially by race/ethnicity [1]. The incidence rates of medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC) are 0.11 and 0.21 per 100 000 person-years with no noted substantial differences by race/ethnicity and sex, respectively.

An escalating incidence during the last decades all over the globe has been reported [2]. This phenomenon is mainly due to an increase in micropapillary (<2 cm) histotype, while there is no substantial change in the incidence of the less common histological categories: follicular, medullary and anaplastic cancers. The increase is attributable to better detection of small papillary carcinomas as a result of improved diagnostic accuracy (neck ultrasound, US and fine needle aspiration cytology, FNAC). It is common experience in thyroid cancer referral centers that nearly 60%–80% of thyroid carcinomas detected nowadays are micropapillary thyroid carcinomas (<1 cm in size) carrying an excellent long-term prognosis [3]. However, more recently, an increased incidence for all size of thyroid tumor has been reported in the USA. During 1997–2005, the annual percentage change (APC) for primary tumor <1.0 cm was 9.9 in man and 8.6 in women. A substantial increase was also observed for tumor >4 cm among men (1988–2005: APC 3.7) and women (1988–2005: APC 5.7) [4]. These data suggested that increased diagnostic scrutiny is not the only explanation, and environmental influence should also be considered.

The only established environmental risk factor for thyroid carcinoma is exposure to ionizing radiation, and the risk, particularly of papillary carcinoma, is greater in subjects of younger age at exposure. An increased incidence of thyroid cancer in children and adolescents was observed in Ukraine, Belarus and certain regions of Russia as early as 4 years after the Chernobyl accident. The pre-Chernobyl incidence of thyroid cancer in Ukrainian children was very low (0.5–1.0 per 1 000 000 children). Following the explosion of the Chernobyl nuclear reactor in 1986, a dramatic increase in the incidence of benign and malignant thyroid tumors (80 times more) was observed in children born or conceived around the time of the accident in a wide area surrounding the reactor [5].

Despite increasing incidence, the mortality from thyroid cancer has tended to decline over the last three decades. It is unclear how much of the decline in mortality is due to better diagnosis rather than to improved treatment of thyroid neoplasm. The age-adjusted death rate was 0.5 per 100 000 men and women per year, increasing from 0.1% under age 20%–30% in the seventh and the eighth decades [2].

diagnosis

Thyroid cancer presents as a thyroid nodule detected by palpation and more often by neck US. While thyroid nodules are common (4%–50% depending on the diagnostic procedures and patients' age) [6], thyroid cancer is rare (~5% of all thyroid nodules). Thyroid US is a widespread technique that is

Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland; E-mail: clinicalguidelines@esmo.org

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used as a first-line diagnostic procedure for detecting and characterizing nodular thyroid disease (I, A). US features associated with malignancy are hypoechogenicity, microcalcifications, absence of peripheral halo, irregular borders, solid aspect, intranodular blood flow and shape (taller than wide). Each of these patterns taken individually is poorly predictive. When multiple patterns suggestive of malignancy are simultaneously present in a nodule, the specificity of US increases but the sensitivity becomes unacceptably low [7, 8]. Fine needle aspiration cytology (FNAC) is an important technique that is used along with US for the diagnosis of thyroid nodules (III, A). FNAC should be performed in any thyroid nodule >1 cm and in those <1 cm if there is any clinical (history of head and neck irradiation, family history of thyroid cancer, suspicious features at palpation, presence of cervical adenopathy) or ultrasonographic suspicion of malignancy. In the case of multinodular goiter, those with suspicious features at US should be submitted to FNAC. FNAC is a very sensitive tool for the differential diagnosis of benign and malignant nodules although there are limitations: inadequate samples and follicular neoplasia. In the event of inadequate samples, FNAC should be repeated, while in the case of follicular neoplasia, with normal thyroid stimulating hormone (TSH) and 'cold' appearance at thyroid scan, surgery should be considered [7, 8]. The use of various immunohistochemical markers in cytologic samples to differentiate papillary thyroid carcinoma from other follicular-derived lesions of thyroid has been explored during the last years but none of the markers appears to be specific enough to be employed as the diagnostic marker for the cytologic diagnosis of papillary thyroid carcinoma [7, 8]. Recently, it has been reported that by molecular testing for thyroid nodules (BRAF, RAS, RET/PTC and PAX8/PPARγ mutations), the presence of any mutation was a strong indicator of cancer because ∼97% of mutation-positive nodules had malignant diagnosis at histology [9, 10] (III, B). Thyroid function test and thyroglobulin (Tg) measurement are of little help in the diagnosis of thyroid cancer. However, measurement of serum calcitonin computed tomography (CT) is a reliable tool for the diagnosis of the few cases of MTC (5%–7% of all thyroid cancers) and has higher sensitivity compared with FNAC. For this reason, measurement of CT should be an integral part of the diagnostic evaluation of thyroid nodules [7] (IV, B).

differentiated thyroid cancer

surgery

The initial treatment of differentiated thyroid carcinoma (DTC) should always be preceded by careful exploration of the neck by US to assess the status of lymph node chains. The initial treatment of DTC is total or near-total thyroidectomy whenever the diagnosis is made before surgery. Less extensive surgical procedures may be accepted in the case of unifocal DTC diagnosed at final histology after surgery performed for benign thyroid disorders, provided that the tumor is small, intrathyroidal and of a favorable histological type (classical papillary or follicular variant of papillary or minimally invasive follicular) (I, A). In the case of widely invasive follicular cancer at final histology, completion thyroidectomy is indicated. The benefit of prophylactic central node dissection in the absence of evidence of nodal disease is controversial. There is no evidence that it improves recurrence or mortality rate, but it permits an accurate staging of the disease that may guide subsequent treatment and follow-up [7, 8] (IV, C). However, it is not indicated in follicular thyroid cancer; compartment-oriented microdissection of lymph nodes should be performed in cases of preoperatively suspected and/or intraoperatively proven lymph node metastases in follicular thyroid cancer (IV, B). In expert hands, surgical complications such as by laryngeal nerve palsy and hypoparathyroidism are extremely rare (<1%–2%) [7].

staging and risk assessment

Several staging systems have been developed by authoritative centers. Each of these staging systems provides good risk stratification based on data available shortly after initial therapy. The most popular is the American Joint Committee on Cancer/International Union against Cancer TNM staging system based mainly on the extent of tumor and age [11]. Although all staging systems are able to predict high or low risk of cancer mortality, they fail to predict the risk of recurrence. To overcome this limitation, both the American Thyroid Association (ATA) and the European Thyroid Association (ETA) have recently published practical guidelines [7, 8] in which they graded the risk of recurrence in three categories of increasing risk on the basis of tumor-related parameters (pTNM and histological variant) integrated with other clinical features, including the result of the post-ablative whole-body scan (WBS) and serum Tg measurement (Table 1).

Recent reports have developed the new concept of 'Ongoing Risk Stratification' or 'Delayed Risk Stratification (DRS)', which better define the patient risk on the basis of the results of the initial treatment [12, 13]. This concept is based on the continuous integration of the initial risk stratification (at the time of diagnosis) with the clinical, radiologic and laboratory data becoming available during follow-up. Although the risk stratifications proposed by ATA [8] and ETA [7] are a good starting point for initial decision-making, they are less accurate in predicting the long-term outcome in DTC patients. Indeed, both systems have a very low positive predictive value (PPV) because of the fact that a large number of patients (∼60%) classified as intermediate/high-risk are in complete remission at the end of follow-up [13]. This drawback is probably due to the lack of consideration of the effects of the initial therapy. When patients are re-stratified according to the results of the 8–12-month control after initial treatment, a significant number of patients who were initially considered (misleadingly) high-risk were re-classified as low-risk and, most interestingly, almost all of these patients continued to be in apparent remission up to the end of follow-up [13]. This DRS allows modulation of the subsequent follow-up excluding a significant number of intermediate/high-risk patients from unnecessary intensive work-up (IV, C).

Table 1. Risk stratification according to the ETA [7] and ATA guidelines [8]

ATA risk stratification		
Low risk	Intermediate risk	High risk
No local or distant metastases All macroscopic tumor has been resected No tumor invasion of locoregional tissues or structures No aggressive histology or vascular invasion If ^{131}I was given, no ^{131}I uptake outside the thyroid bed on the post-therapeutic WBS	Microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery Cervical lymph node metastases or ^{131}I uptake outside the thyroid bed on the post-therapeutic WBS or Tumor with aggressive histology or vascular invasion	Macroscopic tumor invasion Incomplete tumor resection Distant metastases Thyroglobulinemia out of proportion to what is seen on the post-ablative scan
ETA risk stratification		
Very low risk	Low risk	High risk
Complete surgery Patients with unifocal microcarcinoma (<1 cm) with no extension beyond the thyroid capsule and without lymph node metastases	No local or distant metastases No tumor invasion of locoregional tissues or structures No aggressive histology or vascular invasion	Less than total thyroidectomy Tumor invasion of locoregional tissues or structures Cervical lymph node metastases Distant metastases Aggressive histology or vascular invasion

radioiodine ablative therapy

Surgery is usually followed by the administration of ^{131}I activities aimed at ablating any remnant thyroid tissue and potential microscopic residual tumor. This procedure decreases the risk of locoregional recurrence and facilitates the long-term surveillance based on serum Tg measurement and diagnostic radioiodine WBS. In addition, the high activity of ^{131}I makes it possible to obtain a highly sensitive post-therapeutic WBS. According to several guidelines [7, 8], the recommendations for remnant thyroid ablation are modulated on the basis of risk factors. Radioiodine ablation is indicated in high-risk patients (IV, B), whereas it is not indicated in low-risk patients (IV, D). In patients at intermediate risk radioiodine remnant ablation may be indicated, but the decision must be individualized (Table 2) [7, 8].

Effective thyroid ablation requires adequate stimulation by TSH. The method of choice for preparation to perform a radioiodine ablation is based on the administration of recombinant human TSH (rhTSH), while the patient is on levothyroxine (LT4) therapy (I, A). On the basis of several reports [14–16], the latter procedure is considered the method of choice demonstrating equal efficacy compared with THW but better acceptance from the patients. In addition, in the recent years, it has become increasingly apparent that successful thyroid ablation may be achieved using low activities of ^{131}I (1110–1850 MBq) [15, 16] (I, B).

Recent studies demonstrate that rhTSH-assisted radioiodine ablative therapy is associated with similar rates of persistent disease and clinically evident recurrence compared with those observed after traditional thyroid hormone withholding (THW) preparation, at least during short-term follow-up [17, 18]. In addition, preparation with either rhTSH or THW appears to have similar adjuvant therapy effects on small-volume radioiodine-avid (RAI-avid) disease identified outside the thyroid bed at the time of initial radioiodine remnant ablation [15, 19]. RAI-avid metastatic disease discovered at the time of rhTSH-stimulated remnant ablation was successfully treated in ~70% of locoregional lymph nodes [15, 19] and in ~70% of pulmonary micrometastases [19]. In light of these data, the use of rhTSH for post-thyroidectomy ^{131}I ablation represents a safe and effective option for the postoperative management of patients with thyroid cancer.

Table 2. Indication for remnant ablative therapy [8]

RAI is recommended	RAI is not recommended
All patients with Known distant metastases Documented lymph node metastases Gross extrathyroidal extension of the tumor regardless of tumor size Primary tumor size >2 cm even in the absence of other higher risk features[a]	Patients with unifocal cancer <1 cm without other higher risk features[a] Patients with multifocal cancer when all foci are <1 cm in the absence of other higher risk features[a]

[a]Higher risk features: histological subtypes (tall cell, columnar, insular and solid variant as well as poorly DTC and follicular and Hurthle cell cancer), intrathyroidal vascular invasion, gross or microscopic multifocal disease.

short-term follow-up

The aim of follow-up is the early discovery and treatment of persistent or recurrent locoregional or distant disease. The large majority of local recurrences develop and are detected in the first 5 years after diagnosis. However, in a minority of cases, local or distant recurrence may develop in late follow-up, even 20 years after the initial treatment.

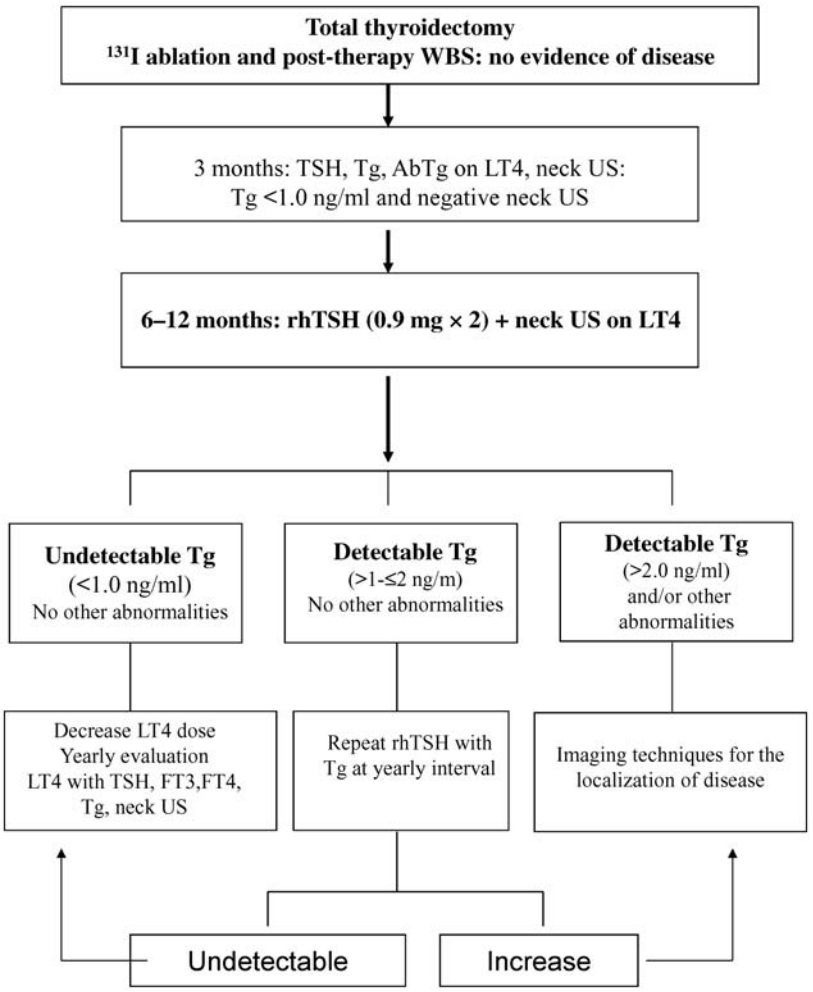

Figure 1 Diagnostic algorithm based on the measurement of both basal and rhTSH-stimulated serum thyroglobulin at the time of the first control post-initial treatment (6–12 months) in patients with differentiated thyroid carcinoma (DTC) [7, 8].

Two to three months after initial treatment, thyroid function tests (FT3, FT4, TSH) should be done to check the adequacy of LT4 suppressive therapy (Figure 1). Follow-up at 6–12 months should ascertain whether or not the patient is free of disease. This follow-up is based on physical examination, neck US, basal and rhTSH-stimulated serum Tg measurement with or without diagnostic WBS [7, 8] (I, A). At this time, most (~80%) of the patients will belong to the low-risk categories and will disclose normal neck US and undetectable (<1.0 ng/ml) stimulated serum Tg in the absence of serum Tg antibodies. Diagnostic WBS does not add any clinical information in this setting and may be omitted. These patients may be considered in complete remission and their rate of subsequent recurrence is very low (<1.0% at 10 years) [7, 8].

Recently, new methods for serum Tg measurement with functional sensitivity below 0.1 ng/ml have become available. Using these assays, some authors have reported that an undetectable basal serum Tg (<0.1 ng/ml) may give the same information as a stimulated serum Tg value, thus avoiding the need for Tg stimulation [20–22] (IV, B). However, the higher negative predictive value (NPV) of these tests is at the expense of a very low specificity and PPV, and the risk is to expose large numbers of patients, probably free of disease, to extensive testing and/or unnecessary treatment. In clinical practice, when basal serum Tg is ≤0.1 ng/ml and neck US is unremarkable, patients may be considered free of disease (NPV = 100%) and can avoid an rhTSH stimulation. On the contrary, when basal serum Tg is >0.1 ng/ml but <1.0 ng/ml, it is not possible to distinguish between the absence or presence of disease. In these cases, rhTSH stimulation testing may still be informative since it may detect those patients in whom serum Tg increases to >1 ng/ml. In these patients, a more intensive follow-up may be useful [21].

long-term follow-up

The subsequent follow-up of patients considered free of disease at the time of their first follow-up will consist of physical examination, basal serum Tg measurement on LT4 therapy and neck US once per year. No other biochemical or morphological tests are indicated unless some new suspicion

arises during evaluation. The question of whether a second rhTSH-stimulated Tg test should be performed in disease-free patients is a matter of debate. Recent studies reported that this procedure has little clinical utility in patients who had no biochemical (undetectable serum Tg) or clinical (imaging) evidence of disease at the time of their first rhTSH-Tg. In this group, the second test confirmed complete remission in almost all patients [20, 23–25]. (IV, B) After initial therapy, ~20% of patients may have detectable basal or stimulated serum Tg levels. If serum Tg is detectable under basal conditions, the chance that the patient has visible disease is very high, and thus imaging techniques must be applied. If serum Tg is detectable in the low range after rhTSH stimulation, the probability of serum Tg changing from detectable to undetectable during follow-up is ~50% [26], and thus observation is all that is required. On the contrary, a trend for serum Tg to increase over time is a hallmark of possible disease to be studied using imaging techniques for the localization of disease and appropriate treatment, including therapeutic doses of ^{131}I [7, 8]. Included in this category are the 5%–10% of DTC patients who presented with local or distant metastases at diagnosis and an additional 5%–10% who develop recurrent disease during follow-up. During the evaluation of metastatic patients, ^{18}fluoro deoxy glucose-positron emission tomography (FDG-PET) scanning should be considered as a diagnostic and prognostic tool [27]. In general, the sensitivity of ^{18}FDG-PET is not superior to that of traditional techniques such as CT and magnetic resonance imaging (MRI), and thus, the main indication for ^{18}FDG-PET is in metastatic patients who have lost radioiodine uptake. ^{131}I-WBS negative and ^{18}FDG-PET positive patients indicate a group of tumors with more aggressive and less differentiated phenotype carrying a worse prognosis with respect to ^{131}I-WBS positive and ^{18}FDG-PET negative patients [27] (IV, C).

treatment of metastatic disease

Treatment of locoregional disease is based on the combination of surgery and radioiodine therapy (IV, B). External beam radiotherapy may be indicated when complete surgical excision is not possible or when there is no significant radioiodine uptake in the tumor [7, 8]. Distant metastases are more successfully cured if they take up radioiodine and are of small size and located in the lungs (not visible at X-rays). Lung macronodules may benefit from radioiodine therapy but the definitive cure rate is very low [28] (IV, B). Bone metastases have the worst prognosis even when aggressively treated by the combination of radioiodine therapy and external beam radiotherapy [7] (IV, B). Brain metastases are relatively rare and usually carry a poor prognosis. Surgical resection and external beam radiotherapy represent the only therapeutic options. Chemotherapy is no longer indicated because of lack of effective results (IV, D) and should be replaced by enrollment of the patients in experimental trials with targeted therapy. Reinducing differentiation in DTC with insufficient uptake of ^{131}I has been attempted with drugs such retinoids and thiazolidinediones but till now with poor results [29].

Regarding DTC, molecules that block kinase activity at different steps in the MAP kinase pathway are logical candidate drugs for DTC patients refractory to conventional therapy. Tyrosine kinase inhibitor (TKIs) being tested against differentiated thyroid cancer in clinical trials include motesanib diphosphate, axitinib, sorafenib, sunitinib and pazopanib (Table 3). None of these is specific to one oncogene protein but they target several TK receptors and proangiogenic growth receptors (e.g. vascular endothelial growth factor, VEGF). The results of phase II–III clinical trials conducted so far are promising with a partial response ranging from 14% to 49% and stable disease from 34% to 68% [30] (II, B) TKIs are generally quite well tolerated; the most common adverse events are fatigue, weight loss, diarrhea and nausea, hypertension,

Table 3. Therapeutic effects of different TKIs in clinical trials enrolling patients with MTC or DTC

Drug	Histotype	No. patients	Phase	PR (%)	SD (%)	SD>6 months (%)	mPFS (weeks)
Motesanib	MTC	91	II	2	81	48	48
	DTC	93	II	14	67	35	40
Sunitinib	MTC	23	II	35	57		28
	MTC	6	II		83		
	MTC	15	II	33	27		
	DTC	31	II	14	68		
Vandetanib	MTC	30	II	20	73	53	
	MTC	19	II	16	64	53	
	MTC	331	III	45	42	83	30.5 months
Sorafenib	MTC	16	II	6	87	56	60
	DTC	41	II	15		53	79
	DTC	30	II	23			
	DTC	31	II	25	34		
XL184	MTC	37	I	29		41	
Axitinib	MTC	11	I	18	27		
	DTC	45	II	31	42		
Pazopanib	DTC	37	II	49			

MTC, medullary thyroid cancer; DTC, differentiated thyroid cancer; PR, partial response; SD, stable disease; mPFS, median progression-free survival.

mucositis and hand foot skin reaction. Another common side effect with some TKIs is the increase of serum Thyroid Stimulating Hormone (TSH), probably due to interference in thyroid hormone metabolism that often requires an adjustment of L-tyroxine therapy. Although preliminary results of these trials are promising and indicate that targeted therapy might become the first line treatment of metastatic refractory thyroid cancer patients in the near future, they are not standard therapy today and should be administered only in the context of clinical trials.

levothyroxine therapy

Thyroid hormone suppression therapy is an important part of the treatment of thyroid cancer. Immediately after surgery thyroid hormone therapy is initiated with dual aim: to replace thyroid hormone and to suppress the potential growth stimulus of TSH on tumor cells (TSH suppressive therapy). The drug of choice is levothyroxine (LT4) and the suppressive dose varies according to age and body mass index [7, 8]. TSH suppressive treatment with LT4 is of benefit in high-risk thyroid cancer patients in whom it may decrease progression of metastatic disease, thus reducing cancer-related mortality (IV, B). No substantial benefits are demonstrated in low-risk patients [31] (IV, D). This provides a rationale to target TSH levels to the lower part of the normal range in low-risk DTC patients as recommended by the ATA [8] and the ETA [7]. In the presence of persistent or metastatic disease, an undetectable serum TSH (<0.1 mU/l) should be maintained during follow-up. In patients free of disease, regardless of their initial risk class, LT4 therapy may be shifted from suppressive to replacement.

medullary thyroid cancer

MTC arises from the parafollicular CT-producing C cells of the thyroid and accounts for between 5% and 8% of all thyroid malignancies, with ~1000 new diagnoses in the USA each year [32]. Since malignant transformed C cells produce and secrete large amounts of peptides, including CEA and CT, with few exceptions, elevated serum CT is a marker of presence of MTC or metastatic MTC after surgery. Up to 75% of MTC cases occur sporadically, while the hereditary form of MTC shows an autosomal dominant pattern of transmission. Familial MTC (FMTC) arises as part of multiple endocrine neoplasia (MEN) syndrome types 2A or 2B or FMTC. Important prognostic factors that predict adverse outcomes include reduced CT doubling time (DT), advanced age at diagnosis, extent of primary tumor, nodal disease and distant metastases [32].

initial treatment and follow-up of medullary thyroid carcinoma

Before surgery, all patients with suspicious MTC should undergo a staging work-up. The goal of preoperative evaluation is to define the extent of disease and to identify the comorbid conditions of hyperparathyroidism and/or pheochromocytoma in the case of hereditary forms. The preoperative biochemical evaluation should include basal serum CT, CEA, calcium and plasma metanephrines and normetanephrines, or 24-h urine collection for metanephrines and normetanephrines (IV, A). Preoperative instrumental imaging includes neck US in all patients, whereas preoperative chest CT, neck CT and three-phase contrast enhanced multidetector liver CT or contrast-enhanced MRI should be performed in patients with documented lymph node metastases or with serum CT >400 pg/ml [32] (IV, B).

For MTC patients with no evidence of lymph node metastases by physical examination and cervical US, treatment consists of total thyroidectomy for both sporadic and hereditary MTC associated with bilateral prophylactic central lymph-node dissection (level V; IV, B). Lateral neck dissection (levels IIA, III, IV, V) may be best reserved for patients with positive preoperative imaging [32] (IV, B). In the presence of distant metastatic disease, less aggressive neck surgery may be appropriate to preserve speech, swallowing and parathyroid function while maintaining locoregional disease control to prevent central neck morbidity (V, C).

After total thyroidectomy, replacement thyroxine treatment is given to maintain serum TSH concentration within the normal range (IV, B). Measurements of serum markers CT (and CEA in specific cases) and the CT and CEA DTs are of paramount importance in the post-surgical follow-up of patients with MTC because it reflects the presence of persistent or recurrent disease (IV, B).

After surgery, serum CT level normalizes (undetectable) in 60%–90% cases of patients with no lymph-node involvement but only in 20% of those with lymph-node metastases.

At this point an undetectable basal serum CT level is a strong predictor of complete remission. Complete remission may be further confirmed if serum CT remains undetectable also after a provocative (pentagastrin or calcium) test [33]. 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 (IV, B). Patients with biochemical remission after initial treatment have only a 3% chance of recurrence during long-term follow-up [32]. On the contrary, if basal serum CT is detectable or becomes detectable after stimulation, the patient is not cured, though imaging techniques will not demonstrate any disease until basal serum CT approaches levels >150 pg/ml [32]. In patients with serum CT concentration <150 pg/ml, localization of disease should be limited to a careful examination by neck US because these CT levels are usually associated with locoregional disease and very rarely with distant metastases [32] (IV, B). In addition to neck US, post-operative MTC patients with detectable serum CT levels <150 pg/ml may be considered for additional imaging [neck and chest CT, liver triphase contrast-enhanced CT or contrast-enhanced MRI, liver US, bone scintigraphy, MRI of the spine and pelvis, ^{18}FDG-PET and 18-F-dihydroxyphenylalanine PET] to serve as baseline examination for future comparison even though these studies are usually negative. Alternatively, additional imaging can be deferred until serum CT rises over time [32] (IV, B). The evaluation of patients with basal CT >150 pg/ml is similar to that of patients with basal serum CT <150 pg/ml. However, the search for distant metastases is mandatory using the aforementioned imaging techniques. In patients with detectable basal serum CT and no evidence of disease, long-term surveillance is

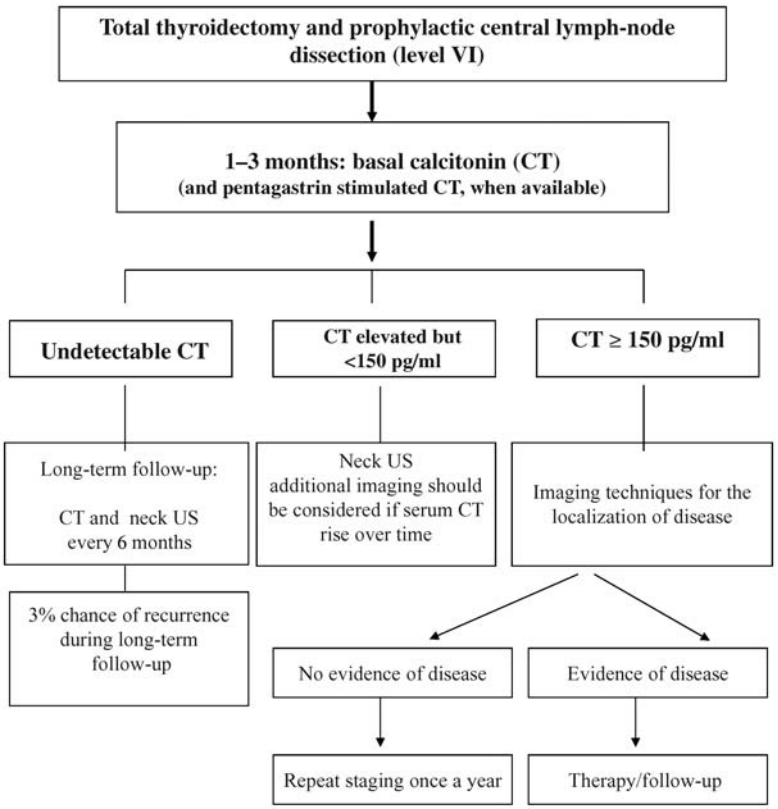

Figure 2 Diagnostic algorithm based on calcitonin levels obtained 1–3 months after initial surgery in patients with medullary thyroid carcinoma [32].

indicated. The optimal timing of this follow-up should be based on CT and CEA DT, which are strongly correlated with disease progression and are significant predictors of survival by multivariate analysis [34] (Figure 2).

local and regional recurrences

Surgery is the main treatment of local and regional recurrences whenever feasible (IV, B). A complete preoperative work-up is performed in search of distant metastases and to localize the recurrence precisely. The extent of surgery will depend on the type of surgical procedures already performed and on the nature of the relapse: if initial surgery was complete, recurrent disease is resected whenever possible; if the extent of initial surgery was incomplete, the primary surgery protocol is resection.

distant metastasis

Distant metastases are the main cause of death in MTC patients. In half of the cases, they are present initially. They are often multiple in organs involved and simultaneously affect multiple organs, such as the liver, lungs and bones. Survival after the discovery of distant metastases is 51% at 1 year, 26% at 5 years and 10% at 10 years [32]. Long survival has been observed in a few patients with metastatic disease even without any systemic treatment and particularly when metastases are discovered at an early stage [32].

In advanced disease mono- or poly-chemotherapy has not shown substantial clinical benefit (<20% response rate). Radiotherapy is often used in the presence of local invasion. In liver metastases, chemoembolization may be effective in reducing tumor mass.

Also in MTC, new compounds (e.g. TKIs) targeting signalling pathways essential for tumor cell survival, proliferation and metastases have been tested (Table 3). Preliminary evidence indicates that they may have important clinical benefits. The most promising TKIs, being tested against MTC in clinical trials, include motesanib diphosphate, vandetanib, sorafenib and sunitinib, resulting in partial responses from 2% to 35% and in disease stabilization rates from 27% to 87% with tolerable and manageable toxicity, as those found in DTC patients [30].

Recently, vandetanib has been approved by FDA and EMA for the treatment of patients with locally advanced/metastatic MTC after therapeutic efficacy has been demonstrated in a phase III trial in patients with advanced MTC [35].

poorly differentiated thyroid carcinoma

Poorly differentiated thyroid carcinoma (PDTC) was introduced as a separate entity in 2004 in the World Health Organization Classification of Tumors [36]. The prevalence of PDTC ranges from 1% to 6% and there is a female predominance and a mean age at presentation of 50 years. PDTC includes aggressive tumor histologies such as trabecular, insular and solid subtypes. PDTC has an intermediate prognosis between DTC and undifferentiated thyroid

Table 4. Summary of recommendations

Topic (Thyroid Cancer)	Recommendations
Diagnosis	• Thyroid ultrasound (US) supplemented by fine needle aspiration cytology (FNAC) should be used as a first-line diagnostic procedure for detecting and characterizing nodular thyroid disease (I, A) • In the event of inadequate samples, FNAC should be repeated, while in the case of follicular neoplasia, with normal TSH and 'cold' appearance at thyroid scan, surgery should be considered (IV, B) • Serum calcitonin (CT) is a reliable tool for the diagnosis of medullary thyroid cancer and its measurement should be an integral part of the diagnostic evaluation of thyroid nodules (IV, B)
Differentiated Thyroid Cancer	• The initial treatment of DTC is total or near-total thyroidectomy whenever the diagnosis is made before surgery. Less extensive surgical procedures may be accepted in case of unifocal DTC diagnosed at final histology after surgery performed for benign thyroid disorders, provided that the tumor is small, intrathyroidal and of favorable histological type (classical papillary or follicular variant of papillary or minimally invasive follicular) (I, A) • One of the several staging systems (AJCC, ATA, ETA) that provide good risk stratification on the basis of data available shortly after initial therapy should be used (II, B) • Surgery is usually followed by the administration of ^{131}I activities aimed at ablating any remnant thyroid tissue and potential microscopic residual tumor. Radioiodine ablation is indicated in high-risk patients (IV, B), whereas it is not indicated in low-risk patients (IV, D). In patients at intermediate risk, the decision must be individualized • Post-surgery thyroid hormone therapy should be initiated in order to replace thyroid hormone (replacement therapy) and to suppress the potential growth stimulus of TSH on tumor cells (suppressive therapy). TSH suppressive treatment with L-T4 is of benefit in high-risk thyroid cancer patients (IV, B). • Two to three months after initial treatment, thyroid function tests (FT3, FT4, TSH) should be carried out to check the adequacy of LT4 suppressive therapy, followed at 6 to 12 months by screening with physical examination, neck US and basal and rhTSH-stimulated serum thyroglobulin measurement with or without diagnostic WBS (I, A) • The subsequent follow-up of patients considered free of disease consists of physical examination, basal serum Tg measurement on LT4 therapy and neck US once per year • Treatment of recurrent loco-regional disease is based on the combination of surgery and radioiodine therapy, supplemented by external beam radiotherapy if surgery is incomplete or there is lack of RAI uptake (IV, B) • Distant metastases are more successfully cured if they are RAI-avid, small and located in the lungs; otherwise, only palliation and survival prolongation is feasible. Chemotherapy is not indicated and clinical trial participation should be encouraged (IV, B)
Medullary Thyroid Cancer	• Before surgery, all patients with suspicious MTC should undergo a staging work-up, including basal serum CT, CEA, calcium and plasma metanephrines and normetanephrines, or 24-h urine collection for metanephrines and normetanephrines (IV, A). • For MTC patients with no evidence of lymph node metastases by physical examination and cervical US, treatment consists of total thyroidectomy with bilateral prophylactic central lymph-node dissection (IV, B). Lateral neck dissection may be best reserved for patients with positive preoperative imaging (IV, B) • After total thyroidectomy, replacement thyroxine treatment should be given to maintain serum TSH concentration within the normal range (IV, B). Measurements of serum markers CT (and CEA in specific cases) and the CT and CEA DTs are of paramount importance in the post-surgical follow-up of patients with MTC (IV, B) • In the event of post-surgery undetectable serum CT after a provocative (pentagastrin or calcium) test, no other diagnostic test is indicated and serum CT should be repeated every 6 months for the first 2–3 years and annually thereafter (IV, B) • In patients with serum CT concentration <150 pg/ml, localization of disease should be limited to a careful examination by neck US (IV, B). Patients with basal CT >150 pg/ml should be screened for distant metastases • Surgery is the main treatment of local and regional recurrences whenever feasible (IV, B) • In advanced disease, mono- or poly-chemotherapy has not shown significant clinical benefit (<20% response rate), while radiotherapy is often used palliatively • Vandetanib has been approved by FDA and EMA for the treatment of patients with locally advanced/metastatic MTC and should be considered for patients with incurable disease

carcinoma. The clinical course of PDTCs is usually aggressive with higher recurrence rate, higher rate of distant metastases and a higher rate of local extrathyroidal invasion with a 5-year survival ranging from 60% to 85% [37]. The initial treatment is total thyroidectomy. Lymph node dissection (central compartment and/or lateral neck dissection) should be considered as regional nodal metastases are present at diagnosis in over 50% of PDTC patients [38] (V, C). TSH suppressive therapy with LT4 should be initiated immediately following surgery. Most studies demonstrate that PDTC respond poorly to RAI, and are often positive on FDG-PET scanning. Patients with unresectable disease or persistent locoregional disease after surgery may take advantage of EBRT (V, C). Administration of chemotherapy, both as single agent

or combination regimens, such as cisplatin and doxorubicin, may achieve only transient and incomplete responses (V, C). Whenever possible, PDTC patients should be included in clinical trials of novel therapies (Table 4).

anaplastic thyroid cancer

Anaplastic thyroid cancer (ATC) is the most aggressive thyroid tumor and one of the most aggressive cancers in humans. Anaplastic thyroid carcinoma affects more women than men, but the female-to-male ratio is of about 2–3:1, lower than that of papillary or follicular histotypes. It arises from the follicular cells of the thyroid gland but does not retain any of the biological features of the original cells, such as uptake of iodine and synthesis of Tg. The peak incidence is in the sixth–seventh decades (mean age at diagnosis 55–65 years) and the prevalence is fortunately very low (<2% of all thyroid tumors). ATC may arise de novo, but in most cases, it develops from a pre-existing well-differentiated thyroid tumor, having undergone additional mutational events, mainly p53 mutation [39].

diagnosis

The diagnosis is usually easy, based on typical clinical aspects: large, hard mass invading the neck and causing compressive symptoms (dyspnea, cough, vocal cord paralysis, dysphagia and hoarseness). About 30% of patients have vocal cord paralysis, and cervical metastases are palpable on examination in 40% of patients. Almost 50% of the patients present distant metastasis, mostly in the lungs but also in bones, liver and brain. Owing to the aggressive behavior of ATC, the latest American Joint Committee on Cancer Staging Manual has classified all ATCs as T4 and stage IV tumors, regardless of their size and overall tumor burden [11].The mean overall survival is often <6 months, regardless of treatment strategy.

treatment

Treatment of ATC has not been standardized, and unfortunately, there is not yet an efficient treatment; surgery, chemotherapy, radiotherapy alone or in combination do not improve survival. Surgery is indicated for local control in resectable lesions. The most common single cytotoxic agent used against anaplastic carcinomas is doxorubicin alone or in combination with cisplatin. The results have been disappointing. Adding bleomycin or other agents does not enhance the efficacy of this combination. Recently, paclitaxel has been used in clinical trial and it has shown some improvement in response rates but not in survival. Novel treatment strategies are necessary, therefore new strategies under investigation include targeted therapy (e.g. axitinib and sorafenib), vascular disrupting agents (such as combretastatin A4 phosphate, human VEGF monoclonal antibodies, e.g. bevacizumab, cetuximab), tumor suppressor gene therapy and cell cycle arrest-inducing agents [40]. So far none of these agents has shown good results in the treatment of ATC so new research is needed to contrast the aggressiveness of this tumor [30].

conflict of interest

All authors have reported no potential conflicts of interest.

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