Differentiated thyroid cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

The incidence of thyroid cancer has been increasing in many countries over the last 30 years (from 3.6/100 000 people in 1973 to 8.7/100 000 people in 2002) while mortality has been slowly decreasing. The incidence increase is attributable to better detection of small papillary carcinomas as a result of improved diagnostic accuracy (neck ultrasound and fine needle aspiration cytology). 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.

diagnosis

Thyroid cancer presents as a thyroid nodule detected by palpation and more frequently by neck ultrasound. While thyroid nodules are frequent (4–50% depending on the diagnostic procedures and patient age), thyroid cancer is rare (~5% of all thyroid nodules). Fine needle aspiration cytology (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, positive family history of thyroid cancer, suspicious features at palpation, presence of cervical adenopathy) or ultrasonographic (hypoechogenicity, microcalcifications, absence of peripheral halo, irregular borders and regional lymphadenopathy) suspicion of malignancy. 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 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 [III, B]. Thyroid function test and thyroglobulin (Tg) measurement are of little help in the diagnosis of thyroid cancer. However, measurement of serum calcitonin is a reliable tool for the diagnosis of the few cases of medullary thyroid cancer (5–7% of all thyroid cancers), and has higher sensitivity compared with FNAC. For this reason measurement of calcitonin should be an integral part of the diagnostic evaluation of thyroid nodules [II, B].

initial treatment

The initial treatment of differentiated thyroid carcinoma (DTC) should always be preceded by careful exploration of the neck by ultrasound to assess the status of lymph node chains. The initial treatment for DTC is total or near-total thyroidectomy whenever the diagnosis is made before surgery and the nodule is ≥1 cm, or regardless of the size if there is metastatic, multifocal or familial DTC. 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 favorable histological type (classical papillary or follicular variant of papillary or minimally invasive follicular). 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 accurate staging of the disease, which may guide subsequent treatment and follow-up. Compartment-oriented microdissection of lymph nodes should be performed in cases of preoperatively suspected and/or intraoperatively proven lymph node metastases. In expert hands surgical complications such as laryngeal nerve palsy and hypoparathyroidism are extremely rare (<1–2%).

Surgery is usually followed by the administration of ¹³¹I aimed at ablating any remnant thyroid tissue and potential microscopic residual tumor. 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) [I, A]. In addition the high activity of $^{131}$I allows a highly sensitive post-therapeutic WBS to be obtained. Radioiodine ablation is recommended in high-risk patients and in low-risk patients while there is no indication in very low-risk patients (those with unifocal T1 tumors, <1 cm in size, with favorable histology, no extrathyroidal extension or lymph node metastases). Effective thyroid ablation requires adequate stimulation by thyroid-stimulating hormone (TSH). The method of choice for preparation for radioiodine ablation is based on the administration of recombinant human TSH (rhTSH) while the patient is on levo-thyroxine (LT4) therapy. A recent multicenter and prospective study has demonstrated that this preparation is highly effective and safe and that the rate of successful ablation is similar to that obtained with LT4 withdrawal [II, B].

Based on these results the use of rhTSH was approved in Europe in February 2005 by the European Medicine Agency (EMEA) and in the USA in December 2007 by the FDA, as preparation for radioiodine ablation of post-surgical thyroid remnants in patients with well-differentiated thyroid carcinoma without evidence of metastatic disease, using a fixed dose of 3700 MBq (100 mCi) of $^{131}$I. However, a recent randomized prospective study has showed that, in patients prepared with rhTSH, a lower dose of 1850 MBq (50 mCi) of $^{131}$I is as effective as 3700 MBq (100 mCi), even in the presence of lymph node metastases and that, further, reduces radiation exposure to the whole body [II, B].

**post-ablation staging and risk assessment**

Conventionally, staging of DTC is based on the pathological results combined with the information derived from the post-ablation $^{131}$I WBS and neck ultrasound at the moment of ablation. Several staging systems have been developed by authoritative centers. 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.

Recently, in accordance with this system, a European Consensus Report defined three risk categories for DTC:

- **Very low risk:** unifocal T1 (<1 cm) N0 M0, no extension beyond the thyroid capsule and favorable histology (classical or follicular variant of papillary and minimal invasive follicular carcinoma);
- **Low risk:** T1 (>1 cm) or T2 N0 M0 or multifocal T1 N0 M0;
- **High risk:** any T3 and T4 or any T, N1, or any M1.

In the American Thyroid Association Guidelines patients are stratified as follows:

- **Low risk:** T1—2 N0 M0 and absence of aggressive histology or vascular invasion;
- **Intermediate risk:** T3 or tumor with aggressive histology or vascular invasion;
- **High risk:** T4 or any T, N1 or M1.

**follow-up**

The aim of the follow-up is the early discovery and treatment of persistent or recurrent locoregional or distant disease. The large majority of local recurrences develops and is detected in the first 3 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.

Two to three months after initial treatment thyroid function tests (FT3, FT4, TSH) should be obtained to check the adequacy of LT4 suppressive therapy. At 6–12 months the follow-up is aimed to ascertain whether the patient is free of disease. This follow-up is based on physical examination, neck ultrasound, rhTSH-stimulated serum Tg measurement with or without diagnostic WBS. At this time most (nearly 80%) of the patients will belong to the low-risk categories and will disclose normal neck ultrasound 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). Patients in remission may be shifted from suppressive to replacement LT4 therapy, with the goal of maintaining a serum TSH level within the normal range. The subsequent follow-up of these patients should be based on yearly physical examination, serum Tg measurement on replacement LT4 and neck ultrasound.

Whether a second rhTSH–Tg test should be obtained during subsequent follow-up is controversial but available evidence suggests that an additional rhTSH-stimulation test is of little clinical utility in patients who had no biochemical (undetectable basal and stimulated serum Tg) or clinical (imaging) evidence of disease at the time of their first rhTSH–Tg [II, B].

Recently, new methods of serum Tg measurement with a functional sensitivity <0.1 ng/ml have become available. Using these systems some authors reported a much higher sensitivity of the assays. In their experience an undetectable basal serum Tg (<0.1 ng/ml) using ultrasensitive assays should give the same information as a stimulated Tg value and thus the authors recommended that rhTSH–Tg testing should be abandoned. However, the higher sensitivity of these tests is at the expense of lower specificity.

**therapy of recurrent or persistent disease**

Patients with evidence of persistent disease, or with detectable levels of serum Tg increasing with time, require imaging techniques for the localization of disease and appropriate treatment, including therapeutic doses of $^{131}$I.

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. When appropriately treated, two-thirds of those patients with local disease and one-third of those with distant disease may achieve complete remission.

Treatment of locoregional disease is based on the combination of surgery and radioiodine therapy [III, B].

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Invited review paper

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External beam radiotherapy may be indicated when complete surgical excision is not possible or when there is no significant radioiodine uptake in the tumor.

Distant metastases are more successfully cured if they take up radioiodine, are of small size located in the lungs (not visible at X-ray). Lung macro-nodules may benefit from radioiodine therapy but the definitive cure rate is very low [III, B]. Bone metastases have the worst prognosis even when aggressively treated by a combination of radioiodine therapy and external beam radiotherapy. Brain metastases are relatively rare and usually carry a poor prognosis. Surgical resection and external beam radiotherapy represent the only therapeutic options. Chemotherapy is restricted to patients with progressive disease not manageable by other treatment modalities. The results are usually disappointing.

Targeted therapy, a new generation of anticancer treatment, aimed at inhibiting specific molecular targets critical in tumor growth and progression is a promising alternative for refractory thyroid cancer. The most natural target for such therapy is the RET proto-oncogene, a tyrosine kinase receptor constitutively active by mutational events in nearly 30–40% of papillary thyroid carcinoma and in the large majority of medullary thyroid cancer. Several molecules have reached the phase II and III clinical trials with promising results [II, C].

**note**

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

**literature**

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