World J. Surg. 24, 942–951, 2000
DOI: 10.1007/s002680010165

WORLD
Journal of
SURGERY

Differentiated Thyroid Cancer: "Complete" Rational Approach

Electron Kebebew, M.D.,[1] Orlo H. Clark, M.D.[2]

[1]Department of Surgery, School of Medicine, University of California, San Francisco, 513 Parnassus Street, San Francisco, California 94143-0470, USA
[2]Department of Surgery, University of California, San Francisco/Mt. Zion Medical Center, 1600 Divisadero Street, San Francisco, California 94143-7921, USA

Abstract. Controversy continues regarding the optimal management of patients with differentiated thyroid cancer because no prospective randomized studies evaluating the merits of (1) extent of thyroidectomy, (2) postoperative radioactive iodine ablation, or (3) thyroid-stimulating hormone (TSH) suppressive therapy exist. Patients with low risk differentiated thyroid cancer enjoy a relatively good prognosis with a mortality rate of about 2% to 5% and a recurrence rate of about 20%. Despite the excellent prognosis in patients considered to be at low risk, total or near-total thyroidectomy in patients with differentiated thyroid cancer has the advantages that: (1) postoperative radioactive iodine can be used to detect and treat residual normal thyroid tissue and local or distant metastases; (2) follow-up serum thyroglobulin levels are a more sensitive marker of persistent or recurrent disease when all thyroid tissue has been removed; and (3) total or near-total thyroidectomy with postoperative ^{131}I ablation and TSH suppressive therapy is associated with better survival and lower recurrence rates. Patients with occult papillary thyroid cancer and minimally invasive follicular thyroid cancer can be treated by thyroid lobectomy because they have a near-normal life expectancy. Virtually all other patients with differentiated thyroid cancer appear to benefit from more extensive initial treatment.

Thyroid cancer, excluding ovarian cancer, is the most common endocrine malignancy with the highest mortality [1]. Thyroid cancers exhibit the full range of malignant behavior from the relatively indolent occult differentiated thyroid cancers to the uniformly aggressive and lethal undifferentiated thyroid cancers. Fortunately, about 98% of thyroid cancers are of the differentiated type [2]. Differentiated thyroid cancers (DTCs) arise from the follicular cells (papillary carcinoma including the follicular variant, and follicular carcinoma with Hürthle cell carcinoma as a subtype) and from the parafollicular cells (medullary thyroid cancer). Many important advances have occurred regarding thyroid carcinogenesis, risk factor assessment, cost-effective and accurate diagnosis, and treatment during the last decade.

Thyroidectomy is the primary treatment for patients with DTC and has proven to be effective and safe. The extent of thyroidectomy for the optimal results in patients with DTC of follicular cell origin remains controversial among experts in the field. This controversy persists largely due to the lack of a prospective randomized controlled trial comparing the extent of thyroidectomy and the use of postoperative ^{131}I ablation in patients with DTC. Such a trial would require a large multicenter trial and a long duration of follow-up.

A general agreement exists that those patients with DTC who are at a high risk (based on AGES, AMES, MACIS, EORTC, or TNM risk classification systems) or those with bilateral tumors or obvious locally invasive thyroid cancers warrant total or near-total thyroidectomy [3–5]. For patients with low risk DTC there is considerable debate on the most appropriate extent of thyroidectomy [3–8]. In the past, three approaches have been proposed by surgeons: (1) thyroid lobectomy; (2) near-total thyroidectomy (total lobectomy and subtotal resection on the other side leaving less than 1 g of thyroid tissue); and (3) total thyroidectomy [9]. The divergent views among experts as to the appropriate extent of thyroidectomy in low risk patients with DTC are best reflected by the practice guidelines published by the American Thyroid Association (ATA) and American Association of Clinical Endocrinologists [3, 5]. These organizations recommend near-total or total thyroidectomy, whereas the Society of Surgical Oncology guidelines state that lobectomy should be performed in low risk patients with DTC [3–5].

The proposed advantages of total thyroidectomy, in order of importance, are (1) radioactive iodine can be used to detect and treat residual normal thyroid tissue or local/distant metastases; (2) the serum thyroglobulin level is a more sensitive marker of persistent or recurrent disease when all normal thyroid tissue has been removed; (3) up to 85% of patients with papillary thyroid cancer have microscopic cancer foci in the contralateral lobe, and these occult cancers are eliminated as possible sites of recurrence; (4) recurrence develops in the contralateral lobe in approximately 7% of patients, and half of these patients die from thyroid cancer; (5) recurrence is lower in patients who underwent bilateral procedures or total thyroidectomy; (6) the 1% risk of DTC progressing to undifferentiated thyroid cancer is decreased; (7) survival is improved for patients with papillary thyroid cancers (PTC) larger than 1.5 cm and for those with follicular thyroid cancer (FTC) that are not minimally invasive; and (8) the need for reoperative thyroid surgery, which is often associated with increased risk of complications, is low [2]. Those who advocate less than total thyroidectomy point out that: (1) total thyroidectomy is associated

Correspondence to: O.H. Clark, M.D.

with a higher complication rate than less extensive surgery; (2) one-half of local recurrences can be cured with surgery; (3) fewer than 5% of recurrences occur in the thyroid bed; (4) tumor multicentricity has little clinical significance; and (5) the prognosis is excellent in patients who have undergone procedures less than total thyroidectomy [2].

We address these issues and discuss a rational treatment approach to patients with DTC of follicular cell origin. Before doing so we provide a working definition for the extent of thyroidectomy procedures because no uniform definition exists in the literature. We also discuss the distinct clinicopathologic feature of DTCs. We follow with a discussion of thyroid cancer risk assessment systems and provide a rational treatment algorithm for patients with DTC. Because there is general consensus regarding the management of patients with medullary thyroid cancer, our discussion does not include DTC of parafollicular origin. In these patients, most experts recommend total thyroidectomy and central neck node dissection as well as screening for possible coexisting pheochromocytomas, primary hyperparathyroidism, and a germ-line *RET* point mutation to document familial disease.

Classification and Distinguishing Clinical Features of DTC

The previous pathologic classification of thyroid carcinoma, founded only on architecture, has been replaced by a classification system that is based on architectural, cytologic, and clinical behavior of these tumors. The ATA, Armed Forces Institute of Pathology (AFIP), and World Health Organization (WHO) classify papillary (pure, mixed papillary-follicular, and follicular variant) and follicular thyroid cancers as DTC [10, 11]. Hurthle cell carcinoma is considered a subtype of FTC and rarely as a subtype of PTC by the ATA and WHO, but as a distinct thyroid cancer by the AFIP [10, 11]. We also consider Hurthle cell carcinoma (HCC) as a distinct DTC subtype exhibiting unique cytologic and clinical features; most importantly, it is an aggressive tumor associated with a slightly worse prognosis [2].

The PTC accounts for about 80% of all thyroid cancers, with the average age at presentation during the third decade. It is more common in women, and more than 90% of patients have survived at the 20-year follow-up [12–15]. Cervical node metastases occurs in 11% to 80% of patients depending on the series and whether prophylactic versus therapeutic cervical node dissection was performed [14–21]. Most series in the United States and Europe report a 30% to 40% cervical node metastasis rate [13, 15–18, 22–25]. Distant metastases from PTC occur in 2% to 14% of patients [7, 13, 20, 21]. Patients with PTC often have multicentric tumors. About 30% of thyroid cancers are multifocal on routine histology sectioning, whereas up to 85% are multicentric when thin sections (0.5 μm) are examined [7, 13, 17, 20, 21, 22]. PTCs that are less than 1 cm (referred to as minimal or occult thyroid cancers) warrant a more conservative surgical therapy because of the good prognosis observed in these patients: 0% to 0.4% mortality rate [13, 15, 23]. These occult PTCs are often multicentric, are smaller than 0.5 cm, and occur with equal frequency in each lobe [2]. The prevalence of occult PTC varies from 0.45% to 36% depending on the country of study, age of the patient, and number of thyroid tissue sections examined [2]. Sixteen percent of patients with occult PTC had cervical node metastases in an autopsy study; few of these individuals had palpable cervical nodes or died directly from thyroid cancer [25]. Because of the good prognosis of patients with occult PTC, a thyroid lobectomy with isthmusectomy is adequate treatment for most patients. Anaplastic thyroid cancers arise from transformation of PTC, which occurs in about 1% of patients [26–29].

The FTC accounts for about 10% to 20% of all thyroid cancers. Similar to PTC, there is a predominant female predilection but patients with FTC are usually about 10 years older (age 40–50 years) than those with PTC; they also present at a higher stage of disease. FTC is usually solitary (90%) rather than multicentric, and it often occurs in association with benign thyroid disorders and in areas of iodine deficiency [30]. FTC tends to invade blood vessels with hematogenous metastases to the lung and bone. The 10-year survival for patients with FTC is worse than for PTC, but when matched for age and stage there is little or no difference in survival [30–34]. Patients with FTC have a lower cervical node metastasis rate (about 10%), and only about 8% have multifocal tumors. More patients with FTC have distant metastases (usually to lung or bone, up to 33%) than in PTC (2–14%) [30–34]. The diagnosis of FTC is established most reliably by permanent histology showing either capsular invasion or angioinvasion. Patients with minimally invasive FTC have an excellent prognosis, and these tumors are almost indistinguishable from benign follicular neoplasm on histology except for the presence of limited capsular invasion or angioinvasion (or both) [30, 31, 34, 35].

As with FTC, HCC can be diagnosed accurately only when there is capsular invasion or angioinvasion (or both) on permanent histology, or when regional or distant metastases are present [36, 37]. Although some experts have proposed a parafollicular cell origin of HCC, most evidence supports a follicular cell origin, including (1) the transition from follicular to Hurthle cells by histologic examination; (2) Hurthle cells demonstrate an intact thyroid-stimulating hormone (TSH) receptor adenylate cyclase system; and (3) HCCs are positive for thyroglobulin but negative for calcitonin on immunohistochemical staining, and they usually secrete thyroglobulin [38]. As previously mentioned, HCC therefore is considered a variant of FTC or rarely a variant of PTC by some experts. However, the unique clinicopathologic profile and prognosis of patients with HCC warrants separate considerations. In addition to the unique oxyphil, polyglonal, hyperchromatic cells observed on histology, higher oncogene expression [Pan-*ras*, N-*myc*, transforming growth factor (TGFα, TGFβ), and insulin-like growth factor-1 (IFG-1)] is observed in HCC than in FTC [39]. Furthermore, most studies comparing cervical node and distant metastases for HCC with PTC and FTC show significant differences [40–45]. DNA ploidy is a good predictor of aggressiveness in HCC but not in FTC [42]. Most importantly, only about 10% of HCCs take up radioactive iodine, whereas about 80% of FTCs and 70% of PTCs do so [41, 46]. Patients with HCC have about a 25% incidence of lymph node metastases [2]. Finally, patients with HCC have a higher tumor recurrence rate and a higher mortality rate (about 30%) at 10 years than do patients with typical PTC or FTC [42].

Patients who have had low dose (up to 60 Gy) radiation exposure have a 1% to 13% risk of developing thyroid cancer that continues to increase for at least three decades [47]. A patient with a thyroid nodule and a history of head and neck irradiation has a 40% risk of having thyroid cancer [48, 49]. Sixty percent of these patients have cancer in the presenting nodule, and in 40% the tumor is situated elsewhere in the thyroid gland [48, 49]. There is general agreement, because of the high frequency of

Table 1. Classification of extent of thyroidectomy.

Nodulectomy
Lumpectomy
Partial thyroidectomy
Subtotal thyroidectomy[a]
Lobectomy/hemithyroidectomy
Near-total thyroidectomy[a]
Total thyroidectomy[a]

[a]Bilateral thyroidectomy has been used to refer to subtotal, near-total or total thyroidectomy by some investigators evaluating the effect of extent of thyroidectomy on survival and differentiated thyroid cancer (DTC) recurrence.

multicentric malignant and benign tumors, that these patients should undergo a total or near-total thyroidectomy to eliminate the risk of leaving residual malignant thyroid tissue [50]. Patients with familial nonmedullary thyroid cancer also have a high incidence of multicentric tumor and invasion [51]. Local recurrence is high in these patients, with about one-third of patients who would be at low risk based on the AMES classification developing recurrences [51]. Total or near-total thyroidectomy should be performed in patients with familial nonmedullary thyroid cancer because (1) the thyroid gland is predisposed to cancer, (2) both benign and malignant thyroid tumors are multifocal, and (3) there is a somewhat more aggressive nature to these tumors.

Thyroidectomy, Lymph Node Dissection, and Complications

As previously mentioned at the Consensus Development Conference for Management of DTC in 1987 in The Netherlands, it was reported that no uniform or agreed on definition of the extent of thyroidectomy exist in the literature [52]. However, it is important when evaluating and discussing treatment outcome that a clear definition or classification be used. Table 1 shows the classification of thyroidectomy procedures. Lumpectomy refers to removal of a neoplasm alone with minimal surrounding thyroid tissue, and partial thyroidectomy involves removal of a neoplasm with a larger margin of normal thyroid tissue. Subtotal thyroidectomy is defined as the bilateral removal of more than 50% of each lobe with the isthmus. Lobectomy or hemithyroidectomy is total removal of one lobe with the isthmus. Near-total thyroidectomy is the total extracapsular removal of one lobe and isthmus with less than 10% (1 g) of the contralateral lobe left behind. When doing a near-total or subtotal thyroidectomy, some thyroid tissue may be left posteriorly or laterally usually in the area of the ligament of Berry to avoid injury to the upper parathyroid gland(s) and the recurrent laryngeal nerve where it enters the larynx posterior to the cricothyroid muscle. Total thyroidectomy is the extracapsular removal of both lobes and the isthmus, leaving behind viable parathyroid glands and intact recurrent laryngeal nerves.

Numerous surgeons have reported that an extracapsular total thyroidectomy is technically feasible and can be done safely. The techniques we use for total thyroidectomy have been described elsewhere [53–55]. Briefly, the side of the nodule or dominant nodule is mobilized first, the middle thyroid veins are ligated and divided laterally, and then the inferior thyroid veins are divided medially on the trachea along with the thyrothymic ligaments. The superior thyroid vessels are identified, individually ligated, and divided close to the thyroid gland to avoid injury to the external laryngeal nerve. The recurrent laryngeal nerve (where it enters posterior to the cricothyroid muscle) and upper parathyroid gland is identified at the level of the cricoid cartilage. The upper parathyroid glands are more dorsal than the lower parathyroid glands, which are usually 1 cm below where the inferior thyroid artery and recurrent laryngeal nerve cross. The upper parathyroid glands are usually easiest to dissect from the thyroid gland on a vascular pedicle. A similar technique is used on the other side to complete the total thyroidectomy. Using this technique 26% of our patients had no radioactive iodine uptake above background levels, and 74% of patients had less than 1% uptake (in the thyroid bed or elsewhere) [55]. When the parathyroid glands are located more anteriorly it might be necessary to leave surrounding thyroid tissue or autotransplant them into the sternocliedomastoid muscle, after confirming it is parathyroid tissue by frozen section.

As previously mentioned, lymph node metastases are common in patients with PTC, are less common in patients with HCC, and are even more uncommon in patients FTC. Even though there is a high rate of cervical node metastases at least microscopically in patients with PTC, most but not all studies have found no significant effect on survival and recurrence in patients with nodal metastases [15–17, 23]. When patients with lymph node metastases are matched for age or have matted nodes, the prognosis is worse [16]. Surgeons from Japan, in contrast to those in Europe and America, perform prophylactic node dissection in patients with PTC and usually do not use ^{131}I ablation [21]. Therapeutic cervical node dissection is recommended by virtually all experts for patients with palpable lymph nodes. These approaches are based on studies documenting that patients with PTC who are treated with prophylactic node dissection have nearly the same survival rate as do patients who are just observed with nonpalpable nodes [15–17, 23]. Cervical node dissection is also associated with a slightly higher risk of complications [2]. Thus therapeutic but not prophylactic cervical node dissection is generally recommended for patients with DTC. In patients with HCC we recommend prophylactic central neck node clearance, similar to what we recommend for patients with medullary thyroid cancer, because most HCCs (90%) do not take up radioactive iodine and have a higher recurrence rate, higher incidence of cervical node metastases (40%), and higher mortality [41, 42]. In patients with lymph node metastases, all lymph nodes in the central neck, adjacent to the tumor, and medial to the carotid artery are removed. Because only about 10% of patients with PTC have contralateral cervical node metastases, a contralateral neck node dissection is not done unless bilateral extensive lymphadenopathy is evident [2]. When lateral neck nodes are involved we perform a modified radical (functional) neck dissection, removing all fibrofatty tissue with the lymph nodes and preserving the sternocleidomastoid muscle, internal jugular vein, vagus nerve, spinal accessory nerve, and sensory nerves. Mediastinal nodes are involved in up to 6% of cases of PTC and can usually be removed through the cervical incision [56].

Complications from thyroidectomy have become less frequent since the technical contributions of surgeons such as Kocher, Halsted, Lahey, Crile, Thompson, Reeve, and Perzik. The complication rate associated with thyroidectomy depends on the experience of the surgeon, extent and type of thyroid disease, anatomic variations and course of the recurrent laryngeal nerve and external laryngeal nerve, the positions of the parathyroid glands, and previous thyroid or parathyroid operation [2]. The major and most common technical complications are permanent recurrent

laryngeal nerve palsy and permanent hypoparathyroidism. In experienced hands, these complication occur in fewer than 2% of patients. Unfortunately, in less experienced hands a complication rate of 14% has been reported [57–71]. Advocates of less than total thyroidectomy report a higher complication rate after total thyroidectomy because of the added risk of dissection on the side contralateral to the pathology. Most large series concerning total thyroidectomy report a comparable low frequency of complications (less than 2%) as reported for lesser procedures. Most of the complications in these series were due to extensive or invasive thyroid cancers involving the recurrent laryngeal nerve. The complication rate is also higher in patients with marked lymphadenopathy who are treated with total thyroidectomy and central and lateral neck dissection [54, 55, 62]. Another contention by the proponents of lobectomy is that total thyroidectomy can be performed only by expert surgeons. However, Reeve and colleagues [69] have reported no significant differences in the complication rates of total thyroidectomy between surgeons at a tertiary care center and those in the community. In fact, a few studies, looking at complication rates of thyroidectomy among surgeons in training under supervision, report low complication rates even when total thyroidectomy was done [70, 71]. Because total thyroidectomy is in essence a bilateral lobectomy, it seems unfounded that total thyroidectomy should be associated with, if any, only a minimally higher complication rate than a lesser procedure. Although we believe that total thyroidectomy is the treatment of choice for any patient with thyroid cancer where radioactive iodine might be considered postoperatively, in some instances it is advisable to leave a small amount of thyroid tissue (near-total thyroidectomy) to avoid injury to the recurrent laryngeal nerve or a parathyroid gland.

Risk Group Analysis and Prognosis in DTC

Many independent prognostic factors have been used to classify risk in patients with DTC, including patient age, gender, lymph node status, extrathyroid invasion, tumor size, histopathologic features, and completeness of thyroid cancer resection. Young patients with small, noninvasive tumors have the best prognosis (low risk group), whereas old patients with large or invasive tumors or distant metastases are at high risk. Some of these classification systems use detailed prognostic factors analyzed by multivariate analysis, some use prognostic factors identified in the literature, and others use weighted combinations of multiple prognostic factors. The major utility of these risk assessment systems is to identify patients with a poor prognosis, hopefully enabling further selection of treatment options (e.g., radioactive iodine). Unfortunately, none of the risk assessment systems includes data that are available preoperatively to guide operative procedures, so they are all postoperative classifications.

In 1979 the European Organization for Research on Treatment of Cancer (EORTC) in a multivariate study of 500 patients with thyroid cancer (PTC, FTC, medullary thyroid cancer, and anaplastic thyroid cancer) proposed a scoring system for patients with thyroid cancer [72]. Patients with scores of less than 50 had a survival rate of 95% at 5 years, whereas patients with scores greater than 109 had only 5% survival at 5 years [72]; however, 94% of the patients with scores over 109 had anaplastic thyroid cancer. The shortcomings of this study, pointed out by a follow-up study, were the short follow-up time and the inclusion of patients with medullary and anaplastic thyroid cancer [73].

In 1987 Hay and the Mayo Clinic group devised the AGES system (*a*ge, histologic *g*rade of tumor, *e*xtrathyroidal invasion and distant metastases, tumor *s*ize) [74]. This system was later modified to exclude grade because there was no uniform acceptance of grades of DTC among pathologists and then included the extent of thyroid resection.

The MACIS scoring system (*m*etastases, *a*ge, *c*ompleteness of resection, extrathyroidal *i*nvasion, tumor *s*ize) uses this information [75]. The MACIS scoring system reliably predicted outcome in patients with PTC among four groups (based on scores < 6.00, 6.00–6.99, 7.00–7.99, and > 8.00) [75].

In 1988 Cady and Rossi [76] from the Lahey Clinic proposed the utility of the AMES (*a*ge, *m*etastases, *e*xtrathyroidal invasion, primary tumor *s*ize) system for selecting patients with PTC and FTC into high and low risk groups. However, they did not separately analyze patients with FTC from patients with PTC. Davis et al. [77] reported that the AMES system did not distinguish low risk patients from high risk patients with FTC.

The SAG system (*s*ex, *a*ge, histologic *g*rade) is another system that identified high and low risk patients with PTC; high risk patients (score > 2) had only a 50% survival rate at 10 years, whereas low risk patients had a 90% survival rate [78]. Common to all the mentioned risk scoring systems is the age of the patient with thyroid cancer. Importantly, age and gender are the only two factors available preoperatively.

The TNM (primary *t*umor size, *n*odal status, distant *m*etastasis status) staging system has also been used to select patients to be at high or low risk of dying from thyroid cancer [79]. The DeGroot classification (similar to the TNM staging system) is yet another risk analysis system using class I (intrathyroidal), class II (cervical node metastases), class III (extrathyroidal extension), and class IV (distant metastases) groups to assign prognosis [15].

For patients with DTC the AMES, DeGroot classification, and TNM staging systems are easiest to use for risk evaluation (Tables 2, 3, 4). However, none of the risk analysis systems can be used to guide extent of surgical resection because only age and gender are known preoperatively.

Several molecular and genetic prognostic factors have also been identified in DTC that predict tumor behavior: (1) Patients with aneuploid PTC and HCC have a worse prognosis. (2) Patients with thyroid cancers with a decreased cyclic adenosine monophosphate (cAMP) response to TSH have a worse prognosis. (3) Patients with thyroid cancers that have a decreased or absent uptake of radioiodine have a worse prognosis. (4) Patients whose tumors have increased epidermal growth factor (EGF) binding have more aggressive tumors [80–84]. (5) Patients whose thyroid cancers have both N-*ras* and *gsp* mutations have more aggressive tumors [85, 86]. (6) Patients whose thyroid cancers have increased expression of c-*myc* mRNA and protein have more aggressive tumors [87, 88]. (7) Some reports suggest that patients with PTC with *RET*/PTC rearrangement mutation are more aggressive [89], although others could not confirm these findings [90, 91]. (8) A *p53* mutation, although rare in DTC, are associated with poorly differentiated DTC and aggressive cancers [92–94].

Most of the retrospective studies in patients with low risk DTC, by various classification procedures, report mortality rates of 2% to 5% at 10 to 20 years compared to the mortality rate of 40% to 50% in patients with high risk DTC [15, 23, 74–76, 95]. The

Table 2. AMES low risk patients with papillary and follicular thyroid cancer.

All young patients (men < 40 years old, women < 50 years old) without distant metastases
All older patients with
Intrathyroidal papillary or follicular thyroid cancer with minor tumor capsular invasion
Primary tumor < 5 cm
No distant metastases

AMES: age, metastases, extrathyroidal invasion, primary tumor size.

Table 3. DeGroot classification for papillary thyroid cancer.

Class	Extent of disease	Risk of death[a]
I	Intrathyroidal	1
II	Cervical node metastases	1
III	Extrathyroidal invasion	5.8-fold increased mortality
IV	Distant metastases	47-fold increased mortality

[a]Risk of death relative to class 1 patients with the best prognosis.

Table 4. TNM staging system for papillary and follicular thyroid cancer.

Stage	Age < 45 years old	Age ≥ 45 years old
I	anyTanyNM0	T1N0M0
II	anyTanyNM1	T2N0M0
		T3N0M0
III		T4N0M0
		anyTN1M0
IV		anyTanyNM1

TNM: primary tumor size; nodal status; distant metastasis status.
T1: ≤ 1 cm; T2: > 1 cm but ≤ 4 cm; T3: > 4 cm; T4: extends beyond gland; N1: regional lymph node metastasis; M1: distant metastasis.

recurrence rate for patients with low risk DTC is about 10% and in the high risk group about 45% [15, 23, 74–76, 95]. Given these data, there is general agreement that high risk patients with DTC should be treated with total or near-total thyroidectomy, radioactive iodine ablation, and TSH suppression. Because of the relatively low mortality and recurrence rates observed for low risk patients with DTC, advocates of thyroid lobectomy contend that this treatment is sufficient in these patients. Unfortunately, among low risk patients who have a recurrence, about 33% to 50% die from DTC [2, 96]. More importantly, most of the large retrospective series with long-term follow-up report decreased recurrence rates and improved survival among patients with DTC who undergo total or near-total thyroidectomy compared to lesser thyroidectomy procedures [15, 23, 95]. This survival benefit in patients undergoing total thyroidectomy is improved when postoperative radioactive iodine (RIA) was used [15, 23]. As previously mentioned, complete and accurate information is often not available preoperatively to distinguish low and high risk patients with DTC, and deaths and recurrences from DTC are observed in patients even with low risk DTC. We therefore recommend total or near-total thyroidectomy for low risk patients with DTC. We recognize that most of these patients do well with lesser procedures. The benefits are small but real, and the complication rate among experienced surgeons should be low (Table 5) [15, 23, 95].

Postoperative Management in DTC

Controversy exists as to whether postoperative RAI ablative treatment offers any benefit to patients with DTC of follicular cell origin. Some experts advocate routine ^{131}I scanning (1–5 mCi) and ablative treatment with 30 to 200 mCi for all patients except those with occult PTC or minimally invasive FTC. Others recommend postoperative ^{131}I treatment only in high risk patients with DTC. Unfortunately, no prospective randomized trials have addressed this question.

Factors that influence uptake of RAI in DTC are (1) serum TSH level, (2) amount of normal thyroid remaining (normal thyroid takes up about 100-fold more RAI than DTC), (3) serum iodine level, (4) degree of tumor differentiation and type of DTC, and (5) the patient's age [97]. Davis et al. [98] reported no benefit of postoperative ^{131}I ablation in patients with invasive FTC. Their study population was small, and many of these patients had only thyroid lobectomy so the ^{131}I therapy probably treated only the remnant normal thyroid tissue. Simpson et al. [99] reported improved survival in patients with microscopically positive tumor margins but otherwise noted no other benefits. However, studies by Mazzaferri and Jhiang [23] and DeGroot et al. [15] in large cohorts with long follow-up times document slightly improved survival and lower recurrence rates even in patients with low risk DTC when postoperative RAI ablation was used. At the University of California, San Francisco patients not treated with ^{131}I ablation had a 2.1-fold greater risk of cancer recurrence than those treated with ^{131}I, although there was no difference in survival [100]. Massin et al. [101] reported a lower rate of lung metastases in patients treated with postoperative ^{131}I. Schlumberger et al. [102] reported that 64% of 33 patients who had a normal chest radiograph and who had pulmonary metastases documented on radioiodine scanning had complete remission, whereas only 8% of 186 patients with an abnormal chest radiograph and a positive RAI scan were successfully treated. Casara et al. [103] confirmed these studies, documenting that 78% of the 42 patients with positive radioiodine scan and negative radiography were successfully treated compared to only 4% ($p < 0.001$) of 54 patients whose chest radiograph and radioiodine scan were positive. Thus ^{131}I treatment is more effective for eradicating small functioning lung metastases detected by chest radiography after total thyroidectomy than when larger functioning metastases were identified on the chest radiograph. Studies by Schlumberger et al. [102] and Pineda et al. [104] have shown that some patients with elevated thyroglobulin (Tg) levels but no RAI uptake using scanning doses of ^{131}I have radioiodine uptake in metastatic tumor or in the thyroid bed when treated with a therapeutic dose (100 mCi). In about one-third of these patients the Tg normalized or decreased, and the lesions observed on follow-up RAI after treatment or computed tomography (CT) scan of the lung were eradicated [97].

Withdrawing thyroid hormone (levothyroxine for 6 weeks and triiodothyronine for 2 weeks) to increase TSH and consumption of a low iodine diet for 2 weeks prior to scanning with radioiodine facilitate treatment of DTC and ablation of residual normal thyroid tissue with RAI. In patients with PTC or FTC who have undergone a total or near-total thyroidectomy, RAI ablates the minimal amount of residual normal thyroid tissue and the metastatic disease in about 75% of patients. Patients who have undergone a total or near-total thyroidectomy usually have their small local or distant metastases effectively identified and ablated with

Table 5. Extent of thyroidectomy and outcome in patients with differentiated thyroid cancer.

Study	Type of thyroid cancer	Median follow-up time (years)	Extent of thyroidectomy	Recurrence	Mortality
Loh et al. [100][a]	PTC and FTC	10.3		Risk ratio	Risk ratio
			Total/near-total	1.0	1.0
			Lobectomy/subtotal	2.5	2.2
			Debulking	11.0	13.5
				($p = 0.0001$)	($p = 0.0001$)
Mazzaferri et al. [23][b]	PTC and FTC	15.7	Total	26%	6%
			Less than total	40%	9%
				($p < 0.002$)	($p = 0.02$)
DeGroot et al. [15][c]	PTC	Mean 12	Total	Decreased	Decreased
			Less than total	($p < 0.001$)	($p < 0.035$)
Hay et al. [95][d]	PTC	16	Total	8.3%	2.4%
			Less than total	22.2%	2.6%
				($p < 0.001$)	($p = 0.27$)

FTC: follicular thyroid cancer; PTC: papillary thyroid cancer.

[a]In this study outcome was evaluated using a Cox model, and the differences in recurrence and mortality were reported as relative risks.

[b]The outcome reported in this study was relative to the extent of thyroidectomy in patients with stage II and III tumors. Stage II: tumors 1.5 to 4.4 cm, any size of tumor if multiple (> 3), or metastases to cervical nodes and tumors of uncertain size that are palpable. Stage III: tumors > 4.5 cm and any size tumor that invades adjacent tissues.

[c]Total thyroidectomy in this study includes total, near-total, and subtotal thyroidectomy. Significant decreases in recurrence and death were reported in all patients who had "total" thyroidectomy with χ^2 test but not with a Cox model.

[d]In this study only low risk patients (defined according to the AMES prognostic scoring system) were studied. Thyroidectomy procedures were classified as unilateral or bilateral (total, near-total, and subtotal thyroidectomy).

the first ^{131}I dose. In general, RAI therapy is most effective in young patients with small or occult metastases. In our experience and that of others, patients with large (> 1 cm) discrete local or distant metastases should have them removed surgically, and then ^{131}I ablation therapy should be used.

The appropriate dose of ^{131}I necessary for thyroid remnant ablation has been debated. DeGroot and Reilly [105] found little difference between a 30 mCi dose and 50 mCi dose of ^{131}I for remnant thyroid ablation, with successful ablation in 80% of patients. In a prospective randomized study, Johansen et al. [106] also showed successful ablation of the thyroid remnant in 80% of patients with both low (29 mCi) and high (100 mCi) ^{131}I doses. Mazzafferi and Jhiang [23] reported no differences in recurrence rates in patients with PTC and FTC who were treated with low versus high doses of ^{131}I. We recommend using outpatient treatment with 30 to 50 mCi of ^{131}I in low risk patients with DTC and inpatient treatment with 100 to 200 mCi of ^{131}I in high risk patients with DTC. When a patient who has undergone total thyroidectomy for DTC has an elevated thyroglobulin level but no ^{131}I uptake on scanning, we recommend treating with 100 mCi and repeating the whole-body scan 5 to 10 days after treatment. About one-third of these patients have ^{131}I uptake, and serum thyroglobulin levels often decrease, documenting a therapeutic effect [97].

The role and level of TSH suppression in patients with DTC has been debated. It has been shown in rats that elevated levels of TSH promote transplantation and growth of thyroid cancers [107]. In human thyroid cancers, TSH stimulates tumor growth and invasion and angiogenesis [108, 109]. It also stimulates thyroglobulin secretion and radioiodone uptake in tumors, and it inhibits thyroid tumor apoptosis [97, 110]. Although there is general agreement that TSH controls thyroid gland function, its role in the regulation of thyroid (normal and neoplastic) growth is less certain. No prospective clinical studies evaluating the benefits of TSH suppression in patients with thyroid cancer are available. Mazzaferri [111] and Massin et al. [101], however, have reported improved long-term survival for patients treated with total thyroidectomy, ^{131}I ablation, plus TSH suppression. Mazzeferri and Jhiang [23], in a larger follow-up study, confirmed their initial findings that patients treated with TSH suppressive doses of thyroid hormone after total or near-total thyroidectomy had a lower recurrence rate and improved survival. Pujol et al. [112] recently reported that patients with adequate TSH suppression (serum TSH level of < 0.1 mU/L) have longer tumor-free periods and improved survival.

Van Herle and Uller [113] were the first to recommend serum Tg assays as a marker of persistent and recurrent disease in patients with DTC. Most DTCs of follicular cell origin synthesize Tg. When a sensitive, accurate assay is used to measure the serum Tg level, it can be a helpful marker for follow-up of patients with DTC and has reduced the need for frequent RAI scanning to follow these patients [114]. Those found to have elevated Tg levels after thyroid hormone withdrawal have either normal residual thyroid tissue or persistent/recurrent DTC [97]. Mueller-Gaertner and Schneider [115] reported 88% sensitivity for Tg determination to detect metastases in patients with DTC when thyroid hormone is withdrawn and 50% sensitivity when patients are receiving thyroid hormone. We have also observed that Tg determination is more sensitive than radioactive scanning for detecting recurrent or persistent DTC and that Tg determination is most sensitive when patients are hypothyroid [116]. Ronga et al. [117] reported that among 233 patients with thyroid cancer 96% had elevated serum Tg levels, but only 48% had RAI uptake in their tumors. Less frequently some patients with persistent or recurrent DTC have no detectable Tg level but show positive RAI uptake [97]. In this scenario, it is possible that the tumor does not synthesize Tg, but more frequently these patients have anti-Tg autoantibodies that falsely lower the Tg level [118]. A serum Tg level ≥ 3 mg/dl in patients without residual thyroid tissue while receiving thyroid hormone and > 10 mg/dl when hypothyroid usually indicates recurrent or metastatic DTC.

Although patients with DTC enjoy a relatively good survival,

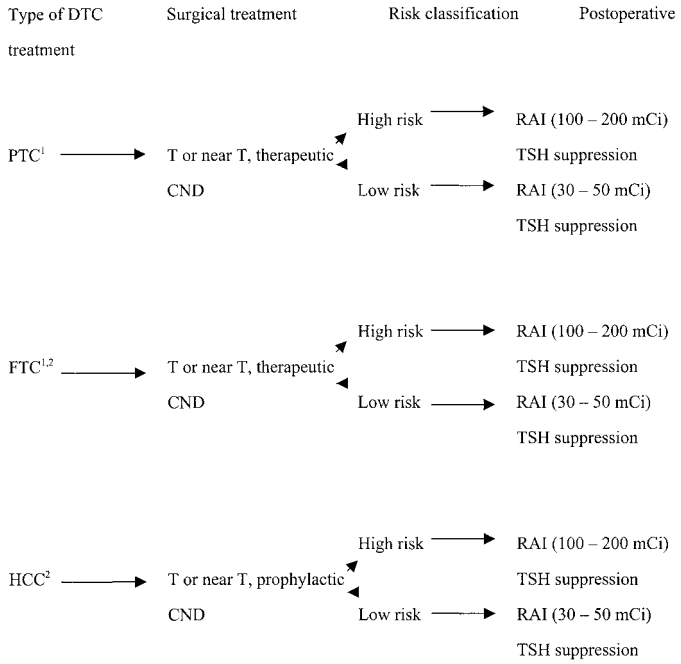

Fig. 1. Rational approach to patients with differentiated thyroid cancer (DTC). [1]In patients with occult papillary thyroid cancer (PTC) and minimally invasive follicular thyroid cancer (FTC), thyroid lobectomy is adequate because of the near-normal life expectancy in these patients. [2]Preoperatively most FTCs and Hurthle cell carcinomas (HCCs) cannot be distinguished reliably from follicular adenoma and Hurthle cell adenoma, respectively. If there is no intraoperative evidence of cancer (large tumor size, lymphadenopathy, or extrathyroidal invasion), a thyroid lobectomy may be performed; if found to be FTC or HCC on final pathology, we recommend a completion thyroidectomy. T: total thyroidectomy; CND: cervical node dissection; RAI: radioactive iodine ablation; TSH: thyroid-stimulating hormone.

optimal management and more complete initial treatment reduces the risk of recurrence and the low risk of death. It must be emphasized that at least one-third of the patients who develop recurrent DTC were dead from their tumor. Although some experts propose lobectomy for patients with low risk DTC, it is currently impossible to identify those patients preoperatively; and total or near-total thyroidectomy appears to decrease recurrence and death. Based on our own experience treating patients with DTC and that reported in the literature, most of the data support total or near-total thyroidectomy, postoperative RAI ablation therapy, and TSH suppression unless these procedures cannot be done with few complications. In Figure 1, we provide a rational approach to patients with DTC. We believe this algorithm represents a "complete" rational approach to patients with DTC that minimizes recurrence and mortality.

Résumé

Le traitement optimal des patients ayant un cancer différencié de la thyroïde est controversé car il n'existe aucune étude prospective randomisée qui a examiné la valeur de 1) la thyroïdectomie étendue, 2) l'ablation complémentaire par iode radioactif ou 3) la thérapie suppressive par TSH. Les patients ayant un cancer différencié, dit à bas risque, ont un relativement bon pronostic avec une mortalité comprise entre 2 et 5% et un taux de récidive d'environ 20%. En dépit de l'excellent pronostic des patients catégorisés comme étant à bas risque, la thyroïdectomie totale ou presque totale pour cancer différencié de la thyroïde offre un certain nombre d'avantages : 1) utilisation de l'iode radioactif en postopératoire pour détecter et/ou traiter du tissu thyroïdien résiduel et les métastases locales ou à distance; 2) les taux sériques de thyroglobuline sont plus sensibles pour détecter soit la maladie persistante ou récidivante après l'ablation totale de tout tissu thyroïdien, et 3) la thyroïdectomie totale ou presque totale combinée avec l'ablation postopératoire par l'I_{131} et, enfin, la survie est meilleure avec un taux de récidive inférieur lorsqu'on utilise la thérapie suppressive par la TSH. Les patients ayant un cancer papillaire occulte ou un cancer folliculaire mini-invasif de la thyroïde peuvent être traités par une lobectomie thyroïdienne car ces patients ont une espérance de vie presque normale. Il apparaît que pratiquement tous les autres patients ayant un cancer différencié de la thyroïde tirent un bénéfice d'un traitement initial agressif.

Resumen

Persiste la controversia sobre cuál es el manejo óptimo del paciente con carcinoma diferenciado de tiroides, por cuanto no se dispone de estudios prospectivos y aleatorizados que determinen los méritos de 1) la amplitud de la tiroidectomía, 2) la ablación postoperatoria con yodo radiactivo o 3) la terapia de supresión de TSH. Los pacientes con cánceres diferenciados de tiroides gozan de pronóstico relativamente bueno, con una mortalidad alrededor del 2% a 5% y una tasa de recurrencia alrededor del 20%. A pesar del excelente pronóstico en pacientes considerados como de bajo riesgo, la tiroidectomía total o la casi total tienen las siguientes ventajas: 1) se puede utilizar el yodo radioactivo en el postoperatorio para detectar y/o tratar tejido tiroideo residual normal y metástasis locales o distantes, 2) en el seguimiento, los niveles séricos de tiroglobulina son un marcador más sensible de enfermedad persistente o recurrente cuando todo el tejido tiroideo ha sido resecado, y 3) la tiroidectomía total o casi total combinada con ablación con 131-I y terapia de supresión de TSH resulta en mejor supervivencia y menores tasas de recurrencia. Los pacientes con carcinoma papilar y cáncer folicular minimamente invasor pueden ser tratados con lobectomía, porque exhiben una expectativa de vida normal. Todos los demás pacientes con cáncer diferenciado de tiroides parecen beneficiarse de un tratamiento quirúrgico primario de mayor extensión.

References

1. Robbins, J., Merino, M.J., Boice, J.D., Ron, E., Ain, K.B., Alexander, H.R., Norton, J.A., Reynolds, J.: Thyroid cancer: a lethal endocrine neoplasm. Ann. Intern. Med. *115*:2, 1991
2. Jossart, G., Clark, O.H.: Well differentiated thyroid cancer. Curr. Probl. Surg. *31*:939, 1994
3. Singer, P.A., Cooper, D.S., Daniels, G.H., Ladenson, P.W., Greenspan, F.S., Levy, E.G., Braverman, L.E., Clark, O.H., McDougall, I.R., Ain, K.V., Dorfman, S.G.: Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. Arch. Intern. Med. *156*:2165, 1996
4. Shaha, A.R., Byers, R.M., Terz, J.J.: Thyroid cancer surgical practice guidelines: scope and format of guidelines. Oncology *11*:1228, 1997
5. Hay, I.D., Feld, S., Garcia, M.: AACE clinical practice guidelines for the management of thyroid carcinoma. Endocr. Pract. *3*:60, 1997
6. Cady, B., Rossi, R., Silverman, M., Wool, M.: Further evidence of the

validity of risk group definition in differentiated thyroid carcinoma. Surgery *98*:1171, 1985
7. Carcangiu, M.L., Zampi, G., Pupi, A., Castagnoli, A., Rosai, J.: Papillary carcinoma of the thyroid: a clinicopathologic study of 241 cases treated at the University of Florence, Italy. Cancer *55*:805, 1985
8. Crile, G., Antunez, A.R., Esselstyn, C.B., Hawk, W.A., Skillern, P.G.: The advantages of subtotal thyroidectomy and suppression of TSH in the primary treatment of papillary carcinoma of the thyroid. Cancer *55*:2691, 1985
9. Clark, O.H., Levin, K., Zeng, Q.H., Greenspan, F.S., Siperstein, A.E.: Thyroid cancer: the case for total thyroidectomy. Eur. J. Cancer Clin. Oncol. *24*:305, 1988
10. Herdinger, C.: Histologic Typing of Thyroid Tumors, Berlin, Springer-Verlag, 1988, p. 7
11. Rosai, J., Carcangiu, M.L., Delellis, R.A.: Atlas of Tumor Pathology: Tumors of the Thyroid Gland, Washington, DC, Armed Forces Institute of Pathology, 1992, p. 161
12. Correa, P., Chen, V.W.: Endocrine gland cancer. Cancer *75*:338, 1995
13. Hay, I.D.: Papillary thyroid carcinoma. Endocrinol. Metab. Clin. North Am. *19*:545, 1990
14. Schelfhout, L.J.D.M., Dreutzberg, C.L., Hamming, J.F., Fleuren, G.J., Smeenk, D., Hermans, J., van de Velde, C.H., Goslings, B.M.: Multivariate analysis of survival in differentiated thyroid cancer: the prognostic significance of the age factor. Eur. J. Cancer Clin. Oncol. *24*:331, 1988
15. DeGroot, L.J., Kaplan, E.L., McCormick, M., Straus, F.H.: Natural history, treatment, and course of papillary thyroid carcinoma. J. Clin. Endocrinol. Metab. *71*:414, 1990
16. Harwood, J., Clark, O.H., Dunphy, J.E.: Significance of lymph node metastasis in differentiated thyroid cancer. Am. J. Surg. *136*:107, 1978
17. McConahey, W.M., Hay, I.D., Woolner, L.B., van Heerden, J.A., Taylor, W.F.: Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. Mayo Clin. Proc. *61*:978, 1986
18. Moreno-Egea, A., Rodriquez-Gonzalez, J.M., Sola-Perez, J., Soria-Cogollos, T., Parrila-Paricio, P.: Multivariate analysis of histopathological features as prognostic factors in patients with papillary thyroid carcinoma. Br. J. Surg. *82*:1092, 1994
19. Simpson, W.J., McKinney, S.E., Curruthers, J.S., Gospodarowicz, M.K., Sutcliffe, S.B., Panzarella, T.: Papillary and follicular thyroid cancer: prognostic factors in 1578 patients. Am. J. Med. *83*:479, 1987
20. Tshcoll-Ducommun, J., Hedinger, C.E.: Papillary thyroid carcinomas: morphology and prognosis. Virchows Arch. Pathol. Anat. *396*: 19, 1982
21. Mizukami, Y., Noguchi, M., Michigishi, T., Nonomura, A., Hashimoto, T., Otakes, S., Nakamura, S., Matsubasa, F.: Papillary thyroid carcinoma in Kanazawa, Japan: prognostic significance of histological subtypes. Histopathology *20*:243, 1992
22. Mazzaferri, E.L.: Papillary thyroid carcinoma: factors influencing prognosis and current therapy. Semin. Oncol. *14*:315, 1987
23. Mazzeferri, E.L., Jhiang, S.M.: Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am. J. Med. *97*:418, 1994
24. Mazzeferri, E.L., Young, R.L.: Papillary thyroid carcinoma: a 10 year follow-up report of the impact of therapy in 576 patients. Am. J. Med. *70*:511, 1981
25. DeGroot, L.J.: Radiation-associated Thyroid Carcinoma. Orlando, FL, Grune & Stratton, 1977, p. 137
26. Allo, M.D., Christianson, W., Koivunen, D.: Not all "occult" papillary carcinomas are "minimal." Surgery *102*:1075, 1988
27. Crile, G.: Changing end results in patients with papillary carcinoma of the thyroid. Surg. Gynecol. Obstet. *132*:460, 1971
28. Harada, T., Kunihiko, I., Shimaoka, K.: Fatal thyroid carcinoma. Cancer *39*:2588, 1977
29. Frazell, E., Foote, F.: Papillary cancer of the thyroid. Cancer *11*:895, 1958
30. Emerick, F.T., Duh, Q.Y., Siperstein, A.E., Burrow, G.N., Clark, O.H.: Diagnosis, treatment, and outcome of follicular thyroid carcinoma. Cancer *72*:3287, 1993
31. Brennan, M.D., Bergstralh, E.J., van Heerden, J.A., McConahey, W.M.: Follicular thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy and outcome. Mayo Clin. Proc. *66*:11, 1991
32. Jorda, M., Gonzalez-Campora, R., Mora, J., Herrero-Zapartero, A., Otal, C., Galera, H.: Prognostic factors in follicular carcinoma of the thyroid. Arch. Pathol. Lab. Med. *117*:631, 1993
33. Mueller-Gaertner, H.W., Grzac, H.T., Rehpenning, W.: Prognostic indices for tumor relapse and tumor mortality in follicular thyroid carcinoma. Cancer *67*:1903, 1991
34. Harness, J.K., Thompson, N.W., McLeod, M.K., Eckhauser, F.E., Lloyd, R.V.: Follicular carcinoma of the thyroid gland: trends and treatment. Surgery *96*:972, 1984
35. Crile, G., Jr., Pontius, K.I., Hawk, W.A.: Factors influencing the survival of patients with follicular carcinoma of the thyroid gland. Surg. Gynecol. Obstet. *160*:409, 1985
36. Grant, C.S., Barr, D., Goellner, J.R., Hay, I.D.: Benign Hurthle cell tumors of the thyroid: a diagnosis to be trusted? World J. Surg. *12*:488, 1988
37. Carcangiu, M.L., Bianchi, S., Savino, D., Voynick, I.M., Rosai, J.: Follicular Hurthle cell tumors of the thyroid gland. Cancer *68*:1944, 1991
38. Clark, O.H., Gerand, P.L.: Thyrotropin receptor adenylate cyclase system in Hurthle cell neoplasms. J. Clin. Endocrinol. Metab. *61*:775, 1985
39. Masood, S., Auguste, L.J., Westerband, A., Belluco, C., Valderama, E., Attie, J.: Differential oncogenic expression in thyroid follicular and Hurthle cell carcinomas. Am. J. Surg. *166*:366, 1993
40. Shaha, A.R., Shah, J.P., Loree, T.R.: Patterns of nodal and distant metastasis based on histologic varieties in differentiated carcinoma of the thyroid. Am. J. Surg. *172*:692, 1996
41. Caplan, R.H., Abellera, R.M., Kisken, W.A.: Hurthle cell neoplasms of the thyroid gland: reassessment of functional capacity. Thyroid *4*:243, 1994
42. Grossman, R.F., Clark, O.H.: Hurthle cell carcinoma. Cancer Control *4*:13, 1997
43. Ditkoff, B.A., Chabot, J., Jin, S.: Hurthle cell cancer of the thyroid: the incidence of multifocal and bilateral disease. Thyroidol. Clin. Exp. *7*:49, 1995
44. Tollefsen, H.R., Shah, J.P., Huvos, A.G.: Hurthle cell carcinoma of the thyroid. Am. J. Surg. *130*:390, 1975
45. Har-el, G., Hadar, T., Segal, K., Levy, R., Sidi, J.: Hurthle cell carcinoma of the thyroid gland: a tumor of moderate malignancy. Cancer *57*:1613, 1986
46. Samaan, N.A., Schultz, P.N., Haynie, T.P., Ordonez, N.G.: Pulmonary metastasis of differentiated thyroid carcinoma: treatment results of 101 patients. J. Clin. Endocrinol. Metab. *60*:376, 1985
47. Greenspan, F.S.: Radiation exposure and thyroid cancer. J.A.M.A. *237*:2089, 1977
48. Wilson, S.D., Komorowski, R., Cerletty, J., Majewski, J.T., Hooper, M.: Radiation-associated thyroid tumors: extent of operation and pathology technique influence the apparent incidence of carcinoma. Surgery *94*:663, 1983
49. Witt, T.R., Meng, R.L., Economou, S.G., Southwick, H.W.: The approach to the irradiated thyroid. Surg. Clin. North Am. *59*:45, 1979
50. Deaconson, T.F., Wilson, S.D., Cerletty, J.M., Komorowski, R.A.: Total or near total thyroidectomy versus limited resection for radiation-associated thyroid nodules: a twelve-year follow-up of patients in a thyroid screening program. Surgery *100*:1116, 1986
51. Grossman, R.F., Tu, S.H., Duh, Q.Y., Siperstein, A.E., Novosolov, F., Clark, O.H.: Familial nonmedullary thyroid cancer: an emerging entity that warrants aggressive treatment. Arch. Surg. *130*:892, 1995
52. Van De Velde, C.J.H., Hamming, J.F., Goslings, B.M., Schelfhout, L.J.D.M., Clark, O.H., Smeds, S., Bruining, H.A., Krenning, E.P., Cady, B.: Report of the consensus development conference on the management of differentiated thyroid cancer in The Netherlands. Eur. J. Cancer Clin. Oncol. *24*:287, 1988
53. Thompson, N.W., Nishiyama, R.H., Harness, J.K.: Thyroid carcinoma: current controversies. Curr. Probl. Surg. *15*:1, 1978
54. Perzik, S.: The place of total thyroidectomy in the management of 909 patients with thyroid disease. Am. J. Surg. *132*:480, 1976
55. Clark, O.H.: Total thyroidectomy: the treatment of choice for patients with differentiated thyroid cancer. Ann. Surg. *196*:361, 1982
56. Frankenthaler, R.A., Sellin, R.V., Cangir, A., Goepfert, H.: Lymph

node metastasis from papillary-follicular thyroid carcinoma in young patients. Am. J. Surg. *160*:341, 1990
57. Schroder, D.M., Chambors, A., France, C.J.: Operative strategy for thyroid cancer: is total thyroidectomy worth the price? Cancer *58*: 2320, 1986
58. Attie, J.N., Moskowitz, G.W., Margouleff, D., Levy, L.M.: Feasibility of total thyroidectomy in the treatment of thyroid carcinoma: postoperative radioactive iodine evaluation of 140 cases. Am. J. Surg. *138*:555, 1979
59. Ready, A.R., Barnes, A.D.: Complications of thyroidectomy. Br. J. Surg. *81*:1555, 1994
60. Moulton-Barrett, R., Crumley, R., Jalilie, S., Segina, D., Allison, G., Marshak, D., Chan, E.: Complications of thyroid surgery. Int. Surg. *82*:63, 1997
61. Flynn, M.B., Lyons, K.J., Tarter, J.W., Ragsdale, R.L.: Local complications after surgical resection for thyroid carcinoma. Am. J. Surg. *168*:404, 1994
62. Harness, J.K., Fung, L., Thompson, N.W., Burney, R.E., McLeod, M.K.: Total thyroidectomy: complications and technique. World J. Surg. *10*:781, 1986
63. Schwartz, A.E., Friedman, E.W.: Preservation of the parathyroid glands in total thyroidectomy. Surg. Gynecol. Obstet. *165*:327, 1987
64. Martensson, H., Terins, J.: Recurrent laryngeal nerve palsy in thyroid gland surgery related to operations and nerves at risk. Arch. Surg. *120*:475, 1985
65. Foster, R.S.: Morbidity and mortality after thyroidectomy. Surg. Gynecol. Obstet. *146*:423, 1978
66. Ley, P.B., Roberts, J.W., Symmonds, R.E., Hendricks, J.C., Snyder, S.K., Frazee, R.C., Smith, R.W., McKennery, J.F., Brindley, G.V.: Safety and efficacy of total thyroidectomy for differentiated thyroid carcinoma: a 20 year review. Am. Surg. *59*:110, 1993
67. Reeve, T.S., Delbridge, L., Cohen, A., Crummer, P.: Total thyroidectomy: the preferred option for multinodular goiter. Ann. Surg. *206*:782, 1987
68. De Roy van Zuidewijn, D.B., Songun, I., Kievit, J., van de Velde, C.J.H.: Complications of thyroid surgery. Ann. Surg. Oncol. *2*:56, 1995
69. Reeve, T.S., Curtin, A., Fingleton, L., Kennedy, P., Mackie, W., Porter, T., Simons, D., Townend, D., Delbridge, L.: Can total thyroidectomy be performed as safely by general surgeons in provincial centers as by surgeons in specialized endocrine surgical units? Arch. Surg. *129*:834, 1994
70. Shindo, M.L., Sinha, U.K., Rice, D.H.: Safety of thyroidectomy in residency: a review of 186 consecutive cases. Laryngoscope *105*:1173, 1995
71. Pederson, W.C., Johnson, C.L., Gaskill, H.V., Aust, J.B., Cruz, A.B.: Operative management of thyroid disease: technical considerations in a residency training program. Am. J. Surg. *148*:350, 1984
72. Byar, D.P., Green, S.B., Dor, P., Williams, E.D., Colon, J., van Gilse, H.A., Mayer, M., Sylvester, R.J., van Glabbeke, M.: A prognostic index for thyroid carcinoma: a study of the E.O.R.T.C. thyroid cancer cooperative group. Eur. J. Cancer *15*:1033, 1979
73. Tennval, J., Biorklund, A., Moller, T., Ranstam, J., Akerman, M.: Is the EORTC prognostic index of thyroid cancer valid in differentiated thyroid carcinoma? Cancer *57*:1405, 1986
74. Hay, I.D., Grant, C.S., Taylor, W.F., McConahey, W.M.: Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery *102*:1088, 1987
75. Hay, I.D., Bergstralh, E.J., Goellner, J.R., Ebersold, J.R., Grant, C.S.: Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery *114*:1050, 1993
76. Cady, B., Rossi, R.: An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery *104*:947, 1988
77. Davis, N.L., Bugis, S.P., McGregor, G.I., Germann, E.: An evaluation of prognostic scoring systems in patients with follicular thyroid cancer. Am. J. Surg. *170*:476, 1995
78. Akslen, L.A.: Prognostic importance of histologic grading in papillary thyroid carcinoma. Cancer *72*:2680, 1993
79. Kukkonen, S.T., Haapiainen, R.K., Franssila, K.O., Sivula, A.H.: Papillary thyroid carcinoma: the new, age-related TNM classification system in a retrospective analysis of 199 patients. World J. Surg. *14*:837, 1990
80. Pasieka, J.L., Zedenius, J., Auer, G., Grinelius, L., Hoog, A., Lundell, G., Wallin, G., Backdahl, M.: Addition of nuclear DNA content to the AMES risk-group classification for papillary thyroid cancer. Surgery *112*:1154, 1992
81. Backdahl, M., Carstensen, J., Auer, G., Tallroth, E.: Statistical evaluation of the prognostic value of nuclear DNA content in papillary, follicular, and medullary thyroid tumors. World J. Surg. *10*:974, 1986
82. Siperstein, A.E., Zeng, Q.H., Gum, E.T., Levin, K.E., Clark, O.H.: Adenylate cyclase activity as a predictor of thyroid tumor aggressiveness. World J. Surg. *12*:528, 1988
83. Beierwaltes, W.H., Nishiyama, R.H., Thompson, N.W., Copp, J.E., Kubo, A.: Survival time and "cure" in papillary and follicular thyroid carcinoma with distant metastases: statistics following University of Michigan therapy. J. Nucl. Med. *23*:561, 1982
84. Duh, Q.Y., Siperstein, A.E., Miller, R.A., Sancho, J.J., Demeure, M.J., Clark, O.H.: Epidermal growth factor receptors and adenylate cyclase activity in human thyroid tissues. World J. Surg. *14*:410, 1990
85. Lemoine, N.R., Mayal, E.S., Wyllie, F.S., Farr, C.J., Hughes, D., Padua, R.A., Thurston, V., Williams, E.D., Wynford-Thomas, D.: Activated ras oncogenes in human thyroid cancers. Cancer Res. *48*:4459, 1988
86. Goretzki, P.E., Lyons, J., Stacy-Philips, S., Rosenau, W., Demeure, M., Clark, O.H., McCormick, F., Roher, H.D., Bourne, H.R.: Mutational activation of RAS and GSP oncogenes in differentiated thyroid cancer and their biological implications. World J. Surg. *16*: 576, 1992
87. Romano, M.I., Grattone, M., Karner, M.P., Moiguer, S., Tetelbaum, F., Romano, L.A., Illescas, E., Padin, R., Cuvea, F., Burdman, J.A.: Relationship between the level of c-myc mRNA and histologic aggressiveness in thyroid tumors. Horm. Res. *39*:161, 1993
88. Terrier, P., Sheng, Z.M., Schlumberger, M., Tubiana, M., Caillou, B., Travagli, J.P., Fragu, P., Parmentier, C., Riou, G.: Structure and expression of c-myc and c-fos proto-oncogenes in thyroid carcinomas. Br. J. Cancer *57*:1405, 1986
89. Jhiang, S.M.: The ret/PTC oncogene in papillary thyroid carcinoma. J. Lab. Clin. Med. *123*:331, 1994
90. Tallini, G., Santoro, M., Helie, M., Carlomagno, F., Salvatore, F., Chiappetta, G., Carcangiu, M.L., Fusco, A.: RET/PTC oncogene activation defines a subset of papillary thyroid carcinomas lacking evidence of progression to poorly differentiated or undifferentiated tumor phenotypes. Clin. Cancer Res. *4*:287, 1998
91. Viglietto, G., Chiappetta, G., Fukunaga, F.H., Visconti, R., Mastro, A., Rigopoulou, D., Martinez-Tello, F.J., Tallini, G., Santoro, M., Fusco, A.: RET/PTC oncogene activation is an early event in thyroid carcinogenesis. Oncogene *11*:1207, 1995
92. Dobashi, Y., Sakamoto, A., Sugimara, H., Mernyei, M., Mori, M., Oyama, T., Machinami, R.: Overexpression of p53 as a possible prognostic factor in human thyroid carcinoma. Am. J. Surg. Pathol. *17*:375, 1993
93. Fagin, J.A., Matsuo, K., Karmakar, A., Chen, D.L., Tang, S.H., Koeffler, H.P.: High prevalence of mutations of the p53 gene in poorly differentiated human thyroid carcinomas. J. Clin. Invest. *91*: 179, 1993
94. Ito, T., Seyama, T., Mizuno, T., Tsuyama, N., Hayashi, T., Hayashi Y., Cohl, K., Nakamura, N., Akiyama, M.: Unique association of p53 mutations with undifferentiated but not with differentiated carcinomas of the thyroid gland. Cancer Res. *52*:1369, 1992
95. Hay, I.D., Grant, C.S., Bergstralh, E.J., Thompson, G.B., van Heerden, J.A., Goellner, J.R.: Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? Surgery *124*:958, 1998
96. Cady, B., Sedgwick, C.E., Meissner, W.A., Wool, M.S., Salzman, F.A., Werber, J.: Risk factor analysis in differentiated thyroid cancer. Cancer *43*:810, 1979
97. Clark, O.H., Hoelting, T.: Management of patients with differentiated thyroid cancer who have positive serum thyroglobulin levels and negative radioiodine scans. Thyroid *4*:501, 1994
98. Davis, N.L., Gordon, M., McGregor, G.I., Robins, R.E.: Efficacy of ^{131}I ablation following thyroidectomy in patients with invasive follicular thyroid cancer. Am. J. Surg. *163*:472, 1992
99. Simpson, W.J., Panzarella, T., Carruthers, J.S., Gospodarowicz,

M.K., Sutcliff, S.B.: Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. Int. J. Oncol. Biol. Phys. *14*:1063, 1988
100. Loh, K.C., Greenspan, F.S., Gee, L., Miller, T.R., Yeo, P.P.: Pathologic tumor-node-metastases (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. J. Clin. Endocrinol. Metab. *97*:3553, 1997
101. Massin, J.P., Savoie, J.C., Garnier, H., Guiraudon, G., Leger, F.A., Bacourt, F.: Pulmonary metastases in differentiated thyroid carcinoma. Cancer *53*:982, 1984
102. Schlumberger, M., Tumbiana, M., De Vathaire, F., Hill, C., Gardet, P., Travagli, J.P., Fragee, P., Lumbrosos, J., Caillou, B., Parmentier, B.: Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. J. Clin. Endocrinol. Metab. *63*:960, 1986
103. Casara, D., Rubello, D., Saladini, G., Nasarotto, G., Favero, A., Girelli, M.E., Busnardo, B.: Different features of pulmonary metastases in differentiated thyroid cancer: natural history and multivariate statistical analysis of prognostic variables. J. Nucl. Med. *34*:1626, 1993
104. Pineda, J.D., Lee, T., Reynolds, J., Robbins, J.: I-131 therapy for thyroid cancer with elevated thyroglobulin and negative diagnostic scan. Thyroid *2*:16, 1992
105. DeGroot, L.J., Reilly, M.: Comparison of 30- and 50-mCi doses of iodine-131 for thyroid ablation. Ann. Intern. Med. *96*:51, 1982
106. Johansen, K., Woodhouse, N.J., Odugbesan, O.: Comparison of 1073 MBq and 3700 MBq iodine-131 in postoperative ablation of residual thyroid tissue in patients with differentiated thyroid cancer. J. Nucl. Med. *32*:252, 1991
107. Nicholas, C.W., Lindsay, S., Sheline, G.E.: Induction of neoplasms in rat thyroid glands by X irradiation of a single lobe. Arch. Pathol. *80*:177, 1965
108. Soh, E.Y., Sobhi, S.A., Wong, M.G., Meng, Y.G., Siperstein, A.E., Clark, O.H., Duh, Q.Y.: Thyroid stimulating hormone promotes the secretion of vascular endothelial growth factor in thyroid cancer cell lines. Surgery *120*:944, 1996
109. Hoelting, T., Tezelman, S., Siperstein, A.E., Duh, Q.Y., Clark, O.H.: Biphasic effects of thyrotropin on invasion and growth of papillary and follicular thyroid cancer in-vitro. Thyroid *5*:35, 1995
110. Kawakami, A., Eguchi, K., Matsuoka, N., Tsuboi, M., Kawabe, Y., Ishikawa, N., Ito, K., Nagataki, S.: Thyroid-stimulating hormone inhibits Fas antigen binding-mediated apoptosis of human thyrocytes in vitro. Endocrinology *137*:3163, 1996
111. Mazzaferri, E.L.: Treating differentiated thyroid carcinoma: where do we draw the line? Mayo Clin. Proc. *66*:105, 1991
112. Pujol, P., Daures, J.P., Nsakala, N., Baldet, L., Bringer, J., Jaffiol, C.: Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. J. Clin. Endocrinol. Metab. *81*:4318, 1996
113. Van Herle, A.J., Uller, R.P.: Elevated serum thyroglobulin: a marker of metastases in differentiated thyroid cancer. J. Clin. Invest. *56*:272, 1975
114. Schlumberger, M., Travagli, J.P., Fragu, P., Gardet, P., Lumbroso, J., Parmentier, C.: Follow-up of patients with differentiated thyroid carcinoma: experience at Institut Gustave-Roussy, Villejuif. Eur. J. Cancer Clin. Oncol. *24*:345, 1988
115. Mueller-Gaertner, H.W., Schneider, C.: Clinical evaluation of tumor characteristics predisposing serum thyroglobulin to be undetectable in patients with differentiated thyroid cancer. Cancer *61*:976, 1998
116. Duren, M., Siperstein, A.E., Shen, W., Duh, Q.Y., Morita, E., Clark, O.H.: Value of stimulated serum thyroglobulin levels for detecting persistent or recurrent differentiated thyroid cancer in high- and low-risk patients. Surgery *126*:13, 1999
117. Ronga, F., Fiorentino, A., Fragasso, G., Fringuelli, F.M., Todino, V.: Complementary role of whole body scan and serum thyroglobulin determination in the follow-up of differentiated thyroid carcinoma. Ital. J. Surg. Sci. *16*:11, 1986
118. Spencer, C.A., Takeuchi, M., Kazarosyan, M., Wand, C.C., Guttler, R.B., Singer, P.A., Fatemi, S., Lo Presti, J.S., Nicoloff, J.T.: Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid cancer. J. Clin. Endocrinol. Metab. *83*:1121, 1998