S1-CONTEMPORARY MANAGEMENT OF DIFFERENTIATED THYROID CANCER

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DIAGNOSIS

Management of differentiated thyroid cancer begins with diagnosis, usually surgical excision, and initial staging postoperatively. Diagnosis is achieved by history and exam, thyroid function tests and calcitonin (CT) assay, ultrasound, most frequently fine needle aspiration (FNA), sometimes isotope scans radiographs, computed axial tomography (CAT) scans or magnetic resonance imaging (MRI), and even positron emission tomography (PET) scans. Diagnostic methods and concepts are extensively reviewed in www.thyroidmanager.org/thyroidcancer to which readers are referred.
Thyrotropin (TSH), free thyroxine (fT4) and thyroid peroxidase antibody (TPO-Ab) assays are needed to document the patient's metabolic status and fitness for operation, to rule out a possible hyper functioning thyroid lesion, and sometimes to help differentiate thyroiditis as the etiology of the lesion of interest. Serum TG measurement is not recommended in routine practice preoperatively because elevated levels are associated with any thyroid growth. Ultrasound exam is currently central to diagnosis, providing information on the size, shape and number of lesions, probability of infiltrative disease, and of involved neck nodes. The key test is of course FNA and its interpretation, supplemented sometimes by assay of tumor genetic markers that can augment, or reduce, the statistical probability that the tumor is malignant. Whole body (WB) Scans for diagnosis of metastatic disease are performed if there is some suggestion of disease spread, but are more commonly conducted after operation. The results of the diagnostic workup may include definite or possible thyroid cancer within a nodule or thyroid lobe, and possible nodal or metastatic disease. Management of cancer in children, and of anaplastic and medullary tumors, is reviewed in Thyroidmanager**.**

COURSE OF DISEASE

Management should be guided by an understanding of the natural history of papillary and follicular thyroid cancers. Age at diagnosis has an important bearing on the patient's subsequent course. The adverse effect of age on prognosis increases gradually with each decade (1). For practical assessment purposes, it is clear that patients diagnosed before age 45 have a much better prognosis than those detected later (2). Age is also directly related to the incidence of undifferentiated tumors and to overall mortality. Pregnancy does not seem to worsen the course of established or previously treated thyroid cancer (3). Overall, women have a better prognosis than men with thyroid cancer (4). Other characteristics of the tumor, including (as would be expected) distant metastases, extra-glandular extension, gross invasion of the tumor capsule, and increasing size also carry a worsened prognosis (4).

Papillary carcinoma has a peak incidence in the third and fourth decades (5). It occurs three times more frequently in women than in men, and accounts for 60-70% of all thyroid cancers in adults and about 70% of those found in children. The disease tends to remain localized in the thyroid gland and in time metastasizes locally to the cervical or upper mediastinal nodes. The lesions are multicentric in 20% or more of patients, especially in children. Using rigid pathologic

criteria, perhaps two-thirds of predominantly papillary thyroid cancers are found to have follicular elements. The natural history of these tumors is generally considered similar to that of pure papillary lesions (6). Metastases may conform to either histologic pattern. At present, the mixed tumors are lumped together with all other papillary cancers. This tumor tends to be indolent and may exist for decades without killing the host. In a Mayo Clinic series of papillary tumors that were detected because of lymph node metastasis or found incidentally during surgery of the thyroid gland, all the patients were unaffected by the tumors over several decades (5). The presentation of papillary thyroid cancer has been changing in the last two decades compared to previous years, with an increasing number of small tumors and less frequent lymph node metastases at presentation (7)

Many papillary tumors present as occult or “minimal’ cancers, incidentally found at neck ultrasound, and measure under 0.5-1 cm in size. The term occult has been used in a variety of ways, including reference to tumors with malignant lymph nodes but no obvious primary, or in reference to tumors under 1.5 cm in diameter. Currently the preferred term is microcarcinoma. Mayo Clinic reports of papillary tumors under 1.5 cm in diameter, treated with conservative subtotal thyroidectomy and node dissection, have stressed their non-lethal nature, but a 1980 follow-up report on 820 patients treated by this group notes that 6 (0.7%) patients eventually died after spread of tumor from such "occult" primaries (8). Patients with appropriately treated minimal tumors have 96-100% survival after 15-30 years.

While the disease may be aggressive in children, it is distinctly less aggressive in young adults, as compared to patients over age 40 (4).Young patients tend to have small primary lesions and extensive adenopathy, but even with local invasion survival is good (9). When papillary cancer occurs in persons over the age of 45, it may show, on microscopic examination, areas of undifferentiation, and pursue a more highly malignant clinical course. The lesions tend to be larger and more infiltrative, and to have fewer local metastases (10). It is possible that persons apparently dying of thyroid cancer in older age actually have had their disease for many years, and that it has simply evolved into a more malignant phase (11, 12).

Papillary carcinoma tends to metastasize locally to lymph nodes, and occasionally produces cystic structures near the thyroid that are difficult to diagnose because of the paucity of malignant tissue. In this case measurement of thyroglobulin in the fluid aspirate is a clue for the correct diagnosis. The presence of nodal metastasis correlates with recurrence but has little effect on mortality in patients under age 45. In patients over 45, the presence of nodes is associated with greater recurrence rates and more deaths (14, 15)**.**

The tumors often metastasize elsewhere, especially to lung or bones. Papillary tumors may metastasize to the lungs and produce a few nodules, or the lung fields may have a snowflake appearance throughout. These tumors are amazingly well tolerated and may allow relatively normal physical activity for 10-30 years. At times, particularly in the follicular variant of papillary thyroid cancer, the pulmonary metastases are active in forming thyroid hormone, and may even function as a source of hormone supply after thyroidectomy. The metastases may progress gradually and result in obstructive and restrictive pulmonary disease. They also may develop arteriovenous shunts, with hypoxia or cyanosis. Such shunts become more prominent during pregnancy, perhaps as an effect of the increased supply of estrogens. The tall cell variant of papillary carcinoma comprises about 10% of total cases, and as noted by several authors appears to be more aggressive than other forms of the disease (16.17). .

The usual net extra mortality in papillary cancer is not great when compared to that of a control population, perhaps 10-20% over 20-30 years (12, 13, and 15). Mortality is rare in patients

diagnosed before age 40, and is mainly observed in patients found to have invasive or metastatic disease at initial diagnosis. About one-half of patients ultimately dying from this lesion do so because of local invasion.
We found that risk of death from cancer was increased by extrathyroidal invasion (6 fold) or distant metastasis (47 fold), age over 45 years (32 fold) and size over 3 cm (6 fold). Thyroiditis, multifocality and the presence of neck nodes had no effect on disease-induced mortality.

Follicular carcinoma has a peak incidence in the fifth decade of life in the United States and accounts for about one-quarter of all thyroid carcinomas (4, 18, and 19). It is often a slowly growing tumor and frequently is recognized as a nodule in the thyroid gland before metastases appear. Variation in the cellular pattern ranges from an almost normal-appearing structure to anaplastic tissue that forms no follicles or colloid. The insular variant of follicular thyroid cancer tends to be more aggressive (20). The tumor is three times as common in women as in men. At operation one-half to two-thirds of these tumors are resectable. Tumors that are small and well circumscribed (not surprisingly) tend to be less lethal than those actively infiltrating local structures at the initial operation. Local adenopathy, which is uncommon, probably carries a greater risk, and extensive invasion of the tumor capsule and thyroid tissue increases mortality (21). Local direct invasion of strap muscles and trachea is characteristic of the more aggressive tumors (22). Resectability depends on this feature, and death may be caused by local invasion and airway obstruction. The "minimally invasive" variant has a far better prognosis than the highly invasive variant.

Follicular carcinomas tend to invade locally and metastasize distantly, rather than to local nodes, and are especially prone to metastasize to bone or lung. In one series (12), one-half had metastasized at the time the diagnosis was originally established. Bony metastases are usually osteolytic, rarely osteoblastic, and the alkaline phosphatase level is rarely elevated. The tumor and metastases often retain an ability to accumulate and hold iodide, and are therefore usually susceptible to treatment with RAI. Indeed, some metastatic tumors synthesize thyroid hormone in normal or even excessive amounts. RAI therapy, as discussed below, improves survival in these patients (21).
Occasionally the primary lesion of a follicular tumor appears to be entirely benign, but distant metastases are found. Invasion of vessels or the capsule, apart from the metastasis, is the only reliable criterion of malignancy. This variant has been called the “benign metastasizing struma” or malignant adenoma. It has a more prolonged course than do other varieties of follicular tumor, and is the type that has offered the best opportunity for the therapeutic use of 131-I. A subset of thyroid carcinomas which have a histologic picture of islands of cells -thus "insular" -has been identified (23). These tumors often look like anaplastic cancers, but sometimes are able to concentrate 131-I and thus are amenable to this treatment. Whether these are properly considered a variety of follicular cancer is uncertain. The important message is that the histology in this instance does not reliably predict the utility of 131-I treatment, suggesting that all patients with thyroid cancer should at some point be studied to determine whether 131-I treatment is possible. The net extra mortality attributable to follicular cancer in the 10 -15 years after diagnosis is 30-50% (12,14,16). Of the patients dying from the lesion, three-fourths do so from the effect of distant metastases and the remainder from locally invasive disease.

Hürthle cell tumors are histologically distinct from other follicular tumors, but they pursue a similar course. They tend to invade and metastasize locally and have a strong propensity to recur after surgery. The course tends to be prolonged. These carcinomas often do not accumulate 131-I. However, in a large survey, Caplan et al (23) found that 4.4% of Hürthle cell neoplasms were hot on scan and 8.9% were “warm”. Serum TG levels may be normal or elevated. Cheung et al recently studied the presence of ret/PTC gene rearrangements in

Hürthle cell tumors and found that many expressed ret/PTC, and also had other evidence of a papillary cancer origin, including focal nuclear hypochromasia, grooves, and nuclear inclusions. Tumors with the ret/PTC gene rearrangement tended to have lymph node metastases, rather than hematogenous spread. Thus Hürthle cell tumors can be classified into Hürthle cell adenomas, Hürthle cell carcinomas, and Hürthle cell papillary thyroid carcinoma (24).

CHOICE OF OPERATIVE PROCEDURE

Surgical treatment often simultaneously finishes the diagnostic work-up, and initiates therapy. Which operative procedure is indicated when FNA is suspicious or indicative of cancer? (Table 1)

In FNA results classified as suspicious for malignancy have nearly 70-80% chance to be malignant, while an FNA indicative of papillary thyroid cancer is almost always true positive at final histology. Thus, we recommend total (or near-total) thyroidectomy as the initial surgical procedure in these categories, regardless of the size of the nodule. "Near-total" thyroidectomy refers to a procedure which intentionally leaves small portions of thyroid tissue near parathyroid glands or at the entry of the recurrent nerve into the larynx, and is associated with a reduction in possibility of hypoparathyroidism and nerve damage. It is frequently used when post-operative 131-I ablation of residual thyroid tissue is intended.

Some authors prefer lobectomy with frozen section examination in cases when the FNA reveals follicular"neoplasm" (the term implying a new abnormal growth, but not declaring its malignant potential). It must be noted that frozen section carries a significant rate of false negative diagnosis, compared to final histology from paraffin sections. If the diagnosis is positive at final histology, a second operation for completion is generally recommended if lobectomy or sub-total thyroidectomy was initially performed. For these reasons, we prefer total (or near-total) thyroidectomy in these cases.

Table 1 **Suggested Surgical Procedures in Thyroid Cancer**

TYPE	**Clinical Class+**	**OPERATION**
Papillary, Follicular	**I**, <1cm	Lobectomy +/- contralateral STT* (if a < 1cm tumor is detected in a resected specimen, do not reoperate)
Papillary, Follicular	1cm, >1cm, or multicentric, or post-irradiation	NTT** or TT , assessment of possible nodes, primarily in the central compartment
Papillary, Follicular	**II**,+ neck nodes by US or FNA pre-op, or at operation	NTT + MND***
Papillary, Follicular	**III**	Resection without mutilation
Papillary, Follicular	**IV**	Resection without mutilation

TT = intended total thyroidectomy; * STT = Subtotal thyroidectomy; ** NTT = Near-total thyroidectomy; *** MND = Modified neck dissection; +for Clinical Class, see Table 3

Among patients with papillary cancer within the gland, some will have cervical lymph node involvement and others will have no obvious spread. The utility of prophylactic central neck

dissection is controversial. Some authoritative centers are in favour, but others, including the authors of this chapter, prefer to perform central neck dissection only when there is a preoperative evidence of lymph node metastases at US, or intraoperative evidence. The same attitude seems indicated for lymph node dissection of other node chains. Whenever a patient treated with lobectomy is found to have a cancer at final histology (sometimes unexpected), the question arises, whether to perform completion thyroidectomy? The indication of several guidelines (25) are in favour of completion thyroidectomy, with the exception of patients with unifocal, small, intrathyroidal, papillary thyroid cancers without evidence of lymph node metastases.

The approach proposed here, is based on several observations. Multicentric involvement is reported to range from 25 to 90%. The wide variation of multicentricity (or intraglandular dissemination) can be explained in part by the finding that the incidence of multicentricity is doubled if one does whole gland histologic sections. There is little or no relationship between the size of a solitary nodule and the incidence of intraglandular dissemination, but an increasing degree of histologic malignancy is associated with the frequency of dissemination. Many extensive studies including those of De Groot et al (26), Mazzaferri et al (18), and Samaan et al (27) supported this procedure. Hay et al. evaluated the efficacy of different surgical approaches to treatment of patients with low risk papillary carcinoma at the Mayo Clinic and concluded that more extensive surgery was not associated with lower case specific mortality rates, but was associated with a lower risk of local regional recurrence. Their data supports the use of bilateral resection as the preferable initial surgical approach (28). Total thyroidectomy carries an increased risk of hypoparathyroidism, recurrent nerve damage, and the necessity for tracheostomy (29). Accidental unilateral nerve damage may reach 5%, but fortunately bilateral injury is rare (30). All surgeons attempt to preserve those parathyroid glands that can be observed and spared, and an attempt is typically made to transplant resected glands into the sternocleidomastoid muscles. Reports range from 1 to a 25% incidence of hypoparathyroidism after total thyroidectomy (15, 31).

TUMOR STAGING AFTER SURGERY

Tumor staging, intended to predict the risk of death or recurrence and guide further therapy, can best be done after initial surgical treatment. The most used staging system is the TNM Staging system which combines simplicity with rather good predictive power (Table 2). Several other staging systems have been developed. The Clinical Class system (Table 3) developed at the University of Chicago classified tumors only on the extent of disease (32), but was found to predict outcome.

Table 2

TNM System of Tumor description and staging developed by the AJCC and UICC

	Definition	
T1	Tumor diameter 2 cm or smaller	
T2	Primary tumor diameter >2 to 4 cm	
T3	Primary tumor diameter >4 cm limited to the thyroid or with minimal extrathyroidal extension	
$T4_a$	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve	
$T4_b$	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels	
TX	Primary tumor size unknown, but without extrathyroidal invasion	
N0	No metastatic nodes	
$N1_a$	Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)	
$N1_b$	Metastasis to unilateral, bilateral, contralateral cervical or superior mediastinal nodes	
NX	Nodes not assessed at surgery	
M0	No distant metastases	
M1	Distant metastases	
MX	Distant metastases not assessed	
Stages		
	Patient age <45 years	*Patient age 45 years or older*
Stage I	Any T, any N, M0	T1, N0, M0
Stage II	Any T, any N, M1	T2, N0, M0
Stage III		T3, N0, M0
		T1, $N1_a$, M0
		T2, $N1_a$, M0
		T3, $N1_a$, M0
Stage IVA		$T4_a$, N0, M0
		$T4_a$, $N1_a$, M0
		T1, $N1_b$, M0
		T2, $N1_b$, M0
		T3, $N1_b$, N0
		$T4_a$, $N1_b$, M0
Stage IVB		$T4_b$, Any N, M0
Stage IVC		Any T, Any N, M1

Table 3- Clinical Class description-

I- Intrathyroidal tumor
II-Positive neck nodes
III- Fixed nodes or invasive tumor in the neck
IV- Distant metastases

Several systems are modified to include known risk factors including age, sex, histology, or genetic analysis. The EORTC classification proposed by the European Thyroid Association is based on age, sex, histology, invasion, and metastases (33). The modified AMES classification includes data on age, extent and size of primary, distant metastases, and DNA ploidy (34). MACIS includes data on age, invasion, metastases, size, and completeness of surgery (35). All of the systems, reviewed by Wong et al (36), appear to be effective in categorizing patients into largely similar low and high risk groups. Invasive disease, metastases, age over 45, and tumor size >4 cm are features placing patients into the high-risk category.
Most recently groups have recently established new criteria for delayed risk assessment based on pathological features combined with clinical features and with the response to initial therapy. Patients in apparent complete remission at follow-up after initial treatment may be defined as low risk, regardless of the initial risk stratification obtained soon after surgery (37). An Italian

study (38) assigned patients to low or high risk group at the moment of the first evaluation done 8-12 months after surgery and radioiodine ablation (if performed). Patients free of disease (negative neck US, undetectable basal and stimulated serum TG and no other evidence of disease) were classified at low risk. Patients with any evidence of persistent disease (including detectable TG) were considered at high risk of recurrence. The authors demonstrated that nearly half of the patients could be shifted from the high risk category (at the time of surgery) to the low risk category. The system was named **Delayed Risk Stratification (DRS).** One advantage of these delayed risk stratification systems is that they give an estimate of the risk of recurrence which is not considered in the TNM classification. Whether these systems actually alter therapeutic plans, which naturally evolve as treatment progresses, is uncertain.

TSH SUPPRESSIVE/REPLACEMENT THERAPY

After operation all patients are kept on TSH-suppressive thyroid hormone therapy with l-thyroxine.

Individuals with known cancer receive therapy aimed at a TSH around 0.1 µU/ml. Pushing TSH below this level has not been associated with better outcome, while over-suppression has been associated with more frequent side effects from clinical or subclinical hyperthyroidism, which is often partially mitigated by beta-blockers. Patients who are considered free of disease, have their replacement lowered to provide a TSH in the low-normal range,

RAI 131-I ABLATION

Most patients who have had a "total" thyroidectomy, and all patients who have had a subtotal resection, will have some functioning thyroid tissue remaining in the normal position after surgery, and will thus be candidates for 131-I ablation. This is done to remove any possible residual tumor in the thyroid bed (thyroid ablation), to make subsequent scans and TG assays more interpretable, and (hopefully) to kill tumor cells elsewhere (adjuvant therapy). There is no unanimity regarding the use of postoperative 131-I ablation in Stage I tumors, since absolutely convincing evidence of its value is lacking (15, 39). But for all patients with papillary and follicular cancers as a group, 131-I ablation correlates with improved survival (13). Our data demonstrated that postoperative 131-I ablation correlated with decreased recurrences for all patients with papillary cancers over 1 cm in size. Samaan et al (27), in a review of 1599 patients, observed that 131-I treatment was the most powerful indicator for disease-free survival.

Ablation after total thyroidectomy can be accomplished in most instances by one dose of 30 mCi (1.1 GBq) 131-I, giving the patients about 10 whole body rads (40). In our practice 80% of patients are ablated successfully with one dose of 30mCi, and the remainder require repeat therapy at the time of their second scan. Other clinicians find this dose insufficient, and give 50-150 mCi (1.85- 5.55 GB) as an inpatient treatment where regulations mandate. In part this difference may depend upon the surgeon, since small remnants of residual thyroid are more easily ablated than large amounts of residual tissue. Low dose (30 mCi) ablation of thyroid tissue after near-total thyroidectomy was recently reviewed by Roos et al. Surveying many studies, they concluded that 30 mCi was as effective as larger doses in inducing ablation, and since it could be administered without hospitalizing the patient, was an appropriate treatment (41). It also minimizes radiation exposure, and damage to the salivary glands. Doses of 100 mCi (3.7 GB) may provide more certain ablation with one dose (although at the expense of greater patient radiation) but there is little difference between ablation rates with doses of 30-75 mCi. There is no data proving that one method or the other provides superior results in terms of survival. We do not routinely use ablation in patients under age 21 with tumors under 1 cm. Patients with tumors above this size, older patients, or those with multicentricity, positive cervical lymph node metastases or a history of neck irradiation are advised to take 131-I. This practice, followed in many clinics, conflicts with some guidelines, as noted below. It has, not

surprisingly, been difficult to prove that the addition of RAI ablation reduces mortality in low-risk papillary thyroid cancer, which already has a 20 year survival rate of >95%. However the treatment makes follow-up more precise and reliable by the absence of residual thyroid tissue on scans and ultrasound, by a TG that should be at or below the limit of detectability, and the reassurance to the patient that the tumor is gone. And there are effectively no reported adverse effects of a 30 mCi dose of RAI in the absence of pregnancy.

The indications for thyroid ablation, based on levels of evidence have been detailed in recent ATA guidelines (25). Three groups of patients are identified, one (at very low risk of recurrence) in which thyroid ablation is felt not indicated due to the lack of evidence of benefit; a second group where the benefit, if any, are not evidence based. In this group, ablation was suggested in selected cases according to the judgement of the treating physician. Finally, a third group, including high risk patients, in which ablation has a strong indication based on good evidence that it may reduce cancer recurrence and possibly deaths.

Irrespective of the protocol and the dose used for ablation, there is always a subgroup of about 20% of patients that will not be successfully ablated with the first RAI course. The factors associated with ablation failure are not fully understood. Ablation failure does not correlate precisely with the dose, with the levels of TSH stimulation, the amount of thyroid residue or the level of urinary iodine excretion (42). In particular, it is not certain whether the use of doses higher than 3.70 GBq (100 mCi) would result in any additional benefit, or whether there is a 'stunning' effect of a diagnostic dose of 131-I on the subsequent ablation rate, although unlikely to occur. A retrospective analysis was performed of all patients (n=389) with well-differentiated thyroid cancer treated at our institution between 1992 and 2001. The therapeutic dose was the only variable found to be associated with success (odds ratio, 1.96 per 1.85 GBq (50 mCi) increment). Our results confirm the presence of a significant percentage of ablation failures (24.4%) despite the use of high ablative doses 3.70-7.40 GBq (100-200 mCi). Higher therapeutic doses are associated with higher rates of successful ablation, even when administered to patients with more advanced stages. Higher diagnostic doses were not associated with higher rates of ablation failure. (43).

The utility of radioactive iodide treatment of patients with papillary and follicular cancer was recently reviewed in a series of articles by Wartofsky, Sherman, and Schlumberger and their associates. Schlumberger concludes that routine radioactive iodide ablation is not indicated in patients with differentiated thyroid carcinomas of less than 1.5 cm in diameter, and advocates restricting RAI ablation to patients with poor prognostic indicators for relapse or death (44). Wartofsky points out a secondary benefit of postoperative low dose 131-I ablation in that, for many patients, it provides a high degree of certainty and peace of mind when subsequent scans are negative and TG is undetectable. Another argument for radioactive iodide ablation and early detection of any recurrence is the data presented by several groups, including Schlumberger and colleagues, that there is a reciprocal relationship between the success of cancer therapy and the size and duration of the lesions.

In patients with TNM Stage II to IV disease, we proceed to destroy all residual thyroid and to treat demonstrable metastases if they can be induced to take up enough 131-I. Use of 131-I therapy is investigated in these patients, regardless of the histologic characteristics of the resected lesion, although significant uptake less frequently is found in Hürthle tumors (23,45) or in patients with anaplastic lesions.

PREPARATION FOR 131-I ABLATION

For many years the standard approach has been to induce hypothyroidism prior to the ablative dose in order to raise TSH to approximately 25-30 uU/ml or greater and stimulate uptake of RAI in residual thyroid or tumor. This may be done by simply leaving the patient without T4 therapy for 3 weeks post op, or at any time. Alternatively patients can be given thyroid hormone suppressive therapy for 6 weeks or so after operation, so that any malignant cells disseminated at the time of thyroidectomy will not be stimulated by TSH. The value of this approach is admittedly unknown. Patients then receive 25 µg L-T3 bid for 3-6 weeks, and therapy is then stopped for 2 weeks to allow endogenous TSH (which may reach 20-60 µU/ml) to stimulate uptake of the 131-I by the remaining fragments of thyroid tissue or metastatic lesions in the neck or elsewhere before proceeding with 131-I therapy. These procedures can induce severe hypothyroidism just before scanning, and this is a significant problem and hazard.

An alternative for the initial ablation or later follow-up is the "half-dose" protocol (46). Half the usual dose of thyroxine is given for six weeks. TSH is tested in the fifth week, and if over 20 uU/ml, scanning is done in the sixth week, or preparation is prolonged if needed. On this protocol patients usually feel quasi-normal and conduct normal activities, in contrast to their function during total hormone withdrawal. On the half-dose protocol, fT4 falls to just below normal, and TSH on average reaches about 60uU/ml in the sixth week. Patients who start with TSH below 0.1 uU/ml may take longer to reach a satisfactory level for Tg testing, which is generally considered to be with TSH at least 30 uU/ml.

Many physicians find it useful to have the patient follow a low iodine diet for 2 weeks prior to the planned treatment in an effort to boost RAIU in the remant or tumor.

Stimulation with Recombinant human TSH --During induced hypothyroidism, patients may experience a wide range of hypothyroid signs and symptoms which may be severe and may result in a substantial impairment of the patients' lives and ability to drive and to work, and occasional tumor growth. Recombinant human TSH (Thyrogen®) has been developed to meet the need for safe, adequate exogenous TSH stimulation in patients with papillary and follicular thyroid carcinoma. The TG level reached after rhTSH stimulation is generally lower than that obtained after thyroid hormone withdrawal, and RAI uptakes in patients undergoing hormone withdrawal are higher, indicating that withdrawal provides a much greater and more prolonged stimulus to thyroid or tumor tissue. However, the diagnostic results are nearly equal. Quality of life is better using rhTSH preparation than during hypothyroidism induced by total thyroid hormone withdrawal, and side effects are minimal. Clinical trials have shown that rhTSH is an effective and safe alternative to thyroid hormone withdrawal during the post-surgical follow-up of papillary and follicular thyroid cancer, although not as sensitive as scanning after hormone withdrawal in some patients. Another factor to consider is the cost, which is roughly $ 2000 per treatment, although for the majority of patients in the USA this is covered by insurance. A few patients have been reported with metastases demonstrated on withdrawal scans that were not evident on rhTSH scans (47). A more prolonged stimulation of residual tissue may be necessary in some instances. It has been found that rhTSH administration induces a reduction of serum vascular endothelial growth factor, even in the absence of thyroid tissue (48). The clinical significance of this observation, if any, is unknown, but it does imply possible action of rhTSH on receptors other than in thyroid tissue. Use of rhTSH in managing thyroid cancer has recently been extensively reviewed (49). Thanks to many studies confirming the properties of rhTSH in stimulating iodine uptake and TG production, rhTSH is now considered an accepted alternative method of preparation for both thyroid ablation and post-surgical follow-up in patients with any form of differentiated thyroid cancer. After any planned period of dietary iodine restriction, two doses of rhTSH are given when the patient is on replacement treatment, and TG assay, dosing

for scan or treatment is done 24 hours after the second injection, and scans are done 48-72 hours later.

Diagnostic scans before first ablation are no longer routinely indicated according to several groups and ATA guidelines (25), based on the evidence that they do not offer additional information compared to the post-therapy scan and based on the possibility of stunning. However some authors point out that pre-ablation or pre-therapy scans can reveal unknown disease that may indicate increased treatment dose requirement, or lack of iodide uptake due to non-functioning or eradicated tumor tissue, which would preclude doing a treatment, or lack of uptake due to unexpected high iodine intake by the patient. If one intends to scan, the usual scanning dose should be no higher than 1-2 mCi 131-I, which has not been shown to induce stunning. 123-I can also be used to reduce radiation, but has a short half-life. Scans should be read at 48 or 72 hours, when body background has diminished. If TSH is sufficiently elevated the initial scan can reveal distant metastases as well as residual thyroid gland. If large thyroid tissue remnants are present, TSH may not become very elevated after hormone withdrawal, but will do so after the first ablation dose. Excess iodine intake in any form, including contrast studies, may suppress RAIU for weeks and should be considered, and avoided,

Some physicians proceed without prior scanning directly to 131-I ablation 2-4 weeks after surgery and perform a post-therapy scan 5-7 days later. Presumed benefits of this approach are patient convenience, less expense, and avoidance of possible thyroid "stunning" by the scan dose. In fact, as noted above stunning has not been demonstrated with the 2mCi 131-I dose. Arguments for doing a pre-ablation scan include finding out the actual percent uptake of the treatment dose in the neck and elsewhere to be considered when counselling about radiation safety required isolation periods, establishing if in fact there is uptake, and recognizing disease that may dictate a larger initial dose. The final word on these different approaches is not in.

It is useful to measure urinary iodine prior to scan or treatment since if elevated significantly (above 500ug/day, especially if >1mg/day) iodine uptake in thyroid or tumor may be suppressed.

Patients with Class I and in many with disease who are under age 45 are given 30 mCi as an out-patient treatment. Older Patients with Class II, III or IV disease are given doses of 75-100 mCi, in some states necessitating inpatient treatment. A post-therapy whole body scans should be mandatory 5-7 days after the ablative dose of 131-I (or after therapeutic doses), since occasionally unsuspected metastasis may be visualized on scans at this time changing the stage of disease and modifying the risk of reoccurrence or death. A stimulated baseline serum TG is always measured at the time of 131-I therapy. At 24 hours after initial ablative treatment, we replace hormone therapy at the prior dose.

OPTIONS IN FOLLOW-UP SCANS AND TREATMENT-INCLUDING RECENTLY DESCRIBED VARIATIONS

After surgery and thyroid ablation, the first important time for follow-up is between 8 and 12 months after initial treatment. At this time we want to understand whether the patients have evidence of complete remission or some evidence of persistent or recurrent disease. In the past, the conventional preparation for follow-up was to obtain a diagnostic total body scan with 131-I after induction of hypothyroidism, with the same methodology as described for ablation, in order to stimulate uptake of 131-I by residual thyroid tissue or tumor cells and production of TG. In recent years it has become common to omit the diagnostic scans after initial ablation, at least in patients deemed to be at low risk, and relying on measurement of stimulated (after rhTSH

administration) serum TG when anti-Tg antibodies are negative (25). In patients known to have residual disease because of elevated baseline TG or ultrasound evidence of metastatic lymph nodes, therapeutic 131-I is often given without preliminary scanning. In several large series, it was demonstrated that at this time of the follow-up, more than 80% of the patients will have evidence of complete remission (negative neck US and undetectable stimulated serum TG levels). These patients do not require additional tests or imaging and their suppressive hormone therapy should be shifted to replacement targeting serum TSH in the low-normal range. In subsequent years, the chance of these patients to have a recurrence is extremely low (<1%) and thus their follow up should be based on basal TG measurement and neck US once a year. On the contrary, when neck US is positive for local disease, or the basal or stimulated TG is elevated the patient should be screened for the localization of the disease and treated accordingly. Exactly what TG level is "elevated" is a shifting target, and depends on the local assay and experience. TG >2 ng/ml after rhTSH or withdrawal of hormone has been one standard. Possibly, with assays now accurate below 0.1ng/ml, a basal or suppressed TG > 0.5-1ng may be considered abnormal. Whether this approach, which essentially eliminates follow-up WB scans in low risk patients, provides satisfactory long-term outcome, is yet to be determined.

FOLLOW -UP TREATMENT BASED ON TG ASSAYS

As assays for thyroglobulin (TG) have become more sensitive and reliable, measurement of TG assumes more and more importance in determining the management of patients followed after thyroidectomy and radioactive iodide ablation treatment for thyroid cancer. Serum TG levels, in the absence of antibodies interfering in the assay, correlate well with tumor burden, although detectable tumor can exist even in the presence of negative TG assays in individuals who are on suppressive doses of thyroid hormone (50). It is proposed that diagnostic 131-I whole body scans can be avoided in patients with undetectable levels of stimulated TG after initial ablation, and that the patients can be monitored with clinical examination, ultrasound, and serial TG measurements on thyroxine treatment during the subsequent follow-up

However, some concerns with this approach have been noted. Mazzaferri and Kloos (51) retrospectively studied 107 patients who were "clinically free of disease" and had undetectable or very low serum TG levels during thyroid hormone therapy. The TG levels on treatment were all 1 ng/ml or less, and 95% were under 0.5 ng/ml in their assay, which was a commercial (Nichols Institute) chemoluminescent antibody assay. In response to the administration of two doses of recombinant TSH and assay of TG on samples taken on the fifth day, 20% were found to have a TG value above 2, with values ranging up to 18 ng/m, and many of these patients ended up with additional 131-I therapy. However, the authors found that diagnostic, pre-ablation radioactive iodide whole body scans often failed to localize the source of the elevated TG, which was found only in post-therapy scans or by other imaging methods. This study suggests that even with a TG level below 1 while on replacement therapy, persistent disease may sometimes be present and be detected by stimulation using recombinant TSH or thyroid hormone withdrawal.

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Wartofsky (52, 53) comments on these studies and supports the idea that TG testing, both on suppression and after TSH stimulation, can help in determining therapy. He suggests that, in patients with a serum TG <0.5ng/ml on suppression, and in a low risk category, that stimulation by recombinant TSH and measurement of TG, rather than scanning, is satisfactory. If the TG remains <1, the patients can be evaluated annually with such a stimulation test. In patients with slightly higher TGs, up to 2, he suggests measuring a recombinant TSH stimulated TG, and scanning. In patients with higher TGs, he suggests that thyroid hormone withdrawal and

radioactive iodide treatment, without initial scanning, may be appropriate. In a study done by the rhTSH-Stimulated Thyroglobulin Study Group (54) and published in 2002, a cut off level of 1 ng/ml for stimulated TG was taken as the safe level for patients with low risk. This group would presumably be monitored by repeat rhTSH stimulated TG assays rather than scans. It is of interest that in this study 14 of the patients with stimulated TG <2ng/ml underwent isotope scanning and 9 were positive. Five had uptake outside the thyroid bed. This group suggests that patients with stimulated TG above 2 would have subsequent thyroid hormone withdrawal and possible 131-I therapy without scanning. A recent "consensus" statement by a group of thyroidologists also supports the categorization of patients into high and low risk groups, and use of TG as described above for following low risk patients (55). Whether this approach, with omission of whole body scans, has any adverse effect on long term outcome is not yet known.

Another option coming "on-line" is the use of ultra-sensitive TG assays (in patients without anti-TG antibodies) since the information appears to partially substitute for rhTSH stimulated TG assays. Several reports indicate (56) that, when using assays with detectability to 0.1ng/ml, an undetectable TG is associated with complete remission in almost all case and may safely be substituted for a TG stimulation test. Detectable values, even if under 0.5ng/nil, probably should be supplemented by a stimulated TG.

TREATMENT USING EMPIRICALLY DETERMINED DOSES OF 100- 150MCI FOR METASTATIC DISEASE

Patients who have significant uptake of 131-I in distant metastases (usually above 0.5% of the tracer) are given 150-250 mCi 131-I. This dose can be tolerated without acute radiation sickness, and is below the level that would promote pulmonary fibrosis if diffuse pulmonary metastases are present, unless uptake in the lungs exceeds 50% (see below). Although use of these empirically derived doses is the most common practice, some centers do careful dosimetry with a tracer dose of 131-I prior to therapy, in order to judge the appropriate, or maximal safe, dose. This requires 2-5 days of observation. The methodology and results have been recently discussed (57). Whether administration of maximally large individual doses is more effective than use of somewhat smaller doses of 131-I has not been established. In perhaps four-fifths of patients accumulating 131-I, it is possible to administer a dose of RAI that should be useful in destroying tumor. For normal thyroid tissue 10,000-15,000 rads is destructive, and a dose of 20,000 rads or more is probably needed for therapy of cancer. Assuming, for example, a standard 150 mCi 131-I dose, and delivery to tumor of about 100 rads per micro Curie retained per gram, a 1% tumor uptake distributed through 10 g of metastatic tissue could provide an effective treatment.

Some groups have attempted to measure tumor volume by use of quantitative I-124 PET scanning if available (58). The effective half-life can be determined from serial counts of the tracer over the metastasis. If 10 g of tumor in the neck accumulated 1% of a 150 mCi dose, and isotope turnover in the tumor was extremely slow, the radiation dose might be as follows: Rads =74 X 0.19 X 150,000 X 0.01 X 6/10= 12,654 rads.

The question of whether a sub-cancericidal doses should be delivered in patients with low levels of tumor isotope accumulation needs further investigation, since radiobiological studies suggest that radiation could preferentially spare the more radio resistant cells, ultimately leaving a more lethal tumor while cumulative exposure to the bone marrow and salivary glands may reach morbidity inducing levels. It may be possible to give conventional x-ray therapy after 131-I in those instances in which 131-I uptake is present but the total dose delivered to the metastasis is less than adequate (59). This procedure may provide another therapeutic approach to the thyroid cancer patient, but it has not yet been given adequate trial. Maxon et al (60) report that

radiation doses of at least 30,000 rads for thyroid ablation, and 8,000 for therapy to metastasis, improve the rate of response.

It is useful to do a scintiscan on patients who have received therapeutic doses of 131-I at 5 - 7days following the treatment, thus using the treatment dose as a more powerful and sensitive scanning dose. While often offering no new information (which may be reassuring to the patrient), this may also reveal unsuspected metastasis, especially in younger patients who have previously had 131-I treatment. Fatourechi et al found that 13% of follow-up scans demonstrated abnormal foci of uptake not seen on diagnostic scans, and changed management in 9% of their patients (45, 61).

The 131-I treatment cycle is repeated at 24-52 weeks, as long as there is no evidence of systemic radiation damage, and as long as the metastases continue to accumulate iodide**.** The total cumulative 131-I dosage may vary from 150 to (rarely) 2,000 mCi (74GB). Both papillary and follicular cancers respond to 131-I therapy. Small metastases from papillary cancer, especially if functional in the lungs but not large enough to be visualized on X-ray, are typically cured. Follicular tumors often have relatively few metastases and high uptake, thus seem ideal targets for therapy. However portions of the metastases, especially in bone, often appear to be resistant and finally continue growth despite 131-I treatment. Nevertheless 131-I therapy is beneficial even in advanced and aggressive tumors. Pelikan et al report their experience on the use of radioactive iodide in treating advanced differentiated thyroid carcinoma and report that up to 50% of patients who have distant metastases can be cured by 131-I therapy (62). Aggressive high dose radioiodine therapy has been advocated for treatment of advanced differentiated thyroid cancer by Menzel and colleagues. These physicians gave repeated doses of 300 mCi (11.1 GBq 131-I) with mean accumulated total activities of, on average, 55 GBq (1500 mCi) per patient. Repetitive high dose therapy appeared beneficial in the majority of patients with papillary carcinoma, but the majority of follicular thyroid cancer patients had progressive disease despite treatment (63).

The National Thyroid Cancer Treatment Cooperative Study Registry Group recently evaluated the therapy of high risk papillary and non-Hürthle cell follicular thyroid carcinoma. The study confirmed the utility and benefit of radioactive iodide therapy to reduce recurrence and cancer-specific mortality among patients in the high risk group (64). Pittas et al. (65) reviewed an extensive series of 146 patients with documented bone metastasis from thyroid carcinoma seen at Memorial Sloan Kettering in New York City. Bone metastases were most common in vertebrae, pelvis, ribs, and femur, and multiple lesions were present in more than half the cases. Overall ten year survival rate was 35%, and from diagnosis of initial bone metastasis, 10 year survival was 13%. Favorable prognostic signs for survival included radioiodine uptake by the metastases and absence of non-osseous metastases. Hürthle cell cancers had a favorable response to treatment, rather surprisingly, whereas undifferentiated thyroid tumors fared the worst.

Arterial embolization has been combined with radioactive iodide treatment for management of large bone metastasis from differentiated thyroid carcinoma with apparent improvement in effect over the use of radioactive iodide alone. In the study by VanTol et al, (66) embolization was not accompanied by any severe complications.

rhTSH is now available for routine use except for high-risk patients, and allows 131-I therapy without induction of hypothyroidism (67). This can increase acceptance of scanning and therefore increase the frequency of diagnostic procedures. Iodide depletion by dietary control

and diuresis, including furosemide or mannitol administration, can also double the fractional uptake of 131-I in metastases (68, 69). Finally, when the diagnostic scan shows no 131-I uptake, even with TSH, the potential benefits from this mode of therapy have probably been exhausted. However, before giving up on 131-I therapy, some authors suggest using empiric 100-150mCi doses of 131-I and obtaining a post-therapy scan, which in some cases may show areas of uptake not seen in the diagnostic scan (see below).

HIGH DOSE RAI THERAPY FOR INVASIVE OR METASTATIC DISEASE

Ablation of thyroid tumors of follicular cell origin with high doses of RAI is a common procedure. Initially heralded as a panacea, it has proven otherwise, although useful.

Efficacy and morbidity of high activity 131-I therapy was assessed in 38 patients with locally advanced or metastatic differentiated thyroid cancer (16 follicular, 20 papillary, one Hürthle cell, one insular) who were treated with high activity radioiodine therapy (9 GBq [250 mCi]) as the cancers had previously not responded to standard activities of 5.5 GBq (150 mCi). After high activity treatment, 9.7% of patients suffered grade 3 and 3.2% suffered grade 4 WHO hematological toxicity. Significant salivary gland morbidity was observed (30% dry mouth, 27% salivary swelling). In this study repeated treatment with high activity (9 GBq) in patients with advanced differentiated thyroid carcinoma appeared to be of no apparent benefit but led to late morbidity (359). However, other investigators have differing results. A retrospective analysis was conducted on 124 differentiated thyroid cancer patients who underwent dosimetric evaluation over a period of 15 years. One hundred four RAI treatments were performed. A complete response at metastatic deposits was attained with absorbed doses of >100Gy. No permanent BM suppression was observed in patients who received absorbed doses of<3Gy to BM. The maximum administered dose was 38.5 GBq (1,040 mCi) with the BM dose limitation. Dosimetry-guided RAI treatment allowed administration of the maximum possible RAI dose to achieve the maximum therapeutic benefit. Estimation of tumor dose rates helped to determine the curative versus the palliative intent of the therapy (71).

131-I THERAPY WITH "NEGATIVE" SCANS

In some patients tracer studies fail to show uptake, but serum TG is elevated (with or without stimulation). Some investigators recommend treating these individuals with large doses of 131-I (100-150 mCi) and report that tumor uptake can be visualized after treatment, and that serum TG may fall (72, 73). The clinical efficacy of this approach is not known. In a few cases reported by Schlumberger et al. (74) and Pineda et al. (75) TG became undetectable, which clearly was a striking and hopeful result. As of this date, there is no data demonstrating that this treatment approach improves prognosis (377).

The utility of radioactive iodide treatment of patients with papillary and follicular cancer was recently reviewed in a series of articles by Wartofsky, Sherman, and Schlumberger and their associates (44). Sherman and Gopal analysed the use of 100 mCi doses of 131-I for treatment of scan-negative TG-positive patients and conclude that this must, at this point, be considered an experimental procedure of uncertain benefit. They argue against its use in young patients with elevated although apparently stable TG values and without radiographic evidence of disease. Fatourechi et al. (77) analysed results of this treatment in a series of patients treated at the Mayo Clinic and concluded that it rarely produced significant effect, although it possibly helped stabilize disease in patients with micro metastases in the lung. It is clearly ineffective in patients who have metastases large enough to be detected on chest X-ray or CAT. Wartofsky et al. (44) suggest that, rather than initial treatment with 131-I of patients who are scan negative and TG-positive, thorough imaging studies are appropriate. These might include a CAT scan of the chest, an MRI of the neck, 99mTc-MIBI, 18-fluorine fluorodeoxyglucose PET scanning, 99mTc-tetrafosmin, or 201Tl thallium. Localization of malignant tissue by any of these means

may allow surgical excision or external radiotherapy. This series of articles provides many very useful thoughts on management of difficult patients with recurrent thyroid carcinoma.

MAXIMAL DOSE PROTOCOLS

The therapeutic protocol used at Memorial Hospital in New York, by Maxon (60), and as well at some other centers, has for years been designed to give maximal-tolerable radiation doses to cancer patients (12). The dose is calculated on the basis of prior isotope tracer kinetics. The aim is to give a blood dose of under 200 rads, or less than 120 mCi (4.4 GB) retained at 48 hours, or 80 mCi (30 GB) retained at 48 hours if diffuse lung metastases are present. This method has theoretical advantages since it potentially provides the most cancericidal dose, but the difficulties of calculating the dose and the occasional adverse reactions have so far prevented this method from being generally employed. The dosimetric approach has been carefully reviewed by Van Nostrand et al (55).

RADIATION PRECAUTIONS

Before radiation therapy, female patients should be carefully screened for pregnancy and lactation. Confirmed or possible pregnancy constitutes an absolute contraindication to therapy because of the risk of damage to the fetus. A patient who has ingested many millicuries of 131-I can cause serious radiation contamination, and appropriate precautions must be followed. If less than 30 mCi 131-I is given, it is permissible to have the patient dispose of urine and feces into general sewage in most regulatory jurisdictions. If amounts of 131-I greater than 30 mCi are given, and in some states the patient may need be kept in a private room in the hospital until less than 30 mCi is retained in the body. Urine can be directly disposed in sewage, or can be collected by the patient and stored in bottles behind protective lead shielding. After physical decay, usually after about 6 weeks, it may be discarded in the sewage. Contaminated bedding and utensils should be stored for 10 half-lives (80 days), thoroughly washed, and monitored for residual contamination before being used again. Alternatively, disposable bedding and utensils may be used.

Table 4. Radiation Exposure to Personnel During Care of a Patient Who Has Received 100 mCi 131-I

Distance From Source – e.g The Patient	Reason for Exposure	Rate (mrad/hr)	Allowable Duration of Exposure Permitted on Basis of 0.1Rad/Week
1/2 in.	Direct handling of therapy dose or urine after therapy	136000	None
1 ft.	Giving personal hygiene to treated patient	240	0.5 hr/week
3 ft.	Making the bed, mopping the floor	27	5.0 hr/week
9 ft.	In chair across the room	3	50.0 hr/week allowable exposure cannot be reached

Personnel caring for a patient who has received 131-I therapy are often concerned about exposure to excessive radiation. This is almost never a real problem. Isotope can, at a practical level, only be passed from the patient to another person via saliva or urine. Monitoring by means of a portable counter is important in making certain that no person receives more than

an allowable radiation dose from the isotope in the patient's body. Table 4 gives a rough estimate of the amount of radiation received while performing ordinary hospital tasks at various distances from a patient who has received 131-I. In general, all ordinary patient care can be performed without hazard. It is best to avoid close contact between hospital personnel and patient during the first 48 hours after therapy because of undue apprehension that may be induced. However, even after doses of up to 100 mCi (3.7 GB), normal personal activities such as eating at the same table, or driving in the same car, carry no risk to others.
The US Nuclear Regulatory Commission has published new guidelines which allow release of patients treated with isotopes from the hospital if the total effective radiation exposure from the treated person to any other individual is not likely to exceed 5mSv (0.5 rads). Grigsby et al (78) found that when using precautions such as those described above in a group of patients given on average about 100mCi 131-I, the exposure to other individuals in their household and to pets did not exceed this level. Guidelines for the optimal radiation protection after treatment with 131-I have been proposed by the American Thyroid Association (79) (WWW.THYROID.ORG) and offer much specific and useful advice.

RADIATION DAMAGE FROM 131-I THERAPY

The use of RAI in large doses is not without hazard. The radiation dose delivered to the whole body, the gonads, or bone marrow is usually assumed to be the same as that of the blood. The blood dose depends on the amount of isotope administered; its distribution space and turnover; the degree of heterogeneity of distribution in the tumor; the uptake, synthesis, and secretion of labelled compound by the tumor; and perhaps other variables. The radiation is usually largely due to inorganic iodide, since little protein bound (PB) 131-I ordinarily appears in the blood. Sometimes tumor destruction is such that much PB131-I appears in the blood and can yield a major fraction of the total whole body radiation dose. As a rough estimate, the blood, gonadal, or bone marrow radiation may be assumed to be 0.3 -1.5 rads/mCi 131-I administered (80), or 45-150 rads per treatment with 100 mCi. The genetic risks are discussed in www.thyroidmanager.org and are not reviewed here. Ordinarily, when 131-I therapy is needed for carcinoma, the necessity of treating the patient outweighs the risks of genetic damage.

Various unwanted effects of radiation may occur in patients receiving large doses of 131-I. Mild radiation sickness is seen. Metastatic deposits or surrounding tissues may become painful over 2-4 weeks from radiation-induced inflamation. Damage to the salivary glands can cause sialadenitis, and xerostomia, and can lead to loss of teeth (81). Increasing salivary flow following treatment may be partially protective. Ovarian function is often temporarily suppressed (82), and if there are pelvic metastases that collect 131-I, the gonads may receive a sterilizing dose. Sperm count may be reduced for months (83). Leukemia occurs with increased frequency in patients who have received large doses of 131-I (usually >600 mCi [22GB]) for cancer (217). Transient or permanent alterations in liver function and lymphoma of the parotid gland have been reported as possible sequelae (85). Pulmonary fibrosis has occurred in patients with functioning lung metastases who have received unusually large doses or who have very active metastases (86). Leukopenia, thrombocytopenia, and anemia are encountered with accumulating doses. A mild effect on the bone marrow is seen with each therapeutic dose, and after several hundred kilocuries, aplastic anemia may develop (87). The hemoglobin level, white cell count, differential count, and platelets should be monitored periodically in order to judge recovery of the marrow between treatments and to prevent excess total radiation damage to the marrow. Large radiation doses may cause transient swelling of metastasis in the brain or spinal canal. Lin et al (88) recently reviewed pregnancies following 131-I treatment of well differentiated thyroid carcinoma among a group of 58 pregnant women and found no evidence of demonstrable adverse effects, but suggest that it would be wise to avoid pregnancy during the first six months after the last administration of 131-I. With the exception of possibly

increased rate of miscarriages which may have been due unstable thyroid function at the time of conception, no other adverse effect of radioiodine has been found on the outcome of 2113 pregnancies after radioiodine treatment and on their offspring (34).

Two special complications need be noted. Occasionally withdrawal of hormone suppression, in preparation for isotope therapy, leads to rapid growth of the tumor, and reinstitution may not seem to return the patient to the prior condition. Special care should be taken if metastases are present in areas such as brain or spinal column, where growth could cause serious sequelae. Glucocorticoids are occasionally given prophylactically in an effort to prevent tumor swelling in this situation.

Disseminated pulmonary metastasis can sometimes be eradicated by 131-I, but radiation pneumonitis or fibrosis may be produced and may be fatal (38, 86). On first observation of pulmonary metastases, this therapy should be considered, but no more than 75 mCi (2.9 GB) should ever be deposited in the lungs in one treatment. Progress of the lesion and pulmonary function should be carefully evaluated before and between treatments (89, 90-94). Occasionally patients present with locally advanced papillary thyroid cancer which is not surgically resectable. In some instances preoperative treatment with radioactive iodide sufficiently reduces the extent of the lesion to allow subsequent definitive surgery (94). One of the most informative studies regarding the effects and limitation of 131-I therapy is given by the series of the Institute Gustave-Roussy periodically updated by Schlumberger et al (95). In their most recent publication the authors report on 444 patients treated with 131-I for distant metastases and the results identified three groups of patients with different outcome after therapy: a group very likely to be cured after a few courses of RAI, represented by young patients with micronodular disease, usually in the lung; a second group whose metastases can be stabilized but not cured after more than 600 mCi (22 GB) as cumulative doses and a third group including older patients with macronodular disease, particularly in the bones, who do not respond to RAI and progress rapidly to exitus. It is apparent from this study that, continuing RAI therapy after 600 mCi usually has no benefit.

FOLLOW-UP OF CANCER PATIENTS: THE SERUM TG ASSAY.

After initial ablation patients are given TSH-suppressive doses of l-thyroxine. This therapy as dual aims: to replace the thyroid hormone function and to inhibit the growth of potential residual disease. Two to three months later serum TSH, free thyroid hormones and TG concentrations are measured during l-thyroxine treatment. The results of these tests will disclose whether the l-thyroxine dose is adequate in suppressing TSH levels without inducing thyrotoxicosis, but will give little information on whether the patient is in remission.To this purpose, the most informative follow-up period is at 6-12 months after initial treatment, when the ablative dose of radioiodine should have exerted its effect. At this point, the patients have been already attributed a risk estimate based on the results of the post-ablative WBS and serum TG measurement (96, 97. This information is important at the moment of the new evaluation. If uptake was seen outside the thyroid bed on the post-therapy WBS, the patient must be considered at high risk of recurrence or persistent disease, while if no uptake is seen outside the thyroid bed on the 131-I post-therapy scan, the Patient is considered at low-risk. The 6-12 month evaluation, consists of careful neck ultrasound to detect the lymph node status and serum TG levels (with negative anti-TG) after stimulation with exogenous (better) or endogenous TSH. These tests are considered by many authors as sufficient to confirm complete remission (negative US and undetectable stimulated TG). Others advocate the usefulness of a diagnostic WBS with radioiodine, aimed to ensure that thyroid ablation has been successful and to search for foci of 131-I uptake outside the thyroid bed. However, two independent studies (357, 99) have shown that this diagnostic WBS is almost always negative

(depending on criteria for positivity) thus adding very little information to that given by neck US and serum TG measurement.

The result of serum TG measurement is the most sensitive predictor of complete remission or persistent disease (provided that anti-Tg autoantibodies are negative) (100-104). Nearly all patients with local or distant disease have detectable or elevated serum TG levels, while patients in stable remission have undetectable serum TG concentrations. Compared to serum TG measurement, the yield of the diagnostic 131-I WBS is lower. A significant proportion of patients may have an elevation of serum Tg in the presence of a negative diagnostic WBS. A retrospective study by Cailleaux et al. (98) has shown that when serum Tg off therapy is undetectable, routine diagnostic WBS usually does not add any further information on the clinical status of the patient. Similar results have been obtained at the Department of Endocrinology, University of Pisa, (99) in a retrospective series of 315 patients who had undetectable serum Tg off l-thyroxine at the time of the first re-evaluation after thyroid ablation. None of these patients had evidence of disease activity at WBS, and 99.4% were in complete and stable remission after 12 years of follow-up. Only two patients (0.6%) had recurrence of lymph node metastases which were treated with radioiodine therapy. Based on these studies it is possible that in the future the need for 131-I scanning may be dictated by the results of serum TG during hypothyroidism or by rhTSH-stimulation
After this follow up, low-risk patients (those with an undetectable stimulated serum Tg, negative neck US and negative WBS, when performed) are considered as cured and may be followed with periodic serum Tg measurement during l-thyroxine therapy. Thyroxine therapy may be decreased to maintain a low but not suppressed serum TSH concentration (0.1-0.4 µU/ml). The risk of recurrence is in fact so low in these patients (representing more than 80% of the total) that overdosage of l-thyroxine is unjustified.

As noted the problem of antibody interference in the TG assay makes this test unreliable in 10-15% of patients. However another aspect of the antibodies should be remembered. If patients are free of thyroid cancer and the thyroid has been ablated, it appears that the antigenic stimulation necessary to maintain an anti-TG titer is gradually lost, and these antibodies disappear with a 3-6 year half-life (302). Thus, the level of anti-Tg antibodies may be used as a surrogate marker of disease. Other approaches, including the search of Tg mRNA in the blood, have been proposed, but none has entered general clinical practice. Fugazzola et al (106) point out that the combination of TG RIA and TG mRNA assay offer better positive and negative predictive value than TG alone. In some studies TG mRNA analysis has proven much less reliable than serum TG assay (107).

In high risk patients, even if considered cured, suppressive doses of l-thyroxine may be continued for some years, because the risk of relapse is greater. Pujol et al evaluated a series of patients over an average of 95 months and compared those who had TSH values constantly under 0.05 mU/l to those who had all TSH values greater than 1mU/l. A lesser degree of TSH suppression was associated with an increased incidence of relapse, with a shorter average relapse-free survival (108). This observation was not sustained in another study (109. The objective of suppressive therapy in these patients should be to attain a serum TSH level of 0.1 µU/ml or less with normal free T3. In this situation, side effects such as osteoporosis, are not observed (110). Clinical and biochemical evaluation is performed annually. If serum Tg becomes detectable during follow-up, the patient should be evaluated for the presence of disease by neck US, first, and by other imaging if neck ultrasound is negative. Some authors prefer to avoid this procedure and directly give a therapeutic dose of 131-I followed by a post-therapy scan. In the absence of uptake after therapeutic doses of 131-I, any further administration of 131-I is not justified, and the site of Tg production should be sought by other

imaging techniques. If 131-I thyroid ablation has not been performed or if the patient has undergone only partial thyroid surgery (subtotal or lobectomy), follow-up should consist of clinical and ultrasound examination and serum Tg measurement. However, in this case, the sensitivity and specificity of serum TG assay is lost. In such patients, any suspicion of persistent or recurrence disease should prompt a completion of the initial treatment with completion thyroidectomy and/or radioiodine ablation.

During follow-up, patients may develop isolated metastases that can be approached surgically. Osseous metastases, especially from follicular cancer, may require radiotherapy or operative procedures for stabilization. Progressive growth of soft tissue or osseous metastases that are not amenable to further suppression with thyroid hormone, 131-I therapy, or radiotherapy should lead to consideration of systemic therapies.

Radiation Therapy, Chemotherapy, Re-differentiation therapy, and use of biological response modifiers such as TKI inhibitors, are discussed elsewhere in this symposium.

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