Controversies in the follow-up and management of well-differentiated thyroid cancer

M D Ringel and P W Ladenson

Divisions of Endocrinology and Oncology, Ohio State University, Columbus, Ohio, USA
1Division of Endocrinology and Metabolism, Johns Hopkins University, 1830 E. Monument Street, Suite 333, Baltimore, Maryland 21287, USA

(Requests for offprints should be addressed to P W Ladenson; Email: ladenson@welch.jhu.edu)

Abstract
Thyroid cancer is a common malignancy with an apparent increasing incidence and a wide spectrum of clinical behavior and therapeutic responsiveness. Recent advances in diagnosis, primary treatment, and long-term monitoring have led to enhanced detection of primary and recurrent disease and improvements in therapy. Controversy still surrounds several issues: the most accurate predictive staging system and histological subclassification scheme, optimal preoperative assessment and surgical extent, appropriate use of radioiodine for remnant ablation, goal for thyrotropin-suppressive thyroid hormone therapy, best practices in immediate postoperative and long-term monitoring, and approach to the patient with thyroglobulin evidence of residual disease. In this paper, recent data related to these controversial issues are critically reviewed.

Introduction
Thyroid cancer is among the most common of endocrine malignancies. In the USA, approximately 20,000 new cases are diagnosed yearly and more than 200,000 patients are monitored for cancer recurrence or progression according to the latest statistics from the American Cancer Society. For reasons that are uncertain, the incidence of thyroid cancer appears to be rising, although the outcome remains excellent with long-term disease-free survival rates approaching 90% over 20 years (Mazzaferri & Jhiang 1994, Hundahl et al. 1998). Despite these overall excellent statistics, patients with more aggressive forms of thyroid cancer have a much worse prognosis and are frequently unresponsive to conventional therapy. For this reason, many clinicians advocate aggressive initial therapy and vigilant long-term monitoring for patients with thyroid cancer in an effort to prevent or detect recurrent disease. The current review focuses on controversies in the initial management of well-differentiated thyroid cancer, monitoring for tumor recurrence or disease progression, and use of radioiodine therapy.

Staging and classification
Primary thyroid cancers can be separated into four histologic groupings, well-differentiated epithelial thyroid cancer (papillary and follicular), poorly differentiated thyroid cancer (insular, tall cell, columnar cell, and other poorly differentiated variants of papillary cancer and anaplastic cancer), medullary thyroid cancer, and unusual thyroid tumors (lymphoma, sarcoma, squamous cell, and others) (Hedinger et al. 1989). Because more than 90% of primary thyroid cancers are well-differentiated papillary or follicular cancers (Hundahl et al. 1998, 2000, Sherman et al. 1998), they will be the primary focus of this review.

Tumor staging
There are a variety of tumor staging systems for well-differentiated thyroid cancer based on several variables, including tumor size, presence of direct local invasion, multifocality, lymphadenopathy, distant metastases, and patient age (Sherman 1999). Some of these stratify only papillary cancer (MACIS, clinical class), while others
were designed to stage all tumor histologies (TNM), European Organisation for Research and Treatment of Cancer (EORTC), or just well-differentiated cancers (AMES and Ohio State). Each of these staging systems groups patients into categories based on tumor size, extent and location of metastases, patient age (except Ohio State), and tumor dedifferentiation. Sherman et al. (1998) applied these staging systems to the National Thyroid Cancer Treatment Cooperative Study (NTCTCS) prospective database and compared them with their own staging system. Disease-specific survival 5 years after diagnosis using the NTCTCS staging system was 100% for stage I and II papillary and follicular carcinoma, 94 and 79% for stage III and IV papillary cancer, and 82 and 37% for stage III and IV follicular cancer. Similar results were obtained using nearly all of the staging systems, although some differences were noted. In this study, as well as in a recent cohort study of the National Cancer Database (Hundahl et al. 1998, 2000), follicular cancer had a worse prognosis than papillary cancer, particularly with higher stage disease. One peculiarity of both the TNM and NTCTCS staging systems is the classification of all patients under the age of 45 years with distant metastases as having less than stage 4 disease. Despite this, the TNM system is the most frequently used as it facilitates unambiguous communication with other subspecialists. The TNM staging system for thyroid cancer is shown in Table 1.

Several histologic features of thyroid cancers that are not included in the TNM staging system are prognostically important. These include the presence or absence of multifocal cancer (Mazzaferri & Jhiang 1994), vascular invasion in papillary or follicular thyroid cancers (Grebe

### Table 1 Current American Joint Committee on Cancer TNM (AJCC) staging system for thyroid cancer.

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<tr>
<th>Tumor</th>
<th>T1: Tumor 2 cm or less in greatest dimension, limited to the thyroid</th>
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<td>T2: Tumor more than 2 cm, but not more than 4 cm in greatest dimension and limited to the thyroid.</td>
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<td>T3: Tumor more than 4 cm in greatest dimension, or any tumor with minimal extrathyroid extension into sternothyroid muscle or perithyroidal soft tissues.</td>
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<td>T4: Excluded.</td>
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<td>T4a: Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve.</td>
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<td>T4b: Tumor invades prevertebral fascia or encases carotid artery.</td>
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<tr>
<th>Nodes</th>
<th>Regional lymph nodes: Central compartment, lateral cervical, and upper mediastinal nodes</th>
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<tr>
<td></td>
<td>N0: No nodal spread</td>
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<td></td>
<td>N1a: Metastasis to level IV (pretracheal, tracheal, and prelaryngeal nodes)</td>
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<td>N1b: Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal nodes.</td>
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<tr>
<th>Metastases</th>
<th>M0: No distant metastases</th>
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<tr>
<td></td>
<td>M1: Presence of distant metastases</td>
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<tr>
<th>Staging for follicular cell-derived thyroid cancer (papillary and follicular) Under 45 years of age</th>
<th>45 years and older</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Any T, any N, M0</td>
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<tr>
<td>Stage II</td>
<td>Any T, any N, M1</td>
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<tr>
<td>Stage III</td>
<td>N/A</td>
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<tr>
<td>Stage IV A</td>
<td>N/A</td>
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<tr>
<td>Stage IV A</td>
<td>N/A</td>
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<td>Stage IV B</td>
<td>N/A</td>
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<td>Stage IV C</td>
<td>N/A</td>
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<th>Staging for anaplastic thyroid carcinoma (all are considered stage IV, regardless of patient age)</th>
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<tr>
<td>Stage IVA</td>
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<td>Stage IV B</td>
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<td>Stage IV C</td>
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et al. 1995, Gardner et al. 2000), autoimmune thyroid disease in the remaining thyroid tissue, and/or incomplete surgical resection (Grebe & Hay 1995).

Histologic subtypes

The importance of histologic tumor dedifferentiation has been debated for different subtypes of papillary and follicular cancer. Certain subtypes, such as the tall and columnar cell variants of papillary cancer and the insular variant of follicular cancer are more common in older patients with higher stage disease and have a worse prognosis than usual forms of thyroid cancer (Burman et al. 1996, Prendiville et al. 2000). However, the independent prognostic significance of the histology itself, as distinct from other factors defining conventional tumor stage, is not entirely clear. Poorly differentiated cancers are occasionally found in conjunction with anaplastic cancer. Furthermore, they are more likely to have mutations in the p53 tumor suppressor gene (Williams 1995, Ruter et al. 1996, Ain 1998, Putti & Bhuiya 2000), suggesting a dedifferentiated phenotype. For these reasons, it is generally recommended that patients with these tumors should be treated more aggressively than those with similar staged well-differentiated cancer, particularly if they are older. The solid variant of papillary cancer has been described in children exposed to radioactive iodine in the Chernobyl nuclear incident of 1986 (Nikiforov & Gnepp 1994, Williams 1995, Michel & Donckier 2002), but the duration of follow-up is not yet adequate to fully evaluate the prognostic importance of this variant. Diffuse sclerosing papillary cancer typically presents as a diffusely enlarging thyroid that is found to have an infiltrating papillary cancer, often with an associated intense lymphocytic infiltrate. These tumors occur more frequently in young women and are almost always metastatic to lymph nodes at diagnosis, but appear otherwise to follow the indolent course typical of papillary cancer (Moreno Egea et al. 1994).

The prognosis for patients with Hürthle cell carcinoma has also been debated. Hürthle cells have abundant eosinophilic staining, mitochondria-laden cytoplasm, but are otherwise well differentiated. They can be present as occasional cells within otherwise typical papillary or follicular carcinomas, but only tumors comprised entirely of this cell type are classified as Hürthle cell carcinomas. Hundahl et al. (1998) reported the outcome of thyroid cancer in 53,856 patients identified in the National Cancer Data Base and determined that patients with Hürthle cell cancer had a lower 10-year survival (75%) than patients with follicular (85%) or papillary cancer (93%). However, several recent publications have reported similar outcomes for conventional follicular cancer and Hürthle cell cancer (Maximo & Sobrinho-Simoes 2000, Bhattacharyya et al. 2003, Lopez-Penabad et al. 2003). The prognosis of Hürthle cell cancers may be due, in part, to the inability of many Hürthle cell malignancies to concentrate iodine. Thus, some authorities recommend a more aggressive initial surgical approach for patients with these tumors, including unilateral neck dissection (Maximo & Sobrinho-Simoes 2000, Stojsadinovic et al. 2002).

Anaplastic thyroid cancers are always categorized as stage IV cancers due to their extremely aggressive behavior and extremely poor clinical outcome, with median survival times of 6–12 months (Hedinger et al. 1989). Advances in chemotherapy and radiation therapy over the past 30 years have had little impact on patient survival or quality of life. It is important to recognize that any focus of anaplastic thyroid cancer within an otherwise well-differentiated tumor alters the patient’s prognosis, regardless of their age (Ain 1999).

Controversies in initial therapy

Initial therapy for thyroid cancer, typically following cytological diagnosis by fine-needle aspiration, consists of thyroidectomy and, in certain cases, radioactive iodine therapy to ablate remnant tissue and perhaps metastatic cancer. These procedures are generally followed by long-term thyroxine therapy at doses intended to reduce circulating levels of thyrotropin (thyroid stimulating hormone, TSH) below normal (Singer et al. 1996). There are still controversies involving the optimal extent of initial surgery, indications for radioiodine therapy, and degree of TSH suppression required, particularly in patients with stage 1 or 2 disease.

What is the appropriate preoperative evaluation?

The extent of preoperative testing in patients with cytologically diagnosed or suspected thyroid cancer deserves careful thought. The serum TSH should be measured, since suppression suggests the possibility of a benign autonomously functioning nodule; whereas an elevated serum TSH indicating hypothyroidism suggests that the patient may need lifelong thyroxine therapy regardless of the extent or diagnostic outcome of surgery. Preoperative serum thyroglobulin measurement has been reported to help differentiate benign from malignant thyroid nodules (Spencer 2000) or to define the optimal extent of surgery, but this has not yet been rigorously demonstrated. Imaging by cervical ultrasound, as noted above, may be helpful in decision making about whether to excise the contralateral lobe and/or perform regional lymph node dissection. In patients with large tumors, particularly those extending beneath the thoracic outlet, and those with clinical suspicion of local invasion or
metastasis (e.g. pain, hemoptysis, dysphagia or odynophagia, dyspnea, hoarseness or dysphonhia, nodule fixation, regional adenopathy, or vocal cord palsy), preoperative magnetic resonance or computed tomographic imaging may be helpful in planning the surgical approach. However, iodinated radiocontrast agents should be avoided whenever possible, since the stable iodine load that they provide can interfere with subsequent radioiodine scanning and therapy for months.

What is the proper extent of initial surgery?

For patients with cytologically diagnosed thyroid cancer, a near total or total thyroidectomy by an experienced surgeon whose permanent complication rate (hypoparathyroidism and/or recurrent laryngeal nerve damage) is less than 2% is generally the procedure of choice. The benefit of bilateral surgery was confirmed by Hay et al. (1998), who reported a significantly lower recurrence rate, but no different cancer-specific mortality in 1685 Mayo Clinic patients. Those with stage 1 and 2 tumors by AMES criteria had a lower 20-year recurrence rate when treated with bi-lobar rather than uni-lobar thyroidectomy (2% vs 14%). These data are consistent with most but not all retrospective data. The lower recurrence rate conferred by bilateral surgery appears to be even more impressive for patients with stage 3 primary tumors (Mazzaferri & Jhiang 1994, Grebe & Hay 1996a, Hundahl et al. 2000, Goss et al. 2002). However, no impact on tumor-specific mortality has ever been demonstrated and, in most studies, radioiodine therapy is effective in reducing recurrence rates in patients with initial regional nodal metastases (Mazzaferri & Jhiang 1994, Grebe & Hay 1996a). In most cases, the tumor stage at the time of surgery helps define the extent of node dissection that is required. For patients with primary lesions that are small (less than 4 cm), confined to the gland, and completely excised, only selective excision of any suspicious regional nodes is sufficient. For large tumors, poorly differentiated cytological features preoperatively, or local extension found at the time of surgery, an ipsilateral modified radical neck dissection is generally advisable.

What is the best management of incidental microscopic papillary carcinoma?

A related controversial issue is the management of incidentally detected microscopic (less than 1 cm diameter) papillary carcinoma. Sometimes a patient undergoing surgery for what ultimately proves to be a benign thyroid nodule or multinodular goiter is also found to have a small papillary cancer histologically. In cases with solitary intrathyroidal and completely excised papillary cancers less than 1.0 cm, there are no data indicating that completion thyroidectomy or postoperative radioiodine ablation further improve the already excellent prognosis. For most patients, only thyroxine therapy to maintain the TSH in the low to normal range is indicated (Cooper et al. 1998). Exceptions in which completion thyroidectomy may be justified include patients with special risk of thyroid cancer by virtue of previous neck irradiation or family history of thyroid cancer, contralateral nodularity by palpation or ultrasound, lymph node metastases, and/or multiple foci of papillary cancer in the excised lobe. Radioiodine ablation of the remaining lobe, an alternative approach that is sometimes entertained (Randolph & Daniels 2002), is generally advisable because multiple ultrasound, the availability of a skilled thyroid surgeon, and patient preference. When a lobectomy is planned, the surgeon should be vigilant intra-operatively for gross evidence of cancer (e.g. invasion or adherence to adjacent tissue or regional adenopathy), which should then prompt removal of the contralateral lobe.

The extent of lymph node dissection at the time of the initial surgery is another topic of great debate. Thyroid cancer frequently metastasizes to ipsilateral cervical and/or upper mediastinal lymph nodes, particularly in patients with papillary thyroid cancer. Some, but not all, studies demonstrate that the presence of regional lymph node metastases at the time of surgery increases tumor recurrence rates (Mazzaferri & Jhiang 1994, Grebe & Hay 1996a, Hundahl et al. 2000, Goss et al. 2002).
How and when should initial (remnant ablative) radioiodine therapy be administered?

There are two rationales for postoperative iodine (I)-131 therapy in treatment of patients with thyroid cancer: (1) to eradicate residual unresected microscopic or gross tumor in remnant thyroid tissue or sites of extrathyroidal metastases; and (2) to ablate remnant thyroid tissue in order to increase the specificity of long-term monitoring for residual cancer. Postoperative radioablation is recommended by nearly all authorities for invasive follicular carcinomas and papillary cancers that are large (greater than 4 cm), locally invasive, extensively involving regional lymph nodes, or incompletely resected. However, use of radioiodine ablation for lesser disease has been long debated. Furthermore, there is controversy regarding the optimal I-131 dose for these indications.

Retrospective and observational studies from both single center and multi-center cohorts suggest that there is a lower recurrence rate after postoperative radioiodine therapy even in stage 2 papillary and follicular cancers (Mazzaferri & Jhiang 1994, Singer et al. 1996, Hundahl et al. 1998, 2000, Wartofsky et al. 1998, Franklyn 1999). On the other hand, data from the Mayo Clinic suggest that patients with small papillary cancers do not benefit from I-131 therapy in terms of lower recurrence (Grebe & Hay 1996a,b). Logue et al. (1994) reported that for patients with stage 1 papillary cancers with tumor within 2 mm of the surgical margin, radioactive iodine was effective in reducing local recurrence rates over a median 10-year follow-up.

In view of these conflicting data, the potential benefits of the radioiodine therapy must be weighed against its risks, transient morbidity, inconvenience and cost. The risks of adverse reactions and long-term complications of postoperative radioiodine therapy are relatively low. The most common complications are due to radiation sialadenitis with resulting short-term pain and swelling and long-term xerostomia and hypogeusia. Sialadenitis occurs in 5–40% of radioiodine-treated patients, and its incidence is related to the dose of radioiodine administered (Van Nostrand et al. 1986, Wartofsky et al. 1998). Nasolacrimal duct obstruction is another related complication (Kloos et al. 2002). With the range of doses typically administered for immediate postoperative radioiodine therapy, transient leukopenia and oligospermia in males have been reported, but without significant clinical consequences. These treatments are, of course, initial contributors to the more serious side-effects of higher cumulative radioiodine doses for persistent disease, including the secondary malignancies reported in some series: leukemia, small intestinal, bladder, and perhaps breast cancers (Edmonds & Smith 1986, Hall et al. 1990, Glanzmann 1992, de Vathaire et al. 1997, Black et al. 1998, Vassilopoulou-Sellin et al. 1999). These have been estimated to occur in approximately 1:300 patients at cumulative radioiodine doses greater than 500 mCi. Radiation pneumonitis is another potential side-effect of high cumulative I-131 doses delivering more than 80 rads to lung tissue in patients with extensive iodine-avid pulmonary metastases.

The optimal administered I-131 dose for initial postoperative radioiodine therapy has also been debated. When the aim is solely to ablate remnant thyroid tissue, the dose typically employed in most centers ranges from 30 to 100 mCi, with reported successful ablation rates of 50–70% and 60–90% respectively (Maxon et al. 1983, Maxon 1999). Paradoxically, it is generally advisable to treat patients who have larger thyroid remnants with a higher fractional radioiodine uptake with a lower I-131 dose, in order to prevent painful radiation thyroiditis. In most regions of the USA, I-131 doses in the 75–100 mCi range can now be administered on an ambulatory basis—an advantage that was previously limited to doses less than 30 mCi. For ablation of known or highly suspected residual cancer tissue, higher I-131 doses are employed, with the dose administered determined by the cancer type, stage, and extent of known residual tumor tissue. For example, patients with microscopically detected positive tumor margins in a small papillary thyroid cancer might be given a dose similar to those employed for remnant ablation alone, i.e. 30–100 mCi; whereas a patient with a large invasive follicular carcinoma with radiological findings suggesting possible distant metastatic disease might be administered as much as 150–200 mCi, or even more with dosimetric guidance.

An alternative approach to empiric dosing for remnant ablation is quantitative dosimetry, as described by Maxon (1999), in which a dose estimated on the basis of preliminary tracer studies to deliver 8000 rads to the thyroid remnant is employed, as long as the whole-body and blood radiation doses are tolerable. In the largest of these reports, remnant ablation was achieved in 92% of patients with neck uptake (Maxon 1999) using a mean dose of 157 mCi. However, the dosimetric calculation required for determining the lesion-specific radiation dose is relatively complex and unavailable at most institutions. Whole-body dosimetry in which the total body exposure to radiation is assessed based on repeated regional and whole-body quantitative imaging and determination of the radioiodine excretion rate can also be used to facilitate remnant ablative dosing (Van Nostrand et al. 2002). This
technique is more frequently applied to treatment of recurrent or residual thyroid cancer (see below).

Should diagnostic I-131 scanning be performed after initial surgery?

A further controversial issue is the requirement for preliminary postoperative imaging before I-131 therapy and the optimal isotope for radioiodine scanning in anticipation of I-131 therapy, or at all. The first rationale for preliminary imaging is that occasional patients (5–10%) will not, in fact, have remaining thyroid tissue, and will not require I-131 therapy at all. Second, quantitation of the remnant’s fractional uptake of radioiodine can assist with both empiric categorical and quantitative dosimetry. Third, rare patients will manifest iodine-avid metastatic disease on such scans, justifying a higher initial I-131 dose. On the other hand, in the vast majority of patients, the findings on such imaging do not actually change the recommended I-131 dose. Furthermore, the preceding doses of I-131 for imaging, typically 2–10 mCi, have been reported in some series to ‘stun’ remnant tissue, preceding doses of I-131 for imaging, typically 2–10 mCi, and will not require I-131 therapy. On the other hand, in the vast majority of patients, the findings on such imaging do not actually change the recommended I-131 dose. Furthermore, the preceding doses of I-131 for imaging, typically 2–10 mCi, have been reported in some series to ‘stun’ remnant tissue, preceding doses of I-131 for imaging, typically 2–10 mCi, and will not require I-131 therapy. On the other hand, in the vast majority of patients, the findings on such imaging do not actually change the recommended I-131 dose. Furthermore, the preceding doses of I-131 for imaging, typically 2–10 mCi, have been reported in some series to ‘stun’ remnant tissue, preceding doses of I-131 for imaging, typically 2–10 mCi, and will not require I-131 therapy.

An alternative is the use of I-123, which is exclusively a γ emitter without the β emissions responsible for the destructive and stunning effects of I-131 (Mandel et al. 2001, Gerard & Cavalieri 2002).

Finally, because patients must have a high circulating TSH level to facilitate uptake of iodine by residual normal and/or malignant thyroid tissue, thyroxine therapy has traditionally been withheld from postoperative patients for a period of 5–6 weeks with the aim of achieving serum TSH concentrations greater than 30 mU/l (Sfakianakis et al. 1975). The resulting transient, but severe iatrogenic hypothyroidism almost universally produces symptoms and reduces quality of life (Ladenson 2002, Pacini 2002), occasionally exacerbates underlying medical or psychiatric conditions (e.g. congestive heart failure and depression), and rarely promotes growth of critically located tumor tissue adjacent to the central nervous system or airways. Short-term tri-iodothyronine is often used to lessen the duration of hypothyroidism.

Following Federal Drug Administration approval of recombinant TSH (TSHα; Thyrogen; Genzyme Corp., Cambridge, MA, USA; rTSH) for long-term thyroid cancer monitoring (see below), early studies have investigated the use of rTSH for postoperative thyroid remnant ablation. In one historically controlled, but non-randomized clinical experience, rTSH preparation for radioiodine therapy was observed to be as effective as radioiodine therapy with hypothyroid preparation. (For a description of the protocol for the administration of rTSH see Fig. 1.) In this study, ten patients were prepared for their first ablative dose of radioiodine with rTSH while maintained on thyroid hormone before being administered 30–250 mCi I-131, based on dosimetric calculations (Robbins et al. 2001c). The success of thyroid tissue ablation, as determined by rTSH scanning the following year, was demonstrated in all patients, four of them had elevated serum thyroglobulin levels, all of those patients were subsequently treated with radioiodine. Post-therapy scans performed after treatment revealed no uptake in three patients, the fourth had uptake in the lateral neck. In a subsequent retrospective study, Robbins et al. (2002a) reviewed 87 patients who underwent radioiodine remnant ablation after thyroid hormone withdrawal compared with the use of rTSH. Eighty-four per cent of those prepared with rTSH versus 81% prepared by thyroid hormone withdrawal had complete resolution of visible thyroid bed uptake after radioiodine remnant ablation. Pacini et al. (2002) recently reported a prospective trial comparing three groups of patients: 50 patients who underwent remnant ablation while hypothyroid; 42 who were stimulated with rTSH while hypothyroid; and 70 given rTSH while euthyroid. They found similar rates of successful ablation in patients prepared with hypothyroidism alone and with hypothyroidism plus rTSH. However, the euthyroid group that received rTSH had a significantly lower rate of ablation with 30 mCi I-131, which does not appear to be sufficient for remnant ablation with this mode of preparation, perhaps due to the accelerated rate of clearance of iodine in patients who are euthyroid or to the dosing regimen used by these investigators. Combining the results of these three studies (Robbins et al. 2001c, 2002a, Pacini et al. 2002), which involved a total of 259 patients, 79% had complete resolution of visible thyroid bed uptake after rTSH, which approximates the typical reported ablation rates of 70–80% that have been achieved after thyroid hormone withdrawal. Clearly, further studies are needed, and a prospective randomized trial comparing rTSH with hypothyroidism in preparation for a 100 mCi dose is in progress. Currently, most authorities consider rTSH-mediated remnant ablation appropriate only for patients at high risk of complications with hypothyroidism.

What is the role of TSH-suppressive therapy?

TSH is one of several important growth factors for thyroid cells, and its trophic effects on thyrocytes can be reduced by TSH-suppressive therapy. The utility of thyroid hormone in reducing the growth and progression of thyroid cancer has been known for over four decades. Since then, TSH-suppressive therapy has been an important component in the management of patients with thyroid cancer.
Several lines of evidence support the long-accepted use of TSH-suppressive thyroid hormone therapy: (1) the biology of the responsiveness of thyroid cancer cells to TSH; (2) inferences from anecdotal clinical observations; (3) clinical outcomes in thyroid cancer patients with or without postoperative TSH-suppressive therapy of varying degrees of intensity; and (4) the circulating thyroglobulin level in response to TSH-suppressive therapy as a surrogate for growth and recurrence. First, from a perspective of biological plausibility, well-differentiated epithelial thyroid cancer cells have TSH receptors, which are more abundant in follicular than in papillary cancers (Ichikawa et al. 1976, Takahashi et al. 1978). Furthermore, thyroid cancer cells in primary culture respond to TSH stimulation with second messenger responses activating the signaling cascades that promote thyrocyte growth (Carayon et al. 1980, Abe et al. 1981, Clark et al. 1981, Saltiel et al. 1981). However, there are contrary biological arguments as well. It is well known that there are other TSH-independent thyrocyte growth factors and oncogenes. In contrast to benign adenomas, activating mutations in the TSH receptor are rare in thyroid cancers, suggesting that TSH receptor activation is not sufficient to cause thyroid cancer (Matsuo et al. 1993, Russo et al. 1995, 1999, Spambalg et al. 1996).

Second, there have been anecdotal reports of thyroid cancers progressing clinically during endogenous TSH stimulation after thyroid hormone withdrawal for diagnostic imaging or radiodine therapy (Sfakianakis et al. 1975, Goldberg & Ditcher 1981). More recently, there have been similar reports of tumor expansion after administration of exogenous thyrotropin (Braga et al. 2001). Another indication that TSH receptor activation can increase the aggressiveness of epithelial thyroid cancers comes from studies reporting the relative extent and prognosis of thyroid cancer in patients with Graves’ disease, who have TSH receptor-stimulating immunoglobulins (Filetti et al. 1988, Belfiore et al. 1990, 2001).

Third, a small number of retrospective non-randomized clinical trials have investigated the impact of TSH-suppressive therapy on tumor recurrence. Mazzaferrri & Jhiang (1994) reported that papillary thyroid cancer patients receiving thyroid hormone therapy postoperatively had a lower cumulative recurrence rate than patients who were not treated with thyroid hormone after surgery. Pujol et al. (1996) evaluated 141 thyroid cancer patients followed for a mean of 11 years at one institution, relating their incidence of tumor recurrence to their serum TSH levels. They demonstrated a lower rate of tumor recurrence for patients with TSH levels less than 0.05 mU/l on 90% of obtained samples, in comparison with those patients with lesser degrees of suppression. This difference was independent of tumor stage, size, or other demographic variables. While the study suggests an important role for TSH-suppressive therapy, the data were limited by relatively few TSH measurements per patient. Subsequently, Cooper et al. (1998) reported data regarding the efficacy of TSH-suppressive therapy from the NTCCSG, which has prospectively collected data on the outcomes of thyroid cancer patients treated in various protocols at 11 centers in North America. In 617 patients followed for a median 4.6 years, a benefit of TSH suppression on tumor recurrence was demonstrable in univariate analysis only for patients with initial stage 3 or 4 tumors.

Controversies remain regarding the intensity and duration of TSH-suppressive therapy required to minimize the risk of tumor recurrence. There is no proven benefit of suppressing TSH concentrations to extremely low levels, such as less than 0.01 or 0.001 mU/l in

Figure 1 Protocol for rTSH administration. In preparation for rTSH administration, if whole-body iodine scanning is to be performed, a low iodine diet should be instituted 2 weeks prior to the first dose being administered. rTSH can be administered in the convenient weekly schedule shown. Intramuscular (IM) injections of 0.9 mg rTSH are administered on days 1 and 2. Laboratory tests are obtained on days 1 and 5. The maximal rise of thyroglobulin in response to rTSH occurs 48–72 h after the second dose is administered. For I-131 scans, 4 mCi are administered orally 24 h after the second dose of rTSH and the scan is obtained 48 h after administration. Alternatively, if I-123 is used as the scanning agent, 1–2 mCi are administered orally 24 h after the second dose and the scan is obtained 24 h later. Tg, thyroglobulin; TSH, thyrotropin; hCG, human chronic gonadotropin.
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...addition of bisphosphonate therapy. 

...women on thyroxine-suppression therapy who are post-menopausal and, if bone loss is detected, to consider the addition of bisphosphonate therapy (Pujol et al. 1996, Cooper et al. 1998).

By definition, TSH-suppressive thyroid hormone therapy causes iatrogenic mild thyrotoxicosis, but this is generally well-tolerated clinically without symptoms or signs in most patients. Overt thyrotoxicosis has long been known to cause accelerated bone loss (Ross et al. 1987, Leb et al. 1994, Liel 1996) and increase the risk of atrial fibrillation (Sawin et al. 1994, Sawin 2002). Over the past 20 years, there has been greater awareness that even mild thyroid hormone excess can have deleterious effects on the skeletal and cardiac systems. Several long-term studies have demonstrated that thyroxine suppression for thyroid cancer may induce bone loss in postmenopausal women, but not in premenopausal women or young men (Campos-Pastor et al. 1993, Florkowski et al. 1993, Hawkins et al. 1994, McDermott et al. 1995, Gouveia et al. 1997). Excess thyroid hormone enhances osteoclastic activity; consequently, estrogen and bisphosphonates appear to be effective in preventing reductions in bone density associated with thyroxine-suppression therapy (Balena et al. 1993, Ongphiphadhanakul et al. 1993, Rosen et al. 1993, 1998, Schneider et al. 1994). Therefore, it is generally recommended to monitor bone density in women on thyroxine-suppression therapy who are post-menopausal and, if bone loss is detected, to consider the addition of bisphosphonate therapy.

Thyrotoxicosis has also been associated with an increase in left ventricular thickness (Ladenson 1996, Fadel et al. 2000, Biondi et al. 2002, Osman et al. 2002). These data, in conjunction with observational data from The Framingham Study that associated atrial fibrillation with serum TSH concentrations less than 0.1 mU/l with mild elevations in thyroxine (Sawin et al. 1994), have led to concerns regarding the safety of thyroxine-suppression therapy in older patients and those with underlying cardiac disease. Periodic clinical assessments, patient awareness of these potential cardiac side-effects, and reduction in the degree of TSH-suppressive thyroxine therapy for patients with low-stage disease or who are in a complete remission for several years are recommended. Complete suppression of TSH in patients with known cardiac disease or arrhythmia may be best performed in conjunction with a cardiologist; β-adrenergic blockade is sometimes indicated. In patients with underlying cardiac disease, complete suppression of TSH may be only warranted in patients with stage 3 or 4 tumors, or aggressive histologic subtypes of thyroid cancer.

Based on these data, it appears that TSH suppression reduces the risk of tumor recurrence for patients with stage 3 or 4 tumors with minimal risk, unless patients have significant underlying cardiac disease. The utility of TSH suppression in patients with stage 1 or 2 tumors is uncertain. However, for most of these patients, the risks of therapy are small; therefore, suppression of TSH to levels less than 0.1 mU/l for patients without underlying cardiac disease for the first 5 years following surgery to minimize the likelihood of early tumor recurrence is recommended. Thereafter, in patients with no clinical, thyroid scans, or serum thyroglobulin evidence of residual disease, a reduction in the thyroxine dose sufficient to maintain a low but detectable TSH level, e.g. 0.1–0.5 mU/l is one widely advocated approach to reduce the likelihood of atrial fibrillation of osteopenia. However, more study is needed in this area to determine if, over a longer period of time, T-4 suppression is beneficial or causes an unacceptably high frequency of adverse effects for individuals with stage 1 or 2 thyroid cancers.

Controversies in monitoring for recurrent thyroid cancer

Periodic I-131 scanning, measurement of serum levels of thyroglobulin, and a variety of radiographic modalities are all used to monitor patients for thyroid cancer recurrence. Limitations of I-131 scanning include the requirement for endogenous or exogenous TSH stimulation as detailed above, and a relatively low sensitivity for neck recurrences. Limitations of thyroglobulin monitoring include inadequate sensitivity during T4-suppression therapy and the presence of interfering anti-thyroglobulin antibodies in approximately 20% of patients. Limitations of neck ultrasound, neck magnetic resonance imaging (MRI), chest computed tomography (CT) and positron emission tomography (PET) scanning include the lack of thyroid cancer specificity and the inability to detect well-differentiated cancer tissue (PET scanning only).

Radioiodine scanning

Radioiodine scanning has traditionally been a central component of monitoring for thyroid cancer recurrence. Patients are withdrawn from thyroxine therapy for 4–6 weeks to allow hypothyroidism to develop with consequent elevations of circulating TSH concentrations to greater than 30 mU/l. Patients are frequently treated with tri-iodothyronine for the first 3–4 weeks of the withdrawal...
to reduce the duration of symptomatic hypothyroidism, and are then deprived entirely of thyroid hormone therapy for 2 weeks. A low-iodine diet and occasionally thiazide diuretics are employed to deplete endogenous stable iodine stores. Once hypothyroidism is confirmed, a whole-body scan is performed 48–72 h after administration of 2–5 mCi I-131.

The location and extent of uptake, the clinical setting, and the degree of thyroglobulin elevation (see below) are used to make an individualized decision regarding the need for additional I-131 therapy. If treatment is required, it is usually administered within 48 h of the scan; otherwise, patients are placed back on thyroid hormone therapy immediately after the scan is interpreted. Limitations of thyroid hormone withdrawal scanning include the likelihood of severe hypothyroid symptoms for several weeks (usually 1 or 2 weeks), rare instances of rapid tumor growth in response to the prolonged elevation of circulating TSH concentrations, the potential to ‘stun’ or partially treat thyroid cancer tissue with the scanning dose, thereby reducing the efficacy of the therapeutic dose, and poor sensitivity of the whole-body scan in detecting disease. Despite the recognition of these problems, radiiodine scanning still has an important role in monitoring patients with thyroid cancer, particularly until a complete remission is achieved.

What is the best preparation for radiiodine scanning?

The development of rTSH has greatly reduced the morbidity for patients who must be monitored for thyroid cancer recurrence. Because rTSH preparation for I-131 scanning does not require withdrawal from L-thyroxine, hypothyroidism and its consequent morbidity do not occur. Potential side-effects of rTSH include transient nausea and fatigue in approximately 20% of patients, but these symptoms are typically mild and short-lived. Overall quality of life is clearly better for patients undergoing rTSH preparation rather than thyroid hormone withdrawal preparation for diagnostic scanning (Haugen et al. 1999, Robbins & Robbins 2003). Rarely, rapid enlargement of tumor masses has been reported following rTSH administration (Robbins et al. 2000, Braga et al. 2001).

In prospective clinical trials, rTSH preparation for I-131 scanning and thyroglobulin stimulation has been shown to have similar sensitivity to scanning after thyroxine withdrawal, provided that both scanning and thyroglobulin levels are included in the monitoring scheme (Haugen et al. 1999, Schlumberger et al. 2000, Robbins & Robbins 2003). These studies demonstrated that rTSH I-131 scans detected 86% of the lesions noted on withdrawal scan, including residual tumor detection in all patients with distant metastases. When a thyroglobulin level greater than 2.0 ng/ml was considered a positive finding, 93% of patients with residual or recurrent thyroid tissue in the thyroid bed and 100% of patients with regional or distant metastases were detected after rTSH preparation.

Robbins et al. (2001b) recently reported a single-site experience comparing rTSH and thyroxine withdrawal preparation for monitoring in 289 consecutive patients with thyroid cancer. In this study, similar to the earlier prospective studies, withdrawal scanning alone was more sensitive than rTSH scanning (80% vs 69%; P, non-significant), but the majority of withdrawal-positive and rTSH-negative scans were in patients with only faint thyroid bed uptake, not patients with regional or distant metastases. When thyroglobulin levels (2.0 ng/ml as the cut-off) were added to the diagnostic criteria, the sensitivity of rTSH monitoring was 98% compared with 96% for withdrawal, with specificities of 82% and 81% respectively. Consequently, these authors concluded that rTSH preparation for the combination of I-131 scanning and thyroglobulin monitoring was equivalent to thyroxine withdrawal. It is important to recognize that the degree of TSH induction of thyroglobulin levels is frequently lower following rTSH administration than after withdrawal of thyroid hormone, stressing the importance of assay sensitivity. In addition, these data do not apply to patients with anti-thyroglobulin antibodies, who were excluded from these prospective and retrospective studies.

These data suggest that in clinical practice, rTSH preparation and thyroxine withdrawal are equivalent in detecting residual or recurrent thyroid cancer, provided serum thyroglobulin can be measured accurately. With regard to rTSH-mediated therapy, there have been encouraging early studies (see above) showing successful remnant ablation and anecdotal reports of therapy for metastases (Robbins et al. 2000, 2002b). However, rTSH is not yet approved for preparation for therapy and its use should be limited for now to patients with a contra-indication to thyroxine withdrawal or inability to surmount an endogenous TSH increase. Furthermore, most patients who are not in complete remission who have a high likelihood of having recurrent disease on diagnostic scan should still be withdrawn from thyroxine in preparation for both scanning and therapy.

Are there important consequences of radiiodine scanning?

The impact of ‘stunning’ from the diagnostic I-131 scan on the efficacy of I-131 treatment is uncertain. ‘Stunning’ refers to the ability of the low-dose radiation exposure of the diagnostic scan to partially damage the thyroid cancer tissue, thereby reducing the ability of the subsequent therapeutic dose to destroy the remaining thyroid cancer
tissue. The frequency of stunning in clinical trials is highly variable, ranging from 5 to 40% of patients (Park et al. 1994, Yagcioglu et al. 1996, Kao & Yen 1998, Hurley 2000). Two variables likely account for these differences in results. First, stunning appears to occur more frequently with administration of higher doses of I-131 for diagnostic scanning, and different doses were employed in these studies. Second, stunning is more likely to occur if there is a delay of several weeks between the diagnostic and therapeutic doses of I-131 and the mean duration between the scan and treatment varied in these studies.

The dose-response of stunning creates a clinical conundrum. Diagnostic scans using higher doses of I-131 (5–10 mCi) result in greater scan sensitivity but also are more likely to reduce the efficacy of the therapeutic dose. One proposed alternative is to utilize rTSH-stimulated thyroglobulin in conjunction with non-I-131 imaging modalities for routine monitoring (see below). A second alternative is to use I-123 rather than I-131 for diagnostic scanning. I-123 exclusively emits only \( \gamma \) radiation without \( \beta \) emissions, and does not appear to cause stunning. Several studies suggest that it may be as accurate in detecting disease as I-131 (Grunwald et al. 1999, Yaakob et al. 1999, Mandel et al. 2001, Siddiqui et al. 2001, Gerard & Cavaliere 2002, de Geus-Oei et al. 2002). The disadvantages of I-123 include its greater cost and the inability to accurately perform dosimetry (see below) to maximize the administered dose of I-131. However, it has become the scanning isotope of choice in many centers.

**Thyroglobulin monitoring**

Thyroglobulin is a thyroid-specific 660 kDa protein that serves as a precursor in thyroid hormone biosynthesis. Because of its tissue specificity, detecting circulating thyroglobulin in patients treated with thyroidectomy and I-131 is evidence for the presence of thyroid tissue, although not necessarily thyroid cancer. The improved sensitivity of thyroglobulin assays over the past two decades and the adoption of an international calibration standard have made thyroglobulin measurement an essential, rather than an adjunctive, part of thyroid cancer monitoring.

TSH stimulates thyroglobulin gene transcription and release of protein, resulting in greater circulating levels of thyroglobulin. Thus, the clinical sensitivity of thyroglobulin testing when TSH levels are elevated is greater than testing during TSH-suppressive therapy (Lo Gerfo et al. 1980). In fact, thyroglobulin levels are detectable in only 60% of thyroid cancer patients with local or distant metastases during \( \text{T-4} \)-thyroxine therapy (Hay & Gorman 1979, Haugen et al. 1999, Pacini 2002, Mazzaferri et al. 2003). Moreover, the amount of circulating thyroglobulin is usually correlated with tumor burden and the extent of disease, thereby making the quantitative thyroglobulin level helpful in determining both the extent of disease and its probable locations. A further advantage of thyroglobulin testing is a very high specificity due to its limited tissue distribution. Thus, in the setting of thyroid cancer following surgery and I-131 therapy, detection of circulating thyroglobulin at any time is highly specific.

The principal limitation of serum thyroglobulin measurement is assay interference by circulating anti-thyroglobulin antibodies. Thyroglobulin, as a very large protein, has many antigenic epitopes. Anti-thyroglobulin autoantibodies are common markers of autoimmune thyroid disease and occur in 4–10% of unselected women and 1–3% of unselected men depending on their age and country of origin (Canaris et al. 2000). In patients with thyroid cancer, anti-thyroglobulin autoantibodies are present in approximately 20% of patients (Nama et al. 1987, Rubello et al. 1990, Hjiyajnaakis et al. 1999, Wingo et al. 1999, Morris et al. 2002, Mazzaferri et al. 2003). The reasons for the higher frequency of the autoantibodies in patients with thyroid cancer are uncertain. In some cases, the presence of anti-thyroglobulin autoantibodies correlates with the presence of chronic lymphocytic thyroiditis or a peri-tumoral lymphocytic infiltration on histopathology. Some studies have associated their presence with a better prognosis, perhaps relating to an immune response against the primary tumor (McConahey et al. 1986), while others have noted that their disappearance is associated with a reduction in tumor burden, presumably leading to a smaller antigenic stimulus (Rubello et al. 1992, Hjiyajnaakis et al. 1999, Quevedo et al. 2002). Regardless of etiology, circulating anti-thyroglobulin autoantibodies usually interfere with measurements of serum thyroglobulin levels. Although many groups have sought to establish thyroglobulin assays that are not altered by anti-thyroglobulin antibodies, due to the heterogeneous nature of the antibodies, none has been convincingly shown to perform reliably.

Most laboratories utilize immunoradiometric (IRMa) or immunochemiluminescent assays (ICMA) methodologies to measure thyroglobulin, while some laboratories prefer radioimmunometric assay methods (RIA). Typically, an adequate thyroglobulin assay will be normalized to the international standard, CRM447, and will have a functional sensitivity of at least 0.5 ng/ml (Spencer et al. 1996, Mazzaferri et al. 2003). IRMA and ICMA assays are usually falsely lowered by anti-thyroglobulin antibodies and RIAs are typically falsely raised (Spencer & Wang 1995). Therefore, it is recommended that anti-thyroglobulin antibodies are measured on the same serum sample as thyroglobulin to assess the accuracy of the thyroglobulin measurement. Some authors have advocated the use
of ‘recovery’ assays as a measure of assessing the degree of interference by anti-thyroglobulin antibodies, since some, but not all antibodies may interfere. This approach is controversial and may be falsely reassuring depending on the specific methodology. Another approach is to perform both RIA and IRMA assays on the same sample. If the results are concordant, then the antibody is probably not interfering with either assay. However, since most anti-thyroglobulin antibodies cause discordant results, both assays are not routinely performed.

Alternative tests for thyroid cancer

Utility of RNA-based assays

Because of difficulties with antibody interference, there has been an interest in developing RNA-based RT-PCR assays for thyroid cancer monitoring using tissue-specific markers (Ringel et al. 1998, 1999, Wingo et al. 1999, Bojunga et al. 2002, Eszlinger et al. 2002, Fugazzola et al. 2002, Span et al. 2003). Published data for assays designed to detect circulating thyroglobulin, thyroid peroxidase, RET oncogene, and the sodium iodide symporter mRNAs from peripheral blood have yielded conflicting results. These disparate results likely relate to sample handling, RNA stability and methodologic differences, as well as technical issues such as ectopic transcription of ‘tissue-specific’ genes. Efforts to quantify these RT-PCR assays demonstrate correlation with the amount of thyroid tissue present in some studies, but in all published reports there is considerable overlap between patients with different stages of disease. Moreover, the quantitation has defined the presence of low levels of probable non-thyroidal expression of thyroglobulin mRNA variants in patients without evidence of thyroid tissue, leading to questions regarding assay specificity (Ringel et al. 1999, Eszlinger et al. 2002, Span et al. 2003). While this method continues to hold promise, further long-term studies and technical improvements are needed prior to clinical use.

Use of PET scanning in thyroid cancer

TSH-stimulated thyroglobulin levels are usually concordant with the amount and location of thyroid cancer tissue detected in simultaneous I-131 scans. However, discordant results, generally a detectable thyroglobulin with a negative radiiodine scan, demonstrate that thyroglobulin is frequently a more sensitive marker of residual or recurrent thyroid cancer than radiiodine scanning. Patients with detectable thyroglobulin levels who have negative radiiodine scans are evaluated by neck ultrasound or MRI, chest CT scans, and, on occasion, PET scans to locate the source of the thyroglobulin. Neck imaging with ultrasound and MRI are the most frequently employed studies since most recurrences will occur in the central compartment of the neck. In the hands of an experienced operator, neck ultrasound is the most convenient and allows for fine-needle aspiration of suspicious nodes at the time of the evaluation. Neck CT is not as useful as MRI because iodinated radiocontrast dye is generally not used due to the potential for subsequent reduction in I-131 scan sensitivity. By contrast, helical chest CT without contrast is the most sensitive test for detecting pulmonary nodules, and is often employed to evaluate for micrometastatic pulmonary metastases.

Recently, PET scanning has become a useful test in the evaluation of patients with elevated thyroglobulin levels and negative whole-body I-131 scans. Conventional PET imaging utilizes 18F-fluorodeoxyglucose (FDG) to measure glucose uptake following intravenous injection. Metabolically active tissue will utilize glucose to a greater degree than quiescent tissue. For many malignancies, PET scanning has become routine for staging and monitoring. PET scanning is useful in identifying metastatic lesions in thyroid cancer, particularly for the more rapidly progressive and therefore metabolically active variants. These PET-positive tumors frequently lose the ability to transport and/or organify iodide and are not detected by I-131 scanning (Tiepolt et al. 2000, Robbins et al. 2001a, Schluter et al. 2001, Larson & Robbins 2002, Lind et al. 2003). Because PET scanning using FDG is not tumor specific, cervical recurrence of thyroid cancer may be difficult to distinguish from reactive cervical adenopathy. For these reasons, PET scan is not yet recommended as a primary imaging modality for patients with well-differentiated thyroid cancer, but has potential utility for patients with negative whole-body I-131 scanning and for patients with poorly differentiated thyroid cancer. Several reports have also reported enhanced FDG uptake in thyroid cancers following TSH stimulation (Grunwald & Biersack 2000, Petrich et al. 2002, Lind et al. 2003). This is biologically plausible, as TSH does increase glucose uptake and metabolism of thyroid cells. TSH-induced enhancement of FDG uptake may distinguish FDG-PET positive thyroid cancer tissue from lymph nodes or other FDG-avid tissue.

Is thyroglobulin monitoring alone sufficient?

Frequently, the location of the recurrent cancer is only detected on an I-131 scan performed after administration of a therapeutic dose of radiiodine (post-therapy scan, see below). The expanding role for thyroglobulin testing in thyroid cancer and the advantages of avoiding I-131 diagnostic scanning (see above) have led several groups to examine the accuracy of TSH-stimulated thyroglobulin following withdrawal of rTSH administration, as a test to monitor for recurrence.
Cailleux et al. (2000) reported data on 256 consecutive patients with thyroid cancer treated previously with thyroidectomy and 100 mCi I-131. Six to 12 months after the radiiodine therapy, the patients underwent thyroxine withdrawal scanning, serum thyroglobulin was also measured; patients with anti-thyroglobulin autoantibodies were excluded from the analysis. Following withdrawal of thyroxine, thyroglobulin was undetectable in 210 of 256 patients, 195 of these 210 patients had negative scans, and the 15 with positive scans had uptake in the thyroid bed only with no evidence of cervical or distant metastases. Over 3 years of follow-up, only two of these 210 patients with undetectable stimulated thyroglobulin demonstrated tumor recurrence. Of the 15 patients with thyroglobulin levels greater than 10 ng/ml, 12 had negative withdrawal scans, but eight demonstrated defined recurrences over the following 3 years. Finally, for the patients with stimulated thyroglobulin in the 1–10 ng/ml range, two of 31 had thyroid bed uptake and only one of 31 had a defined thyroid cancer recurrence over 3 years. These authors therefore suggested that the I-131 withdrawal scan added little to the diagnostic accuracy of thyroglobulin in the absence of anti-thyroglobulin antibodies and treatment decisions could be based on thyroglobulin levels alone. Other investigators (Baudin et al. 2003) have demonstrated the importance of the trend in serum thyroglobulin concentrations after thyroxine withdrawal during follow-up. In this study, 37 patients with elevated serum thyroglobulin levels after withdrawal of L-thyroxine were monitored. In this series, the greatest predictor of tumor recurrence was a further rise in thyroglobulin following withdrawal of L-thyroxine several months later.

Three recently published studies have further evaluated the potential role for rTSH-stimulated thyroglobulin levels alone as the optimal means for monitoring patients with thyroid cancer. Mazzaferri & Kloos (2002) published their single-center experience using rTSH scanning and thyroglobulin measurement to monitor patients with previously treated thyroid cancer for recurrence. Their population included 107 patients thought to be at a low risk for tumor recurrence categorized as ‘clinically free of disease’ based on clinical examination, prior scans, and undetectable thyroglobulin levels during L-thyroxine therapy. Following rTSH administration, 64% had undetectable (less than 0.5 ng/ml) thyroglobulin levels, 18% had levels that stimulated from 0.6 to 2.0 ng/ml, while 19% had levels that stimulated to greater than 2 ng/ml. Eleven patients (10%) were found to have persistent or recurrent thyroid cancer, all of them had thyroglobulin levels greater than 2 ng/ml while none had uptake on rTSH scan. Of the nine additional patients (8%) with rTSH-stimulated thyroglobulin levels greater than 2 ng/ml, no recurrent or residual tissue could be identified using various radiographic modalities, including neck ultrasound and chest CT scan. Overall, an rTSH-stimulated thyroglobulin value greater than 2 ng/ml had a sensitivity of 100% and a specificity of 91%. Thus, in this study, it appeared that the diagnostic I-131 scan did not add to the accuracy of monitoring.

Wartofsky (2002) published a prospective analysis of rTSH-stimulated thyroglobulin as a monitoring tool for recurrent thyroid cancer in 300 patients at ‘low risk’ of having tumor recurrence. Of the patients with undetectable thyroglobulin levels prior to rTSH (n = 248), only 7% stimulated to levels greater than 2 ng/ml. In addition, patients who demonstrated a rise of thyroglobulin greater than 2 ng/ml following rTSH administration (n = 53) were more likely to have detectable thyroglobulin levels basally and were more likely to have uptake on subsequent thyroxine withdrawal I-131 whole-body scan. Diagnostic scanning using an rTSH preparation was not performed in this clinical trial. These data demonstrate that, similar to L-thyroxine withdrawal, rTSH-stimulated thyroglobulin is more sensitive than non-stimulated thyroglobulin levels, and both the level and rise of thyroglobulin following rTSH administration are predictors of the presence of thyroid tissue. Long-term follow-up is needed to determine if the rTSH-stimulated thyroglobulin alone is adequate monitoring for patients with thyroid cancer. However, the studies of Mazzaferri & Kloos (2002) and Wartofsky (2002) only address patients defined as having a low risk of recurrence. To address the best monitoring tests for patients at higher risk of tumor recurrence, and compare their results with a group of low-risk patients, Robbins et al. (2002a) reported their single-center experience in 366 consecutive patients with thyroid cancer undergoing rTSH scanning and thyroglobulin testing. Taken as a total group, including high- and low-risk patients, 76% of patients with thyroglobulin levels greater than 2 ng/ml had metastases on rTSH scan compared with 13% of patients with stimulated thyroglobulin levels less than 2 ng/ml. No low-risk patients, defined as those with prior negative thyroxine withdrawal diagnostic scanning and thyroglobulin levels, had either a positive scan or an rTSH-stimulated thyroglobulin greater than 2 ng/ml. Thus, in this population, low-risk patients were accurately monitored by rTSH-stimulated thyroglobulin levels, but the addition of the I-131 scan improved the accuracy of monitoring in high-risk populations.

Together, these articles suggest that TSH-stimulated thyroglobulin levels following either thyroxine withdrawal or rTSH administration may be sufficient for identifying recurrent or residual thyroid cancer in patients with prior total thyroidectomy and radiiodine therapy thought to
be free of disease based on prior scan data (so-called ‘low-risk’ patients). However, for higher-risk patients, radioiodine scanning will detect additional patients with recurrent or residual disease. Clearly, these data do not include additional studies such as neck ultrasound or MRIs or CT scans of the chest, all of which may be used as adjunctive tests, and further study is required. A suggested algorithm for patients with thyroid cancer who do not have circulating anti-thyroglobulin antibodies is depicted in Fig. 2.

Controversies in the management of recurrent or persistent disease

Once an individual has been identified with recurrent or residual thyroid cancer, a decision must be made regarding the administration of additional therapy, including surgery, radioiodine, and external beam radiation therapy. The management of patients with detectable thyroglobulin levels but negative radioiodine scans and no clear anatomic recurrence on CT, MRI or ultrasound is among the most controversial areas in thyroid cancer management.

Management of the thyroglobulin-positive, scan-negative evaluation

As noted above, in the absence of thyroglobulin antibodies, thyroglobulin testing appears to be a more sensitive marker of recurrent or residual thyroid cancer than diagnostic whole-body I-131 scanning. Thus, the situation where a patient has detectable circulating thyroglobulin levels in the absence of iodine uptake is common. To date, there is no consensus regarding appropriate management of patients with this type of evaluation.

Schlumberger et al. (1997) demonstrated the utility of treating patients with thyroglobulin-positive, scan-negative screening tests and no evidence of lung metastases on chest X-ray. In their study, the authors reported demonstration of uptake on initial post-therapy scan as well as subsequent resolution of pulmonary uptake on post-therapy scan in 20 of 23 patients with repeated doses of I-131 greater than 100 mCi. Pineda et al. (1995) reported similar results in a smaller cohort of patients using a criterion of disease resolution that included thyroxine withdrawal-stimulated thyroglobulin levels below 5 ng/ml. Based largely on these data, there has been a trend toward treating patients with elevated thyroglobulin levels (particularly when greater than
10 ng/ml) with one dose of I-131, and to continue to treat only if an objective response is demonstrated with reductions in serum thyroglobulin levels and/or radiographically determined tumor burden the following year.

To address this question further, Pacini et al. (2001) recently reported their experience in the outcome of their patients who were thyroglobulin positive and scan negative on monitoring prior to 1984, when their policy was clinical follow-up, versus after 1984, when such patients were treated with 100–150 mCi I-131 and then retreated using the paradigm noted above. In the treated group (n = 42), 30 patients had positive post-therapy scans after empiric therapy and 12 patients had negative scans, only the patients with positive scans were treated with additional doses of I-131. The pre-1984 untreated patients (n = 28), and the 42 treated patients were all monitored by ultrasound, chest CT scan, and thyroglobulin levels when off thyroxine therapy at the end of the study. The patient demographics and tumor stages were similar in the two groups. The untreated patients had a longer median follow-up time (11.9 years) compared with the treated group (6.5 years), and lower initial serum thyroglobulin levels (40 ng/ml vs 62 ng/ml) following thyroxine withdrawal. Among 30 patients in the treated group with uptake on post-therapy scan, the uptake was in the thyroid bed in three patients, cervical nodes in 18 patients, and in the lungs in nine cases. These patients were treated with additional I-131 during the course of the study with an average dose of 256 mCi and a high dose of 500 mCi. At the end of the follow-up period, ten of 30 treated patients with initial positive thyroglobulin values and post-therapy scan were in a complete remission, nine patients had > 50% reductions in thyroglobulin levels and negative post-therapy scans, and 11 patients had persistent disease by both measures. The therapy was more effective for patients with pulmonary metastases than for patients with cervical metastases. Results from the patients treated once with negative post-therapy scans were similar, except that one patient died of progressive disease. However, the untreated group also did well. Nineteen of 28 patients developed undetectable serum thyroglobulin levels while hypothyroid, whereas only nine of 28 patients remained positive. Those patients with an initial thyroglobulin below 10 ng/ml after thyroxine withdrawal at initial study were less likely to have a detectable value at the end of follow-up in comparison with those patients with higher values (14% vs 50%), suggesting that the thyroglobulin level may be useful in discriminating patients appropriate for therapy.

The study of Pacini et al. (2001), while not a randomized prospective trial, delineates several important issues. First, radioiodine therapy may be less effective in ablation of small cervical metastases than pulmonary metastases and this emphasizes the role for neck imaging and surgical removal of recurrent cervical thyroid cancer. Second, the outcome of radioiodine therapy depends greatly on the extent of disease present prior to treatment. Third, for those patients with lower levels of thyroglobulin and negative diagnostic radioiodine scans, empirical therapy may not be as beneficial as suggested in earlier studies.

**Dosimetrically calculated radioiodine therapy versus empiric dosing**

The outcomes for radioiodine therapy have generally been reported using fixed dosing regimens, usually 30 150 mCi for initial remnant ablation and 100 200 mCi for treatment of recurrent or residual cancer. Dosimetry represents a method to individualize the dose of radioiodine for an individual patient to maximize effectiveness and minimize risk for the patient (see above). Dosimetry can be broadly categorized into two methods, each of which is designed to provide different information. Whole-body dosimetry calculates the maximal dose of radioiodine that will deliver less than toxic radiation levels to bone marrow and lungs, while lesional dosimetry calculates the dose of radioiodine required to deliver a lethal amount of radiation to a specific tumor mass (see below). Whole-body dosimetry, as described by Berman et al. (1968) and Leeper (1973), has become routine at some institutions in the USA and Europe. Dosimetry calculations require measurement of the rate of radiation clearance from patients following administration of the scanning dose of I-131 prior to therapy (Van Nostrand et al. 2002). Thus, patients with large amounts of iodine-avid metastatic tissue may have prolonged retention of radioiodine and thus have a lower calculated maximum dose than individuals with smaller amounts of thyroid cancer tissue. Thus, whole-body dosimetry theoretically enhances the ‘safety margin’ of I-131 administration and may allow for administration of either larger or smaller I-131 doses than initially planned. Importantly, to date, there are no long-term data demonstrating greater efficacy of this approach than for empiric dosing, and the calculation does not consider the impact prior doses of I-131 might have on the risk of secondary malignancy or other side-effects of I-131. This must be balanced against the potential benefits of minimizing the number of cycles of thyroxine withdrawal required to administer a dose of I-131 able to induce a remission, the method is logical, and there are no known increases in side-effects with nearly 40 years of use in some institutions.

Maxon et al. (1983) and Maxon (1999) pioneered the use of lesional dosimetry, in an effort to calculate the dose delivered directly to the thyroid tissue based on diagnostic iodine scans and calculation of clearance rates. They
estimated that for most cervical lesions, 80,000 rads needed to be delivered to kill the thyroid cancer cells. This type of dosimetry is rarely performed as it is useful only for cervical metastases or isolated distant metastases and is more cumbersome to perform than whole-body dosimetry. However, its use has demonstrated the wide variability in the total dose of I-131 required to achieve remnant ablation following initial surgery (see above).

In summary, while dosimetry has become a more frequently utilized tool to individualize thyroid cancer therapy, there is no proven benefit in comparison with conventional radioiodine and only a few centers are able to perform these calculations on a routine basis. However, data from lesional dosimetry clearly demonstrate the efficacy of this approach for remnant ablation, and whole-body dosimetry has disclosed that empiric conventional dosing of radioiodine will frequently exceed the acceptable radiation dose delivered to the bone marrow. While dosimetrically calculated I-131 has theoretical advantages for treating distant metastases, clinical data that prove improved outcomes are lacking and further studies are required to determine if this approach should replace empiric dosing of I-131.

**Use of agents to increase iodine uptake or retention**

An adjunctive approach to enhancing the efficacy of I-131 therapy for thyroid cancer is to enhance the ability of thyroid cancer cells to transport, organify, or retain the I-. Therapy for thyroid cancer is to enhance the ability of the sodium-iodide symporter enhanced expression of the gene that encodes the sodium-iodide symporter. Retinoids bind the retinoic A and retinoic X receptors (RAR and RXR), RXR binding in particular results in enhanced expression of the gene that encodes the sodium iodide symporter in vitro. 13-cis retinoic acid (Accutane, Roche Laboratories, Nutley, NJ, USA) is an approved medication used in the treatment of acne vulgaris and leukemias and that has metabolites that bind to both RAR and RXRs. Initial reports demonstrated that treating patients with 13-cis retinoic acid prior to administration of I-131 enhanced uptake in some thyroid cancers, particularly follicular cancers (Van Herle et al. 1990, Grunwald et al. 1998, Koerber et al. 1999). Subsequent studies in larger groups of patients have not shown significant efficacy (Gruning et al. 2003) for the majority of patients; however, studies using selective agonists of RXR have been proposed and may be more logical based on the biological effects of RXR and RAR agonists in vitro.

Lithium carbonate has long been known to inhibit the release of iodine from the thyroid. Its use was reported as a treatment for thyrotoxicosis and as an adjunct for I-131 therapy of Graves’ disease in the 1970s. There have been several long-term, non-randomized studies evaluating lithium carbonate use as an adjunct to prolonged I-131 retention in thyroid cancer. In these studies, there appears to be enhanced retention of I-131 as measured dosimetrically (Koong et al. 1999, Sarlis 2001). Administration of lithium requires monitoring blood levels, and can be associated with significant psychiatric and metabolic side-effects, particularly in elderly patients or patients on multiple medications. However, its use in younger patients with thyroid cancer may be justified based on these studies.

**Conclusion**

Thyroid cancer remains the most common classical endocrine malignancy, and its incidence appears to be rising. Long-term survival remains excellent for patients with thyroid cancer, but recurrence rates remain in the 10–20% range; cure in the setting of distant metastases remains uncommon. Over the past two decades, refinements of primary therapies have reduced the morbidities associated with initial therapy, and monitoring for disease recurrence has been greatly enhanced by reliance on TSH-stimulated serum thyroglobulin measurement. There remains a need for targeted chemotherapeutic therapeutic advances for patients with inoperable metastatic disease, particularly in patients with poorly differentiated tumors.

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