Differentiated thyroid carcinoma: defining new paradigms for postoperative management

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Abstract

The demography of differentiated thyroid cancers (DTCs) has changed considerably since the 1990s, when the vast majority of these tumors were clinically evident at the time of diagnosis, and many were associated with regional lymph node involvement. Today's DTCs are more likely to be small, localized, asymptomatic papillary forms that are discovered incidentally, during neck imaging procedure performed for other reasons or during postoperative assessment of a gland removed for benign nodular goiter. The tools available for diagnosing, treating, and monitoring DTCs have also changed and their diagnostic capacities have increased. For these reasons, DTC treatment and follow-up paradigms are being revised to ensure more appropriate, cost-effective management of the current generation of DTCs. This review examines some of the key issues in this area, including the assessment of risks for disease recurrence and thyroid cancer-related death, the indications for postoperative ablation of the thyroid remnant with radioactive iodine and TSH-suppressive doses of levothyroxine, the pros, cons, and rationales for the use of various follow-up tools (serum thyroglobulin assays, neck ultrasound, 2-[18F]fluoro-2-deoxyglucose–positron emission tomography, and whole-body 131I scintigraphy), and temporal strategies for maximizing their efficacy. An algorithm is presented for individualized, risk-tailored management of DTC patients.

Key Words
differentiated thyroid carcinoma
radioiodine remnant ablation
follow-up
neck ultrasound
thyroglobulin
recurrence

Introduction

The incidence of thyroid cancer has been increasing steadily since the 1970s. Data from the Surveillance Epidemiology and End Results Registries show an average annual increase in the USA of 6.6% between 1997 and 2009. The estimated number of patients with thyroid cancer on January 1, 2009, was almost half a million, and roughly three out of four of these individuals were women (http://seer.cancer.gov/statfacts/html/thyro.html; last accessed 20 January 2013). These tumors are fifth on the list of the most common incident cancers among women, and they represent the most rapidly growing category of cancer in both sexes (Eheman et al. 2012).

This trend is almost entirely the result of increases in the diagnosis of differentiated thyroid cancers (DTCs), the papillary type, in particular (Incidence rates of follicular thyroid cancers – like those of the poorly differentiated anaplastic and medullary forms – have remained relatively stable over the past 20–30 years.). DTC treatment and follow-up practices were developed on the basis of experience gained during the latter half of the 20th century.
During those years, papillary thyroid cancers (PTCs) were almost always clinically evident at the time of presentation, and a substantial number were associated with regional lymph node involvement (DeGroot 1994, Mazzaferrri & Jhiang 1994). Today, the vast majority of newly detected PTCs are small, localized, asymptomatic tumors that are discovered incidentally (e.g. during imaging studies of the neck performed for other reasons or postoperatively, after thyroid gland removal for benign nodular goiter; Leenhardt et al. 2004, Davies & Welch 2006, Hall et al. 2009). The tools at our disposal for diagnosing, treating, and monitoring PTCs have also changed and evolved over the past two decades (Table 1; Cooper et al. 2009). The challenge facing us today is the need to revise treatment and follow-up paradigms in light of more recent evidence to ensure more appropriate, cost-effective management of the current generation of DTCs.

This review examines some of the key issues in this area, including the accurate assessment of risks for disease recurrence and thyroid-cancer-related death, the indications for postoperative ablation of the thyroid remnant with radioactive iodine, the pros and cons of various follow-up tools, and temporal strategies for maximizing their efficacy. Finally, an algorithm is presented for individualized, risk-tailored management of DTC patients.

Tailoring management to risk

Given the changes that have occurred in the demography of DTC patients, accurate risk stratification of the current patient population is an essential first step toward improved treatment and follow-up protocols. For patients with DTCs, risk assessment provides the foundation for informed, evidence-based choices regarding subsequent management, including the administration of radioactive iodine after surgery, the use of TSH suppression, the strategies and methods that will be used to detect the signs of disease recurrence, and the frequency, intensity, and duration of the follow-up. Tailoring management strategies to individual risk can increase the cost-effectiveness of care and in many cases improve the patient’s quality of life, by reducing the burden of adverse treatment effects and the stress and costs of ongoing surveillance.

Reliable assessment of the risks faced by an individual patient with DTC requires the use of the right tool at the right time during follow-up. The initial evaluation occurs when the cancer is diagnosed and, in all probability, surgically removed. Staging at this point is conventionally based on the clinicopathologic system elaborated by the American Joint Cancer Committee/Union Internationale Contre le Cancer (AJCC/UICC), which is widely used for all types of cancers. It is based on four variables: patient age, the size and extension of the primary tumor (pT), lymph node involvement (N), and the presence of distant metastases (M).

Both the American Thyroid Association (ATA) Practice Guidelines (Cooper et al. 2009) and the European Thyroid Association (ETA) Consensus Statement (Pacini et al. 2006) endorse the AJCC/UICC staging system for use in patients with DTCs. The main problem with this approach is that the system was designed to predict mortality (Brierley et al. 1997, Orlov et al. 2009), whereas clinicians planning focused follow-ups also need information on the probability of persistent or recurrent disease after surgery. When the AJCC/UICC system was tested in DTC patients to see how well it predicted structural disease recurrence during follow-up, stage IV disease was clearly associated with the highest risk (70%), but the increase in risk across stages I, II, and III was anything but linear (11, 34, and 14% respectively; Tuttle et al. 2010).

The solution proposed by the ATA in its 2009 guidelines was a new system, which classifies the probability of recurrence as high, intermediate, or low (Table 2; Cooper et al. 2009) on the basis of pTχNχM parameters plus other types of information that are generally available shortly after the initial treatment (i.e. thyroidectomy or lobectomy, with or without radioactive iodine therapy). The latter variables include tumor histotype, evidence of vascular invasion, the completeness of the surgical intervention, and the results of the post-treatment whole-body radioiodine scan (RxWBS). As expected, the ATA system has proved to be more effective in predicting the follow-up findings of persistent or recurrent cancer. In a cohort of 588 patients with DTC followed at the Memorial Sloan-Kettering Cancer Center for a median of 7 years after primary treatment, the likelihood of detecting structural disease during the surveillance period increased progressively with the risk level: from ∼3% in low-risk patients to 21% in those with an intermediate-risk and 68% for those assigned to the high-risk category (Tuttle et al. 2010).

Even the ATA risk assessment system, however, has some intrinsic limitations. Little distinction is made between PTCs and follicular thyroid cancers (FTCs), which usually demonstrate different biological behaviors. For instance, for FTCs, the presence of vascular invasion appears to be the major determinant of risk. Thus, the so-called minimally invasive follicular thyroid cancers, which are characterized histologically by tumor capsule...
Table 1  Paradigm shifts in the management of differentiated thyroid cancers.

<table>
<thead>
<tr>
<th>What is the appropriate operation for DTCs?</th>
<th>Old paradigms</th>
<th>Current paradigms*</th>
<th>Future paradigms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thyroidectomy ± neck lymph node dissection</td>
<td>Lobectomy (very low-risk patients) Total thyroidectomy ± neck lymph node dissection Selected&lt;sup&gt;b&lt;/sup&gt; intermediate-risk patients</td>
<td>Depending on the preoperative estimates of the risk</td>
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<tr>
<td>All patients</td>
<td>High-risk patients Early follow-up&lt;sup&gt;c&lt;/sup&gt; Low-risk patients (target TSH: 0.1–0.5 mU/l) Intermediate- and high-risk patients (target TSH: &lt;0.1 mU/l) Long-term follow-up High-risk patients (target TSH: 0.1–0.5 mU/l, for 5–10 years) Patients with persistent disease (target TSH: &lt;0.1 mU/l) Early follow-up&lt;sup&gt;c&lt;/sup&gt; Patients treated with RRA Neck US Serum Tg measurement (rhTSH-stimulated levels or a high-sensitivity assay of basal levels) DstB/WBS (high-risk patients only) Patients not treated with RRA Neck US High-sensitivity assay of basal serum Tg levels Long-term follow-up Neck US Serial measurements of basal Tg with a high-sensitivity assay</td>
<td>Patients with postoperative evidence of disease (and a high risk of persistent disease?)</td>
<td></td>
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<tr>
<td>All patients (target TSH: &lt;0.1 mU/l)</td>
<td>DxWBS Assay of serum Tg levels (basal and during TSH stimulation achieved with thyroid hormone withdrawal) Neck US (when available)</td>
<td>Early follow-up&lt;sup&gt;c&lt;/sup&gt; Neck US Long-term follow-up Serial highly sensitive serum Tg assay (trend over time)</td>
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<tr>
<td>Which diagnostic tools should be used to monitor DTC patients after the initial treatment?</td>
<td>DstB/WBS</td>
<td>How long should DTC patients be followed?</td>
<td>Until death</td>
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<tr>
<td>Which patients should undergo RAI remnant ablation?</td>
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<td>How long should DTC patients be followed?</td>
<td>Until death</td>
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<tr>
<td>Which patients should receive TSH suppression therapy and how much suppression is appropriate?</td>
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<td>How long should DTC patients be followed?</td>
<td>Until death</td>
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</tbody>
</table>

DTC, differentiated thyroid cancer; DxWBS, diagnostic whole-body scintigraphy; RAI, radioactive iodine; RRA, radioactive iodine remnant ablation; rhTSH, recombinant human TSH; Tg, thyroglobulin; US, ultrasonography.

*Based on the most recently published evidence-based international guidelines (Cooper et al. 2009).

<sup>b</sup>Those with higher risk clinicopathological features, such as worrisome histologic subtypes (i.e. tall cell, columnar, insular, and solid variants, as well as poorly differentiated thyroid cancer); invasion of intrathyroidal vasculature; multifocal disease (gross or microscopic); and non-papillary histology (i.e. follicular thyroid cancer and Hürthle cell cancer with vascular invasion).

<sup>c</sup>1–2 years after the initial treatment.

penetration without vascular invasion, are generally regarded as lower risk tumors, irrespective of the tumor size (van Heerden et al. 1992, Sanders & Silverman 1998, D'Avanzo et al. 2004, Lo et al. 2005, Dralle et al. 2013). Most importantly, the ATA risk assessment system fails to consider two factors that can significantly alter the odds of recurrence and death over time: the clinical course of the disease and its response to the initial therapy and any interventions performed thereafter. To address this shortcoming, the Sloan-Kettering group had previously proposed a dynamic risk assessment strategy, which provides for ongoing revision and refinement of the risk estimate as new data emerge during follow-up (Tuttle 2008). In the study cited above (Tuttle et al. 2010), the patients originally staged with the ATA recurrence risk system were subsequently re-assessed on the basis of treatment–response data obtained during the first 2 years after the initial therapy (in this case, total...
thyroidectomy plus postoperative radioiodine ablation of the normal thyroid remnant). Excellent responses (absence of both structural and biochemical evidence of disease) reduced the likelihood of finding persistent/recurrent structural disease in all three ATA risk groups (from 3 to 2% in the low-risk category, from 21 to 2% in the intermediate-risk groups, and from 68 to 14% in those with high-risk disease). Similar findings later emerged from a second retrospective, single-institution study, in which risk was re-classified on the basis of the disease status 1 year after the initial treatment (Castagna et al. 2011a).

These studies showed that, regardless of the initial risk estimate, the likelihood of recurrence in patients with no evidence of disease at the 1–2-year follow-up is quite low (4% in the earlier study and 3.4% in the later one; Tuttle et al. 2010, Castagna et al. 2011a). Most importantly, around 30% (Tuttle et al. 2010) to 50% (Castagna et al. 2011a) of the patients previously classified as ATA intermediate–high-risk could be re-classified as low-risk (no evidence of disease) within 1–2 years of follow-up. With this approach, a substantial proportion of patients with DTCs – including some whose initial staging revealed a high risk of persistent disease – can at some point be channeled into surveillance that is less intensive than originally planned.

What are the current indications and contraindications for postoperative radioactive iodine therapy?

By the late 1990s, patients with DTCs were almost invariably treated postoperatively with radioiodine ($^{131}$I). In the currently advocated risk- and response-based management strategies, this approach is being used much more selectively. Even the specific indications for using radioiodine therapy in the early postoperative management have been questioned over the past few years. Current practice guidelines in Europe and the USA (Pacini et al. 2006, Cooper et al. 2009) cite three rationales for administering radioiodine after total thyroidectomy: i) it eliminates any normal thyroid tissue left after surgery, thereby simplifying subsequent detection of residual/recurrent tumor tissue; ii) it destroys any occult microscopic foci of neoplastic cells within the thyroid remnant or elsewhere in the body, thus improving the long-term outcome (adjuvant therapy); and iii) it can be used to treat known tumor residual tissues. While the ATA and the ETA have defined indications for using radioiodine, the application of this treatment in clinical practice differs between countries and even within them (Haymart et al. 2013). This variation is possibly due to several non-tumor-related factors, such as different restrictions for administering radioactive material, different cohorts of patients, and, last but not the least, different acceptance of the treatment strategy. The latter underlines the need for clear recommendations for the management of DTCs and thus for well-designed clinical trials addressing the gray areas where evidence is ambivalent. Current indications for postoperative radioactive iodine therapy are discussed in more detail below.

Table 2  The American Thyroid Association staging system for predicting the risk of disease recurrence/persistence in patients with differentiated thyroid cancer.

<table>
<thead>
<tr>
<th>Low-risk</th>
<th>Intermediate-risk</th>
<th>High-risk</th>
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<tr>
<td>Meets all of the following criteria: No aggressive tumor histotype (e.g. tall cell, insular, and columnar cell cancers) No vascular invasion; complete macroscopic resection of the tumor</td>
<td>Meets at least one of the following criteria: Aggressive tumor histotype or vascular invasion Microscopic extrathyroidal extension of the tumor neck lymph node metastases or $^{131}$I uptake outside the thyroid bed on the first post-treatment RxWBS</td>
<td>Meets at least one of the following criteria: Macroscopic extrathyroidal extension of the tumor Incomplete resection of the tumor</td>
</tr>
<tr>
<td>No extrathyroidal tumor extension No local or distant metastases No $^{131}$I uptake outside the thyroid bed on the first RxWBS (when done)</td>
<td>Distant metastases</td>
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</tbody>
</table>

RxWBS, post-treatment whole-body scan.

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Normal thyroid remnant ablation

Postoperative administration of radioiodine facilitates subsequent follow-up by eliminating any normal thyroid tissue left behind after surgery. It is widely accepted that the presence of such tissue can diminish the
accuracy of two methods for detecting residual/recurrent thyroid cancer.

The first is the serum thyroglobulin (Tg) assay. The measurement of basal and stimulated Tg levels has been a cornerstone of postoperative surveillance programs for patients with DTCs since the 1980s (Pacini et al. 2006, Cooper et al. 2009). Tg is produced exclusively by cells of thyroid follicular origin, so if all normal thyroid tissues have been eliminated by surgery and postoperative radioiodine remnant ablation (RRA), subsequent findings of detectable Tg levels represent a highly specific marker of tumor recurrence (Pacini et al. 2006, Cooper et al. 2009). If RRA is omitted, the clinical significance of these findings declines since the assay positivity may simply reflect Tg production by residual nests of normal thyrocytes, and there is no specific cutoff level that can reliably distinguish the production of this type from that of persistent or recurrent neoplastic thyroid tissue (Pacini et al. 2006, Cooper et al. 2009). Consequently, the use of RRA is advocated to preserve the diagnostic value of serum Tg assays in the patient’s follow-up.

This is not, however, the only solution. As will be discussed later in this article, while the predictive value of a single serum Tg measurement is undeniably lower in patients who have not undergone RRA, serial Tg measurements can disclose changes over time that can be reliable markers of recurrent disease. In a recent retrospective study, the natural history of ‘benign’ Tg production by unablated postoperative remnants of normal thyroid tissue has been characterized in 290 patients with low-risk PTCs (classified by the ATA system; Durante et al. 2012). Although none of these patients had undergone RRA, around 60% had undetectable Tg levels (<0.2 ng/ml) – without TSH suppression – within the first year of thyroidectomy. In the other cases, Tg levels remained detectable during the first year but declined spontaneously and progressively thereafter. As a result, by the fifth year of the follow-up, the proportion of patients with undetectable levels was close to 80%. In the other 20%, serum Tg levels decreased to low but detectable ones and remained stable for the duration of the follow-up. At the end of the follow-up (median 5 years), all of these individuals were disease-free. Only 1 of the 290 patients experienced recurrence, and it was associated with a gradual increase in previously stable levels of Tg. These data challenge the notion that Tg assays are of little use in the follow-up of patients with DTCs who have not undergone RRA. In some cases, Tg levels will remain within a detectable range during the early phase of the follow-up (the first 5 years), and this will undeniably reduce the diagnostic value of single Tg assay results. However, the temporal trend of consecutive measurements of serum Tg can be a reliable indicator of the presence (rising values) or absence (declining values) of recurrent thyroid cancer in patients undergoing total or near-total thyroidectomy. Short postoperative serum Tg doubling-time (<1 year) has been reported to be independently associated with the likelihood of having loco-regional and distant recurrence, irrespective of radioiodine administration (Miyauchi et al. 2011).

The second follow-up tool the use of which is complicated by the omission of RRA is ¹³¹I scintigraphy. When there is an appreciable thyroid remnant, the normal tissue ¹³¹I uptake can mask the uptake by microscopic foci of neoplastic cells within or near the remnant. The likelihood of detecting extrathyroidal tumor cells is also reduced. In vivo studies in patients with metastatic DTCs have shown that ¹³¹I uptake by the neoplastic foci is consistently lower (and may even drop below the detection level) in the presence of a normal thyroid remnant, which is often much more efficient than the metastatic lesions in incorporating the radioiodine (Schlumberger et al. 2007a). By eliminating this competition, RRA can improve the sensitivity of the ¹³¹I scan for identifying disease recurrence (Pacini et al. 2006, Cooper et al. 2009).

It is important to recall, however, that ~70% of thyroid cancers are confined to the thyroid bed at diagnosis, and in 85% of the remaining cases, the extrathyroidal disease consists exclusively of regional lymph node involvement (http://seer.cancer.gov/statfacts/html/thyro.html; last accessed 20 January 2013). In these cases, ¹³¹I scintigraphy displays a low sensitivity in the detection of persistent/recurrent disease, and enhancing its specificity by ablating the normal thyroid remnant is of considerably less use (Cailleux et al. 2000, Pacini et al. 2003, Torlontano et al. 2003, 2006). Adverse effects must also be considered in these decisions. Exposure to radioiodine significantly increases the probability of second primary malignancies, salivary gland dysfunction, and other complications (Rubino et al. 2003, Brown et al. 2008, Sawka et al. 2009, Van Nostrand 2009). Most of these can have a negative effect on the patient’s quality of life. As for the risk for second primaries, it is generally felt to be radiation dose dependent (Rubino et al. 2003), but some increase in the overall risk – which nonetheless remains very low – has been reported even in patients treated exclusively to ablate the normal remnant, presumably with cumulative activities in the lower range (Iyer et al. 2011).
In light of these considerations, the view that RRA is necessary to facilitate initial staging and follow-up appears somewhat less convincing, and postoperative radioactive iodine therapy is being used with much more caution, especially in low-risk cases (Cooper et al. 2009). If it is used, the ATA guidelines advise using the lowest activity needed to ensure successful remnant ablation (Cooper et al. 2009). The validity of this approach has recently been confirmed by the results of two prospective randomized clinical trials conducted in low-to-intermediate-risk DTC patients (Mallick et al. 2012, Schlumberger et al. 2012). In both studies, low-dose (1.1 GBq (30 mCi)) and high-dose (3.7 GBq (100 mCi)) radioiodine regimens displayed similar efficacies in eliminating normal thyroid residual tissue, regardless of whether the patients were prepared for the procedure with thyroid hormone withdrawal or recombinant human TSH (rhTSH) stimulation.

Destruction of occult foci of neoplastic cells

Postoperative $^{131}$I administration is also used as an adjuvant procedure for destroying any residual microscopic nests of thyroid cancer cells that may be present in the thyroid remnant or elsewhere in the body (Cooper et al. 2009). The elimination of these potential foci is thought to reduce the risk of recurrence and improve the long-term outcome. This rationale is supported largely by data from retrospective studies conducted in the 1990s. In the landmark study by Mazzaferri & Jhiang (1994), 1355 patients with DTC were followed for over 40 years (median 15.7 years). At 30 years, the rates of both recurrence and cancer-related death were approximately threefold lower in the patients who had undergone RRA. Similar conclusions emerged from other studies, which found that RRA significantly reduced disease recurrence (Samaan et al. 1992, DeGroot 1994) and disease-specific mortality rates (Samaan et al. 1992). The publication of these reports was followed by dramatic increases in the use of postoperative $^{131}$I administration, and by the late 1990s, it was being performed in almost all patients.

Other large studies, however, have kindled debates on the true effectiveness of this approach: they found that radioactive iodine adjuvant therapy had no significant effect on long-term outcomes in patients with DTCs (Hundahl et al. 1998, Hay et al. 2002). The conflicting results that emerged from these efforts are largely a reflection of the heterogeneity of the study populations in terms of the risks of recurrence and disease-specific mortality. Even the investigators who had reported benefits with RRA acknowledged that these benefits seemed to be restricted to patients with larger primary tumors (i.e. 1.5 cm or more; DeGroot 1994, Mazzaferri & Jhiang 1994). More recent studies have looked at the effectiveness of RRA as a function of disease stage (Jonklaas et al. 2006, Sacks et al. 2010). The National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) has published its experience with 2936 DTC patients who were prospectively followed for a median period of 3 years (Jonklaas et al. 2006). Benefits from radioiodine therapy were documented only for patients with advanced-stage cancers (NTCTCSG stages III and IV): in this setting, there were significant improvements in the risk ratios for both disease-free survival (1.32, 95% CI 1.02–1.68, $P=0.035$) and disease-specific survival (1.46, 95% CI 1.13–1.87, $P=0.0045$). RRA had no effect, however, on either of these outcomes in patients with stage I or II DTCs.

In light of these findings, it is becoming increasingly clear that radioactive iodine adjuvant therapy needs to be used selectively, and this strategy shift is reflected in the 2009 ATA guidelines (Cooper et al. 2009), which recommend tailoring case management to individual risk levels. A recent multicenter study conducted in Italy (Durante et al. 2010) has retrospectively examined the long-term outcomes of 175 DTC patients with very-low-risk primary tumors (intrathyroidal, unifocal, subcentimeter PTCs with no known high-risk features) who had not received RRA. In a median follow-up of 6.7 years (range 5–23), there were no recurrences and no thyroid-cancer-related deaths. Shortly thereafter, Vaisman et al. (2011) reported that the omission of radioactive iodine therapy is compatible with very low rates of recurrence, even in selected patients with estimated risks classified as low to intermediate. In 120 non-ablated patients with primary tumors measuring 1–4 cm, little or no extrathyroidal extension, and minimal or absent cervical lymph node involvement, the rate of structural disease recurrence was only 4.1% (5 out of 120) after a median follow-up of 5 years (range 0.5–34). A similar approach has been advocated for FTC histotype, for which the absence or the presence of histopathological vascular invasion better discriminates between low- and high-risk patients respectively. In particular, the occurrence of vascular invasion (widely invasive FTCs) should prompt RRA therapy (Cooper et al. 2009, Dralle et al. 2013).

Accurate risk assessment thus appears to be the key to identifying DTC patients who are likely to benefit from postoperative radioactive iodine therapy. In this regard, prophylactic central and/or lateral neck dissection has been advocated to optimize staging (Hartl et al. 2012). However, the prognostic significance of subclinical microscopic
cervical lymph node metastases has been recently questioned (Randolph et al. 2012). Firm conclusions on this issue will have to be based on data regarding the effects of radioiodine not only on recurrence but also on disease-specific survival. These aspects are being addressed in one multicenter prospective randomized trial in low-risk thyroid cancer patients, which is now underway in Europe (http://clinicaltrials.gov/show/NCT01398085; last accessed 31 January 2013).

Elimination of documented residual disease foci

For DTC patients with gross residual disease that is inoperable, radioiodine therapy is currently the most effective treatment that we have to offer. Indeed, it is the only approach that has been demonstrated to significantly improve disease-free survival (Samaan et al. 1992) and, most important, overall survival (Durante et al. 2006), which represents the main outcome in clinical oncology. For several reasons, however, the use of radioiodine for this purpose is also becoming more selective (Tuttle et al. 2011), and clinicians are being encouraged to base their decisions on a careful risk–benefit analysis.

Aside from the risk of long- and short-term adverse effects, one of the main reasons for this shift is the growing awareness that RAI is ineffective in some patients with advanced disease. The selectivity of radioiodine therapy for DTC cells depends on the functional integrity of the complex network of specialized proteins (e.g. the sodium iodide symporter and thyroperoxidase) involved in physiological iodine metabolism and hormonogenesis (Schlumberger et al. 2007a). These functions are usually preserved to some extent in the cells of primary DTCs (Arturi et al. 2001), although varying degrees of impairment can be caused by genetic and epigenetic events involved in the malignant transformation process (Trapasso et al. 1999, Puppin et al. 2005, Durante et al. 2007, Russo et al. 2011). Complete loss of these functions is characteristic of undifferentiated and anaplastic primaries. Iodine uptake in some metastatic thyroid cancer cells is also less efficient than that in their primary tumor counterparts. This phenomenon, too, can be attributed to dedifferentiation, although the iodine-trapping capacity of metastatic thyrocytes may also vary with the site of the lesion (i.e. lymph nodes, bone, lung, and liver; Arturi et al. 2000). Table 3 presents some of the clinical, pathological, and radiological findings associated with radioiodine-refractory thyroid cancer. It is also important to note that promising therapeutic alternatives to radioiodine are finally becoming available. Several novel, molecularly targeted drug therapies are already being tested for this purpose in clinical trials, and others will begin such testing soon (Schlumberger & Sherman 2012).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Features predicting radioiodine-refractory disease.</th>
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<tr>
<td>Clinicopathological features</td>
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<tr>
<td>Age &gt;40 years</td>
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<tr>
<td>Poorly differentiated thyroid cancer</td>
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<td>Large metastases</td>
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<td>Bone metastases</td>
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<td>Functional imaging findings</td>
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<td>RAI scan: at least one lesion without RAI uptake</td>
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<tr>
<td>18FDG–PET scan: FDG-avid lesions, irrespective of their RAI uptake</td>
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<tr>
<td>Response to therapy</td>
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<tr>
<td>At least one lesion that progresses during the first year after RAI therapy</td>
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<tr>
<td>Persistent disease after treatment with cumulative RAI activity of &gt;22 GBq (600 mCi)</td>
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RAI, radioactive iodine; 18FDG–PET, 2-[18F]fluoro-2-deoxyglucose–positron emission tomography; GBq, gigabecquerel.

Which patients stand to benefit from TSH suppression therapy and what degree of suppression is appropriate?

Thyroid cancer cells generally remain responsive to the effects of circulating TSH, which stimulates a variety of cellular processes including cell proliferation (Biondi et al. 2005). This is the rationale cited for the use of TSH-suppressive doses of thyroid hormone therapy, which has been reported to significantly decrease recurrence rates and cancer-related mortality in DTC patients (Mazzaferri & Kloos 2001, McGriff et al. 2002). However, the degree of suppression required to achieve these goals is uncertain. The reduction of TSH levels to <0.1 mU/l has been associated with better clinical outcomes in high-risk thyroid cancer patients (Cooper et al. 1998), but the possibility that milder reductions (0.1–0.5 mU/l) might offer the same benefits has never been explored. Furthermore, TSH suppression produces a state of subclinical hyperthyroidism, which can have negative effects on the bone and heart (Cooper & Biondi 2012). The 2009 ATA guidelines stress the importance of striking a balance between the potential risks and benefits of TSH suppression (Cooper et al. 2009). At the beginning of the follow-up, the degree of TSH suppression should be chosen.
on the basis of the individual patient’s risk for persistent or recurrent disease. Later on, suppression might be discontinued if there is no documented evidence of disease (Table 1).

**What are the best diagnostic methods for detecting persistent/recurrent disease and for identifying patients who are cured and how should these tools be used?**

The early phase of the postoperative follow-up of patients with DTCs (i.e. the first year or 2 years after the initial treatment) has a twofold purpose: to detect persistent disease, which may require additional therapy or at least more active surveillance, and to identify probable cures. As has been discussed previously, most patients will belong to the latter group, and in some the likelihood of recurrence will be low enough to justify less intensive surveillance than that planned on the basis of the initial ATA- or ETA-based risk estimate (Tuttle et al. 2010, Castagna et al. 2011a,b). For the patients who appear to be disease free, the main goal of the successive, long-term phase of the follow-up is the prompt detection of possible recurrence.

Reliable detection of persistent or recurrent disease requires diagnostic tools with a high positive predictive value; those with high negative predictive values are suitable for identifying cases that have been cured. The ATA (Cooper et al. 2009) and the ETA (Pacini et al. 2006) concur that serum Tg assays and neck ultrasonography (US) are the essential tools for monitoring patients with DTCs, but neither association offers any details on the merits or shortcomings of these tools or on how and when should they be used.

**Serum Tg assays**

As has been discussed above, the serum Tg level is a highly specific marker of persistent or recurrent disease in a patient treated with total thyroidectomy and RRA. In patients whose surgery consisted of sub-total thyroidectomy or lobectomy or those who had a total thyroidectomy without RRA, the specificity of a positive Tg assay plummets, since the Tg detected may well be coming from the normal thyroid remnant (Pacini et al. 2006, Cooper et al. 2009). The importance of this shortcoming is highest during the initial postoperative evaluation/phase of the follow-up: as the follow-up continues, the value of the Tg assay increases. Recent studies have shown, in fact, that Tg production by the normal remnant declines spontaneously and sometimes becomes undetectable within the first year of the follow-up. After 5 years, levels are likely to be undetectable in the vast majority of cases (almost 80%) – just as they are in patients who have undergone total thyroidectomies plus RRA (see the previous section for details; Durante et al. 2012). In addition, although benign Tg production in some non-ablated patients never ceases completely, it does stabilize. In contrast, ‘malignant’ Tg production tends to increase over time, and this trend is highly predictive of persistent or progressive neoplastic disease, regardless of whether or not nests of normal thyocytes are still present (Baudin et al. 2003, Torlontano et al. 2004, Miyauchi et al. 2011). In short, in non-ablated patients – who represent an increasingly large proportion of the individuals with DTCs – the initial postoperative serum Tg measurement is per se an unreliable marker of persistent disease, but its specificity increases when it is examined with subsequent measurements: increasing Tg production documented with serial determinations over the course of the follow-up is associated with a positive predictive value for persistent/recurrent disease of roughly 100%. In particular, a Tg doubling-time of <1 year appears to be the strongest correlate of recurrence and cancer-specific survival (Miyauchi et al. 2011).

The sensitivity of a serum Tg measurement varies depending on the patient’s TSH level at the time of the assay. Small foci of neoplastic tissue may not be detected if the Tg assay is done while the patient is on levothyroxine (especially at TSH-suppressive doses) (Mazzaferrì et al. 2003, Bachelot et al. 2005). To maximize sensitivity, Tg production must be measured during endogenous or exogenous TSH stimulation (the former elicited by levothyroxine withdrawal and the latter by the administration of rhTSH; Eustatia-Rutten et al. 2004, Schlumberger et al. 2007b). The latter approach, however, is generally reserved for patients who have undergone RRA (Pacini et al. 2006, Cooper et al. 2009). In these cases, one can be reasonably certain that normal thyroid cells are no longer present, and TSH stimulation will be targeting only residual cancerous cells (if any are present).

The need to measure TSH-stimulated Tg is expected to decline as the availability of high-sensitivity Tg assays increases in clinical settings (Smallridge et al. 2007, Castagna et al. 2011a,b, Malandrino et al. 2011). These assays, which have functional sensitivities of <0.2 ng/ml, may allow earlier detection of ‘malignant’ Tg production even while patients are still taking levothyroxine. A study conducted in 2007 has compared the diagnostic values of seven progressively sensitive Tg assays (Schlumberger et al. 2007b).
A detection limit of 0.9 ng/ml was associated with a low sensitivity in identifying persistent disease (40%). Sensitivity doubled (almost 80%) when the assays with the lowest detection limits (0.11 and 0.02 ng/ml) were tested, but the cost of this improvement was a considerable loss in specificity. Based on their data, the authors concluded that the best trade-off was a functional assay sensitivity between 0.2 and 0.3 ng/ml, which offers an improved diagnostic sensitivity (about 65%) without significantly diminishing the specificity (Schlumberger et al. 2007b). However, the true diagnostic accuracies of the high-sensitivity Tg assays still need to be validated in larger prospective studies. At present, they can be exploited to study the trend of serial serum Tg determinations, which still offers the highest negative (decreasing levels) and positive (rising levels) predictive values (Baudin et al. 2003, Torlontano et al. 2004).

In the presence of serum Tg antibodies, both conventional measurements of TSH-stimulated Tg levels and high-sensitivity assays of basal Tg production may fail to identify patients with clinically significant tumor foci (Spencer et al. 1999). In these cases, serial serum anti-Tg antibody quantification using the same methodology may serve as an imprecise surrogate marker of residual normal thyroid tissue or tumor (Spencer et al. 1998, Chiovato et al. 2003). In a large series of patients with DTC who underwent RRA, those showing a more than 50% decrease in serum anti-Tg antibodies within 6–12 months of ablation had a significantly lower recurrence rate than patients with lower reduction or increasing levels of the antibodies (Kim et al. 2008).

Neck US

Aside from the safety and relatively low cost of ultrasound imaging in general, one of the main reasons neck sonography is so valuable in the postoperative follow-up of PTC patients (Durante & Filetti 2011) is that disease spread or recurrence is almost always associated first with cervical lymphadenopathy. In addition, unlike serum Tg assays and 131I WBS, it performs equally well in patients who have not undergone RRA, it requires no hormone withdrawal or administration of rhTSH, and it provides valuable information for surgeons on the location and preoperative tattooing of the involved nodes.

Neck US has been widely used in patients with DTCs since the 1990s, and the sonographic criteria for identifying cervical lymph node metastases are well established (Leboulleux et al. 2007). In terms of sensitivity, it has repeatedly proved to be superior to stimulated Tg assays and diagnostic WBS in detecting cervical node involvement (Antonelli et al. 1995, Pacini et al. 2003, Torlontano et al. 2003, 2004). In 335 PTC patients whose Tg levels remained undetectable after TSH stimulation at the 1-year postoperative follow-up, neck US disclosed cervical metastases in 7 (2%) cases (Torlontano et al. 2004). Another important advantage of neck US over Tg assays is its high negative predictive value, which approaches 100% in cases of very low-risk DTCs. In a large, long-term study of 312 patients with this type of PTC, those with negative findings on the first postoperative US study (3–12 months after surgery) were all disease free at the end of the follow-up (Durante et al. 2010). To improve the specificity of the examination, nodules that appear suspicious can be biopsied immediately under US guidance (Pacini et al. 2006, Cooper et al. 2009) and the sample submitted for cytologic analysis and/or measurement of Tg levels in the needle-washout fluid (Uruno et al. 2005).

Neck US is thus becoming the mainstay of the postoperative follow-up of DTCs, especially during the early months, when, in the increasingly large proportion of patients with low- or very-low-risk tumors who have not undergone RRA, Tg assay results are difficult to interpret. When the initial postoperative scan is negative, the probability of a favorable long-term outcome is quite high, regardless of serum Tg levels. Even in low-risk patients, however, metastatic disease can still be discovered, sometimes several years after the initial treatment (Ross et al. 2009), so surveillance must be continued. As has been discussed above, the value of serum Tg assays increases with time, as consecutive measurements accumulate and allow increasingly reliable assessments of production trends. In the later phases of the follow-up, greater reliance might be placed on basal Tg assays, which are less expensive and easier to schedule than neck US (Fig. 1). Additional research is needed, of course, to assess the sensitivity of this approach.

All the above-mentioned arguments apply mainly to PTC histotype. As for FTCs, while lymph node metastases involve almost 20% of patients with widely invasive forms, distant metastases are present in as many as one-third of the patients, often in the absence of nodal involvement (Dralle et al. 2013). Thus, staging FTCs requires further complementary imaging modalities (Table 4). Finally, it is important to recall that one of the inherent features of sonographic imaging is inter-operator variability. To reduce the effect of this potential limitation, neck US, as an integral part of thyroid cancer follow-up protocols, should be performed using standardized protocols and in strict compliance with guidelines and criteria.
recommended by the scientific societies. Uniform quality may also be more likely when the examinations are done by specially trained physicians with close and continuous involvement in the overall care of the patient with DTC.

Other tools

Whenever US and/or Tg data are suggestive of persistent/recurrent disease, additional imaging studies may be warranted. These include both cross-sectional modalities such as computed tomography or magnetic resonance imaging and nuclear medicine procedures, such as WBS and 2-[18F]fluoro-2-deoxyglucose–positron emission tomography (18FDG–PET; Table 4; Pacini et al. 2006, Cooper et al. 2009). In addition to detecting neoplastic foci, 18FDG–PET also has important prognostic and treatment implications. Several studies have shown, in fact, that FDG-avid lesions are unresponsive to high-dose radioiodine therapy, and this type of disease carries the highest risk for thyroid cancer-related mortality (Robbins et al. 2006).

How long should the patients who are apparently disease free be followed?

Life-long follow-up is still the rule for patients with DTCs. Once again, however, this practice is rooted largely in data on the outcomes of cases treated at least 20 or 30 years ago (DeGroot 1994, Mazzaferri & Jhiang 1994). Today, in light of the numbers of PTCs being diagnosed, the changing profile of the PTC patient population, and improvements in the methods available for detecting postoperative recurrence, the cost-effectiveness of protracted surveillance is being questioned. In 1994, Mazzaferri & Jhiang analyzed 1077 PTC patients treated during the last four
Table 4  Second-line imaging studies for the work-up of persistent/recurrent disease in patients with DTCs.

<table>
<thead>
<tr>
<th>Imaging procedures</th>
<th>Clinical applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast-enhanced computed tomography</td>
<td>To detect lesions in the brain, neck, chest, and abdomen (triple-phase scanning is required for liver studies)</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>To detect brain, liver, and bone lesions</td>
</tr>
<tr>
<td>Diagnostic 131I whole-body scan</td>
<td>To identify the source of persistent Tg production in intermediate/high-risk patients</td>
</tr>
<tr>
<td>Bone scintigraphy</td>
<td>To stage patients at a higher risk of persistent/recurrent disease, including individuals with widely invasive FTC</td>
</tr>
<tr>
<td>18FDG–PET</td>
<td>To detect skeletal lesions</td>
</tr>
<tr>
<td></td>
<td>To identify occult metastases in patients with elevated Tg levels and negative whole-body scans</td>
</tr>
<tr>
<td></td>
<td>To stage patients with poorly differentiated thyroid cancer or Hürthle cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>To identify patients with distant metastases at a highest risk for cancer-related mortality</td>
</tr>
<tr>
<td></td>
<td>To identify patients unlikely to respond to RAI therapy</td>
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<tr>
<td></td>
<td>To evaluate responses to systemic or local treatment</td>
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</tbody>
</table>

DTC, differentiated thyroid cancer; RAI, radioactive iodine; Tg, thyroglobulin; FTC, follicular thyroid cancer; 18FDG–PET, 2-[18F]fluoro-2-deoxyglucose–positron emission tomography.

decades of the 20th century and found a recurrence rate of more than 20%. After >5 years of follow-up, 40% of the recurrences were identified, and around 20% were detected after the tenth year. In 2013, Durante et al. (2013) conducted a similar analysis of 1020 patients treated between 1990 and 2008. The recurrence rate was markedly lower (1.4%); over 75% of the recurrences were discovered within 5 years of the initial treatment, and none were detected after the eighth year of the follow-up.

The demography of DTC patients seen in general thyroid disease practices has clearly changed. Roughly three out of four of the patients in the 2013 study had stage I tumors. This is approximately five times higher than the percentage reported by Mazzaferrri & Jhiang (even allowing for the fact that the staging criteria used in the two studies were slightly different). In addition, almost half the cases analyzed in the 1994 study were characterized by regional lymph node involvement at the time of the initial therapy — almost twice the rate reported in the 2013 study. Finally, the past 30 years have witnessed a progressive decline in the use of 131I WBS during the follow-up of DTC patients and greater reliance on high-resolution neck US and increasingly sensitive serum Tg assays.

Concluding remarks

Figure 1 shows an algorithm for individualized, risk-tailored management of the DTC patients being seen by today’s endocrinologists. This approach reflects current recommendations made by the ATA and ETA, and it is clearly different from the approaches that had been used 5–10 years ago (Table 1). As our knowledge of the biology and natural history of these tumors expands, the management strategies that we use will continue to evolve. In all probability, the trend will be toward increasingly individualized treatment aimed at optimizing treatment — in terms of efficacy, cost, and quality of life benefits — for all patients with DTCs (right column, Table 1).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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