incidence
Several recent studies have reported an increase in the incidence of thyroid cancer during the last decades in Canada, in the United States and in Europe. This phenomenon is mainly due to an increase in micropapillary (<2 cm) histotype while there is no significant 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 and fine-needle aspiration cytology). It is common experience in thyroid cancer referral centres that nearly 60%–80% of thyroid carcinomas detected nowadays are micropapillary thyroid carcinomas (<1 cm in size) carrying an excellent long-term prognosis. However, more recently, an increased incidence of all sizes of thyroid tumour has been reported in the United States. In 1997–2005 the annual percentage change (APC) for primary tumours <1.0 cm has been 9.9 in man and 8.6 in women. A significant increase was also observed for tumours >4 cm among men (1988–2005: APC 3.7) and women (1988–2005: APC 5.7). These data indicate that increased diagnostic scrutiny is not the only explanation but 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 1000 000 children). Following the explosion of the Chernobyl nuclear reactor in 1986, a dramatic increase in the incidence of benign and malignant thyroid tumours (80 times more) was observed in children born or conceived around the time of the accident in a considerable area surrounding the reactor. Despite increasing incidence, the mortality from thyroid cancer has tended to decline over the last three decades. In the European Union from 1992 to 2002 the mortality for thyroid cancer declined in both men and women (~23% and ~28%, respectively). It is unclear how much of the decline in mortality is due to better diagnosis rather than to improved treatment of thyroid neoplasm.

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’s age), thyroid cancer is rare (~5% of all thyroid nodules). Thyroid ultrasound (US) is a widespread technique that is used as a first-line diagnostic procedure for detecting and characterizing nodular thyroid disease. US features associated with malignancy are hypoechogenicity, microcalcifications, absence of peripheral halo, irregular borders, solid aspect, intranodular blood flow and shape (taller than wide). All these patterns taken singly are 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. Fine-needle aspiration cytology (FNAC) is an important technique that is used along with US for the diagnosis of thyroid nodules. 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. 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 thyroid-stimulating hormone (TSH) and ‘cold’ appearance at thyroid scan, surgery should be considered. The use of various immunohistochemical markers in cytological samples to differentiate papillary thyroid carcinoma from other...
follicular-derived lesions of thyroid have 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 cytological diagnosis of papillary thyroid carcinoma. Two prospective studies reported that by molecular testing of thyroid for nodules BRAF, RAS, RET/PTC and PAX8/PPARγ mutations in cytological material, the difference of any mutation was a strong indicator of cancer because ~97% of mutation-positive nodules had malignant diagnosis at histology. 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.

**differentiated thyroid cancer**

**initial treatment**

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 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 and histology (papillary or follicular) 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 tumour is small, intrathyroidal and of favourable 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 an accurate staging of the disease that may guide subsequent treatment and follow-up. 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 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 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 radiiodine whole body scan (WBS). In addition the high activity of ¹³¹I allows obtaining a highly sensitive post-therapeutic WBS. Radioiodine ablation is recommended for all patients except those at very low risk (those with unifocal T1 tumours, <1 cm in size, with favourable histology, no extrathyroidal extension or lymph node metastases) (Table 1). Effective thyroid ablation requires adequate stimulation by TSH. The method of choice for preparation to perform radioiodine ablation is based on the administration of recombinant human TSH (rhTSH) while the patient is on levo-thyroxine (LT4) therapy. A recent multicentre 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. 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 ¹³¹I. However, a recent randomized prospective study has showed that, in patients prepared with rhTSH, a lower dose of 1850 MBq (50 mCi) of ¹³¹I is equally effective as 3700 MBq (100 mCi), even in the presence of lymph node metastases and that, further, reduces radiation exposure to the whole body.

**staging and risk assessment**

Several staging systems have been developed by authoritative centres. 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 (AJCC/IUAC) TNM staging system based mainly on the extent of tumour and age. Although all staging systems are able to predict high or low risk of cancer mortality, they fail to predict the risk of recurrence. Therefore, the addition of a postoperative clinicopathological staging system should be use in conjunction with the AJCC staging system to improve prediction of risk for recurrence and to dictate the most appropriate therapy. In the recent guidelines, estimate of risk of recurrence and risk of disease-specific death are used to guide both initial treatment and follow-up recommendations. In accordance with this system, a European Consensus Report defined three categories of risk to establish the indication for radioiodine ablation therapy (Table 1): no indication for radioiodine ablation in very low-risk patients [unifocal T1 (<1 cm) N0 M0, no

| Table 1. Risk stratification for DTC patients according to the European Consensus Report |
|---------------------------------|---------------------------------|---------------------------------|
| **Very low risk**               | **Low risk**                    | **High risk**                   |
| Intrathyroidal tumour (T1 ≤1 cm) | Intrathyroidal tumour (T1 >1 cm and T2) | Intrathyroidal tumour (T3)       |
| No aggressive histology         | Aggressive histology            | Micro or macroscopic invasion (T3–T4) |
| No local or distant metastases  | No local or distant metastases  | Locoregional metastases         |
| Complete surgery                | Less than total thyroidectomy   | Incomplete tumour resection     |

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extension beyond the thyroid capsule, favourable histology), definite indication in high-risk (any T3 and T4 or any T, N1, or any M1) and probable indication in low-risk [T1 (>1 cm) or T2 N0 M0 or multifocal T1 N0 M0, or unfavourable histology] (Table 2). Recently, Tuttle et al. have proposed an ‘ongoing risk stratification’ which takes into account the response to therapy. On this basis, patients can be classified as having an excellent, acceptable or incomplete response to therapy. Patients with an excellent response (undetectable basal and stimulated Tg, negative AbTg and negative neck US) 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. Patients with an acceptable response (undetectable basal Tg, stimulated Tg <10 ng/ml, trend of Tg in decline, AbTg absent or declining, substantially negative neck US) require a closer follow-up reserving additional treatment in the case of evidence of disease progression. Patients with an incomplete response (detectable basal and stimulated Tg, trend of Tg stable or rising, structural disease present, persistent or recurrent RAI-avid disease present) 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.

**short-term 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 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. 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 (Table 2). This follow-up is based on physical examination, neck US, basal and 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 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).

**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 a 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. Recently, new methods for serum Tg measurement with a functional sensitivity of <0.1 ng/ml have become available. Using these systems some authors reported a much higher sensitivity of the assays. In their experience 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.

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 131I. Included in this category are the 5%–10% of DTC patients presenting with local or distant metastases at diagnosis and an additional 5%–10% that develop recurrent disease during follow-up. During the evaluation of metastatic patients, 18FDG-PET scanning is gaining more and more attention as a diagnostic and prognostic tool. Several studies have shown that, in differentiated thyroid carcinoma, 18FDG-PET can be used to detect recurrence or metastases with a high degree of sensitivity (80%–90%) and it is particularly indicated for patients who do not take up radioiodine. FDG-PET may also give prognostic information. 131I-WBS-negative and 18FDG-PET-positive patients indicate a group of patients with more aggressive and less differentiated disease carrying a worse prognosis with respect to 131I-WBS-positive and 18FDG-PET-negative patients, who have less aggressive disease and better prognosis.

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**Table 2. Initial treatment and follow-up based on risk stratification**

<table>
<thead>
<tr>
<th>Ablative radiiodine therapy Follow-up</th>
<th>Very low risk</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg on LT4</td>
<td>No indication</td>
<td>Probable indication</td>
<td>Definitive indication</td>
</tr>
<tr>
<td>Stimulated Tg</td>
<td>Every 6–12 months</td>
<td>Every 6–12 months</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td>Neck US</td>
<td>Not useful</td>
<td>At 12 months if Tg on LT4 is undetectable</td>
<td>At 12 months if Tg on LT4 is undetectable</td>
</tr>
<tr>
<td>Diagnostic WBS</td>
<td>Every 6–12 months</td>
<td>Every 6–12 months</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td></td>
<td>Not useful</td>
<td>Nor required if stimulated Tg is undetectable</td>
<td>May be helpful</td>
</tr>
</tbody>
</table>
Treatment of locoregional disease is based on the combination of surgery and radioiodine therapy. External beam radiotherapy may be indicated when complete surgical excision is not possible or when there is no significant radioiodine uptake in the tumour. Distant metastases are more successfully cured if they take up radioiodine, of small size located in the lungs (not visible at X-rays). Lung macro-nodules may benefit from radioiodine therapy but the definitive cure rate is very low. 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 no longer indicated due to lack of effective results and should be replaced by enrollment of the patients in experimental trials with tyrosine kinase inhibitor (TKI). Molecules that block kinase activity at distal steps in the MAP kinase pathway are logical candidate drugs for thyroid cancer, TKIs being tested against differentiated thyroid cancer in clinical trials include motesanib diphosphate, axitinib, gefitinib, sorafenib and sunitinib. None of these is specific for one oncogene protein but they target several TK receptors and pro-angiogenic growth receptors. The results of phase II–III clinical trials conducted so far are promising with a partial response ranging from 14% to 32% and stable disease from 50% to 67%. All together, the preliminary results of these trials are promising and indicate that targeted therapy might become the first-line treatment of metastatic refractory thyroid cancer in the near future.

**levo-thyroxine therapy**

Thyroid hormone suppression therapy is also an important part of the treatment of thyroid cancer and is effective in stopping the growth of microscopic thyroid cancer cells or residual thyroid cancer. Several reports have shown that hormone-suppressive treatment with LT4 benefits high-risk thyroid cancer patients by decreasing progression and recurrence rates, and cancer-related mortality. No significant improvement has been obtained by suppressing TSH in patients with low-risk thyroid cancer. The duration of suppression therapy in cancer patients is currently being debated. According to the current guidelines, low-risk patients free of disease after initial treatment may be shifted from suppressive to replacement LT4 therapy, with the goal of maintaining serum TSH level within the normal range. A significant proportion of patients defined as high risk at the time of diagnosis may appear free of disease at their first follow-up after initial treatment. In these patients, however, the risk of relapse in the long-term follow-up may be significant, therefore it is advisable to maintain these patients on suppressive doses of LT4 therapy (TSH ~0.1 μIU/ml) for 3–5 further years.

**medullary thyroid cancer**

Medullary thyroid cancer (MTC) arises from the parafollicular calcitonin-producing C cells of the thyroid and accounts for between 5% and 8% of all thyroid malignancies, with ~1000 new diagnoses in the United States each year. Since malignant transformed C cells produce and secrete large amounts of peptides, including CEA and calcitonin (CT), with few exceptions, elevated serum CT is a marker of the 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 arises as part of multiple endocrine neoplasia (MEN) syndrome type 2A or 2B or familial MTC (FMTC).

Important prognostic factors that predict adverse outcome include CT doubling time (DT), advanced age at diagnosis, extent of primary tumour, nodal disease and distant metastases.

**initial treatment and follow-up of MTC**

For MTC patients with no evidence of lymph node metastases by physical examination and cervical US the treatment consists in total thyroidectomy for both sporadic and hereditary MTC associated with prophylactic central lymph node dissection (level VI). Lateral neck dissection (levels IIA, III, IV, V) may be best reserved for patients with positive preoperative imaging. In 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. Postoperatively, the TNM classification and other factors, such as the postoperative CT level and the CT and CEA DTs, should be used to predict outcome and to help plan long-term follow-up of patients with MTC. After surgery serum CT level normalizes (undetectable) in 60%–90% of cases in patients with no lymph node involvement but in only 20% of those with lymph node metastases. In patients with detectable CT level after surgery imaging techniques are required to detect metastatic disease, although many patients may have elevated CT levels without evidence of disease. Distant metastases are the main cause of MTC-related death. They occur predominantly in patients who present initially with a large-sized tumour, extra-thyroidal growth and lymph node involvement. Distant metastases often affect multiple organs including lungs, bones and liver, and more rarely the brain, skin and breast.

**therapy of metastatic MTC**

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

Also in MTC, new compounds (e.g. TKI) target signalling pathways essential for tumour cell survival, proliferation and metastases. 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, and all together resulted in a partial response ranging from 6% to 20% and in stable disease from 47% to 87% with tolerable and manageable toxicities.

**anaplastic thyroid cancer**

Anaplastic thyroid cancer (ATC) is the most aggressive thyroid tumour and one of the most aggressive cancers in humans. 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 thyroglobulin. The peak incidence is in the sixth to seventh decades (mean age at diagnosis 55–65 years) and the prevalence is fortunately very low (<2% of all thyroid tumours). ATC may arise de novo but in most cases it develops from a pre-existing well-differentiated thyroid tumour, which has undergone additional mutational events, mainly p53 mutation.

**diagnosis**

The diagnosis is usually easy based on typical clinical aspects: large, hard mass invading the neck and causing compressive symptoms (dyspnoea, cough, vocal cord paralysis, dysphagia and hoarseness). Almost 50% of the patients present with distant metastasis, mostly in the lungs but also in bones, liver and brain. Due to its aggressive behaviour the latest AJCC Staging Manual classifies all ATCs as T4 and stage IV tumours, regardless of their size and overall tumour burden. The mean overall survival is often <6 months, whatever treatment is performed.

**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. 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 but not in survival. Novel treatment strategies are necessary; future treatment strategies include targeted therapy, tumour suppressor gene therapy or induction of cell cycle arrest.

**literature**

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