Management of papillary and follicular (differentiated) thyroid cancer: new paradigms using recombinant human thyrotropin

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Abstract

The incidence of differentiated thyroid cancer (DTC) has increased in many places around the world over the past three decades, yet this has been associated with a significant decrease in DTC mortality rates in some countries. While the best 10-year DTC survival rates are about 90%, long-term relapse rates remain high, in the order of 20–40%, depending upon the patient's age and tumor stage at the time of initial treatment. About 80% of patients appear to be rendered disease-free by initial treatment, but the others have persistent tumor, sometimes found decades later. Optimal treatment for tumors that are likely to relapse or cause death is total thyroidectomy and ablation by iodine-131 (131I), followed by long-term levothyroxine suppression of thyrotropin (TSH). On the basis of regression modeling of 1510 patients without distant metastases at the time of initial treatment and including surgical and 131I treatment, the likelihood of death from DTC is increased by several factors, including age >45 years, tumor size >1.0 cm, local tumor invasion or regional lymph-node metastases, follicular histology, and delay of treatment >12 months. Cancer mortality is favorably and independently affected by female sex, total or near-total thyroidectomy, 131I treatment and levothyroxine suppression of TSH. Treatments with 131I to ablate thyroid remnants and residual disease are independent prognostic variables favorably influencing distant tumor relapse and cancer death rates. Delay in treatment of persistent disease has a profound impact on outcome.

Optimal long-term follow-up using serum thyroglobulin (Tg) measurements and diagnostic whole-body scans (DxWBS) require high concentrations of TSH, which until recently were possible to achieve only by withdrawing levothyroxine treatment, producing symptomatic hypothyroidism. New paradigms, however, provide alternative pathways to prepare patients for 131I treatment and to optimize follow-up. Patients with undetectable or low Tg concentrations and persistent occult disease can now be identified within the first year after initial treatment by recombinant human (rh)TSH-stimulated serum Tg concentrations greater than 2 µg/l, without performing DxWBS. These new follow-up paradigms promptly identify patients with lung metastases that are not evident on routine imaging, but which respond to 131I treatment. In addition, rhTSH can be given to prepare patients for 131I remnant ablation or 131I treatment for metastases, especially those who are unable to withstand hypothyroidism because of concurrent illness or advanced age, or whose hypothyroid TSH fails to increase.

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Introduction
The two most common forms of thyroid cancer, papillary and follicular thyroid cancer, together termed differentiated thyroid cancer (DTC), comprise the majority of thyroid cancers and have the best prognosis. The debate surrounding their management has been fueled by the fact that no prospective randomized trials of treatment have been conducted and none are likely to be done. Each arm of such a study, however, would require nearly 4000 patients to detect a 10% reduction in thyroid cancer mortality after 25 years. Enrollment would take 10 or more years, making the results available in 35 years (Wong et al. 1990). Our knowledge about treatment is woven from a patchwork of large retrospective cohort studies in which patients have been followed for decades, providing the fabric of our management paradigms. Much of the following discussion refers to the management of DTC, because the treatments of papillary and follicular cancer are so similar. Special emphasis is given to new and emerging paradigms, especially those using recombinant human thyrotropin (rhTSH) and sensitive thyroglobulin (Tg) measurements, which is important because patients with DTC often experience tumor relapse decades after treatment.

Incidence and prevalence rates
In the USA in 2001, about 9500 new cases and 1300 deaths occurred from thyroid cancer. Its incidence in the USA has increased nearly 50% since 1973 (Ries et al. 2000) and has been increasing in many other countries, including Canada (Liu et al. 2001), Sweden (Pettersson et al. 1996), Norway (Akslen et al. 1993) and Great Britain (Dos Santos Silva & Swerdlow 1993). This is likely due to exposure of the population to thyroid radiation in the form of external beam radiation used in the past to treat benign conditions in children and in the form of atmosphere fallout of radioactive iodine (Institute of Medicine 1999) and early diagnosis using fine-needle aspiration biopsy (FNA).

Most (80%) thyroid cancers in the USA are papillary cancers, with follicular cancer comprising only 11% of new cases (Hundahl et al. 1998). Papillary and minimally invasive follicular cancers are typically slow-growing tumors that respond well to treatment. Indeed, a few believe that survival is so good that DTC poses little risk to patients younger than 45 years at the time of diagnosis (Cady 2000). Yet the natural history of DTC unfolds over decades. Ten-year cancer-specific mortality rates in almost 54 000 patients diagnosed in the USA between 1985 and 1995 were about 7% for papillary, 15% for follicular and 25% for Hürthle cell cancers (Hundahl et al. 1998). Papillary cancer, the most indolent and most likely to respond to treatment, nevertheless accounts for more than 50% of the cancer deaths, because its incidence is so high.

The prevalence of thyroid cancer in the US population, relatively high because survival is prolonged, is now about 220 000 cases, almost all of which are DTC and many of which will recur.

Recurrence (persistent tumor) rates
Recurrence rates with DTC are high, ranging from 20% to 40% (Mazzaferri & Jhiang 1994). Distant metastases are often discovered decades after initial treatment (Fig. 1), underscoring the need for long-term follow-up. What is usually termed recurrent tumor, however, is in fact often persistent disease that remains below our surveillance radar for

Figure 1 Tumor recurrence rates in 1528 patients after a median of 16.6 years follow-up. There were 359 recurrences (23.5% of patients). Local recurrence (n = 272, 17.8%) is cervical or mediastinal; distant recurrence (n = 114, 7.5%) is sites outside the neck. (A) Number of patients with recurrences at 5-year intervals. (B) Cumulative percent of recurrences, distant recurrences and cancer deaths over 40 years stratified by age at the time of initial treatment. Patients (n = 27) with both local and distant recurrences are shown as distant recurrence. Reproduced with permission from Mazzaferri & Kloos (2002).
years before it reappears as clinically evident cancer. Persistent DTC, however, can now be detected very early using newly devised testing paradigms.

Two-thirds of the cases of persistent tumor are detected within 10 years of treatment, but the others are evident decades later (Fig. 1A) (Mazzaferri & Kloos 2001). Recurrences, including distant metastases, are more common in those younger than 20 and older than 60 years (Fig. 1B) (here and elsewhere, age refers to the patient’s age at the time of initial treatment). Many lead to death. Almost 70% of those who died of cancer were considered disease-free after initial treatment, succumbing to the disease after a relapse. In our experience, 30-year mortality rates are about 12% after local relapse and 43% after distant recurrence.

**Declining mortality rates**

Thyroid cancer mortality rates in the USA have fallen 20% between 1973 and 1996 (Ries et al. 2000), probably as the result of early diagnosis and effective treatment. However, this occurred only in women, probably because they undergo routine examinations more often than do men, in whom thyroid cancer is typically discovered two to three decades later than it is in women.

**Risk stratification**

**Cause of death from thyroid cancer**

Deaths from thyroid cancer are more common in patients older than 45 years at the time of surgery and in those with more advanced tumor stage (Table 1) (Mazzaferri & Kloos 2001). Patients with follicular cancer have higher mortality rates, but tend to be older and with more advanced tumor stage at the time of diagnosis than those with papillary cancer. Few studies give details of the exact cause of death from thyroid cancer. One such study of patients who died of cancer were considered disease-free after initial treatment (Mazzaferri & Jhiang 1994). Among our patients at low risk than among those at high risk (56.8% compared with 35.2%, P < 0.001) according to the age-metastases-extent-size (AMES) staging criteria (Cady 1997). Distant metastases occurred in the low- and high-risk categories, respectively, in 89 and 25 patients. The AJCC/UICC staging system poses similar problems. Most staging systems are derived from multivariate analyses that do not consider recurrence or the effect of treatment, and all rely on some information that is available only after surgery. Relapse-free status and survival cannot be assured by low tumor stage in most staging systems.

Another problem is that staging systems using age to stratify risk fail to predict recurrence-free survival and relapse, mainly because relapse rates are high in young patients (Fig. 1B). For example, 35-year cancer relapse rates were higher among our patients at low risk than among those at high risk (56.8% compared with 35.2%, P < 0.001) according to the age-metastases-extent-size (AMES) staging criteria (Cady 1997). Distant metastases occurred in the low- and high-risk categories, respectively, in 89 and 25 patients. The AJCC/UICC staging system poses similar problems. Most staging systems are derived from multivariate analyses that do not consider recurrence or the effect of treatment, and all rely on some information that is available only after surgery. Relapse-free status and survival cannot be assured by low tumor stage in most staging systems.

Almost none of the multivariate analyses used to construct the clinical staging systems take into account the effects of treatment, tacitly assuming that treatment does not alter outcome. This shortcoming was recognized by the authors of the European Organisation for Research and Cancer Treatment (EORTC) staging system, the first such system to be devised (Byar et al. 1979). Subsequent authors have largely ignored this caveat (Cady & Rossi 1988, Hay 1990, Hay et al. 1993, Shaha et al. 1995).

Clinical staging schemes do not permit meaningful decisions to be made for patients at the time of surgery. They are best reserved for epidemiologic studies, for which the TNM classification of the AJCC and UICC (Table 3) is perhaps most useful.

**Staging systems**

There are many staging systems for thyroid cancer. Most accurately predict mortality rates. Nevertheless, some in the lowest risk strata in most staging systems die of cancer (DeGroot et al. 1994, Hundahl et al. 1998), particularly when risk is simply defined dichotomously as low or high (Cady et al. 1979, American Joint Committee on Cancer 1992). In one study (Kitamura et al. 1999), more than 10% of the patients dying of DTC had an American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) classification of stage 1 or 2 (Table 3).

Another problem is that staging systems using age to stratify risk fail to predict recurrence-free survival and relapse, mainly because relapse rates are high in young patients (Fig. 1B). For example, 35-year cancer relapse rates were higher among our patients at low risk than among those at high risk (56.8% compared with 35.2%, P < 0.001) according to the age-metastases-extent-size (AMES) staging criteria (Cady 1997). Distant metastases occurred in the low- and high-risk categories, respectively, in 89 and 25 patients. The AJCC/UICC staging system poses similar problems. Most staging systems are derived from multivariate analyses that do not consider recurrence or the effect of treatment, and all rely on some information that is available only after surgery. Relapse-free status and survival cannot be assured by low tumor stage in most staging systems.

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Clinical staging schemes do not permit meaningful decisions to be made for patients at the time of surgery. They are best reserved for epidemiologic studies, for which the TNM classification of the AJCC and UICC (Table 3) is perhaps most useful.
Table 1 Risk stratification of clinical variables influencing cancer recurrence and cancer death

A. Patient variables
1. Age < 15 years or > 45 years
2. Male sex
3. Family history of thyroid cancer
4. Previous exposure to thyroidal irradiation (external beam irradiation or exposure to radionuclides from atmospheric fallout or other sources (children))

B. Tumor variables
1. Tumor > 4 cm diameter
2. Bilateral (multifocal) thyroid tumors
3. Extrathyroidal tumor extension
4. Vascular invasion (papillary and follicular carcinoma)
5. Cervical, mediastinal lymph node metastases
6. Tumor subtypes: Hürthle, tall, cell, columnar cell, diffuse sclerosis, insular variants
7. Advanced histologic grade: nuclear atypia, tumor necrosis, vascular invasion
8. Tumor that concentrates $^{131}$I poorly or not at all
9. Distant metastases
10. Tumor that concentrates fluorine-18-fluorodeoxyglucose uptake on PET scan

C. Treatment variables
1. Delay in diagnosis and treatment
2. Less than total or near-total thyroidectomy
3. Delay in completing total thyroidectomy after lobectomy
4. Failure to give $^{131}$I treatment
5. Failure to suppress TSH with levothyroxine

D. Follow-up variables
1. Failure to measure Tg and perform DxWBS
2. Failure to recognize high serum Tg as an indicator of persistent disease

Modified from the National Comprehensive Cancer Network guidelines for the diagnosis and treatment of thyroid cancer (Mazzaferri 1999).

Initial management

Management plan

The five phases of management are: (1) diagnosis, (2) surgery, (3) remnant ablation, (4) thyroid hormone suppression of thyrotropin (THST), and (5) follow-up, including diagnostic studies and treatment. Management in each phase is unique and crucial to optimal long-term outcome, but is not always optimal.

An audit of care found many deficiencies in practice, citing inadequacies in the areas of surgery (20%), suppression of thyroxine ($T_4$) (20%), monitoring by serum Tg (15%) and the use of $^{131}$I treatment (12%) (Kumar et al. 2001). Others identify similar problems in Europe and the USA (Hardy et al. 1995, Hundahl et al. 1998, Vanderpump et al. 1998). Because of these deficiencies, leaders in Great Britain (Kendall-Taylor 2001) called for the establishment of guidelines for the management of thyroid cancer.

National Comprehensive Cancer Network (NCCN) and British Thyroid Association guidelines

Explicit guidelines, established in lieu of prospective randomized trials but based upon the current literature for the diagnosis and management of thyroid cancer, were written by a panel of multidisciplinary experts from USA Cancer Hospitals (Mazzaferri 1999) and by the British Thyroid Association (2002). Both guidelines give explicit advice and assistance in the management of thyroid cancer, providing carefully considered algorithms and comprehensive bibliographies. The British Thyroid Association Guidelines also provide excellent material for patients.

Diagnosis

Fine-needle aspiration (FNA) cytology is the first diagnostic test for a thyroid nodule in a euthyroid patient. Yet diagnosis is sometimes delayed for years because thyroid cancer occurs in an environment teeming with benign nodules (Mazzaferri 1993a, Ross 2002). The diagnostic accuracy is considerably enhanced by ultrasonography and Doppler studies (Marqusee et al. 1997, Papini et al. 2002). In one study the odds ratio of malignancy was 16.8 if ultrasonography showed indistinct or blurred nodule margins, 14.3 with intranodular Doppler flow and 4.9 with microcalcifications (Papini et al. 2002). The sensitivity of ultrasound-guided FNA and Doppler in evaluating 12,001 patients was 93% and the specificity was 75% (Yang et al. 2001).

Despite its efficacy, FNA was not performed before sur-
### Table 2 Cox regression model on cancer recurrence, distant metastasis recurrence and death due to thyroid cancer in 1501 patients with or without distant metastases at the time of initial treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All cancer recurrence (n=1501)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td>1.0</td>
<td>0.2</td>
<td>0.9 to 1.3</td>
</tr>
<tr>
<td>Local tumor invasion</td>
<td>1.4</td>
<td>0.01</td>
<td>1.1 to 2.2</td>
</tr>
<tr>
<td>Lymph node metastases†</td>
<td>1.3</td>
<td>0.01</td>
<td>1.1 to 1.6</td>
</tr>
<tr>
<td>Follicular histology</td>
<td>0.8</td>
<td>0.012</td>
<td>0.7 to 0.96</td>
</tr>
<tr>
<td>Tumor size‡</td>
<td>1.2</td>
<td>0.0001</td>
<td>1.1 to 1.3</td>
</tr>
<tr>
<td>Thyroid remnant $^{131}$I ablation¶</td>
<td>0.8</td>
<td>0.016</td>
<td>0.7 to 0.97</td>
</tr>
<tr>
<td>Treatment with $^{131}$I¶</td>
<td>0.5</td>
<td>0.0001</td>
<td>0.4 to 0.6</td>
</tr>
<tr>
<td>Surgery more than lobectomy§</td>
<td>0.7</td>
<td>0.0001</td>
<td>0.6 to 0.9</td>
</tr>
<tr>
<td><strong>Distant metastasis recurrence (n=1501)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td>1.3</td>
<td>0.0001</td>
<td>1.2 to 1.5</td>
</tr>
<tr>
<td>Follicular histology</td>
<td>1.0</td>
<td>0.864</td>
<td>0.8 to 1.2</td>
</tr>
<tr>
<td>Lymph node metastases†</td>
<td>1.6</td>
<td>0.002</td>
<td>1.2 to 2.2</td>
</tr>
<tr>
<td>Local tumor invasion</td>
<td>1.6</td>
<td>0.927</td>
<td>0.9 to 2.7</td>
</tr>
<tr>
<td>Tumor size‡</td>
<td>1.2</td>
<td>0.001</td>
<td>1.1 to 1.8</td>
</tr>
<tr>
<td>Thyroid remnant $^{131}$I ablation¶</td>
<td>0.6</td>
<td>0.002</td>
<td>0.5 to 0.8</td>
</tr>
<tr>
<td>Treatment with $^{131}$I¶</td>
<td>0.4</td>
<td>0.0001</td>
<td>0.2 to 0.6</td>
</tr>
<tr>
<td>Surgery more than lobectomy§</td>
<td>0.8</td>
<td>0.379</td>
<td>0.6 to 1.2</td>
</tr>
<tr>
<td><strong>Cancer mortality (n=1501)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td>9.5</td>
<td>0.0001</td>
<td>5.3 to 17.1</td>
</tr>
<tr>
<td>Time to treatment**</td>
<td>2.4</td>
<td>0.0001</td>
<td>1.5 to 4.0</td>
</tr>
<tr>
<td>Follicular histology</td>
<td>1.4</td>
<td>0.003</td>
<td>1.1 to 1.8</td>
</tr>
<tr>
<td>Lymph node metastases†</td>
<td>2.0</td>
<td>0.006</td>
<td>1.2 to 3.4</td>
</tr>
<tr>
<td>Tumor size‡</td>
<td>1.2</td>
<td>0.025</td>
<td>1.0 to 1.3</td>
</tr>
<tr>
<td>Local tumor invasion</td>
<td>1.1</td>
<td>0.002</td>
<td>1.0 to 1.2</td>
</tr>
<tr>
<td>Female (versus male)</td>
<td>0.6</td>
<td>0.046</td>
<td>0.4 to 0.99</td>
</tr>
<tr>
<td>Thyroid remnant $^{131}$I ablation¶</td>
<td>0.5</td>
<td>0.0001</td>
<td>0.4 to 0.7</td>
</tr>
<tr>
<td>Surgery more than lobectomy§</td>
<td>0.5</td>
<td>0.0001</td>
<td>0.4 to 0.7</td>
</tr>
<tr>
<td>Treatment with $^{131}$I¶</td>
<td>0.4</td>
<td>0.010</td>
<td>0.2 to 0.8</td>
</tr>
</tbody>
</table>

Reproduced with permission from Mazzaferri & Kloos (2002).

*Age stratified as less than 40 years versus 40 years and older for cancer mortality, and by decade for recurrences and distant recurrences.
†Lymph node metastases present versus absent.
‡Tumor diameter stratified into 1 cm increments from tumors smaller than 1 cm to > 5 cm.
¶Remnant ablation is the use of $^{131}$I in patients with uptake only in the thyroid bed and no evidence of residual tumor; Treatment with $^{131}$I is postoperative treatment of patients with known residual disease.
§Bilateral thyroid surgery versus lobectomy with or without isthmusectomy.
**Time to treatment ≤ 12 months versus > 12 months.

In about 40% of 5584 patients with thyroid cancer in one study in the USA (Hundahl et al. 2000), North American endocrinologists, however, use FNA routinely to evaluate thyroid nodules, performing it early and relying heavily on its results (Bennedbaek & Hegedus 2000). In contrast, evaluations by primary care physicians are more costly and more time consuming, causing a delay of 12 months or longer in almost 30% of the patients managed in one New York study (Ortiz et al. 1998). This increases mortality rates significantly. Mortality rates from thyroid cancer begin rising after 12 months’ delay in diagnosis, increasing up to 40-fold when 10 or more years has elapsed from the time a nodule is first palpated until its treatment (Mazzaferri & Jhiang 1994).

**Initial surgery**

Although debate continues to swirl around the initial treatment of DTC (Mazzaferri & Kloos 2001), total or near total thyroidectomy that leaves less than 2 g (2 cm²) of thyroid tissue is performed in most large centers for the majority of patients. Studies from the USA, Europe and Hong Kong show that most patients at risk for relapse or death from thyroid cancer (tumors 1 cm or larger) are treated with total or near-total thyroidectomy, usually followed by $^{131}$I and levothyroxine treatment (Van De Velde et al. 1988, Baldet et al. 1989, Solomon et al. 1996, Sherman et al. 1998, Mazzaferri 1999, Cailleux et al. 2000, Hundahl et al. 2000, Chow et al. 2002). External beam irradiation, which has a less prominent
Table 3 Definition of TNM and AJCC/UICC clinical stages

<table>
<thead>
<tr>
<th>Definition of TNM</th>
<th>Clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Primary tumor</td>
<td>Patients &lt;45 years with any T, any N, M0</td>
</tr>
<tr>
<td>TX Cannot be assessed</td>
<td>Patients &gt;45 years with T1</td>
</tr>
<tr>
<td>T0 No evidence of primary tumor</td>
<td>Patients &gt;45 years with T2–3</td>
</tr>
<tr>
<td>T1 &lt;1 cm</td>
<td>Patients &gt;45 years with T4 or N1</td>
</tr>
<tr>
<td>T2 1–4 cm</td>
<td>Patients &gt;45 years with M1</td>
</tr>
<tr>
<td>T3 &gt;4 cm</td>
<td>Patients &gt;45 years with T4 or N1</td>
</tr>
<tr>
<td>T4 Tumor of any size beyond thyroid capsule</td>
<td>Patients &gt;45 years with T4 or N1</td>
</tr>
<tr>
<td>N Regional lymph nodes</td>
<td>Patients &gt;45 years with T4 or N1</td>
</tr>
<tr>
<td>NX Cannot be assessed</td>
<td>Patients &gt;45 years with T4 or N1</td>
</tr>
<tr>
<td>N0 Not present</td>
<td>Patients &gt;45 years with T4 or N1</td>
</tr>
<tr>
<td>N1 Present</td>
<td>Patients &gt;45 years with T4 or N1</td>
</tr>
<tr>
<td>M Distant metastases</td>
<td>Patients &gt;45 years with T4 or N1</td>
</tr>
<tr>
<td>M0 None</td>
<td>Patients &gt;45 years with T4 or N1</td>
</tr>
<tr>
<td>M1 Present</td>
<td>Patients &gt;45 years with T4 or N1</td>
</tr>
</tbody>
</table>

Performing lobectomy alone as the definitive surgery may lead to a 5–10% recurrence rate in the opposite thyroid lobe (Hay et al. 1987, Mazzaferri 1993b), a high tumor recurrence rate (Fig. 2) and a high (11%) rate of relapse in the form of pulmonary metastases (Massin et al. 1984). High relapse rates with cervical lymph node metastases and multicentric tumors (Mazzaferri & Jhiang 1994) justify total or near-total thyroidectomy and ¹³¹I ablation. If lobectomy is performed, diagnostic ¹³¹I imaging may miss microscopic metastases in the contralateral lobe or elsewhere when they are most amenable to treatment. We found that surgery consisting of more than lobectomy was an independent variable affecting cancer relapse (Table 2). Others report a similar effect of surgery on tumor recurrence (DeGroot et al. 1994, Chow et al. 2002).

It is more difficult to demonstrate that total or near-total thyroidectomy influences survival, although there is considerable proof that it influences relapse-free survival. One study, for example, found no improvement in survival rates after patients with low-risk papillary cancers (Age, Grade, Extent, Size (AGES) score ≤3.99) underwent more than lobectomy (Hay et al. 1987). The same authors, however, later recommended that bilateral thyroid resection should be performed for low-risk papillary cancer, after finding that the 20-year rates for local recurrence and nodal metastasis were, respectively, 14% and 19% after unilateral lobectomy, compared with 2% and 6% (P = 0.0001) after bilateral thyroid resection (Hay et al. 1998). Others have demonstrated a reduction in cancer mortality by more extensive surgery in patients without distant metastases, but this was mainly attributable to its effect on T4 tumors (DeGroot et al. 1994).

Postoperative ¹³¹I treatment obscures the therapeutic impact of surgery. Patients in our study treated with total or near-total thyroidectomy plus ¹³¹I ablation and levothyroxine had significantly fewer local recurrences and distant relapses than those treated with any other combination, including total thyroidectomy and levothyroxine alone (Mazzaferri & Kloos 2001). Surgery, more than lobectomy, had an independent role in initial management and usually follows ¹³¹I treatment, is best given postoperatively to patients older than 40 years with TNM stage T4 tumors (Simpson et al. 1988, Farahati et al. 1996, Mazzaferri 1999, Chow et al. 2002) or unresectable gross residual disease (Simpson et al. 1988, Mazzaferri 1999).
effect on recurrence and cancer death distinct from 131I, which after a median follow-up of 16.6 years reduced the risk for mortality by 50% (Table 2) (Mazzaferri & Kloos 2001).

The NCCN guidelines

Cervical lymph node metastases are found in 50–80% of cases of papillary cancer, most often in the central paratracheal (Level VI) compartment, followed in descending order by mid-jugular (Level III), supraclavicular (Level IV), and subdigastic nodes (Level I) (Mirallie et al. 1999). In our study, lymph node metastases, especially bilateral cervical and mediastinal, were an independent variable that affected recurrence and survival (Mazzaferri & Kloos 2001). Some report that systematic compartment-oriented dissection of lymph node metastases significantly improves recurrence ($P > 0.0001$) and survival ($P > 0.005$) rates in patients with T1–T3 tumors (Scheumann et al. 1994). The NCCN guidelines recommend total thyroidectomy and, if lymph nodes are involved, bilateral central compartment dissection or lateral modified radical neck dissection, as the primary treatment of high-risk DTC (Mazzaferri 1999). For follicular tumors not identified as cancer before operation, the guidelines suggest lobectomy, followed by total thyroidectomy for minimally invasive follicular cancers larger than 4 cm.

The British Thyroid Association guidelines

Total thyroidectomy and 131I ablation are recommended for papillary cancers larger than 1 cm, and for papillary tumors that are multifocal or have spread beyond the thyroid gland by extension or have metastasized, and for familial tumors and those due to irradiation. Removal of all lymph nodes within the central compartment of the neck (Level VI), which includes those in the pre- and paratracheal regions, is recommended in addition to removing involved lateral lymph nodes by selective dissection. Neither guideline recommends routine radical neck dissection. Lobectomy is advised for follicular tumors not identified as cancer before operation. For follicular cancers larger than 1 cm, the British guidelines advise total thyroidectomy and 131I, and similar treatment of smaller follicular cancers that are widely invasive.

Consensus recommendations

Most US and European specialists opt for total or near-total thyroidectomy when the diagnosis is known (Van De Velde et al. 1988, Baldet et al. 1989, DeGroot et al. 1994, Solomon et al. 1996, Mazzaferri 1999, Cailleux et al. 2000, Hundahl et al. 2000). This also applies to children and young adults, because 60–80% have regional lymph node involvement and 10–20% have distant metastases (Mazzaferri 1991, Hay et al. 1998, Miccoli et al. 1998, Newman et al. 1998, Schlumberger 1998, La Quaglia et al. 2000). Of 50 children aged 15 or younger in our study, 28% developed distant metastases, usually to lung. Only 8% were found on initial presentation, the remaining 20% appearing as relapses (Fig. 1B). Although the overall long-term survival rate in children is greater than 90%, disease-free survival is enhanced by complete tumor resection (Scheumann et al. 1994, Newman et al. 1998).

Completion thyroidectomy

This refers to a separate operation to resect the contralateral lobe when ipsilateral lobectomy has been done. It should be performed when a tumor has the potential for recurrence (Mazzaferri & Kloos 2001). Ablating a large remnant with 131I is not recommended, because it causes radiation thyroiditis with pain and swelling, and may cause thyrotoxicosis. Also, a large thyroid remnant prevents TSH concentrations from increasing above 30 mU/l after the levothyroxine withdrawal that is necessary for tumor 131I uptake (Goldman et al. 1980), without which incomplete tumor ablation results (Burmeister et al. 1991, Maxon et al. 1992).

This surgery has a low complication rate when performed by an experienced surgeon, and may help unmask hidden metastases and enhance survival. Cancer is found in the contralateral lobe in about 50% of cases (Pasieka et al. 1992, Mazzaferri 2000). Lung and lymph node metastases in more than 60% of a group of irradiated children from Chernobyl could only be identified after completion thyroidectomy had been done (Miccoli et al. 1998). In another important study, multivariate analysis found that patients who underwent completion thyroidectomy within 6 months of their initial operation developed significantly fewer lymph node and hematogenous recurrences and survived significantly longer than those in whom the second operation was delayed for longer than 6 months (Scheumann et al. 1996). Completion thyroidectomy should be performed for any patient who has undergone lobectomy for tumor of stage $>T1$ ($>1$ cm), or has recurrent cancer or tumor in the resection margins or metastases (Mazzaferri 1999).

Radioiodine ablation of residual normal thyroid tissue

Some 131I uptake usually is seen in the thyroid bed after total thyroidectomy (Cholewinski et al. 2000). Destruction of this macroscopically normal thyroid tissue with 131I is termed thyroid remnant ablation. Although a few debate this practice (Hay 1990), there are compelling reasons for it (Mazzaferri 1997). Firstly, a large remnant can obscure 131I uptake in cervical or lung metastases (Vassilopoulou-Sellin et al. 1993, Miccoli et al. 1998). Second, the high TSH concentrations necessary to enhance tumor 131I uptake cannot be achieved with a large thyroid remnant (which should be surgically excised) (Goldman et al. 1980). Thirdly, measurement of
TSH-stimulated Tg is the most sensitive way to detect cancer, providing there is no normal thyroid tissue present (Spencer et al. 1998). Fourthly, lung metastases sometimes are seen only on the post-treatment whole-body scan (RxWBS) after 131I remnant ablation (Schlumberger et al. 1997, Wartofsky et al. 1998). Lastly, remnant ablation may destroy microscopic metastases or normal follicular cells destined to become malignant (Sugg et al. 1998), preventing late relapse from an occult cancer (Fig. 1).

Multifocal papillary cancers
Multifocality is common in papillary thyroid cancers (Mazzaferri & Jhiang 1994). Although they have long been considered to be intraglandular metastases and not individual tumors arising de novo, current evidence suggests the opposite. A study found that only two of 17 patients with multifocal tumors had identical RET/PTC gene rearrangements in microscopic multifocal tumors within the same gland, whereas the other 15 patients had diverse RET/PTC rearrangements in tumors within the same thyroid gland, suggesting that individual tumors arise independently in a background of genetic or environmental susceptibility (Sugg et al. 1998). This explains why contralateral lobe recurrences are found years after lobectomy.

Indications for thyroid 131I remnant ablation
This decision is tightly linked to that for performing total or near-total thyroidectomy. Remnant ablation should be done when there is uptake in the thyroid bed in a patient without known foci of cancer after resection of a tumor that has the potential for recurrence (Mazzaferri & Kloos 2001). If there is less than 0.5% thyroid bed uptake at 48 h–12 months after 131I ablation, repeating the ablation is unlikely to be of further benefit. Such a small amount of 131I uptake is unlikely to represent the source of high serum Tg concentrations (>10 µg/l) (Grünwald et al. 1996). As a practical matter, almost every patient who has undergone total or near-total thyroidectomy has 1% or more 131I uptake in the thyroid bed that requires ablation. Once levothyroxine has been withdrawn and the patient has followed a low-iodine diet for imaging, remnant ablation can be done on the same day as a diagnostic whole-body 131I scan (RxWBS), often on an outpatient basis (Mazzaferri & Jhiang 1994, Tsang et al. 1998).

Therapeutic efficacy of 131I remnant ablation
We found lower recurrence and mortality rates after 131I ablation (Mazzaferri 1997, Mazzaferri & Kloos 2001), but not all find this (Hay 1990). Remnant ablation decreased relapse of tumors larger than 1 cm in one study, including low-stage tumors predicted to have a good prognosis; however, it reduced the risk of death only in those with more advanced disease (DeGroot et al. 1990). In yet another study, the rates of pulmonary metastases among 58 patients with DTC were 11% after partial thyroidectomy, 5% after subtotal thyroidectomy and 131I, 3% after total thyroidectomy, and only 1.3% after total thyroidectomy and 131I (Massin et al. 1984). Among 321 patients treated with 131I in 13 Canadian hospitals, mainly to ablate normal thyroid tissue in patients with microscopic residual papillary or follicular cancer, local disease was controlled more often with either postoperative external beam radiotherapy or 131I therapy, or both together, than with levothyroxine alone (P < 0.001) (Simpson et al. 1988). Survival at 20 years of patients treated by surgery alone was less favorable (about 40%) than after treatment with either 131I or external radiation (about 90%, P < 0.01), whereas 131I treatment without obvious residual disease did not increase survival (Simpson et al. 1988). In a later study from Canada of 382 patients with DTC, thyroid ablation with total thyroidectomy and 131I was associated with a significantly lower rate of local relapse, regardless of tumor stage (Tsang et al. 1998).

Among 230 patients who had undergone remnant ablation and 789 treated with levothyroxine alone, the recurrence rate with levothyroxine alone was fourfold (P < 0.0001) and the rate of distant relapse fivefold (P < 0.02) that following remnant ablation after a median follow-up of 18.9 years (Mazzaferri & Kloos 2001). Patients over the age of 40 years with tumors 1.5 cm or larger experienced fewer cancer deaths 40 years after thyroid remnant ablation than after the other treatment strategies (P < 0.0001) (Mazzaferri & Kloos 2001). Multivariate analyses show the extent to which 131I ablation improves outcome. On the basis of regression modeling for 1510 patients without distant metastases at the time of initial treatment, we found remnant ablation was an independent variable that reduced cancer recurrence, distant recurrences and cancer death rates (Table 2). Another study found that the prognostic variables pertaining cancer death were age over 45 years, postoperative gross locoregional residual disease, distant metastasis at presentation, and lack of 131I treatment (Chow et al. 2002). Multivariate analysis showed that patients without distant metastases and obvious residual tumor who underwent thyroid ablation had fewer locoregional relapses (relative risk (RR) = 0.29) and distant metastases (RR = 0.2) than those treated with levothyroxine alone. Total or near-total thyroidectomy followed by 131I treatment thus results in the best outcome.

Choosing the 131I activity for thyroid remnant ablation
Many use about 1110 MBq to ablate a remnant if the amount of thyroid tissue remaining after surgery is small, because it avoids admission to hospital, which is no longer necessary in the USA (Brierley & Maxon 1998). Radiation exposures
of household members of patients given more than 1110 MBq are well below the limit (5.0 mSv) mandated by US national regulations (Grigsby et al. 2000). Small 131I activities have appeal because of the lower cost and lower whole-body radiation to the patient, which has been estimated to be 6.1 mSv for 1110 MBq, 8.5 mSv for 1850 MBq, and 12.2 mSv for 2220 MBq (DeGroot & Reilly 1982). Although 3700 MBq of 131I may cause salivary injury and transient loss of taste, it causes no permanent ovarian or testicular failure and poses virtually no risk for leukemia (Mazzaferri 1986, 2002).

Stratifying 131I ablation treatments into two groups, a low-dose group of 62 patients (46%) treated with 1073–1850 MBq 131I and a high-dose group of 72 patients (54%) treated with 1887–7400 MBq, we found 30-year relapse rates were similar in both groups (4% and 6% respectively, $P = 0.1$). A meta-analysis found that high-dose remnant ablation (2775–3700 MBq) is more efficient than low-dose ablation (about 1110 MBq), particularly after less than total thyroidectomy, suggesting DTC should be treated with total thyroidectomy followed by a higher dose of 131I (2775–3700 MBq) for remnant ablation.

Diagnostic 131I whole-body scans and post-therapy whole-body scans
Performing a whole-body scan is not very useful when there is a large thyroid remnant that prevents TSH from increasing above 30 mU/l or shows a star burst artifact from extensive uptake in the neck obscuring tumor uptake. An RxWBS, which otherwise often detects tumor foci not seen on the DxWBS, should always be performed after 131I therapy (Schlumberger et al. 1997, Cailleux et al. 2000). This is most likely to yield important information when the Tg concentration is $> 10 \mu$g/l in a patient who is clinically free of disease with negative DxWBS, neck ultrasonography and computed tomography.

Thyroid stunning
Administering more than 111 MBq 131I may have a sufficiently harmful effect upon the tissue in which it concentrates to interfere with subsequent 131I uptake for several weeks – a phenomenon termed ‘thyroid stunning’ (Park et al. 1994, Leger et al. 1998, Muratet et al. 1998). Using 64 MBq or 111 MBq 131I or 20 MBq 131I for DxWBS avoids this, but may not identify metastases (Muratet et al. 1997, Leger et al. 1998). A DxWBS with 48–56 MBq 131I produces good images but is very expensive (Mandel et al. 2001). Delaying 131I treatment several weeks after performing a DxWBS may be responsible for stunning (Leger et al. 1998, Muratet et al. 1998), which did not occur in 172 patients treated with 131I within 72 h of having had a 185 MBq 131I DxWBS (Cholewinski et al. 2000). Although a DxWBS is usually performed postoperatively to determine the optimal therapeutic 131I activity, another approach is to perform an RxWBS after empirically administering 3700 MBq 131I on the basis of high Tg concentrations.

Two studies report that stunning has no impact on 131I ablation. One found that 21% of 378 patients showed evidence of thyroid stunning, yet follow-up scans after 131I ablation were negative and serum Tg concentrations were less than 3 µg/l in most of the group (Bajen et al. 2000). Another study found ablation rates after 3700–7400 MBq 131I were respectively 65% and 67% in patients who had or had not undergone a DxWBS with 3700–7400 MBq 131I (Morris et al. 2001). It thus appears that stunning has little or no impact on therapeutic outcome.

False-positive 131I scans
A false-positive scan, which might lead to unnecessary treatment, may be caused by 131I in body secretions, pathologic transudates and areas of inflammation (Greenler & Klein 1989). Metastatic disease may be mimicked by physiologic secretion of 131I in the nasopharynx, salivary and sweat glands, stomach, and genitourinary tract, and from skin contaminated by urine, sputum or tears (Mitchell et al. 2000). Diffuse hepatic 131I uptake on RxWBS, which can be mistaken for hepatic metastases, is a result of 131I-labeled Tg that is seen in 40% of 1110 MBq scans and in 70% of 5550–7400 MBq studies (Chung et al. 1997). This usually represents residual thyroid tissue or metastases (not to the liver) that iodinate Tg, even when there is no visible uptake in the thyroid bed or metastases on RxWBS (Chung et al. 1997).

Follow-up assessments after initial surgical and 131I treatment
The aim of postsurgical follow-up for DTC is the early identification of the small proportion of patients – usually about 20% – who have residual tumor or develop a recurrence. When total thyroidectomy and 131I ablation have been the initial treatment, three powerful tools are available for the follow-up: measurement of basal and TSH-stimulated serum Tg, whole-body radioiodine scans, and neck ultrasonography (Pacini 2002). Serum Tg measurement is the most sensitive and specific marker of DTC. Undetectable serum Tg concentrations that do not increase in response to TSH stimulation are found in most patients who are disease-free, whereas increased serum concentrations of Tg are associated with the presence of residual normal thyroid tissue or metastatic DTC. In the last case, whole-body radioiodine scans under TSH stimulation (either after withdrawal of L-thyroxine treatment or after rTSH stimulation) and neck ultrasonography are the most informative tests for the detection of distant or local metastases that require further treatment. Using this strategy, most patients will achieve definitive cure and will have a normal quality of life.
**Determination of serum Tg**

Serum Tg determinations and DxWBS are the first tests ordinarily used to detect DTC after thyroid ablation. Neither is reliable, however, when there is a large thyroid remnant, because both require high serum TSH concentrations, usually around 25–30 mU/l, to optimize their sensitivity. Although the two tests are complementary (Torrens & Burch 1996), a low TSH-stimulated Tg alone is often sufficient to rule out persistent tumor. The results of Tg assays may vary in different laboratories, even with the use of the international Tg standard (Spencer et al. 1996), but low Tg concentrations alone after TSH stimulation in an assay with a 1 µg/l functional sensitivity will identify patients who are free of disease (Cailleux et al. 2000). Persistent tumor is rarely found when the serum Tg values are less than 2 µg/l after rhTSH stimulation (Haugen et al. 1999) or less than 5 µg/l after levothyroxine withdrawal (Orzata et al. 1994). Nonetheless, a measurable Tg is indicative of thyroid tissue – normal or malignant – since no other tissues falsely increase it.

Six to 12 months after thyroid ablation, when patients are clinically free of disease, the Tg alone after rhTSH can usually serve as a guide for selecting patients who require further testing or treatment; however, the DxWBS after levothyroxine withdrawal or rhTSH only provides evidence of the completion of 131I remnant ablation, but rarely identifies residual disease (Cailleux et al. 2000, Pacini et al. 2001c, 2002, Mazzaferri & Kloos 2002). A 185 MBq DxWBS is relatively useless compared with administering 3700 MBq followed by an RxWBS when the Tg increases above some arbitrary limit suggesting the presence of metastases – usually around 10 µg/l (Schlumberger et al. 1997, Cailleux et al. 2000).

**Antithyroglobulin antibodies (TgAb)**

Found in up to 25% of patients with DTC, compared with about 10% of the general population, TgAb concentrations must be measured in the same serum sample in which Tg is measured, and when present usually invalidate the serum Tg result (Mariotti et al. 1995, Spencer et al. 1998); however, some challenge this point (Schlumberger & Baudin 1998). In the presence of high serum TgAb titers, immunometric assay (IMA) methods are prone to underestimating the serum Tg concentration, increasing the risk of a false-negative test, whereas high Tg concentrations in this situation are likely indicative of residual cancer. Indeed, the presence of TgAb in the serum does not entirely render the serum Tg measurement useless. For instance, even in the presence of interfering TgAbs, a detectable serum Tg measured by IMA is usually indicative of disease, particularly if the concentration increases in response to TSH stimulation. Moreover, a high serum TgAb titer correlates with the presence of tumor, disappearing within 2 years or less of its complete ablation (Spencer et al. 1998).

**Thyroglobulin mRNA**

The detection of circulating tumour cells in patients with DTC may precede the detection of relapse by other diagnostic studies such as serum Tg measurement, and thus may have important therapeutic and prognostic implications. Serum Tg measured by Tg mRNA in the presence of serum TgAb titers is more sensitive than the Tg IMA method for the detection of DTC, but the test is not widely available (Ringel et al. 1998, Wingo et al. 1999, Biscolla et al. 2000). Moreover, some question its clinical value. Tg mRNA expression was found not to be specific for thyroid tissue and not to correlate with a diagnosis of thyroid cancer (Bellantone et al. 2001). Some find no difference in Tg mRNA expression in patients with or without metastasis, reporting no correlation between serum Tg concentrations and the Tg concentrations estimated by mRNA, raising questions regarding both the clinical applicability of Tg RT-PCR and the quantitative measurement of Tg mRNA in peripheral blood (Takano et al. 2001).

**Withdrawal of thyroid hormone suppressive treatment**

Stopping levothyroxine for 4–6 weeks and substituting triiodothyronine (T3) until 2 weeks before doing a DxWBS and measuring Tg has been, until recently, the standard way of inducing hypothyroidism, which causes physical limitations from muscle stiffness, cognitive impairment, emotional dysfunction and, in some studies (Dow et al. 1997), negative psychological alterations and major disruption of a patient’s family, social and work life. Many patients with DTC are middle-aged and active, and some opt to forgo testing because they suffer such debilitating symptoms; if they do submit to it, most are able or unwilling to tolerate hypothyroidism more than once yearly. After levothyroxine has been reinstated, symptoms of hypothyroidism may persist for weeks and TSH concentrations may remain increased for as long as 90 days, which may induce tumor growth (Maini et al. 1994). Some patients are unable to mount an adequate endogenous TSH response to levothyroxine withdrawal because of hypopituitarism, and others have medical conditions such as renal failure or heart failure that preclude inducing hypothyroidism (Mazzaferri & Kloos 2000).

**Recombinant human thyroid-stimulating hormone**

Administering rhTSH increases serum TSH concentrations sufficiently to stimulate thyroidal 131I uptake and Tg release while the patient continues taking levothyroxine (Ladenson et al. 1997). Given on two successive days in a multicenter study, rhTSH produced DxWBS results that were equivalent to those after levothyroxine withdrawal in 66% of the patients, superior in 5% and inferior in 29%, proving that it
stimulates $^{131}$I uptake, albeit with lower sensitivity than after levothyroxine withdrawal (Ladenson et al. 1997). Another multicenter study used different scanning methodology, taking into account the lower renal $^{131}$I clearance in hypothyroidism than with rhTSH, and demonstrated that DxWBS results were superior after rhTSH in 4% and after levothyroxine withdrawal in 8%, and concordant in 89% ($P = NS$) (Haugen et al. 1999). The main findings were that DxWBS and a Tg $\geq 2 \mu g/l$ detected 100% of those with metastatic tumor, although rhTSH-stimulated Tg $\geq 2 \mu g/l$ alone, but not the DxWBS, accomplished the same thing.

A clinical study of 289 patients, many with advanced disease, undergoing routine follow-up testing found that the DxWBS and serum Tg responses were not different in 161 patients prepared for testing by thyroid hormone withdrawal and 128 patients who continued levothyroxine and received rhTSH (Robbins et al. 2001a). No significant differences were found in the positive or negative predictive values between the two groups, but the greatest negative predictive value (97%) was in patients who received rhTSH and had both a negative DxWBS and low rhTSH-stimulated Tg concentrations.

The recommendations are to administer rhTSH 0.9 mg on two consecutive days, followed by at least 4 mCi $^{131}$I on day 3 and a DxWBS and Tg measurement on day 5. Images are acquired after 30 min of scanning or after 140 000 counts. A Tg $\geq 2.0 \mu g/l$ 72 h after the last rhTSH injection indicates that thyroid tissue – normal or malignant – is present, which may be identified on the rhTSH-stimulated DxWBS (Haugen et al. 1999). Mild, transient headache and nausea are its main adverse effects, affecting about 10% of patients, without causing the dysphoria of hypothyroidism (Ladenson et al. 1997).

**Preparation with rhTSH for treatment**

Although initially approved only for diagnostic use in the USA, rhTSH has been given to prepare patients for $^{131}$I thyroid ablation and treatment of residual disease. Since April 1995, rhTSH has been given in a compassionate-use program to more than 100 patients in whom, for one reason or another, levothyroxine could not be stopped (Perros 1999). A number of small studies show its effect in preparing patients for $^{131}$I remnant ablation and treatment of persistent tumor.

Patients prepared by rhTSH stimulation for thyroid remnant ablation given an average of 1070 MBq $^{131}$I after surgery were all found to have complete resolution of visible $^{131}$I uptake in the thyroid bed within 5–13 months (Robbins et al. 2001b). In addition, rhTSH has been used to prepare patients for $^{131}$I treatment of distant metastases.

Hepatic metastases were treated in a 46-year-old woman with follicular thyroid cancer arising from a struma ovarii (Rotman-Pikelny et al. 2000). After the tumor and her thyroid gland were removed, an rhTSH-stimulated DxWBS revealed 17 discrete hepatic foci of $^{131}$I uptake. An amount of rhTSH-stimulated $^{131}$I that would deliver an optimal absorbed radiation dose (> 8000 rad/lesion) without injuring the liver or bone marrow was calculated and administered without an adverse effect. Six months later, her liver metastases showed a significant but partial response. This strategy, which is reported in detail (Rotman-Pikelny et al. 2000), can be applied to determine a safe and effective dose of $^{131}$I for the treatment of thyroid cancer metastases that produce enough thyroid hormone to preclude stimulation of endogenous pituitary TSH secretion.

Others have reported treating distant metastases after stimulation with rhTSH. A study of older patients, some with distant metastases, who were unable to tolerate levothyroxine withdrawal, received 4000 MBq $^{131}$I after being prepared with rhTSH (Berg et al. 2002). After one or two courses of rhTSH-stimulated $^{131}$I treatment, clinical, laboratory and radiological findings improved in about 50% of the patients, including an 80% decrease in $^{131}$I uptake in metastases, lower serum Tg concentrations, and a decrease in bone pain and other symptoms. Patients reported an improvement in their physical condition and quality of life. Despite being elderly and frail, they tolerated treatment well except for transiently increased bone pain, and an enlarging soft-tissue lesion in one patient. Another study of patients with advanced tumor who received rhTSH in preparation for $^{131}$I treatment showed a 30% decrease in serum Tg concentrations, which before treatment ranged from 25 to nearly 30 000 µg/l (Luster et al. 2000). Several patients showed clinical improvement, with decreased or stabilized tumor size, and none had an adverse event. The authors felt that, without the use of rhTSH, $^{131}$I treatment of their patients would not have been possible. In another study, patients with advanced tumor who underwent rhTSH-stimulated $^{131}$I treatment while taking levothyroxine all showed tumor $^{131}$I uptake on the RxWBS (Lippi et al. 2001). Serum Tg concentrations decreased in 50% of the patients 3–12 months later, and one metastatic tumor became smaller. Preparation with rhTSH was well tolerated, but a few patients experienced mild transient fever and nausea and short-lived peritumoral pain and swelling of bone metastases. Another article (Pellegriti et al. 2001) described the treatment of patients with metastatic DTC, with bone and lung metastases or local disease, in whom the use of rhTSH was effective in preventing complications that patients had previously experienced during hypothyroid-induced levothyroxine withdrawal. rhTSH-stimulated $^{131}$I treatment induced a 50% reduction in the size of bone metastases in two patients, and the others remained stable after $^{131}$I treatment. Another article reported the management of a man with papillary thyroid cancer and polycystic renal disease with failure who could not tolerate reduction of renal blood flow induced by hypothyroidism. He was given rhTSH and treated with $^{131}$I on four occasions over 3 years to ablate bilateral lung metastases that
intensely concentrated $^{131}$I on RxWBS, and showed resolution of uptake over time (Mazzaferri & Kloos 2000).

The main complications with rhTSH-stimulated $^{131}$I treatment are transient, but sometimes severe, bone pain, tumor growth, and serious neurologic effects in patients with central neck, bone, brain or vertebral metastases (Braga et al. 2001, Vitale et al. 2002). As with hypothyroid $^{131}$I treatment, patients prepared with rhTSH who have metastases susceptible to causing complications by radiation-induced tumor swelling should be pretreated with glucocorticoids if surgery is not possible. The studies reviewed above show that rhTSH provides sufficient sodium–iodide symporter stimulation in thyroid tissues and metastases to make it possible to treat them with $^{131}$I.

### Serum Tg concentrations during long-term follow-up

Thyroglobulin concentrations during THST should be undetectable or low ($<1 \mu g/l$) in patients who are free of disease, but are more accurate when serum TSH concentrations are increased (Pacini et al. 1985, Haugen et al. 1999). In patients with undetectable Tg concentrations during THST who have no clinically apparent residual cancer, measurement of an rhTSH-stimulated Tg concentration distinguishes those who are truly disease-free from those with tumor who require further diagnostic testing, therapeutic procedures, or both (Pacini et al. 2001c, Haugen et al. 2002, Mazzaferri & Kloos 2002). Patients who are free of disease have undetectable or very low serum Tg concentrations before and after levothyroxine withdrawal (Cailleux et al. 2000).

An increased serum Tg determination shortly after surgery might be indicative of a patient’s tumor status (Lima et al. 2002). One study, for example, found that an initial Tg greater than 70 $\mu$g/l had a 90% positive predictive value for metastases (Ronga et al. 1999). Nevertheless, the Tg may remain high for a year or more after $^{131}$I treatment before spontaneously becoming undetectable (Cailleux et al. 2000, Pacini et al. 2001a,b). During long-term follow-up, Tg should be measured after levothyroxine withdrawal or rhTSH administration, which lowers the false-negative rate well below that of DxWBS (Pacini et al. 1985, Haugen et al. 1999, Cailleux et al. 2000).

One study revealed that the serum Tg in 76% of patients with low basal values ($<2 \mu g/l$) during THST remained low after rhTSH and no $^{131}$I uptake was seen on any DxWBS, whereas Tg in the others increased to 22.0 ± 5.75 $\mu$g/l and half had $^{131}$I uptake visible on DxWBS (David et al. 2001). In contrast, when basal serum Tg was $>2 \mu$g/ml during THST, it increased in response to rhTSH in all patients, increasing to 55.3 ± 12.75 $\mu$g/l, yet $^{131}$I uptake on DxWBS was not evident in 25% of the patients. The authors concluded that an rhTSH-stimulated Tg may identify persistent disease and is of greater diagnostic value than DxWBS in patients with low ($<2 \mu g/l$) basal serum Tg concentrations during THST. This has been substantiated by several other studies.

Haugen et al. (2002) found that 12% of 83 patients previously treated with total thyroidectomy and $^{131}$I ablation had a positive DxWBS that usually (80%) showed uptake only in the thyroid bed, and only one of five that were treated or had further evaluation on the basis of the DxWBS findings had a serum Tg $<2 \mu g/l$. In contrast, 18 patients with a negative DxWBS were treated or further evaluated on the basis of an rhTSH-stimulated Tg $<2 \mu g/l$ (23% of the study group). The authors concluded that an rhTSH-stimulated serum Tg is a more sensitive indicator of tumor than is the DxWBS.

Another study of 72 patients who were clinically free of disease and had serum Tg $<1 \mu g/l$ during THST revealed that rhTSH-stimulated Tg measurements could be used as the only test to identify those with persistent tumor (Pacini et al. 2001c). The Tg remained $<1 \mu g/l$ in 57% of the patients after rhTSH stimulation and in 88% of the latter after levothyroxine withdrawal, none of whom had disease on the hypothyroid DxWBS; in the other 12% in whom the rhTSH-stimulated serum Tg remained $<1 \mu g/l$, the hypothyroid Tg became detectable (1.1–7.8 g/l) but the DxWBS was negative or showed only faint uptake in the thyroid bed. In the 43% in whom serum Tg increased from undetectable during THST to detectable after rhTSH (1.2–23 $\mu$g/l), the hypothyroid DxWBS was positive in 74%, showing thyroid bed uptake in twelve, cervical lymph nodes in seven, and lung metastases in four cases. Thus, an increased rhTSH-stimulated Tg, despite negative DxWBS studies, detected all cases of local or distant metastases.

A study of 107 consecutive patients who were clinically free of disease and undergoing routine follow-up found that 10% had persistent tumor – four with pulmonary metastases and five with regional disease – identified only by an rhTSH-stimulated serum Tg concentration greater than 2 $\mu g/l$ (Mazzaferri & Kloos 2002). A patient’s tumor status, even in retrospect, usually was not predictable on the basis of Tg during THST or initial tumor stage. Among patients with persistent tumor, Tg concentrations during THST were 0.6 $\mu g/l$ or less in 88%, and tumor status in most (82%) was T2N1 or lower. In no case did the rhTSH-stimulated DxWBS show the site of persistent tumor. The sensitivity of an rhTSH-stimulated Tg concentration greater than 2 $\mu g/l$ was 100%, the negative predictive value was 100%, and the false-positive rate was 9%. The rhTSH-stimulated Tg had a substantially better performance than the other tests: the false-negative rates were 64% for Tg higher than 0.5 $\mu g/l$ during THST, 73% for rhTSH-stimulated DxWBS showing any uptake, and zero for an rhTSH-stimulated Tg more than 2 $\mu g/l$.

Together, these studies show that tumor may exist in patients with an undetectable or low serum Tg concentration.
Figure 3 Paradigm for the follow-up of patients with DTC. When baseline serum Tg is less than 2 µg/l during thyroid hormone suppression of TSH, the preferred pathway is to measure rhTSH-stimulated serum Tg concentrations without performing DxWBS. T4, thyroxine; US, ultrasound; CXR, chest X-ray; CT, computed tomography.

during THST that can be identified when the rhTSH-stimulated Tg concentration increases above 2 µg/l. A DxWBS merely provides data concerning the completeness of thyroid ablation, but not persistent tumor. This is the basis of a new paradigm for the follow-up of patients with DTC (Fig. 3).

High-resolution ultrasonography

This is one of the most informative tests for the detection of local metastases that require further treatment, especially when done with power Doppler studies (Lebkowska et al. 2001). Ultrasound and Doppler studies will characterize the presence of cystic versus solid elements, the degree of echogenicity of solid elements, the existence of calcifications, and the regularity and definition of the nodule borders (Haber 2000). Although individual sonographic features of thyroid nodules and masses are not specific for benign or malignant lesions, a constellation of typical features, including hypoechoogenicity, poorly defined irregular margins, and microcalcifications has more diagnostic value. One recent study found that nodules with irregular margins, intranodular vascular spots or microcalcifications were particularly likely to be malignant (Papini et al. 2002).

Precise localization of cervical node metastasis can be achieved with ultrasonography. One retrospective study that mapped the location of cervical lymph node metastases in a series of 119 patients who had undergone total thyroidectomy and bilateral cervical lymph node dissection provides important practical information concerning the location of cervical metastases (Mirallie et al. 1999). Almost 61% of the patients had cervical metastasis, which was bilateral in about 41% of
the cases. The main ipsilateral sites of tumor were paratracheal (50%), mid-jugular (37%) and supraclavicular (17%). Contralateral paratracheal nodes were involved in 21% and mid-jugular nodes in 10%. The lateral compartment was sometimes involved independent of the central compartment.

High-resolution ultrasonography should be performed before proceeding to \(^{131}\)I treatment, especially to exclude malignant cervical lymph nodes that often are best treated with modified neck dissection.

**Post-treatment \(^{131}\)I scans (RxWBS)**

About 4–7 days after \(^{131}\)I treatment, an RxWBS to document tumor \(^{131}\)I uptake often will show tumor foci not detected by the DxWBS (Schlumberger et al. 1997, Cailleux et al. 2000, Mazzaferri & Kloos 2001). An RxWBS most often elicits critical information when the Tg concentration is increased, especially if tumor cannot be found on examination or imaging studies such as chest X-ray, neck ultrasonography and DxWBS. Lung metastases often are found only on an RxWBS performed after 3700 MBq \(^{131}\)I (Schlumberger et al. 1997).

**Tg-positive, DxWBS-negative patients**

Sometimes a high serum Tg concentration is the only indication of metastases. The Tg cutoff for \(^{131}\)I treatment of DxWBS-negative, Tg-positive patients – albeit arbitrary – is about 10 µg/l after levothyroxine withdrawal (Mazzaferri 1995, 1999, Schlumberger et al. 1997).

One study found that about 6% of 283 patients with a high serum Tg who were treated with 3700 MBq \(^{131}\)I had distant metastases detected on the RxWBS that were not seen on a 74 MBq DxWBS (Schlumberger et al. 1986). The frequency of this finding depends on how patients are selected for treatment. Among 89 pairs of DxWBS and RxWBS studies in 79 consecutive patients with hypothyroidism serum Tg concentrations greater than 15 µg/l in our clinic, 9% had a negative 148–185 MBq DxWBS but had lung metastases detected on the RxWBS after 3700–5550 MBq \(^{131}\)I. Another study found that 94% of patients with high Tg concentrations had foci of \(^{131}\)I uptake on the RxWs after 2275–5180 MBq that were not seen on a 5 mCi DxWBS; more than half were in the lung (Pacini et al. 1987). Another study found that 94% of DxWBS-negative, Tg-positive patients had uptake on the RxWBS, 35% of which were in the lung and 65% in the mediastinum (Pineda et al. 1995).

Some question treating patients with Tg-positive DxWBS-negative studies, calling for prospective randomized studies of \(^{131}\)I treatment (McDougall 2001). Such a trial would be unfeasible, because the number of patients required to provide adequate power to the study is impossibly large (Wong et al. 1990). Moreover, \(^{131}\)I treatment for DTC is widely acknowledged as the most efficacious treatment for tumor that cannot be surgically resected and which concentrates \(^{131}\)I (Mazzaferri 1999, British Thyroid Association 2002). The risk for complications of \(^{131}\)I treatment, albeit not trivial (Mazzaferri & Kloos 2001), is far outweighed by the long-term salutary effects of \(^{131}\)I on DTC (Wong et al. 1990).

One study reported 100% 10-year survival in patients with lung metastases detected only by increased Tg concentrations and confirmed by RxWBS (Schlumberger 1999). In contrast, 10-year survival was 91% with a normal chest X-ray and a positive DxWBS, and was considerably worse when the chest X-ray was positive: 63% with lung micronodules and 11% with lung macronodules. Treating lung metastases found only on RxWBS usually reduces the tumor burden, but it may be difficult to achieve their complete eradication. One study of 17 patients with Tg concentrations ranging from 8 to 480 µg/l who were treated with 5550–11 100 MBq \(^{131}\)I found undiagnosed recurrences in the neck (35%), mediastinum (65%) and lung (36%) on RxWBS in 94% of the patients (Pineda et al. 1995). Six months to 5 years later, the RxWBS was negative in 38% after a second treatment, and in 60% of the patients after a third treatment; Tg concentrations decreased in 81% after the first treatment, in 90% after the second treatment, and in 100% of the patients after the third treatment. Therapeutic efficacy of \(^{131}\)I for patients with increased Tg and negative DxWBS was indicated by conversion to negative RxWBS, a statistically significant decrease in the mean Tg concentration, and a reduction of serum Tg to 5 µg/l or less in 50% of patients.

In another retrospective study of patients, the outcome was reported for 42 \(^{131}\)I-treated and 28 untreated patients, after follow-up of 6.7 ± 3.8 and 11.9 ± 4.4 years respectively. At the end of follow-up, 33% of the treated patients had a complete remission — normalization of serum Tg after withdrawal of levothyroxine and a negative DxWBS — and 30% had a negative RxWBS and reduced but detectable serum Tg, 37% had a detectable Tg and a positive RxWBS. Resolution of \(^{131}\)I uptake in lung metastases was observed in 89% and in cervical node metastases in 61% of the cases. Among patients treated only once because the RxWBS was negative, 17% were in remission, 58% had detectable Tg values without evidence of disease, 17% showed lymph-node metastases in the mediastinum, and 8% died of lung metastases. Among 28 untreated patients, none of whom had radiological evidence of disease, serum Tg off levothyroxine became undetectable or significantly reduced in 89%, and was unchanged or increased in 11% of the patients, one of whom developed lung metastases 14 years after the initial diagnosis of cancer.

Some patients with high serum Tg and negative DxWBS studies should not be treated with \(^{131}\)I. A study of patients with metastases in the neck (62%), lung (67%), bone (25%), mediastinum (8%), brain (8%), liver (8%), kidney (4%) and skin (4%) seen on conventional imaging studies, which did not concentrate \(^{131}\)I on an 111 MBq DxWBS and were associ-
The administration of ¹³¹I treatment (Fatourechi et al. 2002) and the suppression of thyrotropin (Pujol et al. 1999) found that disease stage, patient age and ¹³¹I treatment were independent predictors of recurrence in others, post-transcriptional events may cause hNIS dysregulation (Osman et al. 1999). These findings are supported by the observation that disease stage, patient age and ¹³¹I treatment independently predicted disease progression, but that the degree of TSH suppression did not (Cooper et al. 1999). Thyroid hormone suppression of thyrotropin (Mazzaferri & Jhiang 1994, Mazzaferri 1997), but the optimal TSH concentration required to achieve this is debated. A retrospective study found that relapse-free survival was improved with a consistently suppressed TSH (<0.05 µU/ml) compared with relapse when serum TSH concentrations were always 1 µU/ml or higher; moreover, the degree of TSH suppression was an independent predictor of recurrence (Pujol et al. 1996). However, a prospective study of 617 patients found that disease stage, patient age and ¹³¹I treatment independently predicted disease progression, but that the degree of TSH suppression did not (Cooper et al. 1999). Tg concentrations often cannot be decreased by maximally suppressing TSH concentrations (Kamel et al. 1999). These data raise questions about suppressing TSH to undetectable, thyrotoxic ranges to prevent relapse of cancer, although many endocrinologists do this.

As a practical matter, the most appropriate dose of levothyroxine usually is that which reduces the serum TSH to just below the lower limit of the normal range for the assay being used, unless there is evidence of persistent disease, when lower concentrations may be necessary (Mazzaferri 2000). However, the long-term effects of subclinical thyrotoxicosis on the heart and bone must be considered (Toft 2001). Low serum TSH concentrations in individuals aged 60 years or older is associated with increased mortality from all causes, and in particular, mortality due to circulatory and cardiovascular diseases, giving pause to decreasing TSH concentrations to 0.1 µU/ml in patients with thyrotoxicosis (Parle et al. 2001). Subclinical thyrotoxicosis may have arrhythmic effects on the heart (Osman et al. 2002).

Radioiodine (¹³¹I) treatment for residual disease

The therapeutic efficacy of ¹³¹I is related to the capacity of a tumor to concentrate and retain iodine. Sodium–iodide symporter (hNIS) expression is low in some thyroid cancers and, in others, post-transcriptional events may cause hNIS dysfunction (Venkataraman et al. 1999). The unfavorable iodide kinetic characteristics (short half-life) of thyroid cancers can be partially improved by thyroid ablation and low-iodide diet. Up to two-thirds of metastases concentrate ¹³¹I, but when tumors do not concentrate it, even after meticulous patient preparation and large amounts of the isotope, ¹³¹I administration provides no therapeutic benefit (Némec et al. 1979, Samaan et al. 1985, Schlumberger et al. 1986). This is more common after age 40, in patients with advanced tumors and with Hürthle cell cancers and in tall cell and insular variant tumors (Samaan et al. 1985, Fatourechi et al. 2002).

Low-iodine diet

Restricting iodine intake to about 50 µg can increase thyroidal ¹³¹I uptake and can double the dose of gray per 3700 MBq of ¹³¹I administered (Maraucă et al. 1984); however, it may increase total body radiation as result of delayed ¹³¹I clearance. The diet can be very tedious, but the target iodine intake can be achieved by restricting the use of iodized salt, dairy products, eggs and seafood (Lakshmanan et al. 1988). Dietary restrictions should be started 2 weeks before ¹³¹I treatment and continued for several days thereafter. A low-iodine cookbook is available without charge from the Thyroid Cancer Survivors’ Association (Guljord 2000). The patient must avoid pharmaceutical agents (e.g. radiocontrast material) with iodine.

Efficacy of postoperative ¹³¹I treatment of residual cancer

Radioiodine therapy refers to the treatment of thyroid cancer within the thyroid bed and in metastatic sites (Maxon 1999). There are three approaches to ¹³¹I treatment: empiric fixed doses, upper bound limits that are set by blood and whole-body dosimetry, and quantitative tumor dosimetry (Brierley & Maxon 1998). Full discussion of these approaches is beyond the scope of this review, but they are summarized elsewhere (Brierley & Maxon 1998, Mazzaferri & Kloos 2001).

Surgery is the preferred treatment, but if it cannot be undertaken then ¹³¹I is the treatment of choice, providing the tumor concentrates it (Mazzaferri 1999). In one large study of 1599 patients with DTC, ¹³¹I treatment was the single most important factor accounting for disease-free survival (Samaan et al. 1992). Patients with low-risk tumors had significantly fewer recurrences and deaths after ¹³¹I treatment than those treated with levothyroxine alone; however, ¹³¹I conferred only a slight advantage to patients with high-risk tumors (Samaan et al. 1992). On the basis of regression modeling of 1510 patients without distant metastases, we found that ¹³¹I treatment of residual disease was an independent variable that favorably reduced the likelihood of recur-
ence, distant recurrence and death from thyroid cancer (Table 2).

External radiation therapy

Relapse-free survival, especially in patients older than 40 years with invasive papillary thyroid cancer (T4) and lymph-node metastases (N1) with and without extranodal extension, may be improved by external beam radiation treatment given as postoperative adjunctive treatment (Philips et al. 1993, O’Connell et al. 1994, Farahati et al. 1996, Brierley et al. 1996, Tsang et al. 1998, Esik et al. 2001). Patients with microscopic residual papillary cancer after surgery are more commonly rendered disease-free by external beam radiotherapy (90%) than without it (26%) (Simpson et al. 1988). Patients with microscopically invasive follicular cancer are also more often rendered disease-free when external beam radiation treatment is given (53%) than when it is not (38%) (Simpson et al. 1988). In another study, the relative risk of locoregional failure was reduced (RR 0.35) by postoperative external beam radiotherapy, particularly in those with gross postoperative regional tumor (RR 0.36) (Chow et al. 2002).

Fluorine-18-fluorodeoxyglucose positron emission tomography

Progressive dedifferentiation of thyroid cancer cells leads to a loss of iodine-concentrating ability, with resultant false-negative 131I DxWBS in about 20% of all DTC metastatic lesions (Wang et al. 1999). Fluorine-18-fluorodeoxyglucose (FDG) uptake is an indicator of poor functional tumor differentiation and a poor prognosis of thyroid cancer, and should be considered in patients suspected of having persistent DTC, particularly those with increased serum Tg values and a negative DxWBS, because it can localize tumor that does not concentrate iodine but which produces Tg. A multicenter study comparing FDG-positron emission tomography (PET) with 131I DxWBS, and other scintigraphy tests, found that the specificity of whole-body FDG-PET was 90% and the sensitivity was 75% among all DTC patients (Wang et al. 1999). Fluorine-18-fluorodeoxyglucose (FDG) uptake is an indicator of poor functional tumor differentiation and a poor prognosis of thyroid cancer, and should be considered in patients suspected of having persistent DTC, particularly those with increased serum Tg values and a negative DxWBS, because it can localize tumor that does not concentrate iodine but which produces Tg. A multicenter study comparing FDG-positron emission tomography (PET) with 131I DxWBS, and other scintigraphy tests, found that the specificity of whole-body FDG-PET was 90% and the sensitivity was 75% among all DTC patients (n = 222) and 75% for those with a negative 131I DxWBS (n = 166) (Grünwald et al. 1999). In contrast, the sensitivity and specificity of DxWBS were respectively 50% and 99%. Nonetheless, FDG-PET and DxWBS used together detected tumor in 93% of the patients, which was significantly better than the results using other scans.

FDG-PET is sensitive enough to detect small cervical lymph node metastases, but they nonetheless remain the most common cause of a false-negative test (Stokkel et al. 1999, Wang et al. 1999). It localized occult DTC in 71% of patients who had increased serum Tg concentrations and a negative 131I DxWBS, and it changed the clinical management in 51% of the patients (Wang et al. 1999). It had a positive predictive value of 92% in patients with increased Tg concentrations and a negative predictive value of 93% in those with low Tg concentrations. FDG-PET scans were never positive in stage 1 tumors, but were always positive in stage 4 tumors with increased serum Tg concentrations. Others report similar results (Alnafisi et al. 2000).

A positive FDG-PET study in a patient with lung metastases correlates well with poor 131I uptake of the isotope by the tumor and a lack of therapeutic response. Multivariate analysis demonstrated that the single strongest predictor of survival with DTC was the volume of FDG-avid disease (Wang et al. 2000). Three-year survival of patients with FDG volumes of ≤125 ml and >125 ml was respectively 96% and 18%. No cancer death occurred in a PET-negative patient with distant metastases. Conversely, patients older than 45 years with distant metastases that concentrate FDG were at the highest risk for death.

The influence of serum TSH concentrations on FDG uptake in metastases has not yet been fully clarified. Hypothyroidism has no effect on FDG uptake (Wang et al. 1999). However, rhTSH stimulates FDG uptake by DTC (Petrich et al. 2002).

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