Current Concepts in the Follow-Up of Patients with Differentiated Thyroid Cancer

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Follow-up of patients with differentiated (papillary and follicular) thyroid cancer after total thyroidectomy and thyroid ablation has been traditionally based on periodic serum thyroglobulin determination and ^{131}I diagnostic whole body scan until complete remission is achieved. With more sensitive technologies, persistent or recurrent disease can be detected in early stages, presumably allowing for a better outcome. Furthermore, the burden of follow-up procedures can be reduced in low risk patients with no evidence of persistent disease. In the last decade, technical innovations and clinical research have changed the approach to follow-up of DTC patients considerably; yet some areas remain controversial. In this article we provide an up-to-date review of the approach to the follow-up of these patients.

Staging systems and risk stratification in DTC

Postoperative staging for thyroid cancer has several purposes: a) facilitates prognostication for an individual patient; b) helps to tailor decisions regarding postoperative adjunctive therapy to the patient; c) contributes to decision-making regarding the frequency and intensity of follow-up; and d) enables accurate communication between health-care professionals regarding a patient.

At least nine systems have been proposed for staging of thyroid cancer [1]. These systems take into account a number of prognostic factors for outcome in multivariate analysis of retrospective studies. Age at diagnosis is one of the most important prognostic features of DTC. Death is more likely to occur if the patient is older than 40 at the time of diagnosis. Men are twice as likely as women to die from thyroid cancer. Patients with primary tumors > 4 cm will have a higher cancer-related death rate. Overall, papillary carcinoma has a long-term survival rate higher than follicular carcinoma, and invasion into tissues surrounding the thyroid is associated with a poorer prognosis. Unlike most other solid tumors, lymph node metastases do not appear to be as important for survival. Distant metastases at initial staging predict a higher death rate. These and other risk factors are weighted differently among the various systems in predicting outcome, but no system has demonstrated superiority.

The TNM classification was first introduced in 1997 by the American Joint Committee on Cancer [2]. It relies on the extent of primary tumor, regional lymph node involvement, distant metastases, age, and histology. Despite the fact that it does not take into account several additional independent prognostic variables, its utility in predicting disease mortality and its requirement in the cancer registry has made it the staging method of choice for all DTC patients. However, the TNM system was developed to predict mortality, not recurrence. For evaluation of recurrence, a classification of risk has been adopted [3,4]. The low risk group is defined as no local or distant metastases, all macroscopic tumors resected, no invasion of loco-regional tissues, no aggressive histology or vascular invasion, and ^{131}I uptake only in the thyroid bed on the first whole body scan. Intermediate risk requires a primary tumor 4 cm or larger, microscopic invasion into perithyroidal soft tissue, aggressive histology, or vascular invasion. The high risk group is defined as macroscopic tumor invasion, incomplete tumor resection, local or distant metastases, or ^{131}I uptake outside the thyroid bed on the first post-treatment whole body scan.

The role of serum thyroglobulin

Following total thyroidectomy and thyroid ablation, all patients are started on suppressive doses of thyroxine, and serum thyroglobulin levels are used as a marker of disease. Immunometric assays are now used almost universally for measuring thyroglobulin levels, albeit with some limitations. First is the suboptimal

DTC = differentiated thyroid cancer

functional sensitivity, which currently stands at 0.9 ng/ml despite the very good analytical sensitivity of 0.2 ng/ml. Most studies show a limited efficacy of Tg level to detect active disease when the patient is on thyroxine suppression (Tg-on) with thyroglobulin detection limit of 3 ng/ml, although more recent studies with a 1 ng/ml detection limit have shown similar results. If a supersensitive assay with a thyroglobulin functional sensitivity closer to 0.2 ng/ml could be developed for commercial use, the use of Tg-on in detecting recurrence should be reconsidered [5]. Second, there is a large variability (47%) between different IMA methods that persists (37%) after standardization with the human thyroglobulin reference material (CRM 457) [6]. Third, interference in thyroglobulin assays by anti-Tg antibodies can occur in up to 20% of patients [6,7]. Whether these antibodies cause incorrectly high or low values depends on the type of thyroglobulin method used. The IMA method typically reports falsely low thyroglobulin values when Tg antibodies are present, leading to a delay in treatment. Alternatively, an inappropriately high thyroglobulin level can be a problem with some of the radioimmunoassay methods and leads to unnecessary scans or treatment. The use of recovery tests for detection of TgAb interference could solve this problem, but it has been reported to be unreliable [6]. The National Academy of Clinical Biochemistry recommended routine use of CMR-457 standardization, but discouraged the use of recovery tests [7].

The combination of high resolution ultrasonography and stimulated thyroglobulin is the most reliable method for detection of recurrent disease

It is now well accepted that an undetectable thyroglobulin level on suppression (Tg-on) is unreliable for the detection of active disease. Up to 21% of patients with undetectable Tg-on (< 1 ng/ml) will show a rise to above 2 ng/ml after withdrawal, and 36% of these patients will harbor metastases [8]. Recently, a single determination of stimulated serum thyroglobulin (Tg-off) levels was proposed for the follow-up of low risk DTC patients, with neck ultrasound as additional surveillance; however, the use of the whole body scan is discouraged [8,9]. Both the American Thyroid Association and the European Thyroid Association have endorsed these recommendations [3,4], and a 2 ng/ml cutoff level is now used for diagnosing persistent disease based on 10 studies showing that tumor is rarely found below this level [8].

Schlumberger et al. [9] recommended sparing whole body scan in low risk patients with undetectable Tg-off and no evidence of disease at 6–12 months after total thyroidectomy and thyroid ablation. The supporting data for their recommendation came from seven recent retrospective studies [10-16]. Together, these studies included a total of 1248 patients, of whom 916 were Tg-off negative, with only 24 of them having extra-thyroidal radioiodine uptake on whole body scan; and 332 were Tg-off positive, with 157 of them having extra-thyroidal radioiodine uptake on whole body scan. This combination of a good negative predictive value for Tg-off alone, together with the poor sensitivity of whole body scan in Tg-off positive patients, guided the authors' conclusions.

Two points, however, should be addressed: First, when considering intra- and extra-thyroidal uptake together, the number of Tg-off negative with whole body scan-positive patients in all studies combined rose from 24/916 (2.5%) to 183/916 (20%), meaning that remnant ablation could not be completed in a significant proportion of patients. The ability to discern between intra- and extra-thyroidal bed uptake and the significance of not re-treating these 20% with thyroid remnants is not clear. Second, patients with low detectable Tg-off levels, in the range of 2–10 ng/ml, may well have no persistent disease, representing false positives [15,17]. In such cases, some authors recommended a policy of wait and see, based on serial Tg determinations and reserving ^{131}I treatment for those showing rising thyroglobulin levels [9,17]. Additional support for their recommendations comes from evidence that neck ultrasound performed by an experienced operator is the most sensitive means of detecting neck recurrences [14]. In the real world, however, the intra- and/or inter-operator variation in neck ultrasound is far from satisfactory. Finally, while long-term survival is known to be very favorable in DTC compared to other malignant diseases, the efficacy of a "loose" surveillance, allowing for elimination of "unnecessary" investigations as recently proposed [8], is yet to be proven.

The role of ultrasound

Neck ultrasound has been found to be a very effective tool for detecting regional disease, including patients with undetectable serum Tg-off levels. In one study of 456 low risk papillary thyroid cancer patients followed for 5 years, whole body scan detected node metastases in 13 subjects and ultrasound in 38 (31 Tg-off positive and 7 negative), with a negative predictive value, for negative thyroglobulin and ultrasound combined, of 98.8% at first follow-up [18]. In another study, Tg-off combined with neck ultrasound was found to have a sensitivity of 96.3% and a negative predictive value of 99.5% compared to 21% and 89% respectively for whole body scan alone, 85% and 98.2% respectively for Tg-off alone, and 92.7% and 99% respectively for Tg-off/whole body scan combined [19].

Based on current improvements in neck ultrasound, sonographic criteria for management of thyroid nodules have been published by several medical associations [3,4], including a recent consensus statement from the American Society of Radiologists [20]. The highest predilection for malignancy is found with a predominantly solid composition, microcalcifications, irregular margins, intranodular vascularization, and size > 1.0 cm in diameter. However, in patients after total thyroidectomy and iodine therapy, any thyroid tissue should be considered abnormal. A

Tg = thyroglobulin
IMA = immunometric assay

cervical lymph node is suspicious if it has a heterogeneous texture, cystic areas within, or a rounded shape causing mass effect; size however, is less important. In these cases there is a need for ultrasound-guided fine-needle aspiration.

The role of whole body scan

Diagnostic whole body scan is performed after thyroid-stimulating hormone stimulation, either following thyroid hormone withdrawal or after recombinant TSH administration. The scan is acquired 48–72 hours after administration of 2-5 mCi (74–185 MBq) ^{131}I. In recent years, dxWBS has been found less sensitive than stimulated-thyroglobulin measurement in detecting persistent/recurrent disease, and the yield of dxWBS has been questioned in patients who have undetectable thyroglobulin levels off-thyroxine [8-10]. Cailleux et al. [12] reported data on 256 consecutive patients studied 6–12 months after thyroidectomy and radioiodine therapy. Following withdrawal of thyroxine, stimulated thyroglobulin was undetectable in 210 of 256 patients, with only 2 of these 210 patients demonstrating tumor recurrence in neck lymph nodes after 3 years of follow-up. The relapse could have been detected on neck ultrasound and on serum thyroglobulin during follow-up. Mazzaferri and Kloos [13] studied 107 consecutive patients with dxWBS and rTSH-stimulated thyroglobulin. None of the 87 among 107 patients whose serum thyroglobulin was < 2 ng/ml was found to have a positive scan, although 8% of patients with thyroglobulin > 2 ng/ml had negative scans. Overall, rTSH-stimulated Tg value > 2 ng/ml had a sensitivity of 100% and a specificity of 91%. Thus, in this study, it appeared that the dxWBS did not add to the accuracy of monitoring

Empiric treatment with ^{131}I should be considered when stimulated thyroglobulin is detectable and no visible lesion apparent on conventional imaging

Cooper [4], Mazzaferri [8] and Schlumberger [9] and their teams all suggested that the 80–90% of patients whose thyroglobulin levels are not stimulated with rTSH may be safely followed by monitoring thyroglobulin levels on thyroxine, clinical examination, and high resolution ultrasound of the neck. This approach is currently limited to low risk patients, especially those with a prior negative dxWBS, in view of the study of Robbins and co-authors [10] who referred 366 patients after rTSH to dxWBS and serum thyroglobulin. Data showed that 76% of patients in whom stimulated thyroglobulin rose to > 2 ng/ml had residual disease on rTSH scan, but the same was true for 13% of those whose stimulated thyroglobulin was 2 ng/ml or less. The authors concluded that although Tg-off alone may be sufficient in low risk patients, especially those who had a prior negative dxWBS, the addition of dxWBS is essential for monitoring a high risk population.

Recombinant human TSH (Thyrogen^{TM})

The usual protocol for withdrawal whole body scan includes cessation of thyroxine for 4–6 weeks and measurement of thyroglobulin and TSH before a whole body scan, aiming to reach a TSH level above 25–30 mU/L, which will allow for ^{131}I uptake. Thyroid hormone withdrawal may lead to severe hypothyroid symptoms for several weeks, and in rare instances to rapid tumor growth. This morbidity has been significantly reduced by the introduction of rTSH, and its use prior to dxWBS together with thyroglobulin stimulation has similar sensitivity to a scan after thyroxine withdrawal [21]. Most patients, however, remain asymptomatic during the first 2 weeks of thyroxine withdrawal. Three recent studies [22-24] reported that a suitable TSH elevation could be reached in most patients 14–21 days of withdrawal, suggesting that thyroxine withdrawal can be shortened to 3 weeks. Furthermore, in most studies showing the advantage of avoiding hypothyroidism by using rTSH, the comparison was done against 4–6 weeks of withdrawal with TSH levels well above 50 mU/L. In a recent study [25] comparing rTSH and withdrawal for primary treatment, the withdrawal group reached a mean TSH of 83 mU/L, three times higher than the cutoff at 25–30 mU/L selected as sufficient. If a 25–30 mU/L TSH level provides reliable stimulation for ^{131}I trapping, a shortened protocol would have minimized the benefits of rTSH.

The advent of rTSH has raised the question of the relative sensitivity and specificity of thyroglobulin measurements (and DxWBSs for that matter) performed after rTSH injection as compared to those performed after thyroid hormone withdrawal. A recent meta-analysis of 46 individual studies determined that the sensitivity and specificity of thyroglobulin levels determined after thyroid hormone withdrawal were 96% and 95%, respectively. The corresponding values for thyroglobulin after rTSH injection were slightly lower, 92% and 88%, but still considered adequate [26]. Similar conclusions were reached by Robbins and Robbins [21] in their comprehensive review published one year earlier. From a strictly diagnostic point of view, rTSH and thyroid hormone withdrawal can be considered essentially equivalent in terms of sensitivity and specificity, and both the ATA and the ETA recommend either rTSH-stimulated or thyroid hormone withdrawal studies interchangeably [3,4]. Because of the morbidity associated with thyroid hormone withdrawal, and because of the excellent diagnostic accuracy of post-rTSH thyroglobulin level determination, there is a growing tendency to avoid the former whenever possible.

TSH = thyroid-stimulating hormone
dxWBS = diagnostic whole body scan
rTSH = recombinant TSH

ATA = American Thyroid Association
ETA = European Thyroid Association

Management of Tg-positive ^{131}I WBS-negative patients

Patients with detectable thyroglobulin but negative whole body scan and no recurrence on anatomic conventional imaging represent one of the most controversial issues in thyroid cancer management. When neck ultrasound and chest computed tomography do not disclose disease that is potentially curable by surgery, a therapeutic trial with radioiodine has been suggested to help localize persistent tumor or to treat surgically incurable disease. This high ^{131}I activity was found to increase the sensitivity of the whole body scan, with visualization of neoplastic foci not seen with diagnostic doses of ^{131}I.

Several agents have been proposed to enhance the efficacy of ^{131}I therapy for thyroid cancer by means of increasing the ability of the cancer cells to transport, organify, or retain the ^{131}I beyond the effects of TSH [27].

- A strict low iodine diet is recommended for 1–2 weeks prior to radioiodine ablation or therapy of metastatic disease.
- Lithium has been shown to inhibit the release of iodine from normal thyroid cells, and pretreatment with lithium carbonate increases the retention of radioiodine with resultant increase in radiation to the lesions. Koong et al. [28] found that lithium pretreatment increased retention in 24 of 31 individual lesions in 15 patients, with doubling of radiation to the lesions, but no long-term outcomes were reported from this cohort.
- Redifferentiating agents: binding of retinoids to retinoic X receptors results in enhanced expression of the gene that encodes the sodium iodide importer *in vitro*. In preliminary studies, treating patients with 13-cis retinoic acid (Roaccutane®), or metabolites that bind to both retinoic A receptors and retinoic X receptors, enhanced uptake in some thyroid cancers, particularly follicular cancers, but subsequent studies in larger groups of patients did not show significant efficacy for the majority of patients. Thus, conflicting reports have ensued either supporting or rejecting this approach [29].

Poorly differentiated, rapidly progressive thyroid cancer lesions often lose the ability to concentrate radioiodine and exhibit increased metabolic activity, as reflected in enhanced glucose utilization. They are thus detected by F18-fluorodeoxyglucose, using positron emission tomography. The latter has become the method of choice in DTC patients with negative dxWBS and detectable thyroglobulin, and has a sensitivity ranging from 71 to 89% in detecting metastases [30]. FDG-avid lesions are seldom destroyed by radioiodine therapy alone, and identification of multiple FDG-avid distant metastases may spare the patient aggressive local curative maneuvers. Furthermore, FDG-PET is an independent prognostic indicator in thyroid cancer [31].

Recent studies have reported enhanced FDG uptake following TSH stimulation [32,33], using withdrawal or rTSH. This is biologically plausible, as TSH stimulation increases expression of glucose transporters and glucose uptake of cultured thyroid cells. Petrich et al. [32] compared FDG-PET images obtained under TSH suppression with those obtained under stimulation with rTSH and found more "tumor-like lesions" (78 versus 22) in more patients (19 versus 9) after rTSH. Chin and team [33] also evaluated prospectively the impact of rTSH stimulation using paired FDG-PET scans both on thyroid hormone suppression and rTSH stimulation within 1 week. All lesions seen on TSH suppression scans were seen on the rTSH stimulation studies, but the latter identified four additional lesions not seen on TSH suppression, and one patient was positive on rTSH stimulation alone.

Several non-iodine single-photon emitters such as ^{201}Tl, ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin and ^{111}In-DTPA-octreotide, have been suggested for patients with negative dxWBS and detectable serum thyroglobulin. These non-iodine isotopes do not require withdrawal of thyroxine therapy, with sparing the patient prolonged hypothyroidism. The primary value of ^{201}Tl, ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin is in imaging of regional nodal disease and they are less reliable in visualizing bony and pulmonary metastases. Conflicting data have been reported concerning the comparison of FDG and ^{111}In-DTPA-octreotide [34].

Approach to anti-TgAb-positive patients

It has been recognized for more than 30 years that endogenous thyroglobulin antibodies have the potential to interfere with measurement of Tg protein, including recovery assays [16,17]. Accordingly, TgAb should be measured in every specimen sent for thyroglobulin assay and a change in TgAb values over time should be sought. Antigenic stimulation should cease once the thyroid had been completely ablated, and autoantibody production is therefore expected to decrease over time (6 to 12 months) in patients who are judged to be disease free after thyroid ablation. In contrast, anti-TgAb concentrations remain unchanged or exhibit an increase among patients with persistent or progressive thyroid cancer. However, a temporary rise in TgAb level may occur during the first 6 months after radioiodine therapy. This may even be a sign of the effectiveness of treatment since TgAb values return to the original value or below after 6 months [35]. In the absence of disease, anti-TgAb will progressively decrease and disappear within the first 2 years of follow-up [35].

Thyroglobulin mRNA in peripheral blood

The measurement of circulating mRNA from thyroid tumor cells as a potential indicator of recurrent or persistent thyroid cancer was first introduced in the late 1990s [36]. Initial studies suggested that thyroglobulin mRNA determinations may be as sensitive as protein measurements, and may be of particular use in patients with anti-TgAb that interfere with currently available plasma thyroglobulin assays. The method is based on several premises that must be validated. The first is that a sufficient number of cancer cells are consistently present in the circulation, even in the presence of minimal disease (sensitivity). The second major requirement for this test to be valid is that normal thyroid cells are never present in the circulation and that non-thyroid cells never express mRNA species (specificity). Normal thyroid cells do, of course, express thyroglobulin and thyrotropin receptor,

FDG = F18-fluorodeoxyglucose
PET = positron emission tomography

and significant amounts of these mRNA species have been found in the peripheral blood of normal healthy controls [37]. This suggests that the test may be valid only in patients with no normal thyroid tissue. Another, more critical point is that thyroglobulin mRNA may be expressed in very low concentrations by other cells in the body, including peripheral lymphocytes, through a process known as illegitimate transcription. Published studies suggest that neither of these two basic premises has been met by the currently available assays, given the low sensitivity and negative predictive value (82% and 43% respectively) reported in one study [38] and even lower specificity demonstrated in another [37]. In view of the proven and potential pitfalls of measurement of circulating thyroglobulin or TSH receptor mRNA, and the lack of standardized methodology and large-scale well-controlled studies, these determinations must still be considered experimental.

Follow-up after partial thyroidectomy

When DTC is confined to one lobe and the tumor consists of a single focus less than 10 mm in diameter with a well-differentiated histology, hemithyroidectomy of the affected lobe is an accepted choice for primary treatment and iodine therapy can be withheld [3,4]. In these patients, thyroglobulin levels cannot be used as a marker of persistent/recurrent disease since the remaining thyroid tissue normally synthesizes it, but a progressive rise in thyroglobulin over time may suggest tumor recurrence. Neck ultrasound is the most reliable method for the follow-up of these patients. It should be done at regular time intervals, at least once a year, with fine-needle aspiration performed if new lesions are detected. Because the potential for microscopic DTC foci to be present in the contralateral lobe, long-term thyroxine therapy is recommended to maintain TSH levels at the lower limit of normal [3,4].

Suppressive therapy during follow-up

The rationale for TSH-suppression therapy comes from experimental and clinical evidence showing that TSH behaves as a growth factor for thyroid epithelial cells. Several retrospective studies show a significantly lower recurrence rate for patients treated with suppressive doses of thyroxine [39,40]. Nevertheless, several adverse effects have been associated with long-term TSH suppression therapy, mainly increased bone turnover, increased risk for supra-ventricular tachycardia, and exacerbation of ischemic heart disease [27]. Initial suppression of TSH to levels < 0.1 mU/L is recommended for all patients, except those with microscopic occult disease that can be treated to achieve TSH levels of 0.1–0.5 mU/L. For low risk patients with no evidence of disease after 1 year, thyroxine dose may be decreased to maintain a TSH level of 0.1–0.5 mU/L. High risk patients should be maintained on TSH levels < 0.1 mU/L for 3–5 years after achievement of remission, as recommended by the ETA [3], or 5–10 years as recommended by the ATA [4]. In all cases overt hyperthyroidism should be avoided.

Conclusions

The TNM staging should be applied to all patients with differentiated thyroid cancer and the patient-risk stratification, as described above, should be considered in the planning of follow-up. Thyroglobulin assays should be calibrated against the international CRM-457 standard and anti-TgAb should be measured in all thyroglobulin samples. After radioiodine ablation, subsequent dxWBS is not necessary in low risk patients who are clinically free of residual tumor and have an undetectable serum thyroglobulin level following either thyroxine withdrawal or rTSH administration, and negative neck ultrasound. However, for higher risk patients, radioiodine scanning is suggested for possible detection of recurrent or residual disease. Empiric radioactive iodine therapy should be considered in patients with elevated or rising serum thyroglobulin levels in whom conventional imaging failed to reveal the tumor site. When post-therapy whole body scan is negative, no additional radioiodine should be given and FDG-PET scan is suggested. In case of interference of thyroglobulin measurement by TgAb, follow-up cannot rely on serum thyroglobulin results and should comprise clinical examination, neck ultrasound and a diagnostic ^{131}I whole body scan.

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