

Review**Unresolved issues, dilemmas and points of interest in thyroid cancer: A current perspective****Nicholas J Sarlis¹, Loukas Gourgiotis²***¹The University of Texas – M. D. Anderson Cancer Center, Houston, Texas 77030, USA, and ²National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, USA***ABSTRACT**

Thyroid cancer (TC) is the commonest endocrine malignancy. In the overwhelming majority of cases, thyroid carcinomas are well-differentiated malignancies that respond favorably to treatment; however, this outcome cannot be absolutely guaranteed. The absence of large prospective randomized clinical trials in TC – due to its low incidence and protracted clinical course in cases with persistent/recurrent metastatic disease – results in considerable debates regarding the optimal treatment and follow-up regimens in this malignancy. Some of these debates originated several decades ago, yet are still ongoing despite interim advancements in other domains of oncology. Here we discuss what we believe are the issues of major controversy in TC; these are mentioned in the following non-exhaustive list: (i) the optimal management of solitary and multiple thyroid nodules; (ii) the role of basal calcitonin measurements in the diagnostic investigation of nodular thyroid disease; (iii) the extent of the initial operation after establishment of the diagnosis of TC; (iv) the intensity and frequency of radioactive iodine (RAI; ¹³¹I) therapies (especially in patients with persistent/recurrent metastatic disease); (v) the degree and duration of long-term thyroid hormone suppression therapy (THST) required for optimal outcomes in TC patients; (vi) the optimal management of patients with RAI-refractory disease or other “high-risk” clinicopathologic features; and, finally, (vii) the optimal algorithm for lifelong follow-up of TC patients after their initial treatment. We present elements of the above controversies as pertinent to the various types of TC. We have opted for breadth rather than depth of commentary, at the same time providing the reader with extended up-to-date bibliography.

Key Words: Thyroid cancer, Radioiodine, Thyroid hormone suppression therapy, Follow-up, Thyroid nodules, Calcitonin, Thyroglobulin, Thyroidectomy.

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INTRODUCTION

In this contribution, we focus on current controversies and dilemmas in thyroid carcinoma (TC). We categorize these, as yet unresolved, questions, dilemmas, and issues as relevant to TC biological behavior, diagnostic approach at the time of initial presentation, and clinical management (including antitumor

ABBREVIATIONS

ACTH	adrenocorticotropin
ATC	anaplastic thyroid cancer
BTA	British Thyroid Association (U.K.)
CCH	C-cell hyperplasia
CEA	carcinoembryonic antigen
CG-A	chromogranin-A
CNS	central nervous system
CRH	corticotropin-releasing hormone
CT	computed tomography
DSV	diffuse sclerosing variant
EBRT	external beam radiotherapy
FA	follicular adenoma
FAP	familial adenomatous polyposis coli
FDG-PET	¹⁸ F-fluorodeoxyglucose positron emission tomography
FMTC	familial MTC
FNAB	fine needle aspiration biopsy
FPTC	familial PTC
FTC	follicular thyroid cancer
FV	follicular variant
HCC	Hurthle-cell carcinoma
5-HT	5-hydroxytryptamine (serotonin)
IRMA/ICMA	immuno(radio/chemilumi)metric assay (for thyroglobulin)
LCH	Langerhans'-cell histiocytosis
MDACC	M. D. Anderson Cancer Center (Houston, TX)
MEN	multiple endocrine neoplasia
MIBG	meta-iodobenzylguanidine
MRI	magnetic resonance imaging
MRND	modified radical neck dissection
MSKCC	Memorial-Sloan Kettering Cancer Center (New York, NY)
MSO	malignant struma ovarii
MTC	medullary thyroid cancer
NCCN	National Comprehensive Cancer Network (U.S.)
NCI	National Cancer Institute (Bethesda, MD)
PET	positron emission tomography
PTC	papillary thyroid cancer
RAI	radioactive iodine; ¹³¹ I
rhTSH	recombinant human TSH
RIA	radioimmunoassay
SEER	Surveillance, Epidemiology, and End Results
SV	solid variant
TC	thyroid cancer; thyroid carcinoma
TCV	tall cell variant
Tg	thyroglobulin
TH	thyroid hormone
THST	thyroid hormone suppression therapy
T/NTT	total or near-total thyroidectomy
TSH	thyrotropin
U/S	ultrasonography
VIP	vasoactive intestinal peptide
WBS	whole body scan
WDHA	watery diarrhea-hypokalemia-achlorhydria syndrome

therapy and long-term follow-up). These points are presented for each pathologic type of TC, including rare malignancies. Throughout this review, we intersperse interesting, yet under-appreciated, management details (“pearls”) pertinent to each section. If the clinician who deals with TC patients (among others, the Endocrinologist, Nuclear Medicine specialist, Pathologist, Oncologist, Surgeon, and Radiation Therapist) pays due attention to these details, s/he could potentially improve therapy outcome and follow-up strategy design in selected TC cases, especially those of patients with “clinically aggressive” disease.

I. CONTROVERSIES IN TC DIAGNOSIS AT INITIAL PRESENTATION

The epidemiology, diagnosis, differential diagnosis, and treatment of TC are inextricably entwined with those of nodular goiter and other benign thyroid disorders. Thyroid nodules are common. Their prevalence in two population-based studies – Framingham, MA, USA, and Whickham, England, UK – was 4.2 and 3.2%, respectively^{1,2}. However, the true prevalence of thyroid nodules demonstrated at autopsy is much greater, i.e. up to 50% in subjects with “clinically normal” thyroid glands³. With the increased use of newer imaging modalities, such as high-resolution neck ultrasonography (U/S), the discovery of thyroid incidentalomas has become commonplace. In two studies where patients were evaluated with neck U/S for primary hyperparathyroidism, thyroid nodules were found in up to 46% of them^{4,5}. Furthermore, almost half of the patients presenting with a solitary clinically palpable thyroid nodule have additional nodule(s) detected by U/S; most of these are “unexpected” or occult lesions⁶. Several studies have shown that the risk of malignancy is the same in clinically obvious vs. occult (impalpable) thyroid nodules, i.e. around 5%-6%^{7,8}. These epidemiologic data can be a source of considerable anxiety for individual patients, despite the fact that clinically apparent TC remains a rather uncommon malignancy (in comparison with most other solid organ or head & neck malignancies). In the United States, according to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), TC prevalence in the general population is less than 0.1%. This statistic notwithstanding, clinically inapparent – or occult – TC, defined as a lesion smaller than 10 mm that is

unexpectedly found during autopsy or surgery, is quite common. The prevalence of “clinically silent” TC in North America averages 3.6%⁹, but rates as high as 36% have been reported in other countries^{10,11}, possibly related to differences in iodine sufficiency of the ambient diet and the differential effect of a variety of other factors, including population age and ethnicity.

From the above data, it appears that clinically occult TC has minimal clinical importance. The very same data pose the dilemma of optimal management of incidentally discovered thyroid nodules, given the fact that the size threshold—among experienced examiners—for palpation of thyroid nodules is 1.0-1.5 cm. Most experts advocate fine needle aspiration biopsy (FNAB) of all thyroid nodules larger than 1.0 cm^{12,13}. By applying the above criterion and assuming that ~40-50% of the population harbors inapparent thyroid nodules, as well as that ~30% of these nodules will be greater than 1.0 cm in size, one would then conclude that ~10-12% of the population could be candidates for a diagnostic FNAB. Theoretically, if all the above individuals were biopsied, and with an estimated 5% malignancy rate, up to 0.6%-0.7% of the general population could end up with a diagnosis of TC! This rationale could well create a public health conundrum, considering that the majority (>80%) of the TCs diagnosed in this manner would never become clinically significant during an individual’s lifetime. Therefore, it has been proposed that only nodules with certain ultrasonographic criteria should undergo FNAB. These criteria include: nodule size >1.5 cm, irregular margins, presence of microcalcifications, and an intranodular vascular pattern, the latter being assessed by Doppler color flow U/S techniques¹⁴. Additional studies that focus on the optimal management of nodules that do not meet the above criteria for FNAB, or are too small to biopsy, are needed for refinement of currently available guidelines [available at Internet site: http://www.ace.com/clin/guidelines/thyroid_nodules.pdf; site last accessed on July 7, 2004¹⁵]. This is especially true, as a few occult TCs may present with local or, rarely, even distant dissemination¹⁶.

In the context of the diagnostic evaluation of thyroid nodules, the role of thyroid scintigraphy (¹²³I or ^{99m}Tc) is currently thought to be limited. Nevertheless, we believe that a thyroid scan should be performed only in cases of patients with: decreased se-

rum thyrotropin (TSH), suspicion of ectopic thyroid tissue, or retrosternal extension of a goiter or mass¹⁷. Scintigraphically “hot” thyroid nodules are more likely to show cytologic features of “follicular neoplasm” on FNABs, as most of them are indeed benign (hyperfunctioning or “autonomous”) follicular adenomas¹⁸. Of note, hyperfunctioning follicular TCs (FTCs) are rare¹⁹.

The role of “screening” baseline plasma calcitonin measurements in the context of initial diagnosis of MTC remains controversial. Several studies have shown that FNAB can miss a diagnosis of MTC in up to 20% of cases, suggesting that an elevated basal calcitonin level in a patient with nodular thyroid disease is much more informative for MTC than an FNAB²⁰. A basal calcitonin level (measured with a reliable double-site immunometric assay [IRMA or ICMA]) of less than 10 pg/ml can be considered “normal”, with values above 100 pg/ml being clearly abnormal and requiring definite diagnosis with thyroidectomy²⁰. Unfortunately, these cutoff values leave a “gray area” for calcitonin levels between 10 and 100 pg/ml, a range that is predictive of MTC in only 13%-15% of cases²¹. Stimulation with pentagastrin + calcium can be useful in cases like these, since stimulated calcitonin levels above 100 pg/ml are highly indicative of MTC or the precancerous condition of C-cell hyperplasia (CCH)²²⁻²⁵. Of note, these issues are further complicated by the current lack of availability of pentagastrin in North America.

Despite the aforementioned caveats, FNAB is the method of choice for the initial evaluation of thyroid nodules. The results of the FNAB are usually categorized into four diagnostic groups: benign (negative), malignant (positive), suspicious (indeterminate), and unsatisfactory (non-diagnostic)²⁶. Unsatisfactory specimens are usually hypocellular/paucicellular, account for 5-15% of FNABs, and, in their presence, FNA sampling should be repeated²⁷. Re-biopsy yields satisfactory results in about half of the cases, and U/S-guided FNAB can further increase this rate to ~70%. Despite this fact, an incidence of ~10%-15% of unsatisfactory specimens remains. The risk of malignancy in nodules that have been subjected to multiple FNABs that yielded unsatisfactory specimens can be as high as 10%²⁸. Tissue core biopsy (TCB) or thyroid surgery may be necessary for diagnosis in these cases. An ipsilateral hemithyroidectomy and isthmusectomy can

be used as the initial approach, particularly if the nodule is growing over time. The surgical pathology results from study of permanent sections usually provide the definitive answer with regard to the presence or absence of malignancy. The value of intraoperative frozen sections in such cases remains debatable (M. Merino, NIH, Bethesda, MD; personal communication).

The management of “suspicious” lesions, i.e. nodules that yielded adequate FNAB specimens that were still cytologically “indeterminate”, remains controversial. These lesions include: hypercellular follicular lesions (especially when associated with a dearth of colloid and/or absence of lymphocytic thyroiditis features in the cytopathology specimen), follicular neoplasms, Hurthle-cell neoplasms, benign specimens with marked cellular atypia^{29,30}. Approximately 20-25% of these “suspicious” lesions are eventually proven to be malignant (usually FTCs, but also follicular variant of PTCs, and, rarely, even MTCs) (30; A. Fili, NIH, Bethesda, MD; personal communication). Therefore, the currently recommended approach for cytologically suspicious lesions is surgical resection with an ipsilateral hemithyroidectomy and isthmusectomy³¹. The surgical specimen may also be examined by frozen section. As mentioned above, the diagnostic value of frozen sections in this setting remains a debatable issue. Some authorities believe that frozen sections are of limited value in regards to providing a definitive diagnosis of TC and, hence, unable to provide assistance with the decision to proceed (or not) with completion thyroidectomy during the time of the actual operation^{32,33}; others disagree with that assessment (A. El-Naggar, M. D. Anderson Cancer Center [MDACC], Houston, TX; personal communication).

II. CONTROVERSIES IN PAPILLARY TC (PTC): PATHOLOGY AND PROGNOSIS

PTCs represent the majority (80%) of TCs³⁴. In autopsy and surgical pathology studies, microscopic occult PTC (“papillary microcarcinoma”) occurs in 5-35% of the population, either as an independent focus or in the form of microscopic malignant cell clusters within an otherwise benign nodule (e.g. nodular hyperplastic goiter or follicular adenoma). Notably, most such microcarcinomas never become apparent by clinical or imaging methods and, hence, remain well below clinical detectability³⁵. The factors that “drive”

only a minority of these “microcancers” to develop into clinically evident PTC remain unknown.

Patient characteristics indicating poorer PTC prognosis are: age at diagnosis <15 or >45, male sex, family history of TC, and previous exposure to neck radiation³⁶. Tumor variables associated with worse PTC prognosis are: size >4.0 cm; multifocality presence of extrathyroidal extension; presence of vascular invasion; aggressive tumor histological subtype (see below); advanced histologic grade with nuclear atypia; tumor aneuploidy; presence of areas of tumor necrosis; and presence of distant metastases³⁶. Whether the presence of microscopic cervical and anterosuperior mediastinal lymph node metastases alters prognosis remains debatable. On the other hand, there is little doubt that bulky macroscopic cervical lymphadenopathy, as well as presence of mediastinal nodes deeper than the confines of the anterosuperior mediastinum (the latter, even when only microscopically infiltrated), can affect prognosis in a negative way. The overall 10-yr survival of patients with PTC is ~90-93%³⁴.

In addition to the “ordinary” or “common” variant of PTC, there are several subtypes (or variants) of PTC. These variants include³⁷: the relatively frequent “follicular variant” (PTC-FV, referred to as “mixed papillary-follicular” TC in older literature); the diffuse sclerosing variant (DSV); the tall-cell variant (TCV); the trabecular cell variant; the columnar-cell variant; the solid variant (SV; rare, specifically associated with radiation-induced PTC); and the cribriform variant (specifically occurring in the context of the autosomal dominant syndrome of familial adenomatous polyposis [FAP]). Apart from PTC-FV, all the above variants have been variably considered to demonstrate a more aggressive clinical behavior vs. that seen with “ordinary” PTC³⁸⁻⁴².

Very rarely, PTC may arise as part of a genetic neoplasia syndrome, such as Cowden syndrome⁴³, Peutz-Jeghers syndrome⁴⁴, FAP⁴⁵ or Carney complex⁴⁶. Very few pedigrees have also been described with familial PTC (FPTC) in the absence of other syndromic features^{47,48}. Extremely rarely, PTC can develop within a benign struma ovarii⁴⁹.

III. CONTROVERSIES IN FOLLICULAR TC (FTC): PATHOLOGY AND PROGNOSIS

Follicular TC (FTC) represents 11%-13% of TCs³⁴.

Usually, these tumors are encapsulated. The same patient and tumor characteristics as for PTC are pertinent for prognosis of FTC (see previous section). The 10-yr survival for “minimally-invasive” FTCs is 85%, in contradistinction to ~45% for “grossly invasive” (or “more-than-minimally invasive”) FTCs⁵⁰. Overall, FTCs are believed to have an increased malignant potential vs. PTCs of the same stage, and tend to spread hematogenously to distant sites (mediastinum, lungs, bone, CNS, etc.)⁵¹.

There are three additional subtypes (or variants) of FTC, other than the “ordinary” one. These variants include: the Hurthle- (or oxyphilic-) cell variant (or Hurthle-cell carcinoma [HCC]); the poorly-differentiated variant; and the insular variant. A considerable body of evidence suggests that these FTC variants may behave in a more aggressive fashion than “ordinary” FTC⁵²⁻⁵⁴. Very rarely, a tumor may present with mixed follicular and medullary components (FTC-MTC “mixed” or “collision” tumors)⁵⁵. Additionally, also rarely, FTC can develop within a benign struma ovarii⁵⁶.

As mentioned previously, at the time of initial diagnosis, FNAB is inadequate in differentiating among benign follicular adenomas (FAs), FTCs (and its subtypes), and PTCs-FV⁵⁷. This distinction eventually has to be made by examination of surgical pathology or tissue core biopsy specimens. In contrast to other solid malignancies, immunohistochemical study of “standard” proliferative markers (e.g. p53, Ki67, PCNA, etc.) and other epithelial differentiation markers does not usually differentiate between benign and malignant lesions⁵⁸; however, staining for galectin-3 has recently been reported to be consistently positive in FTCs, yet is rare in FAs⁵⁹.

It is worth noting at this point that efforts towards prognostication of final outcome in patients with PTC and FTC based on clinical features at the time of initial presentation have been going on for more than 5 decades. These efforts have resulted in a multitude of staging systems specifically for TC. The aim of staging systems is to provide reliable risk assessment with regard to morbidity, mortality, and incidence of recurrence, so that they provide guidance to the clinician regarding the aggressiveness of primary or secondary treatment applied and the vigor of follow-up measures. Overall, the currently existing staging systems have not entirely achieved that goal, as TC dem-

onstrates one of the widest ranges of malignant behavior of any other tumor type emanating from a cell of a defined histogenetic origin. On the other hand, staging systems can be very useful in long-term epidemiologic studies, as well as clinical research, since they aid in risk group stratification for retrospective analysis of TC natural history and treatment outcomes, as well as the design of prospective trials of novel treatment approaches. The currently published staging systems for TC include: pTNM (pathological tumor-node-metastasis system, adopted by the American Joint Committee on Cancer [AJCC] and the Union Internationale Contre le Cancer [UICC]), NTCTCS (National Thyroid Cancer Treatment Cooperative Study; “National Registry group”), EORTC (European Organization for Research and Treatment of Cancer), MACIS (Metastasis, age, completeness of resection, invasion, & size), AGES (Age, grade, extent, size), and AMES (Age, distant metastasis, extent & size of primary tumor), Clinical Class/University of Chicago, and Ohio State University (OSU) staging systems. The most extensively used and validated systems are pTNM and NTCTCS. We also believe that these two systems reflect the biology of TC better than the other available staging systems. The pTNM system was revised in 2002^{60,61}, while NTCTCS has not been altered since its initial conception more than 15 years ago^{62,63}. These two systems are shown in Tables 1 and 2.

IV. PTC AND FTC: CONTROVERSIES AND DEBATES IN THEIR MANAGEMENT AND FOLLOW-UP

PTC and FTC management comprises 5 major phases: diagnosis, initial surgery, remnant ablation, thyroid hormone suppression of TSH (THST), and long-term follow-up. Considerable debate surrounds all these phases, mainly due to the absence of prospective randomized trials on TC management. Practice guidelines have recently been published by experts from comprehensive cancer centers in the U.S.^{15,64}, as well as the British Thyroid Association (BTA)⁶⁵. The relevant Internet sites are as follows: http://www.nccn.org/physician_gls/f_guidelines.html, http://www.aace.com/clin/guidelines/thyroid_carcinoma.pdf, and <http://www.british-thyroid-association.org/guidelines.htm> (sites were last accessed on July 7, 2004). Nevertheless, consensus has not been reached

Table 1. Thyroid Carcinoma Staging according to the TNM/UICC System, 6th Edition (2002) (60,61)

Primary Tumor Size	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor size: maximal 2 cm, limited to the thyroid
T2	Tumor size: >2 cm and ≤4 cm, limited to the thyroid
T3	Tumor size: >4 cm, limited to the thyroid, or any tumor with minimal extrathyroid extension (i.e., to sternothyroid muscle or perithyroid soft tissues)
T4	T4a: tumor extends beyond the thyroid capsule and invades subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve T4b: tumor invades prevertebral fascia, mediastinal vessels, or encases carotid artery
Presence of Regional Lymph Node Metastasis	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis in Level VI (pretracheal and paratracheal, including prelaryngeal and Delphian lymph nodes)
N1b	Metastasis in other unilateral, bilateral, or contralateral cervical or mediastinal lymph nodes
Presence of Distant Metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Derivant TNM/UICC Clinicopathologic Stages	
Stage I	Tx Nx M0 <45 yrs T1 N0 M0 ≥45 yrs
Stage II	Tx Nx M1 <45 yrs T2 N0 M0 ≥45 yrs
Stage III	T3 N0 M0 ≥45 yrs T1–3 N1a M0 ≥45 yrs
Stage IV	A: T1–3 N1b M0 ≥45 yrs or T4a N0–1 M0 ≥45 yrs B: T4b Nx M0 ≥45 yrs C: Tx Nx M1 ≥45 yrs

Abbreviations: UICC: Union Internationale Contre le Cancer, yrs: years of age

among the experts participating in the these panels.

i) Surgery

In almost all cases of PTCs and FTCs greater than 1.0 cm, a total or near-total thyroidectomy (T/NTT)

is the initial surgical treatment of choice. Lobectomy alone—as the definitive initial surgery—is associated with a 5-10% recurrence in the contralateral lobe⁶⁶, and a ~25%-30% recurrence rate in the ipsilateral thyroid bed and neck lymph nodes³⁶. There is also higher incidence of pulmonary metastases following lobectomy alone for PTC vs. performing a more complete surgery⁶⁶. There is evidence of increased relapse-free survival with T/NTT, although it is more difficult to demonstrate an effect on overall survival. Mazzaferri et al. showed that T/NTT reduces the risk of mortality by 50% after a median follow-up of 16 years. This effect was independent from subsequent administration of RAI treatment(s)⁶⁷. It has to be noted, however, that a remarkable total of 22,000 patient-years of follow-up was necessary to demonstrate the above effect of T/NTT. The guidelines published by the National Comprehensive Cancer Network (NCCN) in the U.S. recommend a total thyroidectomy with bilateral central compartment dissection; if lymph nodes are involved, lateral modified radical neck dissection is additionally advised⁶⁴. The British Thyroid Association (BTA) recommends a total thyroidectomy plus removal of all lymph nodes in the central compartment of the neck, along with selective dissection of lateral cervical lymph nodes; there is no recommendation for routine radical neck dissection or more extensive explorations in multiple anatomical levels of cervical lymph nodes⁶³. In selected cases of PTCs and FTCs with adverse prognostic factors, assuming that these are recognized and appreciated at the preoperative stage after appropriate risk stratification, a more aggressive surgical approach can be used. Moreover, a study suggested that in cases where a completion thyroidectomy is needed, if the latter is performed within 6 months from the initial partial thyroid resection, there is a significant survival advantage and a lower recurrence rate, as opposed to a completion operation performed more than 6 months after initial surgery⁶⁸.

ii) Thyroid remnant RAI ablation

The universal treatment of all PTC/FTC patients with RAI for the ablation of thyroidal postoperative remnants, as well as RAI activity (“dose”) to be administered, remain controversial issues. Most authors, including ourselves, believe that remnant ablation in all patients is justified for the following reasons: (a) it facilitates the subsequent follow-up of patients using

Table 2. The National Thyroid Cancer Treatment Cooperative Study (NTCTCS) Registry Staging Classification for WDTC

Parameters considered	Tumor Type			
	Papillary TC		Follicular TC	
	Age <45	Age ≥45	Age <45	Age ≥45
Primary tumor size (cm)				
<1	I	I	I	II
1-4	I	II	I	III
>4	II	III	II	III
Primary tumor description				
Microscopic multifocal	I	II	I	III
Macroscopic multifocal or macroscopic tumor capsule invasion	I	II	II	III
Extraglandular invasion				
Microscopic	I	II	I	III
Macroscopic	II	III	II	III
Poor differentiation	NA	NA	III	III
Metastases				
Cervical lymph node metastases only	I	III	I	III
Extracervical lymph node metastases (or worse)	III	IV	III	IV

(N.B.: Disease stage assigned to patients is the highest stage determined by any of the above clinicopathologic features).

Abbreviations: TC: thyroid carcinoma; WDTC: well-differentiated thyroid cancer.

serum thyroglobulin (Tg) as a tumor marker; (b) a large remnant might obscure the detection of cervical or lung metastases in long-term follow-up⁶⁹; (c) the presence of a large remnant renders it difficult to achieve an appropriately elevated serum TSH—and thus RAI uptake by the tumor—in case RAI therapy is needed for tumor metastases; and (d) RAI ablation can also be cytotoxic for concomitant micrometastases, as well as normal thyrocytes within the remnant that have a defined (above zero) lifelong potential for malignancy⁵⁵.

In order to achieve optimal conditions for RAI ablation, serum TSH needs to be >25 mU/L. In the past, this was achieved by increasing endogenous (pituitary) TSH by instituting iatrogenic hypothyroidism after thyroidectomy. Recently, with the advent of recombinant human TSH (rhTSH), one can bypass the hypothyroid preparation and its associated morbidities. On-going studies are focusing on the question of relative efficacy of such an approach vs. “classic” hypothyroidism with regard to rates of achieving RAI ablation, but preliminary data suggest that rhTSH administration is equivalent to hypothyroid preparation⁷⁰.

The optimal RAI dose for ablation is debatable

and, to a certain degree, depends on the amount of thyroid tissue left behind after thyroidectomy. Lower doses (~ 30 mCi; 1.11 GBq) are appealing because they can be given on an outpatient basis. However, a recent meta-analysis showed that doses between 75-100 mCi (2.78-3.7 GBq) are more efficient than doses of 30 mCi (1.11 GBq) in achieving complete remnant ablation³⁶. Patients with more sinister prognostic factors would probably benefit from RAI ablation doses at the higher end of the spectrum (100-125 mCi; 3.7-4.63 MBq). Of note, a post-therapy RAI whole body scan should be performed after remnant ablation, as it can occasionally detect previously unappreciated or unsuspected sites of local or metastatic spread.

iii) Thyroid hormone suppression therapy (THST)

Although THST has been shown to significantly reduce recurrence and TC-specific mortality rates in both single institution studies⁷¹ and meta-analyses⁷², the minimum degree of TSH suppression to achieve this effect remains debatable. In PTC/FTC patients, the levothyroxine (LT4) dose needed to maintain serum TSH suppressed is ~2.1-2.4 µg/kg/day, as opposed to the replacement therapy doses of 1.6-1.8 µg/kg/day

used in patients with hypothyroidism caused by non-malignant disease⁷³. To add more complexity to this issue, the LT4 dose required to achieve THST is dependent on the subject's age, with younger patients needing higher doses per unit weight than older patients⁷⁴.

In a French study by Pujol et al, persistently undetectable serum TSH levels (<0.05 mU/L) were associated with a longer relapse-free survival, as opposed to a serum TSH always being >1.0 mU/L; in the same study, the degree of TSH suppression was an independent predictor of disease recurrence⁷⁵. Other studies, however, were unable to reproduce these results. In our opinion, for the vast majority of PTC/FTC patients, keeping a serum TSH just below the lower limit of normal (i.e. in the range of 0.1-0.4 1.0 mU/L) is appropriate. If there is evidence of persistent, recurrent or "clinically aggressive" disease, lower levels of "target" TSH may be considered, although one would always have to balance the risk-benefit ratio, given the fact that long-term subclinical hyperthyroidism is associated with increased risk of all-cause mortality. Finally, in low-risk patients who have reached a status of no evidence of disease and remain without recurrence for more than 10 years, a cogent argument can be made for those patients to continue LT4 therapy in hormonal replacement rather than TSH-suppressive doses (S. Sherman, MDACC, Houston, TX; personal communication).

iv) Long-term follow-up

The main methods of monitoring patients with PTC and FTC for the exclusion of persistent/recurrent disease are: measurement of serum thyroglobulin (Tg) levels, RAI whole body scans (WBSs), and neck U/S. A suggested scheme of follow-up of PTC/FTC patients after primary therapy is shown in Figure 1. In this scheme, specific emphasis is placed on the detection of persistent/recurrent disease, which should lead to appropriate therapeutic action (see section [v.]).

iv – a) Tg levels

The appropriate use of Tg as a TC "marker" presumes that patients have already undergone a T/NTT followed by thyroid remnant RAI ablation; otherwise, Tg levels are unreliable for use as TC markers during follow-up. Ideally, serum Tg assays should be performed in the same laboratory, since measured val-

ues can differ among different clinical chemistry laboratories, even when international Tg standards are used⁷⁶. Tg levels above the following cut-off points indicate the presence of thyroid tissue, either normal (remnant) or malignant [even when a RAI WBS is negative], since Tg is only produced by thyroid tissue: >0.5-1.0 ng/ml, while on THST⁷⁷; >8.0 ng/ml while off TH therapy⁷⁸; and >2.0 ng/ml after stimulation with recombinant human TSH (rhTSH; Thyrogen[®])⁷⁹. It has to be noted that with newer, more reliable Tg assays, the cutoff Tg level of 8.0 ng/ml—assessed under hypothyroid conditions as an indicator of possible persistent thyroid tissue or recurrent disease—may be viewed by most authorities in the field as inordinately high. Indeed, we and others often see patients with biopsy-proven, low-volume persistent/recurrent PTC/FTC who have Tg levels under hypothyroid conditions in the range of 2.0-8.0 ng/ml. On the other hand, no systematic study exists to date assessing the validity of cutoff levels of serum Tg levels lower than 8.0 ng/ml—measured under hypothyroid conditions—as an independent proof of evidence of clinically significant residual disease in PTC/FTC patients, especially when imaging studies for disease localization are unrevealing. Over the last decade, most algorithms for the diagnosis of residual/recurrent disease are based primarily on serum Tg analysis, as reflected in recently published follow-up guidelines by both U.S.⁸⁰ and European⁸¹ investigators.

In cases where residual/recurrent disease is suspected because of Tg levels above certain cutoff values (depending on the clinical circumstances), then imaging with other modalities (e.g. neck U/S, diagnostic RAI WBS, or ¹⁸F-fluorodeoxyglucose positron emission tomography [FDG-PET]) is both appropriate and necessary for the detection of such clinically occult disease which, in fact, may be amenable to further therapy (surgery, RAI or other modalities).

Anti-Tg antibodies are found in ~20% of patients with PTC/FTC. When anti-Tg antibodies are present, IRMA/ICMA-based Tg measurement methods are prone to underestimate the "true" serum Tg levels, thus increasing the possibility of missing metastatic disease. Additionally, serial serum anti-Tg antibody measurements usually parallel serial serum Tg measurements (by radioimmunoassay [RIA] techniques)⁸². However, it is debatable whether anti-Tg antibodies concentrations are clinically useful as tumor markers

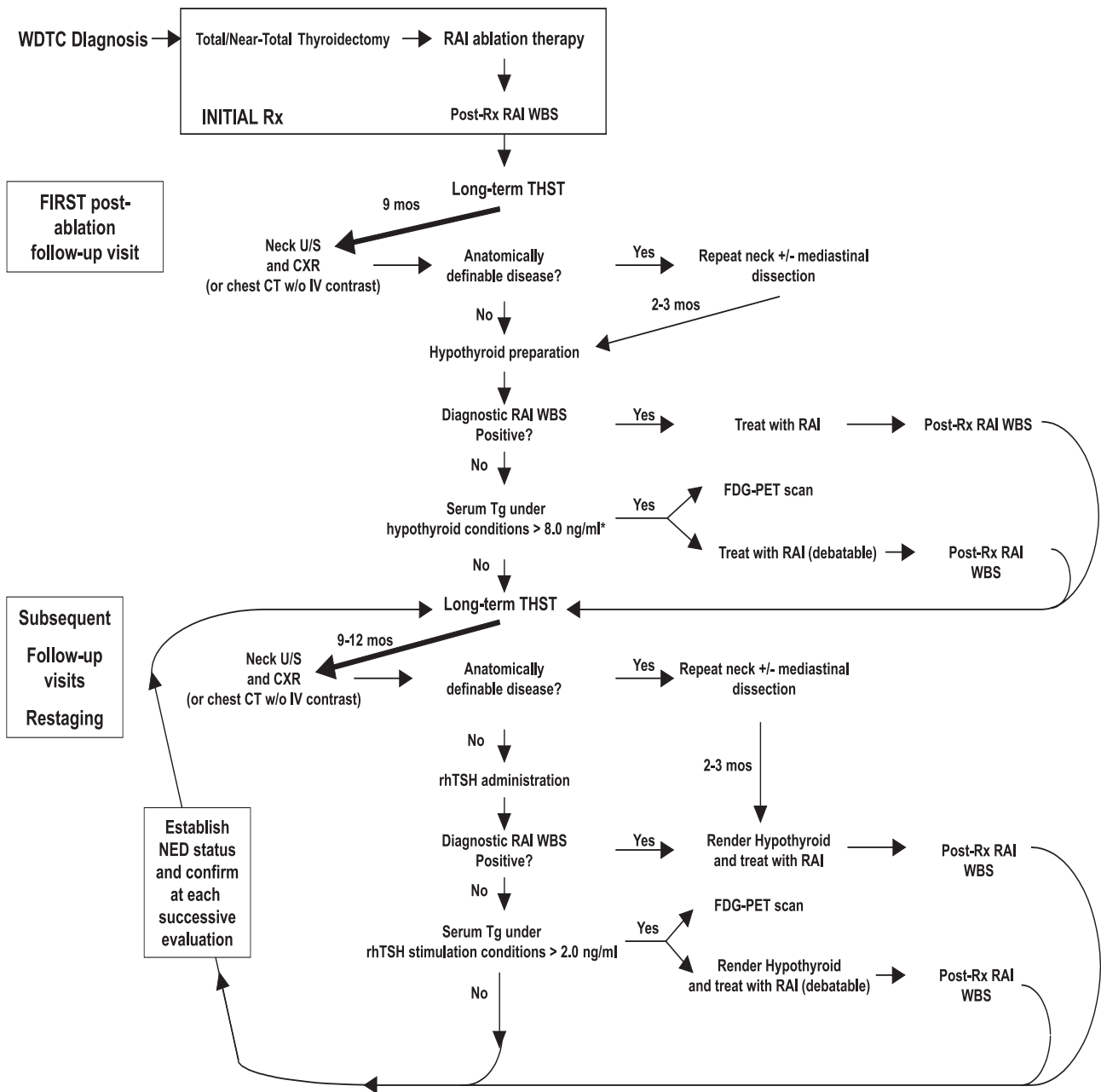


Figure 1. Algorithm for the follow-up of pediatric patients with well-differentiated thyroid carcinoma (WDTC) after total/near-total thyroidectomy and initial ¹³¹I remnant ablation. In the proposed scheme, special emphasis is placed on the detection and eradication – whenever feasible – of persistent/recurrent metastatic disease in all patients who do not achieve no evidence of disease (NED) status. Different cutoff serum Tg values are used as corroborating evidence of residual/recurrent disease, depending on how TSH stimulation is achieved (thyroid hormone withdrawal vs. recombinant human thyrotropin [rhTSH] administration). For more details, refer to the text. Of note, RAI treatment for thyroid remnants can also be administered under stimulation with rhTSH. This is still considered an “off-label” use of rhTSH and should preferably be limited to tertiary center specialists with experience in the treatment of TC. Abbreviations: CT: computed tomography, CXR: chest X-ray, FDG-PET: ¹⁸F-fluoro-deoxyglucose positron emission tomography, IV: intravenous, RAI: radioiodine (¹³¹I), Rx: therapy, TH: thyroid hormone, THST: thyroid hormone suppressive therapy, U/S: ultrasonography, WBS: whole body scan, w/o: without.

*: The serum Tg cutoff value of 8.0 ng/ml – when measured under hypothyroid conditions, as a surrogate indicator of the presence of persistent/recurrent disease after adequate primary therapy – may be inordinately high. In many cases, we proceed with extensive diagnostic imaging evaluation in patients with Tg levels in the range of 2.0-8.0 ng/ml. When newer studies on this subject become available, it is highly likely that this cutoff Tg level will decrease significantly (in the range of 0.5-2.0 ng/ml).

for following individual TC patients over time. Qualitative and, more recently, quantitative methods of measuring Tg mRNA (extracted from peripheral whole blood samples) have been applied in cases wherein the presence of anti-Tg antibodies renders serum Tg measurements invalid^{83,84}. However, these methods are not widely available, not always specific for TC, and not better – or cheaper – in a clinical practice setting than new Tg ICMAs/IRMAs. Consequently, their general use in TC patients is not yet advocated⁸⁵. Another caveat in using serum Tg alone for monitoring disease status in PTC/FTC is the patient with dedifferentiated TC, whose tumor has lost the ability to synthesize and/or secrete Tg, or secretes abnormal Tg molecules that cannot be detected by currently available Tg assays^{86,87}.

iv – b) RAI whole body scans

The role of the RAI diagnostic WBS has changed dramatically with the introduction of rhTSH for monitoring of patients with PTC/FTC. Until recently, iatrogenic hypothyroidism achieved by withdrawal of TH therapy – with all the associated repercussions for the patient's quality of life – was required to proceed with a diagnostic RAI WBS. Hypothyroidism is no longer required, as iodine uptake by thyrocytes can be adequately stimulated by administration of exogenous rhTSH.

Traditionally, ¹³¹I has been used for the performance of diagnostic RAI WBSs. However, the administration of “tracer” doses (2-5 mCi; 74-185 MBq) of a β -particle emitter, such as ¹³¹I, for the performance of the scan has been claimed to induce “stunning” of the remnant tissue^{88,89}, thus reducing the uptake of the subsequent therapeutic ¹³¹I dose. This stunning phenomenon seems to be more important in ¹³¹I ablation of thyroidal remnants, but some investigators believe that stunning occurs to a considerable degree in malignant thyroid cells as well, thus affecting the efficacy of ¹³¹I administered for TC therapy⁹⁰. In view of the above considerations, ¹²³I has recently been used for the performance of diagnostic RAI WBSs with success⁹¹. ¹²³I is a pure γ -emitter RAI with much shorter half-life than ¹³¹I. Tracer doses of ¹²³I for scanning are in the range of 0.5-4 mCi (18.5-148 MBq). The above notwithstanding, ¹²³I is more expensive than equal-activity doses of ¹³¹I, and there is limited experience with regard to the appropriate interpretation of ¹²³I scintigraphy for TC detection.

The above issues, i.e. convenience in patients' scheduling of follow-up visits and the possibility of stunning, have led many experts to dispute the necessity of performing a diagnostic RAI WBS altogether, at least in most low-risk TC cases, since an rhTSH-stimulated serum Tg above 2.0 ng/ml can readily and reliably detect the presence of disease in patients with persistent TC. Indeed, in these patients, a diagnostic RAI WBS is positive in only 30-50% of cases⁹². Despite extensive experience reported by the Memorial-Sloan Kettering Cancer Center ([MSKCC], New York, NY)^{93,94}, there is no consensus as yet for the role of rhTSH in monitoring disease status in “high-risk” TC patients.

From the above, it is obvious that there are patients with detectable stimulated serum Tg (either after LT4 Rx discontinuation or post-rhTSH administration) and a negative diagnostic WBS. In cases such as these, we and others⁹⁵ propose the use of non-RAI-based disease localizing modalities (U/S, computed tomography [CT], magnetic resonance imaging [MRI], bone imaging or FDG-PET) in efforts to identify disease amenable to surgical extirpation or other therapies (e.g. external beam radiotherapy; EBRT). In some of these cases, metastases are detected only after the administration of larger (therapeutic) RAI doses (usually in the range of 150-300 mCi; 5.6-11.1 GBq) and subsequent performance of a “post-therapy” RAI WBS (usually performed 2-7 days after RAI therapy administration)^{96,97}. In some of such cases, if the post-therapy RAI WBS is positive, then further RAI treatment(s) may be carefully considered aiming for induction of disease remission, or at least stabilization⁹⁸⁻¹⁰⁰, although this approach remains controversial (101,102; J. Reynolds, NIH, Bethesda, MD; personal communication). The above notwithstanding, if the post-therapy RAI WBS is negative, the patient's disease is deemed non-avid to iodine and further RAI administration is of no clinical benefit³⁶, or may in fact be harmful^{103,104}.

It is important to emphasize at this point the role of an adequate preparation before a diagnostic RAI WBS and anticipated RAI therapy with depletion of the iodine body stores. This is achieved by implementing 2-3 weeks of low iodine diet prior to the administration of the RAI tracer dose, leading to increase the RAI uptake from thyroid tissue, which can in turn increase (up to 200%) the radiation doses deposited

therein (in cGy per 100 mCi [3.7 GBq])^{105,106}.

The possibility of “false positive” RAI WBSs certainly exists but is rare. False positive WBSs can be caused by: body secretions, inflammatory processes, non-specific mediastinal or gallbladder uptake, as well as, very rarely, RAI accumulation by non-thyroid malignancies¹⁰⁷. Physiologic iodine uptake from the nasopharynx, salivary and sweat glands, mammary glands, stomach and genitourinary tract, or contamination of skin or hair can also give the impression of a positive scan. Diffuse hepatic uptake is commonly seen due to hepatic clearance of RAI-labeled Tg and other iodinated proteins (such as iodo-albumin), originating from thyroid remnants or metastatic disease¹⁰⁸. Thus, low-level, diffuse hepatic RAI uptake does not signify the presence of liver metastases from PTC/FTC, which are exceedingly rare¹⁰⁹.

iv – c) Ultrasonography and chest radiography

Neck U/S can accurately identify locoregional metastasis or tumor recurrence¹¹⁰. Serial neck U/S exams are recommended in most, but not all, consensus guidelines on TC follow-up. Additionally, chest X-ray has customarily been used in the periodic evaluation of patients with TC, although its sensitivity is at least 30% below that of a diagnostic RAI WBS (in the subgroup of patients with iodine-avid metastatic TC deposits to the lung)¹¹¹. The presence of deposits demonstrable by simple chest radiograms portends a more grave prognosis vs. when such deposits are invisible¹¹². Over the last 15 years, chest CT has been used for the diagnosis of micronodular or military TC spread or lymphangitis pulmonis due to this malignancy, and has proven to be significantly more sensitive than simple chest radiograms¹¹³. On the other hand, in order for the chest CT to achieve its maximal sensitivity for disease detection, iodinated IV radiographic contrast administration is necessary. This precludes the use of this modality prior to the performance of diagnostic RAI WBSs or administration of RAI therapy, due to “cold” (stable) iodine contamination that abrogates RAI uptake by malignant thyrocytes. Stable iodine contamination after administration of IV contrast material can interfere with subsequent RAI uptake by TC deposits for up to 9 months, depending on the amount and type of contrast material administered¹¹⁴.

Finally, additional radiographic studies, such as CT, MRI, FDG-PET, ^{99m}Tc-MDP bone scan, bone X-

ray metastatic survey, and ¹¹¹In-pentetreotide scintigraphy (OctreoScan[®]), are not recommended routinely for follow-up of PTC/FTC patients, but have their utility in selected patients with residual/recurrent or metastatic disease¹¹⁵.

v) Management of Residual/Recurrent PTC/FTC after Initial Therapy

Non-physiologic RAI uptake after primary TC therapy with T/NTT and successful thyroidal ablation correlates with the presence of functional TC. Most PTCs/FTCs accumulate enough RAI to allow effective therapy by ingestion of this radionuclide, but therapeutic success requires a high degree of stimulation by TSH, as well as the achievement of a very low whole body iodine status prior to therapy in order to increase the avidity of RAI uptake by TC cells. Therapeutic doses are generally continued to be given, as long as iodine-avid lesions persist—that show response to continuing therapy—or until a maximum cumulative lifetime RAI dose is reached.

In patients with evidence of non-resectable residual/recurrent TC after initial therapy, further RAI therapy may be given either empirically using “fixed-size” RAI therapy doses (150-200 mCi [5.55-7.4 GBq] per administration)—according to the University of Michigan protocol [reviewed by Beierwaltes¹¹⁶—or “maximum tolerated”/“maximally safe” doses. In most centers, the upper threshold for empirically administered RAI therapy doses is 300 mCi (11.1 GBq) per administration, although seminal studies from the MSKCC group had demonstrated that single administrations of RAI doses up to 750 mCi could be safe in highly selected cases, at least with regard to acute RAI-induced toxicity¹¹⁷. These “maximally safe” doses are determined quantitatively by a pre-therapy study using RAI tracer with the method of “whole body and blood dosimetry”. The latter procedure allows calculation of the expected whole body (WB) and whole blood/bone marrow acute radiation exposure from the administered RAI dose after estimating the radiation dose delivered to critical tissues [in rads/mCi (or rads/GBq) of administered RAI activity], as well as the expected retention of RAI in pulmonary metastases—if any—, according to the MSKCC protocol developed in the mid-1960s¹¹⁸. We would like to emphasize here that what is ultimately important in RAI therapy of TC is the absorbed radiation dose (in cGy) to the tumor, and how it compares with absorbed radiation dos-

es to the bone marrow and lungs so that a balance between benefit and risks can be achieved. Thus, it is these absorbed radiation doses to the tumor and critical host tissues that are biologically relevant, and not the activity of ^{131}I administered to the patient (measured in mCi [or MBq]).

It is believed that dosimetry can minimize the risk of the two limiting acute complications of high-dose RAI therapy, i.e. bone marrow suppression and pulmonary fibrosis. The details of dosimetric protocols have been reviewed exhaustively in earlier publications^{89,119,120}. Of note, dosimetry is not always predictive of the degree and timing of emergence of acute radiation side effects and cannot predict long-term stochastic side effects, such as development of secondary (radiation-induced) malignancies over time¹²⁰. Finally, the availability of dosimetry is limited to only a few cancer centers internationally.

Lithium carbonate has been shown to increase iodine retention by PTC/FTC cells and, consequently, prolongs the period of intratumoral residence of RAI after therapy with RAI¹²¹. Thus, lithium can be useful as an adjunct to RAI therapy, at least in cases in which radioiodine turnover by the tumor is rapid. Although formal serial tumoral iodine uptake studies are required to document tumor turnover rates, lithium can also be used empirically in clinically aggressive, “high-risk” PTC/FTC cases. Lithium toxicity should be avoided by closely monitoring serial serum lithium levels, obtained on a daily or every-other-day basis, until the time of RAI therapy administration.

Limiting factors for RAI therapy are bone marrow toxicity (mainly leukopenia and thrombocytopenia) and radiation pneumonitis. Leukemia, small intestine, stomach, and bladder cancer (as well as perhaps breast cancer) are rare, yet serious, long-term potential complications of RAI therapy and tend to occur more frequently with cumulative life-time RAI doses above 1,200-1,500 mCi (44.4-55.5 GBq)¹²². Sialoadenitis with significant xerostomia and ageusia/dysgeusia, as well as transient oligospermia in males may occur with single RAI therapy doses in the range of 150-300 mCi (5.55-11.1 GBq), but are rarely permanent. Recently, amifostine has been used for the prevention of sialadenitis in a small number of cases receiving high-dose RAI with anecdotal success¹²³.

Despite occasional achievement of extensive par-

tial—or even complete—tumor responses after RAI therapy in patients with disseminated PTC/FTC, there is no statistical evidence that such therapy improves survival in “high-risk” patients, although it may decrease rate of disease progression. In fact, several cancer centers with treatment teams of conservative treatment philosophies (such as the Mayo Clinic, Rochester, MN) opt not to use further RAI therapies in patients with persistent TC once a cumulative RAI dose of 600-900 mCi (22.2-33.3 GBq) has been reached, even in the presence of persistently positive previous post-therapy RAI WBSs and/or history of prior partial tumor response(s) to RAI, thus designating these patients as “RAI-resistant”. Although we certainly agree that the majority of such patients will never be rendered disease-free by RAI alone, we also believe that in selected cases clinical “control” of symptomatic or life-threatening metastases can be achieved. Indeed, achievement of very long progression-free intervals has been documented in some cases after repeated courses of high-dose (“maximally safe”) RAI therapy, with cumulative life-time RAI doses reaching 4,500 mCi (4.5 Ci; 166.5 GBq) (111, 124; H. Maxon; Hilton Head, SC; personal communication; K. Ain, Lexington, KY; personal communication)].

On the other hand, once TC cells cease concentrating RAI, further treatment presents a serious clinical dilemma. Approximately 30% of locoregional non-resectable recurrences from PTC/FTC fail to concentrate adequate amounts of RAI for their eradication by RAI alone¹²⁵. The therapeutic options for patients harboring tumors that do not respond to RAI therapy are limited and generally ineffective with regard to disease eradication. Occasionally, however, significant long-term palliation can be achieved with judicious use of: palliative surgical debulking of recurrent disease; EBRT; chemotherapy; or a combination of the above modalities.

Extensive (debulking) metastasectomies in PTC/FTC, especially in cases of RAI non-avid tumors, are justified in selected cases and may have a favorable short-term effect on prognosis and quality of life¹²⁶. Electron beam EBRT is moderately effective as a local therapy directed usually against persistent/recurrent disease in the neck and upper mediastinum, CNS/paraspinal structures and accessible bone sites. EBRT is employed when RAI cannot be used or when a local complication poses an imminent threat to limb or

life [summarized in¹²⁷]. Heavy particle (e.g. proton) beam therapy for PTC/FTC, particularly in disease persisting in locations previously subjected to conventional EBRT, is currently under investigation¹²⁸.

Chemotherapy is only minimally effective for the control of PTC/FTC and is considered only when other therapy options are impossible to implement or have been exhausted. Currently, the most effective single agent is doxorubicin (Adriamycin[®]), given either alone or in combination with other agents. Other chemotherapy drugs that have been used in PTC/FTC—either anecdotally or in small case series—include: cisplatin, cyclophosphamide, etoposide, carboplatin and, more recently, paclitaxel (Taxol[®]), all with generally modest results. In major cancer centers, including the NCI and MDACC, the combination of paclitaxel and carboplatin has been used for disease control in metastatic refractory TC with variable success, although formally reported data are lacking. Anecdotally, some patients who showed early responses to paclitaxel and became refractory to this agent may show responses to docetaxel (Taxotere[®]) (M. Kies, MDACC, Houston, TX; personal communication). EBRT combined with either low-dose doxorubicin (\pm cisplatin) or paclitaxel (\pm carboplatin) (used as “radiosensitizers”) can occasionally eradicate locally invasive, inoperable TC deposits that threaten the larynx, trachea, esophagus or other structures of the thoracic inlet, but will not prevent the subsequent development of distant metastases¹²⁹. The latter, of course, eventually become limiting for survival¹³⁰.

Finally, retinoic acid analogs, such as high-dose oral isotretinoin, have been used anecdotally aiming at “re-differentiation” of metastatic PTC/FTC deposits, i.e. in efforts to induce the accumulation and retention of iodine by the TC cell, thus allowing for the re-introduction of high-dose RAI therapies for disease control^{131,132}. Heretofore, this aim has remained elusive, although new compounds, such as histone deacetylase inhibitors¹³³, and other transcriptional modulators, such as valproate¹³⁴, are under investigation.

V. CONTROVERSIES IN ANAPLASTIC TC (ATC): PATHOLOGY AND PROGNOSIS

ATC represents 8-10% of TCs³⁴. This is an undifferentiated carcinoma, thought to arise from “transformation” of a long-standing PTC (or, more rarely,

FTC or nodular goiter) in ~50% of cases¹³⁵. There are four major histological subtypes of ATC: giant-, spindle-, squamoid-, clear-cell variants. However, the final clinical outcome in patients with this malignancy is the same regardless of its histologic subtype¹³⁶. The previously described subtype of “small-cell” ATC should no longer be used, since most of these cases were in fact thyroid lymphomas, poorly differentiated MTCs or metastases to the thyroid from other primary malignancies¹³⁷. ATCs also usually lose their ability to produce/secrete Tg and, hence, Tg cannot be used as a tumor marker in this malignancy¹³⁸. At the time of initial diagnosis, ~50% of ATC patients have distant metastases—mainly in the lungs, bones, liver, and brain/intraspinal; paraspinal tissues—, whilst another 25% of patients develop distant deposits during the course of the disease¹³⁹. The prognosis is dismal, with most patients succumbing to the disease within a few months after initial diagnosis because of either locoregional disease—and associated complications (e.g. airway obstruction)—or galloping distant metastases¹³⁹.

VI. CONTROVERSIES IN ATC MANAGEMENT

ATC is almost uniformly fatal. Hence, in almost all cases the only aim of treatment is palliation. If there is no extracervical disease and functional surgical excision of the primary tumor site is feasible, then T/NTT with bilateral modified radical neck dissections (MRNDs) is recommended¹⁴⁰. EBRT can result in local disease “control”, although recurrences occur frequently¹⁴¹. Systemic chemotherapy has been disappointing in altering the fatal outcome of the disease. Combination chemotherapy with doxorubicin and cisplatin + bleomycin showed only minimal improvement in clinical response vs. doxorubicin alone^{142,143}. In a recent trial, paclitaxel resulted in a 53% combined (partial and minimal) response rate; there was no patient with complete response to paclitaxel, and the partial responses were relatively short-lived¹⁴⁴. Newer taxanes, such as docetaxel (Taxotere[®]), as well as epothilones, may show promise in ATC therapy¹⁴⁵, although they have not been studied formally in this malignancy. Of note, aggressive cytotoxic therapy with a taxane and cisplatin (or carboplatin) combination usually mandates rescue with hematopoietic growth factor administration due to potentially severe and/or prolonged therapy-induced cytopenias¹⁴⁶, and

should be reserved for younger and healthier patients with metastatic ATC. Currently, the use of combination therapies (radiation, chemotherapy and aggressive surgical intervention) should be considered the “standard of care” for patients with resectable ATC¹⁴⁷.

VII. CONTROVERSIES IN MEDULLARY TC (MTC): PATHOLOGY AND PROGNOSIS

MTC represents 6%-8% of TCs³⁴. This malignancy is derived from the calcitonin-producing parafollicular (or C-) cells, which are of neuroectodermal origin. Hence, MTCs are not iodine-avid and their growth is not TSH-dependent. Furthermore, these malignancies do not produce/secret Tg. MTCs overall show more malignant potential than “ordinary” PTCs or “minimally-invasive” FTCs. MTC is believed to develop through a pre-malignant stage of C-cell hyperplasia (CCH), subsequently leading to the formation of “micro-MTC”, and eventually macroscopic malignancy¹⁴⁸.

It is important for the clinician to keep in mind that MTC can be associated with paraneoplastic manifestations due to the production of various substances by the tumor (with corresponding clinical syndromes in brackets), including: 5-HT (5-hydroxytryptamine or serotonin) [flushing, carcinoid syndrome]¹⁴⁹; adrenocorticotropin (ACTH)/corticotropin releasing hormone (CRH) [ectopic Cushing's syndrome]^{150,151}; prostaglandins [flushing, diarrhea]; brady- and tachykinins [flushing, hypotension]; and vasoactive intestinal peptide (VIP) [watery diarrhea-hypokalemia-achlorhydria [WDHA] syndrome]¹⁵².

Calcitonin secretion by the tumor renders this neuropeptide a useful marker for MTC at the time of initial diagnosis (with the limitations discussed in the section of diagnostic evaluation of thyroid nodules) and, more importantly, during follow-up after initial therapy. Plasma calcitonin levels correlate directly with tumor mass in that an approximately spherical MTC lesion of 1.0 cm in diameter corresponds to a plasma calcitonin level of ~1,000 pg/ml¹⁵³. The above notwithstanding, some MTCs are partially dedifferentiated, thus having diminished or completely lost ability of calcitonin secretion; in these tumors, plasma calcitonin cannot be used as a reliable tumor marker¹⁵⁴. On the other hand, almost all MTCs retain their ability to express and secrete carcinoembryonic antigen

(CEA) and, hence, even in tumors that have lost their calcitonin expression capacity, serum CEA can be used as a surrogate marker of tumor burden¹⁵⁵. The role of chromogranin-A (CG-A) in the diagnosis of residual/recurrent MTC remains under investigation¹⁵⁶.

Sporadic MTC accounts for ~80% of all MTC cases, the remaining 20% of cases developing in the realm of one of three familial syndromes with autosomal dominant inheritance pattern, often associated with other endocrine neoplasms. These syndromes are: Multiple Endocrine Neoplasia (MEN) types -2A and -2B, and familial MTC (FMTC)^{95,157}. Patients with MTCs occurring in a familial pattern universally harbor germline activating mutations of the RET proto-oncogene. In these syndromes, there is definite correlation between the clinical phenotype and the site (codon) of the mutation along the RET oncogene sequence¹⁵⁸. On the other hand, there is variable biological aggressiveness of MTCs occurring among family members who carry the very same RET mutation, a fact suggesting that other variables (both genetic and environmental) are important in determining malignant potential in MTC¹⁵⁹. It is important to screen for RET mutations in all MTC cases, even those in which the tumor is “apparently sporadic”, since ~6% of patients harboring these “apparently sporadic” tumors are found to carry germline RET mutations; this has important implications for the patients and their families¹⁶⁰. Patients with MTC who undergo genetic screening for RET oncogene mutations should always undergo genetic counseling prior to consenting for such testing, due to the social, familial, psychological, and potentially financial implications of positive genetic testing results¹⁶¹.

Regarding prognosis in MTC, patients under 40 years of age at the time of diagnosis have a 10-year survival of ~75%, as opposed to ~50% for those above 40 years of age at the time of diagnosis¹⁶². Of note, the familial syndromes associated with MTC show significant differences in aggressiveness of the malignancies that develop in their context. The following order of MTC aggressiveness has been observed¹⁶³: MEN2B >> MEN2A > FMTC.

VIII. MTC: CONTROVERSIES IN ITS MANAGEMENT AND FOLLOW-UP

MTC remains a predominantly surgical disease. T/

NTT and central neck compartment dissection should be done in all cases, with consideration to be given to ipsilateral MRND and/or mediastinal dissection¹⁶². Bilateral neck dissections are recommended for all familial cases, as well as multifocal, apparently sporadic MTC¹⁶². For members of families of MEN2 who are proven to be carriers of RET gene mutation, prophylactic thyroidectomy is recommended. The timing of the surgery is controversial, but it depends on the actual codon of the RET gene where the mutation is localized¹⁶⁵:

- Children with MEN2B and/or RET codon 883, 918 or 922 mutations are classified as having the highest risk for aggressive MTC development (“level 3 risk”), and should have T/NTT within the first 6 months – preferably within the first month – of life.
- Children with RET codon 611, 618, 620 or 634 mutations are classified as having a moderately high risk for aggressive MTC development (“level 2 risk”), and should have T/NTT performed before the age of 5.
- Children with RET codon 609, 768, 790, 791 804 and 891 mutations are classified as having the least high risk of developing aggressive MTC (“level 1 risk”). There is little consensus on the management of patients with these mutations. Some advocate T/NTT by the age of 5. Others suggest that thyroidectomy by age 10 is appropriate, while yet other clinicians recommend periodic pentagastrin-stimulated calcitonin testing only, withholding surgery until the first occurrence of an abnormal stimulated calcitonin result.

Postoperative EBRT should be offered to patients with high risk of recurrence in the thyroid bed, as well as those who present with cervical, supraclavicular or mediastinal lymphadenopathy¹⁶⁶. Of note, there is no role of RAI ablative therapy in the postoperative management of MTC. Peripheral levels of calcitonin and CEA are used for monitoring disease activity after the initial operation. Patients with persistently elevated – or increasing – calcitonin levels harbor residual or recurrent/metastatic MTC and, in these cases, additional imaging should be performed for localization of the disease deposits, leading to potential further surgical treatment. Imaging is done with conventional modalities, such as neck U/S and CT/MRI. Additional imaging modalities, such as scintigraphy

with ¹¹¹In-pentetreotide (OctreoScan®)¹⁶⁷, ¹³¹I- (or ¹²³I-) meta-iodobenzylguanidine (MIBG)¹⁶⁸, ¹³¹I- or ⁹⁰Y-labeled anti-CEA antibodies¹⁶⁹, or positron emission tomography (PET) with ¹⁸F-fluoro-deoxyglucose (FDG)¹⁷⁰ – or fluoro-dopamine¹⁷¹ – can be used in selected cases. Additionally, selective venous catheterization of the neck/mediastinal venous systems can be useful in localizing disease¹⁷². The use of MTC-seeking radionuclides for imaging has led to their consideration as potential therapeutic agents, although the current experience with ⁹⁰Y-labeled anti-CEA antibodies or ¹³¹I-MIBG is limited to a few cancer centers^{168,173}.

IX. RARE THYROID TUMORS: CONTROVERSIES IN THEIR DIAGNOSIS AND MANAGEMENT

In addition to the above categories of TC, rarely, other tumorous conditions also occur that either originate in or extend to the thyroid gland¹⁷¹. These are as follows:

- Mucoepidermoid TC (with or without peritumoral sclerosis and eosinophilic infiltrates)¹⁷⁵.
- Thyroid lymphoma. This is usually a non-Hodgkin’s T-lymphocyte large-cell immunoblastic lymphoma; more rarely, thyroid lymphomas can be low-grade “MALTomas”. There is definite association of the development of thyroid lymphoma with long-standing Hashimoto’s thyroiditis. Thyroid lymphoma occurs primary in the elderly¹⁷⁶.
- Sarcoma (fibro-, lympho-, lipo-, carcinosarcoma, Kaposi sarcoma)¹⁷⁷⁻¹⁸⁰.
- Hemangioendothelioma; Angiosarcoma^{181,182}.
- Thyroid teratoma. (This is usually a benign tumor in childhood and adolescence, yet it shows highly malignant behavior in adults.)¹⁸³
- Primary thyroid thymoma¹⁸⁴.
- Plasmocytoma¹⁸⁵.
- Langerhans’-cell histiocytosis (LCH)¹⁸⁶.
- Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy)¹⁸⁷.
- Metastatic tumors to the thyroid (metastases from: lung, breast, kidney, colon, pancreas, ovary, esophagus, bladder, vaginal primary carcinoma, metastases from melanoma, and metastases from car-

cinoma of unknown primary [CUP])¹⁸⁸⁻¹⁹⁰.

- Malignant neuroendocrine thyroid tumors, including chemodectomas and paragangliomas¹⁹¹.

The prognosis of these rare tumors of the thyroid gland remains only partially known, primarily due to the rarity of the above entities. Similarly, there are no set treatment guidelines for these entities. When we are confronted with patients having these rare thyroid tumors, we are acutely reminded of the need for the application of an extended differential diagnosis, especially in cases of thyroid nodules with unusual or atypical cytopathologic or histopathologic features, and subsequent need for referral to a tertiary/referral cancer center.

- Finally, we would like to mention the entity of malignant struma ovarii (MSO). This is a rare teratomatous tumor that originates from thyroid cellular elements in the ovary. Malignant transformation of formerly benign strumae ovarii to MSO most commonly are associated with an FTC-like phenotype, although, rarely MSOs are encountered with PTC-like histologic differentiation. The pattern of metastases from MSO primaries is different from that of TCs originating in the thyroid, due to the site of origin of the malignancy. MSOs frequently demonstrate lymphatic spread to the abdominal lymph nodes, peritoneum, and liver¹⁹². Treatment in the absence of widely metastatic disease consists of ipsilateral salpingo-oophorectomy and extensive regional node dissection. If metastatic disease exists at presentation, then local surgery should be followed by T/NTT, and administration of high-dose RAI therapy under hypothyroid conditions¹⁹³.

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