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Abstract. Differentiated thyroid carcinoma (DTC), either papillary or follicular, has usually a very good prognosis with an overall mortality of less than 10%. In recent decades, the clinical presentation of DTC has been changing from advanced cases requiring intense treatment and surveillance to cancer detected by fortuitous neck ultrasonography requiring less aggressive treatment and follow-up.

The initial treatment for DTC is total or near-total thyroidectomy whenever the diagnosis is made before surgery. Central compartment and possible lateral neck dissections should be performed when nodal metastases are present in the respective nodal basins. Post-operatively, radioactive iodine ablation with ¹³¹I followed by thyroid stimulating hormone (TSH) suppression is indicated in certain patients to improve locoregional control and reduce recurrence. After initial treatment (thyroidectomy and radioiodine ablation), the objectives of the follow-up of DTC is to maintain adequate thyroxine therapy and to detect persistent or recurrent disease through the combined use of neck ultrasound and basal and stimulated serum thyroglobulin (Tg) with or without diagnostic whole body scan (WBS). Recent advances in the radioiodine therapy and follow-up of DTC are related to the use of recombinant human TSH (rhTSH) in order to stimulate Tg production and radioiodine uptake, and the ultrasensitive methods for Tg measurement during follow-up.

Keywords: thyroglobulin, differentiated thyroid cancer, recombinant human TSH, neck ultrasound, whole body scan, radioiodine therapy.

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy although representing less than 1% of all human tumors. The follicular thyroid epithelium can give rise to differentiated and undifferentiated carcinomas. Differentiated thyroid carcinoma (DTC) includes the papillary and follicular histotype and their variants accounting for more than 80% of all thyroid cancers. Undifferentiated (or anaplastic) thyroid cancer is still derived from the follicular epithelium but it is characterized by the almost complete loss of thyroid differentiation. Frequently, it can arise on the background of pre-existent papillary or follicular carcinoma. Undifferentiated thyroid carcinoma account for about 5% of thyroid carcinoma. The incidence of thyroid cancer has been increasing in many countries over the last 30 years (from 3.6/100000 people in 1973 to 8.7/100000 people in 2002) while mortality has been slowly decreasing (1). This phenomenon is mainly due to an increase in small papillary (< 2 cm) tumors 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). Despite increasing incidence, the mortality from thyroid cancer has been declining over the last three decades. In the European Union from 1992 to 2002 the mortality for thyroid cancer declined in both man and women (-23 % and -28% respectively) (2). It is unclear how much of the decline in mortality is due to early diagnosis or to improved treatment of the disease. The age-adjusted death rate was 0.5 per 100,000 per year. Approximately 0.1% died under age 20; 0.9% between 20 and 34; 2.3% between 35 and 44; 8.1% between 45 and 54; 17.5% between 55 and 64; 24.1% between 65 and 74; 30.3% between 75 and 84; and 16.8% in patients older than 85 years (2).

TREATMENT OF DIFFERENTIATED THYROID CARCINOMA

SURGERY

The initial treatment for DTC is total or near-total thy-

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roidectomy 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). The initial treatment of DTC should always be preceded by careful exploration of the neck by ultrasound to assess the status of lymph node chains. Clinically evident lymph node metastases are present in approximately one third of patients with papillary thyroid carcinoma at presentation. Microscopic metastases are present in one half. The most common site of lymph node involvement is the central compartment (level 6) The lateral lymph node chains (levels 2-4) are the next most common sites of cervical node involvement. Lymph nodes in the posterior triangle of the neck (level 5) may also develop metastases. Unlike papillary carcinoma, cervical metastases from follicular carcinomas are uncommon. The benefit of prophylactic central node dissection in the absence of evidence of nodal disease is controversial. There is no evidence that in papillary thyroid carcinoma may improve recurrence or mortality rate, but allows accurate staging of the disease that may guide subsequent treatment and follow-up (3,4). Compartment-oriented dissection of lymph nodes should be performed in case of preoperatively suspected and/or intraoperatively proven lymph node metastases. Prophylactic lymph nodes dissection is not indicated in follicular thyroid cancer. In expert hands surgical complications such as laryngeal nerve palsy and hypoparathyroidism, are extremely rare (<1-2 %) (3,4).

RADIOIODINE ABLATIVE THERAPY

Surgery is usually followed by the administration of ¹³¹I activities aimed to ablate any remnant thyroid tissue and potential microscopic residual tumor. This procedure does not seem to have an influence on mortality rate, but in most series seems to reduce the risk of regional recurrence and facilitates the long term surveillance based on serum Tg measurement and diagnostic radioiodine WBS. In addition, the high activity of ¹³¹I allows obtaining a highly sensitive post-therapeutic WBS. According to several guidelines (3,4) the recommendations for remnant thyroid ablation are modulate on the bases of risk factors. Radioiodine ablation is indicate in high risk patients whereas it is not indicate in low risk patients. In patients at intermediate risk radioiodine remnant ablation may be indicate but the decision must be individualized (3,4).

Effective thyroid ablation requires adequate stimulation by TSH. This may be achieved by thyroid hormone withdrawal (THW) or after recombinant human TSH (rhTSH) administration. The latter procedure is considered the method of choice based on several reports (5-7) demonstrating equal efficacy compared to THW but better acceptance from the patients. In addition, in the recent years it is increasingly apparent that successful thyroid ablation may be achieved using low ac-

tivities of ¹³¹I (1110- 1850 MBq) (6,7).

Recent studies demonstrate that rhTSH-assisted radioiodine ablative therapy is associated with similar rates of persistent disease and clinically evident recurrence than those observed after for traditional THW preparation, at least in the short term follow-up (8,9). In light of these data, the use of rhTSH for post-thyroidectomy ¹³¹I ablation represents a safe and effective option for the postoperative management of patients with thyroid cancer. In addition, preparation with either rhTSH or THW appears to have similar adjuvant therapy effects on small-volume RAI-avid disease identified outside the thyroid bed at the time of initial radioiodine remnant ablation (6,10). Radioiodine-avid metastatic disease discovered at the time of rhTSH-stimulated remnant ablation was successfully treated in about 70% of locoregional lymph nodes (6,10) and in about 70% of pulmonary micrometastases (10).

FOLLOW-UP

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 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 .

Two to three months after initial treatment thyroid function tests (FT3, FT4, TSH) should be obtained to check the adequacy of Levothyroxine (LT4) suppressive therapy. At 6 to 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, basal and rhTSH stimulated serum Tg measurement with or without diagnostic WBS (3,4). At this time most (nearly 80%) of the patients will belong to the low risk category and will disclose normal neck ultrasound and undetectable (<1.0 ng/ml) basal and 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 (11,12). Recently, new methods for serum Tg measurement with functional sensitivity below 0.1 ng/ml became available. Using these assays some authors reported that an undetectable basal serum Tg (<0.1 ng/ml) may give the same information of a stimulated serum Tg value, thus avoiding the need for Tg stimulation (13-20). However, the higher negative predictive value (NPV) of these tests is at the expenses of a very low specificity and positive predictive value (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 ultrasound 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 less than 1.0 ng/ml, it is not possible to distinguish between ab-

sence or presence of disease. In these cases, rhTSH stimulation test may be still informative since it may detect those patients in whom serum Tg increases to more than 1 ng/ml. In these patients a more intensive follow-up may be useful (19).

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 ultrasound 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 control after initial therapy. In this group, the second test confirmed complete remission in almost all patients (11,12,21-24).

At the time of the first control after initial therapy, about 20% of patients may have detectable basal or stimulated serum Tg levels. If serum Tg is detectable in basal condition the chance that the patient has visible disease are very high and thus imaging techniques must be applied. If serum Tg is detectable in the low range after rhTSH stimulation and the chance of serum Tg to convert from detectable to undetectable during follow-up is about 50% (25) and thus observation is all that is required. On the contrary, a trend of serum Tg to increase over the time is an hallmark of possible disease to be localized by imaging techniques including therapeutic doses of ¹³¹I (3,4). During the evaluation of metastatic patients, ¹⁸F-DG-PET scanning is gaining more attention as a diagnostic and prognostic tool (26). In general, the sensitivity of ¹⁸F-DG-PET is not superior to that of traditional techniques such as CT and MRN, thus the main indication for ¹⁸F-DG-PET is in metastatic patients who have lost radioiodine uptake. ¹³¹I-WBS negative and ¹⁸F-DG-PET positive patients indicate a group of tumors with more aggressive and less differentiated phenotype carrying a worse prognosis with respect to ¹³¹I-WBS positive and ¹⁸F-DG-PET negative patients. (26).

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