2014 American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer

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ABSTRACT

Background: Thyroid nodules are a common clinical problem, and differentiated thyroid cancer is becoming increasingly prevalent. Since the American Thyroid Association's guidelines for the management of these disorders were published in 2006 and revised in 2009, significant scientific advances have occurred in the field. The aim of this guideline is to inform clinicians, patients, researchers, and health policy makers on updated published evidence relating to the diagnosis and management of thyroid nodules and differentiated thyroid cancer.

Methods: The specific clinical questions addressed in this guideline were based on prior versions of the guidelines, stakeholder input, and input of task force members. Task force panel members were educated on knowledge synthesis methods, including: electronic database searching, review and selection of relevant citations, and critical appraisal of selected papers. Published English language articles on adults were eligible for inclusion. The American College of Physicians (ACP) Guideline Grading System was used for critical appraisal of evidence and grading strength of recommendations for therapeutic interventions. As an ACP grading system is not intended for appraisal of studies evaluating diagnostic tests, we developed a similarly formatted system to appraise the quality such studies and resultant recommendations. The guideline panel had complete editorial independence from the ATA. Competing interests of guideline task force members were regularly updated and communicated to the ATA as well as the rest of the panel members.

Results: The revised guidelines for the management of thyroid nodules include recommendations regarding initial evaluation, clinical and ultrasound criteria for fine-needle aspiration biopsy, interpretation of fine-needle aspiration biopsy results, use of molecular markers and management of benign thyroid nodules. Recommendations regarding the initial management of thyroid cancer include those relating to screening for thyroid cancer, staging and risk assessment, surgical management, radioiodine remnant ablation, and TSH suppression therapy using levothyroxine. Recommendations related to long-term management of differentiated thyroid cancer include those related to surveillance for recurrent disease using imaging and serum thyroglobulin, thyroid hormone therapy, management of recurrent and metastatic disease, consideration for clinical trials and targeted therapy, as well as directions for future research.

Conclusions: We have developed evidence-based recommendations to inform clinical

decision making in the management of thyroid nodules and differentiated thyroid cancer. They represent, in our opinion, contemporary optimal care for patients with these disorders.

INTRODUCTION

THYROID NODULES are a common clinical problem. Epidemiologic studies have shown the prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world (1;2). In contrast, high-resolution ultrasound (US) can detect thyroid nodules in 19–68% of randomly selected individuals with higher frequencies in women and the elderly (3;4). The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer which occurs in 7–15% depending on age, sex, radiation exposure history, family history, and other factors (5;6). Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises the vast majority (>90%) of all thyroid cancers (7). In the United States, approximately 63,000 new cases of thyroid cancer will be diagnosed in 2014 (8) compared with 37,200 in 2009 when the last ATA guidelines were published. The yearly incidence has nearly tripled from 4.9 per 100,000 in 1975 to 14.3 per 100,000 in 2009 (9). Almost the entire change has been attributed to an increase in the incidence of papillary thyroid cancer (PTC). Moreover, 25% of the new thyroid cancers diagnosed in 1988-89 were $\leq$ 1cm compared with 39% of the new thyroid cancer diagnoses in 2008-9 (9). This tumor shift may be due to the increasing use of neck ultrasonography and early diagnosis and treatment (10), trends that are changing the initial treatment and follow-up for many patients with thyroid cancer. By 2019, one study predicts that papillary thyroid cancer will be come the third most common cancer in women at a cost of 19-21 billion dollars in the U.S. (11). Furthermore, patients with a recent diagnosis of cancer were >2.5-fold more likely to file for bankruptcy than those without a cancer diagnosis (12). Amazingly, patients with thyroid cancer had one of the highest risks for filing bankruptcy (approximately 3.5-fold), suggesting that the increasing incidence and treatment of thyroid cancer can carry many risks. Optimization of long-term health outcomes of individuals with thyroid neoplasms is critically important.

In 1996, the American Thyroid Association (ATA) published treatment guidelines for patients with thyroid nodules and DTC (13). Over the last 15-20 years, there have been many advances in the diagnosis and therapy of both thyroid nodules and DTC, but clinical controversy exists in many areas. A long history of insufficient peer-reviewed research funding for high quality clinical trials in the field of thyroid neoplasia, may be an important contributing factor to existing clinical uncertainties (11). Methodologic limitations or conflicting findings of older studies present a significant challenge to modern-day medical decision-making in many aspects

of thyroid neoplasia. Although not a specific focus of this guideline, we recognize that feasibility and cost considerations of various diagnostic and therapeutic options also present important clinical challenges in many clinical practice settings.

AIM AND TARGET AUDIENCE

Our objective in this guideline is to inform clinicians, patients, researchers, and health policy makers about the best available evidence (and its limitations), relating to the diagnosis and treatment of thyroid nodules and differentiated thyroid cancer. This document is intended to inform clinical decision-making. This guideline should not be interpreted as a replacement for clinical judgement and should be used to complement informed, shared patient-healthcare provider deliberation on complex issues. It is important to note that national clinical practice guidelines may not necessarily constitute a legal standard of care in all jurisdictions (14). If important differences in practice settings present barriers to meaningful implementation of the recommendations of this guideline, interested physicians or groups (in or outside of the USA) may consider adapting the guidelines using established methods (15;16)(ADAPTE Collaboration, 2009 http://www.g-i-net)(Can-Implement © Guideline Adaptation and Implementation Planning Resource. 2012 Version 3.0 http://www.cancerview.ca/idc/groups/public/documents/webcontent/can_implement_guide_lines.pdf). As our primary focus was reviewing the quality of evidence related to health outcomes and diagnostic testing, we have decided a priori, not to focus on economic resource implications in this guideline. As part of our review, we have identified some knowledge gaps in the field, with associated future research priorities.

Other groups have previously developed guidelines, including the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons (17), the British Thyroid Association and The Royal College of Physicians (epub? 2014), and the National Comprehensive Cancer Network (https://www.nccn.org). The European Thyroid Association has published consensus guidelines for postoperative US in the management of DTC (18). The European Association of Nuclear Medicine has also published consensus guidelines for radioiodine (RAI) therapy of DTC (19). The Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons has recently revised guidelines on treatment of patients with thyroid tumors (20). Given the existing controversies in the field, differences in critical appraisal approaches for existing evidence, and differences in clinical practice patterns

across geographic regions and physician specialties, it should not be surprising that all of the organizational guidelines are not in complete agreement for all issues. Such differences highlight the importance of clarifying evidence uncertainties with future high quality clinical research.

METHODS

The ATA guidelines were published in 2006 (21) and revised in 2009 (22). Because of the rapid growth of the literature on this topic, plans for revising the guidelines within approximately four years of publication were made at the inception of the project. A task force chair was appointed by the ATA President with approval of the Board. A task force of specialists with complementary expertise (Endocrinology, Surgery, Nuclear Medicine, Radiology, Pathology, Oncology, Molecular Diagnostics, and Epidemiology) was appointed. In order to have broad specialty and geographic representation, as well as fresh perspectives, one-third of the task force is to be replaced for each iteration of the guidelines, as per ATA policy. Upon discussion among the panel members and the Chair with other Chairs of other ATA guideline committees, the Americal College of Physicians' Grading System was adopted for use in this guideline, relating to critical appraisal and recommendations on therapeutic interventions (23)(Tables 1 and 2). An important component of this guideline was judged to be critical appraisal of studies of diagnostic tests, however, the ACP Guideline Grading System is not designed for this purpose. We reviewed a number of appraisal systems for diagnostic tests, but some of the complexity and time-consuming nature of some systems limited their feasibility for implementation in our group in our group (24-28). We drafted , revised, and piloted use of a newly developed diagnostic test appraisal system that was acceptable to panel members which included consideration of the following methodologic elements: consecutive recruitment of patients representative of clinical practice, use of an appropriate reference gold standard, directness of evidence (eg. target population of interest, testing procedures representative of clinical practice, and relevant outcomes), precision of diagnostic accuracy measures (eg. width of confidence intervals for estimates such as sensitivity, specificity), and consistency of results among studies using the same test (Tables 3 and 4). In the majority of circumstances in this guideline (unless otherwise specified), the outcome of interest for the diagnostic test was the diagnosis of thyroid cancer (relative to a histologic gold standard). However, prognostic studies were also graded using the diagnostic study critical appraisal framework. In terms of strength of

recommendation for use of diagnostic studies, we modeled our approach on the ACP system for therapeutic studies, as previously described, but the target outcome was the accuracy in establishing a definitive diagnosis, largely relating to the diagnosis of new or recurrent malignancy (unless otherwise specified). Diagnostic tests or risk stratification systems used for estimation of prognosis were also appraised using the diagnostic test grading system. An important limitation of our diagnostic test appraisal system is that it does not specifically examine the clinical utility of a test in improving long-term health outcomes by execution of the test as part of an intended therapeutic strategy (unless specifically noted). However, much as possible, we tried to separate recommendations on the diagnostic accuracy of a test, from therapeutic management based on the test result, with the latter grading being more rigorous, and based on longer term outcomes (whenever possible). It is important to note that according to our diagnostic test grading system, a body of well-executed non-randomized diagnostic accuracy studies could be considered high quality evidence; yet, a therapeutic strategy incorporating the use of the diagnostic test would require one or more well-executed randomized controlled trials to be considered high quality evidence. In developing and applying our diagnostic test critical appraisal system, we considered American societal values, relating to the importance of informing patients about potentially helpful tests developed for their clinical situation (with counseling on relevant limitations) and the role of patients in informed, shared decision-making relating to diagnostic and therapeutic strategies. Such input was based on thoughtful consideration of stakeholder input, including input from physician stakeholders who were committee members. As this was a preliminary, pilot, utilization of this diagnostic test critical appraisal system by our group, we have labeled recommendations using this system in the manuscript (diagnostic test recommendation), moreover, we anticipate the future iterations of guidelines will likely incorporate further refinements to the system, or even possible adoption of another system, if superior and feasible to execute by contributing physicians.

Prior to initiating the reviews, all task force members were provided written and verbal group advice on conducting electronic literature searches, critical appraisal of articles, and rationale for formulating strength of recommendations from a panel member with Epidemiology (via e-mail documents, a teleconference meeting on February 21, 2012). For each question, a primary reviewer performed a literature search, appraised relevant literature, generated recommendations, accompanying text and a relevant bibliography. This was then reviewed by

the secondary reviewer, revised as needed, and presented for review by the entire panel. Feedback and suggestions for revisions from the Chair and panel members were obtained via email, regularly scheduled teleconferences, and face-to-face meetings held in conjunction with scientific meetings. Once the manuscript was drafted, all suggestions for revisions were regularly reviewed by all panel members in the form of a tracked changes draft manuscript and teleconferences. The draft document continued to be revised until no further suggestions for further revisions were requested by any panel members. Thus, general consensus on acceptability of recommendations and manuscript was achieved, with the fundamental understanding that that not all recommendations may be feasible in all practice settings, and adaptation of the guideline recommendations may need in some practice settings.

Formal stakeholder input in development of this guideline was sought from ATA membership in an online survey distributed in October 2011. Thyroid cancer survivor group leadership input was sought from three North American thyroid cancer groups via e-mail correspondence in January to March of 2012. We also reviewed any letters, editorials, or reviews of the 2009 iteration of the guideline (22) that were collected by the current Chair of the committee. Pre-publication verbal feedback on some of the key guideline recommendations was received at a formal Satellite Symposium held in conjunction with the Endocrine Society meeting in Chicago on June 19, 2014. Feedback and suggestions were formally discussed by the panel, and incorporated in the guideline development as much as possible. The organization of management guideline recommendations is shown in Table 5.

The medical opinions expressed here are those of the authors, and the committee had complete editorial independence from the ATA in writing the guideline. No funding was received by individual committee members from the ATA or industry, for work on these guidelines. Competing interests of all committee members were reviewed at inception of the group, yearly, and upon completion of the guidelines, and are included with this document. The following groups reviewed and endorsed the final document: the ATA Board of Directors and (in alphabetical order) by the American Association of Clinical Endocrinologists (AACE), American College of Endocrinology, British Association of Head and Neck Oncologists (BAHNO), The Endocrine Society, European Association for Cranio-Maxillo-Facial Surgery (EACMFS), European Association of Nuclear Medicine (EANM), European Society of Endocrine Surgeons (ESES), European Society for Paediatric Endocrinology (ESPE),

International Association of Endocrine Surgeons (IAES), and Latin American Thyroid Society (LATS). (need to reach out for endorsements)

[A1] THYROID NODULE GUIDELINES

A thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma. Some palpable lesions may not correspond to distinct radiologic abnormalities (29). Such abnormalities do not meet the strict definition for thyroid nodules. Nonpalpable nodules detected on US or other anatomic imaging studies are termed incidentally discovered nodules or "incidentalomas." Nonpalpable nodules have the same risk of malignancy as do sonographically-confirmed palpable nodules of the same size (30). Generally, only nodules >1 cm should be evaluated, since they have a greater potential to be clinically significant cancers. Occasionally, there may be nodules <1 cm that require evaluation because of suspicious US findings, associated lymphadenopathy, or other high-risk clinical factors such as a history of childhood head and neck irradiation or a history of thyroid cancer in one or more first-degree relatives. In very rare cases, some nodules <1 cm lack these sonographic and clinical warning signs yet may nonetheless cause future morbidity and mortality. This remains highly unlikely, and given the unfavorable cost/benefit considerations, attempts to diagnose and treat all such small thyroid cancers in an effort to prevent exceedingly rare outcomes is deemed to cause more harm than good. In general, the guiding clinical strategy acknowledges that most thyroid nodules are low risk, and many thyroid cancers pose minimal risk to human health and can be effectively treated.

[A2] What is the role of thyroid cancer screening in people with familial follicular-cell derived differentiated thyroid cancer?

■ RECOMMENDATION 1

Screening people with familial follicular cell-derived differentiated thyroid cancer may lead to an earlier diagnosis of thyroid cancer, but the panel cannot recommend for or against ultrasound screening since there is no evidence that this would lead to reduced morbidity or mortality. (**No recommendation, Insufficient evidence**)

Screening programs for patients at risk of oncological disease are usually advocated based on the following evidence: a) a clear demonstration that the patient is indeed at risk; b) demonstration that familial disease is more aggressive than sporadic disease, thus implying that earlier diagnosis by screening may be clinically important; c) demonstration that screening allows the detection of the disease at an earlier stage; d) early diagnosis has an impact on subsequent outcome, both recurrence and survival.

Family members of patients with non-medullary differentiated thyroid cancer may be considered at risk based on epidemiological evidence showing that 5-10% of DTCs have a familial occurrence. However, in most of the pedigrees only two members are affected. There is controversy on whether two family members are sufficient to define a real familial disease rather than a fortuitous association. The probability estimates reported by Charkes (31) suggests that when only two first-degree family members are affected the probability that the disease is sporadic is 62%. This probability decreases when the number of affected family members is three or more. In contrast, the study by Capezzone et al, which was statistically adjusted to minimize risk of 'insufficient follow-up bias', (32) demonstrates that even when only two family members are affected, the disease display the features of "genetic anticipation" (occurrence of the disease at an earlier age and with more aggressive presentation in the subsequent generation compared with the first generation) which is considered good evidence for a distinct clinical entity possibly representing true familial disease. Appearance of the disease at an earlier age has been found also by Moses et al. (33). More advanced disease at presentation and slightly worst outcome have been reported in familial cases by Capezzone et al (32). More frequent multicentricity has been reported by Ito et al. (34), but disease-free and overall survival were similar to sporadic cases. In the study by Park et al (35), FNMTCs with parent-offspring relationship were found to have higher recurrence rate compared with sporadic cases and the second generation had even higher rates compared with the first generation. Mazeh et al. (36) found that familial DTC patients had more aggressive disease compared with sporadic cases regardless of the number of family members affected. In contrast, Robenshtok et al. (37) found that staging at diagnosis and outcomes were not different in familial DTC patients compared with sporadic DTC patients.

It is not possible to speculate on the impact of screening in preventing or reducing recurrence and deaths, since no interventional screening programs have ever been reported in at

risk family members. Patients with familial differentiated thyroid cancer should have a careful history and directed neck examination as a part of routine health maintenance.

[A3] What is the appropriate laboratory and imaging evaluation for patients with clinically or incidentally discovered thyroid nodules?

[A4] Serum TSH measurement

■ RECOMMENDATION 2

A) Serum TSH should be measured during the initial evaluation of a patient with a thyroid nodule. (**Strong recommendation, Moderate-quality evidence**)

B) If the serum TSH is subnormal, a radionuclide thyroid scan should be performed. (**Strong recommendation, Moderate-quality evidence**)

C) If the serum TSH is normal or elevated, a radionuclide scan should not be performed as the initial imaging evaluation (**Strong recommendation, Moderate-quality evidence**)

With the discovery of a thyroid nodule, a complete history and physical examination focusing on the thyroid gland and adjacent cervical lymph nodes should be performed. Pertinent historical factors predicting malignancy include a history of childhood head and neck irradiation, total body irradiation for bone marrow transplantation (38), exposure to ionizing radiation from fallout in childhood or adolescence (39), familial thyroid carcinoma, or thyroid cancer syndrome (e.g., PTEN hamartoma tumor syndrome (Cowden's disease), familial adenomatous polyposis, Carney complex, multiple endocrine neoplasia [MEN] 2, Wermer syndrome) in a first-degree relative, rapid nodule growth and/or hoarseness. Pertinent physical findings suggesting possible malignancy include vocal cord paralysis, cervical lymphadenopathy, and fixation of the nodule to surrounding tissues.

With the discovery of a thyroid nodule >1 cm in any diameter or diffuse or focal thyroidal uptake on F18-flurodeoxyglucose positron emission tomography (FDG-PET) scan, a serum TSH level should be obtained. If the serum TSH is subnormal, a radionuclide thyroid scan should be obtained to document whether the nodule is hyperfunctioning ("hot", i.e., tracer uptake is greater than the surrounding normal thyroid), isofunctioning ("warm", i.e., tracer uptake is equal to the surrounding thyroid), or nonfunctioning ("cold", i.e., has uptake less than the

surrounding thyroid tissue)(40). Since hyperfunctioning nodules rarely harbor malignancy, if one is found that corresponds to the nodule in question, no cytologic evaluation is necessary. If overt or subclinical hyperthyroidism is present, additional evaluation is required. Higher serum TSH, even within the upper part of the reference range, is associated with increased risk of malignancy in a thyroid nodule, as well as more advanced stage thyroid cancer (41;42).

[A5] Serum thyroglobulin measurement

■ **RECOMMENDATION 3**

Routine measurement of serum Tg for initial evaluation of thyroid nodules is not recommended. (**Strong recommendation, Moderate-quality evidence**)

Serum Tg levels can be elevated in most thyroid diseases and are an insensitive and nonspecific test for thyroid cancer (43-45).

[A6] Serum calcitonin measurement

■ **RECOMMENDATION 4**

The panel cannot recommend either for or against routine measurement of serum calcitonin in patients with thyroid nodules. (**No recommendation, Insufficient evidence**)

The utility of serum calcitonin has been evaluated in a series of prospective, non-randomized studies (46-50). These data suggest that the use of routine serum calcitonin for screening may detect C-cell hyperplasia and medullary thyroid cancer (MTC) at an earlier stage and overall survival consequently may be improved. However, most studies relied on pentagastrin stimulation testing to increase specificity. This drug is not available in the United States, Canada and some other countries, and there remain unresolved issues of sensitivity, specificity, assay performance, cut-offs using calcium stimulation (51) and cost-effectiveness. Two retrospective studies have shown improved survival in patients diagnosed with MTC after routine calcitonin testing compared with historical controls (49;52), but were unable to show a decreased number of MTC related deaths. A cost-effectiveness analysis suggested that calcitonin screening would be cost effective in the United States (53). However, prevalence estimates of MTC in this analysis included patients with C-cell hyperplasia and microMTC,

which have uncertain clinical significance. Based on the retrospective nature of the survival data, unresolved issues of assay performance, lack of availability of pentagastrin in North America, and potential biases in the cost-effective analysis, the task force cannot recommend for or against the routine measurement of serum calcitonin as a screening test in patients with thyroid nodules, although there was not uniform agreement on this recommendation. There was, however, agreement that serum calcitonin may be considered in the subgroup of patients where an elevated calcitonin may change the diagnostic or surgical approach (ie – patients considered for less that total thyroidectomy, patients with suspicious cytology not consistent with PTC). If the unstimulated serum calcitonin determination has been obtained and the level is greater than 50-100 pg/mL, medullary cancer is more commonly present (54).

There is emerging evidence that a calcitonin measurement from a thyroid nodule FNA washout may be helpful in the preoperative evaluation of patients with a modestly elevated basal serum calcitonin (20-100 pg/ml) (55).

[A7] ^{18}FDG-PET scan

■ **RECOMMENDATION 5**

A) Focal FDG-PET uptake within a sonographically confirmed thyroid nodule conveys an increased risk of thyroid cancer, and fine needle aspiration is recommended. (**Strong recommendation, Moderate-quality evidence**)

B) Diffuse FDG-PET uptake, in conjunction with sonographic and clinical evidence of chronic lymphocytic thyroiditis, does not require further imaging or fine needle aspiration. (**Strong recommendation, Moderate-quality evidence**)

^{18}FDG-PET is increasingly performed during the evaluation of patients with both malignant and non-malignant illness. While FDG-PET imaging is not recommended for the evaluation of patients with newly detected thyroid nodules or thyroidal illness, the incidental detection of abnormal thyroid uptake may nonetheless be encountered. Importantly, incidental FDG-PET uptake in the thyroid gland can be either focal or diffuse. Focal FDG-PET uptake in the thyroid is incidentally detected in 1-2% of patients, while an additional 2% of patients demonstrate diffuse thyroid uptake (56-58).

Focal thyroid uptake most often corresponds to a clinically relevant thyroid nodule, and ultrasound examination is thus recommended to define thyroid anatomy. Importantly, focal FDG-PET uptake increases malignancy risk in an affected nodule, and therefore clinical evaluation and FNA is recommended. A recent meta-analysis confirmed that approximately 1 in 3 (~35%) FDG-PET positive thyroid nodules proved cancerous (56), with higher mean SUVmax in malignant compared to benign nodules (6.9 vs. 4.8, $p<0.001$). In contrast, diffuse thyroid uptake most often represents benign disease corresponding to macrophage uptake in the setting of Hashimoto's disease or other diffuse thyroidal illness. However, if detected, diffuse FDG-PET uptake in the thyroid should also prompt sonographic examination to ensure there is no evidence of clinically relevant nodularity. Most patients with diffuse FDG-PET uptake demonstrate diffuse heterogeneity on sonographic examination, and no further intervention or FNA is required. It is appropriate to evaluate thyroid function in these patients.

[A8] Thyroid sonography

■ **RECOMMENDATION 6**

Thyroid sonography should be performed in all patients with known or suspected thyroid nodules. (**Strong recommendation, High-quality evidence**)

Diagnostic thyroid/neck US should be performed in all patients with a suspected thyroid nodule, nodular goiter, or radiographic abnormality suggesting a thyroid nodule incidentally detected on another imaging study (e.g., computed tomography (CT) or magnetic resonance imaging (MRI) or thyroidal uptake on FDG-PET scan). Thyroid US can answer the following questions: Is there truly a nodule that corresponds to an identified abnormality? How large is the nodule? What is the nodule's pattern of ultrasound imaging characteristics? Is suspicious cervical lymphadenopathy present? Is the nodule greater than 50% cystic? Is the nodule located posteriorly in the thyroid gland? These last two features might decrease the accuracy of FNA biopsy performed with palpation (59;60).

Ultrasound should evaluate the following: thyroid parenchyma (homogeneous or heterogeneous) and gland size; size, location, and sonographic characteristics of any nodule(s); the presence or absence of any suspicious cervical lymph nodes in the central or lateral compartments. The ultrasound report should convey nodule size (in 3 dimensions) and location

(e.g. right upper lobe) and a description of the nodule's sonographic features including: composition (solid, cystic proportion, or spongiform), echogenicity, margins, presence and type of calcifications, and shape if taller than wide, and vascularity. The pattern of sonographic features associated with a nodule confers a risk of malignancy, and combined with nodule size, guides FNA decision making (61;62) (see Recommendation 8).

In the subset of patients with low serum TSH levels who have undergone radionuclide thyroid scintigraphy suggesting nodularity, ultrasound should also be performed to evaluate both the presence of hyperfunctioning nodules concordant with functioning areas on the scan, which do not require FNA, as well as other nonfunctioning nodules that meet sonographic criteria for FNA (63).

[A9] Ultrasound (US) for FNA decision making.

■ **RECOMMENDATION 7**

FNA is the procedure of choice in the evaluation of thyroid nodules, when clinically indicated (**Strong recommendation, High-quality evidence**)

FNA is the most accurate and cost-effective method for evaluating thyroid nodules. Retrospective studies have reported lower rates of both nondiagnostic and false-negative cytology from FNA procedures performed using US-guidance compared to palpation (64;65). Therefore, for nodules with a higher likelihood of either a nondiagnostic cytology (>25–50% cystic component) (60) or sampling error (difficult to palpate or posteriorly located nodules), US-guided FNA is preferred. If the diagnostic US confirms the presence of a predominantly solid nodule corresponding to what is palpated, the FNA may be performed using palpation or US-guidance.

[A10] Recommendations for diagnostic FNA of a thyroid nodule based on sonographic features

■ **RECOMMENDATION 8**

Thyroid nodule diagnostic FNA is recommended for (Figure 2):

A) Nodules $\geq$ 1cm with high suspicion sonographic pattern (**Strong recommendation, Moderate-quality evidence**)

B) Nodules ≥ 1 cm with intermediate suspicion sonographic (**Strong recommendation, Low-quality evidence**)

C) Nodules ≥ 1.5cm with low suspicion sonographic pattern (**Weak recommendation, Low-quality evidence**)

D) Nodules ≥ 2cm with very low suspicion sonographic pattern (e.g. - spongiform) (**Weak recommendation, Moderate-quality evidence**)

Thyroid nodule diagnostic FNA is not required for:

E) Nodules that do not meet the above criteria. (**Strong recommendation, Moderate-quality evidence**)

F) Nodules that are purely cystic (**Strong recommendation, Moderate-quality evidence**)

Thyroid ultrasound (US) has been widely used to stratify the risk of malignancy in thyroid nodules, and aid decision-making about whether FNA is indicated. Studies consistently report that several US gray scale features in multivariable analyses are associated with thyroid cancer, the majority of which are papillary thyroid cancer. These include the presence of microcalcifications, nodule hypoechogenicity compared with the surrounding thyroid or strap muscles, irregular infiltrative or microlobulated margins, and a shape taller than wide measured on a transverse view. Features with the highest specificities (median >90%) for thyroid cancer are microcalcifications, irregular margins, and tall shape although the sensitivities are significantly lower for any single feature (66-70) (71-73). Up to 55% of benign nodules are hypoechoic compared to thyroid parenchyma, making nodule hypoechogenicity less specific. In addition, subcentimeter benign nodules are more likely to be hypoechoic than larger nodules (67). Multivariable analyses confirm that the probability of cancer is higher for nodules with either microlobulated margins or microcalcifications than for hypoechoic solid nodules lacking these features (66). Macrocalcifications within a nodule, if combined with microcalcifications, confer the same malignancy risk as microcalcifications alone (66;70). However, the presence of this type of intranodular macrocalcification alone is not consistently associated with thyroid cancer (74). On the other hand, a nodule that has interrupted peripheral calcifications, in association with a soft tissue rim outside the calcification, is highly like to be malignant and the

associated pathology may demonstrate tumor invasion in the area of disrupted calcification (75;76).

In a recent study comprised of 98% PTC, intranodular vascularity did not have independent predictive value for malignancy in multivariate logistic regression model including gray scale features (68). Two other studies and a meta-analaysis with higher proportions of FTC (10-22%) have shown that intranodular vascularity was correlated with malignancy (62;70;77). FTC exhibits others differences in sonographic features compared to PTC. These tumors are more likely to be iso- to hyperechoic, noncalcified, round (width greater than anterioposterior dimension) nodules with regular smooth margins (78). Similarly, the follicular variant of papillary cancer (FVPTC) is also more likely than conventional PTC to have this same appearance as FTC (75). Distant metastases are rarely observed arising from follicular cancers < 2 cm in diameter, therefore justifying a higher size cutoff for hyperehoic nodules (79).

The vast majority (82-91%) of thyroid cancers are solid (66;69) (71;73;80). Of 360 consecutively surgically removed thyroid cancers at the Mayo clinic, 88% were solid or minimally cystic (<5%), 9% were <50% cystic and only 3 % were more than 50% cystic (81). Therefore, FNA decision making for partially cystic thyroid nodules must be tempered by their lower malignant risk. In addition, evidence linking sonographic features with malignancy in this subgroup of nodules is less robust, originating from univariate rather than multivariable analyses. However, eccentric position of the solid component on one side of the cyst wall and presence of microcalcifications consistently confer a higher risk of malignancy (81-83). Other findings such as lobulated margins or increased vascularity of the solid portion are not as robust risk factors (82;83). On the other hand, spongiform appearance of mixed cystic solid nodules is strongly correlated with benignity (62;66;67;84). Spongiform and other mixed cystic solid nodules may exhibit bright reflectors on ultrasound imaging, caused by colloid crystals or posterior acoustic enhancement of the back wall of a microcystic area. These may be confused with microcalcifications by less proficient sonographers, and a recent meta-analysis confirmed that operator experience is correlated with accurate evaluation of internal calcifications (62). Therefore, because of potential for misclassification, FNA may still be warranted for nodules interpreted as spongiform with a higher size cutoff. Lastly, pure cysts, although rare (<2% of thyroid lesions), are highly likely to be benign (62;85;86).

Given the nuances in sonographic appearances of different thyroid cancer histologies, as

well as the challenges posed by partially cystic nodules, some authors have suggested risk stratification based upon a constellation of sonographic features (85-87). In the absence of sonographically suspicious cervical lymph nodes, features associated with the highest risk for thyroid cancer can be used to triage smaller nodules for fine-needle biopsy, whereas nodules with sonographic appearance suggesting lower risk might be considered for fine needle biopsy at a larger size as determined by maximal diameter (Figures 1 and 2, Table 6). The sonographic appearance for the vast majority of thyroid nodules can be generally classified in the following categories of ultrasound patterns which combine several individual sonographic characteristics. Since the interobserver variability in reporting individual characteristics is moderate even within controlled studies (68), the use of patterns exhibiting correlated sonographic features may be more robust:

<u>High suspicion [malignancy risk >70-90% (85;86;88)]:</u> Solid hypoechoic nodule or solid hypoechoic component in a partially cystic nodule with one or more of the following features: irregular margins (e.g infiltrative, microlobulated, spiculated), microcalcifications, taller than wide shape, disrupted rim calcifications with small extrusive hypoechoic soft tissue component, or evidence of extrathyroidal extension (Figure 2, Table 6). A nodule demonstrating this ultrasound pattern is highly likely to be a papillary thyroid cancer. Nodules with the high suspicion pattern and <u>≥</u> 1cm should undergo diagnostic fine needle biopsy to refute or confirm malignancy. However, in the absence of evidence of extrathyroidal extension, metastatic cervical lymph nodes, or distant metastases, micropapillary thyroid cancers (<1cm) often have an indolent course but this may depend upon patient age (89;90). Although no distant metastases or deaths occurred in a recent observational series of 1235 Japanese patients with biopsy proven papillary thyroid cancer, tumor growth and new appearance of of lymph metastases occurred more frequently in patients younger than 40 years of age compared with those over age 60 (5.9% vs. 2.2% for size increase; 5.3% vs. 0.4% for new nodal metastases, $p<0.05$). Thus although a sonographically suspicious subcentimeter thyroid nodule without evidence of extrathyroidal extension or sonographically suspicious lymph nodes may be observed with close sonographic follow up of the nodule and cervical lymph nodes, rather than pursuing immediate FNA, patient age and preference may modify decision making.

Intermediate suspicion [malignancy risk 10-20% (85;86;88)]: Hypoechoic solid nodule with a smooth regular margin, without microcalcifications, extrathyroidal extension, or taller than wide shape (Figure 2, Table 6). This appearance has the highest sensitivity (60-80%) for papillary thyroid cancer, but a lower specificity than the above high suspicion pattern, and fine needle biopsy should be considered for these nodules ≥ 1cm to refute malignancy.

Low suspicion [malignancy risk 5-10% (85;86;88)]: Isoechoic or hyperechoic solid nodule, or partiallycystic nodule with eccentric uniformly solid areas without microcalcifications, irregular margin or extrathyroidal extension, or taller than wide shape (Figure 2, Table 6). Only about 15% -20% of thyroid cancers are iso- or hyperechoic on ultrasound, and these are generally the follicular variant of papillary thyroid cancer or follicular thyroid cancers (67). Fewer than 20% of these nodules are partially cystic. Therefore, these appearances are associated with a lower probability of malignancy and observation may be warranted until ≥ 1.5cm.

Very low suspicion [<3% (62;85;86;88)]: Spongiform or partially cystic nodules without any of the sonographic features described in the low, intermediate or hight suspicion patterns have a low risk of malignancy and may be observed until ≥ 2cm (Figure 2, Table 6).

Benign [<1% (85;86;88)]: Purely cystic nodules are very unlikely to be malignant and fine needle biopsy is not indicated for diagnostic purposes (Figure 2, Table 6). Aspiration with or without ethanol ablation may be considered as a therapeutic intervention if a cyst is large and symptomatic; cytology should be performed if aspirated.

Sonographic evaluation of the anterior cervical lymph node (central and bilateral) compartments should be performed whenever thyroid nodules are detected. If ultrasound detects cervical lymph nodes that are sonographically suspicious for thyroid cancer, FNA of the suspicious lymph node should be performed for cytology and washout for thyroglobulin measurement if indicated. In addition, this scenario also warrants US FNA of a subcentimeter nodule that is likely to represent the primary tumor based upon sonographic features.

Although there are several known clinical risk factors for thyroid cancer in patients with thyroid nodules including, immobility with swallowing, pain, cough, voice change, growth, lymphadenopathy and history of childhood irradiation (either therapeutic e.g. cranial radiation in

childhood leukemia or for benign conditions, e.g. enlarged thymus or tonsils) or familial thyroid cancer (91), these have not been incrementally included in multivariable analyses of grayscale sonographic features and thyroid cancer risk. However, given the higher pre-test likelihood of thyroid cancer associated with these clinical risk factors, FNA can be considered at lower size cut-offs for all of the sonographic appearances described above.

Ultrasound elastography (USE) has similarly been used investigated for its ability to modify thyroid cancer risk assessment among clinically relevant thyroid nodules. Elastography is a measurement of tissue stiffness. Performance requires an ultrasound machine, as well as a required elastography computational module which most often must be purchased separately. An initial propsective study of 92 selected, non-randomized patients suggested a near 100% positive and negative predictive value (92). However, more recent, larger trials have confirmed substantially different results. Moon and colleagues retrospectively studied 703 thyroid nodules in comparison to gray-scale ultrasound (74). Performance of USE was inferior to that of gray-scale ultrasound assessment. The largest prospective study of 706 patients with 912 thyroid nodules was recently published by Azizi et al (93). In this study, the positive predictive value of USE was only 36%, comparable to that of microcalcifications. The negative predictive value of USE was 97% in a population with cancer prevalence of 9%. Thus, while USE holds promise as a means by which to non-invasively assess cancer risk, its performance is highly variable and operator dependent. Perhaps most importantly, USE can only be effectively applied to solid nodules, thus excluding its utility for cystic or partially cystic nodules. Furthermore, to be amenable to direct pressure and determination of tissue strain, the index nodule must not overlap with other nodules in the anterioposterior plane. Obese patients, those with multinodular goiters and coalescent nodules, or patients in whom the nodule is posterior or inferior are not candidates for this USE. Thus, at present, USE cannot be widely applied to all thyroid nodules in a similar fashion to gray-scale or color ultrasound examination. The committee therefore believes USE (when available) may prove a helpful tool for pre-operative risk assessment in those patients in whom accurate assessment can be performed. However, the committee cannot presently recommend its universal use or widespread adoption. Importantly, the ability to perform (or not perform) USE should not modify the recommendation for traditional gray-scale sonographic evaluation.

Finally, while most thyroid nodules meeting the above sonographic patterns and sizes should undergo FNA, we acknowledge that a conservative approach of active surveillance management may be appropriate as an alternative to FNA in selected patients. These may include: patients with very low risk tumors (e.g. – no clinical or radiographic evidence of invasion or metastases), patients at high surgical risk or those with a relatively short life span in whom the benefits of intervention may be unrealized.

[A11] What is the role of fine-needle aspiration (FNA), cytology interpretation and molecular testing in patients with thyroid nodules?

■ RECOMMENDATION 9

Thyroid nodule FNA cytology should be reported using diagnostic groups outlined in the Bethesda System for Reporting Thyroid Cytopathology (**Strong recommendation, Moderate-quality evidence**)

To address a significant variability in the reporting of cytological findings in thyroid FNA samples, the 2007 National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference provided consensus recommendations known as the Bethesda System for Reporting Thyroid Cytopathology (94;95). The Bethesda system recognizes six diagnostic categories and provides an estimation of cancer risk within each category based upon literature review and expert opinion (Figure 1, Table 7). These categories are: (i) nondiagnostic/unsatisfactory; (ii) benign; (iii) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); (iv) follicular neoplasm/suspicious for follicular neoplasm (FN), a category that also encompasses the diagnosis of Hürthle cell neoplasm/suspicious for Hürthle cell neoplasm; (v) suspicious for malignancy (SUSP), and (vi) malignant. Recent studies that applied the criteria and terminology of the Bethesda System to a large series of patients have shown a relatively good concordance in reporting FNA cytology, with 89-95% of samples being satisfactory for interpretation and 55-74% reported as definitively benign and 2-5% as definitively malignant (96-99). The remaining samples are cytologically indeterminate, including AUS/FLUS in 2-18% of nodules, FN in 2-25%, and SUSP in 1-6%. In these studies, the probability of malignancy for each Bethesda category demonstrated significant variability, but was overall compatible with the range predicted by the Bethesda System, with the

exception of the AUS/FLUS diagnosis, where the risk of malignant outcome in some studies was significantly higher than predicted (Table 7) (98;100). Recently, a blinded prospective evaluation of inter-observer concordance using Bethesda classification was performed. These data confirm an inherent limitation to the reproducibility of interpreting any cytology specimen (101). Specimens labeled AUS/FLUS and Suspicious for Malignancy were associated with the highest discordance rates. Nonetheless, classification using the Bethesda system has proven highly beneficial, allowing practicioners to speak with the same terminology and better convey malignant risk. Ideally, the risk of malignancy in each of the six diagnostic categories should be independently defined at each cytology center or institution to guide clinicians on risk estimates and help choose appropriate molecular testing for patients with indeterminate cytology.

[A12] Nondiagnostic cytology

■ **RECOMMENDATION 10**

(A) For a nodule with an initial nondiagnostic cytology result, FNA should be repeated with US guidance and, if available, on-site cytologic evaluation (**Strong recommendation, Moderate-quality evidence**)

(B) Repeatedly nondiagnostic nodules without a high suspicion sonographic pattern require close observation or surgical excision for histopathologic diagnosis (**Weak recommendation, Low-quality evidence**)

(C) Surgery should be considered for histopathologic diagnosis if the cytologically nondiagnostic nodule is a high suspicion sonographic pattern, growth of the nodule is detected during ultrasound surveillance, or clinical risk factors for malignancy are present (**Weak recommendation, Low-quality evidence**)

Nondiagnostic or unsatisfactory FNA biopsies are those that fail to meet the established quantitative or qualitative criteria for cytologic adequacy (i.e. the presence of at least six groups of well-visualized follicular cell, each group containing at least 10 well-preserved epithelial cells, preferably on a single slide) (94;102). After an initial nondiagnostic cytology result, repeat FNA with US guidance and, if available, on-site cytologic evaluation, will substantially increase the rate of specimen adequacy (103-107). It has been suggested that repeat FNA should be performed no sooner than 3 months after the initial FNA to prevent false-positive interpretation

due to biopsy-induced reactive/reparative changes (108). However, if clinical and ultrasound features are suspicious for malignancy, a shorter waiting period may be appropriate. One study questioned the necessity for a 3 month waiting period after the first FNA as it did not find a correlation between the diagnostic yield/accuracy of repeated FNA and the waiting time between the procedures (109). Repeat FNA with ultrasound guidance will yield a diagnostic cytology specimen in 60-80% of nodules, particularly when the cystic component is <50% (60;106;110). Nodules with larger cystic portion have a higher chance to yield nondiagnostic samples on the initial and repeated FNA.

Most nodules with a nondiagnostic cytology interpretation are benign. In large series of patients classified based on the Bethesda System, nondiagnostic samples constituted 2-16% of all FNA samples, of which 7-26% were eventually resected (96-98). The frequency of malignancy among all initially nondiagnostic samples was 2-4% and among those nondiagnostic samples that were eventually resected was 9-32%.

Sonographic features are also useful for indentifying which nodules with repeat nondiagnostic FNA cytology results are more likely to be malignant. Of 104 nodules with 2 nondiagnostic cytology results, thyroid cancer was found in 25% of those with microcalcifications, irregular margins, a taller than wide shape or hypoechogenicity, but in only 4% lacking these features (111).

In some studies, the use of thyroid core-needle biopsy (112) and molecular testing for BRAF (113) or a panel of mutations (114) helped to facilitate appropriate management of these patients, although the full clinical impact of these approaches for nodules with nondiagnostic cytology remains unknown. Some studies have found that core biopsy offers a higher adequacy rate, but may be less sensitive for the detection of papillary cancer (115;116). Mutational testing may be informative in samples considered inadequate by qualitative criteria (i.e. due to poor preparation or poor staining of cells), but is unlikely to be contributory in samples with insufficient quantity of cells.

[A13] Benign cytology

■ RECOMMENDATION 11

If the nodule is benign on cytology, further immediate diagnostic studies or treatment are not required (**Strong recommendation, High-quality evidence**)

Accurate FNA cytology diagnosis depends upon a number of factors including the skill of the operator, FNA technique, specimen preparation and cytology interpretation. Ultrasound guided FNA with real time visualization of needle placement in the target nodule decreases the false negative rate of a benign cytology diagnosis (117-120). Although prospective studies are lacking, malignancy rates of only 1-2% have been reported in large retrospective series that analyzed the utility of systematic repeat FNA in nodules with prior benign cytology results (121-125).

Studies have also attempt to correlate nodule size with accuracy of FNA cytology. Several surgical series have reported higher malignancy rates in nodules >3-4cm, but these suffer from both selection bias (only a subset of patients underwent preoperative FNA) and potential sampling error (FNA performed by palpation) (126;127). Two recent reports of consecutive US FNA evaluation in over 1400 nodules >3cm with initial benign cytology followed for a mean of 3 years confirm a similar false negative rate <1.5% (128;129). Interestingly, in both these studies 66% of the missed cancers were found in nodules with high suspicion pattern, despite initial benign cytology. A recent retrospective study analyzed the long-term followup of 2010 cytologically benign nodules from 1369 patients. Over a mean followup of 8.5 years 18 false negative malignancies were detected. However, no deaths attributable to thyroid cancer were identified in this entire cohort. These data confirm that an initially benign FNA confers negligible mortality risk during long-term follow-up despite a low but real risk of false negatives in this cytologic category (130).

[A14] Malignant Cytology

■ **RECOMMENDATION 12**

If a cytology result is diagnostic for primary thyroid malignancy, surgery is generally recommended. (**Strong recommendation, Moderate-quality evidence**)

A cytology diagnostic for a primary thyroid malignancy will almost always lead to thyroid surgery. However, an active surveillance management approach can be considered as an alternative to immediate surgery in:

A) patients with very low risk tumors (e.g. papillary microcarcinomas without clinically evident metastases or local invasion, and no convincing cytologic or molecular (if performed) evidence of aggressive disease),

B) patients at high surgical risk because of co-morbid conditions,

C) patients expected to have a relatively short life span (e.g. serious cardiopulmonary disease, other malignancies, very advanced age), or

D) patients with concurrent medical or surgical issues that need to be addressed prior to thyroid surgery.

Following thyroid surgery for papillary thyroid microcarcinoma (PTMC) defined as a tumor 1 cm or less in size, disease-specific mortality rates have been reported to be < 1 %, loco-regional recurrence rates are 2-6%, and distant recurrence rates are 1-2% (131;132). It is quite likely that these excellent outcomes are more related to the indolent nature of the disease rather than to the effectiveness of treatment, since two prospective clinical studies of active surveillance from Japan reported similar clinical outcomes in 570 patients with biopsy-proven PTMC that was not surgically removed and that were followed for up to 15 years (90;133). In the study by Ito et al, observation was offered to 340 patients with PTMC that did not have (i) location adjacent to the trachea or on the dorsal surface of the lobe close to the recurrent laryngeal nerve, (ii) FNA findings suggestive high-grade malignancy; (iii) presence of regional lymph node metastases; or (iv) signs of progression during follow-up. Of those, most of patients showed stable tumor size on average follow up of 74 months, whereas 6% showed tumor enlargement by US on 5-year follow-up, and 16% on 10-year follow-up. Furthermore, 1.4% and 3.4% of patients at 5-year and 10-year follow-up showed evidence for lymph node metastases. Of 340 patients, 109 (32%) underwent surgical treatment after observation, including those with tumor enlargement and new lymph node metastases. None of the patients treated with surgery after observation developed tumor recurrence on average follow-up of 76 months. In the study by Sugitani et al, 230 patients with asymptomatic PTMC were followed on average for 5 years. Of those, tumor size enlargement was observed in 7% of patients, and 1% developed apparent lymph node metastasis. 7% of patients underwent surgery after 1-12 years of follow up, and no recurrences were identified in those on limited follow up, suggesting that the delayed surgery did not affect the outcome. A more recent study by Ito and colleagues followed 1235 patients with PTMC under active surveillance for an average of 60 months (89). Only 43 patients (3.5%) had

clinical progression of disease by their stated criteria (tumor growing to > 12 mm or appearance of new lymph node metastases). Interestingly, the younger patients (< 40 years old) had an 8.9% rate of clinical progression, while those 40-60 years old had a 3.5% rate of progression and those > 60 years old had the lowest rate of clinical progression (1.6%).

Despite the evidence that cautious observation is a safe and effective alternative to immediate surgical resection, very few PTMC patients outside of those two centers in Japan are given the option of an active surveillance approach. This is in part due to reports in the literature of a small percentage of patients with PMC presenting with clinically significant regional or distant metastases (131;132;134). Unfortunately, no clinical features (90;135-140) can reliably differentiate the relatively small number of PTMC patients destined to develop clinically significant progression from the larger population of people that harbor indolent PTMCs that will not cause significant disease.

Similarly, well-known thyroid cancer oncogenes, such as BRAF, when taken in isolation, are not able to specifically identify those microcarcinomas that are expected to progress and spread outside of the thyroid. Prevalence of BRAF V600E mutations in microcarcinomas with lymph node metastasis and tumor recurrence is significantly higher, and in some studies BRAF mutation was associated with lymph node metastasis from PTMC on multivariate analysis (139;141;142). These studies showed that although the presence of BRAF V600E mutation identifies 65-77% of patients with PTMC that develop lymph node metastases, the BRAF status taken in isolation has a low positive predictive value for detecting PTMC with extrathyroidal spread and therefore has a limited role for guiding patient management. However, as discussed above, recent data suggest that specific molecular profiles, such as coexistence of BRAF with other oncogenic mutations (such as PIK3CA, AKT1) and presence of TERT or TP53 mutation may serve as a more specific markers of less favorable outcome of papillary thyroid cancer. Therefore, it is likely that finding of one of these genetic profiles in a small tumor would suggest that it represents an early stage of a clinically relevant PTC. Future studies are expected the impact of molecular profiling on clinical management of patients with PTMC.

[A15] Indeterminate cytology (AUS/FLUS, FN, SUSP)

[A16] What are the principles of the molecular testing of FNA samples?

Footnote: The final draft for the sections (A15-A19) and recommendations (13-16) were revised and approved by a subgroup of 7 members of the task force no perceived conflicts or competing interests in this area.

Molecular markers may be classified according to intended use; that is, diagnostic (classification of a disease state), prognostic, or predictive purposes (providing information on the estimated probability of therapeutic benefit or harm of a specific therapy) (143). Furthermore, companion use of predictive molecular markers involves the identification of patient subgroups in whom a therapeutic intervention is proven to be either beneficial or harmful, with intended implications for appropriate clinical stratification of therapies (143). Validation studies of molecular marker tests may include examination of: a) analytic validity (including test accuracy and reproducibility in ascertaining the molecular event), b) clinical validity (the performance of the test in distinguishing different groups of patients, based on biology or expected disease outcome, including measures of sensitivity and specificity or predictive values), and c) clinical utility (examination of the test's ability to improve outcomes, with direct clinical decision-making implications) (143). Furthermore, an NCCN Tumor Markers Task Force has indicated that the clinical utility of a molecular test should be founded in strong evidence proving that use of the marker "improves patient outcomes sufficiently to justify its incorporation into routine clinical practice".

The principal proposed use of molecular markers in indeterminate thyroid FNA specimens is diagnostic (ruling out or in the presence of thyroid malignancy), with the implication of a companion use to inform decision-making on primary surgical treatment (ie. the decision to perform surgery or surgical extent). However, the focus of this section is restricted to the clinical validity testing of molecular testing of indeterminate FNA specimens. It is important to note that long-term outcome data on companion use of molecular marker status to guide therapeutic decision-making is currently lacking and so we do not know if implementation of molecular marker use in routine clinical practice would result in a significant overall benefit in health outcomes in patients with thyroid nodules. Surgical decision-making on indeterminate FNA specimens is reviewed in another section of these guidelines, with some reference to molecular marker testing (if performed). As summarized in a Disease State Commentary from the AACE Thyroid Scientific Committee, use of molecular marker testing on indeterminate FNA speciments should not be intended to replace other sources of information or clinical judgment (144). The pre-test probability of malignancy (based on clinical risk factors, cytology, ultrasound findings), feasibility considerations, and patient preferences are some additional factors that need to be considered in decision-making related to molecular marker testing of FNA specimens.

A number of molecular approaches have been studied in the clinical setting of indeterminate FNA cytologic interpretation (145). One could surmise that an ideal 'rule-in' test would have a positive predictive value (PPV) for histopathologically-proven malignancy similar to a malignant cytologic diagnosis (98.6%), and an ideal 'rule-out' test would have a negative predictive value (NPV) similar to a benign cytologic diagnosis (96.3%) (PV estimates based on a recent meta-analysis of performance of the Bethesda system) (98), and these would hold true with a reasonable degree of precision and reproducibility.

RECOMMENATION 13

If molecular testing is being considered, patients should be counseled regarding the potential benefits and limitations of testing, and about the possible uncertainties in the therapeutic and long-term clinical implications of results.

(Strong recommendation, Low-quality evidence)

The largest studies of preoperative molecular markers in patients with indeterminate FNA cytology have respectively evaluated a panel of genetic mutations and rearrangements (BRAF, RAS, RET/PTC, PAX8/PPARγ) (146), a gene expression classifier (GEC) (mRNA expression of 167 genes) (147), and galectin-3 immunohistochemistry (cell blocks) (148). These respective studies have been subject to various degrees of blinding of outcome assessment (146-148).

Mutational testing has been proposed for use as a 'rule-in' test due to relatively high reported specificity and PPV. Although BRAF V600E single mutation testing has been estimated to have a specificity of approximately 99% (pooled data from 1117 nodules with histopathologic confirmation from multiple studies), the sensitivity has been deemed to be too low to reliably rule-out the presence of malignancy (149). Therefore, mutational panels have been expanded to include multiple mutations/translocations , including BRAF, NRAS, HRAS, and KRAS point mutations, as well as RET/PTC1, RET/PTC3, and PAX8/PPARγ rearrangements (100;114;146;150-152). Mutational panel testing is limited by a relatively low sensitivity (mean sensitivity values of 48% to 63% in indeterminate nodule subgroups in respective prospective and retrospective studies of histopathologically confirmed specimens (146;152); therefore, they cannot reliably rule out malignancy with a negative test in nodules with indeterminate cytology. Although similar mutations are sought, there are some differences

in techniques used to perform mutational testing by various groups (146;152), and it is not known how such differences could affect test performance, as direct, head-to-head comparisons of these tests within the same population are lacking. In order to improve test sensitivity, expansion of mutational marker panels is being studied (153;154). The currently available mutational panels have been proposed to be most useful when surgery is favored; however, this is based on the assumption that the surgical approach would be altered with a positive test, but long-term outcome data proving the overall benefit of this therapeutic strategy are needed. It is important to acknowledge that algorithms employing mutational testing as a means to inform decision-making on extent of primary thyroid surgery (ie. lobectomy or total thyroidectomy) (146) were developed at a time when the ATA guidelines favored total thyroidectomy for most PTCs >1cm in diameter (22). However, this does not reflect recommendations in these guidelines (see Recommendation 34 on surgical management of malignant cytology nodules). Furthermore, long-term outcome data from a strategy of using molecular markers in indeterminate FNA specimens to stratify surgical approach are currently lacking.

Use of a GEC has been proposed as a 'rule-out' test due to relatively high sensitivity and NPV, as reported in a prospective, multi-center, study (147). The relatively low specificity of the GEC test (mean values 48% - 53% in indeterminate nodules subject to histopathologic confirmation) suggests the test cannot definitively rule-in malignancy in indeterminate nodules. In a retrospective analysis of GEC results from 5 institutions, Alexander et al reported that the prevalence of GEC benign readings by institution varied up to 29%, which was not statistically significant (155). The distribution of recruitment from each of the five study sites was highly variable (total n=339 nodules), with two sites contributing only 30 and 37 patients, and the other three sites accounting for the majority of the study population. The prevalence of histopathologically-confirmed malignancy in GEC 'suspicious' nodules ranged from 33% to 80% in the 48 nodules in the AUS/FLUS group across institutions (no 95% CI reported, p=0.11), and from 33% to 67% in the 65 nodules in the FN cytology group (no 95% CI reported, p=0.87) (155). For the 174 patients with GEC 'benign' readings, 4 patients were recommended for surgery (2%), and 41% (71 patients) of this group had short documented follow-up for a mean of 8.5 months (median 8 months, range 1-24 months); ultimately, 6% of patients in this group (11/174) had surgery, with one histopathologically-confirmed malignancy (155). The reproducibility of GEC NPV measures in different populations of patients with indeterminate

cytology thyroid nodules has been recently questioned in two smaller, unblinded single-institution studies (156;157). Neither of these studies reported on precision (95% CI) of predictive estimates in indeterminate cytology nodules (156;157) or any degree of blinding, making it difficult to interpret the findings. However, such data highlight the need for additional independent research examining the reproducibility of diagnostic efficacy of the GEC in more institutions, and the importance of reporting precision estimates for diagnostic accuracy measures. Furthermore, as in the case of other molecular-based diagnostic tests in the field, long-term outcome data from clinical utility studies are needed to inform potential future clinical practice implications of the GEC.

Immunohistochemical stains such as galectin-3 and HBME-1 have been examined in multiple studies of histologically-confirmed thyroid FNA samples with indeterminate cytology, with reports of relatively high rates of specificity, but low sensitivity, for cancer detection (148;158;159). Two of these studies were reported to be prospective (148;158), but only one of the studies reported any degree of blinding (blind centeral histopathologic review) (148). Immunohistochemical stains require the availability of a cell block to perform the staining. Additional diagnostic molecular marker strategies are also under development. Specifically, mRNA markers (160-162), as well as miRNA markers (163-168), have shown initial diagnostic utility in FNA samples with indeterminate cytological diagnoses, but they have not been thoroughly validated. Finally, peripheral blood thyrotropin receptor mRNAassay has been reported to have a 90% PPV and 39% NPV in FNA-based assessment of thyroid nodules with atypical or suspicious cytology in a single center, prospective validation study (169).

In summary, there is currently no single optimal molecular test that can definitively rule in or rule out malignancy in all cases of indeterminate cytology, and long-term outcome data proving clinical utility are needed.

■ RECOMMENDATION 14

If intended for clinical use, molecular testing should be performed in CLIA/CAP certified molecular laboratories, as reported quality assurance practices may be superior compared to other settings. (**Strong recommendation, Low-quality evidence**)

Many molecular marker tests are available in hospital-based molecular pathology laboratories and in reference laboratories. Importantly, all molecular marker tests intended for clinical use should be performed only in CLIA/CAP-certified molecular laboratories after appropriate analytical and clinical validation of all assays in each laboratory (143). In a survey of American molecular genetic testing laboratory directors, laboratory process quality assurance score (for multiple relevant domains) was associated with the presence of CLIA certification (170). In a large, international survey of medical genetic testing laboratory directors, accreditation of the laboratory was associated with a higher quality assurance index score (171).

[A17] AUS/FLUS Cytology

■ **RECOMMENDATION 15**

(A) For nodules with AUS/FLUS cytology, after consideration of worrisome clinical and sonographic features, investigation such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment in lieu of proceeding directly with a strategy of either surveillance or diagnostic surgery. Informed patient preference and feasibility should be considered in clinical decision-making. (**Weak recommendation, Moderate-quality evidence**)

(B) If repeat FNA cytology and/or molecular testing are not performed or inconclusive, either surveillance or diagnostic surgical excision may be performed for an AUS/FLUS thyroid nodule, depending on clinical risk factors, sonographic pattern, and patient preference. (**Strong recommendation, Low-quality evidence**)

Based on the Bethesda System, this diagnostic category is reserved for specimens that contain cells with architectural and/or nuclear atypia that is more pronounced than expected for benign changes but not sufficient to be placed in one of the higher risk diagnostic categories (94;172). Although this diagnostic category has been recommended for limited use and an expected frequency in the range of 7%, recent reports based on the Bethesda System have found this cytologic diagnosis to be used in 1-27% of all thyroid FNA samples (100;173). In studies that utilized the criteria established by the Bethesda System, the risk of cancer for patients with AUS/FLUS nodules who underwent surgery was 6–48%, with a mean risk of 16% (173).

A repeat FNA yields a more definitive cytologic diagnosis in many cases, whereas 10-30% of nodules are repeatedly AUS/FLUS (99;174-176). The rate of malignancy on surgical follow-

up has been shown to be similar for patients with a single AUS/FLUS diagnosis, two successive AUS/FLUS diagnoses, and patients with a benign cytologic interpretation following the initial AUS/FLUS diagnosis, arguing against the role of repeat FNA (177). Use of thyroid core-needle biopsy was reported by some to be more informative than repeated FNA for sampling nodules that were AUS/FLUS on initial FNA (112), although morbidity is higher. Therefore, routine performance of this approach requires further investigation and is not justified.

The refinement of risk stratification of nodules with AUS/FLUS cytology using molecular testing has been examined in multiple studies. The interpretation of molecular testing is complex, however, and its utility is strongly influenced by the prevalence of cancer in the tested population of nodules. Only two molecular tests have been separately evaluated and validated for the individual AUS/FLUS, FN, and SUSP categories. Mutational testing for BRAF in AUS/FLUS samples has high specificity for cancer, but low sensitivity (178;179). Testing for a panel of mutations (BRAF, NRAS, HRAS, KRAS, RET/PTC1, RET/PTC3, PAX8/PPARγ) offers a significantly higher sensitivity of 63-80% (146;150). One prospective, blinded, single-center study of 137 patients with indeterminate thyroid nodules had a lower sensitivity (48%) than the other mutation panel studies (151). This study had different methodologic approaches than the other studies and did not include HRAS mutations, which may explain the lower sensitivity. In the largest-to-date prospective study of nodules with AUS/FLUS cytology (653 consecutive nodules, of which 247 had surgical follow-up) from a single institution, detection of any of these mutations using RT-PCR with fluorescent melting curve analysis was reported to convey an 88% risk of cancer among nodules with surgical follow-up; 63% of cancers on final histopathology were identified with a positive mutation preoperatively (22 of 35), and 94% of nodules that were negative on mutation analysis had benign final histopathology (209 of 222) (146). Positive testing for BRAF, RET/PTC or PAX8/PPARγ was specific for a malignant outcome in 100% of cases, whereas RAS mutations had an 84% risk of cancer and a 16% risk of benign follicular adenoma. A recent study utilizing RT-PCR with liquid bead array flow cytometry reported on 11 AUS/FLUS cytology nodules that had malignant histopathologic confirmation, of which 7 had a negative molecular test and 4 had a positive test (152). There were also 11 AUS/FLUS cytology nodules which had benign histopathologic confirmation, of which 9 had a negative molecular test result and 2 had a positive result. Unfortunately, the

specific calculations for sensitivity, specificity, predictive values, and 95% CIs were not reported for the AUS/FLUS subgroup (152).

Molecular testing using the GEC has been studied for its diagnostic use in nodules with AUS/FLUS cytology. A multi-institutional study of 129 FNA samples with AUS/FLUS cytology and surgical follow-up reported a 90% sensitivity (95% CI 74%-98%) and 95%NPV (95% CI 85%-99%), but only a 53% specificity (95% CI 43%-63%) and 38% PPV (95% CI 27%-50%) for cancer (147). Although the specificity of the GEC was low (53%, 95% CI 43%-63%), the negative test result was reported to decrease the risk estimate of malignancy in AUS/FLUS nodules in this study from 24% to 5%.This observation has led to a clinical extrapolation suggesting that nodules that have negative GEC test results may be followed without surgery (147). The reproducibility of the test's performance in the AUS/FLUS subgroup has not been independently confirmed. In two recent studies, there were insufficient data for analysis in the AUS/FLUS subgroup to draw any meaningful conclusion (156;157). In addition, published follow up for the GEC is currently limited to a mean of 8.5 months (155), so long-term outcome data are needed to ensure durability of benign GEC findings with correlation to clinical and histologic outcomes.

Several recent studies (180-184) have examined the feasibility of using sonographic features to estimate risk of malignancy in nodules with AUS/FLUS cytology. The positive predictive value of suspicious sonographic features has been estimated to range from 60% to 100% depending on the pre-test probability of malignancy of AUS/FLUS cytology and the specific sonographic criteria selected in respective studies. A limitation of all of these studies is that a gold-standard surgical excisional diagnosis was not required for confirmation of malignancy and long-term follow-up data were generally lacking. The prevalence of suspicious sonographic features among studies of AUS/FLUS cytology nodules ranged from 18% to 50%, assuming that one or more suspicious features were deemed to be sufficient to be categorized as a sonographically suspicious nodule. The findings of these studies must be interpreted in the context of each study's overall risk of malignancy for this cytology classification because of its effect on the positive predictive values obtained by subsequent application of sonographic features to cytologically AUS/FLUS nodules. From the four Korean studies (overall malignancy rate 40-55%), the reported cancer risk in AUS/FLUS nodules with the high suspicion sonographic pattern is 90-100% (180-183), and the presence of even one suspicious ultrasound

feature (irregular margins, taller than wide shape, marked hypoechogenicity or microcalcifications) increases the cancer risk to 60-90%. However, when the reported cancer rate in AUS/FLUS nodules is lower, e.g. 23% in Brazil (184), the high suspicion sonographic pattern still raises the risk of malignancy but the positive predictive value is lower at 70%. Nonetheless, the incidence of cancer in AUS/FLUS nodules with either the high suspicion pattern ultrasound or just one suspicious ultrasound feature is significantly higher than that generally accepted for this cytology category. To date, no studies have included sonographic imaging when analyzing molecular testing with mutation panels or the gene expression classifier. Further research in this area is needed.

[A18] Follicular Neoplasm/Suspicious for Follicular Neoplasm (FN) Cytology

■ **RECOMMENDATION 16**

(A) Diagnostic surgical excision is the long-established standard of care for the management of follicular neoplasm/suspicious for follicular neoplasm (FN) cytology nodules. However, after consideration of clinical and sonographic features, molecular testing may be used to supplement malignancy risk assessment data, in lieu of proceeding directly with surgery. Informed patient preference and feasibility should be considered in clinical decision-making. (**Weak recommendation, Moderate-quality evidence**)

(B) If molecular testing is either not performed or inconclusive, surgical excision may be considered for removal and definitive diagnosis of an FN/SFN thyroid nodule. (**Strong recommendation, Low-quality evidence**)

This diagnostic category of the Bethesda System is used for cellular aspirates (i) comprised of follicular cells arranged in an altered architectural pattern characterized by cell crowding and/or microfollicle formation and lacking nuclear features of papillary carcinoma or (ii) comprised almost exclusively of oncocytic (Hürthle) cells (94;185;186). This is an intermediate risk category in the Bethesda System, with a 15-30% estimated risk of malignancy. Studies that applied the Bethesda System reported the use of this diagnostic category in 1-25% (mean, 10%) of all thyroid FNA samples, with the risk of cancer on surgery found to range from 14-33% (mean, 26%) (173).

The refinement of risk stratification of nodules with FN/suspicious for FN/Hürthle cell neoplasm cytology has been examined using ancillary molecular testing. In one study, molecular testing using the GEC was reported to have a 94% NPV (95% CI 79%-99%), and a 37% PPV (95% CI 23%-52%) in this Bethesda subgroup (147). A recent unblinded study from the Mayo Clinic utilizing a prospective patient registry reported the following diagnostic accuracy estimates in a subgroup of 31 indeterminate nodules from the same Bethesda subgroup that were subject to histopathologic confirmation: sensitivity 80% (4/5 nodules), specificity 12% (3/26 nodules), PPV 15% (4/27), and NPV 75% (3/4) (157). The relatively small number of indeterminate nodules in this study is an important limitation. Furthermore, precision estimates (95% CIs) for the diagnostic accuracy measures were not reported but could be assumed to be relatively wide given the small sample size.

Testing for a panel of mutations (BRAF, RAS, RET/PTC, RAX8/PPARγ, etc.) is expected to detect one of the mutations in 18-39% of FN samples, and this confers an 87% risk of cancer, whereas the rest of mutation-positive nodules are benign neoplasms (146;150). These benign tumors are follicular adenomas driven by oncogenic RAS mutation with uncertain malignant potential (187). Nodules lacking all of these mutations still have a substantial cancer risk (14%), which is due to the presence of a subset of tumors that lack any of the mutations tested by this panel (146). Expansion of the current panels to include additional mutations which can be tested in thyroid FNA samples using new techniques such as next generation sequencing may further improve the NPV of mutational panels (153;154).

[A19] Suspicious for Malignancy (SUSP) Cytology

■ **RECOMMENDATION 17**

(A) If the cytology is reported as suspicious for papillary carcinoma (SUSP), surgical management should be similar to that of malignant cytology, depending on clinical risk factors, sonographic feastures, patient preference, and possibly results of mutational testing (if performed). (**Strong recommendation, Low-quality evidence**)

(B) After consideration of clinical and sonographic features, mutational testing for BRAF or the mutation marker panel (BRAF, RAS, RET/PTC, PAX8/PPARγ, etc.) may be considered in nodules with SUSP cytology if such data would be expected to alter surgical decision-making. (**Weak recommendation, Moderate-quality evidence**)

This diagnostic category of the Bethesda System is reserved for aspirates with cytologic features that raise a strong suspicion for malignancy (mainly for PTC) but are not sufficient for a conclusive diagnosis (94;188). This is the highest risk category of indeterminate cytology in the Bethesda System, with an estimated cancer risk of 60-75% (188). Studies that utilize the Bethesda System have reported this cytologic diagnosis in 1-6% of thyroid FNAs and found malignancy after surgery in 53-87% (mean, 75%) of these nodules (173). Due to the high risk of cancer, the diagnosis of suspicious for papillary carcinoma is an indication for surgery.

Mutational testing has been proposed to refine risk prior to surgery, assuming that surgical management would change based on a positive test result. BRAF mutations are detected in 20-60% of nodules with this cytologic diagnosis and confer close to 100% probability of cancer (178;189;190). Testing for a panel of mutations (BRAF, RAS, RET/PTC, RAX8/PPARγ) offers better sensitivity, and a positive test confers >95% risk of cancer (146;150). Nodules with SUSP cytology and negative for all above mutations have a 28% risk of cancer (146). Molecular testing using the GEC has a positive predictive value that is similar to cytology alone (76%) and a NPV of 85% (147), and currently does not contribute to the management of patients with this cytologic diagnosis.

[A20] What is the utility of FDG-PET scanning to predict malignant or benign disease when FNA cytology is indeterminate (AUS/FLUS, FN, SUSP)?

■ **RECOMMENDATION 18**

^{18}FDG-PET imaging is not routinely recommended for the evaluation of thyroid nodules with indeterminate cytology. (**Weak recommendation, Moderate-quality evidence**)

Eight studies have been performed, and are the subject of two metanalyses (191-200). While early data suggested a high negative predictive value for FDG-PET in this setting, most studies failed to use the Bethesda System for Reporting Thyroid Cytopathology and included numerous small nodules < 1cm in diameter (199). A more recent metanalysis included 7 studies, of which 5 were prospective (200). The cancer prevalence was 26% inclusive of all combined data, confirming a typical study cohort. Sensitivity and specificity of FDG-PET were 89% and 55% respectively, resulting in a 41% positive predictive value and 93% negative predictive

value. Most recently, however, a prospective analysis of 56 nodules with indeterminate FNA cytology used both FDG-PET and thyroid ultrasound to further evaluate the nodules (198). In multivariate analysis, the authors demonstrated no additional diagnostic benefit or improved risk assessment when adding FDG-PET to that already obtained from thyroid ultrasound, bringing into question the incremental benefit of PET imaging in patients with cytologically indeterminate thyroid nodules.

[A21] What is the appropriate operation for cytologically indeterminate thyroid nodules?

■ RECOMMENDATION 19

When surgery is considered for patients with a solitary, cytologically indeterminate nodule, thyroid lobectomy is the recommended initial surgical approach. This approach may be modified based on molecular testing when performed (see Recommendations 13-16) (**Strong recommendation, Moderate-quality evidence**)

■ RECOMMENDATION 20

A) Because of increased risk for malignancy, total thyroidectomy may be preferred in patients with indeterminate nodules which are cytologically suspicious for malignancy, positive for known mutations specific for carcinoma, sonographically suspicious, large (>4 cm), or in patients with familial thyroid carcinoma or history of radiation exposure, if completion thyroidectomy would be recommended based on the indeterminate nodule being malignant following lobectomy. (**Strong recommendation, Moderate-quality evidence**)

B) Patients with indeterminate nodules who have bilateral nodular disease, those with significant medical comorbidities, or those who prefer to undergo bilateral thyroidectomy to avoid the possibility of requiring a future surgery on the contralateral lobe, may undergo total or near-total thyroidectomy, assuming completion thyroidectomy would be recommended if the indeterminate nodule proved malignant following lobectomy. (**Weak recommendation, Low-quality evidence**)

The primary goal of thyroid surgery for a thyroid nodule that is cytologically indeterminate (AUS/FLUS or FN or SUSP) is to establish a histological diagnosis and definitive removal, while reducing the risks associated with remedial surgery in the previously operated

field if the nodule proves to be malignant. Surgical options to address the nodule should be limited to lobectomy (hemithyroidectomy) with or without isthmusectomy, near-total thyroidectomy (removal of all grossly visible thyroid tissue, leaving only a small amount [<1 g] of tissue adjacent to the recurrent laryngeal nerve near the ligament of Berry), or total thyroidectomy (removal of all grossly visible thyroid tissue). Removal of the nodule alone, partial lobectomy, or subtotal thyroidectomy, leaving >1 g of tissue with the posterior capsule on the uninvolved side, are inappropriate operations for possible thyroid cancer (201).

Decisions regarding the extent of surgery for indeterminate thyroid nodules are influenced by several factors (202), including the estimated pre-surgical likelihood of malignancy based upon clinical risk factors (>4cm, family history, and/or radiation history) (203-206), sonographic pattern (Table 6, Figure 2)(181;182), cytologic category (Table 7), and ancillary test findings (see molecular testing section [A15-19]). These risk factors, as well as patient preference, presence of contralateral nodularity or coexistent hyperthyroidism, and medical comorbidities, impact decisions regarding thyroid lobectomy with the possible need for subsequent completion thyroidectomy vs. total thyroidectomy up front.

Nodules that are cytologically classified as AUS/FLUS or FN and 'benign' using the Afirma gene expression classifier, or AUS/FLUS and negative using the known mutation panel have an estimated 5-6% risk of malignancy (146;147). Nodules that are cytologically classified as FN and negative using the known mutation panel have an estimated 14% risk of malignancy which is slightly lower than the risk based upon the Bethesda classification alone (146).

Nodules that are cytologically classified as AUS/FLUS or FN, and 'suspicious' using the Afirma gene expression classifier have an estimated 37-44% risk of malignancy which is slightly higher than the risk based upon the Bethesda classification alone (Table 7)(147;155).

Nodules that are cytologically classified as SUSP and 'benign' using the Afirma gene expression classifier or negative using the known mutation panel, also have an estimated 15-28% risk of malignancy.

In contrast, nodules that are cytologically classified as AUS/FLUS or FN and that are positive for known *RAS* mutations associated with thyroid carcinoma have an estimated 84% risk of malignancy and should be considered in a similar risk category to cytologically suspicious for malignancy (Table 7) (207). Nodules that are cytologically classified as AUS/FLUS or FN or SUSP and that are positive for known *BRAFV600E, RET/PTC, PAX8/PPAR*γ mutations have an

estimated risk of malignancy of >95% and should be considered in a similar category to cytologically diagnosed thyroid carcinoma (178;189;190).

Sonographic pattern of nodules with AUS/FLUS cytology may aid in risk stratification and management. In one study, sonographically benign or very low risk appearing nodules with AUS/FLUS cytology were noted to be malignant in only 8% of cases, compared to 58% when sonographic suspicious was low or intermediate, and 100% when sonographic suspicion of malignancy was high (182). Another study supported this finding with sonographic findings highly suspicious for malignancy (taller than wide shape, irregular borders, and/or marked hypoechogenicity) having >90% specificity and positive predictive value for malignancy (181).

The risks of total thyroidectomy are significantly greater than that for thyroid lobectomy, with a recent meta-analysis suggesting a pooled relative risk (RR) significantly greater for all complications, including: recurrent laryngeal nerve injury (transient RR=1.7, permanent RR=1.9); hypocalcemia (transient RR=10.7, permanent RR=3.2); and hemorrhage/hematoma (RR=2.6) (208). Further, total thyroidectomy is associated with the rare but potential risk of bilateral recurrent laryngeal nerve injury necessitating tracheostomy. Surgeon experience likely influences the risks of thyroidectomy, with higher volume surgeons having lower complication rates (209;210).

Total thyroidectomy necessitates thyroid hormone replacement, while lobectomy is associated with an incidence of postoperative biochemical hypothyroidism estimated at 22%, with clinical or overt hypothyroidism estimated at 4% (211). A significantly increased risk of hypothyroidism following lobectomy has been reported in the presence of autoimmune thyroid disease (eg. as reflected by the presence of thyroid antibodies), or high normal/elevated TSH (208;211). Hypothyroidism is not an indication for thyroidectomy, and its use as justification for total thyroidectomy over lobectomy should be weighed against the higher risks associated with total thyroidectomy. In contrast, co-existent hyperthyroidism, may be an indication for total thyroidectomy depending upon the etiology.

Thyroid lobectomy (hemithyroidectomy) provides definitive histological diagnosis and complete tumor removal for cytologically indeterminate nodules with a lower risk of complications compared to total thyroidectomy, and may be sufficient for smaller, solitary, intrathyroidal nodules that ultimately prove malignant. As the likelihood of malignancy increases, the potential need for a second operation also increases, if the cytologically

indeterminate nodule ultimately proves malignant and if completion thyroidectomy would be recommended. Intraoperative evaluation, with or without frozen section, can occasionally confirm malignancy at the time of lobectomy allowing for conversion to total thyroidectomy if indicated. The individual patient must weigh the relative advantages and disadvantages of thyroid lobectomy with possible total thyroidectomy or subsequent completion thyroidectomy vs. initial total thyroidectomy.

[A22] How should multinodular thyroid glands (i.e. - 2 or more clinically relevant nodules) be evaluated for malignancy?

■ RECOMMENDATION 21

A) Patients with multiple thyroid nodules >1cm should be evaluated in the same fashion as patients with a solitary nodule >1cm, excepting that each nodule >1cm carries an independent risk of malignancy and therefore multiple nodules may require FNA. (**Strong recommendation, Moderate-quality evidence)**

B) When multiple nodules >1cm are present, those with a suspicious sonographic patern (Table 6, Figure 2) should be aspirated preferentially. FNA should be performed preferentially based upon nodule sonographic pattern and respective size cut-off (Table 6, Figure 2). (**Strong recommendation, Moderate-quality evidence)**

C) If none of the nodules have a high or moderate suspicion sonographic pattern, and multiple sonographically similar very low or low suspicion pattern nodules coalesce with no intervening normal parenchyma, the likelihood of malignancy is low and it is reasonable to aspirate only the largest nodules (> 2cm) while observing the others with serial US examinations. **(Weak recommendation, Low-quality evidence)**

■ RECOMMENDATION 22

A low or low-normal serum TSH concentration in patients with multiple nodules may suggest that some nodule(s) may be autonomous. In such cases, a technetium $^{99\,m}$Tc pertechnetate or ^{123}I thyroid scan should be considered and directly compared to the US images to determine functionality of each nodule >1 cm. FNA should then be considered only for those isofunctioning or nonfunctioning nodules, among which those with high suspicion sonographic pattern should be aspirated preferentially. **(Weak recommendation, Low-quality evidence)**

Patients with multiple thyroid nodules have the same risk of malignancy as those with solitary nodules (29;70). However, one large study found that a solitary nodule had a higher likelihood of malignancy than did a nonsolitary nodule ($p < 0.01$), although the risk of malignancy per patient was the same and independent of the number of nodules (73). A recent systematic review and meta-anlysis confirmed the slightly higher risk of malignancy in a solitary nodule compared with a nodule in a MNG, although this appeared to hold true mostly outside of the United States and in iodine-deficient populations (212). A diagnostic US should be performed to delineate the nodules, but if only the "dominant" or largest nodule is aspirated, the thyroid cancer may be missed (70). Therefore, multiple thyroid nodules >1cm may require aspiration, based on sonographic pattern (Recommendation 8, Table 6, Figure 2), to fully exclude clinically relevant thyroid cancer. Radionuclide scanning may also be considered in patients with multiple thyroid nodules with the goal of identifying and aspirating appropriate hypofunctioning nodules. Such imaging may prove especially useful when the serum TSH is in the low or low-normal range. Similarly, sonographic risk assessment of each nodule can assist in identifying those nodules with the highest likelihood of cancer (see section [A10]).

[A23] What are the best methods for long-term follow-up of patients with thyroid nodules?

[A24] Recommendations for initial follow-up of nodules with benign FNA cytology

■ **RECOMMENDATION 23**

Given the low false negative rate of US FNA cytology and the higher yield of missed malignancies based upon nodule sonographic pattern rather than growth, the follow up of thyroid nodules with benign cytology diagnoses should be determined by risk stratification based upon ultrasound pattern.

A) Nodules with high suspicion US pattern: repeat US and US FNA (**Strong recommendation, Moderate-quality evidence**)

B) Nodules with low to intermediate suspicion US pattern: repeat US at 12-24 months. If sonographic evidence of growth (20% increase in at least two nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume), the FNA could be repeated or

continue observation with repeat US and FNA if continued growth (**Weak recommendation, Low-quality evidence).**

C) Nodules with very low suspicion US pattern (including spongiform nodules): the utility of surveillance US and assessment of nodule growth as an indicator for repeat FNA is not known. If US is repeated, it should at ≥ 24 months (**No recommendation, Insufficient evidence)**

[A25] Recommendation for follow-up of nodules with two benign FNA cytology results

D) If a nodule has undergone repeat US FNA with a second benign cytology result, ultrasound surveillance for this nodule for continued risk of malignancy is no longer indicated (**Strong recommendation, Moderate-quality evidence**)

Given that there is a low but discrete false negative rate for nodules with benign FNA cytology results, is there an optimal way to identify these missed malignancies? Although the risk of malignancy after two benign cytology results is virtually zero (121-125;213), routine rebiopsy is not a viable or cost-effective option because of the low false negative rate of an US FNA benign cytology result. Prior guidelines have recommended repeat FNA for nodules that grow during serial sonographic observation. However, nodule growth can be variably defined. Because of interobserver variation, Brauer reported a 50% increase in nodule volume as the minimally significant reproducibly recorded change in nodule size, which is equivalent to a 20% increase in 2 of the 3 nodule dimensions. If a 50% volume increase cut off is applied, only 4-10% of nodules were reported to be larger at a mean of 18 months (125;214). However, using cut offs of a 15% volume increase based upon internally assessed interobserver coefficients of variation, published series report that 32- 50% of nodules increase in size over a 4-5 year period (215;216). Because of the stringent methodology of these studies, adoption of a 15% volume increase as statistically significant is not practically applicable. Furthermore, there are no follow up studies of nodule growth that extend observation beyond 5 years to help inform decision-making about longterm surveillance. Additional research would be valuable as indefinite follow up of nodules with benign cytology is costly and may be unecessary.

Recent investigations of repeat US FNA in nodules with initial benign cytology report higher detection rates for missed malignancy for those nodules with high suspicion sonographic

pattern rather than size increase (213;217). Kwak et al reported a significantly higher malignancy rate of 20.4% in nodules with benign cytology that exhibited either marked hypoechogenicity, irregular borders, microcalcifications or a taller than wide shape versus a 1.4% risk in those that exhibited a 15% volume increase but lacked these US features. Importantly, the low risk of malignancy did not differ between US negative nodules that grew and those that demonstrated no interval size change (1.4% vs. 0.5%, p= 0.18). Similarly, Rosario et al detected cancer in 17.4% of nodules with benign cytologic diagnoses and suspicious US features versus 1.3% of those without suspicious characteristic that grew, using criteria of a 50% volume increase. High suspicion sonographic pattern is present in approximately 10% of nodules with prior FNA benign cytology results. These studies indicate the use of suspicious US characteristics rather than nodule growth should be the indication for repeat FNA despite an initial benign cytology diagnosis. Repeat US and FNA should be repeated within 12 months as guided by clinical judgement. Given the low false negative rate of US FNA cytology and the higher yield of missed malignancies based upon nodule sonographic pattern rather than growth, the follow up of thyroid nodules with benign cytology diagnoses should be determined by risk stratification based upon ultrasound pattern as defined in Recommendation 8. If follow up US for surveillance is performed and the nodule size is stable, the utility of subsequent US imaging for detection of potential malignancy by nodule growth assessment is very low and if performed, the time interval for any additional US exam should be at least as long that between the initial benign FNA cytology result and first follow up. However, even if a repeat US is not indicated based upon benign cytology, US pattern or stability in nodule size, larger nodules may require monitoring for growth that could be symptomatic and thus prompt surgical intervention despite benign cytology.

One recent study evaluated the long-term consequences of a false-negative benign cytology (130). 1,369 patients with 2,010 cytologically benign thyroid nodules were followed for a mean of 8.5 years. 18 false-negatives were identified, although only a subset of patients underwent repeat FNA or thyroid surgery. 30 deaths were documented in the entire cohort over this time period and none were attributable to thyroid cancer. These data support that an initial benign cytology conveys an overall excellent prognosis and a conservative follow-up strategy is reasonable.

[A26] Follow-up for nodules that do not meet FNA criteria

■ **RECOMMENDATION 24**

Nodules may be detected on ultrasound that do not meet criteria for FNA at initial imaging (Recommendation 8). The strategy for sonographic follow up of these nodules should be based upon the nodule's sonographic pattern.

A) Nodules with high suspicion US pattern: repeat US 6-12 months (**Weak recommendation, Low-quality evidence**)

B) Nodules with sonographic features of low to intermediate suspicion US pattern: consider repeat US at 12-24 months. **(Weak recommendation, Low-quality evidence).**

C) Nodules with very low suspicion US pattern (including spongiform nodules) and pure cyst: the utility and time interval of surveillance US for risk of malignancy is not known. If US is repeated, it should be at $\geq$ 24 months **(No recommendation, Insufficient evidence)**

D) Nodules < 5 mm without high suspicion US pattern do not require routine sonographic FU and if repeated, the US should be performed at 24 months or later (**Weak recommendation, Low-quality evidence)**

Ultrasound studies demonstrate that up to 50% of adults have thyroid nodules. The vast majority of these are subcentimeter and FNA evaluation is generally not indicated. In addition, based upon both sonographic pattern and size cutoffs (Recommendation 8), many supracentimeter nodules may also be followed without FNA. No prospective studies address the optimal cost effective surveillance strategy for these nodules that have not undergone FNA. However, findings from studies correlating sonographic features and malignancy risk in aspirated nodules can be extrapolated to inform a follow up strategy for this group of nodules that do not meet FNA criteria at time of their initial detection. For example, the interval for follow up sonography for a nodule that is hypoechoic and taller than wide should be shorter than that for an isoechoic solid nodule with smooth borders.

US FNA should be performed based upon follow-up ultrasound imaging if the nodule subsequently meets criteria based upon Recommendation 8.

[A27] What is the role of medical or surgical therapy for benign thyroid nodules?

■ **RECOMMENDATION 25**

Routine TSH suppression therapy for benign thyroid nodules in iodine sufficient populations is not recommended. Though modest response to therapy can be detected, the potential harm outweighs benefit for most patients. (**Strong recommendation, High-quality evidence**)

■ RECOMMENDATION 26

Individual patients with benign, solid or mostly solid nodules should have adequate iodine intake. If inadequate dietary intake is found or suspected, a daily supplement (containing 150 mcg iodine) is recommended. (**Strong recommendation, Moderate-quality evidence**)

■ RECOMMENDATION 27

A) Surgery may be considered for growing nodules that are benign after repeat FNA if they are large (>4cm), causing compressive or structural symptoms, or based upon clinical concern. (**Weak recommendation, Low-quality evidence**)

B) Patients with growing nodules that are benign after FNA should be regularly monitored. Most asymptomatic nodules demonstrating modest growth should be followed without intervention. (**Strong recommendation, Low-quality evidence**)

■ RECOMMENDATION 28

Recurrent cystic thyroid nodules with benign cytology should be considered for surgical removal or percutaneous ethanol injection (PEI) based on compressive symptoms and cosmetic concerns. Asymptomatic cystic nodules may be followed conservatively. (**Weak recommendation, Low-quality evidence**)

■ RECOMMENDATION 29

There are no data to guide recommendations on the use of thyroid hormone therapy in patients with growing nodules that are benign after FNA (**No recommendation, Insufficient evidence**)

Evidence from multiple prospective, randomized controlled trials, and from 3 meta-analyses suggest that thyroid hormone supplementation in doses that suppress the serum TSH to

subnormal levels may result in a decrease in nodule size and may prevent the appearance of new nodules in regions of the world with borderline low iodine intake (218-220). However, the effect is modest, with most studies suggesting an average 5-15% reduction in nodule volume when treated with suppressive levothyroxine therapy for 6-18 months. Two high-quality meta-analyses confirm that 6-8 patients will require suppressive levothyroxine therapy to achieve one successful treatment response (221;222). The extent of TSH suppression achieved in high-quality studies is variable, though the majority suppressed TSH <0.2mIU/L, with many <0.1mIU/L. Hyperthyroidism to this degree has been significantly associated with an increased risk of cardiac arrhythmias and osteoporosis, as well as adverse symptomatology. Together, these data confirm that levothyroxine suppressive therapy demonstrates modest (though usually clinically insignificant) efficacy in nodule volume reduction, but increases the risk of adverse consequences related to iatrogenic thyrotoxicosis. One large prospective, randomized trial demonstrated that sufficient dietary iodine intake (150mcg daily) also reduced nodule size slightly more than placebo (223). The consumption of adequate dietary iodine is recommended for all adults, and is without harm when not excessive.

Cystic nodules that are cytologically benign can be monitored for recurrence (fluid reaccumulation) which can be seen in 60–90% of patients (224;225). For those patients with subsequent recurrent symptomatic cystic fluid accumulation, surgical removal, generally by hemithyroidectomy, or percutaneous ethanol injection (PEI) are both reasonable strategies. Four controlled studies demonstrated a 75–85% success rate after PEI compared with a 7–38% success rate in controls treated by simple cyst evacuation or saline injection. Success was achieved after an average of two PEI treatments. Complications included mild to moderate local pain, flushing, dizziness, and dysphonia (224;225) (226;227).

[A28] How should thyroid nodules in pregnant women be managed?

[A29] FNA for thyroid nodules discovered during pregnancy

■ RECOMMENDATION 30

A) FNA of clinically relevant thyroid nodules (refer to section [A10]) should be performed in euthyroid and hypothyroid pregnant women. (**Strong recommendation, Moderate-quality evidence**)

B) For women with suppressed serum TSH levels that persist beyond 16 weeks gestation,

FNA may be deferred until after pregnancy and cessation of lactation. At that time, a radionuclide scan can be performed to evaluate nodule function if the serum TSH remains suppressed. (**Strong recommendation, Moderate-quality evidence**)

It is uncertain if thyroid nodules discovered in pregnant women are more likely to be malignant than those found in nonpregnant women, since there are no population-based studies to address this question. Pregnancy does not appear to modify microscopic cellular appearance, thus standard diagnostic criteria should be applied for cytologic evaluation (228). Serial evaluation of nodules throughout pregnancy has demonstrated that thyroid nodules will enlarge slightly throughout gestation, though this does not imply malignant transformation (229). The recommended evaluation of a clinically relevant nodule in a pregnant patient is thus the same as for a non-pregnant patient, with the exception that a radionuclide scan is contraindicated. In addition, for patients with nodules diagnosed as DTC by FNA during pregnancy, delaying surgery until after delivery does not affect outcome (230). Surgery performed during pregnancy is associated with greater risk of complications, longer hospital stays, and higher costs (231).

[A30] Approaches to pregnant patients with malignant or indeterminate cytology

■ **RECOMMENDATION 31**

A) PTC discovered by cytology in early pregnancy should be monitored sonographically. If it grows substantially (as defined in section [A24]) before 24-26 weeks gestation, or if sonography detected cervical lymph nodes are suspicious for metastatic disease, surgery should be considered during pregnancy. However, if the disease remains stable by midgestation, or if it is diagnosed in the second half of pregnancy, surgery may be deferred until after delivery. (**Weak recommendation, Low-quality evidence**).

B) In pregnant women with FNA that is suspicious for or diagnostic of PTC, thyroid hormone therapy to keep the serum TSH 0.1-1.0mU/L is recommended. (**Weak recommendation, Low-quality evidence**).

If FNA cytology found during pregnancy is consistent with PTC, surgery has been generally recommended. However, there is no consensus about whether surgery should be performed during pregnancy or after delivery.

The application of molecular testing to pregnant women with clinically relevant, cytologically indeterminate thyroid nodules remains uncertain. Importantly, data confirm that the prognosis of women with well-differentiated thyroid cancer identified but not treated during pregnancy is similar to that of nonpregnant patients. Because of this, surgery may be generally deferred until postpartum (230;232) and no further testing is required. However, unique circumstances can arise where more precise cancer risk assessment impacts clinical decision making. Theoretically, molecular marker analysis could be helpful in this regard. However, as there are no published data validating the performance of any molecular marker in this population the committee cannot recommend for or against their use in pregnant women. Observational data that nodular growth may be related to parity and therefore it is theoretically possible that changes in a nodule's RNA expression may occur during gestation altering performance of the Afirma gene expression classifier while the mutational panel (BRAF, RAS, PAX8/PPARγ, RET/PTC) would be more likely to demonstrate similar performance to that of a nonpregnant population.

When surgery is advised, there is no consensus about whether surgery should be performed during pregnancy or after delivery. To minimize the risk of miscarriage, surgery during pregnancy should be done in the second trimester before 24 weeks gestation (233). However, PTC discovered during pregnancy does not behave more aggressively than that diagnosed in a similar-aged group of nonpregnant women (230;234). A retrospective study of pregnant women with DTC found there to be no difference in either recurrence, or survival rates, between women operated on during or after pregnancy (230). Further, retrospective data suggest that treatment delays of less than 1 year from the time of thyroid cancer discovery do not adversely affect patient outcome (235). A separate study reported a higher rate of complications in pregnant women undergoing thyroid surgery compared with nonpregnant women (236). If FNA cytology is indeterminate, monitoring may be considered with further evaluation may be delayed until after delivery. Some experts recommend thyroid hormone suppression therapy for pregnant women with FNA suspicious for or diagnostic of PTC, if surgery is deferred until the postpartum period (231).

[B1] DIFFERENTIATED THYROID CANCER: INITIAL MANAGEMENT GUIDELINES

Differentiated thyroid cancer, arising from thyroid follicular epithelial cells, accounts for the vast majority of thyroid cancers. Of the differentiated cancers, papillary cancer comprises about 85% of cases compared to about 12% that have follicular histology, including conventional and oncocytic (Hürthle cell) tumors , and <3% that are poorly differentiated tumors (237). In general, stage for stage, the prognoses of PTC and follicular cancer are similar (235;238).

[B2] Goals of initial therapy of DTC

The basic goals of initial therapy for patients with DTC are to improve overall and disease-specific survival, reduce the risk of persistent/recurrent disease and attendant morbidity, and permit accurate disease staging and risk stratification, while minimizing treatment-related morbidity and unnecessary therapy. The specific goals of initial therapy are to:

1. Remove the primary tumor, disease that has extended beyond the thyroid capsule, and clinically significant lymph node metastases. Completeness of surgical resection is an important determinant of outcome, while residual metastatic lymph nodes represent the most common site of disease persistence/recurrence (239-241).

2. Minimize the risk of disease recurrence and metastatic spread. Adequate surgery is the most important treatment variable influencing prognosis, while radioactive iodine treatment, TSH suppression, and other treatments each play adjunctive roles in at least some patients (242-244).

3. Facilitate postoperative treatment with radioactive iodine, where appropriate. For patients undergoing RAI remnant ablation, or RAI treatment of residual or metastatic disease, removal of all normal thyroid tissue is an important element of initial surgery (245).

4. Permit accurate staging and risk stratification of the disease. Because disease staging risk stratification should be used to guide initial prognostication, disease management, and follow-up strategies, accurate postoperative risk assessment is a crucial element in the management of patients with DTC (246;247).

5. Permit accurate long-term surveillance for disease recurrence.

6. Minimize treatment-related morbidity. The extent of surgery and the experience of the surgeon both play important roles in determining the risk of surgical complications (209;210;248;249).

[B3] What is the role of preoperative staging with diagnostic imaging and laboratory tests?

[B4] Neck imaging - Ultrasound

■ RECOMMENDATION 32

A) Preoperative neck US for cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant or suspicious for malignancy cytologic or molecular findings. (**Strong recommendation, Moderate-quality evidence**)

B) US-guided FNA of sonographically suspicious lymph nodes ≥ 8-10 mm in the smallest diameter should be performed to confirm malignancy if this would change management. (**Strong recommendation, Moderate-quality evidence**)

C) The addition of FNA-Tg washout in the evaluation of suspicious cervical lymph nodes is appropriate in select patients, but interpretation may be difficult in patients with an intact thyroid gland. (**Weak recommendation, Low-quality evidence**)

Differentiated thyroid carcinoma (particularly papillary carcinoma) involves cervical lymph node metastases in 20–50% of patients in most series using standard pathologic techniques (80;135;250-252), and may be present even when the primary tumor is small and intrathyroidal (253). The frequency of micrometastases may approach 90%, depending on the sensitivity of the detection method (254;255). However, the clinical implications of micrometastases are likely less significant compared to macrometastases. Preoperative US identifies suspicious cervical adenopathy in 20–31% of cases, potentially altering the surgical approach (256;257) in as many as 20% of patients (258-260). However, preoperative US identifies only half of the lymph nodes found at surgery, due to the presence of the overlying thyroid gland (261).

Sonographic features suggestive of abnormal metastatic lymph nodes include enlargement, loss of the fatty hilum, a rounded rather than oval shape, hypoechogenicity, cystic change, calcifications, and peripheral vascularity (Table 8). No single sonographic feature is adequately sensitive for detection of lymph nodes with metastatic thyroid cancer. One study correlated the sonographic features acquired 4 days preoperatively directly with the histology of 56 cervical lymph nodes identified in 19 patients. Some of the most specific criteria were short

axis >5 mm (96%), presence of cystic areas (100%), presence of hyperechogenic punctuations representing either colloid or microcalcifications (100%), and peripheral vascularity (82%). Of these, the only one with sufficient sensitivity is peripheral vascularity (86%). The others have sensitivities of <60% and would not be adequate to use as a single criterion for identification of malignant involvement (261). As shown by earlier studies (262;263), the ultrasonographic feature with the highest sensitivity is absence of a hilum (100%), but this has a low specificity of 29%. Microcalcifications have the highest specificity; any lymph nodes with microcalcifications should be considered abnormal (261) (Table 8).

The location of the lymph nodes may also be useful for decision-making. Malignant lymph nodes are much more likely to occur in levels III, IV, and VI than in level II (Fig. 3)(261;263), although this may not be true for PTC tumors arising in the upper pole of the thyroid, which have a higher propensity to demonstrate skip metastases to levels III and II (264). Figure 3 illustrates the delineation of cervical lymph node Levels I through VI.

Confirmation of malignancy in lymph nodes with a suspicious sonographic appearance is achieved by US-guided FNA aspiration for cytology and/or measurement of Tg in the needle washout. A Tg concentration <10ng/mL is reassuring, and the probability of N1disease increases with higher Tg levels (265). This FNA measurement of Tg is valid even in patients with circulating Tg autoantibodies (266;267). Tg washout may be helpful, particularly in cases where the lymph nodes are cystic, cytologic evaluation of the lymph node is inadequate, or the cytologic and sonographic evaluations are divergent (i.e. normal cytologic biopsy of a large lymph node with microcalcifications). (268). In a retrospective study of 241 lymph nodes in 220 patients who underwent US-guided FNA with Tg in FNA (FNA-Tg) washout fluid measurements for suspicious lymph nodes, additional FNA-Tg helped to diagnose a metastatic lymph node with one or two suspicious US features but did not offer incremental benefit for those lymph nodes with highly suspicious US features in which FNA alone was sufficient for diagnosis. False positive Tg washout may occur, particularly in lymph nodes in the central compartment when the thyroid gland is still present (269). There is no standardization of FNA-Tg procedures or assays to date, which makes this additional diagnostic tool sometimes difficult to interpret (270).

Accurate staging is important in determining the prognosis and tailoring treatment for patients with DTC. However, unlike many tumor types, the presence of metastatic disease does

not obviate the need for surgical excision of the primary tumor in DTC (271). Because metastatic disease may respond to RAI therapy, removal of the thyroid as well as the primary tumor and accessible locoregional disease remains an important component of initial treatment even in patients with metastatic disease.

[B5] Neck imaging - CT/MRI/PET

■ **RECOMMENDATION 33**

A) Preoperative use of cross-sectional imaging studies (CT, MRI) with intravenous contrast is recommended as an adjunct to ultrasound for patients with clinical suspicion for advanced disease including invasive primary tumor, or clinically apparent multiple or bulky lymph node involvement. (**Strong recommendation, low-quality evidence**)

B) Routine preoperative FDG-PET scanning is not recommended. (**Strong recommendation, low-quality evidence**)

Since US evaluation is operator-dependent and cannot always adequately image deep anatomic structures and those acoustically shadowed by bone or air, alternative imaging procedures may be preferable or useful as an adjunct in some clinical settings. Patients displaying bulky or widely distributed nodal disease on initial ultrasound exam may present with involvement of nodal regions beyond typical cervical regions some of which maybe difficult to visualize on routine preoperative ultrasound including the mediastinum, infra-clavicular, retropharyngeal and parapharyngeal regions. In a study of 37 consecutive patients who had preoperative CT and US and subsequently underwent total thyroidectomy and neck dissection, the sensitivity of CT was better than US for the evaluation central and lateral compartment lymph nodes examined together (77% vs 62%, p=0.002), but there were no differences between the two imaging modalities when the central and lateral compartments were examined separately (272). In a series of 299 consecutively registered patients with pathologically proven papillary thyroid cancer who underwent preoperative CT and ultrasound, ultrasound was more accurate than CT in predicting extrathyroidal tumor extension and multifocal, bilobar disease ($p<0.05$). The accuracy of staging was better overall with US ($p<0.01$), and US had greater sensitivity than CT at predicting lateral compartment metastases (p=0.041) (273). However another study

showed that combined preoperative mapping with US and CT was superior to US alone in the preoperative detection of nodal disease especially in the central neck (274). The sensitivities of MRI and PET for the detection of cervical lymph node metastases are relatively low (30–40%) (275).

Invasive DTC has been reported to occur in 10-15% of patients at the time of diagnosis (276). For this group of patients, cross-sectional imaging can also be a useful supplement for preoperative planning to accurately delineate the extent of laryngeal, tracheal, esophageal or vascular involvement (274) (277). Endoscopy of the trachea and or esophagus, with or without ultrasonography, at the beginning of the initial operation looking for evidence of intraluminal extension can also be helpful in cases of suspected areodigestive tract invasion.

Locally invasive primary tumor may be associated with characteristic signs and symptoms including progressive dysphagia, respiratory compromise, hemoptysis, rapid tumor enlargement, significant voice change or the finding of vocal cord paralysis, and mass fixation to the airway or neck structures. Certain sonographic features of the primary tumor, including extrathyroidal extension especially with posterior capsular extension and extension into the mediastinum, may also prompt axial imaging (272). Chest CT is useful in defining the inferior border of disease and in determining the extent to which mediastinal structures are involved in cases with significant caudal spread. CT findings may influence management by indicating the need for sternotomy and/or tracheal or laryngeal resection/reconstruction, which would likely require assembling additional resources and personnel in preparation for surgery. Neck CT with contrast can therefore be useful in delineating the extent of laryngeal, tracheal, and/or esophageal involvement in tumors displaying aggressive local invasion, as well as delineating bulky nodal disease which may harbor significant extranodal extension that involves muscle and/or blood vessels. Preoperative knowledge of these features of the primary tumor or metastases could significantly influence the surgical plan (Yeh M, Bauer A, Bernet V, Ferris R,Loevner L,Mandel S, Orloff L, Randolph G Steward D Preoperative Imaging for Thyroid Cancer Surgery: Recommendations from the American Thyroid Association Surgical Affairs Committee submitted Thyroid.). FDG PET scanning maybe sensitive in some patients for neck or mediastinal involvement, and may reveal distant metastases as well.

When cross-sectional imaging is performed, use of intravenous (IV) contrast is an important adjunct, as it helps to delineate the anatomic relationship between the primary tumor

or metastatic disease and these other structures. Iodine is generally cleared within 4-8 weeks in most patients, so concern about iodine burden from IV contrast causing a clinically significant delay in subsequent whole body scans or radioactive iodine treatment after the imaging followed by surgery is generally unfounded(278). The benefit gained from improved anatomic imaging generally outweighs any potential risk of a several week delay in RAI imaging or therapy. When there is concern, a urinary iodine to creatinine ratio can be measured.

[B6] Measurement of serum Tg and Tg antibodies

■ **RECOMMENDATION 34**

Routine preoperative measurement of serum Tg or Tg antibodies is not recommended. (**Weak recommendation, Low-quality evidence**)

Data from a systematic review and meta-analysis suggested that high preoperative concentrations of serum Tg may predict a higher sensitivity for postoperative surveillance with serum Tg (279). Preoperative Tg antibodies do not appear to be an independent preoperative predictor of stage in patients with DTC, but the evidence is limited. In a cross-sectional analysis of 1,770 patients with perioperative Tg antibodies status data in the National Thyroid Cancer Treatment Cooperative Study (a large thyroid cancer registry that included 11 North American centers and enrolled patients between 1987-2011), serum Tg antibodies status was not significantly associated with stage of disease on multivariate analysis, or with disease-free or overall survival on univariate or multivariate analyses. (280). Evidence that preoperative measurement of serum Tg impacts patient management or outcomes is not yet available.

[B7] Operative approach for a biopsy diagnostic for follicular cell-derived malignancy.

■ **RECOMMENDATION 35**

A) For patients with thyroid cancer >4 cm, or with gross extrathyroidal extension (clinical T4), or clinically apparent metastatic disease to nodes (clinical N1) or distant sites (clinical M1), the initial surgical procedure should include a near-total or total thyroidectomy and gross removal of all primary tumor unless there are contraindications to this procedure. (**Strong Recommendation, Moderate-quality evidence**)

B) For patients with thyroid cancer >1 cm and <4 cm without extrathyroidal extension,

and without clinical evidence of any lymph node metastases (cN0), the initial surgical procedure can be either a bilateral procedure (near-total or total thyroidectomy) or a unilateral procedure (lobectomy). Thyroid lobectomy alone may be sufficient initial treatment for low risk papillary and follicular carcinomas; however, the treatment team may choose total thyroidectomy to enable RAI therapy or to enhance follow-up based upon disease features and/or patient preferences. (**Strong Recommendation, Moderate-quality evidence**)

C) If surgery is chosen for patients with thyroid cancer <1 cm without extrathyroidal extension and cN0, the initial surgical procedure should be a thyroid lobectomy unless there are clear indications to remove the contralateral lobe. Thyroid lobectomy alone is sufficient treatment for small, unifocal, intrathyroidal carcinomas in the absence of prior head and neck irradiation, familial thyroid carcinoma, or clinically detectable cervical nodal metastases. (**Strong Recommendation, Moderate-quality evidence**)

Surgery for thyroid cancer is an important element of a multifaceted treatment approach. The operation must be compatible with the overall treatment strategy and follow-up plan recommended by the managing team. Consideration should be given to referring cases with high risk features (clinicial N1 disease, concern for RLN involvement or grossly invasive disease) to experienced surgeons as both completeness of surgery and experience of the surgeon can have a significant impact on clinical outcomes and complication rates (209;210;248) (249).

Previous guidelines have endorsed total thyroidectomy as the primary initial surgical treatment option for nearly all differentiated thyroid cancers greater than 1 cm with or without evidence of loco-regional or distant metastases(22). This was based on retrospective data that suggested that a bilateral surgical procedure would improve survival (281), decrease recurrence rates (282-284), allow for routine use of RAI remnant ablation, and facilitate detection of recurrent/persistent disease during follow-up. However, recent data have demonstrated that in properly selected patients, clinical outcomes are very similar following unilateral or bilateral thyroid surgery (285-288) (285;289). Furthermore, since the requirement for routine use of RAI ablation was one of the major reasons given in support of total thyroidectomy in low to intermediate risk patients, our current more selective approach to RAI ablation in these patients requires a critical reassessment of this indication. In some patients, the presence of the remaining lobe of the gland may obviate the life-long need for exogenous thyroid hormone

therapy. Finally, as our follow-up management paradigm has moved away from diagnostic whole body RAI scanning and toward a greater reliance on neck ultrasonography and serial serum Tg measurements (even in patients that did not receive RAI remnant ablation), we must also question whether total thyroidectomy and RAI remnant ablation is required to facilitate follow-up in low to intermediate risk patients.

In an analysis of 52,173 papillary thyroid cancer patients diagnosed between 1985 and 1998 from the National Cancer Data Base (43,227 total thyroidectomy, 8,946 lobectomy), Bilimoria et al demonstrated a slightly higher 10 year relative overall survival for total thyroidectomy as opposed to thyroid lobectomy (98.4% vs 97.1% respectively, $p < 0.05$) and a slightly lower 10 year recurrence rate (7.7% vs 9.8% respectively, p,0.05) (281). When analyzed by size of the primary tumor, statistically significant differences in survival and recurrence was seen for all sizes greater than 1 cm based on the extent of initial surgery. However, data on extrathyroidal extension, completeness of resection and other co-morbid conditions which could have had a major impact on survival and recurrence risk were not available. Therefore, it is unclear how often lobectomy was done based on proper selection of low to intermediate risk patients versus how often lobectomy was done in high risk patients because of co-morbid conditions, inability to obtain a complete resection, or status of the contralateral recurrent laryngeal nerve. This is an important distinction because thyroid lobectomy patients was associated with extrathyroidal extension in 7% (288), external beam radiation therapy in 1-2% (287), radioactive iodine therapy in 12-18% (281;288) and high risk features in 8% (288). Given the small magnitude of differences reported for survival and recurrence between the total thyroidectomy and the lobectomy patients, it is quite possible that the slightly poorer outcomes seen in the lobectomy group could have been significantly influenced by lobectomy patients with concurrent high risk features.

Previously, Haigh et al had analyzed 5,432 papillary thyroid cancer patients from the SEER data based (4,612 total thyroidectomy and 820 lobectomy) and found no difference in 10 year overall survival between total thyroidectomy and thyroid lobectomy when risk stratified by the AMES classification system (288). Interestingly, patients selected for thyroid lobectomy included 7% with extrathyroidal extension, 1% with distant metastases, 5% with primary tumors greater than 5 cm, and 8% classified as AMES high risk.

More recently, two additional studies have analyzed the SEER database and both have failed to demonstrate a significant difference in survival when comparing total thyroidectomy with thyroid lobectomy (286;287). Barney et al included 23,605 differentiated thyroid cancer cases diagnosed between 1983 and 2002 (12, 598 total thyroidectomy, 3,266 lobectomy) and found no difference in 10 year over all survival (90.4% for total thyroidectomy vs 90.8% for lobectomy) or 10 year cause specific survival (96.8% for total thyroidectomy vs 98.6% for lobectomy). Furthermore, in a multivariate analysis that included age, T, N, M, gender, year of diagnosis, extent of surgery and RAI use, no difference in overall survival or cause specific survival was seen with respect to the extent of initial surgery. Mendelsohn et al (287) analyzed 22,724 papillary thyroid cancer patients diagnosed between 1998 and 2001 (16,760 total thyroidectomy, 5,964 lobectomy) and found no difference in overall survival or disease specific survival when comparing total thyroidectomy with lobectomy. Interestingly, of the patients that had lobectomy, 1.6% received external beam irradiation, 16% had extrathryoidal extension, 9% were greater than 4 cm, and 20% received RAI ablation (once again indicating that lobectomy was done in some high risk patients).

Consistent with the SEER data analyses, two single center studies also confirm that lobectomy is associated with excellent survival in properly selected patients (285;289). After a median follow-up of 8 years, only 1 disease specific death was seen in a cohort of 889 papillary thyroid cancer patients with T1-T2 tumors treated with either total thyroidectomy (n=528) or lobectomy (n=361) (289). Furthermore, Matsuzu et al reported a cause specific survival rate of 98% after a median of 17 years of follow-up in properly select papillary thyroid cancer patients treated with lobectomy and ipsilateral neck dissection (285).

Given the propensity for papillary thyroid cancer to be multifocal (often involving both lobes), it is not surprising that some studies have demonstrated a lower risk of loco-regional disease recurrence following total thyroidectomy as compared to thyroid lobectomy (282-284). However, with proper patient selection, loco-regional recurrence rates of less than 1-4% and completion thyroidectomy rates of less than 10% can be achieved following thyroid lobectomy (289;290). Furthermore, the few recurrences that develop during long term follow-up are readily detected and appropriately treated with no impact on survival (285;289;290).

Therefore, we conclude that in properly selected low to intermediate risk patients, the extent of initial thyroid surgery probably has little impact on disease specific survival. While

recurrence rates can be quite low in properly selected patients, it is likely that the lowest rates of recurrence during long term follow-up would be associated with a total thyroidectomy. But since salvage therapy is quite effective in the few patients that recur after thyroid lobectomy, a conservative management approach to up front surgery accepting a slightly higher risk of loco-regional recurrence is an acceptable management strategy. Finally, a more selective use of RAI coupled with a greater reliance on neck US and serial serum Tg measurements for detection of recurrent disease is likely to significantly decrease the mandate for total thyroidectomies in low and intermediate risk patients done solely to facilitate RAI remnant ablation and follow-up.

Near-total or total thyroidectomy is necessary if the overall strategy is to include RAI therapy postoperatively, and thus is recommended if the primary thyroid carcinoma is >4 cm, there is gross extra-thyroidal extension, or regional or distant metastases are present. For tumors that are between 1 and 4 cm in size, either a bilateral thyroidectomy (total or near-total) or a unilateral procedure (thyroid lobectomy) may serve as the surgical platform for an overall treatment plan. Older age (>45 years), contralateral thyroid nodules, a personal history of radiation therapy to the head and neck, or familial DTC may be criteria for recommending a bilateral procedure either because of plans for RAI therapy, to facilitate follow-up strategies, or to address suspicions of bilateral disease (239;247;285;289).

The relationship between surgeon volume and patient outcomes has been studied extensively over the last 20 years. Institutional studies examining outcomes following thyroidectomy by high-volume surgeons have been published demonstrating overall safety. In one of the first studies examining the relationship between surgeon volume and thyroidectomy outcomes at a state level, Sosa et al. found a strong association between higher surgeon volume and favorable patient outcomes, especially with regard to recurrent laryngeal nerve injury and wound complications (209). This was especially pronounced for patients undergoing total thyroidectomy for thyroid cancer. Others have made similar observations (210;291;292). In a recent study of patients undergoing thyroidectomy in the Health Care Utilization Project Nationwide Inpatient Sample (HCUP-NIS), surgeons were divided into low- (<10 cases/yr; encompassing 6072 surgeons), intermediate- (10-100 cases/yr; 11544 surgeons), and high-volume (>100 cases/yr; 4009 surgeons) categories (293). Over 80% of thyroid resections were performed by low- and intermediate-volume surgeons. On average, high-volume surgeons had

the lowest complication rates for patients who underwent total thyroidectomy for cancer at 7.5%; intermediate-volume surgeons had a rate of 13.4%, and low-volume surgeons 18.9%, ($p<0.001$).

From robust population level data such as these, it can be concluded that referral of patients to high-volume thyroid surgeons is associated, on average, with superior outcomes. However, such referral is not always possible, given the relative scarcity of high-volume surgeons and their geographic distribution. In addition, there are some data suggesting that other factors, such as surgeon age, should be considered (294). Therefore, conclusions at a population level cannot always be applied to individual surgeons and patient circumstances. It may, however, be reasonable to consider sending patients with more extensive disease and concern for grossly invasive disease to a high volume surgeon experienced in the management of advanced thyroid cancer.

It is worth noting that even high-volume surgeons have a higher overall postoperative complication rate when performing total thyroidectomy compared to lobectomy (295). Using the HCUP-NIS, these authors found that high-volume thyroid surgeons had a complication rate of 7.6% following thyroid lobectomy but a rate of 14.5% following total thyroidectomy. For low-volume surgeons, the complication rates were 11.8% and 24.1%, respectively. Therefore, patients should carefully weigh the relative benefits and risks of total thyroidectomy vs. thyroid lobectomy, even when surgery is performed by high-volume surgeons.

[B8] Lymph node dissection

■ **RECOMMENDATION 36**

A) Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. (**Strong Recommendation, Moderate-quality evidence**)

B) Prophylactic central-compartment neck dissection (ipsilateral or bilateral) should be considered in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes (cN0) who have advanced primary tumors (T3 or T4), clinically involved lateral neck nodes (cN1b), or if the information will be used to plan further steps in therapy. (**Weak Recommendation, Low-quality evidence**)

C) Thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTC (cN0) and for most follicular

cancer. (**Strong Recommendation, Moderate-quality evidence**)

■ **RECOMMENDATION 37**

Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy. (**Strong Recommendation, Moderate-quality evidence**)

Regional lymph node metastases are present at the time of diagnosis in a majority of patients with papillary carcinoma and a lesser proportion of patients with follicular carcinoma (259;296;297). Although PTC lymph node metastases are reported by some to have no clinically important effect on outcome in low risk patients, a study of the Surveillance, Epidemiology, and End Results (SEER) database found, among 9904 patients with PTC, that lymph node metastases, age >45 years, distant metastasis, and large tumor size significantly predicted poor overall survival outcome on multivariate analysis (298). All-cause survival at 14 years was 82% for PTC without lymph node metastases and 79% with nodal metastases ($p < 0.05$). Another SEER registry study concluded that cervical lymph node metastases conferred an independent risk of decreased survival, but only in patients with follicular cancer and patients with papillary cancer over age 45 years (299). However, characteristics of the lymph node metastases can further discriminate the risk of recurrence to the patient, especially in those patients with clinically evident metastasis, multiple metastases, larger metastases, and/or extracapsular nodal extension (300;301), compared to those with more limited microscopic nodal disease (297). Common to all of these studies is the conclusion that the effect of the presence or absence of lymph node metastases on overall survival, if present, is small and probably most significant in older patients.

The cervical node sites are well-defined (302), and the most common site of nodal metastases is in the central neck which is cervical level VI (Fig. 3). A recent consensus conference statement describes the relevant anatomy of the central neck compartment, delineates the nodal subgroups within the central compartment commonly involved with thyroid cancer, and defines the terminology relevant to central compartment neck dissection (303). In many patients, lymph node metastases in this area do not appear abnormal on preoperative imaging (258;296;304-306) or by inspection at the time of surgery (297), defining a cN0 group.

The role of therapeutic lymph node dissection for treatment of thyroid cancer node metastases is well-accepted for cN1 disease (298;307-309). However, the value of routine prophylactic level VI (central) neck dissection for cN0 disease remains unclear. Central compartment dissection (therapeutic or prophylactic) can be achieved with low morbidity by experienced thyroid surgeons (310-312). Value for an individual patient depends upon the utility of the staging information to the treatment team in specific patient circumstances (312;313). Based on limited and imperfect data, prophylactic dissection has been suggested to improve disease-specific survival (314) local recurrence (306;315), and post-treatment thyroglobulin levels (306;316). It has also been used to inform use of adjuvant RAI (305;308;311;317) and improve the accuracy of the estimates of risk of recurrence (317-319). However, in several studies, prophylactic dissection has shown no improvement in long-term patient outcome, while increasing the likelihood of temporary morbidity, including hypocalcemia (296;307;308;310;320-324).

The removal of cN0 level VI lymph nodes detects a substantial number of patients with pN1 disease; however, the direct effect of this on long-term outcome is small at best (325;326). The use of staging information for the planning of adjuvant therapy depends upon whether this information will affect the team-based decision-making for the individual patient. For these reasons, groups may elect to include prophylactic dissection for patients with some prognostic features associated with an increased risk of metastasis and recurrence (older or very young age, larger tumor size, multifocal disease, extrathyroidal extension, known lateral node metastases) to contribute to decision-making and disease control (306;312;316). Alternatively, some groups may apply prophylactic level VI dissection to patients with better prognostic features if the patient is to have a bilateral thyroidectomy, and if the nodal staging information will be used to inform the decision regarding use of adjuvant therapy (305;311;317). Finally, for some groups it appears reasonable to use a selective approach that applies level VI lymph node dissection at the time of initial operation only to patients with clinically evident disease based on preoperative physical exam, preoperative radiographic evaluation or intraoperative demonstration of detectable disease (cN1) (297;320;327).

The information from prophylactic central neck dissection must be used cautiously for staging information. Since microscopic nodal positivity occurs frequently, prophylactic dissection often converts patients from clinical N0 to pathologic N1a, upstaging many patients

over age 45 from American Joint Committee on Cancer (AJCC) stage I to stage III (296;305-308). However, microscopic nodal positivity does not carry the recurrence risk of macroscopic clinically detectable disease (297). Thus microscopic nodal upstaging may lead to excess radioactive iodine utilization and patient follow-up. Alternatively, the demonstration of uninvolved lymph nodes by prophylactic dissection may decrease the use of radioiodine for some groups (305;311;317). These effects may account for some of the existing extreme variability in utilization of radioactive iodine for thyroid cancer (328).

Studies of the BRAF V600E mutation have suggested an association between presence of the mutation and the risk of nodal disease (329-331) although results across all patients with papillary thyroid carcinoma are mixed (332-335). However, BRAF V600E mutation has a limited positive predictive value for recurrence and therefore BRAF V600E mutation status in the primary tumor should not impact on the decision for prophylactic central neck dissection (336).

The above recommendations should be interpreted in light of available surgical expertise. For patients with small, noninvasive, cN0 tumors, the balance of risk and benefit may favor thyroid lobectomy and close intraoperative inspection of the central compartment, with the plan adjusted to total thyroidectomy with compartmental dissection only in the presence of involved lymph nodes.

Lymph nodes in the lateral neck (compartments II–V, Fig. 3), level VII (anterior mediastinum), and rarely in Level I may also be involved by thyroid cancer (251;297;337;338). For those patients in whom nodal disease is evident clinically on preoperative US and nodal FNA cytology or Tg measurement, or at the time of surgery, surgical resection by compartmental node dissection may reduce the risk of recurrence and possibly mortality (339-341).

[B9] Completion thyroidectomy

■ **RECOMMENDATION 38**

A) Completion thyroidectomy should be offered to those patients for whom a bilateral thyroidectomy would have been recommended had the diagnosis been available before the initial surgery. Therapeutic central neck lymph node dissection should be included if the lymph nodes are clinically involved. (**Strong Recommendation, Moderate-quality evidence**)

B) Radioactive iodine ablation in lieu of completion thyroidectomy is not recommended routinely; however, it may be used to ablate the remnant lobe in selected cases. (**Weak Recommendation, Low-quality evidence**)

Completion thyroidectomy may be necessary when the diagnosis of malignancy is made following lobectomy for an indeterminate or nondiagnostic biopsy. In addition some patients with malignancy may require completion thyroidectomy to provide complete resection of multicentric disease, and to allow for efficient RAI therapy. However, since intrathyroidal PTC can be managed with either lobectomy or total thyroidectomy (See Recommendation 35B), a completion thyroidectomy is not always required. The surgical risks of two-stage thyroidectomy (lobectomy followed by completion thyroidectomy) are similar to those of a near-total or total thyroidectomy (342-344). The marginal utility of prophylactic lymph node dissection for cN0 disease argues against its application in re-operations.

Ablation of the remaining lobe with radioactive iodine has been used as an alternative to completion thyroidectomy (345;346). There are limited data regarding the long-term outcomes of this approach. The data suggest similar clinical outcome with a slightly higher proportion of patients with elevated thyroglobulin. This approach may be helpful in patients for whom completion thyroidectomy carries some increased risk and for whom a delay in the length of time required to achieve destruction of the normal thyroid which follows RAI (as opposed to surgical resection) is acceptable. In one unblinded, multi-center, randomized controlled equivalence trial comparing dose activities in achieving successful ablation of a remaining lobe in patients with T1b or T2 primary tumor, who had surgical contraindications or declined completion thyroidectomy, the remnant ablation success rate was significantly higher using 100 mCi (75% success rate), compared to 30 mCi (54%), although mild to moderate short-term neck pain was more frequently reported in the high dose group (66%) compared to the low dose group (51%) (347). Prednisone treatment for neck pain was used more frequently in the high dose group (36% of patients) compared to the low dose activity group.

[B10] What is the appropriate perioperative approach to voice and parathyroid issues?

[B11] Preoperative care communication

■ RECOMMENDATION 39

Prior to surgery, the surgeon should communicate with the patient regarding surgical risks, including nerve and parathyroid injury, through the informed consent process and communicate with associated physicians, including anesthesia personnel, regarding important findings elicited during the preoperative workup. **(Strong recommendation, Moderate-quality evidence)**

The preoperative consent process should include explicit discussion of the potential for temporary or permanent nerve injury (and its clinical sequelae, including voice change, swallowing disability, risk of aspiration, and tracheostomy) as well as hypoparathyroidism, bleeding, scarring, disease recurrence, need for additional postoperative treatment , need for thyroid hormone and surveillance thyroid function tests. The conversation should be informed by the operating surgeon's own rates of complications. Results of the preoperative evaluation regarding extent of disease, risk stratification, and integrity of the airway should include results from imaging, cytology, and physical examination (348-352).

[B12] Preoperative voice assessment

■ **RECOMMENDATION 40**

All patients undergoing thyroid surgery should have preoperative voice assessment as part of their pre-operative physical examination. This should include the patient's description of vocal changes, as well as the physician's assessment of voice. **(Strong recommendation, Moderate-quality evidence)**

■ **RECOMMENDATION 41**

Preoperative laryngeal exam should be performed in all patients with:

A) Preoperative voice abnormalities **(Strong recommendation, Moderate-quality evidence)**

B) History of cervical or upper chest surgery which places the RLN or vagus nerve at risk **(Strong recommendation, Moderate-quality evidence)**

C) Known thyroid cancer with posterior extrathyroidal extension or extensive central nodal metastases. **(Strong recommendation, Low-quality evidence)**

Voice alteration is an important complication of thyroid surgery affecting patients' quality of life (with regard to voice, swallowing, and airway domains), and it can have medico-legal and cost implications (353-361).

Preoperative assessment provides a necessary baseline reference from which to establish perioperative expectations (362). Also, preoperative voice assessment may lead one to identify preoperative vocal cord paralysis or paresis which provides presumptive evidence of invasive thyroid malignancy and is important in extent of surgery planning and perioperative airway management (363-365). Contralateral nerve injury at surgery in such patients could cause bilateral cord paralysis with airway implications.

Preoperative voice assessment should include the patient's historical subjective response to questions regarding voice abnormalities or changes, as well as the physician's objective assessment of voice, and should be documented in the medical record (Table 9) (366). Voice and laryngeal function may be further assessed through laryngoscopy , and the application of validated quality of life and auditory perceptual assessment voice instruments (362). It is important to appreciate that vocal cord paralysis, especially when chronic, may not be associated with significant vocal symptoms due to a variety of mechanisms, including contralateral vocal cord compensation. Voice assessment alone may not identify such individuals (362).

Incidence rates for preoperative vocal cord paresis or paralysis for patients with benign thyroid disease at preoperative laryngoscopy range from 0 to 3.5% and up to 8% in patients with thyroid cancer (367-371). Finding vocal cord paralysis on preoperative examination strongly suggests the presence of locally invasive disease. Approximately 10 to 15% of thyroid cancers present with extrathyroidal extension, with the most common structures involved including strap muscle (53%), the RLN (47%), trachea (30%), esophagus (21%), and larynx (12%).(365;372-374)(https://www.nccn.org).

Undiagnosed preoperative laryngeal nerve dysfunction conveys greater risk during total thyroidectomy of postoperative bilateral nerve paralysis, respiratory distress, and need for tracheostomy. Preoperative patient counseling is potentially improved. Also, preoperative identification of vocal cord paralysis is important because surgical algorithms in the management of the invaded nerve incorporate nerve functional status (375).

Laryngeal exam should be performed if during preoperative voice evaluation voice is abnormal. In addition, any patient with a history of neck surgery which placed at risk either the

recurrent laryngeal nerve (such as past thyroid or parathyroid surgery) or the vagus nerve (such as carotid endarterectomy, cervical esophagectomy, and anterior approach to the cervical spine) or a history of prior external beam radiation to the neck should have laryngeal exam even if the voice is normal. Correlation between vocal symptoms and actual vocal cord function is poor given the potential for 1) variation in paralytic cord position, 2) degree of partial nerve function, and 3) contralateral cord function/compensation; therefore, vocal symptoms may be absent in patients with vocal cord paralysis. Vocal cord paralysis may be present in 1.5 to 30% of such postsurgical patients; it can be asymptomatic in up to one third (363;376-382).

Laryngeal exam is recommended in patients with the preoperative diagnosis of thyroid cancer if there is evidence for gross extrathyroidal extension of cancer which extends posteriorly or extensive nodal involvement , even if the voice is normal. Laryngeal exam should be performed in the above noted high risk settings but can be performed in other patients based on the surgeon's judgment.

[B13] Intraoperative Voice and Parathyroid Management

■ RECOMMENDATION 42

A) Visual identification of the recurrent laryngeal nerve (RLN) during dissection is required in all cases. Steps should also be taken to preserve the external branch of the superior laryngeal nerve (EBSLN) during dissection of the superior pole of the thyroid gland. **(Strong recommendation, Moderate-quality evidence)**

B) Intraoperative neural stimulation (with or without monitoring) may be considered to facilitate nerve identification and confirm neural function. **(Weak recommendation, Low-quality evidence)**

■ RECOMMENDATION 43

The parathyroid glands and their blood supply should be preserved during thyroid surgery. **(Strong recommendation, High-quality evidence)**

RLN injury rates are lower when the nerve is routinely visualized as compared to surgeries where the nerve is simply avoided (362;376;383). If the superior laryngeal nerve can be visualized and preserved, that is ideal. If the nerve cannot be visually identified, steps should

be taken to avoid the nerve; this can be done by staying close to the thyroid capsule at the superior pole and by skeletonizing the superior vascular pedicle. Intraoperative nerve monitoring can be used to facilitate this dissection (379). Studies with or without intraoperative nerve monitoring (IONM) demonstrate similar patient outcomes with regard to nerve injury rates (380), but studies likely have been underpowered to detect statistically significant differences (373;384). A recent systematic review meta-analysis of 20 randomized, non-randomized prospective and retrospective studies, suggested no statistically significant benefit of intraoperative neuromonitoring compared to visualization alone during thyroidectomy for the outcomes of overall, transient, or permanent recurrent laryngeal nerve palsy when analyzed per nerve at risk or per patient (385). However, secondary subgroup analyses of high risk patients (including those with thyroid cancer) suggested statistically significant heterogeneity (variability) in treatment effect for overall and transient recurrent laryngeal nerve injury, when analyzed per nerve at risk. A significant proportion of surgeons, including high volume surgeons, use IONM to facilitate nerve management and several studies show improved rates of nerve paralysis with the use of neural monitoring in reoperative and complex thyroid surgery (361;386-390). Neural stimulation at the completion of lobectomy can be used as a test to determine the safety of contralateral surgery with avoidance of bilateral vocal cord paralysis and has been associated with a reduction of bilateral paralysis when loss of signal occurs on the first side (388;391-393).

Typically, parathyroid gland preservation is optimized by gland identification via meticulous dissection. If the parathyroid(s) cannot be located, the surgeon should attempt to dissect on the thyroid capsule and ligate the inferior thyroid artery very close to the thyroid, since the majority of parathyroid glands receive their blood supply from this vessel. There are exceptions to this rule; for example, superior glands in particular may receive blood supply from the superior thyroid artery. If the parathyroid glands are inadvertently or unavoidably removed (e.g. they are intrathyroidal, or require removal during a central lymph node dissection) or devascularized, confirmation of cancer-free parathyroid tissue should be performed, and then the glands can be autotransplanted into the strap or sternocleidomastoid muscles. It is important to inspect the thyroidectomy and/or central lymphadenectomy specimen when removed and before sending it to pathology to look for parathyroid glands that can be rescued.

[B14] Postoperative Voice Care

■ RECOMMENDATION 44

Patients should have their voice assessed in the postoperative period. Formal laryngeal exam should be performed if the voice is abnormal **(Strong recommendation, Moderate-quality evidence)**

■ RECOMMENDATION 45

Important intraoperative findings and details of postoperative care should be communicated by the surgeon to the patient and other physicians who are important in the patient's postoperative care. **(Strong recommendation, Low-quality evidence)**

Voice assessment should occur after surgery and should be based on the patient's subjective report and physician's objective assessment of voice in the office (369). Typically this assessment can be performed at 2 weeks to 2 months after surgery. Early detection is important for facilitating prompt intervention, which is associated with better long-term outcome (394-396). Many options exist for the management of RLN paralysis, including voice therapy, vocal cord injection techniques, and open vocal cord medialization. Rates of vocal cord paralysis after thyroid surgery can only be assessed by laryngeal exam postoperatively.

Communication of intraoperative findings and postoperative care from the surgeon to other members of the patient's thyroid cancer care team is critical to subsequent therapy and monitoring approaches. Important elements of communication include: 1) Surgical anatomic findings, including RLN and parathyroid status (including nerve monitoring loss of signal information if monitoring is employed); 2) Surgical disease findings, including evidence for extrathyroidal spread, completeness of tumor resection, presence and distribution of nodal disease; and 3) Postoperative status, including voice /laryngeal exam, laboratory data regarding calcium/parathyroid hormone levels and need for calcium and/or vitamin D supplementation, and the surgical pathology report (397).The surgeon remains engaged in the patient's pursuant care to facilitate appropriate communication and may remain engaged subsequent to endocrinologic consultation depending on regional practice patterns.

[B15] What are the basic principles of histopathologic evaluation of thyroidectomy samples?

■ RECOMMENDATION 46

A) In addition to the basic tumor features required for AJCC/UICC thyroid cancer staging including status of resection margins, pathology reports should include additional information helpful for risk assessment including the presence of vascular invasion and the number of invaded vessels, number of lymph nodes examined and involved with tumor, size of the largest metastatic focus to the lymph node, and presence or absence of extranodal extension of the metastatic tumor. (**Strong recommendation, Moderate-quality evidence**)

B) Histopathologic variants of thyroid carcinoma associated with more unfavorable (e.g. - tall cell, columnar cell, and hobnail variants of PTC, widely invasive FTC, poorly differentiated carcinoma) or more favorable (e.g. - encapsulated follicular variant without invasion, minimally-invasive FTC) outcome should be identified during histopathologic examination and reported. (**Strong recommendation, Low-quality evidence**)

C) Histopathologic variants associated with familial syndromes (cribriform-morular variant of papillary carcinoma often associated with familial adenomatous polyposis, PTEN-hamartoma tumor syndrome associated follicular carcinoma) should be identified during histopathologic examination and reported. (**Weak recommendation, Low-quality evidence**)

Pathologic examination of thyroid samples establishes the diagnosis and provides important information for risk stratification of cancer and post-surgical patient management. Histopathologically, papillary carcinoma is a well differentiated malignant tumor of thyroid follicular cells that demonstrates characteristic microscopic nuclear features. Although a papillary growth pattern is frequently seen, it is not required for the diagnosis. Follicular carcinoma is a well-differentiated malignant tumor of thyroid follicular cells that shows transcapsular and/or vascular invasion and lacks the diagnostic nuclear features of papillary carcinoma. Oncocytic (Hürthle cell) follicular carcinoma shows the follicular growth pattern but is composed of cells with abundant granular eosinophilic cytoplasm, which has such appearance because of accumulation of innumerable mitochondria. This tumor is currently designated by WHO as a histopathologic variant of follicular carcinoma (398). However, oncocytic follicular carcinoma tumors have some differences in biological behavior as compared to the conventional

type follicular carcinoma, such as the ability to metastasize to lymph nodes and a possibly higher rate of recurrence and tumor-related mortality (238;399;400). Moreover, a growing body of genetic evidence suggests that oncocytic tumors develop via unique molecular mechanisms and therefore represent a distinct type of well differentiated thyroid cancer (401).

Traditionally, follicular carcinomas have been subdivided into minimally invasive (encapsulated) and widely invasive. In this classification scheme, minimally invasive carcinomas are fully encapsulated tumors with microscopically identifiable foci of capsular or vascular invasion, whereas widely invasive carcinomas are tumors with extensive, frequently extrathyroidal, invasion. More recent approaches consider encapsulated tumors with only microscopic capsular invasion as minimally-invasive, whereas angioinvasive tumors are placed into a separate category (402-404). Such approach is preferable, as it distinguishes encapsulated tumors with capsular invasion and no vascular invasion, which are highly indolent tumors with mortality <5%, from angioinvasive follicular carcinomas, which depending on the number of invaded blood vessels have mortality ranging from 5 to 30% (405).

In addition to establishing a diagnosis for each nodule in a thyroidectomy or lobectomy specimen, pathology report must provide characteristics required for AJCC/UICC TNM staging, such as tumor size and presence of extrathyroidal extension and lymph node metastasis. Extrathyroidal extension is defined as tumor penetration through the thyroid capsule into the adjacent tissues. It is subdivided into *minimal*, which is invasion into immediate perithyroidal soft tissues or sternothyroid muscle (T3 tumors), and *extensive*, which is tumor invasion into subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (T4a tumors). The size of the metastatic focus in a lymph node (297) and tumor extension beyond the capsule of a lymph node (300;406;407) affects cancer risk. Therefore, pathology report should indicate the size of the largest metastatic focus to the lymph node and the presence or absence of extranodal tumor extension, as well as the number of examined and involved LN.

Additionally, the presence of vascular (blood vessel) invasion is an unfavorable prognostic factor (408-410), and should be evaluated and reported. Vascular invasion is diagnosed as direct tumor extension into the blood vessel lumen or a tumor aggregate present within the vessel lumen, typically attached to the wall and covered by a later of endothelial cells. Invasion of multiple (4 or more) blood vessels appears to entail poorer outcomes, particularly in

follicular carcinoma (411-413). Therefore, the number of invaded blood vessels (less than 4 or more) should be stated in the pathology report.

More than 10 microscopic variants of papillary carcinoma have been documented (414). Some of them are associated with more aggressive or, in opposite, more indolent tumor behavior and can contribute for risk stratification. The variants with more unfavorable outcomes are the tall cell, columnar cell, and hobnail variants. The tall cell variant is characterized by predominance of tall columnar tumor cells whose height is at least 3 times their width. These tumors present at an older age and more advanced stage than classic papillary carcinoma (415-418) and demonstrate a higher recurrence rate and decreased disease-specific survival (415-417;419;420), which was found to be independent of patient age and tumor size and stage (421;422). *BRAF* V600E mutation is found in ~80% of these tumors (423;424).

The columnar cell variant of papillary carcinoma is characterized by predominance of columnar cells with pronounced nuclear stratification (425;426). These tumors have a higher risk of distant metastases tumor-related mortality, the latter seen mostly in patients with an advanced disease stage at presentation (425-428). *BRAF* V600E mutation is found in one-third of these tumors (425).

Papillary carcinoma with prominent hobnail features is a rare recently described variant characterized by the predominance of cells with a hobnail appearance with apically placed nuclei and bulging of the apical cell surface (429;430). *BRAF* V600E mutation is frequency found in these tumors (429). This variant of papillary carcinoma appears to be associated with frequent distant (typically to lung) metastases and increased risk of tumor-related death (429).

Other variants of papillary carcinoma, such as the solid variant and diffuse sclerosing variant, may be associated with a less favorable outcome, although the data remain conflicting. The solid variant tumors appear to be more frequently associated with distant metastases that are present in about 15% of cases, and with a slightly higher mortality rate, which was 10-12% in two studies with 10 and 19 years mean follow-up (431;432). However, among children and adolescents with post-Chernobyl papillary carcinoma, which frequently was of the solid variant, the mortality was very low (<1%) during the first 10 years of follow-up (433;434). Importantly, the solid variant of papillary carcinoma should be distinguished from poorly differentiated thyroid carcinoma, with which it shares the insular, solid, and trabecular growth patterns. The distinction is based primarily on the preservation of nuclear features and lack of necrosis and

high mitotic activity in the solid variant, as outlined by the Turin diagnostic criteria for poorly differentiated thyroid carcinoma (435). The distinction is important to make because poorly differentiated thyroid carcinoma has a much poorer prognosis, with the 5-year survival of 72% and 10-year survival of 46% in a series of 152 patients diagnosed using the Turin criteria (436).

The prognostic implication of the diffuse sclerosing variant of papillary cancer remains controversial. This variant is characterized by diffuse involvement of the thyroid gland and a higher rate of local and distant metastases at presentation, and has lower disease-free survival is than classic papillary carcinoma (437-439). The frequency of distant, predominantly lung, metastases varies between the reported series and is 10-15% based on almost 100 published cases summarized by Lam and Lo in 2006 (440) and more recent reports. Nevertheless, the overall mortality appears to be low, with a disease-specific survival of approximately 93% at 10 years of follow-up. Diffuse sclerosing variant tends to be found in younger patients in whom response to treatment is high.

Encapsulated follicular variant of papillary carcinoma is, in contrast, associated with a low risk of recurrence, particularly in the absence of capsular or vascular invasion. This variant is characterized by the follicular growth pattern with no papillae formation and total tumor encapsulation, and the diagnosis rests on the finding of characteristic nuclear features of papillary carcinoma. Most of the tumors show no invasive growth, whereas in about one-third of cases tumor capsule invasion and/or vascular invasion are found (441;442). Whereas in the past the encapsulated follicular variant was relatively rare, at present time half to two-thirds of all follicular variant papillary carcinomas belong to this subtype (443). The behavior of these tumors is usually quite indolent. A summary of 6 studies that reported 107 cases of encapsulated follicular variant, revealed 25% with lymph node metastases and 1% with distant metastases (444). Among these 107 patients, 1 died of disease and 2 were alive with disease, whereas the rest (97%) of patients were alive and well with various follow-up periods. In a study of 61 cases of encapsulated follicular variant, lymph node metastases were observed in 5% and there was no distant metastasis (441). With median follow-up of 11 years, one patient developed tumor recurrence, and this tumor had invasion. No adverse events were found in any of the encapsulated and non-invasive tumors, including 31 patients treated with lobectomy only. Similarly, no evidence of recurrence was found in 61 out of 62 encapsulated or well-circumscribed follicular variant of PTC in another series of patients with median follow-up of

9.2 years, and the only case that developed recurrence had a positive resection margin after initial surgery (445). In another study of a cohort of thyroid tumors followed on average for 12 years, none of 66 patients with encapsulated follicular variant of papillary carcinoma died of disease (442). Despite a low probability, some patients with encapsulated follicular variants may present with distant, particularly bone, metastases or develop metastasis on follow-up (446;447). Tumors prone to metastatic behavior often have a thick capsule and significant intratumoral fibrosis, and virtually all of them reveal vascular invasion or invasion of the tumor capsule. Therefore, pathologic evaluation of these tumors should include microscopic examination of the entire tumor capsule to rule out invasion, as well as careful evaluation of the tumor to rule out the presence of poorly differentiated carcinoma areas or other unfavorable diagnostic features such as tumor necrosis or high (≥3 per 10 HPFs) mitotic activity (448). In the absence of these features, a completely excised non-invasive encapsulated follicular variant of papillary carcinoma is expected to have a very low risk of recurrence or extrathyroidal spread, even in patients treated by lobectomy.

Similarly, excellent clinical outcomes are seen in follicular thyroid cancers that manifest only capsular invasion without vascular invasion (449-451). However, when vascular invasion is present, some studies (413;449;452-455), but not all (451;456), suggest a greater extent of vascular invasion (more than 4 foci of vascular invasion, or extracapsular vascular invasion) is associated with poorer outcomes.

Some histopathologic variants of thyroid carcinomas are important to recognize because of their association with familial tumor syndromes. Cribriform-morular variant of papillary carcinoma is frequently seen in patients with familial adenomatous polyposis (FAP) due to a germline mutation in the adenomatous polyposis coli (*APC)* gene (457;458). It is characterized by the prominent cribriform architecture and formation of whorls or morules composed of spindle cells. The presence of aberrant β-catenin immunoreactivity provides a strong evidence for this tumor variant (459-461). Approximately 40% of patients with this variant of papillary carcinoma are found to have FAP, whereas the rest have no evidence of the inherited disease (459;462). Although no microscopic tumor features can distinguish between familial and sporadic disease, tumor multifocality is more common in the setting of the familial disease (459;462). Since many patients with cribriform-morular variant have FAP and thyroid cancer can precede clinically detectable colonic abnormalities in ~40% of patients (462), this diagnosis

should raise the possibility of the familial disease and prompt consideration for colonic examination and genetic counseling.

Follicular carcinoma may develop in a manifestation of the PTEN hamartoma tumor syndrome (PHTS), which is caused by a germline mutation in the *PTEN* gene (463-465). The histopathologic appearance of thyroid glands in these patients is very characteristic and should allow pathologists to suspect this syndrome (464;465). The glands typically have numerous sharply-delineated, frequently encapsulated thyroid *nodules* that microscopically are well-delineated, cellular, with variable growth patterns (466;467)(464;465). Individuals affected by this syndrome also have a high risk for malignant tumors of breast and endometrium, and in light of the characteristic appearance of thyroid tumors, genetic counseling should be recommended.

Well differentiated papillary and follicular cancers should be histologically distinguished from poorly differentiated carcinoma. Poorly differentiated carcinoma is an aggressive thyroid tumor characterized by a partial loss of the features of thyroid differentiation that occupies morphologically and behaviorally an intermediate position between well differentiated papillary and follicular carcinomas and fully dedifferentiated anaplastic carcinoma. Another term used in the past for this tumor is "insular carcinoma". Diagnostic criteria for poorly differentiated carcinoma are based on the consensus Turin proposal and include the following 3 features: (i) solid/trabecular/insular microscopic growth pattern, (ii) lack of well developed nuclear features of papillary carcinoma, and (iii) one of the following: convoluted nuclei (evidence for partial loss of differentiation in papillary cancer), tumor necrosis, or 3 or more mitoses per 10 high power fields (468). Poorly differentiated carcinomas have signifciantly worse ourtcome as compared to well differentiated PTC and FTC, with a 10-year survival of ~50% (468-470). Patient age over 45 years, larger tumor size, presence of necrosis and high mitotic activity are additional factors that may influence a more unfavorable outcome in patients with poorly differentiated thyroid cancer (468;471). Tumor with insular, solid, or trabecular architecture but lacking other diagnostic features of poorly differentiated carcinoma do not demonstrate such an aggressive behavior and threfore should not be connsidered as poorly diferentiated. On the other hand, some studies suggest that the presense of high mitotic rate (≥5 mitoses/10 high power fields or Ki-67 labeling index ≥4%) or tumor necrosis predicts a less favorable outcome irrespective of the presence of the solid/trabecular/insular growth pattern (472;473).

[B16] What is the role of postoperative staging systems and risk stratification in the management of DTC?

[B17] Postoperative staging

■ RECOMMENDATION 47

AJCC/UICC staging is recommended for all patients with DTC, based on its utility in predicting disease mortality, and its requirement for cancer registries (**Strong recommendation, Moderate-quality evidence**)

Postoperative staging for thyroid cancer, as for other cancer types, is used: 1) to provide prognostic information, which is of value when considering disease surveillance and therapeutic strategies, and 2) to enable risk-stratified description of patients for communication among health care professionals, tracking by cancer registries, and research purposes.

It is important to emphasize that accurate initial staging requires a detailed understanding of all pertinent risk stratification data, whether it was obtained as part of pre-operative testing, during the operation(s), or as part of post-operative follow-up. It is also important to emphasize that in many cases the written pathology report of the surgical specimen does not convey critical risk factors such as pre-operative vocal cord paralysis, extent of gross extrathyroidal invasion, completeness of resection, or remaining gross residual disease. Without these critical pieces of information, it is likely that initial risk stratification will be inaccurate and potentially misleading. Details and suggestions for effectively communicating specific risk factors between health care providers are detailed in a recent publication of the Surgical Affairs Committee of the American Thyroid Association (397).

[B18] AJCC/UICC TNM staging

Over the years, multiple staging systems have been developed to predict the risk of mortality in patients with differentiated thyroid cancer (474). Each of the system uses some combination of age at diagnosis, size of the primary tumor, specific tumor histology, and extrathyroidal spread of the tumor (direct extension of the tumor outside the thyroid gland, loco-regional metastases, and/or distant metastases) to stratify patients into one of several categories with differing risks of death from thyroid cancer. Recently, a nomogram was developed and validated using the SEER data base which provides a mathematical approach to integrating these important clinical predictive features into a specific mortality risk estimate for an individual

patient (475). Using an approach similar to the MACIS system from the Mayo Clinic (239), a quantitative approach based on histology, age, lymph node metastases, tumor size and extra-thyroidal extension utilizing TNM staging has recently been proposed and validated (476;477)

While none of the staging systems has been shown to be clearly superior to the other systems, several studies have demonstrated that the AJCC/UICC TNM system (Table 10) and the MACIS system consistently provide the highest proportion of variance explained (PVE, a statistical measure of how well a staging system can predict the outcome of interest) when applied to a broad range of patient cohorts (246;456;478-482), and have been validated in retrospective studies as well as prospectively in clinical practice.

Unfortunately, none of the staging systems designed to predict mortality from thyroid cancer can account for more than small proportion (5-30%, corresponding to PVE values of 0.05 to 0.30) of the uncertainty associated with eventual death from thyroid cancer (246;456;478-482). This relative inability to accurately predict the risk of death from thyroid cancer for an individual patient may be related to the failure of current staging systems to adequately integrate the risk associated with other potentially important clinico-pathologic features such as the specific histology (well differentiated thyroid cancer vs. poorly differentiated thyroid cancer), molecular profile, size and location of distant metastases (pulmonary metastases vs. bone metastases vs. brain metastases), functional status of the metastases (RAI avid vs. FDG PET avid) and effectiveness of initial therapy (completeness of resection, effectiveness of RAI, external beam irradiation or other systemic therapies). Furthermore, recent studies have questioned the use of the age of 45 years old as a cutoff to upstage patients using the AJCC/UICC TNM system (Jonklass, J, JCEM 97:E878, 2012; Bischoff LA, Endo Practice 19:995, 2013).

Even though the various staging systems designed to predict mortality from thyroid cancer were developed and validated using cohorts that were either exclusively or predominantly papillary thyroid cancer patients, several small studies have demonstrated that MACIS and TNM/AJCC staging systems were also predictive in follicular thyroid cancer patients (456;483;484). Currently, none of the mortality risk systems incorporate molecular testing results. This may need to be re-evaluated as studies emerge using molecular testing including BRAFV600E, TERT and TP53 or combinations of markers. For example, in one study that analyzed more than 400 differentiated thyroid cancers,TERT mutation was found to be an

independent predictor of mortality (HR 10.35; 95% CI 2.01-53.24) for all differentiated cancers and for papillary carcinomas (485).

[B19] What initial stratification system should be used to estimate the risk of persistent/recurrent disease?

■ **RECOMMENDATION 48**

A) The 2009 ATA Initial Risk Stratification System is recommended for DTC patients treated with thyroidectomy, based on its utility in predicting risk of disease recurrence and/or persistence. (**Strong recommendation, Moderate-quality evidence**)

B) Additional prognostic variables (such as the extent of lymph node involvement, mutational status, and/or the degree of vascular invasion in follicular thyroid cancer), not included in the 2009 ATA Initial Risk Stratification system, may be used to further refine risk stratification for DTC as described below (and in Fig 4) in the Modified Initial Risk Stratification system. However, the incremental benefit of adding these specific prognostic variables to the 2009 Initial Risk Stratification system has not been established. (**Weak recommendation, Low-quality evidence**)

C) Since BRAF mutational status appears to add little incremental prognostic value to clinico-pathological staging systems, BRAF testing is not routinely recommended for initial post-operative risk stratification in DTC. (**Weak recommendation, Moderate-quality evidence**)

Because the AJCC/TNM risk of mortality staging system does not adequately predict the risk of recurrence in differentiated thyroid cancer (486-489), the 2009 version of the ATA thyroid cancer guidelines proposed a three tiered clinico-pathologic risk stratification system that classified patients as either low, intermediate, or high risk of recurrence (22). Low risk patients were defined as having intrathyroidal papillary thyroid cancers with no evidence of extrathyroidal extension, vascular invasion, or metastases. Intermediate risk patients demonstrated either microscopic extrathyroidal extension, cervical lymph node metastases, RAI avid disease in the neck outside the thyroid bed, vascular invasion or aggressive tumor histology. High risk patients had gross extrathyroidal extension, incomplete tumor resection, distant metastases, or in appropriate post-operative serum Tg values (Table 12).

The 2009 ATA risk stratification system was somewhat different than staging systems proposed by a European Consensus conference (490) and the Latin American Thyroid Society (LATS) (491) which classifies patients as either being at very low risk (unifocal, intrathyroidal T1aN0M0), low risk (T1b N0M0, T2N0M0 or multifocal T1N0M0) or high risk (any T3 or T4, any N1, or any M1). The European and LATS very low risk and low risk would be classified as ATA low risk, while the ETA high risk category would be subdivided between ATA intermediate risk (minor extrathyroidal extension, N1 disease) and ATA high risk (gross extrathyroidal extension, M1, incomplete tumor resection).

Subsequent studies have retrospectively validated the 2009 ATA risk of recurrence staging system through analysis of independent datasets originating from three respective continents (Table 11). These studies have reported the estimates of patients who subsequently had no evidence of disease (NED) in each ATA Risk Category after total thyroidectomy and radioactive iodine remnant ablation: a) Low Risk 78-91% NED, b) Intermediate Risk 52-64% NED, and c) High Risk 31-32% NED (488;489;492;493). In these datasets, NED was defined as a stimulated Tg < 1 ng/mL with no other radiological or clinical evidence of disease. Prospectively collected validation data for the ATA initial risk stratification system is needed.

Three additional studies, in which the ATA risk classification system was retrospectively evaluated, have also suggested that the ATA risk of recurrence model may be applied in low and intermediate risk patients in the absence of RAI remnant ablation (290;494;495). Over a median follow-up period that ranged from 5-10 years, structural disease recurrence was identified in less than 1-2% of ATA low risk patients and 8% of ATA intermediate risk patients who underwent thyroid surgery without RAI ablation as initial therapy (290;494;495).

The type of persistent disease also varies according to ATA initial risk stratification, with 70-80% of the persistent disease in ATA low risk patients being manifest by abnormal serum Tg levels (suppressed or stimulated Tg >1 ng/mL) without structurally identifiable disease, while only 29-51% of the ATA intermediate risk patients, and 19-21% of ATA high risk patients are classified as having persistent disease on the basis of biochemical abnormalities (488;489;493). With increasing ATA risk level, the relative risk of having structural persistent/recurrent disease increases. Thus the ATA low risk patients appear to be at highest relative risk of isolated thyroglobulinemia which may be of less clinical significance than structural disease persistence or recurrence.

Similar to what was seen with the staging systems designed to predict risk of mortality from thyroid cancer (See section [B18] above), the proportion of variance explained by the ATA risk of recurrence system was suboptimal ranging from 19% to 34% (488;492). More recently, a novel mathematical clinico-pathologic staging system from the University of Yonsei yielded similar results with a PVE of 11.9% in predicting disease recurrence (496).

[B20] Potential impact of specific clinico-pathologic features on the risk estimates in PTC

As originally conceived, the ATA initial risk stratification system was a three tiered system in which clinico-pathologic features available at the time of initial treatment were used to classify DTC patients as either low, intermediate, or high risk of having either recurrence or persistent disease. However, as with any categorical staging system, the risk of recurrence within the individual risk categories (low, intermediate and high) can vary depending on the specific clinical features of individual patients (Figure 4). In addition, the three tiered system did not specifically address the risk of recurrence associated with specific DTC histologies, multifocality, genotype, extent of vascular invasion, or extent of metastatic lymph node involvement.

For example, while intrathyroidal PTCs of all sizes are included in the ATA low risk category, the risk of structural disease recurrence can vary from 1-2% in unifocal papillary microcarcinomas, to 4-6% in multifocal papillary microcarcinomas (131;137), to 5-6% in 2-4 cm intrathyroidal PTC (497), and 8-10% in intrathyroidal PTC > 4 cm (497). Similarly, while all DTC patients with loco-regional lymph node metastases were classified as intermediate risk in the 2009 ATA risk stratification system, the risk of structural disease recurrence can vary from 4% in patients with fewer than 5 metastatic lymph nodes, to 5% if all involved lymph nodes are < 0.2 cm, to 19% if more than 5 lymph nodes are involved, to 21% if more than 10 lymph nodes are involved, to 22% if macroscopic lymph node metastases are clinically evident (clinical N1 disease), and 27-32% if any metastatic lymph node is greater than 3 cm (297;498). As defined by the ATA surgical affairs committee task force on thyroid cancer nodal surgery, ≤ 5 pN1 micrometastases (<0.2 cm in largest dimension) are classified as lower risk N1 disease (<5% risk of recurrence)(297). Clinical N1 disease, > 5 metastatic lymph nodes, or any metastatic lymph node > 3 cm in largest dimension are classified as higher risk N1 disease (> 20% risk of

recurrence) (297). Identification of extranodal extension of the tumor through the metastatic lymph node capsule has also been associated with an increased risk of recurrent/persistent disease (300;407). As extranodal extension is tightly linked to both the number of involved lymph nodes (300;407), minor extrathyroidal extension (407;499), it is difficult to estimate the risk associated with extranodal extension independent of these other risk factors. Nonetheless, a 10 year recurrence rate of 2% was seen in patients with three or fewer metastatic lymph nodes with extranodal extension while a recurrence rate of 38% was reported in patients with 3 or more metastatic lymph nodes with extracapsular extension (407).

It is also important to differentiate the clinical significance of minor extrathyroidal extension (ATA intermediate risk) from gross extrathyroidal invasion of surrounding structures (ATA high risk). The risk of recurrence associated with minor extrathyroidal extension (pT3 disease manifest by minimal extrathyroidal extension) ranges from 3-9% (500-504) while the risk of recurrence in patients with gross extrathyroidal extension (pT4a disease involving the subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve) ranges from 23-40% (487;500;502-505).

Encapsulated follicular variant of papillary thyroid carcinoma also appears to be associated with a low risk of recurrence (441;445;506). Only 2 recurrences were reported in the 152 patients (1.3% risk of recurrence) described in these three reports. No recurrences were described in the 42 patients that had encapsulated FVPTC without capsular or lymphovascular invasion in the Liu series (441). However, the Baloch report included a single patient with encapsulated FVPTC that developed a bone metastases despite not having lymphovascular invasion or lymph node metastases identified at the time of diagnosis (506). Therefore, intrathyroidal FVPTC is best classified as a low risk tumor that is unlikely to recur or metastasize.

Well differentiated follicular thyroid cancers demonstrating only capsular invasion (without vascular invasion) usually have an excellent prognosis with recurrence rates of 0 – 7% and can be classified as a low risk tumor (449-451). Encapsulated, minimally invasive FTC with only minor vascular invasion (small number of foci confined to intra-capsular vessels) appears to also have a low recurrence rate approximating 0-5% (413;455). Furthermore, some studies (413;449;452-455), but not all (451;507), suggest a greater extent of vascular invasion (more than 4 foci of vascular invasion, or extracapsular vascular invasion) is associated with poorer

outcomes even in encapsulated follicular thyroid cancers. However, FTC is considered ATA high risk if extensive vascular invasion is present as recurrence rates as high as 30-55% have been reported (412;449;452;455).

In papillary thyroid cancer, most (408-410;508-511), but not all (512) studies demonstrate that vascular invasion is associated with worse clinical outcomes. Recurrence rates were significantly higher if vascular invasion was present in the studies by Gardner (16-20% with vascular invasion, 3-6% without), Nishida (28% with vascular invasion, 15% without), and Falvo (30% with vascular invasion, 5% without), but not in the studies by Furlan (512) or Akslen (509). Vascular invasion in PTC was also associate with higher rates of distant metastases (410;511) and disease specific mortality (509;510).

[B21] Potential impact of BRAF V600E and other mutations on risk of recurrence estimates in PTC

In a pooled univariate analysis of 1,849 papillary thyroid cancer patients, BRAF V600E mutation was associated with increased disease specific mortality, although this was not significantly associated with mortality in a multivariate analysis (330). In a systematic review and meta-analysis of 14 publications that included 2,470 papillary thyroid cancer patients from 9 different countries, BRAF V600E mutation was associated with a significantly higher risk of recurrence than BRAF wild type tumors (24.9% vs. 12.6%, $p<0.00001$, 95% CI 1.61-2.32) (513). In the studies included in this meta-analysis, the risk of recurrence in BRAF V600E positive tumors ranged from 11-40% (median 26.5%) while the risk of recurrence in BRAF wild type tumors was ranged from 2-36% (median 9.5%). Because BRAF V600E mutation is tightly linked with the presence of aggressive histologic phenotypes, lymph node metastases, and extrathyroidal extension, it is difficult to determine the proportion of risk that is attributable to the BRAF mutation versus that attributable to the other clinico-pathologic features. Some studies (514;515), but not all (516-518) have demonstrated that BRAF V600E mutation is an independent predictor of risk of recurrence in multivariate analysis. Furthermore, a recent publication demonstrated a small, but statistically significant, improvement in risk stratification if BRAF status was used in conjunction with 2009 ATA initial risk stratification system (519). Among 2,167 patients included in the largest meta-analysis reported to date, BRAF V600E had a sensitivity of 65% in identifying those tumors that subsequently recurred, but had a positive

predictive value of only 25% in predicting the risk of recurrence (513). Based on this data, it appears that the BRAF status in isolation is not sufficient to substantially contribute to risk stratification in most patients.

However, recently published data suggest that a more accurate tumor prognostication is possible based on a broader genetic analysis. Specifically, as discussed below, a growing body of data suggest that more aggressive clinical course can be expected in tumors that carry (i) BRAF V600E in combination with other driver oncogenic mutations; (ii) TERT mutations, isolated or in combination with BRAF, or (iii) TP53 mutations.

The potential role of BRAF status in isolation as an aid to risk stratification in patients clinico-pathologically classified as ATA low risk is currently being evaluated. In a cohort of low risk patients with intrathyroidal PTC (< 4 cm, N0, M0; 33% with BRAF mutation), the overall risk of having structural disease recurrence over 5 yrs of follow up was 3% (515). However, BRAF V600E mutated tumors had a recurrence rate of 8% (8/106) compared with only 1% (2/213) in BRAF wild type tumors (p= 0.003, Fisher's exact). Furthermore, in multivariate analysis, the only clinico-pathological significant predictor of persistent disease after 5 years of follow up was the presence of mutated BRAF V600E. If these findings are verified in additional studies, it is possible that BRAF testing could be used to help further risk stratify patients with intrathryoidal PTC into patients at very low risk of recurrence (BRAF wild type) and those at intermediate risk of recurrence (BRAF V600E mutation).

The impact of BRAF status on the risk of recurrence in the very low risk patients (intrathyroidal unifocal papillary microcarcinomas less than 1 cm) appears to be small. Even though BRAF mutation is present in 30-67% of papillary microcarcinomas (141;142;423;516;520-526), the overall clinical recurrence rate is quite low ranging from 1-6% (243;516). In a series of 99 papillary microcarcinoma patients with an overall recurrence rate of 7%, no recurrences were detected in the patients with BRAF V600E mutated, intrathyroidal, unifocal tumors. Conversely, BRAF V600E mutated multifocal PMC with extrathyroidal extension demonstrated a 20% recurrence rate (139) Therefore, in the absence of data demonstrating that BRAF V600E mutation is associated with increased structural recurrence in very low risk tumors, we have classified intrathyroidal papillary microcarcinomas (T1a, N0, M0) harboring BRAF V600E mutations with no other worrisome features (such as extrathyroidal extension, aggressive histology, vascular invasion, or lymph node metastases) as ATA low risk

tumors. The few patients (about 10% of PMC patients) that demonstrate multifocal PMC with extrathyroidal invasion and BRAF V600E mutation would be considered ATA intermediate risk for recurrence. Based on this data, there appears to be little role for BRAF mutational testing as an aid to risk stratification in PMC tumors that do not demonstrate other worrisome clinico-pathologic features.

More recent data suggest that aggresive behavior of a given thyroid tumor, including high probability of tumor recurrence, is likely when the tumor harbor more than one known oncogenic mutation, and specifically BRAF mutation co-occuring with PIK3CA, TP53, AKT1, or RET/PTC mutation (423;527;528). Such combination of several mutations is seen in a much smaller fraction of PTC as compated to a 40-45% incidence of BRAF, and is expected to serve as a more specific marker of unfavorable outcome of PTC.

Two other molecular markers that appear to confer an increased risk of tumor recurrence and tumor related mortality are TP53 and TERT mutations. TP53 mutations have been known to occur mostly in poorly differentiated and anaplastic thyroid cancers. However, more recent broad genotypic analyses identified TP53 mutations in 2/57 (3.5%) well differentiated PTC and 4/36 (11%) of well differentiated FTC (154). Both PTCs in this series that were positive for TP53 mutation also showed mutation in BRAF (or BRAF and PIK3CA) and developed lung metastases. All 4 TP53-positive FTC (with no other co-existing mutations) were oncocytic, and 3 out of 4 of those were widely invasive FTC.

Finally, recent studies identified TERT promoter mutations as a likely predictor of more unfavorable outcome for thyroid cancer. TERT mutations were found in 7-22% of PTC and 14-17% of FTC, but with a significiantly higher prevalence in dedifferentiated thyroid cancer (485;529-531). In some (485;529), but not all (530) reports, TERT mutations were found more often in PTC carrying BRAF mutation. In the largest reported series (332 PTC and 70 FTC followed on average for 8 years), TERT mutation was an independent predictor of disease-free survival (OR 4.68; 95%CI 1.54-14.27) and mortality (HR 10.35; 95% CI 2.01-53.24) for well differentiated thyroid cancer (485). Furthermore, the combination of a TERT mutation and a BRAF mutation within the same tumor was associated with a high risk of structural disease recurrence (532). These results, although pending confirmation in other studies, suggest that these molecular markers, alone or in combination, will be helpful for risk stratification of thyroid

cancer and provide significantly more accurate risk assesement than BRAF mutational status taken in isolation.

It is important to emphasize that the identification of a molecular predictor of recurrence or mortality does not necessarily imply that more aggressive therapies (more extensive surgery, RAI therapy, aggressive thyroid hormone therapy with TSH suppression, BRAF inhibitors) will have a significant impact clinical outcomes. As with any molecular or clinico-pathological risk factor, intervention studies are required to determine which at risk patients may benefit from additional therapies.

[B22] Potential impact of Post-operative serum Tg on risk estimates

Several studies have demonstrated the clinical utility of a serum thyroglobulin measurement (either TSH stimulated or non-stimulated) obtained a few weeks after total thyroidectomy (post-operative Tg) and before RAI remnant ablation as a tool to aid in initial risk stratification and adjuvant therapy decision making (See Recommendations 50B and 50C) .

[B23] Proposed modifications to the 2009 ATA initial risk stratification system

While the 2009 risk stratification system has proven to be a valuable tool for initial risk stratification in papillary thyroid cancer, modifications are required to better incorporate our new understanding regarding the risks associated with the extent of lymph node involvement, mutational status, and specific follicular thyroid cancer histologies (Table 12). While the modified 2009 risk stratification system continues to classify intrathyroidal PTC without vascular invasion as low risk, the category was expanded to include patients with small volume lymph node metastases (clinical N0 or ≤ 5 pathologic N1 micrometastases ,<0.2 cm in largest dimension), intrathyroidal encapsulated follicular variant of papillary thyroid cancer, intrathyroidal well differentiated follicular cancer with capsular or minor vascular invasion (< 4 vessels involved), and intrathyroidal papillary microcarcinomas that are either BRAF wild type or BRAF mutated. Similarly, the modified 2009 intermediate risk category continues to include patients with microscopic invasion of the tumor into perithyroidal soft tissues, vascular invasion, uptake outside the thyroid bed at the time of remnant ablation, and aggressive histologies, but it has been modified to include only a subset of patients with lymph node metastases (clinical N1

or >5 pathologic N1 with all involved lymph nodes < 3 cm in largest dimension), intrathyroidal papillary thyroid cancer with a primary tumor of 1-4 cm that are BRAF mutated (if known), and multifocal papillary microcarcinoma with extrathyroidal extension and BRAF mutated (if known). Finally, the high risk category continues to include patients with macroscopic extrathyroidal extension, incomplete tumor resection, distant metastases, and post-operative serum Tg suggestive of distant metastases, but has been expanded to include patients with large volume lymph node involvement (any metastatic lymph node ≥ 3 in largest dimension), and follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion or extracapsular vascular invasion). While these modifications are based on our current literature review of the impact of the individual risk factors, future studies will be required to validate this proposed modification to and determine if the additional modifying factors provide significant incremental improvement in risk stratificaiton.

[B24] Risk of recurrence as a continuum of risk

While the ATA initial risk stratification system provides a meaningful and valuable tool for predicting risk of recurrence when used as a three tiered categorical staging system, additional insights can be gained if one appreciates that the risk of structural disease recurrence is a continuum of risk that ranges from less than 1% in very low risk patients to greater than 50% in high risk patients (See Figure 4). Therefore, individualized management recommendations should be based not only on the categorical risk of recurrence estimate, but also on a more individualized estimate of risk in which the ATA low and intermediate risk categories are further characterized on the basis of respective clinical or pathologic features, such as the size of the primary tumor, number and size of loco-regional lymph node metastases (as well as extra-nodal extension), specific histologic variant, vascular invasion, extent of extrathyroidal extension, or other potentially important factors.

While the risk estimates presented in this section may be useful in guiding initial treatment selections (extent of initial surgery, need for RAI ablation), it is important to recognize that these risk estimates likely reflect not only the biology of tumor, but also the impact of initial therapy which varied from thyroid lobectomy to total thyroidectomy with varying extents of lymph node dissection either with or without RAI ablation across the various studies. Additional

studies are needed to better define the risk of recurrence in most of these clinical scenarios in patients randomized to receive one of several initial treatment options (lobectomy vs. total thyroidectomy, extent of lymph node dissection, with or without RAI ablation).

[B25] How should initial risk estimates be modified over time?

■ RECOMMENDATION 49

Initial recurrence risk estimates should be continually modified during follow-up, because the risk of recurrence and disease specific mortality can change over time as a function of the clinical course of the disease and the response to therapy (**Strong recommendation, Low-quality evidence**)

While initial staging systems provide important insights into an individual patient's risk of recurrence and disease specific mortality, they provide static, single point estimates of risk based only on data available at the time of initial therapy. None of the currently available initial staging systems are capable of using new data obtained during the course of follow-up to modify the initial risk estimate. For example, an ATA low risk patient that demonstrates a rising serum Tg associated with cervical lymphadenopathy highly suspicious for recurrent disease at some point during follow-up would still be classified as "ATA low risk" despite the presence of clinical data demonstrating a high risk of recurrence. Conversely, an ATA high risk patient that has no evidence of disease over 30 years of appropriate follow-up would still be classified as "ATA high risk" despite having a risk of recurrence that is significantly lower than would have been predicted at the time of initial therapy.

Therefore, while the initial staging systems can be informative in guiding therapeutic and early diagnostic follow-up strategy decisions, a risk stratification system that incorporates individual response to therapy into a real time, dynamic risk stratification scheme is needed to provide an individualized approach to ongoing management (533;534). One approach that has been proposed is to use the risk estimates from the initial staging systems to guide initial management recommendations and then to incorporate a response to therapy assessment during follow-up to modify these initial risk estimates in an ongoing, dynamic process (535).

Multiple studies have now shown that many patients initially classified as intermediate or high risk of recurrence using initial staging systems can be re-classified as having a subsequent

low risk of recurrence based on having an excellent response to initial therapy (488;489;536-552). Furthermore, the PVE (proportion of variance explained) values associated with staging systems that incorporated response to therapy variables into revised risk estimates were significantly higher (62% - 84%) than those seen with initial staging systems (< 30%) (488;492). These data indicate that long term outcomes can be more reliably predict using systems that adjust to new data over time.

[B26] Proposed terminology to classify response to therapy and clinical implications

All clinical, biochemical, imaging (structural and functional), and cytopathologic findings obtained during follow-up should be used to re-define the clinical status of the patient and to assess their individual response to therapy. Ideally, the global consideration of the composite findings of such an assessment would allow for the disease status to be classified into one of several discrete response to therapy risk strata as proposed by Tuttle et al (488;533). Potential challenges in applying this specific system in routine clinical practice include: lack of validation in specific subgroups of patients (such as those who had less than total thyroidectomy or those not treated with radioactive iodine), the lack of published prospective data utilizing this system in clinical care, and some inconsistency with other authors in classifying the significance of varying levels of detectable thyroglobulin levels or imaging findings.

The response to therapy re-staging system was also not designed or specifically tested by developers to guide specific therapeutic decisions on primary therapy (such as use of adjuvant treatment), as it has been designed for use after primary therapy is completed. Prospective studies of the value of this system for guiding extent of primary treatment, including adjuvant treatment decisions, are needed. However, given that there is emerging evidence that such a re-classification system has potential to be of great importance in ongoing clinical care of DTC patients after primary treatment, the details are described herein.

It is acknowledged that appropriate clinical application of such a system is highly dependent on the availability of high quality biochemical testing and structural, and functional imaging with appropriate interpretation (e.g. standardized radiologic reporting). Therefore, applicability may be limited in settings where these procedures are not available or feasible

The concept and initial validation of the four response to therapy categories presented here were described by Tuttle et al (488) as modified in Vaisman (290). As originally conceived,

these clinical outcomes described the best response to initial therapy during the first 2 years of follow-up (488;533), but are now being used to describe the clinical status at any point during follow-up.

- **Excellent response**: no clinical, biochemical or structural evidence of disease
- **Biochemical incomplete response:** abnormal thyroglobulin or rising anti-thyroglobulin antibody levels in the absence of localizable disease
- **Structural incomplete response**: persistent or newly identified loco-regional or distant metastases
- **Indeterminate response**: non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant. This includes patients with stable or declining anti-thyroglobulin antibody levels without definitive structural evidence of disease.

The majority of published studies examining response to therapy in DTC have been performed in populations of patients whose primary treatment consisted of total thyroidectomy and RAI ablation. While the following sections will provide the details of multiple studies examining response to therapy, a simplified overview of the clinical implications of the response to therapy re-classification system in patients treated with total thyroidectomy and RAI ablation, based on the research from Tuttle et al (488;489), and supported by other studies described in Table 13. Specific suggestions with regard to the application of response to therapy assessments in patients treated with total thyroidectomy without RAI ablation or with thyroid lobectomy have recently been published by Momesso et al (553).

[B27] Excellent response: no clinical, biochemical or structural evidence of disease after initial therapy (remission, no evidence of disease)

These patients have no clinical, biochemical or structural evidence of disease identified on risk appropriate follow-up studies (Table 13). If a total thyroidectomy and RAI ablation was done, an excellent response was usually defined as a TSH stimulated Tg of less than 1 ng/mL in

the absence of structural or functional evidence of disease (and in the absence of thyroglobulin antibodies) (488;489;536-552) . An excellent response to initial therapy is achieved in 86-91% of ATA low risk patients, 57-63% of ATA intermediate risk patients, and 14-16% of ATA high risk patients (488;489;492).

In twenty retrospective studies, the risk of recurrence over 5-10 years of follow-up ranged from 1 to 4% (median 1.8%) in patients who had an excellent response to therapy by 6-18 months after total thyroidectomy and RAI remnant ablation (488;489;536-552;554).

The potential impact of this reclassification is the most dramatic in the two thirds of ATA intermediate risk patients who achieve an excellent response and therefore have their risk of having recurrent/persistent disease decreased from 36-43% (predicted by initial ATA risk stratification) to 1-2% (predicted by response to therapy re-classification) (488;489). Because of the very low risk of structural disease recurrence in ATA low risk patients (1-3%), reclassification based on an excellent response to therapy has less practical implications than in the intermediate and high risk patients.

While many of the studies reviewed primarily low risk DTC patients (537;539;546-549;552), the same low risk of recurrence following achievement of excellent response to therapy was seen in other studies that had substantial numbers of intermediate risk patients (488;489;492;538;542;543;555). Furthermore, most studies also demonstrate that the few high risk patients that achieve an excellent response to therapy also have subsequent recurrence rates in the 1-2% range (492;544;545;551). The one exception is the 14% risk of recurrence seen in the few ATA high risk patients that achieved remission in a series from Memorial Sloan-Kettering Cancer Center (488), which is likely due to the known referral bias of unusual and very high risk cases. Nonetheless, high risk patients that achive an excellent response to therapy may require somewhat more intense follow-up than ATA low and intermediate risk patients demonstrating an excellent response to therapy. It is important to note that patients at intermediate to high risk of recurrence may require additional structural or functional imaging to rule out disease that may not be detected by US and Tg measurements prior to being classified as having an excellent response (553). The details of choice of follow-up tests are found in another section of this guideline [C4-C13], (Figures 5-8).

While most studies have assessed response to therapy using TSH stimulated Tg values obtained 6-18 months after initial therapy (488;489;536;537;539-541;544-546;548-551), at least

15 other studies have evaluated the response to surgical therapy using a stimulated Tg obtained at the time of RAI remnant ablation (556). Patients demonstrating an excellent response to therapy at this very early time point have a very low risk of disease recurrence (556).

Four additional studies used non-stimulated sensitive Tg assays to define an excellent response to therapy at various time points after initial therapy with total thyroidectomy and radioactive iodine remnant ablation (538;546;552;557). A recurrence rate of 1.5% was seen in cohort of 589 DTC patients who had a non-stimulated Tg < 0.27 ng/mL at 3 months after initial therapy (546). Malandrino et al reported recurrence rates of 0% in low risk patients, 1% in intermediate risk patients and 2.7% in high risk patients who demonstrated non-stimulated Tg values less than 0.15 ng/mL at 9-18 months after initial therapy (538). Smallridge et al described a 4.3% recurrence rate in 163 low to intermediate risk DTC patients with non-stimulated Tg < 0.1 ng/mL, measured a median of 1.8 yrs after initial surgery (557). Finally, Giovanella et al reported a 1.6% recurrence rate over 5-6 years of follow up in 185 low risk patients who have a non-stimulated Tg < 0.2 ng/mL and normal post-operative neck US 6 months after remnant ablation (552).

Further studies are needed to refine the precise Tg value cut-off used to define what should be an excellent response to therapy in patients treated with total thyroidectomy with or without radioactive iodine remnant ablation. In addition to determining whether TSH stimulated Tg values are clinically helpful in patients at very low risk for recurrence, Tg cut points need to be defined for patients whose primary treatment consisted of thyroid lobectomy or total thyroidectomy without adjuvant RAI ablation.

In summary, once a patient achieves an excellent response to therapy, the initial risk of recurrence estimate should be modified and the patient re-classified as having a subsequent very low risk of recurrence. This re-classification into a very low risk of recurrence status can occur as early as several weeks (or several months) after initial therapy and is applicable to all DTC patients initially stratified as ATA low or intermediate risk of recurrence and to the few ATA high risk patients that achieve an excellent response to therapy. Appropriate re-classification into a the excellent response category with its very low risk of recurrence should lead to re-evaluation of intensity of diagnostic surveillance procedures and treatment, as discussed in other sections of this clinical practice guideline [C4-C13], (Figures 5-8).

[B28] Biochemical incomplete response: abnormal thyroglobulin values in the absence of localizable disease.

These patients have persistently abnormal suppressed and/or stimulated Tg values or rising anti-thyroglobulin antibodies without structural evidence of disease that can be detected using risk appropriate structural and functional imaging (Table 13). Previous studies have used non-stimulated Tg values > 1 ng/mL or TSH stimulated Tg values > 10 ng/mL to define a biochemical incomplete response to therapy in patients treated with total thyroidectomy and RAI ablation (488;489;492).

This is not an uncommon outcome being seen in 11-19% of ATA low risk patients, 21-22% of ATA intermediate risk patients, and 16-18% of ATA high risk patients (488;489).

Clinical outcomes in these patients are usually very good with as many as 56-68% being classified as having no evidence of disease at final follow-up while 19-27% continue to have persistently abnormal Tg values without structural correlate and only 8-17% developing structurally identifiable disease over 5-10 years follow-up (488;489;558). No deaths have been reported in patients with a biochemical incomplete response to therapy followed for up to 10 years (489;558).

Anti-thyroglobulin antibody levels measured over time in the same assay can provide clinically useful information (559). Rising anti-thyroglobulin antibody titers (or new appearance of anti-thyroglobulin antibodies) are associated with an increase risk disease recurrence (560-565). Conversely, patients rendered free of disease with initial therapy will usually demonstrate a decline in anti-thyroglobulin antibody titers over several years (562;566;567).

Vaisman et al further demonstrated that the transition to no evidence of disease status occurred without any additional radioactive iodine or surgical therapy (beyond levothyroxine suppressive therapy) in 34% of patients classified as having a biochemical incomplete response to initial therapy (558). These observations are consistent with several previous studies that have demonstrated that abnormal serum Tg values can gradually decline over time without additional radioactive iodine or surgical therapy, in the absence of structurally identifiable disease (549;550;568;568-572).

A small percentage of patients with a biochemical incomplete response to therapy will demonstrate progressive increases in the non-stimulated Tg values over time. In patients treated with total thyroidectomy and radioactive iodine remnant ablation, clinically significant increases

in unstimulated serum Tg values over time as described by Tg doubling times (<1year, 1-3 years, or >3 years) (573) or rate of rise in unstimulated Tg of ≥0.3 ng/mL/year over time (574), identify patients at increased risk of developing structurally identifiable loco-regional or distant metastases.

Just as with the excellent response to therapy category, additional studies are needed to more precisely define what Tg levels define an incomplete biochemical response to therapy. The specific cut point that defines an "abnormal Tg" is dependent on the corresponding TSH value, the amount of residual normal thyroid tissue remaining after thyroidectomy, whether or not RAI ablation was performed, and the duration of time since ablation since Tg values often decline for months to years after ablation. To define a biochemical incomplete response, previous studies have used non-stimulated Tg values > 5 ng/mL at 6 months (575), non-stimulated Tg values > 1 ng/mL more than 12 months after ablation (488;489;492) or TSH stimulated Tg values > 10 ng/mL more than 1 year after ablation (488;489). The precise Tg value for defining a biochemical incomplete response to therapy in patients treated with lobectomy or total thyroidectomy without ablation has not been adequately defined. In addition, some studies also classified patients with persistent or rising anti-Tg antibodies in the absence of structurally identifiable disease as having a biochemical incomplete response to therapy (488;489;576).

In summary, a biochemical incomplete response is seen in approximately 15-20% of DTC patients. Fortunately, many of these patients are eventually reclassified as having no evidence of disease at final follow-up, often without any additional radioactive iodine or surgical treatments.

[B29] Structural incomplete response: persistent or newly identified loco-regional or distant metastases

These patients have structural or functional (FDG-PET, RAI scan) evidence of loco-regional or distant metastases (488;489;558). This category includes both patients with biopsy proven disease and also patients in whom structural or functional disease is identified which is highly likely to be metastatic disease based on the clinical scenario (Table 13). A structural incomplete response to initial therapy is seen in 2-6% of ATA low risk patients, 19-28% of ATA intermediate risk patients, and 67-75% of ATA high risk patients (488;489).

Despite additional treatments, the majority of patients classified as having a structural incomplete response will have persistent structural and/or biochemical evidence of persistent

disease at final follow-up (489;558). Depending on the definition used to describe patients as free from disease, higher rates of remission (29-51%) have been described following surgical intervention for patients with persistent/recurrent loco-regional disease (577-579). While no deaths were reported over a follow up period that extended to 15 years in patients with biochemical incomplete response to therapy, death from disease was seen in 11% of patients with a loco-regional incomplete response and 57% of patients structurally identifiable distant metastases (489;558).

In summary, a structural incomplete response to initial therapy identifies a cohort of DTC patients that may not be cured with additional therapies and consequently demonstrate the highest risk of disease specific mortality of any of the response to therapy categories. It is important to emphasize that persistent/recurrent loco-regional structural disease may have a higher likelihood of responding to additional treatments and has significantly lower disease specific mortality rates than persistent/recurrent distant metastases.

[B30] Indeterminate response: biochemical or structural findings which cannot be classified as either benign or malignant (acceptable response).

These patients have biochemical, structural, or functional findings that cannot be confidently classified as either excellent response or persistent disease (290;488;489;557;580)(Table 13). Rather than forcing these patients into either the excellent or incomplete response to therapy categories, some investigators have recommended a separate category for these patients so that they can be continued to be carefully observed with selected patients identified for further evaluation with testing designed to establish the presence/absence of disease (488;489).

For example, this category includes patients with subcentimeter avascular thyroid bed nodules or atypical cervical lymph nodes that have not been biopsied, faint uptake in the thyroid bed with undetectable stimulated Tg on follow up imaging, or nonspecific abnormalities on functional or cross sectional imaging. Also included in this category patients with non-stimulated Tg values that are detectable but < 1 ng/ml, TSH stimulated Tg values between 1 and 10 ng/mL and patients with stable or declining Tg antibodies in the same assay over time in the absence of structural disease (488;489).

This issue was exemplified in a recent study evaluating the prognostic value of a highly sensitive Tg assay in which the response to therapy could not be definitively established in 16

patients that had small indeterminate pulmonary micronodules without other evidence for persistent disease (557). A similar situation arises when trying to determine the response to therapy in the 34% of patients that demonstrated non-specific subcentimeter thyroid bed nodules after total thyroidectomy (580). Similarly, it is often difficult to be certain whether or not very low level detectable Tg values represent persistent disease or simply remnant normal thyroid cells remaining after initial therapy.

An indeterminate response to initial therapy is seen in 12-29% of ATA low risk patients, 8-23% of ATA intermediate risk patients, and 0-4% of ATA high risk patients (488;489). The clinical outcomes in patients with an indeterminate response to therapy are intermediate between patients with an excellent response and those with incomplete responses. Two series have demonstrated that only 13-20% of patients with an indeterminate response to therapy are reclassified as persistent/recurrent disease over approximately 10 years of follow-up. In the remaining 80-90% of patients, the non-specific findings either remain stable or resolve with observation alone.

In summary, the majority of patients with an indeterminate response to therapy remain disease free during prolonged follow-up. However, up to 20% of these patients will eventually have biochemical, functional or structural evidence of disease progression and may require additional therapies.

[B31] Using risk stratification to guide disease surveillance and therapeutic management decisions.

Risk stratification is the cornerstone of individualized thyroid cancer management. Initial risk estimates are useful to guide the wide variety of clinical management decisions that need to be made around the time of initial diagnosis and treatment. As described in this document, initial management decisions are largely made by balancing the estimates of the risk of recurrence and risk of disease specific mortality with the potential benefits and risks of proposed therapies. However, in clinical practice many other risk estimates can also significantly influence surveillance and therapeutic decision making including: the risk of failing initial therapy, the risk of having non-RAI avid disease, the risk of disease recurring without making appreciable amounts of serum thyroglobulin, the risk of adjuvant RAI therapy, the risk of additional thyroid surgery, the risk of additional lymph node surgery, the risk of external beam irradiation, and the

risk of systemic therapy. Individual management recommendations require that the risks and benefits of potential surveillance and therapeutic management decisions be carefully evaluated in the context of the specific clinico-pathologic features of each patient.

Nonetheless, initial risk estimates can be used to guide recommendations with regard to the extent of thyroid surgery, the need for and extent of cervical lymph node dissection, the need for and administered activities of radioiodine, the need for and degree of TSH suppression, the need for and details of external beam irradiation, the need for and types of systemic therapy, the need for and types of studies required for initial staging, and the intensity and type of follow-up studies required for evaluating response to therapy in the early years following initial therapy. This approach tailors the aggressiveness of intervention and follow-up to the specific risks associated with the tumor in an individual patient.

In summary, this risk adapted management approach utilizes initial risk estimates to guide early surveillance and therapeutic management decisions. These initial management plans are then modified over time as additional data is accumulated that allows for re-stratification based their individual response to therapy. This system tailors the extent and intensity of therapy and follow-up studies to real time risk estimates that evolve over time for individual patients.

[B32] Should postoperative disease status be considered in decision-making on RAI therapy for patients with DTC?

■ **RECOMMENDATION 50**

A) Post-operative disease status (ie. the presence or absence of persistent disease) should be considered in deciding whether additional treatment (eg. radioactive iodine, surgery, or other treatment) may be needed. (**Strong recommendation, Low-quality evidence**)

B) Post-operative serum thyroglobulin can help in assessing the persistence of disease or thyroid remnant and predicting potential future disease recurrence. (**Strong recommendation, Moderate-quality evidence**)

C) The optimal cut-off value for postoperative serum thyroglobulin or state in which measured (on thyroid hormone therapy or after TSH stimulation) to guide decision-making regarding RAI administration is not known (**No Recommendation, Insufficient evidence**)

D) Postoperative diagnostic radioiodine whole-body scans may be useful when the extent of the thyroid remnant cannot be accurately ascertained from the surgical report or neck

ultrasonography, or when the results would alter either the decision to treat or the activity of RAI that is administered. If performed, pretherapy diagnostic scans should utilize ^{123}I (1.5–3 mCi) or low-activity ^{131}I (1–3 mCi), with the therapeutic activity optimally administered within 72 hours of the diagnostic activity. (**Weak recommendation, Low-quality evidence**)

Postoperative disease status is a relevant consideration in post-operative treatment decision-making after initial consideration of clinic-pathologic stage. Evaluation of postoperative disease status may be performed by a number of means including serum thyroglobulin, neck ultrasonography and iodine radioisotope scanning. There are currently no randomized controlled trials comparing any particular postoperative diagnostic strategy with the intention of modulating decision-making on RAI remnant ablation or RAI treatment for differentiated thyroid cancer.

[B33] Utility of Post-operative serum Tg in clinical decision making

Serum thyroglobulin measurements (with thyroglobulin antibodies), with or without neck ultrasound, are frequently performed as part of the early post-operative evaluation. The predictive value of the post-operative Tg value will be significantly influenced by a wide variety of factors including: the amount of residual thyroid cancer and/or normal thyroid tissue, the TSH level at the time of thyroglobulin measurement, the functional sensitivity of the Tg assay, the Tg cut off used for analysis, the individual risk of having RAI avid loco-regional or distant metastasis, the time elapsed since total thyroidectomy, and the sensitivity of the post therapy scanning technique (SPECT CT vs planar imaging).

Multiple studies have confirmed an increase risk of recurrence following total thyroidectomy and RAI remnant ablation in patients that had a post-operative TSH stimulated thyroglobulin > 1-2 ng/mL at the time of ablation (556;581-587)(Polacheck 2011, Peltarri 2010). In multivariate analysis, the post-operative Tg is often found to be an independent predictor of persistent/recurrent disease (581;582;587)(Polachek 2011, Peltarri 2010). Furthermore, the risk of having recurrent/persistent disease increases as the post-operative Tg rises (585;587) . Using receiver operator curve analyses, thyroid hormone withdrawal post-operative Tg values between 20 and 30 ng/mL achieve the optimal balance of sensitivity and specificity for predicting recurrent/persistent disease (588-590). Furthermore, high level post-

operative stimulated Tg values (> 10-30 ng/mL) are also associated with poorer survival (587;589;591). Conversely, post-operative stimulated Tg values less than 1-2 ng/mL are strong predictors of remission (585;587). Even in ATA low and intermediate risk patients that did not receive RAI remnant ablation, a non-stimulated post-operative thyroglobulin < 1 ng/mL was associated with excellent clinical outcomes and recurrence rates < 1% (592). Therefore, a post-operative serum Tg can provide valuable information with regard to the likelihood of achieving remission or having persistent/recurrent disease in response to an initial therapy.

A thyroglobulin measurement <10ng/mL may not distinguish between the presence of nodal disease from thyroid remnant, when evaluated using concurrent radioactive iodine scans with SPECT/CT (single photon emission computed tomography/computed tomography) (593). In one of the prospective studies mentioned previously, a thyroglobulin treatment threshold of >5 ng/mL was suggested as an indication for RAI treatment (584). However, in a recent retrospective review of consecutive low risk patients treated with total thyroidectomy without radioactive iodine, an unstimulated thyroglobulin of ≥ 2 ng/mL with a concomitant median TSH level of 0.48 mIU/L was reported to detect all patients with disease recurrence (76 patients followed for a median of 2.5 years)(594). Thus, there is some uncertainty as to what degree of postoperative stimulated or unstimulated thyroglobulinemia (with or without neck ultrasound interpretation), may be appropriate to prompt RAI treatment. Moreover, detection of unexplained inappropriate thyroglobulinemia may prompt consideration of further investigation for its cause (eg. imaging studies).

The post-operative Tg can also be used to predict the likelihood of identifying RAI avid metastatic thyroid cancer outside the thyroid bed on the post-therapy scan at the time of remnant ablation. No uptake outside the thyroid bed was identified in 63 low risk patients with a non-stimulated post-op Tg of < 0.4 ng/mL (581) or in 132 low risk patients with a thyroid hormone withdrawal Tg of < 1 ng/mL (595). However, RAI avid metastatic foci outside the thyroid bed was detected in 12% of intermediate risk patients with a suppressed Tg of < 0.6 ng/mL (596), 5.6% of intermediate/high risk patients with a suppressed Tg < 1 .0 ng/ml (597) and 6.3% of intermediate/high risk patients with a thyroid hormone withdrawal stimulated Tg of < 2 ng/mL (598). The likelihood of finding RAI avid metastatic disease on the post therapy scan is substantially lower (2.8%) if the post-operative Tg is undetectable in 3 different Tg assays than if it is undetectable only in a single assay (30%) (599). Conversely, the likelihood of identifying

either loco-regional or distant metastases on the post therapy scan increases as either the suppressed or stimulated Tg values rise above 5-10 ng/mL (582;596;597;600). Therefore, neither a stimulated or suppressed post-operative Tg < 1 ng/mL can completely eliminate the possibility that a post-therapy RAI scan will identify metastatic foci outside the thyroid bed. However, post-operative Tg values greater than 5-10 ng/mL increase the likelihood of identifying RAI avid metastatic disease on the post therapy scan.

The post-operative serum Tg value can also be used to predict the likelihood of successful remnant ablation. Post-operative thyroid hormone withdrawal stimulated Tg values > 5-6 ng/mL were associated with higher rates of failed ablation after administered activities of both 30 mCi (601) and 100 mCi (602). A TSH stimulated Tg > 6 ng/mL was associated with a 5-fold greater risk of failing ablation after 30 mCi administered activity prepared with thyroid hormone withdrawal (601).

It does appear that a post-operative Tg value (either TSH stimulated or non-stimulated) is an important prognostic factor that can be used to guide clinical management. Given a disappearance half life of 1-2 days (603-610), the post-operative Tg should reach its nadir by 3-4 weeks post-operatively in nearly all patients. In low risk patients, a suppressed or stimulated Tg < 1 ng/mL is very reassuring and further confirms classification of the patients as low risk. In intermediate risk patients, post-operative Tg values < 1 ng/mL are reassuring, but do not completely rule out the presence of small volume RAI avid metastastic disease. However, even without RAI ablation many intermediate patients have excellent clinical outcomes. Therefore, it is not clear that additional therapy is required in these intermediate risk patients with post-operative Tg values < 1 ng/mL even though small volume RAI avid disease may still be present after thyroidectomy.

On the other hand, post-operative Tg values (stimulated or non-stimulated) greater than 10 -30 ng/mL increase the likelihood of having persistent/recurrent disease, failing initial RAI ablation, having distant metastases, and dying of thyroid cancer. Therefore, post-operative Tg values greater than 10 ng/mL will likely lead to additional evaluations possibly even additional therapies.

With regard to decision-making on the need for RAI remnant ablation, it appears that the post-operative serum Tg value will be more helpful in identifying patients that may benefit from RAI ablation rather than in identifying patients that do not require ablation. For example, a

post-operative Tg value > 5-10 ng/mL may lead to selection of RAI ablation in an ATA low risk patient, or ATA intermediate risk patient that otherwise would not have required RAI ablation (selective use) in order to improve initial staging and facilitate follow-up. Conversely, in high risk patients, a post-operative Tg value < 1 ng/mL does not rule out RAI avid disease and therefore is unlikely to alter the decision to proceed with RAI ablation.

[B34] Potential role of post-operative US in conjunction with post-operative serum Tg in clinical decision making

In a prospective study of 218 differentiated thyroid cancer patients, Lee et al. reported that a stimulated thyroglobulin after thyroid hormone withdrawal (with goal TSH of > 30 mIU/L), at the time of administration of 100 to 200 mCi of I-131 (for remnant ablation or treatment), was associated with the following negative predictive values for biochemical or structural recurrence at 6 to 12 months: 98.4% for ATA low risk patients, 94.1% for ATA Intermediate Risk, and 50% in ATA High Risk group (611). They further reported that he negative predictive values increased to 97.2%, and 100% for ATA intermediate and high risk patients, respectively when the stimulated thyroglobulin values were combined with negative neck ultrasound findings at baseline (with no change in low risk patients). Similar significant decreases in the risk of recurrence was seen when ATA intermediate and high risk patients had a normal post-operative neck ultrasound (612).

[B35] Role of post-operative radioisotope diagnostic scanning in clinical decision making

Iodine radioisotope diagnostic testing may include I-131 or I-123 diagnostic imaging with or without single photon emission computed tomography – computed tomography (SPECT-CT), and/or radioactive iodine uptake measurements. Postoperative radioactive iodine planar imaging (I-123 or I-131, with or without SPECT-CT) has been reported to yield information that could alter clinical management (such as altering disease status assessment) in 25% to 53% of patients, as reported in single-center, retrospective studies (593;613;614). However, in a multivariable analysis of retrospective data, Hu et al reported that the use of 5 mCi of I-131 between 4 to 11 days prior to remnant ablation, was independently associated with an increased risk of remnant ablation failure (615). In contrast, in a smaller retrospective study, the

administration of 3-5 mCi of I-131 for scanning two to five days prior to ablation in 37 patients was not associated with any significant reduction in remnant ablation success, compared to no pre-therapy scanning in 63 patients (I-131 therapeutic activity of 100-200 mCi used in both groups) (616). A possible relationship between I-131 diagnostic scan dose activity on remnant ablation success was suggested in another retrospective study, in which success was lower following the use of 3 mCi as compared to 1 mCi of I-131, 9 days before therapeutic administration of 100 mCi (617). In two small randomized controlled trials, there was no significant impact of I-131 scanning compared to I-123 scanning, in impacting rate of successful remnant ablation (618;619). The timing of whole body diagnostic scans following administration of radioisotopes in reviewed studies ranged from about 24 to 72 hours for I-131 (593;614;615;617-619), and was 24 hours for I-123 (613;614;618). The tailoring of RAI therapeutic dose activity according to radioactive iodine neck uptake (measured 24 hours after administration of 1 mCi of I-131), was associated with a lower rate of remnant ablation success than fixed dosing, in another single-center retrospective observational study (620). Furthermore, in a multivariable analysis of retrospective data (adjusted for relevant risk factors), Verberg et al reported that the use of 1 mCi of I-131 for calculation of radioactive iodine neck uptake two days before remnant ablation, was independently associated with an increased risk of remnant ablation failure (621).

There continues to be some debate on the utility of post-operative iodine radioisotope diagnostic scanning (with or without SPECT/CT) in guiding RAI therapeutic decision making. Although potentially valuable information on disease status and the presence of radio-iodine avid disease may be obtained by such testing, it is not known whether a routine strategy of RAI therapeutic decision-making based on such results, would benefit many patients. Furthermore, there are some questions on potentially negative impact of such testing on RAI therapeutic efficacy as relating to the outcome of successful remnant ablation.

[B36] What is the role of radioactive iodine (RAI) (including remnant ablation, adjuvant therapy, or therapy of persistent disease) after thyroidectomy, in the primary management of differentiated thyroid cancer?

■ RECOMMENDATION 51 (details in Table 14)

A) RAI remnant ablation is not routinely recommended after thyroidectomy for ATA low

risk DTC patients. (**Weak recommendation, Low-quality evidence**)

B) RAI remnant ablation is not routinely recommended after lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma, in absence of other adverse features. (**Strong recommendation, Moderate-quality evidence**)

C) RAI remnant ablation is not routinely recommended after thyroidectomy for patients with multi-focal papillary microcarcinoma, in absence of other adverse features. (**Weak recommendation, Low-quality evidence**)

D) RAI should be considered after total thyroidectomy in ATA intermediate risk level differentiated thyroid cancer patients. (**Weak recommendation, Low-quality evidence**)

E) RAI therapy is routinely recommended after total thyroidectomy for ATA high risk differentiated thyroid cancer patients (**Strong recommendation, moderate-quality evidence**)

Depending on the post-operative risk stratification of the individual patient, the primary goal of post-operative administration of radioactive iodine (RAI) after total thyroidectomy may include: 1) *remnant ablation* (to facilitate detection of recurrent disease and initial staging by tests such as thyroglobulin measurements or whole body RAI scans), 2) *adjuvant therapy* (intended to improve disease-free survival by theoretically destroying suspected, but unproven metastatic disease, especially in those at increased risk of disease recurrence), or 3) *RAI therapy* (intended to improve disease-specific and disease-free survival by treating persistent disease in high risk patients). Additional considerations in RAI decision-making may include: patient co-morbidities (and the potential impact of therapeutic doses of RAI or preparation for the procedure), feasible or preferred disease surveillance procedures, patient preferences (the latter being particularly important when clear data on therapeutic efficacy are lacking), or others. It is important to note that in patients with low risk DTC, disease surveillance may be accomplished without RAI ablation using neck ultrasound and thyroglobulin with thyroglobulin antibody measurements while on levothyroxine therapy.

We categorized the results of our review according to the ATA Risk of Recurrence Risk stratification (outlined in a preceding section of this guideline). However, given that the ATA risk classification is relatively new and the majority of studies examining therapeutic efficacy of post-surgical RAI remnant ablation or therapy (adjuvant or for persistent disease), have been performed with attention to traditional mortality risk stratification systems such as the

AJCC/TNM system, MACIS, National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG), or others, it was necessary to extrapolate the results of many studies according to estimated ATA risk level. We have also categorized some of the results of our evidence review according to the AJCC/TNM risk of mortality stratification system, as this system has been in use longer in our field (Table 14). Evaluation of post-operative disease status and recommendations for radioiodine remnant ablation and adjuvant therapy can be found in algorithms in Figures 5-8.

ATA Low Risk: Studies examining the impact of RAI remnant ablation on long-term thyroid cancer outcomes in ATA low risk patients are subject to limitations due to their observational nature (and potential for bias), as well as limited statistical power to detect relatively uncommon events (such as disease-related mortality). By definition the risk of disease-specific mortality is low, the risk of persistent/recurrent disease is low (around 3%) and there is no demonstration that delayed discovery and treatment of persistent disease may decrease the chance of cure in these patients. In a retrospective multi-center registry study, 1298 differentiated thyroid cancer patients categorized as ATA low risk level, were followed for a median of 10.3 years, and there was no significant effect of RAI remnant ablation on overall or disease-free survival, using respective multivariable and stratified propensity analysis techniques (494). Prospective data from the National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) suggest that overall, disease-specific, and disease-free survival are not improved by RAI treatment in NTCTCSG Stage I and II patients (ie. patients aged <45 years with no distant metastases or patients aged ≥45 years with primary tumor < 4cm in diameter, no extra-thyroidal extension, and no nodal metastases), also using multivariable analyses and propensity analyses (622;623). In two systematic reviews examining results of multivariable adjusted analyses, with a focus on low risk differentiated thyroid cancer using classic clinic-pathologic staging systems such as TNM/AJCC, the majority of studies did not show a significant effect of RAI remnant ablation in reducing thyroid cancer-related death, and conflicting findings of studies relating to outcomes of disease recurrence (624;625). It is important to note that in the studies summarized in this section on ATA low risk disease (or equivalent), patients with multifocal papillary thyroid cancer were generally included (if no other adverse features meeting criteria for upstaging were noted). To date, there is little evidence to suggest that RAI may improve disease-specific mortality in low risk differentiated thyroid cancer patients, and there is some conflicting

evidence on effect on recurrence, with newer data using the ATA risk system, suggesting lack of a significant effect. Furthermore, the majority of the best available observational evidence, suggests that RAI remnant ablation is unlikely to improve disease-specific or disease-free survival in papillary microcarcinoma (< 1 cm, uni- or multi-focal), in absence of other higher risk features (136;626-630). In a recent retrospective analysis of of 704 papillary microcarcinoma patients whose initial risk level was ATA low or intermediate and were followed for a median of 64 months, there was no significant reduction in recurrence rates in patients treated with RAI compared to those not treated with RAI using a propensity score analysis (627). With respect to microcarcinomas of follicular cancer and Hürthle cell cancer, a recent SEER registry secondary data analysis suggested no disease-specific survival benefit in patients treated with RAI in a multivariable analysis adjusted for age, histology, disease extent, type of surgery and external beam radiation (total number of patients in this study was 564) (631). A limitation of interpreting this data on follicular and Hürthle cell microcarcinomas is that some of the patients in the study had some adverse features and were not all considered low risk, however the authors adjusted for relevant variables in their multivariable analysis (631). The role of RAI remnant ablation in ATA low risk DTC should be clarified in the future, following completion of randomized controlled trials, such as the Iodine or Not (IoN) trial for low and intermediate risk patients (632) and ESTIMABL2 for low risk patients.

ATA Intermediate Risk: We did not find studies specifically examining RAI treatment efficacy in the ATA Intermediate risk group, thus, results of studies using alternative classification systems were extracted as they applied to this risk category. Multivariable adjusted analyses from SEER suggest that post-surgical RAI treatment is associated with improved overall survival for aggressive papillary thyroid cancer histologies such as: Tall cell, Diffuse Sclerosing, and Insular variants (633;634). There is some evidence from multivariable and propensity analyses that there may be a benefit of adjuvant RAI treatment in improving overall and disease-specific survival as well as disease-free survival in patients with nodal metastases aged ≥45 years, as such patients would be included in the NTCTCSG stage III category (622). Furthermore, in a single center retrospective study from Hong Kong examining data from a subgroup of 421 patients with node-positive papillary thyroid cancer, lymph node failure-free survival was improved with post-surgical radioactive iodine treatment, with the greatest treatment benefits observed in patients with N1b disease, as well as with lymph nodes >1 cm in

diameter (635). RAI therapeutic efficacy in patients <45 years of age with nodal metastases are unclear, as such patients are categorized as Stage I by the NTCTCSG system and no significant benefit of RAI treatment was observed for the Stage I group in that study, with no specific subgroup analysis reported according to node positivity (622). A single-center retrospective study from the Mayo Clinic examining 20-year cause-specific mortality and recurrence rate, suggested no significant benefit in papillary thyroid cancer patients with a MACIS score of <6 who had positive lymph nodes, using respective univariate analyses (247); given that age is incorporated in the MACIS score, it is possible that age was a contributing factor in the results of that analysis. In a subgroup of 352 patients with microscopic extra-thyroidal extension from a single center retrospective study, post-surgical radioactive iodine treatment was associated with a reduction in rate of local relapse (635). However, in the NTCTCSG study, microscopic extra-glandular invasion would be classified as NTCTCSG stage I for those < 45 years of age and II for those ≥45 years of age, and those stages were associated with lack of clear benefit of RAI. For patients with ATA intermediate risk DTC, limited risk-group specific data examining RAI efficacy is available, but existing data suggest that the greatest potential benefit may be observed with adverse thyroid cancer histologies, increasing volume of nodal disease, lymph node disease outside the central neck, and advancing patient age. Benefits on survival or recurrence can be expected primarily in patients with higher risk of recurrent or persistant disease that is iodine-avid. More studies are needed, including randomized controlled trials, to characterize RAI treatment efficacy in ATA intermediate risk patients. The adjuvant therapeutic efficacy of RAI treatment in improving long-term thyroid cancer outcomes in the situation of isolated microscopic central neck nodal disease in absence of other adverse features is unknown, so the relatively good overall prognosis of this group (as outlined in the preceding section of this guideline) as well as the uncertainty RAI therapeutic efficacy for this subgroup, are important considerations in RAI decision-making. Clearly more research is needed to understand the therapeutic efficacy in various subgroups of patients in the ATA intermediate risk category.

ATA High Risk: A prospective multicenter study reported a significant improvement in overall and disease-specific mortality, as well as disease-free survival in NTCTCSG stage III and IV patients, after statistical adjustment using multivariable and propensity stratified analyses (622). Furthermore, prospectively collected data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry, suggest that post-surgical RAI therapy is associated with

improved overall survival in patients with papillary thyroid cancer with distant metastases (when distant metastases combined with age >45 years, tumor size > 2cm, and positive lymph nodes at primary diagnosis) (636). Data from SEER also suggest that overall survival in patients with follicular thyroid cancer with distant metastases more than doubled in patients receiving post-surgical RAI treatment (636). Thus, routine post-surgical RAI treatment is recommended in patients with ATA high risk DTC.

[B37] What is the role of molecular marker status in therapeutic RAI decision-making?

■ **RECOMMENDATION 52**

The role of molecular testing in guiding post-operative RAI use has yet to be established, therefore no molecular testing to guide post-operative RAI use can be recommended at this time. (**No recommendation, Insufficient evidence**)

There are currently insufficient data, to know whether the presence or absence of the BRAF V600E mutation, or other genetic alterations, in papillary thyroid cancer may impact the success of adjuvant therapy or remnant ablation in papillary thyroid cancer, or, if adjustments in administered activity are warranted for any planned treatments. In a recent subgroup analysis of 134 papillary thyroid cancer patients of TNM stage T1aN0M0, 37 of whom did not receive postoperative RAI and 97 of whom received postoperative RAI, the rate of macroscopic structural disease recurrence was 0% in the no RAI group (24% of whom were BRAF positive) and 2.6% in 39 BRAF positive patients who received RAI, and 1.7% in BRAF negative patients to received RAI (mean follow-up of 5.3 years for the entire study) (515). In the same study, in the 97 T1aN0M0 patients who received post-operative RAI, the rate of biochemical persistence of disease (defined by a stimulated thyroglobulin of >1 ng/mL), was 13% in the 39 BRAF positive patients and 1.7% in the BRAF negative patients; the standard dose activity for remnant ablation in this study was 30 mCi in most cases (515). The relatively small number of patients who did not receive post-operative RAI and the relatively small number of structural disease recurrences in the T1aN0M0 subgroup of papillary thyroid cancer patients in this study may preclude meaningful analysis of RAI therapeutic efficacy. Comparison of two treatment modalities without randomization introduces biases and decreases the relevance of any study to low level of evidence. ESTIMABL2 study will analyze the relevance of BRAF status on outcome (registration number NCT01837745). There are no studies examining therapeutic

efficacy of RAI in ATA high risk patients, but the presence or absence of a BRAF V600E mutation in that situation would be unlikely to alter RAI decision-making at present. Thus, the role of molecular testing in guiding post-operative RAI use has yet to be established and more research in this area is clearly needed. Moreover, in general, randomized controlled trials examining RAI therapeutic efficacy are needed, and ideally these should be appropriately stratified for ATA recurrence risk level and other important prognostic variables.

[B38] How long does thyroid hormone need to be withdrawn in preparation for RAI remnant ablation/treatment or diagnostic scanning?

■ RECOMMENDATION 53

A) If thyroid hormone withdrawal is planned prior to RAI therapy or diagnostic testing, levothyroxine should be withdrawn for 3-4 weeks, with or without T3 substitution in the initial weeks. Serum TSH should be measured prior to radioisotope administration to evaluate degree of TSH elevation. (**Strong recommendation, Moderate-quality evidence**)

B) A goal TSH of > 30 mIU/L has been generally adopted in preparation for RAI therapy or diagnostic testing, but there is uncertainty relating to the optimum TSH level associated with improvement in long-term outcomes. (**Weak recommendation, Low-quality evidence**)

Thyrotropin stimulation before RAI remnant ablation/therapy or scanning has been a long-established standard of care, as early observational research suggested that a TSH >30 mIU/L was required for incompletely resected thyroid tumors to significantly concentrate I-131 (637). There have been two randomized controlled trials comparing various thyroid hormone withdrawal protocols prior to therapeutic or diagnostic iodine radioisotope administration (638;639). Lee et al reported on an open-label, single-center, study, in which 291 patients with well-differentiated thyroid cancer (TNM stage T1-T3, N0/N1a,M0) were randomized to either: a) withdrawal L-T4 for 4 weeks (n=89), b) withdrawal of LT-4 for 4 weeks with substitution of T3 for the first 2 weeks (n=133), c) or recombinant human thyrotropin (with withdrawal of L-T4 for a few days from the time of the first rhTSH injection to radioisotope administration) (n=69) (639). In this trial, all patients received 30 mCi of I-131 for remnant ablation, and were prescribed a 2 week low iodine diet pre-ablation. Although randomization method was unclear,

the baseline characteristics (including pre-ablation urinary iodine measurements) were well-balanced among groups. Furthermore, the pre-ablation TSH was >30 in all patients in all groups in this trial, with no significant difference in mean pre-ablation TSH levels . Moreover, the primary outcome, which was the rate of successful remnant ablation at 12 months, was not significantly different among groups (range 91.0 to 91.7% among groups). Upon administration of questionnaires in a double-blind fashion, there was no significant difference in quality of life during preparation for RAI ablation, between the T4 withdrawal group and the T4 withdrawal with T3 substitution group; however, quality of life in both withdrawal groups pre-remnant ablation was significantly worse than after rhTSH preparation (639). Long-term outcome data from this trial was not reported. In a single-center trial, Leboeuf et al randomized 20 individuals with well-differentiated thyroid cancer awaiting RAI remnant ablation or diagnostic scanning, to L-T4 withdrawal and either: b) substitution of T3 (50 µg per day, divided as 2 capsules) for 21 days, followed by 2 weeks off T3 or b) identical appearing placebo for T3 (2 pills per day) for 21 days (638). In both groups, either the T3 or placebo was withdrawn for another 2 weeks and weekly measurements were performed for serum TSH, free T4, and free T3 (638). The primary outcome was hypothyroid symptom score (Billewicz scale), which was ascertained in a double-blind fashion at time of L-T4 withdrawal and every 2 weeks until the end of the study. The randomization method was a computer generated number sequence; the L-T3 group was significantly older than the placebo group (mean age 64 compared to 46) suggesting some possible imbalance in randomization (638). Disease stage of participants was not reported. Approximately 15% of participants withdrew from this trial (2 in placebo group and 1 in the T3 group). Leboeuf et al reported no significant difference between the two thyroid hormone withdrawal protocol groups for hypothyroid symptom scores at any time point in the trial in a per-protocol analysis. At the time of ablation or whole body scanning, the mean TSH was not significantly different between groups. Yet the time needed to reach a TSH value >30 mIU/L from T4 withdrawal was significantly lower in the T4/placebo group (17 days, standard deviation [SD] 9) compared to the T3 group (32 days, SD 4) (p=0.006), which corresponded to 11 days after T3 discontinuation (638). In summary, available evidence from recent randomized controlled trials, suggest that either direct L-T4 withdrawal or L-T4 withdrawal with substitution of T3 in initial weeks, are associated with similar short-term quality of life and hypothyroid symptom scores; moreover, remnant ablation success rate appears comparable.

There is some conflicting observational evidence on whether any specific pre-RAI administration TSH level is associated with success of remnant ablation (640-644). For example, in a secondary analysis of a RAI remnant ablation dose activity RCT, Fallahi et al reported that pre-RAI TSH of >25 following (L-T4 and T-3) thyroid hormone withdrawal was significantly associated with increased likelihood of successful remnant ablation (odds ratio 2.36, 95% confidence interval 1.28-4.35, p=0.006), after adjustment for RAI dose activity, baseline serum thyroglobulin, on-levothyroxine TSH level, sex, age, histology, baseline RAI uptake, and extent of surgery) (640). However, in two retrospective studies, each including several hundred DTC patients who underwent thyroid hormone withdrawal, no significant association was observed between pre-RAI TSH and rate of successful remnant ablation, in respective multivariable analyses adjusted for relevant variables such as disease extent, I-131 dose activity, and gender (643;644). However, results of these two studies may not necessarily be extrapolated to TSH levels below 30 mU/L, given patients with such TSH thresholds were not generally considered eligible for RAI ablation in these studies. Pre-RAI ablation TSH was not a significant predictor of becoming disease-free without further treatment in a secondary subgroup analysis of 50 patients who underwent thyroid hormone withdrawal, but the small number of patients in this subgroup may have limited the statistical power for a multivariable analysis (642). In summary, there is some uncertainty on the optimal level pre-RAI treatment TSH following thyroid hormone withdrawal, in considering long-term outcome effects.

[B39] Can rhTSH (Thyrogen™) be used as an alternative to thyroxine withdrawal for remnant ablation or adjuvant therapy in patients who have undergone near-total or total thyroidectomy?

■ RECOMMENDATION 54

A) In patients with ATA low risk and ATA intermediate risk DTC without extensive LN involvement (ie. T1-T3, N0/Nx/N1a, M0), in whom radioiodine remnant ablation is planned, preparation with rhTSH stimulation is an acceptable alternative to thyroid hormone withdrawal for achieving remnant ablation, based on evidence of superior short-term quality of life, non-inferiority of remnant ablation efficacy, and multiple consistent observations suggesting no significant difference in long-term outcomes. (**Strong recommendation, Moderate-quality evidence**)

B) In patients with ATA intermediate risk DTC who have extensive lymph node disease (multiple clinically-involved LN) in absence of distant metastases, preparation with rhTSH stimulation may be considered as an alternative to thyroid hormone withdrawal, prior to adjuvant radioactive iodine treatment (**Weak recommendation, Low-quality evidence**)

C) In patients with ATA high risk DTC with attendant higher risks of disease-related mortality and morbidity, more controlled data from long-term outcome studies are needed, before recombinant human thyrotropin preparation for RAI adjuvant treatment can be recommended. (**No recommendation, Insufficient evidence**)

D) In patients with DTC of any risk level with significant co-morbidity that may preclude thyroid hormone withdrawal prior to iodine radioiodine administration, recombinant human thyrotropin preparation should be considered. Significant co-morbidity may include: a) a significant medical or psychiatric condition that could be acutely exacerbated with hypothyroidism leading to a serious adverse event, or b) in ability to mount an adequate endogenous TSH response with thyroid hormone withdrawal. (**Strong recommendation, Low-quality evidence**)

Recombinant human thyrotropin (rhTSH, trade name Thyrogen) is currently approved by the United States Food and Drug Administration and Health Canada for use in preparation for radioactive iodine remnant ablation in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastases (FDA: http://www.accessdata.fda.gov; Health Canada: http://webprod.hc-sc.gc.ca). Data from an compassionate use observational study suggests that rhTSH raises serum TSH measurements in patients who are unable to mount an endogenous TSH rise and appears to reduce the risk of hypothyroid-related complications in patients with significant medical or psychiatric co-morbidity (645). Some of the complications that were reported to be avoided by use of rhTSH included: worsening of psychiatric illness, respiratory compromise, central nervous system compromise, aggravation of congestive heart failure, and aggravation of coronary artery disease (645).

Multiple randomized controlled trial (RCTs) have focused on short-term remnant ablation outcomes in low and intermediate risk DTC with lower risk features, using rhTSH compared to thyroid hormone withdrawal. In 6 randomized controlled trials (RCTs) of patients with well-differentiated thyroid cancer without distant metastases undergoing radioactive iodine remnant ablation (T1-T3, N1 or N0, all M0), the rate of successful remnant ablation, was not significantly different after rhTSH preparation compared to thyroid hormone withdrawal, using I-131 dose activities ranging from 30 to 100 mCi (639;646-650). Patients with resected cervical lymph node metastases were included in 5 of these RCTs (639;647-650), and these may be assumed to be confined to the central neck, given the extent of primary surgery described in these studies. In one trial, a further inclusion restriction was <5 positive nodes at time of primary surgery (650). Some potential limitations of the existing RCTs in this area include lack of blinding of patients and treating physicians (as it was not feasible). In 5 of the randomized controlled trials which examined health-related quality of life around the time of remnant ablation, this outcome was significantly worse in patients who underwent thyroid hormone withdrawal compared to rhTSH preparation, and this was attributed to hypothyroid symptoms (639;647-650). However, in 3 of these randomized controlled trials which examined longer term quality of life, there was no significant difference in measurements between patients who had received rhTSH compared to those who had thyroid hormone withdrawal preparation, 3 or more months after radioactive iodine remnant ablation (647;649;650). A smaller RCT including a total of 25 individuals who had incidentally discovered PTC in the course of thyroidectomy for multinodular goiter, showed that mean thyroglobulin measurements were similar at various time points out to about 20 months in 13 individuals who were prepared for remnant ablation using rhTSH within a week after thyroidectomy, compared to those prepared by L-T4 abstinence for 4-6 weeks postoperatively (651). A meta-analysis pooling data from 1535 patients in all 7 trials described herein, suggested that the rates of remnant ablation success were not significantly different using rhTSH compared to thyroid hormone withdrawal (risk ratio 0.97, 95% CI 0.94, 1.01) (652). Furthermore, a pooled analysis suggested that quality of life measures were superior on the day of remnant ablation in the rhTSH group, with no significant difference between groups 3 months later (652).

There are some limited long-term outcome data following rhTSH preparation for RAI treatment compared to thyroid hormone withdrawal. In one aforementioned RCT in ATA low

and intermediate risk disease (648), follow-up data was reported a median of 3.7 years later for 51 of the original 63 patients, and rates of reoperation for cervical neck recurrence were essentially identical between groups (4% of patients), with no deaths (653). In the same study, repeat treatment with I-131 for detectable thyroglobulin or imaging evidence of disease was performed in 4/28 patients in the rhTSH group and 5/23 patients in the hypothyroid group in this study (653). The low number of thyroid cancer-related deaths and recurrences in this small trial limit the ability to make meaningful statistical comparisons of long-term outcomes. In another RCT including 44 mixed risk level DTC patients, who were subjected to either rhTSH preparation (N=24) for RAI treatment within a week after surgery or a 4-6 weeks of L-T4 abstinence (N=20), after a mean follow-up period of about 52 months, only one individual in the rhTSH group was histologically proven to have recurrent disease (lymph nodes and bone) (654). However, this study was likely underpowered to detect meaningful differences in this outcome and the final data analysis would be limited by lack of data available at the final follow-up (ie. in progress) for 18% of the trial participants (654). In one prospective (642) and two retrospective (655;656) observational studies or largely ATA low and intermediate risk DTC patients, no significant difference was observed in the long-term presence of clinically significant disease, regardless of whether recombinant human thyrotropin or thyroid hormone withdrawal was used in preparing for therapeutic radioactive iodine for DTC patients). In a subgroup analysis of 183 DTC patients with level N1b nodal disease from one of the aforementioned retrospective studies, the rate of no evidence of disease at last follow-up was not significantly different in patients prepared with thyroid hormone withdrawal (26.8%) compared to those prepared with rhTSH (33.7%) (655). In a smaller retrospective, multi-center study, Pitoia et al reported that in 45 consecutive thyrogobulin antibody-negative patients with T3-T4 /N1-Nx/M0 disease, the absence of persistence or recurrence of disease after a mean follow-up of about 3 years was 72% in patients pre-treated with rhTSH and 59% in those pre-treated with thyroid hormone withdrawal (p=0.03) (657). In a multi-center, retrospective analysis of patients with T4 disease with or without nodal or distant metastases (T4, N0/N1, M0/M1), the rate of stimulated thyroglobulin < 2 ng/mL thyroglobulin antibody-negative patients was 67.7% (42/62) in patients prepared for RAI treatment with rhTSH, compared to 57.8% (37/64) in those prepared with thyroid hormone withdrawal (6 month follow-up) (658). In a retrospective analysis of 175 patients with RAI avid metastatic disease to lungs and/or bone, the authors observed no

significant difference in overall survival after a mean follow-up period of 5.5 years, among patients prepared prior to RAI treatment with either rhTSH alone for all RAI treatments, thyroid hormone withdrawal for all RAI treatments, nor thyroid hormone withdrawal for initial treatments followed by rhTSH for subsequent treatment(s) (659). In this study, whole-body and blood dosimetry studies were performed in all patients, so the results may not be extrapolated to RAI fixed dosing. Some important differences among groups in this study that could have impacted the findings included differences in cumulative RAI activity received and longer follow-up in groups who had thyroid hormone withdrawal (659). Although the authors performed a multi-variable analysis examining for predictors of overall survival, and method of thyrotropin stimulation was not significant, this model did not adjust for these variables. In a two-center retrospective analysis comparing responses to treatment using RECIST 1.1 criteria in 56 patients with distant metastastic disease pre-treated with either rhTSH or thyroid hormone withdrawal prior to RAI, there was no differences in outcomes between groups after a mean follow-up period of about 6 years (660). Also in this study, there were important baseline differences among groups, such as rates of use of dosimetry and mean cumulative RAI dose activity. Rates of xerostomia, leukopenia, or thrombocytopenia were not significantly different between treatment groups in this study. The overall mortality rate was 20% in the rhTSH group (3/15) and 7.3% in the thyroid hormone withdrawal group (3/41) (p=0.188) (660), although the study was likely not sufficiently large to examine differences in this important outcome. The findings of the latter study cannot be readily extrapolated to fixed dosing RAI treatment regimens, as 80% of the individuals in the rhTSH group and 46% in the thyroid hormone withdrawal group had dosimetry-based RAI treatment. Randomized controlled trials comparing rhTSH to thyroid hormone withdrawal preparation pre-RAI treatment, are clearly needed to guide clinical care in higher risk DTC patients.

[B40] What activity of ^{131}I should be used for remnant ablation or adjuvant therapy?

■ RECOMMENDATION 55

If radioactive iodine remnant ablation is performed after total thyroidectomy for ATA low risk thyroid cancer or intermediate risk disease with lower risk features (ie. low volume central neck nodal metastases with no other known gross residual disease nor any other adverse

features), a low administered dose activity of approximately of 30 mCi (1.11 GBq) is generally favored over higher administered dose activities. (**Strong recommendation, High-quality evidence**)

■ RECOMMENDATION 56

When RAI is used for initial adjuvant therapy to treat suspected or documented microscopic residual disease in ATA intermediate and high risk patients, administered activities of 30-150 mCi are generally recommended (in absence of known distant metastases). Routine use of higher administered activities in this setting does not appear to reduce structural disease recurrence for T3 and N1 disease. (**Weak recommendation, Low-quality evidence**)

Successful remnant ablation can be defined by an undetectable stimulated serum thyroglobulin, in absence of interfering thyroglobulin antibodies, with or without confirmatory nuclear or other imaging studies. An alternative definition in cases where thyroglobulin antibodies are present, is the absence of visible RAI uptake on a subsequent diagnostic RAI scan. In this section, we only included published original randomized controlled trials (RCTs), or systematic reviews/meta-analyses of such studies, examining the impact of various I-131 dose activities on the rate of successful remnant ablation or thyroid cancer outcomes (including thyroid cancer-related deaths or recurrences) in adult patients with well-differentiated thyroid carcinoma who had been treated with total or near-total thyroidectomy and who were not known to have any gross residual disease following surgery. Our search yielded 6 RCTs (640;647;649;661-663), the majority of which had had no blinding of patients and healthcare providers (647;649;661-664).

In the trial by Fallahi et al, the randomization program was prepared and executed by a technologist in the lab where the I-131 activities were prepared for dispensing in coded vials, without revealing the administered dose activity to participants and healthcare providers (640). The pathologic stage of disease of patients included in trials was TNM stage pT1 to pT3 in 4 trials (647;661;662;664), whereas only pT1 or pT2 patients were eligible in one trial (649), and primary tumor size or tumor size staging was not reported in two trials (640;663). Some patients with known small volume lymph node disease were included in 5 of the trials (647;649;661;662;664), but patients with known lymph node disease were excluded from one

trial (640) and lymph node staging was not reported in another trial (663). Although the specific levels and size of lymph node metastases at baseline were not clearly reported, data reported on surgical extent suggested that these were consistent with relatively non-bulky central neck nodal metastases resected in the course of thyroidectomy with or without central neck dissection (647;649;661;662;664).

The I-131 activities compared were as follows: 30 mCi compared to 100 mCi in 4 trials (640;647;649;661), 50 mCi compared to 100 mCi in 2 trials (662;663), or 30 mCi compared to 60 mCi or 100 mCi in one study comprised of pooled longterm outcome data from two staged smaller trials from the same group (664).

The rate of successful remnant ablation was reported to be not inferior using a dose activity of 30 mCi as compared to 100 mCi in three trials after preparation with thyroid hormone withdrawal (647;649) (661), and two trials after preparation with recombinant human thyrotropin (647;649), including data from the two large factorial design trials in both comparisons (647;649) . Pilli et al. reported that a dose activity of 50 mCi was not inferior to 100 mCi in achieving successful remnant ablation, following preparation with recombinant human thyrotropin (662). In contrast, Zaman et al. suggested that 100 mCi may be superior to 50 mCi following thyroid hormone withdrawal, but the small size (40 patients) and lack of reporting of statistical comparisons, are important limitations of this study. The third largest trial (341 patients randomized), Fallahi et al., reported that a dose activity of 100 mCi was superior to 30 mCi in achieving successful remnant ablation after thyroid hormone withdrawal (640). The rate of initial successful remnant ablation (as defined by the primary authors), was highly variable among trials, and the following rates were reported following initial administration of 100 mCi of I-131: 64% in the trial from Fallahi et al. (640), 56% in the trial from Maenpaa et al (661), 89% in the trial from Mallick et al (647), 67% in the trial from Pilli et al. (662), 94% in the trial from Schlumberger et al. (649), and 60% in the trial from Zaman et al. (663). The reasons explaining variability in the rates of successful radioactive iodine remnant ablation among trials are not completely understood, but could potentially be due to differences in study populations, completeness of surgery (including size of the remaining remnant), or sensitivity of techniques used to evaluate outcomes (such as thyroglobulin assays or diagnostic imaging studies).

Short-term side effects in the weeks following remnant ablation have been reported to be more frequent in patients treated with 100 mCi as compared to 30 mCi dose activities by Mallick

et al. (647) and a similar trend was reported by Maenpaa et al. (661). Repeat treatment with additional I-131 has been reported to be more frequent in patients treated with 30 mCi as compared to higher dose activities in three trials (640;647;664), but not in one trial (661) . Long-term outcome data from randomized trials in this area are limited by relatively low event rates, potentially underpowering statistical analyses. Kukulska et al. followed 390 patients that had been randomized to either 30 mCi, 60 mCi, or 100 mCi dose activities for remnant ablation, and reported the following event rates after median period of 10 years following treatment: local relapse in 2% following an initial 30 mCi dose activity compared to 3% for initial dose activities of 60 mCi or 100 mCi (reported to be not significantly different), and distant metastatic recurrence in 0% of the patients in all of the treatment groups (664). Maenpaa et al. followed 160 patients who were randomized to either 30 mCi or 100 mCi for a median of 51 months and reported the following outcomes: reoperation for resection of thyroid cancer in lymph nodes in 7% and 8% of patients for treated with dose activities of 30 mCi and 100 mCi respectively, distant metastatic recurrence in 0% and 4% of patients treated with dose activities of 30 mCi and 100 mCi respectively, and no thyroid cancer-related deaths in any of the treatment groups (661) .

Overall, the rate of successful remnant ablation patients who have undergone total or near-total thyroidectomy, appears to be not inferior in patients treated with 30 mCi compared to 100 mCi in the majority studies comparing these activities, and in particular in studies achieving the highest successful ablation rates. Rates of short-term adverse effects may be higher after administration of 100 mCi I-131 compared to 30 mCi, in a small number of trials examining these outcomes. Limited long-term randomized controlled trial data on the impact of various dose activities for remnant ablation are available, but thyroid cancer-related recurrences or deaths do not appear to be higher with the use of lower initial dose activities for remnant ablation, compared to higher dose activities. Four recent systematic reviews and meta-analyses reported results that are supportive of these conclusions (665-668), although some of the pre-defined study inclusion criteria in these reviews were generally not as strict as defined in our review (particularly for variables such as the extent of primary surgery or the stringency of thyroglobulin threshold in the definition of success of remnant ablation); it is also important to note that in some of these meta-analyses, statistically significant heterogeneity (variability) of treatment effect was noted for the pooled analyses on successful remnant ablation (665;667;668).

In the 2009, the ATA guidelines task force recommended a fixed dose activity of between 100 and 200 mCi for adjuvant RAI treatment if residual microscopic disease is suspected or documented), or if an aggressive histologic variant of DTC was present (22). Since that time, at least 4 retrospective, single-studies have compared clinical outcomes following various adjuvant RAI fixed dose activities in ATA intermediate and ATA higher risk patients, without distant metastases (669-672). In comparing rates of disease persistence or recurrence in 225 ATA Intermediate risk DTC patients treated with 30 to 50 mCi compared to ≥100 mCi of adjuvant RAI, Castagna et al reported no significant difference in rates of successful remnant ablation nor long-term disease recurrence/persistence between groups (669). However, there were some statistically significant differences between the treatment groups that may have influenced these results, including higher numbers of men, individuals with lateral neck nodal disease, and longer follow-up period (which may increase rate of detection), in the higher dose activity group of this study (669). In another study including 176 DTC patients with a primary tumor size ≤2cm in diameter and microscopic extrathyroidal extension, no significant differences were found in comparing rates of successful remnant ablation and long-term recurrences in patients treated with 30 mCi I-131 compared to 149 mCi (670). In this study, no recurrences were noted in either group after median follow-up of 7.2 years. Although the mean primary tumor size was higher in the higher dose activity group compared to the lower dose activity group in this study ($p<0.001$), the difference in mean tumor diameter was only 2 mm, so it may be of questionable clinical significance (670). Kruijff et al reported the results multiple secondary subgroup analyses on data from 341 patients with T3 PTC, in which a post-surgical I-131 dose activity of ≤75 mCi, was compared to >75mCi (671). In this study, the respective rates of disease recurrence, mortality and stimulated thyroglobulin > 2 µg/L, were not significantly different in the lower dose activity group (ie. 7%, 3%, 72%), compared to the higher dose activity group (12%, 1.7%, 64%) (respective p-values 0.55, 0.43, 0.40). Furthermore, in this study, a multivariable analysis using data from 1,171 mixed risk DTC patients without distant metastases, suggested that there was no significant in risk of disease recurrence with the use of >75 mCi of I-131 post-operatively compared to ≤75 mCi (higher dose activity hazard ratio 1.57, 95% CI 0.61 to 3.98, p=0.341, after adjustment for age, gender, primary tumor size, presence of vascular invasion, multifocality, and lymph node positivity, with a mean follow-up period 60 months) (671). In another study comparing rates of disease structural recurrence/persistence in

181 patients with positive N1b lymph nodes, Sabra et al reported no statistically significant difference among the following approximate fixed dose activity categories: 75-139 with median 102 mCi (31%), 140 to 169 with median mCi (32%), 170 to 468 with median 202 mCi (23%) (p=0.17) (672). Consistent with this finding, no significant correlation between RAI dose activity and best clinical response was observed in this study. In respective secondary subgroup analyses, the authors reported that a dose response was apparent in individuals ≥45 years of age, but not younger individuals, but the authors cautioned about the use of RAI dose fixed activities exceeding 150 mCi because of concerns about potential toxicity in the context of renal impairment (672). In the three studies utilizing either thyroid hormone withdrawal or recombinant human thyrotropin for RAI treatment preparation (669;671;672), insufficient data was reported to make any meaningful interpretation on any relationship between dose activity in context of preparation method, for meaningful clinical interpretation. In one study, RAI adjuvant treatment was performed post-operatively, presumably without initiation of thyroid hormone, as recombinant human thyrotropin was not reported to be used (670). None of the aforementioned studies (669-672) reported on RAI toxicity nor quality of life outcomes; furthermore, T4 disease was not included in these studies. Overall, there is little evidence to suggest that increasing dose activity of adjuvant RAI is necessarily associated with improvement of clinical outcomes for patients with ATA intermediate and high-risk disease without evidence of persistent disease. There is an important unmet need for randomized controlled trials examining thyroid cancer-related outcomes, quality of life, and toxicities in patients with ATA intermediate or higher level thyroid cancer, in absence of gross residual disease or distant metastases.

[B41] Is a low-iodine diet necessary before remnant ablation?

■ RECOMMENDATION 57

A low-iodine diet for approximately 1 to 2 weeks, should be considered for patients undergoing RAI remnant ablation or treatment. (**Weak recommendation, Low-quality evidence**)

It is important for healthcare providers to inquire about a history of possible high dose iodine exposure (e.g., intravenous contrast, amiodarone, or others), in considering timing of

scheduling of RAI therapy or imaging. There are no studies examining whether the use of a low iodine diet in preparation for radioactive iodine remnant ablation or treatment impacts long-term disease-related recurrence or mortality rates. In a recent systematic review of observational studies in this area, the most commonly studied LIDs allowed for ≤50 µg/day of iodine for 1 to 2 weeks and that the use of LIDs appeared to be associated with reductions in urinary iodine excretion as well as increase in I-131 uptake, compared to no LID (673). There is conflicting evidence on the impact of a LID on the outcome of remnant ablation success (673), with the best available evidence largely restricted to retrospective analyses, using historical controls (674;675). In a study including a total of 120 patients, the use of a 4-day LID (with seafood restriction for 1 week), was associated with a higher rate of remnant ablation success (defined by absent neck activity and stimulated thyroglobulin < 2 µg/L) compared to no LID (674). In a study including a total of 94 patients, comparing a more stringent LID to a less stringent diet of restricted salt/vitamins/seafood, each for 10 to 14 days, there was no significant difference in rate of successful remnant ablation, using a visually negative I-131 scan to define that outcome (675). The optimal stringency and duration of LID (if any), prior to therapeutic RAI, is not known. In a randomized controlled trial, including 46 patients, the increase in I-131 uptake and reduction in urinary iodine excretion was not significantly different between patients who followed a LID for 2 weeks compared to 3 weeks, prior to RAI scanning (676), suggesting that there may be little reason to extend the LID past 2 weeks. However, a lack of association between urinary iodine excretion and rate of successful thyroid ablation has been reported in patients not specifically prescribed a LID (677); the absence of a specific LID comparison group in this study may limit the generalizability of the findings to situations where a specific LID is prescribed. Such findings may suggest, however, that the routine measurement of urinary iodine excretion, outside of possibly a research setting or suspected iodine contamination, may not be necessary. Although LIDs may be boring or unpalatable, serious side effects are relatively infrequent (673), with case reports of potentially life-threatening hyponatremia, occurring largely in elderly patients who were subject to thyroid hormone withdrawal, often in the presence of metastatic disease, sometimes concurrently treated with thiazide diuretics, and in the majority of cases, with a LID duration of longer than week (678). It is important to avoid restriction of non-iodized salt during the LID. Some examples of low iodine diet descriptions for patients, may be found at the following websites: American Thyroid Association (http://www.thyroid.org/faq-low-iodine-

diet/), Thyroid Cancer Survivors Association-Thyca (http://thyca.org/rai.htm#diet), Light of Life Foundation (http://www.checkyourneck.com/About-Thyroid-Cancer/Low-Iodine-Cookbook), and Thyroid Cancer Canada (http://www.thyroidcancercanada.org/userfiles/files/LID_English_Aug_2013_final.pdf).

[B42] Should a posttherapy scan be performed following remnant ablation?

■ RECOMMENDATION 58

A post-therapy whole-body scan (with or without single-photon emission tomography/computed tomography [SPECT-CT]), is recommended after RAI remnant ablation or treatment, to inform disease staging and document the RAI-avidity of any structural disease. (**Strong recommendation, Low-quality evidence**)

The literature on the utility of posttherapy RAI scans is largely based on single-center retrospective studies (593;679-682), many of which included a relatively large proportion of ATA intermediate and high risk differentiated thyroid cancer (DTC) patients (593;679;680). In comparing the results of pretherapy I-131 scans to posttherapy scans, and the rate of newly discovered lesions on posttherapy scans was reported to be between 6% and 13%. In a study examining post-remnant ablation scans in 60 DTC patients, the results were reported to alter the disease stage in 8.3% of individuals (681). In older literature, it had been reported that posttherapy scanning demonstrated new findings in 31% of 39 cases studied, but the detection of thyroid foci was included in that outcome, whereas almost a third of the patients (12/39) had a sizeable portion of their thyroid remaining following primary surgery (682). In the recent posttherapy scan literature, the I-131 dose activities ranged from 30 to 300 mCi (679-681), and the timing of scans was between 2 and 12 days following therapeutic RAI (593;679-681;683)(}(684), with some studies prescribing a prepatory low iodine diet (593;681)(}(684), and others reporting not prescribing such a diet (679;680). In one study, post-therapy scan images were compared on the third and 7th day following ablative or therapeutic RAI administration for mixed risk DTC (following thyroid hormone withdrawal) (684). The authors of this study reported that the concordance of lesions detected on both scans was 80.5% (108 of 135 patients), with 7.5% of early scans providing more information than late scans and 12% of late scans providng more information than early scans (684). A limitation in interpreting the

posttherapy scan literature is that all of the lesions identified on posttherapy scans were not always confirmed to represent with structural evidence of disease (ie. using cross-sectional imaging, histopathology, or longterm outcome data), and readers of posttherapy scans were generally not specifically blinded to the results of other investigations, such as pretherapy RAI scans.

The potential utility of the combination of RAI postherapy scanning in conjunction with SPECT-CT has been examined in multiple prospective (683;685;686) and retrospective studies (687-689). The majority of these studies (683;685) (686-688), have independently confirmed the presence of disease by means such as alternative imaging studies, histopathology, or clinical follow-up. In a single-center study of 170 patients with mixed risk level well-differentiated thyroid cancer, the combination RAI posttherapy scanning and neck/thorax SPECT-CT, was estimated to have a sensitivity of 78% (95% confidence interval [CI] 60 – 90%), with a specificity of 100% (where negative or indeterminate scans were grouped as negative), for the outcome of persistent/recurrent disease (median study follow-up period of 29 months) (683). Furthermore, in a multivariable analysis reported in this study, posttherapy RAI scanning with SPECT-CT significantly independently predicted an increased risk of future disease persistence/recurrence (hazard ratio 65.2, 95% CI 26.0 – 163.4) (683). In a single-center study of 81 DTC patients who underwent I-131 postherapy scanning in conjunction with SPECT-spiral CT of the neck, 1.6% of the 61 patients with negative cervical scintigraphy/SPECT-CT had evidence of abnormal cervical scintigraphy 5 months later, whereas 3 of the 20 patients (15%) with positive or indeterminate cervical postterapy scintigraphy/SPECT-CT, had abnormal cervical scintigraphy 5 months later (687). The incremental value of SPECT/CT in impacting therapeutic planning appears to be greatest in studies where its use reserved for situations of posttherapy scan diagnostic uncertainty (impacted therapy in 24.4% [8/33] of cases, all of which went on to surgery) (685), or when disease is advanced and whole body scan is inconclusive (impacted management in 35% [8/23] of such patients in another study) (686). The routine addition of neck/chest SPECT-CT to all posttherapy scans, has been estimated to alter post-surgical American Thyroid Association recurrence risk estimate in 6.4% (7/109) of patients (689), impact therapeutic planning in about 2% of cases (688), and reduce the need for additional cross-sectional imaging in 20% of cases (29/148). In one study examining the use of routine cervical/thoracic SPECT-CT in conjunction with posttherapy scanning, the SPECT-CT portion

identified non-iodine-avid lesions in 22% of patients (32/148), although the underlying pathologic diagnosis or long-term clinical significance of these lesions was not clearly reported (ie. “tiny” lung nodules in 19 patients, mediastinal lymph nodes <5mm in 10 patients, and osteolytic bone metastases in 3 patients) (689). In situations where SPECT-CT may not be feasible to perform in conjunction with a post-therapy RAI scan, clinical judgment needs to prevail on the utility of alternative cross-sectional imaging studies, considering factors such as clinic-pathologic stage, the completeness of surgery, inappropriate thyroglobulinemia, and, if performed, post-therapy RAI scan result.

[B43] Early management of DTC after initial therapy

[B44] What is the appropriate degree of initial TSH suppression?

■ RECOMMENDATION 59

A) For high-risk thyroid cancer patients, initial TSH suppression to below 0.1 mU/L is recommended. (**Strong recommendation, Moderate-quality evidence**)

B) For intermediate-risk thyroid cancer patients, initial TSH suppression 0.1- 0.5 mU/L is recommended. (**Weak recommendation, Low-quality evidence**)

C) For low risk patients who have undergone remnant ablation and have undetectable serum Tg levels, TSH may be maintained at the lower end of the reference range (0.5–2 mU/L) while continuing surveillance for recurrence. Similar recommendations hold for low-risk patients who have not undergone remnant ablation and have undetectable serum Tg levels. (**Weak recommendation, Low-quality evidence**)

D) For low risk patients who have undergone remnant ablation and have low level serum Tg levels, TSH may be maintained at or slightly below the lower limit of normal (0.1–0.5 mU/L) while continuing surveillance for recurrence. Similar recommendations hold for low-risk patients who have not undergone remnant ablation, although serum Tg levels may be measurably higher and continued surveillance for recurrence applies. (**Weak recommendation, Low-quality evidence**)

DTC expresses the TSH receptor on the cell membrane and responds to TSH stimulation by increasing the expression of several thyroid specific proteins (Tg, sodium-iodide symporter) and by increasing the rates of cell growth (690). Suppression of TSH, using supra-physiologic

doses of LT4, is used commonly to treat patients with thyroid cancer in an effort to decrease the risk of recurrence (244;622;691-693). A meta-analysis supported the efficacy of TSH suppression therapy in preventing major adverse clinical events (RR = 0.73; CI = 0.60–0.88; $p < 0.05$) (691). A large randomized controlled trial from Japan (694) showed that disease-free survival was equivalent in patients with normal TSH (0.4-5 mU/L) compared with those on LT4 suppression therapy (TSH <0.01 mU/L). Extent of residual disease is uncertain in these patients in that most did not undergo total thyroidectomy or radioiodine ablation and Tg levels were not monitored or reported, making direct comparisons to a North American approach difficult.

Retrospective and prospective studies have demonstrated that TSH suppression to below 0.1 mU/L may improve outcomes in high-risk thyroid cancer patients (244;695), though no such evidence of benefit has been documented in low-risk patients. Higher degrees of suppression to <0.03 mU/L may offer no additional benefit (692). A prospective cohort study (622) of 2936 patients found that overall survival improved significantly when the TSH was suppressed to undetectable levels in patients with NTCTCSG stage III or IV disease and suppressed to the subnormal to undetectable range in patients with NTCTCSG stage II disease; however, in the latter group there was no incremental benefit from suppressing TSH to undetectable levels. Suppression of TSH was not beneficial in patients with NTCTCSG stage I disease. In another study, there was a positive association between serum TSH levels and the risk for recurrent disease and cancer-related mortality (696). Adverse effects of TSH suppression may include the known consequences of subclinical thyrotoxicosis, including exacerbation of angina in patients with ischemic heart disease, increased risk for atrial fibrillation in older patients (697), and increased risk of osteoporosis in postmenopausal women (694;698-700). Therefore, optimal TSH goals for individual patients must balance the potential benefit of TSH suppression with the possible harm from subclinical thyrotoxicosis espeically in patients with medical conditions that can be exacerbated with aggressive TSH suppression.

[B45] Is there a role for adjunctive external beam irradiation or chemotherapy?

[B46] External beam irradiation

■ RECOMMENDATION 60

There is no role for routine adjuvant external beam radiation therapy to the neck in patients with DTC after initial complete surgical removal of the tumor (**Strong**

recommendation, Low-quality evidence).

The application of adjuvant neck/thyroid bed/loco-regional radiation therapy in DTC patients remains controversial. In particular, the use of radiation therapy within the context of initial/primary surgery/thyroidectomy has no meaningful literature support. There are reports of responses among patients with locally advanced disease (701;702) and improved relapse-free and cause-specific survival in patients over age 60 with extrathyroidal extension but no gross residual disease (703), and selective use can be considered in these patients. It remains unknown whether external beam radiation might reduce the risk for recurrence in the neck following adequate primary surgery and/or RAI treatment in patients with aggressive histologic subtypes (704). However, in the context of certain individual patients undergoing multiple and frequent serial neck re-operations for palliation of locoregionally recurrent disease, adjuvant external beam radiation therapy may sometimes be of consideration. In such contexts, the risks of anticipated additional serial re-operations versus the risks of external beam radiation therapy must be carefully weighed to arrive at optimal decisions for individual patients. The approach to patients with gross incomplete surgical resection of disease is addressed in another section (Recommendation 72).

[B47] Systemic adjuvant therapy

■ **RECOMMENDATION 61**

There is no role for routine systemic adjuvant therapy in patients with DTC (beyond RAI and/or TSH suppressive therapy using levothyroxine). (**Strong recommendation, Low-quality evidence**)

There are no clinical trial data to indicate that any adjuvant therapy beyond RAI and/or TSH suppressive therapy using levothyroxine has a net beneficial role in DTC patients. Furthermore, as the prognosis of DTC patients in complete remission and without any indication of active systemic disease is very good - and as toxicities, and even the risk of death, from use of kinase inhibitor therapies are appreciable – toxicities/risks have strong potential to exceed expected therapeutic benefit in the adjuvant context in most patients with DTC.

Whether populations of DTC patients might be identifiable who have sufficiently great

future risks from recurrent disease to justify the corresponding risks attendant to the application of adjuvant systemic therapy (beyond RAI and/or TSH suppressive therapy using levothyroxine) remains uncertain. Doxorubicin may act as a radiation sensitizer in some tumors of thyroid origin (705), and could be considered for patients with locally advanced disease undergoing external beam radiation. It is in particular also uncertain whether patients with rising thyroglobulin in the setting of no identifiable progression of anatomical disease have sufficiently high future risks from disease to justify the application of adjuvant systemic therapy beyond RAI and/or TSH suppressive therapy using levothyroxine.

[C1] DTC: LONG-TERM MANAGEMENT AND ADVANCED CANCER MANAGEMENT GUIDELINES

[C2] What are the appropriate features of long-term management?

Accurate surveillance for possible recurrence in patients thought to be free of disease is a major goal of long-term follow-up. Tests with high specificity allow identification of patients unlikely to experience disease recurrence, so that less aggressive management strategies can be used that may be more cost effective and safe. Similarly, patients with a higher risk of recurrence are monitored more aggressively because it is believed that early detection of recurrent disease offers the best opportunity for effective treatment. A large study (706), found that the residual life span in disease-free patients treated with total or near-total thyroidectomy and ^{131}I for remnant ablation and, in some cases, high dose ^{131}I for residual disease, was similar to that in the general Dutch population. In contrast, the life expectancy for patients with persistent disease was reduced to 60% of that in the general population but varied widely depending upon tumor features. Age was not a factor in disease-specific mortality when patients were compared with aged matched individuals in the Dutch population. Treatment thus appears safe and does not shorten life expectancy. Although an increased incidence of second tumors in thyroid cancer patients has been recognized after the administration of high cumulative activities of ^{131}I (707;708) this elevated risk was not found to be associated with the use of ^{131}I in another study (709), and RAI therapy in low-risk patients did not affect median overall survival in another (710). Patients with persistent or recurrent disease are offered treatment to cure or to delay future morbidity or mortality. In the absence of such options, therapies to palliate by substantially

reducing tumor burden or preventing tumor growth are utilized, with special attention paid to tumors threatening critical structures.

A second goal of long-term follow-up is to monitor thyroxine suppression or replacement therapy, to avoid under-replacement or overly aggressive therapy (711).

[C3] What are the criteria for absence of persistent tumor (excellent response)?

In patients who have undergone total or near-total thyroidectomy and thyroid remnant ablation, disease-free status comprises all of the following (summarized in Table 13):

1) no clinical evidence of tumor,

2) no imaging evidence of tumor by radioiodine imaging (no uptake outside the thyroid bed on the initial posttreatment WBS if performed, or, if uptake outside the thyroid bed had been present, no imaging evidence of tumor on a recent diagnostic or post-therapy WBS) and/or neck US, and

3) low serum Tg levels during TSH suppression (Tg <0.2 ng/mL) or after stimulation (Tg <1 ng/mL) in the absence of interfering antibodies.

[C4] What are the appropriate methods for following patients after initial therapy?

[C5] What is the role of serum Tg measurement in the follow up of DTC?

■ RECOMMENDATION 62

A) Serum thyroglobulin should be measured by an assay that is calibrated against the CRM457 standard. Ideally, serum Tg should be assessed longitudinally in the same laboratory and using the same assay for a given patient. Thyroglobulin antibodies should be quantitatively assessed with every measurement of serum Tg. (**Strong recommendation, High-quality evidence**)

B) During initial follow-up, serum Tg on thyroxine therapy should be measured every 6-12 months. More frequent Tg measurements may be appropriate for ATA high risk patients. (**Strong recommendation, Moderate-quality evidence**)

C) In ATA low and intermediate risk patients that achieve an excellent response to therapy, the utility of subsequent Tg testing is not established. The time interval between serum Tg measurements can be lengthened to at least 12-24 months. (**Weak recommendation, Low-quality evidence**)

D) Serum TSH should be measured at least every 12 months in all patients on thyroid hormone therapy (**Strong recommendation, Moderate-quality evidence**)

E) ATA high risk patients (regardless of response to therapy) and all patients with biochemical incomplete, structural incomplete, or indeterminate response should continue to have Tg measured at least every 6-12 months for several years. (**Weak recommendation, Low-quality evidence**)

■ RECOMMENDATION 63

A) In ATA low-risk and intermediate-risk patients who have had remnant ablation and negative cervical US, serum Tg should be measured at 6-18 months on thyroxine therapy in a sensitive Tg assay (<0.2 ng/ml) or after TSH stimulation to verify absence of disease (excellent response). (**Strong recommendation, Moderate-quality evidence**)

B) Repeat TSH stimulated Tg testing is not recommended for low and intermediate risk patients with an excellent response to therapy. (**Weak recommendation, Low-quality evidence**)

C) Subsequent TSH stimulated Tg testing may be considered in patients with an indeterminate, biochemical incomplete or structural incomplete response following either additional therapies or a spontaneous decline in Tg values on thyroid hormone therapy over time in order to reassess response to therapy. (**Weak recommendation, Low-quality evidence**)

The necessity of subsequent stimulated testing is uncertain for those found to have no evidence of disease, because there is rare benefit seen in this patient population from repeated TSH-stimulated Tg testing (541;545;548;712). The use of sensitive methods for serum Tg may obviate the need for rhTSH stimulation in low risk patients with a Tg on LT4 treatment below 0.1-0.2 ng/mL (353;538;546;546;552;557;713).

[C6] Serum thyroglobulin measurement and clinical utility

Measurement of serum Tg levels is an important modality to monitor patients for residual or recurrent disease. Most laboratories currently use immunometric assays to measure serum Tg, and it is important that these assays are calibrated against the CRM-457 international standard. Despite improvements in standardization of thyroglobulin assays, there is still a twofold difference between some assays (279;714), leading to the recommendation that measurements in

individual patients over time be performed in the same assay. Immunometric assays are prone to interference from Tg autoantibodies, which commonly cause falsely low serum Tg measurements. Moreover, variability in Tg autoantibody assays may result in falsely negative antibody levels associated with a misleadingly undetectable serum Tg due to the antibodies that are present but not detected (715). Assays for Tg autoantibodies suffer from a similar variance and lack of concordance as do Tg assays (559;716), and both Tg and Tg autoantibody assays may be affected by heterophile antibodies (717;718). The presence of Tg autoantibody should be suspected when the surgical pathology indicates the presence of background Hashimoto thyroiditis (719). While there is no method that reliably eliminates Tg antibody interference, radioimmunoassays for Tg may be less prone to antibody interference (720-722). However, radioimmunoassays for Tg are not as widely available, may be less sensitive than immunometric assays in detecting small amounts of residual tumor, and their role in the clinical care of patients is uncertain. In the absence of antibody interference, serum Tg has a high degree of sensitivity and specificity to detect thyroid cancer, especially after total thyroidectomy and remnant ablation. In patients with low risk for recurrence, serum Tg measurement at the time of remnant ablation may be useful for prediction of subsequent disease-free status (556).

Most data come from studies using methods with a functional sensitivity of 1ng/mL. Functional sensitivity of many contemporary assays is $\leq$ 0.1ng/mL, which may lead to greater reliance of Tg on thyroid hormone therapy instead of performing Tg determination following TSH stimulation. Because TSH stimulation generally increases basal serum Tg by 5-10 fold, significant serum Tg levels (>1-2ng/mL) found after TSH stimulation when using an assay with a functional sensitivity of 0.5-1ng/mL may already be predicted in patients on LT4 treatment without TSH stimulation by a highly sensitive Tg assay when Tg levels are above 0.2ng/mL.

The highest degrees of sensitivity for serum Tg are noted following thyroid hormone withdrawal or stimulation using rhTSH (723). Serum Tg measurements obtained during thyroid hormone suppression of TSH, and, less commonly following TSH stimulation, may fail to identify patients with relatively small amounts of residual tumor (534;599;724;725). These minimal amounts of residual disease are often located in the neck, and performing neck US in these patients offers the best opportunity to recognize or exclude neoplastic disease even when serum Tg is undetectable (266;726;727). Conversely, even TSH-stimulated Tg measurement may

fail to identify patients with clinically significant tumor, due to anti-Tg antibodies or less commonly to defective or absent production and secretion of immunoreactive Tg by tumor cells (599;724). Tg levels should be interpreted in light of the pretest probability of clinically significant residual tumor. An aggressive or poorly differentiated tumor may be present despite low basal or stimulated Tg; in contrast, a minimally elevated stimulated Tg may occur in patients at low risk for clinically significant morbidity (728). Nevertheless, a single rhTSH-stimulated serum Tg <0.5 ng/mL in the absence of anti-Tg antibody has an approximately 98–99.5% likelihood of identifying patients completely free of tumor on follow-up (541;542;544;548;712). Repeating rhTSH-stimulated Tg measurements may not be necessary in most cases when surveillance includes an undetectable basal serum Tg and ultrasonography (555;568). However, there may remain 0.5-3% of patients who will manifest clinical or biochemical recurrence in spite of an initial rhTSH-stimulated Tg of <0.5 ng/ml (543). An undetectable rhTSH-stimulated serum Tg after five years of follow-up may have 100% predictive value for cure (545).

Initial follow-up for low-risk patients (about 85% of postoperative patients) who have undergone total or near-total thyroidectomy and ^{131}I remnant ablation should be based mainly on TSH-suppressed Tg and cervical US, followed by TSH-stimulated serum Tg measurements if the TSH-suppressed Tg testing is undetectable (534;729). However, a Tg assay with a functional sensitivity of 0.1-0.2 ng/mL may reduce the need to perform TSH-stimulated Tg measurements during the initial and long-term follow-up of some patients. In one study of this assay, a T_4-suppressed serum Tg <0.1 ng/mL was only rarely (2.5%) associated with an rhTSH-stimulated Tg >2 ng/mL; however, 61.5% of the patients had baseline Tg elevation >0.1 ng/mL, but only one patient was found to have residual tumor (713). In another study of the same assay (730), a TSH-suppressed serum Tg level was >0.1 ng/mL in 14% of patients, but the false-positive rate was 35% using an rhTSH-stimulated Tg cutoff of >2 ng/mL, raising the possibility of unnecessary testing and treatment. In low risk patients not undergoing ablation, an ultrasensitive Tg was < 1ng/ml in 91%, and < 2 ng/ml in 96% of patients was seen at 9 months after thyroidectomy (594). In a second generation assay, a cut-off of 0.15 ng/ml was shown to have a NPV of 98.6% and 91% specificity for residual disease or potential recurrence (538). The only prospective study also documented increased sensitivity of detection of disease at the expense of reduced specificity (714), and ROC curves have shown that a Tg level on thyroid hormone therapy around 0.2-0.3 ng/mL portends the best sensitivity and specificity for detecting persistent

disease, and indication a rhTSH stimulated Tg level. Employing these sensitive Tg assays, it was concluded that an annual serum Tg on L-T4 treatment with periodic neck ultrasound are adequate for detection of recurrence without need for rhTSH stimulation testing in those patients with a serum Tg<0.2-0.3 ng/mL on thyroid hormone therapy; however, rhTSH stimulation may help to differentiate among patients with a serum Tg>0.2-0.3ng/mL those with a small increase from those with a stimulated Tg>1.5-2ng/mL who are at a higher risk of persistent disease (557). In patients at low to intermediate risk of recurrence, the utility of an undetectable post-operative non-stimulated Tg level is uncertain, with some studies (583;595;596) observing radioiodine avid metastatic foci (usually in neck lymph nodes) in 6-12% of such patients, while another study (581) noted negative scans in 63/63 patients when the baseline Tg was < 0.2 ng/ml. The different results likely relate to both the degree of intermediate vs. higher risk patients in the respective cohorts, the amount of residual thyroid tissue, the elapsed time since surgery, the cut-off for functional sensitivity of the Tg assays, as well as the sensitivity of the post-RAI imaging techniques.

Approximately 20% of patients who are clinically free of disease with serum Tg levels <1 ng/mL during thyroid hormone suppression of TSH (729) will have a serum Tg level >2 ng/mL after rhTSH or thyroid hormone withdrawal at 12 months after initial therapy with surgery and RAI. In this patient population, one third will have identification of persistent or recurrent disease and of increasing Tg levels, and the other two thirds will remain free of clinical disease and will have stable or decreasing stimulated serum Tg levels over time (569;575). However, there may be little likelihood of a rise in serum Tg to >2 ng/ml when basal serum Tg is <0.1 ng/ml if a second generation Tg ICMA with a functional sensitivity of 0.05 ng/ml is employed (731). There is good evidence that a Tg cutoff level above 2 ng/mL following rhTSH stimulation is highly sensitive in identifying patients with persistent tumor (729;732-737). However, the results of serum Tg measurements made on the same serum specimen differ among assay methods (279). Therefore, the Tg cutoff may differ significantly among medical centers and laboratories. Further, the clinical significance of minimally detectable Tg levels is unclear, especially if only detected following TSH stimulation. However, ROC curves have shown that a Tg/T4 level around 0.2-0.3ng/mL portends the best sensitivity and specificity for detecting persistent disease, and indication a rhTSH stimulated Tg level. In these patients, the trend in serum Tg over time will typically identify patients with clinically significant residual disease. A

rising unstimulated or stimulated serum Tg indicates disease that is likely to become clinically apparent (569;738). Tg doubling time may have utility as a predictor of recurrence, analogous to the use of calcitonin doubling time for medullary thyroid cancer (573;739).

[C7] Antithyrogloublin antibodies

The presence of anti-Tg antibodies, which occur in approximately 25% of thyroid cancer patients (740) and 10% of the general population (741), will falsely lower serum Tg determinations in immunometric assays (742). The use of recovery assays in this setting to detect significant interference is controversial (742;743). Serum anti-Tg antibody should be measured in conjunction with serum Tg assay by an immunometric method. Although assay standardization against the International Reference Preparation 65/93 has been recommended (559), a wide ranging variability in assay results and analytical sensitivity of the assay remains (744;745). Use of recovery methods for anti-Tg antibody may suffer variable interferences (559). Anti-Tg antibody may rise transiently post-operatively as an apparent immune reaction to the surgery itself and will more predictably rise after ablation therapy. Anti-Tg antibody should be measured in a different assay if the routine anti-Tg antibody is negative in a patient with surgically proven Hashimoto thyroiditis. It may be useful to measure anti-Tg antibodies shortly after thyroidectomy and prior to ablation as high levels may herald the likelihood of recurrence in patients without Hashimoto thyroiditis (744). Similarly, recurrent or progressive disease is suggested in those patients initially positive for anti-Tg antibody who then become negative but subsequently have rising levels of anti-Tg antibody. Falling levels of anti-Tg antibody may indicate successful therapy (565;744) . Thus, serial serum anti-Tg antibody quantification using the same methodology may serve as an imprecise surrogate marker of residual normal thyroid tissue, Hashimoto thyroiditis, or tumor (559;560;566). Following total thyroidectomy and radioactive iodine remnant ablation, thyroglobulin antibodies usually disappear over a median of about 3 years in patients without evidence of persistent disease (562;566;567). Several studies demonstrate an increased risk of recurrence/persistent disease associated either with a new appearance of antithyroglobulin antibodies or rising titers (560) (561-565). From a clinical perspective, anti-thyroglobulin antibody levels that are declining over time are considered a good prognostic sign while rising antibody levels, in the absence of an acute injury to the thyroid, significantly increases the risk that the patient will subsequently diagnosed with persistent or

recurrent thyroid cancer.

Recent development of liquid chromatography-tandem mass spectrometry assay of thyroglobulin holds promise for accurate Tg measurement in the presence of Tg autoantibodies (746-748) but further studies will be required to validate the assays in terms of functional analytic sensitivity, correlations with immunoassay results, and patient outcomes (749).

[C8] What is the role of serum Tg measurement in patients who have not undergone radioiodine remnant ablation?

■ RECOMMENDATION 64

Periodic serum Tg measurements on thyroid hormone therapy and neck ultrasonography should be considered during follow-up of patients with DTC who have undergone less than total thyroidectomy, and in patients who have had a total thyroidectomy but not RAI ablation. While specific cutoff levels of Tg that optimally distinguish normal residual thyroid tissue from persistent thyroid cancer are unknown, rising Tg values over time are suspicious for growing thyroid tissue or cancer. (**Strong recommendation, Low-quality evidence**)

In low and intermediate risk patients who underwent a total thyroidectomy without remnant ablation, the same strategy of follow-up is used, based on serum Tg determination on LT4 treatment and on neck US at 9-12 months. In most of these patients, neck US does not reveal any suspicious findings and the serum Tg is <1 ng/mL on LT4 treatment, or is low (<2ng/mL) and will remain at a low level or will decrease with time to undetectable level (<1ng/mL) (495). There is no need for routine rhTSH stimulation, because Tg will increase to a value above 1 ng/mL in 50% of the cases, even in those without residual cancer and the magnitude of increase being related to the size of normal thyroid remnants (727). These patients are followed on an annual basis with serum TSH and Tg determination.

In the few patients with a serum Tg that remains elevated over time, especially for those with a rising Tg, remnant ablation with I-131 may be considered with a post therapy-WBS if neck US is negative. There is no evidence in these low risk patients, that a delayed treatment over the post-operative treatment may adversely affect the outcome.

A cohort of 80 consecutive patients with very low-risk papillary thyroid microcarcinoma who had undergone near-total thyroidectomy without postoperative RAI treatment was studied

over 5 years (727). The rhTSH-stimulated serum Tg levels were ≤1 ng/mL in 45 patients (56%) and >1 ng/mL in 35 (44%) patients in whom rhTSH-stimulated Tg levels were as high as 25 ng/mL. The diagnostic WBS (DxWBS) revealed uptake in the thyroid bed but showed no pathological uptake in any patient, and thyroid bed uptake correlated with the rhTSH-stimulated serum Tg levels ($p < 0.0001$). Neck ultrasonography identified lymph node metastases in both Tg-positive and Tg-negative patients. The authors concluded that for follow-up of this group of patients: 1) diagnostic WBS was ineffective at detecting metastases; 2) neck ultrasonography as the main surveillance tool was highly sensitive in detecting node metastases; and 3) detectable rhTSH-stimulated serum Tg levels mainly depended upon the size of thyroid remnants, which suggests that serum Tg determination should be performed primarily on thyroid hormone therapy when using a sensitive (FS ≤0.2 ng/ml) Tg assay. In a series of 290 low risk patients who had not undergone remnant ablation (495), serum Tg levels on LT4 became undetectable (<1ng/mL) within 5-7 years in 95% of the cohort and was <0.1ng/mL in 80% of a subset of these patients when using a sensitive assay confirming the utility of Tg measurement on thyroid hormone treatment for routine follow-up. The frequency of follow-up is uncertain in patients who have not received RAI ablation and have sufficient residual thyroid tissue to produce measurable levels of serum Tg, the magnitude of which will depend upon the mass of residual tissue and the degree of TSH suppression. It appears reasonable to consider periodic measurement of Tg as surveillance for a trend in rising values. Other retrospective analyses have indicated that there is little need for a WBS (750) especially in the presence of an rhTSH-stimulated serum Tg of <0.2 ng/ml (751).

[C9] What is the role of US and other imaging techniques (RAI SPECT-CT, CT, MRI, PET-CT) during follow-up?

[C10] Cervical ultrasonography

■ RECOMMENDATION 65

A) Following surgery, cervical US to evaluate the thyroid bed and central and lateral cervical nodal compartments should be performed at 6–12 months and then periodically, depending on the patient's risk for recurrent disease and Tg status. (**Strong recommendation, Moderate-quality evidence**)

B) If a positive result would change management, ultrasonographically suspicious lymph

nodes ≥ 8-10 mm (see Recommendation 71) in the smallest diameter should be biopsied for cytology with Tg measurement in the needle washout fluid. (**Strong recommendation, Low-quality evidence**)

C) Suspicious lymph nodes less than 8-10 mm in smallest diameter may be followed without biopsy with consideration for FNA or intervention if there is growth or if the node threatens vital structures. (**Weak recommendation, Low-quality evidence**)

D) Low-risk patients who have had remnant ablation, negative cervical US, and a low serum Tg on thyroid hormone therapy in a sensitive assay (<0.2 ng/ml) or after TSH-stimulation (Tg <1 ng/ml) can be followed primarily with clinical examination and Tg measurements on thyroid hormone replacement. (**Weak recommendation, Low-quality evidence**)

Cervical ultrasonography is performed with a high frequency probe (≥ 10 MHz), and is highly sensitive in the detection of cervical metastases in patients with DTC (259;727;752). It should interrogate all lymph node compartments and the thyroid bed. Frequently, neck US does not distinguish thyroid bed recurrences from benign nodules (580;753). When an abnormality is found during the year after surgery in patients without any other suspicious findings, including low serum Tg on thyroid hormone therapy, follow-up may be performed with neck US.

A correlation performed between US findings and pathology at surgery (261) has shown for LN > 7mm in the smallest diameter, that a cystic appearance or hyperechoic punctuations in a context of thyroid cancer should be considered as malignant; lymph nodes with hyperechoic hilum are reassuring; the type of vascularization (central vs peripheral) has a high sensitivity/ specificity; a round shape, a hypoechoic appearance or the loss of the hyperechoic hilum by themselves does not justify a FNAB.

Interpretation of neck US should take into account all other clinical and biological data. In fact, the risk of recurrence is closely related to the initial lymph node status: most LN recurrences occur in already involved compartments; the risk increases with higher number of N1 and higher number of N1 with extra-capsular extension (300) and with macroscopic than with microscopic lymph node metastases (297;754).

In low and intermediate risk patients, the risk of LN recurrence is low (<2%) in patients with undetectable serum Tg level and is much higher in those with detectable/elevated serum Tg. In fact, 1g of neoplastic thyroid tissue will increase serum Tg by ~1ng/ml during LT4 treatment

and by ~2-10 ng/ml following TSH stimulation (731;743). Neck US can detect N1 as small as 2-3 mm in diameter (in whom serum Tg may be low or undetectable), but benefits of their early discovery (<8-10mm) is not demonstrated.

FNAB for cytology and Tg measurement in the aspirate fluid is performed for suspicious lymph nodes ≥8-10 mm in their smallest diameter. US guidance may improve the results of FNAB, in particular for small lymph nodes and those located deep in the neck. However, FNAB is not contributive in a significant proportion (up to 20%) of patients. The combination of cytology and serum Tg determination in the aspirate fluid increases sensitivity (755-757). In cases of lymph node metastases, the Tg concentration in the aspirate fluid is most often elevated (> 10 ng/mL), and concentrations above this level is highly suspicious (265;267;269). A Tg concentration in the aspirate fluid between 1 and 10 ng/mL is infrequent and moderately suspicious, and control of FNA with a Tg measurement in the aspirate fluid should be considered. Also, up to half of the FNAB performed for suspicious US findings are benign, demonstrating that selection of patients for FNAB need to be improved (265;267;758). Non suspicious and small nodes (<8-10 mm in the smallest diameter) can be monitored with neck US.

[C11] Diagnostic whole-body RAI scans

■ **RECOMMENDATION 66**

After the first treatment WBS performed following RAI remnant ablation, low-risk and intermediate-risk patients (lower risk features) with an undetectable Tg on thyroid hormone with negative antithyrogolublin antibodies and a negative US (excellent response to therapy) do not require routine diagnostic WBS during follow-up. (**Strong recommendation, Moderate-quality evidence**)

■ **RECOMMENDATION 67**

A) Diagnostic WBS, either following thyroid hormone withdrawal or rhTSH, 6–12 months after remnant ablation can be useful in the follow-up of patients with high or intermediate risk (higher risk features) of persistent disease (see risk stratification system, section [B19]) and should be done with ^{123}I or low activity ^{131}I. (**Strong recommendation, Low-quality evidence**)

B) SPECT/CT radioiodine imaging is preferred over planar imaging in patients with

uptake on planar imaging to better anatomically localize the radioiodine uptake and distinguish between likely tumors and nonspecific uptake (**Weak recommendation, Moderate-quality evidence**)

Following RAI ablation, when the posttherapy scan does not reveal uptake outside the thyroid bed, subsequent DxWBS have low sensitivity and are usually not necessary in low-risk patients who are clinically free of residual tumor and have an undetectable serum Tg level on thyroid hormone and negative cervical US (534;729;750;759).

Diagnostic WBS is indicated in three primary clinical settings: 1) patients with abnormal uptake outside the thyroid bed on post-therapy WBS, 2) patients with poorly informative post-ablation WBS because of large thyroid remnants with high uptake of I-131 (>2% of the administered activity at the time of WBS) that may hamper the visualisation of lower uptake in neck lymph nodes, and 3) patients with thyroglobulin antibodies, at risk of false negative Tg measurement, even when neck US does no show any suspicious finding (Rosario). I-123 is preferred over I-131 in these rare indications for diagnostic WBS, because it delivers lower radiation doses to the body and provides a better quality of images.

I-131 or I-123 whole body scintigraphy (WBS) includes planar images of a dual-head single photon emission computed tomography (SPECT) gamma-camera of the whole body and spot images of the neck, mediastinum and on any abnormal focus of radioiodine uptake. It may be performed after the administration of either a diagnostic (usually 2-5mCi) or a therapeutic activity (30-150mCi) of radioiodine. Because of the lack of anatomical landmarks on planar images, it is often difficult to differentiate uptake in normal thyroid remnants from lymph node metastases (especially when thyroid remnants are large), uptake in lung metastases from rib lesions or accumulation of radioiodine in intestine or bladder from a pelvic bone lesion. Hybrid cameras combine a dual-head SPECT gamma-camera with a CT scanner in one gantry. This allows direct superimposition of functional and anatomical imaging. The radiation dose delivered to the patient by the low dose CT scan is 2–5 mSv, a dose that is much lower than the dose delivered by the administration of 100 mCi of I-131 (around 50mSv).

Whole body SPECT/CT performed after the administration of a diagnostic or a therapeutic activity (30mCi or more) of radioiodine is associated with (i) an increased number of patients with a diagnosis of metastatic lymph node (ii) a decreased frequency of equivocal

findings (685;689;760-763). Furthermore, the CT portion of the SPECT/CT provides additional information on non–iodine-avid lesions; SPECT/CT changed tumor risk classifications in 25% of the patients according to the International Union Against Cancer classification and in 6% of the patients according to the American Thyroid Association risk of recurrence classification; the SPECT/CT changed treatment management in 24 to 35% of patients, by decreasing the rate of equivocal findings. Finally, SPECT/CT avoids the need for further cross-sectional imaging studies such as contrast CT or magnetic resonance imaging. Neoplastic lesions with low uptake of radioiodine or without any uptake may be a cause of false negative SPECT/CT.

I-124 emits positrons, allowing PET/CT imaging in DTC patients. It is used as a dosimetric and also as a diagnostic tool to localize disease. In fact the I-124 PET/CT permits for each neoplastic focus an accurate measurement of its volume, of the uptake and half life of I-124 in the lesion, therefore allowing a reliable individual dosimetric assessment for each neoplastic focus.

The sensitivity of I-124 PET for the detection of residual thyroid tissue and/or metastatic DTC was reported to be higher than that of a diagnostic I-131 planar WBS (99% *vs.* 66%), but compared with that of a post-therapeutic I-131 WBS in only two small series of patients was similar in one study, except for lung miliary, but this was not confirmed by another study (764-766). I-124 PET/CT has not yet been compared with 1-131 SPECT/CT in large series of patients with DTC. Furthermore, I-124 is not yet widely available for clinical use and is primarily a research tool at this time.

[C12] ^{18}FDG-PET scanning

■ **RECOMMENDATION 68**

A) ^{18}FDG-PET scanning should be considered in high risk DTC patients with elevated serum Tg (generally > 10 ng/ml) with negative radioiodine imaging (**Strong recommendation, Moderate-quality evidence**)

B) ^{18}FDG-PET scanning may also be considered 1) as part of initial staging in poorly differentiated thyroid cancers and invasive Hürthle cell carcinomas, especially those with other evidence of disease on imaging or because of elevated serum Tg levels, 2) as a prognostic tool in patients with metastatic disease to identify lesions and patients at highest risk for rapid disease progression and disease-specific mortality, and 3) as an evaluation of posttreatment response

following systemic or local therapy of metastatic or locally invasive disease. (**Weak recommendation, Low-quality evidence**)

^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is primarily considered in high risk DTC patients with elevated serum Tg (generally > 10 ng/ml) with negative radioiodine imaging. In a meta-analysis of 25 studies that included 789 patients, the sensitivity of FDG-PET/CT was 83% (ranging from 50 to 100%) and the specificity was 84% (ranging from 42 to 100%) in non I-131 avid DTC (767). Factors influencing FDG-PET/CT sensitivity included tumor de-differentiation, larger tumor burden and to a lesser extent, TSH stimulation.

FDG-PET is more sensitive in patients with aggressive histological subtype, including poorly differentiated, tall cell, and Hürthle cell thyroid cancer. FDG uptake on PET in metastatic DTC patients is a major negative predictive factor for response to radioiodine treatment and an independent prognostic factor for survival (768;769). It can also identify lesions with high FDG uptake (SUV) that may be more aggressive and should be targeted for therapy or close monitoring. It is complementary to I-131 WBS, even in the presence of detectable I-131 uptake in metastases, because FDG uptake may be present in neoplastice foci with no I-131 uptake.

In patients with a TSH stimulated Tg ≤10 ng/mL, the sensitivity of FDG is low, ranging from less than 10% to 30%. It is therefore recommended to consider FDG-PET only in DTC patients with a stimulated Tg level equal to or above 10ng/mL. Of course, this level needs to be adapted and lowered in case of aggressive pathological variant of thyroid cancer that may produce low amount of serum Tg. Furthermore, in patients with undetectable Tg levels but with persistent Tg antibodies the level of serum Tg cannot be reliably assessed and FDG-PET may localize disease in some of these patients.

The sensitivity of FDG-PET scanning may be improved with TSH stimulation. A multicentric prospective study on 63 patients showed an increase in the number of lesions detected on the FDG-PET/CT performed after rhTSH stimulation compared to the FDG-PET/CT performed on thyroid hormone treatment and without TSH stimulation (770). However, the sensitivity for detecting patients with at least one tumor site was not improved by the rhTSH stimulation. In this study, the lesions found only by rhTSH-PET contributed adequately to an altered therapeutic plan in four patients (6%), and the clinical benefit of identifying these

additional small foci remains to be proven. Its clinical benefit might be higher in patients with normal neck and chest CT scan and normal neck ultrasonography. A meta-analysis on 7 studies including the previous study and totalizing 168 patients confirmed these results and showed that FDG-PET/CT performed following TSH stimulation altered clinical management in only 9% of patients.

Results of FDG-PET/CT might alter the indications for I-131 treatment or the decision for surgical removal of small tumor foci with FDG uptake. The frequency of false positive lesions varies among series from 0 to 39%, and this high number justifies a FNAB with cytology and Tg measurement in the aspirate fluid in cases where surgery is planned, based on FDG-PET results. The higher sensitivity of neck ultrasonography for the detection of small metastatic lymph node should be noted, with FDG-PET being more sensitive for some locations such as the retropharyngeal or the retro-clavicular regions.

[C13] CT and MRI imaging

■ **RECOMMENDATION 69**

A) Cross-sectional imaging of the neck and upper chest (CT, MRI) with intravenous contrast should be considered 1) in the setting of bulky and widely distributed recurrent nodal disease where ultrasound may not completely delineate disease, 2) in the assessment of possible invasive recurrent disease where potential aerodigestive tract invasion requires complete assessment or 3) when neck ultrasound is felt to be inadequately visualizing possible neck nodal disease (high Tg, negative neck US) (**Strong recommendation, Moderate-quality evidence**).

B) CT imaging of the chest without intravenous contrast (imaging pulmonary parenchyma) or with intravenous contrast (to include the mediastinum) should be considered in high risk DTC patients with elevated serum Tg (generally > 10 ng/ml) with or without negative radioiodine imaging (**Strong recommendation, Moderate-quality evidence**)

C) Imaging of other organs including MRI brain, MR skeletal survey, and/or CT or MRI of the abdomen should be considered in high risk DTC patients with elevated serum Tg (generally > 10 ng/ml) and negative neck and chest imaging, who have symptoms referable to those organs, or who are being prepared for TSH-stimulated RAI therapy and may be at risk for complications of tumor swelling (**Strong recommendation, Low-quality evidence**)

In patients with elevated or rising Tg or Tg Ab and no evidence of disease on neck US or RAI imaging (if performed), CT imaging of the neck and chest may be considered. The frequency of positive anatomic imaging increases with higher serum Tg levels above 10 ng/ml. CT is the most frequently recommended first line technique to search for lymph node metastases in patients with squamous cell carcinoma of the head and neck, and an injection of contrast medium is mandatory for the analysis of the neck and mediastinum (771). Radioiodine can be administered 4-8 weeks following the injection of contrast medium, because at that time a majority of the iodine contamination has disappeared in most patients (278). Diagnostic CT scan may complement neck US for the detection of macrometastases in the central compartment, in the mediastinum and behind the trachea (272-274), and is the most sensitive tool for the detection of micro-metastases in the lungs. Before revision surgery is contemplated, presumptive recurrent neck targets must be defined by high-resolution radiographic anatomic studies such as ultrasound or spiral axial CT scan in complement of FDG-PET or RAI, and must be robustly defined to allow for adequate preoperative mapping and definitive surgical localization. In addition to nodal assessment axial scanning including CT scan with contrast has utility in the evaluation of primary recurrent invasive disease and relationships with vessels. Such patients may present with hoarseness, vocal cord paralysis on laryngeal exam, progressive dysphagia or mass fixation to surrounding structures respiratory symptoms including stridor or hemoptysis and lesions with rapid progression/enlargement. Such lesions are incompletely evaluated with ultrasound alone and axial CT scanning with contrast medium is indicated.

The use of MRI has also been advocated for imaging the neck and the mediastinum. It is performed without and with injection of gadolinium chelate as contrast medium and does not require any injection of iodine contrast medium. The performance of MRI for imaging the neck and mediastinum have not been directly compared with CT on large numbers of thyroid cancer patients (772-774). Compared to CT scan, it may better delineate any involvement of the aerodigestive tract (775;776). It is often used as second line imaging technique in patients with demonstrated or suspicious lesions in the supra-hyoid region on CT scan in order to better delineate these lesions from soft tissues. In the lower part of the neck, movements of the aerodigestive axis during the procedure that may last several minutes will decrease the quality of images (374). Endoscopy of the trachea and or esophagus, with or without ultrasonography, looking for evidence of intraluminal extension can also be helpful in cases of suspected

areodigestive tract invasion. MRI is less sensitive than CT scan for the detection of lung micronodules.

Finally, whether these imaging techniques (CT and MRI) should be performed for diagnostic purposes or whether an FDG-PET scan should be performed as the first line imaging procedure for diagnosis is still a matter of debate: in the past, CT scan with injection of contrast medium was more sensitive for the detection of lymph node metastases (777), but with modern PET/CT apparatus, the CTscan of the PET/CT is reliable as a CTscan used for radiology, and most lesions can be found on FDG-PET scanning, even if no injection of contrast medium has been performed. Delineation between lymph node metastases or local recurrence and vessels or the aerodigestive axis is often not well visualized on FDG-PET/CT in the absence of contrast injection, and if necessary other imaging techniques (CT and MRI with contrast medium) may be performed especially for a preoperative work-up. As a result, most patients with extensive disease should be considered for FDG-PET/CT and CT imaging with contrast and some patients will also be considered for MRI imaging.

This imaging strategy is applied in patients with elevated serum Tg and no other evidence of disease, starting with a FDG-PET/CT (767;778). In the past an empiric treatment was used in such patients, but recent studies have shown that FDG-PET imaging is more sensitive and should be performed as first line, with empiric RAI treatment being considered only for those patients with no detectable FDG uptake.

[C14] Using ongoing risk stratification (response to therapy) to guide disease long-term surveillance and therapeutic management decisions

Ongoing risk stratification allows the clinician to continue to provide individualized management recommendations as the risk estimates evolve over time. While the specific details of how surveillance and therapeutic strategies should be modified over time as a function of response to therapy re-classification within each ATA risk category remains to be defined, we do endorse the following concepts (more details in Table 13):

Excellent Response: An excellent response to therapy should lead to a decrease in the intensity and frequency of follow up and the degree of TSH suppression (this change in management will be most apparent in ATA intermediate and high risk patients)

Biochemical Incomplete Response: If associated with stable or declining serum Tg values, a biochemical incomplete response should lead to continued observation with ongoing TSH suppression in most patients. Rising Tg or Tg antibody values should prompt additional imaging and potentially additional therapies.

Structural Incomplete Response: A structural incomplete response may lead to additional treatments or ongoing observation depending on multiple clinico-pathologic factors including the size, location, rate of growth, RAI avidity, FDG avidity, and specific pathology of the structural lesions.

Indeterminate Response: An indeterminate response should lead to continued observation with appropriate serial imaging of the non-specific lesions and serum Tg monitoring. Non-specific findings that become suspicious over time or rising Tg or Tg Ab levels can be further evaluated with additional imaging or biopsy.

[C15] What is the role of TSH suppression during thyroid hormone therapy in the long-term follow-up of DTC?

■ **RECOMMENDATION 70**

A) In patients with structural or biochemical incomplete response to therapy, the serum TSH should be maintained below 0.1 mU/L indefinitely in the absence of specific contraindications. (**Strong recommendation, Moderate-quality evidence**)

B) In patients with an excellent (clinically and biochemically free of disease) or indeterminate response to therapy, but who presented with high risk disease, consideration should be given to maintaining thyroid hormone therapy to achieve serum TSH levels of 0.1–0.5 mU/L for up to 5 years after which the degree of TSH suppression can by reduced with continued surveillance for recurrence. (**Weak recommendation, Low-quality evidence**)

C) In patients with an excellent (clinically and biochemically free of disease) or indeterminate response to therapy, especially those at low risk for recurrence, the serum TSH may be kept within the low reference range (0.5–2 mU/L). (**Strong recommendation, Moderate-quality evidence**)

D) In patients who have not undergone remnant ablation who demonstrate an excellent or indeterminate response to therapy with a normal neck US, and low or undetectable suppressed serum Tg, and Tg or TgAb that are not rising, the serum TSH can be allowed to rise to the low reference range (0.5–2 mU/L). (**Weak recommendation, Low-quality evidence**)

A meta-analysis has suggested an association between thyroid hormone suppression therapy and reduction of major adverse clinical events (691). The appropriate degree of TSH suppression by thyroid hormone therapy is still unknown, especially in high-risk patients rendered free of disease. A constantly suppressed TSH (0.05 mU/L) was found in one study to be associated with a longer relapse-free survival than when serum TSH levels were always 1 mU/L or greater, and that the degree of TSH suppression was an independent predictor of recurrence in multivariate analysis (695). Conversely, another large study found that disease stage, patient age, and ^{131}I therapy independently predicted disease progression, but that the degree of TSH suppression did not (244). A third study showed that during LT_4 therapy the mean Tg levels were significantly higher when TSH levels were normal than when TSH levels were suppressed (<0.5 mU/L) but only in patients with local or distant recurrence (779). A fourth study of 2936 patients found that overall survival improved significantly when the TSH was suppressed to <0.1 mU/L in patients with NTCTCSG stage III or IV disease and to a range of 0.1 to about 0.5 in patients with NTCTCSG stage II disease; however, there was no incremental benefit from suppressing TSH to undetectable levels in stage II patients, and suppression of TSH was of no benefit in patients with stage I disease (622), and higher degrees of suppression to TSH of <0.03 mU/L provided no additional benefit (692). Another study found that a serum TSH threshold of 2 mU/L differentiated best between patients free of disease and those with relapse or cancer-related mortality (696). A prospective study showed that DFS for low risk patients without TSH suppression was not inferior to patients with TSH suppression (780). No prospective studies have been performed examining the risk of recurrence and death from thyroid cancer associated with varying serum TSH levels, based on the criteria outlined above in [C14] for the absence of tumor at 6–12 months post-surgery and RAI ablation.

A recent observational study demonstrated increased risk of all-cause and cardiovascular mortality in DTC patients compared with a control population (781). The authors also showed that survival in the DTC patients was lower when the serum TSH was <0.02 mU/L, which is

particularly relevant in patients with an excellent response to therapy in whom overtreatment should be avoided. An approach to balancing the risks of thyroxine suppression against the risks of tumor recurrence or progression has been presented in a recent review (693). This review helped to define patients at low, intermediate and high risk of complications from TSH suppression therapy. Table 15 provides recommendations for TSH ranges based on response to thyroid cancer therapy weighed against risks of levothyroxine therapy, which is adapted from the review by Biondi and Cooper (693). In patients at high risk of adverse effects on heart and bone by TSH suppression therapy, the benefits of TSH suppression should be weighed against the potential risks. In peri- and postmenopausal women at risk for bone loss, adjunctive therapy with calcium supplements, Vitamin D, and other bone enhancing agents should be considered. β-adrenergic blocking drugs may be considered in older patients to obviate increases in left ventricular mass and tachycardia (782) (783).

[C16] What is the most appropriate management of DTC patients with metastatic disease?

Metastases may be discovered at the time of initial disease staging, or may be identified during longitudinal follow-up. If metastases are found following initial therapy, some patients may subsequently experience a reduction in tumor burden with additional treatments that may offer a survival or palliative benefit (784-788). The preferred hierarchy of treatment for metastatic disease (in order) is surgical excision of locoregional disease in potentially curable patients, ^{131}I therapy for RAI-responsive disease, external beam radiation or other directed treatment modalities such as thermal ablation, TSH-suppressive thyroid hormone therapy for patients with stable or slowly progressive asymptomatic disease, and systemic therapy with kinase inhibitors (preferably by use of FDA-approved drugs or participation in clinical trials), especially for patients with significantly progressive macroscopic refractory disease. Clinical trials or kinase inhibitor therapy may be tried before external beam radiation in special circumstances, in part because of the morbidity of external beam radiation and its relative lack of efficacy. However, localized treatments with thermal (radiofrequency or cryo-) ablation (789), ethanol ablation (790), or chemo-embolization (791), may be beneficial in patients with a single or a few metastases, in those with metastases at high risk of local complications, and should be performed in such patients before the initiation of any systemic treatment. These modalities may

control treated metastases, may avoid local complications and may delay initiation of systemic treatment. Additionally, surgical therapy in selected incurable patients is important to prevent complications in targeted areas, such as the central nervous system (CNS) and central neck compartment. Conversely, conservative intervention with TSH-suppressive thyroid hormone therapy may be appropriate for selected patients with stable asymptomatic local metastatic disease, and most patients with stable asymptomatic non-CNS distant metastatic disease.

[C17] What is the optimal directed approach to patients with suspected structural neck recurrence?

■ RECOMMENDATION 71

Therapeutic compartmental central and/or lateral neck dissection, sparing uninvolved vital structures, should be performed for patients with biopsy proven persistent or recurrent disease for central neck nodes greater than or equal to 8 mm and lateral neck nodes greater than or equal to 10 mm in the smallest dimension which can be localized on anatomic imaging . (**Strong recommendation, Moderate-quality evidence**)

Persistent or recurrent nodal disease may result in local invasion and is the source of considerable patient and physician anxiety (792). However, several observational studies suggest low-volume recurrent nodal disease can be indolent and can be managed through active surveillance although not all lesions in these series are documented as malignant (580;793). Bulky or invasive recurrent disease is best treated surgically (282;794-797).

The judgment to offer surgery for recurrent nodal disease in the neck is made with equipoise in two opposing decision elements: 1) the risks of revision surgery (which are typically higher than primary surgery due to scarring from previous surgery (798) balanced with 2) the fact that surgical resection generally represents the optimal treatment of macroscopic gross nodal disease over other treatment options. An important element in this decision-making process is the availability of surgical expertise specifically in the performance of revision thyroid cancer nodal surgery, which is a discrete surgical skill set. The decision to treat cervical nodal recurrence surgically should be made with an appreciation of distant disease presence and progression but may be undertaken even in the setting of known distant metastasis for palliation of symptoms and prevention of aerodigestive tract obstruction. The decision for treatment and surgery specifically is best derived through collaborative team approach involving surgery,

endocrinology and importantly the patient and family (799). Therefore, cytologic confirmation of disease can be deferred if the findings of the FNA will not lead to additional evaluation or treatment. While we generally recommend cytologic confirmation of abnormal radiographic findings prior to surgical resection, we recognize that this may not be necessary (or possible) in every case (e.g. radiographic findings with a very high likelihood of malignancy, or the specific location of the lymph node makes it difficult/impossible to biopsy).

[C18] Nodal Size Threshold

Surgery is considered with the recognition of clinically apparent, macroscopic nodal disease through radiographic analysis including ultrasound (Table 8) and/or axial (CT) scanning rather than through isolated thyroglobulin (Tg) elevation (274;297;800). Given the risks of revision nodal surgery a clearly defined preoperative radiographic target is mandatory. The risks of surgery relate in part to the exact location of the target node(s) and whether the compartment in question has been previously dissected such as recurrent central neck nodes after primary thyroidectomy. This target must be defined by high-resolution radiographic anatomic studies such as ultrasound or spiral CT scan with contrast, as a complement to FDG-PET/CT or RAI-SPECT/CT and must be robustly defined to allow for adequate preoperative mapping and definitive surgical localization(274;800). Ultrasound guided FNA for cytology with Tg measurement in the aspiration sample can be performed in the setting of radiographically suspicious nodal recurrence keeping in mind that Tg rinsing may be positive with thyroid bed persistent benign thyroid remnant tissue if the patient has not been treated with radioactive iodine. Charcoal tattoing under US guidance may help the surgeon to localize the lymph node to be removed during surgery (305).

FNA biopsied malignant central neck nodes greater than or equal to 8 mm and lateral neck nodes greater than or equal to 10 mm which can be localized on anatomic imaging (ultrasound+/- axial CT) can be considered surgical targets [Tufano 2014 submitted Thyroid, Urken 2014 submitted Thyroid(274;801;802) Short axis nodal diameter measurement is optimally employed in surgical decision-making for nodal malignancy. Smaller lesions are probably best managed with active surveillance (observation) with serial cross sectional imaging reserving FNA and subsequent intervention for documented structural disease progression. However, multiple factors in addition to size should be taken into account when considering surgical options including proximity of given malignant nodes to adjacent vital structures and the

functional status of the vocal cords. Patient co-morbidities, patient motivation and emotional concerns should also be taken into account as well as primary tumor factors (high-grade histology, Tg doubling time, radioactive iodine avidity, FDG-PET avidity, and presence of molecular markers associated with aggressive behavior). Through thorough patient and multidisciplinary collaborative discussions, metastatic nodes greater than 8-10 mm can be carefully observed in properly selected patients with serial clinical and radiographic follow-up offering surgery if they progress during follow-up and conservative follow up if they are stable over time.

[C19]Extent of Nodal Surgery

Because of the increased risk of recurrence with focal "berry picking" techniques, compartmental surgery is recommended (803;804). Planned compartmental dissection should be titrated and be more limited depending on the surgeons judgment of procedural safety as it relates to scarring/distortion of anatomy (from prior surgery and or past radiation therapy) and the perception of impending complications. Typical revision lateral neck dissection involves regions 2, 3, and 4 while revision central neck dissection includes at least one paratracheal region with pre-laryngeal and pretracheal sub compartments. Bilateral central neck dissection due to its risks of bilateral nerve injury and permanent hypoparathyroidism is offered only when dictated by disease distribution.

Basal Tg decreases by 60 to 90% after compartmental dissection for recurrent nodal disease in modern series but only 30 to 50% of patients have unmeasurable basal Tg after such surgery and it is difficult to predict who will respond to surgery with Tg reduction (578;579;585;801;805-819). However most series suggest surgery results in high clearance rate of structural disease in over 80% of patients (Urken submitted Thyroid 2014)(802;818).

[C20] Ethanol Injection

Percutaneous ethanol injection (PEI) for patients with metastatic lymph node (LN) is gaining interest as a nonsurgical directed therapy for patients with recurrent DTC. Most of the studies limited PEI to patients who had undergone previous neck dissections and RAI treatment, those who had FNA proven DTC in the LN and those with no known distant metastases.

One of the first studies examining the effectiveness of local metastatic LN control by PEI treated 14 patients with 29 LN (790). Twelve of 14 patients had good locoregional control in this study with short-term follow-up (mean 18 months). The largest study to date treated 63 patients with 109 metastatic LN between the years 2004-2009 (820). 92 LN (84%) were successfully ablated in this retrospective study with a mean follow-up of 38 months, and most required 1-3 treatment sessions. There were no major complications.

A recent study retrospectively reviewed 25 patients who had 37 LN ablated between the years 1994-2012, with a relatively long follow-up of a mean of 65 months (821). All LN were successfully 'ablated' in 1-5 treatment sessions by lack of flow on US. Most of the LN decreased in size and 46% completely disappeared. Serum Tg levels were reduced in most patients and brought into an acceptable range (< 2.4 ng/ml) in 82% of patients with negative Tg antibodies. There were no serious or long-term complications. Another recent study also demonstrated safety and efficacy of PEI in 21 patients with 41 metastatic LN (822). These investigators treated patients with only one session and 24% of patients had a recurrence at the site of the injection.

Limitations of many of the studies included small numbers of patients, relatively short-term FU, and many patients with small LN (<5-8 mm) were treated.

A general consensus from studies and reviews is that PEI should be considered in patients who are poor surgical candidates. Many patients will likely need more than one treatment session and LN > 2 cm may be difficult to treat with PEI. Focal PEI treatment does represent a non surgical form of "berry picking" which has been condemned in the surgical literature for many years as incomplete treatment. Formal neck compartmental dissection is still the first-line therapy in DTC patients with clinically apparent or progressive LN metastases. When deciding for the optimal strategy of care for patients LN metastases, previous treatment modalities should also be taken into consideration.

[C21] Radiofrequency or Laser Ablation

The use of radiofrequency ablation (RFA) with local anesthesia in the treatment of recurrent thyroid cancer has been associated with a mean volume reduction that ranges between approximately 55-95% (823;824), and complete disappearance of the metastatic foci in 40-60% of the cases (789;824;825). As with alcohol ablation, multiple treatment sessions are often

required. Complications include discomfort, pain, skin burn and changes in the voice (826). Similar to ETOH ablation techniques, it appears that RFA may be most useful in high risk surgical patients or in patient refusing additional surgery rather than as a standard alternative to surgical resection of metastatic disease (825-827). More recently, preliminary findings using ultrasound guided laser ablation for treatment of cervical lymph node metastases have been reported (828).

[C22] Other therapeutic options

While sterotactic radiation can be successfully used to treat isolated metastatic disease foci, it is seldom considered for loco-regional recurrences unless the disease is not surgically resectable. Furthermore, empiric RAI therapy for structurally identifiable disease that is not RAI avid by diagnostic scanning is very unlikely to have a significant tumoricidal effect and is therefore not generally recommended (829). Likewise, systemic therapies (such as cytotoxic chemotherapy or kinase inhibitors) for loco-regional disease are considered only after all surgical and radiation therapy options have been exhausted.

[C23] What is the surgical management of aerodigestive invasion?

■ RECOMMENDATION 72

When technically feasible, surgery for aerodigestive invasive disease is recommended in combination with RAI and/or external beam radiotherapy. (**Strong Recommendation, Moderate-quality evidence**)

For tumors that invade the upper aerodigestive tract, surgery combined with additional therapy such as ^{131}I and/or external beam radiation is generally advised (830;831)). Patient outcome is related to complete resection of all gross disease with the preservation of function, with techniques ranging from shaving tumor off the trachea or esophagus for superficial invasion, to more aggressive techniques when the trachea is more deeply invaded (e.g., direct intraluminal invasion) including tracheal resection and anastomosis or laryngopharyngoesophagectomy (832-834). Surgical decision making can be complex and must balance oncologic surgical completeness with preservation of upper aerodigestive track head and neck function. In some circumstances such surgery represents a possible attempt for cure and in

other circumstances offers significant regional neck palliation in patients with distant metastasis with impending asphyxiation or significant hemoptysis (374;831) .

[C24] How should RAI therapy be considered for locoregional or distant metastatic disease?

For regional nodal metastases discovered on DxWBS, RAI may be employed in patients with low volume disease or in combination with surgery, although surgery is typically preferred in the presence of bulky disease or disease amenable to surgery found on anatomic imaging such as US, CT scanning, or MRI, and ethanol ablation may be used in some patients for isolated lymph node metastases. Radioiodine is also used adjunctively following surgery for regional nodal disease or aerodigestive invasion if residual RAI avid disease is present or suspected. Significant variation exists nationally in the US in regard to radioiodine use, irrespective of the degree of disease or risk of recurrence (835;836). However, there are no randomized, controlled clinical trials demonstrating better patient outcomes after radioiodine therapy. One retrospective analysis indicated that a delay in radioiodine therapy of six months or more was associated with disease progression and reduced survival (837). In one study of 45 patients with persistent serum Tg elevation after reoperation for locoregional recurrence, adjuvant RAI therapy demonstrated no benefit (838).

[C25] Administered activity of ^{131}I for locoregional or metastatic disease

■ **RECOMMENDATION 73**

A) Although there are theoretical advantages to dosimetric approaches to the treatment of locoregional or metastatic disease, no recommendation can be made about the superiority of one method of RAI administration over another (empiric high activity vs blood and/or body dosimetry vs lesional dosimetry) (**No Recommendation, Insufficient evidence)**

B) Empirically administered amounts of ^{131}I exceeding 150 mCi that often potentially exceed the maximum tolerable tissue dose should be avoided in patients over age 70 years. (**Strong recommendation, Moderate-quality evidence)**

Despite the apparent effectiveness of ^{131}I therapy in many patients, the optimal therapeutic activity remains uncertain and controversial (835;839). There are three approaches to

^{131}I therapy: empiric fixed amounts, therapy determined by the upper limit of blood and body dosimetry (840;841), (842-847), and quantitative tumor or lesional dosimetry (848;849). Dosimetric methods are often reserved for patients with distant metastases or unusual situations such as renal insufficiency (850;851), children (852;853), the elderly, those with extensive pulmonary metastases or when therapy with rhTSH stimulation is deemed necessary (854). Comparison of outcome among these methods from published series is difficult (835;837;840). No prospective randomized trial to address the optimal therapeutic approach has been published. One retrospective study concluded that patients with loco-regional disease were more likely to respond after dosimetric therapy than after empiric treatment (855). Another study demonstrated improved efficacy of administration of dosimetric maximal activity after failure of empiric dosage (856). Arguments in favor of higher activities cite a positive relationship between the total ^{131}I uptake per tumor mass and outcome (848), while others have not confirmed this relationship (857). In the future, the use of ^{123}I or ^{131}I with modern SPECT/CT or ^{124}I PET-based dosimetry may facilitate whole-body and lesional dosimetry (858-860). In certain settings, e.g., in the patients with radiation-induced thyroid cancer seen after the Chernobyl accident, radioiodine treatment may be associated with good outcomes even in high risk patients with metastatic disease (861).

The efficacy of RAI therapy is related to the mean radiation dose delivered to neoplastic foci and also to the radiosensitivity of tumor tissue (862). The radiosensitivity is higher in patients who are younger, with small metastases from well differentiated papillary or follicular carcinoma and with uptake of RAI but no or low FDG uptake.

The maximum tolerated radiation absorbed dose (MTRD), commonly defined as 200 rads (cGy) to the blood, is potentially exceeded in a significant number of patients undergoing empiric treatment with various amounts of ^{131}I. In one study (863) 1–22% of patients treated with ^{131}I according to dosimetry calculations would have theoretically exceeded the MTRD had they been empirically treated with 100–300 mCi of ^{131}I. Another study (864) found that an empirically administered ^{131}I activity of 200 mCi would exceed the MTRD in 8–15% of patients younger than age 70 and 22–38% of patients aged 70 years and older. Administering 250 mCi empirically would have exceeded the MTRD in 22% of patients younger than 70 and 50% of patients 70 and older. These estimates imply the need for caution in administering empiric

activities higher than 100-150 mCi in certain populations such as elderly patients.

[C26] Use of rhTSH (Thyrogen™) to prepare patients for ^{131}I therapy for locoregional or metastatic disease.

■ RECOMMENDATION 74

There are currently insufficient outcome data to recommend rhTSH-mediated therapy for all patients with metastatic disease being treated with ^{131}I. (**No Recommendation, Insufficient evidence)**

■ RECOMMENDATION 75

Recombinant human TSH–mediated therapy may be indicated in selected patients with underlying co-morbidities making iatrogenic hypothyroidism potentially risky, in patients with pituitary disease who are unable to raise their serum TSH, or in patients in whom a delay in therapy might be deleterious. Such patients should be given the same or higher activity that would have been given had they been prepared with hypothyroidism or a dosimetrically determined activity. (**Strong Recommendation, Low-quality evidence)**

No randomized trial comparing thyroid hormone withdrawal therapy to rhTSH-mediated therapy for treatment of metastatic disease has been reported, but there is a growing body of nonrandomized studies exploring the use of rhTSH to prepare patients for therapy of metastatic disease (660;865-874). One small comparative study showed that the radiation dose to metastatic foci is lower with rhTSH than that following withdrawal (875). Many of these case reports and series report disease stabilization or improvement in some patients following rhTSH-mediated ^{131}I therapy, but whether the efficacy of this preparation is comparable to thyroid hormone withdrawal is unknown. Extreme or prolonged elevations of TSH from either THW or rhTSH may acutely stimulate tumor growth and mass of metastases (870;876-878). With metastatic deposits in the brain or in close relation to the spinal cord or the superior vena cava, such swelling may severely compromise neurologic function or produce a superior vena caval syndrome, respectively. When distant metastases are evident, MRI imaging of the brain and spine is recommended to detect the presence of critical metastases prior to treatment. When detected, institution of temporary high dose corticosteroid therapy is recommended in an attempt to limit the risk of acute tumor swelling and compromised function. Dexamethasone has been

employed in doses of 2-4 mg q 8 hrs starting 6-12 hours prior to rhTSH and radioiodine dosing or after 10-12 days of THW, with the steroids continued in a tapering dosage schedule for one week post-therapy, or for 48-72 hrs after rhTSH administration, or for 72 hrs after re-institution of thyroxine therapy when THW was employed (867). In patients with these critical metastases, consideration should be given to preparation with either a reduced dose of rhTSH or to attenuating the degree and duration of endogenous TSH elevation after THW while monitoring serum TSH levels. Satisfactory radioiodine treatment with either empiric or dosimetric activities should be feasible after achieving TSH levels of 30-50 mU/L. When THW has been employed, levothyroxine therapy should recommence once the dose of radioiodine is administered in order to reduce the duration of TSH elevation.

[C27] Use of lithium in ^{131}I therapy

■ **RECOMMENDATION 76**

Since there are no outcome data that demonstrate a better outcome of patients treated with lithium as an adjunct to ^{131}I therapy, the data are insufficient to recommend lithium therapy. (**No Recommendation, Insufficient evidence)**

Lithium inhibits iodine release from the thyroid without impairing iodine uptake, thus enhancing ^{131}I retention in normal thyroid and tumor cells (879). One study (880) found that lithium increased the estimated ^{131}I radiation dose in metastatic tumors an average of more than twofold, but primarily in those tumors that rapidly cleared iodine. On the other hand, a different study was unable to document any clinical advantage of lithium therapy on outcome in patients with metastatic disease, despite an increase in RAI uptake in tumor deposits (881). Lithium use may be associated with adverse events and needs to be precisely managed.

[C28] How should distant metastatic disease to various organs be treated?

The overall approach to treatment of distant metastatic thyroid cancer is based upon the following observations and oncologic principles:

1. Morbidity and mortality are increased in patients with distant metastases, but individual prognosis depends upon factors including histology of the primary tumor, distribution

and number of sites of metastasis (e.g., brain, bone, lung), tumor burden, age at diagnosis of metastases, and ^{18}FDG and RAI avidity (786;873;882-888).

2. Improved survival is associated with responsiveness to directed therapy and/or RAI (786;873;882-888).

3. In the absence of demonstrated survival benefit, certain interventions can provide significant palliation or reduce morbidity (791;889-891).

4. Treatment of a specific metastatic area must be considered in light of the patient's performance status and other sites of disease; e.g., 5–20% of patients with distant metastases die from progressive cervical disease (888;892).

5. Longitudinal re-evaluation of patient status and continuing re-assessment of potential benefit and risk of intervention is required.

6. In the setting of overall poor anticipated outcome of patients with radiographically evident or symptomatic metastases that do not respond to RAI, the complexity of multidisciplinary treatment considerations and the availability of prospective clinical trials should encourage the clinician to refer such patients to tertiary centers with particular expertise.

8. Mutation profiling of metastatic tumor (to detect abnormalities in genes such as BRAF, TERT, Ras, or Pax8-PPARγ) may prove to be of value for estimating patient prognosis or for predicting response to treatments such as targeted kinase inhibitors. However, evidence is currently insufficient to support a prognostic role of any specific gene testing for prognosis, and is absent to support selection of any specific therapy proven to enhance patient outcomes. Thus, routine mutation profiling cannot be recommended at this time outside of research settings.

There is little if any benefit derived from the treatment of radioiodine refractory differentiated thyroid cancer with radioiodine (893). Although radioiodine refractory tumors often may harbor BRAF V600E mutations and radioiodine avid tumors are overrepresented with RAS mutations, radioiodine therapy has not been shown to be effective in patients with either mutation (894). However, in one preliminary trial, a new MEK inhibitor increased expression of the sodium iodide symporter allowing increased radioiodine uptake and treatment in a subgroup of patients (895).

[C29] Treatment of pulmonary metastases

■ **RECOMMENDATION 77**

A) Pulmonary micrometastases should be treated with RAI therapy, and repeated every 6–12 months as long as disease continues to concentrate RAI and respond clinically, because the highest rates of complete remission are reported in these subgroups. (**Strong recommendation, Moderate-quality evidence)**

B) The selection of RAI activity to administer for pulmonary micrometastases can be empiric (100–200 mCi, or 100-150 mCi for patients ≥70 yo) or estimated by dosimetry to limit whole-body retention to 80 mCi at 48 hours and 200 cGy to the red bone marrow. (**Strong recommendation, Moderate-quality evidence**)

■ RECOMMENDATION 78

Radioiodine-avid macronodular metastases may be treated with RAI and treatment may be repeated when objective benefit is demonstrated (decrease in the size of the lesions, decreasing Tg), but complete remission is not common and survival remains poor. The selection of RAI activity to administer can be made empirically (100–200 mCi) or by lesional dosimetry or whole-body dosimetry if available in order to limit whole-body retention to 80 mCi at 48 hours and 200 cGy to the red bone marrow. (**Weak Recommendation, Low-quality evidence**)

In the management of the patient with pulmonary metastases, key criteria for therapeutic decisions include 1) size of metastatic lesions (macronodular typically detected by chest radiography; micronodular typically detected by CT; lesions beneath the resolution of CT); 2) avidity for RAI and, if applicable, response to prior RAI therapy; and 3) stability (or lack thereof) of metastatic lesions. Pulmonary pneumonitis and fibrosis are rare complications of high-dose radioactive iodine treatment. Dosimetric approaches to therapy with a limit of 80 mCi whole-body retention at 48 hours and 200 cGy to the red bone marrow should be considered in patients with diffuse ^{131}I pulmonary uptake (896). If pulmonary fibrosis is suspected, then appropriate periodic pulmonary function testing and consultation should be obtained. The presence of pulmonary fibrosis may limit the ability to further treat metastatic disease with RAI (897).

Patients with pulmonary micrometastases that are RAI-avid have the highest rates of complete remission after treatement with radioiodine (882;887;898;899). These pateints should be treated with RAI therapy repeated every 6–12 months as long as disease continues to

concentrate RAI and respond clinically.

A precise definition of a 'responding clinically' is not feasible given the wide variation in disease presentation and response to therapy. A meaningful response to RAI treatment is generally associated with a significant reduction in serum Tg and/or in the size or rate of growth of metastases or structurally apparent disease. In contrast, a reduction in serum Tg and in RAI uptake with no concomitant decrease or with an increase in tumor size suggests refractoriness to RAI therapy. In the presence of widespread metastases, especially when in bone, additional RAI may temporarily stabilize progression but is unlikely to result in cure, and the risks of bone marrow suppression or pulmonary fibrosis should generate caution when considering repeated doses of RAI. Absolute neutrophil count (ANC) and platelet counts are the usual markers of bone marrow suppression, and pulmonary function testing including DLCO can be markers of pulmonary toxicity. Other approaches (see sections C36-C41) should be considered once maximal cumulative tolerable radiation doses have been administered.

Macronodular pulmonary metastases may also be treated with RAI if demonstrated to be iodine avid. How many doses of RAI to give and how often to give it is a decision that must be individualized based on the disease response to treatment, age of the patient, and the presence or absence of other metastatic lesions (882;887). The presence of significant side effects including bone marrow suppression and salivary gland damage may temper enthusiasm for additional RAI therapy (900), and risk of second malignancies after radioiodine treatment remains controversial (901-903).

No clear benefit may be gained by treatment of patients with elevated serum thyroglobulin who have metastases that are non-avid for radioiodine on diagnostic RAI WBS (904). While some reduction in serum thyroglobulin may be observed after such empiric therapy, one analysis concluded that there was no good evidence either for against such treatment (905). In one small retrospective series of patients with structural disease but negative 131-I whole body scans, additional RAI therapy was associated with stability of disease in 44% but progression of structural disease in 56% of the patients (829).

[C30] RAI treatment of bone metastases.

■ RECOMMENDATION 79

A) RAI therapy of iodine-avid bone metastases has been associated with improved

survival and should be employed, although RAI is rarely curative. (**Strong recommendation, Moderate-quality evidence**)

B) The RAI activity administered can be given empirically (100–200 mCi) or determined by dosimetry. (**Weak recommendation, Low-quality evidence**)

RAI therapy for patients with bone metastases is rarely curative, but some patients with RAI-avid bone metastases may benefit from this therapy (786;887). A dosimetrically determined administered dose of RAI may be benifical for patients with bone metastases (848), although this is not proven in controlled studies. Patients undergoing RAI therapy for bone metastases should also be considered for directed therapy of bone metastases that are visible on anatomical imaging (section [C37]). This may include surgery, external beam radiation, and other focal treatment modalities. These patients should also be considered for systemic therapy with bone-directed agents (section [C47]).

[C31] When should empiric RAI therapy be considered for Tg-positive, RAI diagnostic scan–negative patients?

■ RECOMMENDATION 80

In the absence of structurally evident disease, stimulated serum Tg <10 ng/mL with thyroid hormone withdrawal or <5ng/mL with rhTSH (indeterminate response) can be followed with continued thyroid hormone therapy alone, reserving additional therapies for those patients with rising serum Tg levels over time or other evidence of structural disease progression. (**Weak recommendation, Low-quality evidence**)

■ RECOMMENDATION 81

Empiric radioactive iodine therapy (100–200 mCi) may be considered in patients with more significantly elevated serum Tg levels (see Recommendation 80), rapidly rising serum Tg levels or rising Tg antibody levels, in whom imaging (anatomic neck/chest imaging and/or ^{18}FDG-PET/CT) has failed to reveal a tumor source that is amenable to directed therapy. The risk of high cumulative administered activities of RAI must be balanced against uncertain long-term benefits. If empiric RAI therapy is given and the posttherapy scan is negative, the patient

should be considered to have RAI-refractory disease and no further RAI therapy should be administered. (**Weak recommendation, Low-quality evidence**)

■ **RECOMMENDATION 82**

If persistent nonresectable disease is localized after an empiric dose of RAI, and there is objective evidence of significant tumor reduction, then consideration can be made for RAI therapy to be repeated until the tumor has been eradicated or the tumor no longer responds to treatment. The risk of repeated therapeutic doses of RAI must be balanced against uncertain long-term benefits. (**Weak recommendation, Low-quality evidence**)

Factors to consider when selecting patients for empiric RAI therapy include the level of serum Tg elevation and the results of ^{18}FDG-PET scanning, if performed. Since tumors that are ^{18}FDG-PET positive generally do not concentrate RAI (906)), RAI therapy is much less likely to be efficacious (906;907) and RAI therapy is unlikely to alter the poorer outcome in such patients (768). Because of this, some have argued that ^{18}FDG-PET scanning should be performed prior to empiric RAI therapy (908).

The cutoff value of serum Tg above which a patient should be treated with an empiric dose of RAI is not clear. Most studies have reported primarily on patients with Tg levels after T_4 withdrawal of 10 ng/mL or higher; it has been suggested that a corresponding level after rhTSH stimulation would be 5 ng/mL (284;726;909-911). Patients with a suppressed (575) or stimulated (912) serum Tg of 5 ng/mL or higher are unlikely to demonstrate a decline without therapy, and have higher rates of subsequent structural recurrence than those with lower serum Tg levels (912). In addition, a rising serum Tg indicates disease that is likely to become clinically apparent, particularly if it is rapidly rising (573;913;914).

If serum Tg levels suggest residual or recurrent disease, but diagnostic RAI WBS imaging is negative and structural imaging does not reveal disease that is amenable to directed therapy (surgical, thermal ablation, EBRT, alcohol ablation, see section [C17 and C38]), then empiric therapy with RAI (100–200 mCi) can be considered for two purposes: 1) to aid in disease localization, and/or 2) as therapy for nonsurgical disease. This approach may identify the location of persistent disease in approximately 50% of patients (910;915;916) although the reported range of success is wide. From a therapeutic perspective, over half of patients

experience a fall in serum Tg after empiric RAI therapy in patients with negative DxWBS (remove 417,418 and replace with (904;911;917;918), however, there is no evidence for improved survival with empiric therapy in this setting (726;909;910). Further, there is evidence that Tg levels may decline without specific therapy in a significant proportion of patients with Tg levels < 10 ng/ml (489;569-571;575;726;726;912-914;917;919-921). The most compelling evidence for benefit from empiric RAI therapy is for pulmonary metastases, which are not amenable to surgical management or external beam radiotherapy, and RAI response rates are reasonable (726;788;922).

[C32] What is the management of complications of RAI therapy?

■ RECOMMENDATION 83

The evidence is insufficient to recommend for or against the routine use of measures to prevent salivary gland damage after RAI therapy. (**No recommendation, Low-quality evidence**)

■ RECOMMENDATION 84

Patients with xerostomia are at increased risk of dental caries and should discuss preventive strategies with their dentists. (**Weak recommendation, Low-quality evidence**)

■ RECOMMENDATION 85

Surgical correction should be considered for nasolacrimal outflow obstruction, which often presents as excessive tearing (epiphora) but also predisposes to infection. (**Strong recommendation, Low-quality evidence**)

While RAI appears to be a reasonably safe therapy, it is associated with a cumulative dose-related low risk of early-and late-onset complications such as salivary gland damage, dental caries (923), nasolacrimal duct obstruction (924), secondary malignancies (707;708;903;925;926), and may likely contribute to long-term dysphagia (927). Therefore, it is important to ensure that the benefits of RAI therapy, especially repeated courses, outweigh the potential risks. There is probably no dose of RAI that is completely safe nor is there any

maximum cumulative dose that could not be used in selected situations. However, with higher individual and cumulative doses there are increased risks of side effects as discussed previously.

For acute transient loss of taste or change in taste and sialadentitis, recommended measures to prevent damage to the salivary glands have included hydration, sour candies, amifostene and cholinergic agents (928), but evidence is insufficient to recommend for or against these modalities. One study suggested sour candy may actually increase salivary gland damage when given within 1 hour of RAI therapy, as compared to its use until 24 hours posttherapy (929). Another study showed that the use of lemon slices within 20 min of 124I administration resulted in increased radiation absorbed dose to the salivary glands (930). For chronic salivary gland complications, such as dry mouth and dental caries, cholinergic agents may increase salivary flow (928).

[C33] How should patients who have received radioiodine therapy be monitored for risk of secondary malignancies?

■ **RECOMMENDATION 86**

Although patients should be counseled on the risks of second primary malignancy (SPM) with RAI treatment for DTC, the absolute increase in risk of developing second primary malignancy attributable to RAI treatment is considered small, and does not warrant specific screening for SPMs, to any extent greater than age-appropriate general population health screening. (**Weak recommendation, Low-quality evidence**)

Most long-term follow-up studies variably report a very low risk of secondary malignancies (bone and soft tissue malignancies, including breast, colorectal, kidney, and salivary cancers, and leukemia) in long-term survivors (707;708). A meta-analysis of two large multicenter studies showed that the risk of second malignancies was significantly increased at 1.19 (95% CI: 1.04–1.36; $p < 0.010$), relative to thyroid cancer survivors not treated with RAI, although the absolute increase in SPM risk attributable to RAI is considered to be small (903). The risk of leukemia was also significantly increased in thyroid cancer survivors treated with RAI, with a relative risk of 2.5 (95% CI: 1.13–5.53; $p < 0.024$) (903). Studies on T1N0 papillary thyroid cancer from the SEER registry suggeseted that the excess risk of leukemia after RAI treatment was greater in young individuals compared with older individuals. The excess risk of

leukemia was significantly greater in patients aged <45 years (standardized incidence rate, SIR 5.32; 95% CI, 2.75, 9.30 for those aged <45 years versus SIR of 2.26; 95% CI, 1.43, 3.39 in older individuals) (902). The risk of secondary malignancies is dose related (708), with an excess absolute risk of 14.4 solid cancers and of 0.8 leukemias per gigabecquerel of ^{131}I at 10,000 person-years of follow-up. Cumulative ^{131}I activities above 500–600 mCi are associated with a significant increase in risk. There appears to be an increased risk of breast cancer in women with thyroid cancer (707;925;931). It is unclear whether this is due to screening bias, RAI therapy, or other factors. An elevated risk of breast cancer with ^{131}I was not observed in another study (709). The use of laxatives may decrease radiation exposure of the bowel, particularly in patients treated after prolonged withdrawal of thyroid hormone, and vigorous oral hydration will reduce exposure of the bladder and gonads (19).

[C34] What other testing should patients receiving RAI therapy undergo?

■ RECOMMENDATION 87

Patients receiving therapeutic doses of RAI should have baseline CBC and assessment of renal function. (**Weak recommendation, Low-quality evidence**)

Published data indicate that when administered activities are selected to remain below 200 cGy to the bone marrow, minimal transient effects are noted in white blood cell and platelet counts (896). However, persistent mild decrements in white blood cell count and/or platelets are not uncommon in patients who have received multiple RAI therapies. Further, radiation to the bone marrow is impacted by several factors, including renal function. The kidneys are a major means of iodine excretion from the body, and physiologic radioisotope study research in non-thyroidectomized individuals has shown that renal impairment significantly reduces radioactive iodine excretion (932).

[C35] How should patients be counseled about radioiodine therapy and pregnancy, nursing and gonadal function?

■ RECOMMENDATION 88

Women of childbearing age receiving RAI therapy should have a negative screening evaluation for pregnancy prior to RAI administration and avoid pregnancy for 6–12 months after receiving RAI. (**Strong recommendation, Low-quality evidence**)

■ RECOMMENDATION 89

Radioactive iodine should not be given to nursing women. Depending on the clinical situation, RAI therapy could be deferred until lactating women have stopped breast-feeding or pumping for at least 6–8 weeks. A diagnostic 123-I or low dose 131-I scan may be considered in recently lactating women to detect breast uptake that may warrant deferral of therapy. (**Strong recommendation, Moderate-quaity evidence**)

■ RECOMMENDATION 90

Men receiving cumulative radioiodine activities $\geq$ 400 mCi should be counseled on potential risks of infertility. (**Weak recommendation, Low-quality evidence**)

Women about to receive radioactive iodine therapy should first undergo pregnancy testing. Gonadal tissue is exposed to radiation from RAI in the blood, urine, and feces. Temporary amenorrhea/oligomenorrhea lasting 4–10 months occurs in 20–27% of menstruating women after ^{131}I therapy for thyroid cancer. Although the numbers of patients studied are small, long-term rates of infertility, miscarriage, and fetal malformation do not appear to be elevated in women after RAI therapy (933-935). One large retrospective study suggested that pregnancy should be postponed for 1 year after therapy because of an increase in miscarriage rate (936), although this was not confirmed in a subsequent study (937). Ovarian damage from RAI therapy may result in menopause occurring approximately 1 year earlier than the general population, but this result was not associated with cumulative dose administered or the age at which the therapy was given (938). Radioiodine is also significantly concentrated in lactating breast tissue (939). Therefore, radioactive iodine should not be given to women who are nursing. A diagnostic 123-I or low dose 131-I scan can be employed in recently lactating women to detect breast uptake that may warrant deferral of therapy (614). Dopaminergic agents might be useful in decreasing breast exposure in recently lactating women, although caution should be exercised given the risk of serious side effects associated with their routine use to suppress postpartum lactation (940).

In men, RAI therapy may be associated with a temporary reduction in sperm counts and elevated serum follicle-stimulating hormone (FSH) levels (941;942). Higher cumulative activities (500–800 mCi) in men are associated with an increased risk of persistent elevation of serum FSH levels, but fertility and risks of miscarriage or congenital abnormalities in subsequent pregnancies are not changed with moderate RAI activities (~ 200 mCi) (943;944). Permanent male infertility is unlikely with a single ablative activity of RAI, but theoretically there could be cumulative damage with multiple treatments. It has been suggested that sperm banking be considered in men who may receive cumulative RAI activities ≥400 mCi (942). Gonadal radiation exposure is reduced with good hydration, frequent micturition to empty the bladder, and avoidance of constipation (945). Some specialists recommend that men wait 3 months (or one full sperm cycle) to avoid the potential for transient chromosomal abnormalities.

[C36] How is radioiodine-refractory DTC defined?

■ RECOMMENDATION 91

Radioiodine-refractory structurally-evident DTC is defined in patients with appropriate TSH stimulation and iodine preparation in four basic ways: 1) the malignant/metastatic tissue does not ever concentrate radioiodine (no uptake outside the thyroid bed at the first diagnostic or therapeutic WBS), 2) the tumor tissue loses the ability to concentrate radioiodine after previous evidence of RAI-avid disease, 3) radioiodine is concentrated in some lesions but not in others; 4) metastatic disease progresses despite significant concentration of radioiodine.

When a patient with DTC is classified as refractory to radioiodine, there is no indication for further radioiodine treatment. (**Strong recommendation, Moderate-quality evidence**)

The prognosis of patients with DTC is usually favorable, even when metastatic radioiodine-avid disease is present. For this reason, I-131 is considered the gold standard in the treatment of metastatic disease. However, a significant subgroup of DTC patients with advanced disease does not respond or become refractory to I-131, with most of these patients dying within 3-5 years, but there are long term survivors with very slowly progressive disease.

I-131 refractory DTC includes four categories of patients (946): 1) the malignant/metastatic tissue does not take-up I-131 since the first discovery of the disease (at the time of the first treatment course): in these patients there is no evidence that treatment with

radioiodine may be of any benefit; similarly, a patient with morphological disease with an absence of I-131 uptake on a diagnostic WBS should be considered refractory, because even when uptake is seen on post-therapy scan, it will not be high enough to induce any benefit; 2) the tumor tissue loses the ability to take up I-131 after previous evidence of uptake: this occurs in patients with often large and multiple metastases and is due to the eradication by I-131 treatment of differentiated cells able to pick-up radioiodine but not of poorly differentiated cells that do not pick-up I-131 and that will progress; 3) I-131 uptake is retained in some lesions but not in others: this is frequent in patients with multiple large metastases as shown by I-124 studies on PET scan (858) and by comparing results of FDG-PET scan with I-131 WBS and in such patients, progression is likely to occur in metastases without uptake (in particular when FDG uptake is present) and radioiodine treatment will not be beneficial on the overall outcome of the disease; 4) metastatic disease progresses despite significant uptake of I-131. It has been clearly shown that when progression occurs during the months following a radioiodine treatment course, there will not be any tumor response to subsequent I-131 treatment course (even with higher activities), and in these patients there is no indication to proceed to other I-131 treatment courses. The definition of any of these possibilities depends on imaging modalities, including a post-therapy I-131 whole body scan combined with other imaging modalities, such as CT scan, MRI or F-18 fluorodeoxyglucose (FDG) positron emission tomography/computerized tomography (PET/CT).

Predictive factors for tumor response to radioiodine treatment are indeed the presence of I-131 uptake by tumor, and among those patients with radioiodine uptake, younger age, well differentiated histotype, small metastases and low FDG uptake. Indeed these parameters are closely interrelated (768;769;788), and may permit to predict the outcome of radioiodine treatment at the time of the discovery of the metastases. About two-thirds of patientswith metastases demonstrate I-131 uptake in their metastases, and only half of them will be cured with repeated courses of I-131 treatment.

Less clear is the case of patients with visible radioiodine uptake in all the known lesions, who are not cured despite several treatment courses but whose disease remains stable and does not progress according to RECIST criteria. It is controversial whether these patients (particularly after receiving more than 600 mCi of I-131) should be considered I-131 refractory and whether radioiodine treatment should be abandoned in favor of other treatment modalities. The probability to obtain a cure with further treatments is low and side effects may increase,

including the risk of secondary cancers and leukemias (707;708;788;903). Several parameters should then be taken into consideration for the decision to continue treatments, including response to previous treatment courses and absence of tumor progression since a previous treatment, high or significant level of I-131 uptake at the previous treatment course, low FDG uptake in tumor foci, and good tolerance (absence of side effects).

[C37] Which patients with metastatic thyroid cancer can be followed without additional therapy?

■ RECOMMENDATION 92

Patients with I-131 refractory metastatic DTC that is asymptomatic, stable or minimally progressive, not likely to develop rapidly progressive, clinically significant complications, and do not have indications for directed therapy can be monitored on TSH-suppressive thyroid hormone therapy with serial radiographic imaging every 3-12 months. (**Weak recommendation, Low-quality evidence**)

Patients with I-131 refractory metastatic DTC often have an indolent clinical course, with no apparent symptoms or adverse impact from their disease burden for many years. In the absence of tolerable therapies with significant likelihood of inducing durable complete remission or improving overall survival, treatment should be limited to interventions that prevent morbidity or palliate symptoms. Thus, once I-131 refractory metastatic disease is identified, attention should be directed toward 1) determining the extent of metastatic disease by staging imaging studies such as CT, FDG-PET/CT or MRI as described in sections [C9-13]; 2) assessing degree of current or potential symptoms from the disease; 3) understanding the co-morbidities that might influence the choice of therapies for the metastatic disease; and 4) determining the rate of progression of radiographically-evident lesions. Serial assessment of the size and development of metastatic lesions can be enhanced by applying criteria similar to RECIST, as commonly used to assess tumor response in clinical trials (947). Representative soft tissue metastatic lesions, typically > 1 cm, are identified as "targets" on cross-sectional imaging, with the longest diameter of each lesion measured. Disease extent can be considered to be stable or minimally progressive if the sum of the longest diameters of the target lesions increases less than 20% in the absence of new metastatic foci on sequential imaging over 12-15 months of follow-up. No study has

identified an appropriate frequency for repeat imaging, but it is reasonable to repeat the staging imaging studies within 3-12 months based on the disease burden and locations of lesions (893;948). More frequent assessment could be considered once metastatic disease is identified and/or in response to intercurrent patient symptoms, and less frequent imaging performed once a pattern of stability is identified. The development of progressive disease, either by RECIST assessment identifying at least 20% increase in sum of longest diameters of target lesions, the appearance of significant new metastatic lesions, or development of disease-related symptoms should warrant consideration of appropriate systemic therapies [section C41] beyond TSH-suppressive thyroid hormone and/or directed therapies [sections C15 and C38]. Although serum thyroglobulin levels should be measured as biomarkers of the disease extent, patients should not be identified as progressive and requiring more aggressive therapy solely on the basis of rising levels of thyroglobulin; accelerating increases in thyroglobulin levels should, however, lead to consideration of more frequent and comprehensive imaging in efforts to identify previously occult structural correlates.

[C38] What is the role for directed therapy in advanced thyroid cancer?

■ **RECOMMENDATION 93**

A) Both thermal ablation (RFA and cryoablation) and stereotactic radiation show a high efficacy in treating individual distant metastases with relatively few side effects and may be considered as valid alternatives to surgery. (**Weak recommendation, Moderate-quality evidence)**

B) Thermal ablation or stereotactic radiation should be considered prior to initiation of systemic treatment when the individual distant metastases are symptomatic or at high risk of local complications. (**Strong recommendation, Moderate-quality evidence)**

Several local treatment modalities other than surgery may be used to treat brain, lung, liver and bone lesions from thyroid carcinoma. These local treatment modalities should be considered prior to initiation of systemic treatment when the individual distant metastases are symptomatic or at high risk of local complications. They may also be helpful in case of progression in a single lesion in patients with an otherwise controlled disease during systemic treatment. In these patients, benefits can be achieved in preventing local complications, in

improving symptoms such as pain, in delaying the initiation of systemic treatments, and even in improving survival. These techniques can be a less aggressive alternative to surgery, and may be indicated in cases of lung metastases associated insufficient respiratory reserve, poor patient clinical status, or after multiple previous surgical resections, local recurrence at the site of previous surgery or refusal of additional surgery.

In selected patients, they may be an alternative to surgery as first line treatment, and they may induce local tumor control with a similar efficacy to surgical resection. Of interest, long term benefits in terms of disease control have been reported in patients with a single or few metastases and in whom the disease is slowly progressive.

Interventional radiology (thermal ablation and cement injections) or stereotactic body radiotherapy (SBRT), including IMRT (intensity modulated RT) or stereotactic radiosurgery techniques, are the most frequently used techniques. The main principle of these techniques is to treat selectively the lesion, to be minimally invasive, to be well tolerated with relatively few side effects. The indications and the feasibility of each technique depend on the location and the size of the lesion to be treated. Experience on metastases from thyroid cancer is scarce, and most available data have been obtained in patients with metastases from non thyroid cancers.

Percutaneous thermal ablation is aimed to destroy tumor foci by increasing (radiofrequency ablation) or decreasing (cryoablation) temperatures sufficiently to induce irreversible cellular damages.

Radiofrequency ablation (RFA) is performed for liver, lung and bone tumor foci. Clinical trials showed high efficacy of RFA on liver lesions, especially from colorectal cancer with long-term local disease control ranging from 40-80 %, depending on lesion size, and a prolonged overall survival in treated patients (949;950).

In a total of 100 lung lesions including primary lung tumors and metastases, RFA was both efficient and well tolerated with a complete tumor control rate of 93% at 18-months (951). A multicenter prospective trial on 183 lung metastases from cancer other than colorectal showed a complete response rate of 88 % at 1 year and an overall survival of 92% and 64% at 1 year and at 2 years, respectively (952). Recurrence occurs more frequently in lesions > 3 cm and can be detected early after ablation (within 3 months) by FDG PET/CT (769;953). Cases of delayed recurrence have also been reported, and long term follow up is needed. RFA is indicated for lung lesions < 3 cm of diameter, without soft tissue or mediastinum invasion and without contact

with large vessels. Furthermore, repeated treatments can be performed on the same lesion and multiple lesions can be treated in the same patient.

Radiofrequency ablation or cryoablation of bone lesions showed promising results with a rapid (1-7 days) and long lasting pain control (954;955). Cryoablation is a safe technique to cure or to stabilize bone lesions, is frequently associated with cementoplasty to consolidate the bone and avoid subsequent complications and can treat larger lesions than RFA.

Local disease control was achieved in the few reported cases of lung and bone metastases from thyroid cancer treated by thermal ablation (825;953;956). The association of cryoablation and cementoplasty seems promising in purely lytic bone metastases from thyroid cancer. Furthermore, in 3 patients with liver metastases from thyroid cancer (2 medullary thyroid cancer and 1 follicular thyroid cancer) thermal ablation was feasible and reduced local symptoms(957). Multidisciplinary treatment for metastases from thyroid cancer especially for bone metastases, including for example thermal ablation and/or cementoplasty associated to systemic treatment (radioactive iodine, bone-directed agents or chemotherapy) can improve the patient's quality of life by reducing pain and prolonging time to skeletal events, delaying initiation of systemic treatment and even by improving patient survival (958).

The toxicity of thermal ablation is generally low, but pneumothorax or pleural effusion were observed in up to 50% of RFA procedures for lung lesions, but rarely required further treatments, local pain or transient neurological deficit or vertebral fracture can occur in case of ablation of bone lesions (5-6%) and intestinal perforation, abdominal pain or intraperitoneal bleeding were observed following ablation of liver lesions (951;959).

Stereotactic beam radiation therapy (SBRT) allows for delivering high radiation doses in few fractions to the target tumoral lesion with a high degree of precision, minimizing the irradiation of normal surrounding tissue. It has been used in several trials to treat brain, liver, lung and bone metastases.

For patients with few (1-3) brain metastases, SBRT is as effective as surgery and can be repeated in case of appearance of new brain lesions. Results do not depend on the modality used for SBRT. It is usually well tolerated, and brain necrosis that occurred in less than 10% of cases is usually limited and had no clinical consequences. The patient outcome depends mostly on the progression rate of extra cerebral lesions (960).

Data on lung and liver metastases are available only in retrospective studies on low numbers of patients and with a median follow-up of less than 1 year in most cases and in one prospective study (953). They showed a local control rate ranging from 63% to 98% in lung lesions, from 57% to 100% in liver lesions with a cumulative dose delivered ranging from 20-75 Gy in 5-15 fractions. The local tumor control seems to be long lasting with complete response ranging form 70 to 90 % at 2-3 years. Furthermore, rare (<3%) grade 3-4 toxicities (pneumonitis, pleural effusion, intestinal complications) were reported (961). These toxicities are much less common that those associated with percutaneous treatment modalities. The local control rate seems to be dose-related but the optimal protocol for SBRT is still not established.

Concerning bone lesions, radiotherapy plays an important role because it can complement surgery in case of incomplete resection or be used alone for pain relief or palliation. In many cases, usual RT can be given. However, the major limitation of RT in spine lesions is the cumulated dose to the spinal cord. SBRT compared to standard RT demonstrated a higher efficacy on tumour control and for limiting irradiation to the spinal cord, especially in patients who need to be re-irradiated. A local tumoral control rate of bone lesions for SBRT ranging from 88 to 100% was reported especially for lesions that were previously surgically resected, and a pain relief rate of 30-83%. SBRT protocols differed among studies with a maximum of 30 Gy administrated in 1-5 fractions but a single-dose of 12.5-15 Gy seems to achieve similar results (962). Spinal myelopathy or vertebral fractures are the most important side effects, especially in case of large volume lesions.

Published experience using thermal ablation and stereotactic radiation in thyroid cancer patients is limited, and recommendations are currently based on more robust evidence in other solid tumors. Randomized prospective studies comparing the efficacy and tolerability of these different techniques are lacking, and their choice in clinical practice is based on local experience, lesion location as well as patient status and preference.

[C39] Treatment of brain metastases

■ RECOMMENDATION 94

While surgical resection and stereotactic external beam radiotherapy are the mainstays of therapy for CNS metastases, RAI can be considered if CNS metastases concentrate RAI. If RAI is being considered, stereotactic external beam radiotherapy and concomitant glucocorticoid

therapy are recommended prior to RAI therapy to minimize the effects of a potential TSH-induced increase in tumor size and RAI-induced inflammatory response (**Weak recommendation, Low-quality evidence**)

Brain metastases typically occur in older patients with more advanced disease and are associated with a poor prognosis (873). Surgical resection and stereotactic external beam radiotherapy are the mainstays of therapy (873;963)(Henriques de Figueirdo, Thyroid 24:270, 2014). There are few data showing efficacy of RAI. Stereotactic radiation therapy is preferred to whole brain irradiation because life expectancy in patients with brain metastases may be prolonged, and stereotactic irradiation induces less short and long term toxic damages to the brain compared with whole brain irradiation, and it may be effective even in patients with multiple brain lesions.

[C40] Who should be considered for clinical trials?

■ RECOMMENDATION 95

Patients should be considered for referral to participate in prospective therapeutic clinical trials based upon specific eligibility requirements for given studies and the likelihood that the patient may benefit from study participation. Clinicians considering referral of patients for trials should review available treatment options and eligibility criteria, preferably through discussions with trial center personnel and review of trial materials at the website www.clinicaltrials.org (**Strong recommendation, Moderate-quality evidence**)

A therapeutic clinical trial is a systematic investigation of the effectiveness and safety of a potential new, modified, or combination of treatments, potentially including medications, surgery, radiation therapy, and/or other novel or revised approaches. A broad variety of such trials may exist at any given time, which can generally be identified through online databases such as www.clinicaltrials.org, best supplemented with direct contact with the institutions conducting trials of particular interest so as to assure trial availability and patient eligibility. There is limited evidence that enrollment into clinical trials is associated with lower overall cancer-specific mortality for patients with common cancers, even within contexts in which approved and "standard of care" therapies already exist (964). The reasons for this association

are unclear, but there is no evidence to suggest that trial participation is deleterious to patiet outcomes, and it may be beneficial. Participation in a clinical trial should be considered in any situation wherein there exists no effective or proven standard of care, or when a standard of care is being compared with a promising new or investigational therapy. Adjuvant therapy trials may be appropriate for patients at high risk for disease recurrence following primary treatment who wish to pursue aggressive therapy. For patients with radioiodine refractory carcinoma that is locally advanced or metastatic, clinical trials may be appropriate in the setting of disease that is considered progressive by RECIST criteria, especially if progression occurred after use of an approved kinase inhibitor such as sorafenib, and/or if approved therapies are otherwise unaffordable to a specific patient. Patients demonstrated to have specific therapeutically targetable tumor alterations, such as mutations in BRAF, or PAX8-PPARγ or ALK rearrangements, can also be considered for trials testing therapies specifically targeting these alterations. However, given the indolent nature of metastatic disease in most patients, therapeutic clinical trial participation should not be considered for patients with stable, asymptomatic metastatic disease unless agents with significant likelihood of complete remission or prolongation of survival are available (see section [C37]).

[C41] What is the role of systemic therapy (kinase inhibitors, other selective therapies, conventional chemotherapy, bisphosphonates) in treating metastatic DTC?

Systemic therapeutics of several types *in selected clinical contexts* appear to provide clinical benefit in treating metastatic DTC (965). Benefit has been demonstrated in the form of improved progression free survival (delay in time to disease progression) in three randomized, double-blinded, placebo-controlled, clinical trials (vandetanib, (966); sorafenib, (967); lenvatinib, (968). Benefit has also been demonstrated in the form of induced durable tumor regression (969-971).

However, randomized clinical trial data are not yet available to address many additional critical questions, including effects of systemic therapies of various types on: i) survival and ii) quality of life – and also to address critical issues of optimal patient selection/inclusion/exclusion criteria for therapyand duration of treatment.

To date, no clinical trial has demonstrated an overall survival advantage or improved quality of life from use of any therapy in RAI-refractory DTC. Because improvement in overall

survival is less likely to be demonstrated in phase 3 trials with a cross-over design, demonstrated benefits in PFS can only be used as potential surrogate markers of benefits in overall survival. However, sorafenib has recently been approved for DTC by the US FDA and European EMA on the basis of improved progression-free survival when compared to placebo (967). Consequently, therapeutic decisions are presently based upon the convergence of "expert opinion" and patient preference/philosophy, thus emphasizing the critical need to address the above questions definitively through clinical trials. It is also important to involve highly skilled clinicians familiar with RAI-refractory disease and these systemic therapies in decision making until definitive guidelines can be developed based upon more rigorous data. In the absence of definitive data related to improved overall survival and/or quality of life to inform evidence-based recommendations, expert consensus has been recently published (893).

It should be highlighted also that, broadly construed, systemic therapy encompasses not only more recently emerging "targeted" approaches - but also historical "mainstay" therapies including TSH suppression and RAI. Although more "novel" approaches have attracted attention recently, it is important to optimally apply fundamental approaches. In this regard, therapeutic RAI should also be used to optimal effect prior to the initiation of more recent/novel therapies. To accomplish this requires attention to detail, including assurance of adequate TSH stimulation, patient adherence to low-iodine pre-RAI therapy dietary restrictions, and avoidance of proximal preceding iodine contamination from IV contrast agents - with verification by urinary iodine concentration measurements in selected cases. In this context, occasional patients previously declared "RAI-refractory" can be found instead to have RAI-responsive disease when such details are attended to if previously neglected.

Also important is the consideration of alternatives to the use of systemic therapy – such as the application of surgery or other localized approaches (including radiation therapy or thermal ablation approaches). In patients where the threats imposed by cancer are more localized, directed approaches may have greater potential to control localized disease and symptoms when compared to systemic therapies. Such approaches are therefore important to consider, especially in the context of the absence of data to indicate survival benefit or improved quality of life from the application of systemic therapies in advanced RAI-refractory DTC.

It is also critically important to assure that the disease prompting therapy represents metastatic thyroid cancer. In particular, because pulmonary nodules attributable to benign causes

are common, the presence of pulmonary nodules does not in-and-of-itself justify the application of systemic therapy. Thus, in cases of diagnostic uncertainty where the result would have definitive therapeutic implications, biopsy is required, especially when thyroglobulin levels are low/unhelpful (such as in the presence of anti-thyroglobulin antibodies). Conversely, stable, asymptomatic pulmonary nodules of a few millimeters in size likely do not justify invasive assessment or systemic therapy.

The introduction of systemic therapy requires that both the clinician and the patient agree that clinical benefits are expected to exceed risks for that individual patient. The problem in this determination, however, is that it is often very difficult to precisely define such risks and benefits – as risks and benefits vary greatly depending upon patient context, and as they are often poorly articulated in the literature. It is also critical to weigh not just risks of death and injury – but also risks of systemic therapies on quality of life, especially as viewed by a particular patient considering treatment. Hence, the decision is not based solely on benefits and risks of therapy, but also on patient value judgments. Issues of risks and benefits are reviewed in this context in conjunction with each therapeutic modality below. Finally, it is important that the involved care team (physicians, PA, NP, nurses) be experienced in the use and management of toxicities associated with these therapies.

[C42] Kinase Inhibitors

■ **RECOMMENDATION 96**

A) Kinase inhibitor therapy should be considered in RAI-refractory DTC patients with metastatic, rapidly progressive, symptomatic and/or imminently threatening disease not otherwise amenable to local control using other approaches. Kinase inhibitors that are FDA approved for differentiated thyroid carcinoma, or other available kinase inhibitors (preferably within the context of therapeutic clinical trials), can be considered since the impact of these agents on overall survival and quality of life remains to be defined. (**Weak recommendation, Moderate-quality evidence**)

B) Patients who are candidates for kinase inhibitor therapy should be thoroughly counseled on the risks and benefits of this therapy as well as alternative therapeutic approaches including best supportive care. Appropriate informed consent should be obtained and documented in the medical record prior to initiation of any therapy, regardless of whether the

patient is being treated in the context of a clinical trial. (**Strong Recommendation, Low-quality evidence**)

Cytotoxic chemotherapy had historically produced disappointing results in patients with DTC (972). Kinase inhibitors, many of which share the common target of the VEGF receptor, (e.g. sorafenib, pazopanib, sunitinib,lenvatinib, axitinib, cabozantinib and vandetanib) have recently emerged as highly promising therapies for metastatic RAI-refractory DTC (965). Kinase inhibitors, however, are associated with numerous adverse effects including diarrhea, fatigue, induced hypertension (requiring initiation of antihypertensive therapy in about half of all previously normotensive individuals), hepatotoxicity, skin changes, nausea, and changes in taste. These potential side effects have high probability of negatively impacting quality of life and/or necessitating dosage reductions in nearly two-thirds of treated patients, and treatment discontinuation in up to 20% of patients. Furthermore, these agents are also associated with more serious and potentially fatal risks including of thrombosis, bleeding, heart failure, hepatotoxicity, GI tract fistula formation and intestinal perforation (973) . Overall, the risk of therapy-related death in cancer patients treated with oral kinase inhibitors is about 1.5-2% (relative risk 2.23, $p<0.023$, compared with randomized placebo treated control cancer patients) based upon meta-analysis of results from 10 recently published randomized trials conducted in several cancers (973). While risk of drug-related death is relatively low, this knowledge of potentially fatal therapeutic outcomes should prompt considerable restraint in the use of tyrosine kinase inhibitors in patients with stable or slowly progressive disease who likely have a disease-specific mortality that may also be low over 1-3 years.

Three randomized placebo-controlled clinical trials (phase 2, vandetanib; phase 3, sorafenib and lenvatinib) had been published or presented by the time of the writing of these guidelines, each demonstrating delayed time to disease progression among kinase inhibitor-treated, relative to placebo-treated, patients (966) (967) (968). Sorafenib or vandetanib treatement were each associated with PFS prolonged by 5 months, with <15% objective response rates, but with no improvement on overall survival demonstrated to date. Assessments comparing sorafenib to placebo outcomes demonstrated overall lower quality of life among sorafenib-treated patients relative to those treated with placebo, despite improved PFS. Lenvatinib therapy was associated with longer median PFS by 14.7 months, with a RECIST

response rate of 65%, with some complete responses also reported. No statistically significant impact of lebvatinib therapy on overall survival, however, has yet been observed; moreover, lenvatinib toxicities were reported in 100% of treated patients (968).

Axitinib, pazopanib, cabozantinib and sunitinib also have activity in metastatic DTC based upon phase 2 therapeutic trials (969-971). No multi-arm comparison "superiority" phase 3 trial data in DTC are available to inform decision making with regard to selection among available, and mostly similarly-targeted, kinase inhibitors. Kinase inhibitor response rates (RECIST criteria) in DTC range as high as ~50-65%, with many responders attaining durable disease control of median duration 1-2 years (968;970). Sorafenib was approved by the US FDA in December 2013, and by EMA in April 2014, for use in patients with RAI-refractory, progressive DTC on the basis of prolongation of PFS. Recent regulatory approval in DTC and the larger amount of published studies on outcomes in response to sorafenib therapy in DTC (974-977) prompt prominent consideration of sorafenib as a first-line therapy.

Despite encouraging trial results, the extent to which any kinase inhibitor may prolong overall survival, and in which contexts, remains undefined. None of the yet-completed randomized trials have demonstrated survival benefit for kinase inhibitor therapy relative to placebo, perhaps in part reflecting crossover from placebo to kinase inhibitor therapy among progressing placebo-treated trial patients, raising the question of whether delay of therapy initiation adversely affected patient outcomes among enrolled trial patients.

In some contexts, however, the decision to initiate kinase inhibitor therapy is straightforward. For example, patients with oxygen dependence attributable to DTC lung metastases are not only adversely affected by their cancers, but also imminently threatened. Such patients have potential to gain symptomatic benefit even in the absence of definite extension of life. On the other extreme, many patients with metastatic DTC are asymptomatic from their cancers and are not expected to be threatened by their cancers in the foreseeable future. These patients should remain on TSH-suppressive treatment as their primary therapeutic intervention rather than be exposed to kinase inhibitor therapy. For patients with disease between these two extremes, it is critical that risks and benefits of therapy, anticipated side effects, goals, patient context, and the therapeutic philosophy of each particular patient be thoroughly vetted so as to best individualize therapy. This decision is ideally made within the

context of specialized centers with comprehensive knowledge of the natural history of the disease and of the effects of available therapies.

As a general 'expert consensus' guideline, structurally progressive, symptomatic and/or imminently threatening DTC (disease progression is expected to require intervention and/or to produce morbidity or mortality in <6 months), that is RAI-refractory and not amenable to satisfactory control using directed approaches (e.g. surgery, radiation therapy, thermal ablation), should prompt consideration of kinase inhibitor therapy. Specific characteristics impacting enthusiasm for starting such therapy are outlined in Table 16.

Patients who are candidates for kinase inhibitor therapy should be thoroughly counselled with regard not only to potential benefits, but also with regard to potential side effects and risks of therapy, as well as with regard to alternative therapeutic approaches including best supportive care, as should be the case with any medical therapeutic decision making (978). Such extensive and comprehensive discussions are particularly important to undertake in the context of kinase inhibitor therapy because of the high probability of side effects of these agents and because of their presently uncertain effects on patient overall survival and quality of life.

Another critical and complex question often faced in treating patients with kinase inhibitor therapy is that of when treatment should be discontinued once initiated. In general, therapy should be continued so long as net benefit exceeds net detriment. In case of slow RECIST disease progression after significant tumor response, treatment may be maintained so long as overall disease control is maintained providing that toxities are mannagable; progression rate should be taken into account, and when global progression is rapid, therapy should be discontinued. However, there are times when focal/oligometastatic disease progression amenable to directed therapies is noted. In such instances, superimposed locoregional therapies in the setting of maintained systemic therapy can sometimes be in the best interest of a particular patient. For instance, in the setting of regressed lung metastases and yet progression at a solitary bony site, maintained systemic therapy with superimposed directed radiation therapy may be reasonable.

[C43] Patients who fail first-line kinase inhibitor therapy

■ **RECOMMENDATION 97**

Patients who incur disease progression in response to initial kinase inhibitor therapy without prohibitive adverse effects should be considered for second-line kinase inhibitor therapy. Ideally, such therapy should be undertaken within the context of therapeutic clinical trials. (**Weak recommendation, Low-quality evidence**)

DTC patients who progress through first-line line kinase inhibitor therapy commonly respond to a second similarly-targeted agent, and thus should be considered candidates for second-line kinase inhibitor therapy (968;979). Hence, the selection of an agent for initial therapy may be in some senses less critical, as many patient will go on to receive several kinase inhibitors over their disease courses. In the near future, other treatment modalities, such as radioiodine resensitization therapy, immunotherapy, or drugs directed to other targets may also offer additional therapeutic options.

[C44] Management of toxicities from kinase inhibitor therapy

■ **RECOMMENDATION 98**

Active surveillance and timely intervention in response to emergent toxicities are critical components of management in patients receiving kinase inhibitor therapy. (**Strong recommendation, Low-quality evidence**)

Patients treated with kinase inhibitors are subject to many potential toxicities that can negatively impact quality of life or even be fatal; as a consequence, great care must be taken not only in selecting appropriate patients for therapy, but also in monitoring patients once receiving kinase inhibitor therapy (978). Some toxicities (e.g. fatigue, diarrhea, GI symptoms, cutaneous effects) will be symptomatic and can more easily be addressed upon close communication with patients. However, there are also more serious potential toxicities that might not be expected to immediately lead to patient symptoms (e.g. hepatotoxicity, prolonged QTc) that require proactive screening (Table 17).

Hypertension and hepatotoxicity are especially important to serially monitor and rapidly address. Cardiotoxicity is also important to be aware of and to monitor according to patient risk factors, agent used, and induced symptoms/signs. In particular, sunitinib induces a decreased cardiac ejection fraction in about 20% of treated patients (980). Furthermore, all kinase inhibitors

can induce QTc prolongation that should prompt careful consideration of co-administered drugs and periodic electrocardiography. Also important is that kinase inhibitor half-life is long; consequently, severe toxicities should prompt complete cessation of kinase inhibitor therapy for an adequate amount of time to allow drug levels to decline before resumption at a lower dosage.

Serum TSH level frequently increases during kinase inhibitor therapy; this should lead to frequent TSH assessment in conjunction with therapy initiation and upon therapy cessation, with responsive modifications thyroid hormone therapy where indicated.

[C45] Other Novel Agents

■ RECOMMENDATION 99

Agents without established efficacy in DTC should be used only within the context of therapeutic clinical trials. (**Strong recommendation, Low-quality evidence**)

A variety of novel agents have been and/or are being tested as candidate therapeutics in progressive metastatic RAI-refractory DTC (965;981). At the time of the writing of these guidelines, however, only kinase inhibitors have shown sufficient promise to consider use other than within the context of therapeutic clinical trials. Agents of particular interest for further testing include BRAF kinase inhibitors, as PTC frequently harbors the constitutively activating BRAF V600E mutation, and as these agents have already shown efficacy and been approved for use in BRAF mutant melanoma (982), (983;984). Inhibitors of MEK kinase and other signaling pathways are also of considerable investigational interest. In addition, promising initial results in response to use of kinase inhibition to "re-sensitize" RAI-refractory tumors to RAI have been reported (895). Data developed to date, however, do not yet favor the use of these novel approaches over use of VEGFR-directed kinase inhibitors unless within the context of therapeutic clinical trials.

[C46] Cytotoxic Chemotherapy

■ RECOMMENDATION 100

Cytotoxic chemotherapy can be considered in RAI-refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to control through other approaches including kinase inhibitors. Too few

data exist to recommend specific cytotoxic regimens, and use within the context of a therapeutic clinical trial is preferred. (**Weak recommendation, Low-quality evidence**)

Historically, cytotoxic chemotherapy has produced disappointing results when used to treat RAI-refractory DTC (972). Cytotoxic chemotherapy, however, may have selective benefit in patients unresponsive to kinase inhibitors and perhaps also in some patients with poorly differentiated thyroid cancer (985). Data are limited and primarily anecdotal.

[C47] Bone-Directed Agents

■ RECOMMENDATION 101

Bisphosphonate or denosumab therapy should be considered in patients with diffuse and/or symptomatic bony metastases from RAI-refractory DTC, either alone or concomitantly with other systemic therapies. Adequate renal function, calcium and vitamin D25 levels should be documented prior to each dose, and dental evaluation should take place before initial use. (**Strong recommendation, Moderate-quality evidence**)

Bony metastatic disease represents a particularly challenging clinical problem in patients with RAI-refractory DTC, especially given the high rate of multiple skeletal related events in patients following detection of an initial bone lesion (986). Patients with a small number of threatening and/or symptomatic bony lesions are generally best treated with focal approaches such as radiation therapy and/or surgery and/or thermoablation. Many patients, however, suffer from diffuse progression of bony metastases that are not amenable to effective control using focal therapies alone. In such patients, focal therapy to symptomatic lesions or lesions at high risk of complications may be beneficial and should be performed before initiation of systemic treatment.

Unfortunately, kinase inhibitors appear to be less effective in controlling bony metastatic disease in comparison to disease at other soft tissue sites such as lungs and lymph nodes. Bony progression through kinase inhibitor therapy commonly occurs despite maintained benefit with respect to disease at other metastatic sites. Hence, kinase inhibitor therapy cannot be relied upon to control diffuse bony metastases in many patients with RAI-refractory DTC.

In other solid tumors, bone-directed therapeutics including bisphosphonates (especially zoledronic acid) and the RANK-ligand-directed agent denosumab have been shown to delay time to occurrence of subsequent skeletal-related adverse events (fracture, pain, neurologic complications) and to improve symptoms, and these agents may provide benefit for patients with diffuse bony metastases (987;988) . The determination of benefit across several tumor types suggests that such benefit may be broadly generalizable, prompting FDA approval for their general use in patients with solid tumor bony metastases. Two small studies have suggested benefit from bisphosphonates specifically within the context of DTC bony metastases (891;989).

Risks of bisphosphonates and RANK ligand-directed agents include hypocalcemia, which can be severe, prompting the recommended concomitant use of supplemental calcium and vitamin D therapy. Moreover, these agents also moderately increase the risk of non-healing oral lesions and jaw osteonecrosis; thus, candidates for this therapy should undergo dental/oral surgical evaluation prior to their initiation so as to minimize these risks (987).

Recent studies have overall shown equivalence or superiority of denosumab to zoledronic acid in delaying bone related adverse events in solid tumors, with similar risk of jaw osteonecrosis, greater incidence of hypocalcemia, and lessor nephrotoxicity (990). However, no thyroid-specific data related to the efficacy of denosumab have yet been published.

Expert consensus is that bone-directed therapy should be strongly considered in patients with multiple progressing and/or symptomatic bony metastases, likely best beginning with bisphosphonate/zoledronic acid (assuming calcium and renal function permit). Candidates for such therapy should be cleared by their dentist/oral surgeon prior to therapy initiation; in addition, calcium/vitamin D therapy should be ongoing in conjunction with any intended bone-directed therapeutic. In general, there is consensus that q3 month (rather than q1 month) zoledronic acid therapy is a reasonable initial approach in terms of dosing interval – but randomized trial data are unavailable to definitively clarify this issue.

Expert consensus is that bone-directed therapy should be used in the setting of diffuse bony metastases *even if kinase inhibitor therapy is intended or ongoing.* If the patient's renal function is impaired, there is sometimes justification for alternatively beginning with RANK ligand-directed/denosumab therapy, as this agent seems to produce fewer adverse renal effects, albeit the oral/jaw effects are similar to bisphosphonates in magnitude.

[D1] WHAT ARE DIRECTIONS FOR FUTURE RESEARCH?

[D2] Optimizing molecular markers for diagnosis, prognosis and therapeutic targets

Significant progress has been made over the last several years in understanding the genetic mechanisms of thyroid cancer and creating molecular tests for cancer diagnosis in thyroid nodules. This process is currently going through the accelerated phase, which is expected to continue into the future. The papillary thyroid carcinoma project that is being finished by The Cancer Genome Atlas (TCGA) and work from multiple research labs led to the identification of mutations and other driver genetic alterations in more than 90% of thyroid cancers, making it one of the best characterized human cancers from the genetic standpoint. Moreover, the next generation sequencing (NGS) technology may allow detection of most of these alterations in a limited cell sample obtained by FNA. This is expected to result in a significantly improved accuracy of cancer detection in thyroid nodules as compared to the currently available clinical tests. If such progress continues, it is expected that future molecular tests will be able to predict the risk of cancer in thyroid nodules with high accuracy, eliminating the uncertainty of indeterminate FNA cytology. Furthermore, as the cost of next generation sequencing of human DNA continues to decrease and the analytical tools becomes more efficient, it should be expected that the cost of molecular testing will decrease, enabling cost-efficient utilization of testing.

Molecular markers are expected to have a significant impact on cancer prognostication. Whereas BRAF can be considered as a relatively sensitive prognostic marker for papillary cancer, it is not specific and can not be used in isolation for tumor prognostication. However, recent results obtained by broad tumor genotyping show that several specific molecular signatures (such as presence of several driver mutations; TP53 mutation; TERT mutation in isolation or in combination with BRAF) are found in a small fraction of well differentiated papillary and follicular cancers and in associated with more aggressive tumor behavior. It is expected that these molecular signatures will be confirmed and perhaps further improved in additional studies and will offer a more specific detection of well differentiated thyroid cancers that have high risk of tumor recurrence and cancer-related mortality. Furthermore, research may inform how such data may inform therapeutic decision-making (eg. surgical extent [if any], treatment with multi-kinase and specific kinase inhibitors or their combination). Discoveries of

new genes involved in pathogenesis of thyroid cancer, such as those of ALK and NTRK3, are expected to offer new effective therapeutic targets. Finally, new therapeutic approaches to target genes commonly mutated in thyroid cancer, such as RAS, are in development and expected in enter clinical trials in the future. Prospective, long-term outcome studies, ideally in the form of randomized controlled trials, will be needed to define the optimal surgical and post-surgical management of patients based in these molecular signatures. Such research may enable personalized, evidence-based care of patients with thyroid cancer across the disease trajectory.

[D3] Active surveillance of DTC primary tumors

Our Japanese colleagues have provided compelling data that an active surveillance management approach to papillary microcarcinoma is a safe and effective alternative to immediate surgical resection in properly selected patients (90;133). These data led to the discussion in section [A14] which endorses active surveillance for DTC patients with "very low risk tumors" which would include papillary microcarcinomas without clinically evident metastases or local invasion and without known high risk cytologic or molecular characteristics. These data have also led to recommendation 8E that FNA is not required for suspicious thyroid nodules < 1 cm without other high risk features (cervical adenopathy, question of extrathyroidal invasion). Section [A14] could also allow for active surveillance of primary tumors greater than 1 cm and other histological subtypes provided they could be classified as "very low risk tumors."

Unfortunately, no clinical features or molecular abnormality in isolation can reliably differentiate the relatively small number of PTMC patients destined to develop clinically significant progression from the larger population of people that harbor indolent PTMCs that will not cause significant disease. Therefore, additional studies are needed to identify specific risk factors that would favor surgical resection over active surveillance. Possible risk factors could include the specific molecular profile of the tumor, other clinical risk factors (e.g., age, gender, ethnic background), structural risk factors (size of the primary tumor, location of the tumor within the thyroid gland), plans for future pregnancy, or additional imaging findings (e.g., specific US, CT or MRI characteristics of the tumor).

Furthermore, additional studies are needed to define important management issues that arise during an active surveillance follow-up approach. These issues include the frequency of

US evaluations required during follow-up, optimal TSH goals, the potential role of serum Tg in follow-up, and specific indications for surgical intervention (e.g., what measurements should be used to define a clinically significant increase in the size of the primary tumor? what constitutes clinically significant lymph node metastases?).

Finally, studies that examine decision-making and acceptability of an active surveillance approach to thyroid cancer in patients, family members, and clinicians are required to better understand how to implement this novel management approach outside of Japan.

[D4] Improved risk stratification

Accurate risk stratification is the cornerstone of nearly all decision making in thyroid cancer management. While the AJCC/UICC TNM staging provides valuable information with regard to disease specific mortality, it accounts for less than 30% of the proportion of variance explained (PVE, a statistical measure of how well a staging system can predict the outcome of interest) (246;456;478-480;991;992) (482). Additional studies are needed to determine inclusion of additional prognostic variables into the AJCC staging system could improve its predictive ability. Potential variables for consideration include: the specific histology (well differentiated thyroid cancer vs. poorly differentiated thyroid cancer), molecular profile, size and location of distant metastases (pulmonary metastases vs. bone metastases vs. brain metastases), functional status of the metastases (RAI avid vs. FDG PET avid) and effectiveness of initial therapy (completeness of resection; effectiveness of RAI, external beam irradiation or other systemic therapies).

With regard to predicting the risk of recurrence, the 2009 ATA Risk Stratification system has now been validated in multiple studies and certainly provides a useful starting point for initial risk stratification. However, the PVE provided by the ATA risk of recurrence system was suboptimal ranging from 19% to 34% (488;492) . In an attempt to improve the prognostic ability of the 2009 ATA Risk Stratification system, additional prognostic variables (such as such as the extent of lymph node involvement, mutational status, and/or the degree of vascular invasion in follicular thyroid cancer) were included in a Modified 2009 Initial Risk Stratification System (See Recommendation 48). However, additional studies will be required to determine if there is any significant incremental benefit of adding these specific prognostic variables to the 2009 Initial Risk Stratification system.

In order to optimize ongoing management, it is necessary to continually modify risk estimates over time as new data is obtained (See Recommendation 49). Dynamic (ongoing) risk stratification systems provide PVE values of 62%-84% indicating that they are more likely to predict clinical outcomes than initial static staging systems. Since these systems have been primarily optimized and validated on differentiated thyroid cancer patients that had total thyroidectomy and RAI remnant ablation, additional studies are needed to refine the definitions of excellent, biochemical incomplete, structural incomplete, and indeterminant responses in patients treated with total thyroidectomy without RAI ablation and in patients treated with less than total thyroidectomy(553). Furthermore, additional studies are needed to define what types of cross sectional/functional imaging are required to rule out structural disease in order to classify a patient as having a biochemical incomplete response to therapy (based on initial risk, serum Tg, signs/symptoms, or other imaging results).

Another area of significant research interest centers on identifying specific clinical situations where the molecular findings provide clinically meaningful information that goes beyond what is predicted by standard clinico-pathological staging. Molecular findings that provide these types of prognostic information or guide optimal initial/ongoing treatment decisions have the potential to significantly alter clinical management.

[D5] Improving our understanding of the risks and benefits of DTC treatments

In achieving a better understanding of the risks and benefits of DTC treatments (such as extent of primary surgery or secondary surgery for recurrence, radioactive iodine ablation/treatment, and thyroid hormone suppressive therapy), more prospective long-term outcome research is needed, and in particular, randomized controlled trials. In the case of relatively uncommon adverse effects of treatments, propective surveillance research is also needed. Prospective collection of data on quality of life and related outcomes, (when relevant), is also needed in DTC trials. Using an evidence-based approach to knowledge synthesis (systematic reviews, meta-analyses, and clinical practice guidelines) of data can also enable evidence-informed clinical practice. Barriers need to be overcome to dissemination and implementation of clinical practice guideline recommendations. Evidence-based guidelines may need to be formally adapted to various practice settings to enable their implementation. Furthermore, plain language educational materials, including decision aids or other decision

support tools should be developed to be used as an adjuct in physician counseling of patients about diagnostic and treatment options.

[D6] Issues with measurement of Tg and Tg antibodies

Current methodologies for both thyroglobulin (Tg) and anti-Tg antibodies (TgAb) remain problematic in many ways that hopefully will be overcome in the future. For Tg assays, these include interference with Tg measurement by the presence of anti-Tg and heterophile antibodies and the use of a host of different methods with varying results in terms of sensitivity or detection limits. Assay calibration or standardization may be successful only if the same certified reference standard is employed, which currently is CRM-457. While more "ultrasensitive" Tg assays have been developed, we need to determine the true clinical significance or utility of measurable levels below 0.2 ng/ml (either on suppression or after TSH stimulation) as indicating evidence of residual disease or outcome. Recently developed mass spectrometry (MS) based assays have offered some promise, but are yet to be validated (749). Nor have competitive immunoassays provided the answer in view of their unpredictability (715). In regard to TgAb, we need to better characterize the various epitopes of interfering antibodies to better understand their effect in different sera in order to interpret the associated spectrum of results obtained for measurable Tg. We will need to do better than approximating Tg levels by the ratio of ICMA Tg to Tg measured by competitive immunoassay (993). Authoritative bodies such as the National Academy of Clinical Biochemistry (NACB) should consider mandating specific methodology rather than recommending general guidance. It remains to be seen whether the future standard might entail adoption of a modified ICMA, RIA, or MS methodology.

[D7] Management of metastatic cervical adenopathy detected on ultrasound

With the advent of improved technology, increased utilization, and specialized operator experience, ultrasound imaging can identify small volume metastatic cervical lymph nodes. From the surgical pathology literature analyzing specimens from prophylactic lateral and central neck dissections with normal preoperative cervical lymph node sonography, up to 90% of with papillary cancers less 1 cm have metastatic level VI lymph nodules and up to 40% have metastatic lateral neck lymph nodes (320;994;995). Yet, in the absence of these dissections, this is not the observed clinical locoregional recurrence rate for these patients. It should not be

surprising then, that during extended surveillance, US will be able to detect small volume metastatic disease that may represent a stable reservoir of residual cancer. On the other hand, grossly involved metastatic lymph nodes were at one time minimally invaded by metastatic thyroid cancer. The challenge is to differentiate between low volume metastatic disease that progresses with potential clinical consequences, and that which remains stable. To date, only one study has addressed this question and no sonographic, pathologic, demographic, or molecular feature predicted outcome (793). In addition, it is unclear if growth itself is a harbinger of decreased survival. Therefore, first, observational studies using standardized US scanning protocols are required to define the magnitude of this scenario and define predictors of disease progression. Subsequently, randomized controlled interventional trials could be designed to address change in outcome, such as development of additional locoregional disease, appearance of distant metastases, or disease-specific survival.

[D8] Novel therapies for systemic RAI-refractory disease

Efforts to develop additional and further-improved systemic therapeutic approaches to RAI-refractory metastatic DTC are presently pursuing a variety of approaches. First, the question arises as to whether kinase inhibitors with already demonstrated clinical activity in DTC can be made more effective as single agents. For example, based upon data indicating strong correlation between achieved pazopanib level and extent of clinical response in DTC, indicating absence of response to pazopanib therapy in the lowest quintile of pazopanib drug levels, one clinical trial is presently examining the feasibility and potential benefits of individualization of pazopanib therapy with the goal of achieving target drug levels in the highest achievable fraction of patients, in hopes of improving the fraction of patients benefiting (NCT01552356). Another study is examining the differential impacts of continuous vs. intermittent pazopanib dosing in thyroid cancer (NCT01813136).

Generally predicated upon identification of synergistic interactions in preclinical models, several studies are examining the question of whether therapy combining several agents may improve outcomes in thyroid cancer. Although the majority of combinatorial studies assess effects of multiple co-administered small molecule therapeutics, several are using kinase inhibitors in combination with radioactive iodine (RAI) in efforts to enhance RAI-avidity and clinical efficacy in the context of RAI-refractory disease (e.g. NCT00970359). Still other trials

are focusing on novel non-traditional therapies, including even engineered candidate virotherapeutics (e.g. NCT01229865).

Alternatively, another active area of investigation involves efforts to specifically therapeutically target specific alterations (mutations, translocation) found in patient thyroid cancers in efforts to individualize therapy and potentially thereby improve outcomes in the process; one such recent example is the use of the BRAFV600E inhibitor vemurafenib in BRAFV600E PTC (NCT01286753).

[D9] Survivorship care

The American Cancer Society estimates that there will be almost 63,000 new cases of thyroid cancer diagnosed in 2014, but only about 1900 deaths from thyroid cancer (http://www.cancer.org/cancer/thyroidcancer/detailedguide/thyroid-cancer-key-statistics). According to SEER database statistics, there are more than 500,000 people living with thyroid cancer in the U.S. alone (http://seer.cancer.gov/statfacts/html/thyro.html). Despite these large numbers of patients living with thyroid cancer, there is only a modest amount of peer-reviewed literature studying thyroid cancer survivors.

The majority of literature involving thyroid cancer survivors relates directly to the short term and long term effects of thyroid cancer therapies: surgery, radioiodine and lifetime thyroid hormone therapy. There is very little information regarding the impact of the diagnosis itself, as well as the effect of living with persistent disease such as those with thyroglobulin positive, scan negative thyroid cancer. A thoughtful and comprehensive analysis of thyroid cancer survivors will likely require both qualitative studies with in-depth interviews of survivors that will represent as many demographics of thyroid cancer patients as possible. Additionally, or as a next step, the development and/or utilization of a validated survey type instrument. This instrument would be designed to assess the quality of life of thyroid cancer survivors in a more quantitative manner, will allow for rigorous statistical analyses, and will help to identify areas to target that may improve the lives of thyroid cancer survivors (996) .

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Disclaimer

It is our goal in formulating these guidelines, and the ATA's goal in providing support for the development of these guidelines, that they assist in the clinical care of patients, and share what we believe is current, rational, and optimal medical practice. In some circumstances, it may be apparent that the level of care recommended may be best provided in limited centers with specific expertise. Finally, it is not the intent of these guidelines to replace individual decision making, the wishes of the patient or family, or clinical judgment.

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Table 1. Interpretation of the American College of Physicians' Guideline Grading System (for Therapeutic Interventions)

Recommendation	Clarity of Risk/Benefit	Implications
Strong Recommendation	Benefits clearly outweigh harms and burdens, or visa versa	**Patients:** most would want course of action; a person should request discussion if intervention not offered **Clinicians:** most patients should receive the recommended course of action **Policymakers:** the recommendation can be adopted as policy in most circumstances
Weak Recommendation	Benefits closely balanced with harms and burdens	**Patients:** many would want course of action but some may not – a decision may depend on individual circumstances **Clinicians:** Different choices will be appropriate for different patients – management decision should be consistent with patients' preferences and circumstances **Policymakers:** policymaking will require careful consideration and stakeholder input
No Recommendation	Balance of benefits and risks cannot be determined	Decisions based on evidence cannot be made

Table 2. Recommendations (for Therapeutic Interventions) based on strength of evidence*

Recommendation and Evidence Quality	Description of supporting evidence*	Interpretation
Strong Recommendation		
High-quality evidence	RCT without important limitations or overwhelming evidence from observational studies	Can apply to most patients in most circumstances without reservation
Moderate-quality evidence	RCT with important limitations or strong evidence from observational studies	Can apply to most patients in most circumstances without reservation
Low-quality evidence	Observational studies/case studies	May change when higher-quality evidence available
Weak Recommendation		
High-quality evidence	RCT without important limitations or overwhelming evidence from observational studies	Best action may differ based on circumstances or patients' values
Moderate-quality evidence	RCT with important limitations or strong evidence from observational studies	Best action may differ based on circumstances or patients' values
Low-quality evidence	Observational studies/case studies	Other alternatives may be equally reasonable
Insufficient	Evidence is conflicting, poor quality or lacking	Insufficient evidence to recommend for or against

RCT – randomized, controlled trial
*This description of supporting evidence refers to therapy, therapeutic strategy, or prevention studies. The description of supporting evidence is different for diagnostic accuracy studies.

Table 3. Interpretation of the American Thyroid Association Guideline Grading System for Diagnostic Tests

Recommendation	Accuracy of Diagnostic Information versus Risks and Burden of Testing*	Implications
Strong Recommendation	Knowledge of the diagnostic test result clearly outweighs risks and burden of testing or vice versa	**Patients:** In the case of an accurate test for which benefits outweigh risks/burden, most would want the diagnostic to be offered (with appropriate counseling) a patient should request to discuss the test if it is not offered. In contrast, for a test in which risks and burden outweigh the benfits, most patients should not expect for the test to be offered. **Clinicians:** In the case of an accurate test for which benefits outweigh risks/burden, most patients should be offered the diagnostic test (and provided relevant counseling). Counseling about the test should include a discussion of the risks, benefits, and uncertainties related to testing (as applicable), as well as the implications of the test result. In contrast, for a test in which risks and burden outweigh the perceived benefits, most patients should not be offered the test, or if the test is discussed, the rationale against the test should, for the particular clinical situation, be explained. **Policymakers:** In the case of an accurate test for which benefits outweigh risks/burden, availability of the diagnostic test should be adopted in health policy. In contrast, for a test in which risks and burden outweigh the perceived benefits, some restrictions on circumstances for test use may need to be considered.
Weak Recommendation	Knowledge of the diagnostic test result	**Patients:** most would want to be informed about the diagnostic test, but

	closely balanced with risks and burden of testing	some would not want to seriously consider undergoing the test – a decision may depend on the individual circumstances (eg. risk of disease, co-morbidities, or other), the practice environment, feasibility of optimal execution of the test, and consideration of other available options. **Clinicians:** different choices will be appropriate for different patients, and counseling about the test (if being considered) should include a discussion of the risks, benefits, and uncertainties related to testing (as applicable), as well as the implications of the test result. The decision to perform the test should include consideration of the patients' values, preferences, feasibility, and the specific circumstances. Counseling the patient on why the test may be helpful or not, in her/his specific circumstance, may be very valuable in the decision-making process. **Policymakers:** policymaking decisions on availability of the test will require discussion and stakeholder involvement.
No Recommendation	Balance of knowledge of the diagnostic test result cannot be determined	Decisions on the use of the test based on evidence from scientific studies cannot be made.

* Frequently this guideline, the diagnosis of thyroid cancer (relative to a histologic gold standard) was the diagnostic outcome (unless otherwise specified). However, prognostic, disease staging, or risk stratification studies were also included in the grading scheme of diagnostic studies. For disease staging systems, the implication for use would be on the part of the clinician, in reporting results in the medical record and communicating them to the patient (at applicable time point in disease or follow-up trajectory), as opposed to offering a specific choice of staging/risk stratification system to the patient.

Table 4. Recommendations (for Diagnostic Interventions) based on strength of evidence

Recommendation and Evidence Quality	Methodologic Quality of Supporting Evidence	Interpretation
Strong Recommendation		
High-quality evidence	Evidence from one or more well-designed non-randomized diagnostic accuracy studies (ie. observational – cross-sectional or cohort) or systematic reviews/meta-analyses of such observational studies (with no concern about internal validity or external generalizability of the results)	Implies the test can be offered to most patients in most applicable circumstances without reservation
Moderate-quality evidence	Evidence from non-randomized diagnostic accuracy studies (cross-sectional or cohort), with one or more possible limitations causing minor concern about internal validity or external generalizability of the results	Implies the test can be offered to most patients in most applicable circumstances without reservation
Low-quality evidence	Evidence from non-randomized diagnostic accuracy studies with one or more important limitations causing serious concern about internal validity or external generalizability of the results	Implies the test can be offered to most patients in most applicable circumstances, but the utilization of the test may change when higher-quality evidence becomes available
Weak Recommendation		
High-quality evidence	Evidence from one or more well-designed non-randomized diagnostic accuracy studies (ie. observational – cross-sectional or cohort) or systematic reviews/meta-analyses of such observational studies (with no concern about internal validity or external generalizability of the results)	The degree to which the diagnostic test is seriously considered may differ depending on circumstances or patients' or societal values
Moderate-quality evidence	Evidence from non-randomized diagnostic accuracy studies (cross-sectional or cohort), with one or more possible limitations causing minor concern about	The degree to which the diagnostic test is seriously considered may differ depending on individual patients'/practice circumstances or patients' or societal values

	internal validity or external generalizability of the results	
Low-quality evidence	Evidence from non-randomized diagnostic accuracy studies with one or more important limitations causing serious concern about internal validity or external generalizability of the results.	Alternative options may be equally reasonable.
Insufficient	Evidence may be of such poor quality, conflicting, lacking (ie. studies not done), or not externally generalizable to the target clinical population such that the estimate of the true effect of the test is uncertain and does not permit a reasonable conclusion to be made.	Insufficient evidence to recommend for or against routinely offering the diagnostic test.

Table 5. Organization of the 2014 ATA Guidelines for Thyroid Nodules and DTC

* - New section/recommendation
** - Substantially changed recommendation compared with 2009
Questions are in ***bold***
R – recommendation, F – Figure, T - Table

Page	***Location key***	***Sections and subsections***	***Item***
	[A1]	**THYROID NODULE GUIDELINES**	
	[A2]	***What is the role of thyroid cancer screening in people with familial follicular-cell derived differentiated thyroid cancer?****	R1*
	[A3]	***What is the appropriate laboratory and imaging evaluation for patients with clinically or incidentally discovered thyroid nodules?***	
	[A4]	*Serum TSH measurement*	R2
	[A5]	*Serum thyroglobulin measurement*	R3
	[A6]	*Serum calcitonin measurement*	R4
	[A7]	*^{18}FDG-PET scan**	R5*
	[A8]	*Thyroid sonography*	R6
	[A9]	*Ultrasound (US) for FNA decision making*	R7
	[A10]	*Recommendations for diagnostic FNA of a thyroid nodule based on sonographic features***	R8** F1**, F2**, T6**
	[A11]	***What is the role of fine-needle aspiration (FNA), cytology interpretation and molecular testing in patients with thyroid nodules?****	R9**, F1**, T7**
	[A12]	*Nondiagnostic cytology*	R10
	[A13]	*Benign cytology*	R11
	[A14]	*Malignant Cytology*	R12
	[A15]	*Indeterminate cytology (AUS/FLUS, FN, SUSP)***	
	[A16]	***What are the principles of the molecular testing of FNA samples?****	R13-14
	[A17]	*AUS/FLUS Cytology **	R15**
	[A18]	*Follicular Neoplasm/Suspicious for Follicular Neoplasm (FN) Cytology **	R16**
	[A19]	*Suspicious for Malignancy (SUSP) Cytology **	R17**
	[A20]	***What is the utility of FDG-PET scanning to predict malignant or benign disease when FNA cytology is indeterminate (AUS/FLUS, FN, SUSP)?****	R18*
	[A21]	***What is the appropriate operation for cytologically indeterminate thyroid nodules?****	R19-20**

	[A22]	***How should multinodular thyroid glands (i.e. - 2 or more clinically relevant nodules) be evaluated for malignancy?***	R21-22
	[A23]	***What are the best methods for long-term follow-up of patients with thyroid nodules?***	
	[A24]	*Recommendations for initial follow-up of nodules with benign FNA cytology* **	R23A-C**
	[A25]	*Recommendation for follow-up of nodules with two benign FNA cytology results* *	R23D*
	[A26]	*Follow-up for nodules that do not meet FNA criteria* *	R24*
	[A27]	***What is the role of medical or surgical therapy for benign thyroid nodules?***	R25-29
	[A28]	***How should thyroid nodules in pregnant women be managed?***	
	[A29]	*FNA for thyroid nodules discovered during pregnancy*	R30
	[A30]	*Approaches to pregnant patients with malignant or indeterminate cytology*	R31
	[B1]	**DIFFERENTIATED THYROID CANCER: INITIAL MANAGEMENT GUIDELINES**	
	[B2]	*Goals of initial therapy of DTC*	
	[B3]	***What is the role of preoperative staging with diagnostic imaging and laboratory tests?***	
	[B4]	*Neck imaging - Ultrasound*	R32 F3, T6, T8*
	[B5]	*Neck imaging - CT/MRI/PET* **	R33**
	[B6]	*Measurement of serum Tg and Tg antibodies*	R34
	[B7]	*Operative approach for a biopsy diagnostic for follicular cell-derived malignancy* **	R35**
	[B8]	*Lymph node dissection*	R36-37, F3
	[B9]	*Completion thyroidectomy*	R38
	[B10]	***What is the appropriate perioperative approach to voice and parathyroid issues?****	
	[B11]	*Preoperative care communication* *	R39*
	[B12]	*Preoperative voice assessment* *	R40-41*, T9*
	[B13]	*Intraoperative Voice and Parathyroid Management* *	R42-43*
	[B14]	*Postoperative Voice Care* *	R44-45*
	[B15]	***What are the basic principles of histopathologic evaluation of thyroidectomy samples?****	R46*
	[B16]	***What is the role of postoperative staging systems and risk stratification in the management of DTC?***	
	[B17]	*Postoperative staging*	R47
	[B18]	AJCC/UICC TNM staging	T10
	[B19]	*What initial stratification system should be used to estimate*	R48**,

		*the risk of persistent/recurrent disease?***	T11*, T12**
	[B20]	*Potential impact of specific clinico-pathologic features on the risk estimates in PTC **	
	[B21]	*Potential impact of BRAF V600E and other mutations on risk of recurrence estimates in PTC **	
	[B22]	*Potential impact of Post-operative serum Tg on risk estimates **	
	[B23]	*Proposed modifications to the 2009 ATA initial risk stratification system **	T12**
	[B24]	*Risk of recurrence as a continuum of risk **	F4*
	[B25]	***How should initial risk estimates be modified over time?****	R49
	[B26]	*Proposed terminology to classify response to therapy and clinical implications **	
	[B27]	*Excellent response: no clinical, biochemical or structural evidence of disease after initial therapy (remission, no evidence of disease)**	T13*
	[B28]	*Biochemical incomplete response: abnormal thyroglobulin values in the absence of localizable disease **	T13*
	[B29]	*Structural incomplete response: persistent or newly identified loco-regional or distant metastases **	T13*
	[B30]	*Indeterminate response: biochemical or structural findings which cannot be classified as either benign or malignant (acceptable response).**	T13*
	[B31]	*Using risk stratification to guide disease surveillance and therapeutic management decisions.**	
	[B32]	***Should postoperative disease status be considered in decision-making on RAI therapy for patients with DTC?***	R49
	[B33]	*Utility of Post-operative serum Tg in clinical decision making*	
	[B34]	*Potential role of post-operative US in conjunction with post-operative serum Tg in clinical decision making*	
	[B35]	*Role of post-operative radioisotope diagnostic scanning in clinical decision making*	
	[B36]	***What is the role of radioactive iodine (RAI) (including remnant ablation, adjuvant therapy, or therapy of persistent disease) after thyroidectomy, in the primary management of differentiated thyroid cancer?***	R51 T14
	[B37]	*What is the role of molecular marker status in therapeutic RAI decision-making?**	R52*
	[B38]	***How long does thyroid hormone need to be withdrawn in preparation for RAI remnant ablation/treatment or diagnostic scanning?***	R53
	[B39]	***Can rhTSH (Thyrogen™) be used as an alternative to thyroxine withdrawal for remnant ablation or adjuvant therapy in patients who have undergone near-total or total***	R54

		thyroidectomy?	
	[B40]	***What activity of ^{131}I should be used for remnant ablation or adjuvant therapy?*****	R55-56**
	[B41]	***Is a low-iodine diet necessary before remnant ablation?***	R57
	[B42]	***Should a posttherapy scan be performed following remnant ablation?***	R58
	[B43]	*Early management of DTC after initial therapy*	
	[B44]	***What is the appropriate degree of initial TSH suppression?***	R59
	[B45]	***Is there a role for adjunctive external beam irradiation or chemotherapy?***	
	[B46]	*External beam irradiation*	R60
	[B47]	*Systemic adjuvant therapy*	R61
	[C1]	**DTC: LONG-TERM MANAGEMENT AND ADVANCED CANCER MANAGEMENT GUIDELINES**	
	[C2]	***What are the appropriate features of long-term management?***	
	[C3]	***What are the criteria for absence of persistent tumor (excellent response)?***	
	[C4]	***What are the appropriate methods for following patients after initial therapy?***	
	[C5]	***What is the role of serum Tg measurement in the follow up of DTC?*****	R62-63**
	[C6]	*Serum thyroglobulin measurement and clinical utility*	
	[C7]	*Antithyrogloublin antibodies*	
	[C8]	***What is the role of serum Tg measurement in patients who have not undergone radioiodine remnant ablation?***	R64
	[C9]	***What is the role of US and other imaging techniques (RAI SPECT-CT, CT, MRI, PET-CT) during follow-up?***	
	[C10]	*Cervical ultrasonography*	R65
	[C11]	*Diagnostic whole-body RAI scans*	R66-67
	[C12]	*^{18}FDG-PET scanning*	R68
	[C13]	*CT and MRI imaging**	R69*
	[C14]	*Using ongoing risk stratification (response to therapy) to guide disease long-term surveillance and therapeutic management decisions**	
	[C15]	***What is the role of TSH suppression during thyroid hormone therapy in the long-term follow-up of DTC?*****	R70** T15*
	[C16]	***What is the most appropriate management of DTC patients with metastatic disease?***	
	[C17]	***What is the optimal directed approach to patients with suspected structural neck recurrence?***	R71
	[C18]	*Nodal Size Threshold*	
	[C19]	*Extent of Nodal Surgery*	
	[C20]	*Ethanol Injection**	
	[C21]	*Radiofrequency or Laser Ablation**	

	[C22]	*Other therapeutic options**	
	[C23]	***What is the surgical management of aerodigestive invasion?***	R72
	[C24]	***How should RAI therapy be considered for locoregional or distant metastatic disease?***	
	[C25]	*Administered activity of ^{131}I for locoregional or metastatic disease***	R73**
	[C26]	*Use of rhTSH (Thyrogen™) to prepare patients for ^{131}I therapy for locoregional or metastatic disease.*	R74-75
	[C27]	*Use of lithium in ^{131}I therapy*	R76
	[C28]	***How should distant metastatic disease to various organs be treated?***	
	[C29]	*Treatment of pulmonary metastases*	R77-78
	[C30]	*RAI treatment of bone metastases*	R79
	[C31]	***When should empiric RAI therapy be considered for Tg-positive, RAI diagnostic scan–negative patients?***	R80-82
	[C32]	***What is the management of complications of RAI therapy?***	R83-85
	[C33]	***How should patients who have received radioiodine therapy be monitored for risk of secondary malignancies?***	R86
	[C34]	***What other testing should patients receiving RAI therapy undergo?***	R87
	[C35]	***How should patients be counseled about radioiodine therapy and pregnancy, nursing and gonadal function?***	R88-90
	[C36]	***How is radioiodine-refractory DTC defined?****	R91*
	[C37]	***Which patients with metastatic thyroid cancer can be followed without additional therapy?****	R92*
	[C38]	***What is the role for directed therapy in advanced thyroid cancer?*****	R93**
	[C39]	*Treatment of brain metastases*	R94
	[C40]	***Who should be considered for clinical trials?****	R95*
	[C41]	***What is the role of systemic therapy (kinase inhibitors, other selective therapies, conventional chemotherapy, bisphosphonates) in treating metastatic DTC?*****	
	[C42]	*Kinase Inhibitors**	R96*, T16*
	[C43]	*Patients who fail first-line kinase inhibitor therapy* *	R97*
	[C44]	*Management of toxicities from kinase inhibitor therapy**	R98*, T17*
	[C45]	*Other Novel Agents**	R99
	[C46]	*Cytotoxic Chemotherapy*	R100
	[C47]	*Bone-Directed Agents***	R101**
	[D1]	**DIRECTIONS FOR FUTURE RESEARCH**	
	[D2]	*Optimizing molecular markers for diagnosis, prognosis and therapeutic targets*	

	[D3]	*Active surveillance of DTC primary tumors*	
	[D4]	*Improved risk stratification*	
	[D5]	*Improving our understanding of the risks and benefits of DTC treatments*	
	[D6]	*Issues with measurement of Tg and Tg antibodies*	
	[D7]	*Small cervical lymph node metastases*	
	[D8]	*Novel therapies for systemic RAI-refractory disease*	
	[D9]	*Survivorship care*	

Table 6. Sonographic patterns and estimated risk of malignancy for thyroid nodules.

Sonographic Pattern	US features	Estimated risk of malignancy	Consider biopsy
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule ***with*** one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension	>70-90%*	≥ 1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins ***without*** microcalcifications, extrathyroidal extension, or taller than wide shape	10-20%	≥ 1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, ***without*** microcalcification, irregular margin or extrathyroidal extension, or taller than wide shape.	5-10%	≥ 1.5 cm
Very low suspicion	Spongiform or partially cystic nodules ***without*** any of the sonographic features described in low, intermediate or high suspicion patterns	< 3%	≥ 2 cm
Benign	Purely cystic nodules (no solid component)	< 1%	No biopsy**

* - the estimate is derived from high volume centers, the overall risk of malignancy may be lower given the interobserver variability in sonography
** - aspiration of the cyst may be considered for symptomatic or cosmetic drainageUS FNA should be considered for lymph nodes that are sonographically suspicious for thyroid cancer
Note: *US FNA should be considered for lymph nodes that are sonographically suspicious for thyroid cancer (see Table 8)*

Table 7. The Bethesda system for reporting thyroid cytopathology: Diagnostic categories and risk of malignancy[1]

Diagnostic category	Estimated/predicted risk of malignancy by the Bethesda system (%)[1]	Actual risk of malignancy in nodules surgically excised (%, median (range))[2]
Nondiagnostic or Unsatisfactory	1-4	20 (9-32)
Benign	0-3	2.5 (1-10)
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)	5-15	14 (6-48)
Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN)	15-30	25 (14-34)
Suspicious for Malignancy (SFM)	60-75	70 (53-97)
Malignant	97-99	99 (94-100)

[1]As reported in The Bethesda System by Ali &Cibas, 2010
[2]Based on the meta-analysis of 8 studies reported by Bongiovanni et al. (173). The risk was calculated based on the portion of nodules in each diagnostic category that underwent surgical excision.

Table 8: Ultrasound features of lymph nodes predictive of malignant involvement. (adapted from Leboulleux et al. (261))

Criterion	Sensitivity % (95% CI)	Specificity % (95% CI)
Size >1 cm	68 (48-84)	75 (55-89)
Shape (ratio of long axis to short axis <2.0)	46 (28-66)	64 (44-81)
Punctate calcifications	46 (28-66)	100 (88-100)
Peripheral hypervascularity	86 (67-96)	82 (63-94)

Table 9. Preoperative factors which may be associated with laryngeal nerve dysfunction.

History: Voice abnormality, dysphagia, airway symptoms, hemoptysis, pain, rapid progression.
Physical exam: Extensive, firm mass fixed to the larynx or trachea.
Imaging : Mass extending to/beyond periphery of thyroid lobe posteriorly and/or tracheoesophageal infiltration, or bulky cervical adenopathy along the course of the RLN or vagus nerve.

Table 10. AJCC 7th edition/TNM Classification System for Differentiated Thyroid Carcinoma

	Definition
T0	No evidence of primary tumor
T1a	Tumor ≤1 cm, without extrathyroidal extension
T1b	Tumor >1 cm but ≤2 cm in greatest dimension, without extrathyroidal extension
T2	Tumor >2 cm but ≤4 cm in greatest dimension, without extrathyroidal extension.
T3	Tumor >4 cm in greatest dimension limited to the thyroid -or- Any size tumor with minimal extrathyroid extension (e.g., extension into sternothyroid muscle or perithyroidal soft tissues).
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.
T4b	Tumor of any size invading prevertebral fascia or encasing carotid artery or mediastinal vessels
N0	No metastatic nodes
N1a	Metastases to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes).
N1b	Metastases to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)
M0	No distant metastases
M1	Distant Metastases

Patient age < 45 years old at diagnosis

I	Any T	Any N	M0
II	Any T	Any N	M1

Patient age ≥ 45 years old at diagnosis

I	T1a	N0	M0
	T1b	N0	M0
II	T2	N0	M0
III	T1a	N1a	M0
	T1b	N1a	M0
	T2	N1a	M0
	T3	N0	M0
	T3	N1a	M0
IVa	T1a	N1b	M0
	T1b	N1b	M0
	T2	N1b	M0
	T3	N1b	M0

	T4a	N0	M0
	T4a	N1a	M0
	T4a	N1b	M0
IVb	T4b	Any N	M0
IVc	Any T	Any N	M1

The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010), Springer Publishing. This is a modified version of that staging system.
Need AJCC approval for use?

Table 11. ATA risk of recurrence stratification system: clinical outcomes following total thyroidectomy and RAI remnant ablation.

ATA Risk	Study	NED	Biochemical Incomplete**	Structural Incomplete
Low	Tuttle 2010	86%	11%	3%
	Castagna 2011	91%	ND*	ND*
	Vaisman 2012	88%	10%	2%
	Pitoia 2013	78%	15%	7%
Intermediate*	Tuttle 2010	57%	22%	21%
	Vaisman 2012	63%	16%	21%
	Pitoia 2013	52%	14%	34%
High	Tuttle 2010	14%	14%	72%
	Vaisman 2012	16%	12%	72%
	Pitoia 2013	31%	13%	56%

NED – no evidence of disease

ND – not determined

*Because the ATA intermediate and high risk groups were merged into a single "high risk" group in the Castagna series, risk of persistent/recurrence for these subgroups were not presented.

**Proportion of patients with a biochemical incomplete response. Definition: suppressed Tg > 1 ng/mL, TSH-stimulated Tg > 10 ng/ml, or rising Tg Ab levels in the absence of structural disease.

***Proportion of patients with persistent/recurrent disease that is structural. Definition: structural disease that is either biopsy proven or highly suspicious for disease with or without abnormal serum Tg.

Table 12. ATA 2009 risk stratification system with proposed modifications

ATA Low Risk	Papillary Thyroid Cancer (with all of the following) • No local or distant metastases; • All macroscopic tumor has been resected • No tumor invasion of locoregional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • No vascular invasion • ***Clinical N0 or ≤ 5 pathologic N1 micrometastases (<0.2 cm in largest dimension)**** • If 131I is given, there are no RAI avid metastatic foci outside the thyroid bed on the first post-treatment whole-body RAI scan ***Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer**** ***Intrathyroidal, well differentiated follicular thyroid cancer with only capsular invasion**** ***Intrathyroidal, well differentiated follicular thyroid with minor vascular invasion**** Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including V600E BRAF mutated (if known)*
ATA Intermediate Risk	Microscopic invasion of tumor into the perithyroidal soft tissues ***Clinical N1 or >5 pathologic N1 with all involved lymph nodes < 3 cm in largest dimension**** RAI avid metastatic foci in the neck on the first post-treatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion. ***Intrathyroid, papillary thyroid cancer, primary tumor 1-4 cm, V600E BRAF mutated (if known)**** ***Multifocal papillary microcarcinoma with extrathyroidal extension and V600E BRAF mutated (if known)****
ATA High Risk	Macroscopic invasion of tumor into the perithyroidal soft tissues (gross extrathyroidal extension), Incomplete tumor resection Distant metastases

	Pathologic N1 with any metastatic lymph node ≥ 3 in largest dimension*
	Post-operative serum thyroglobulin suggestive of distant metastases
	Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)*

***Proposed modifications, not present in the original 2009 initial risk stratification system.** *See sections [B19]-[B23] and Recommendation 48B.*

Table 13. Clinical implications of response to therapy re-classification in differentiated thyroid cancer patients treated with total thyroidectomy and RAI remnant ablation

Category	Definitions[1]	Clinical Outcomes	Management Implications
Excellent Response	Negative imaging *and either* Suppressed Tg <0.2 ng/mL* *or* TSH stimulated Tg < 1 ng/mL*	1-4% recurrence[2] <1% disease specific death[2]	An excellent response to therapy should lead to an early decrease in the intensity and frequency of follow up and the degree of TSH suppression
Biochemical Incomplete Response	Negative imaging *and* Suppressed Tg > 1 ng/mL* *or* Stimulated Tg > 10 ng/mL* *or* Rising Anti-Tg Ab levels;	At least 30% spontaneously evolve to NED[3] 20% achieve NED after additional therapy[1] 20% develop structural disease[1] <1% disease specific death[1]	If associated with stable or declining serum Tg values, a biochemical incomplete response should lead to continued observation with ongoing TSH suppression in most patients. Rising Tg or Tg antibody values should prompt additional investigations and potentially additional therapies.
Structural Incomplete Response	Structural or functional evidence of disease With any Tg level +/- Tg Ab	50-85% continue to have persistent disease despite additional therapy. [4] Disease specific death rates as	A structural incomplete response may lead to additional treatments or ongoing observation depending on multiple clinico-pathologic factors including the size, location, rate of growth, RAI avidity, FDG avidity, and specific pathology of the

		high as 11% with loco-regional metastases and 50% with structural distant metastases[1]	structural lesions.
Indeterminate Response	Non-specific findings on imaging studies Faint uptake in thyroid bed on RAI scanning Non-stimulated Tg detectable, but less than 1 ng/mL Stimulated Tg detectable, but less than 10 ng/mL or Tg antibodies stable or declining in the absence of structural or functional disease	15-20% will have structural disease identified during follow-up[1] In the remainder, the non-specific changes are either stable, or resolve. [1] <1% disease specific death[1]	An indeterminate response should lead to continued observation with appropriate serial imaging of the non-specific lesions and serum Tg monitoring. Non-specific findings that become suspicious over time can be further evaluated with additional imaging or biopsy.

NED denotes a patient as having no evidence of disease at final follow-up
* In the absence of anti-Tg antibodies

[1] Tuttle Thyroid 2010, and Vaisman Clin Endo 2012
[2]Tuttle thyroid 2010, Castagna Eur J Endo 2011, Vaisman Clin Endo 2012, Berger Eur J Nucl Med Mol Imaging 2011, Malandrino JCEM 2011**,** Soyluk, Thyroid 2011, Piccardo J Endo Invest 2010**,** Castagna JCEM 2008, Kloos JCEM 2005, Kloos JCEM 2010, Han Thyroid 2012**,** Rosario Thyroid 2012, Brassard JCEM 2011**,** Pelttari Eur J Endo 2010, Klubo-Gwiezdzinska Clin Endo 2011**,** Crocetti Thyroid 2008, Torlontano JCEM 2004, Verburg Eur J Nucl Med Mol Imaging 2010, Giovanella Clin Chem Lab Med 2009.
[3]Castagna J Endo Invest 2011, Bilo Europ J of Nuclear Med and molecular imaging 2010, Baudin JCEM 2003, Pineda JCEM 1995, Alzahrani J of Endo Invest 2005, Crocetti Thyroid 2008, Valadao Thyroid 2006, Torlontano JCEM 2004, Castagna J Endo Invest 2011
[4]Vasiman Thyroid 2011, Vaisman Clin Endo 2011,Schuff Laryngoscope 2008, Al-saif JCEM 2010, Yim JCEM 2011

Table 14. Characteristics according to the ATA Risk Stratification System and AJCC/TNM Staging System that may Impact Post-operative RAI Decision-making

ATA recurrence risk ***Staging*** ***T*** ***N*** ***M***	**Description**	**Body of Evidence Suggests RAI Improves Disease-Specific Survival?**	**Body of Evidence Suggests RAI Improves Disease-Free Survival?**	**Post-Surgical RAI Indicated?**
ATA low risk ***T1a*** ***N0,Nx*** ***M0,Mx***	Tumor size ≤1cm (uni-or multi-focal)	No	No	No
ATA low risk ***T1b,T2*** ***N0, Nx*** ***M0,Mx***	Tumor size >1-4 cm	No	Conflicting observational data	Not routine – may be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk)
ATA low to intermediate risk ***T3*** ***N0,Nx*** ***M0,Mx***	Tumor size >4 cm	Conflicting data	Conflicting observational data	Consider - Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cut-offs subject to some uncertainty*
ATA low to intermediate risk ***T3*** ***N0,Nx*** ***M0,Mx***	Microscopic extra-thyroidal extension, any tumor size	No	Conflicting observational data	Consider - Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI
ATA low to intermediate risk ***T1-3*** ***N1a*** ***M0,Mx***	Central compartment neck lymph node metastases	No, except possibly in subgroup of patients ≥ 45 years of age (NTCTCSG Stage III)	Conflicting observational data	Consider – Generally favored, due to somewhat higher risk of persistent or recurrent disease, especially with increasing number of large (>2-3 cm) or clinically evident lymph nodes or presence of extra-nodal extension. Advancing age may also favor RAI use.* However, there is insufficient data to mandate RAI use in patients with few (<5) microscopic nodal metastases in central compartment in absence of other adverse features.
ATA low to intermediate risk ***T1-3*** ***N1b*** ***M0,Mx***	Lateral neck or mediastinal lymph node metastases	No, except possibly in subgroup of patients ≥ 45 years of age	Conflicting observational data	Consider - Generally favored, due to higher risk of persistent or recurrent disease, especially with increasing number of macroscopic or clinically evident lymph nodes or presence of

				extra-nodal extension. Advancing age may also favor RAI use.*
ATA high risk ***T4*** ***Any N*** ***Any M***	Any size, gross extra-thyroidal extension	Yes (observational data)	Yes (observational data for disease persistence and recurrence)	Yes
ATA high risk ***M1*** ***Any T*** ***Any N***	Distant metastases	Yes (observational data)	Yes (observational data)	Yes

*Recent data from the NTCTCSG (National Thyroid Cancer Treatment Cooperative Study Group) have suggested that a more appropriate prognostic age cut-off for their and other classification systems could be 55 years, rather than 45 years, particularly for women

ETE – extrathyroidal extension

Table 15. TSH targets for long-term thyroid hormone therapy

Response to cancer therapy

Risk of LT4 therapy	Excellent	Indeterminate	Biochemical incomplete	Structural incomplete
Minimal	No Suppression. TSH target 0.5*-2.0 mU/L	Mild Suppression. TSH target 0.1-0.5*mU/L	Moderate or Complete Suppression. TSH target <0.1 mU/L	
Moderate				
High				

* - 0.5 mU/L represents the lower limit of the reference range for the TSH assay which can be 0.3-0.5 mU/L depending on the specific assay

Table 16. Factors to review when considering kinase inhibitor therapy

Factors Favoring Kinase Inhibitor Therapy	Factors Discouraging Kinase Inhibitor Therapy
Clinically significant anatomical disease progression in 6 months or less despite optimal TSH suppression in RAI-refractory disease not amenable to control using focal therapeutic approaches (e.g. surgery, radiation therapy, ablation)	Comorbidity including: • Active or recent intestinal disease (e.g. diverticulitis, inflammatory bowel disease, recent bowel resection) • Liver disease • Recent bleeding (e.g. ulcer/GI bleed) or coagulopathy • Recent cardiovascular event(s) (e.g. CVA, MI) • Cachexia/low weight/poor nutriture • Poorly controlled hypertension • Prolonged QTc interval/history of significant arrhythmia (includes ventricular and bradyarhymias) • Untreated brain metastases (controversial) • Recent suicidal ideation (suicide has been reported in depressed patient receiving TKIs)
Symptomatic disease (e.g. exertional dyspnea, painful unresectable adenopathy))	
Imminently threatening disease (tumor progression expected to require intervention and/or to produce morbidity or mortality in <6 months; e.g. pulmonary lesions or lymphadenopathy likely to rapidly invade airways or cause bronchial obstruction	
Diffuse disease progression (e.g. in multiple lung metastases; as opposed to focal progression) NOTE: bony metastases are often poorly responsive to kinase inhibitor therapy (see **Bone Directed Agents** in section [C46]).	Life expectancy based upon other co-morbidity estimated to be too brief to justify systemic therapy

Table 17. Potential toxicities and recommended screening or surveillance approaches in patients started on kinase inhibitor therapy

Toxicity	Recommended Screening/Surveillance
Hypertension	Frequent blood pressure monitoring, most critical during the first 8 weeks of therapy; if hypertension is induced, therapy should be individualized to patient response • Note: effective and expeditious management of hypertension is critical - and may reduce potential for cardiotoxicity; if antihypertensive therapy is needed, calcium channel blockers (e.g. amlodipine) may be most effective.
Hepatotoxicity	Serial assessment of AST, alkaline phosphatase and Bilirubin - most critical during the first 8 weeks of therapy • Note: dose reduction of kinase inhibitor therapy is commonly required due to hepatic toxicity
Cardiotoxicity	ECG pre-therapy, and frequently during therapy • Hold (or do not initiate) kinase inhibitor therapy if QTc>480 msec Echocardiogram, elective - but recommended in any patient with cardiac history; especially important in patient with hypertension, symptoms consistent with congestive heart failure or coronary artery disease and in patients receiving sunitinib
Hypothyroidism	TSH should be assessed frequently, with levothyroxine dosage altered in response to rising TSH if observed
Nephrotoxicity	Serial serum creatinine, UA w/ protein determination,
Hematological toxicities	Serial CBC/diff
Pancreatitis	Serial Amylase
Teratogenicity	Pre-therapy pregnancy testing and effective contraception in women and men of childbearing potential

Figure legends

Figure 1. Algorithm for evaluation and management of patients with thyroid nodules based on US pattern and FNA cytology. R – Recommendation in text.

Figure 2. ATA nodule sonographic patterns and risk of malignancy

Figure 3. Lymph node compartments separated into levels and sublevels. Level VI contains the thyroid gland, and the adjacent nodes bordered superiorly by the hyoid bone, inferiorly by the innominate (brachiocephalic) artery, and laterally on each side by the carotid sheaths. The level II, III, and IV nodes are arrayed along the jugular veins on each side, bordered anteromedially by level VI and laterally by the posterior border of the sternocleidomastoid muscle. The level III nodes are bounded superiorly by the level of the hyoid bone, and inferiorly by the cricoid cartilage; levels II and IV are above and below level III, respectively. The level I node compartment includes the submental and submandibular nodes, above the hyoid bone, and anterior to the posterior edge of the submandibular gland. Finally, the level V nodes are in the posterior triangle, lateral to the lateral edge of the sternocleidomastoid muscle. Levels I, II, and V can be further subdivided as noted in the figure. The inferior extent of level VI is defined as the suprasternal notch. Many authors also include the pretracheal and paratracheal superior mediastinal lymph nodes above the level of the innominate artery (sometimes referred to as level VII) in central neck dissection (302).

Figure 4. Risk of structural disease recurrence in patients without structurally identifiable disease after initial therapy. The risk of structural disease recurrence associated with selected clinico-pathological features are shown as a continuum of risk with percentages (ranges, approximate values) presented to reflect our best estimates based on the published literature reviewed in the text. In the left hand column, the three tiered risk system proposed as the Modified Initial Risk Stratification System is also presented to demonstrate how the continuum of risk estimates informed our modifications of the 2009 ATA Initial Risk System (See recommendation 48). (≈ approximately) **(***) While analysis of BRAF and or TERT status is not routinely recommended for initial risk stratification, we have included these findings to assist

clinicians in proper risk stratification in cases where this information is available.

Figure 5. Clinical decision making and management recommendations in ATA low risk differentiated thyroid cancer patients that have undergone total thyroidectomy. R – Recommendation in text.

Figure 6. Clinical decision making and management recommendations in ATA low risk differentiated thyroid cancer patients that have undergone less than total thyroidectomy (lobectomy or lobectomy with isthmusectomy). R – Recommendation in text.

Figure 7. Clinical decision making and management recommendations in ATA intermediate risk differentiated thyroid cancer patients that have undergone total thyroidectomy. R – Recommendation in text.

Figure 8. Clinical decision making and management recommendations in ATA high risk differentiated thyroid cancer patients that have undergone total thyroidectomy and have no gross residual disease remaining in the neck. R – Recommendation in text.

Figure 1

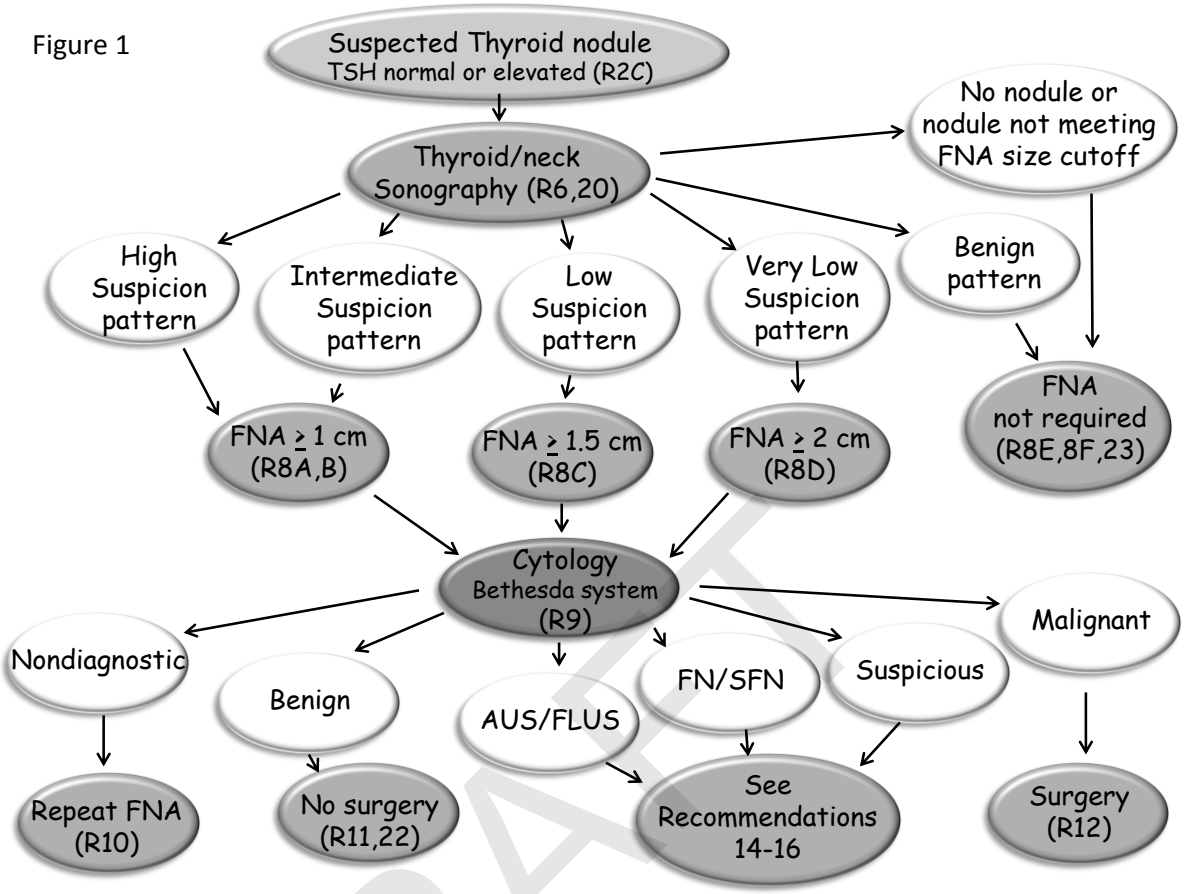


Figure 2

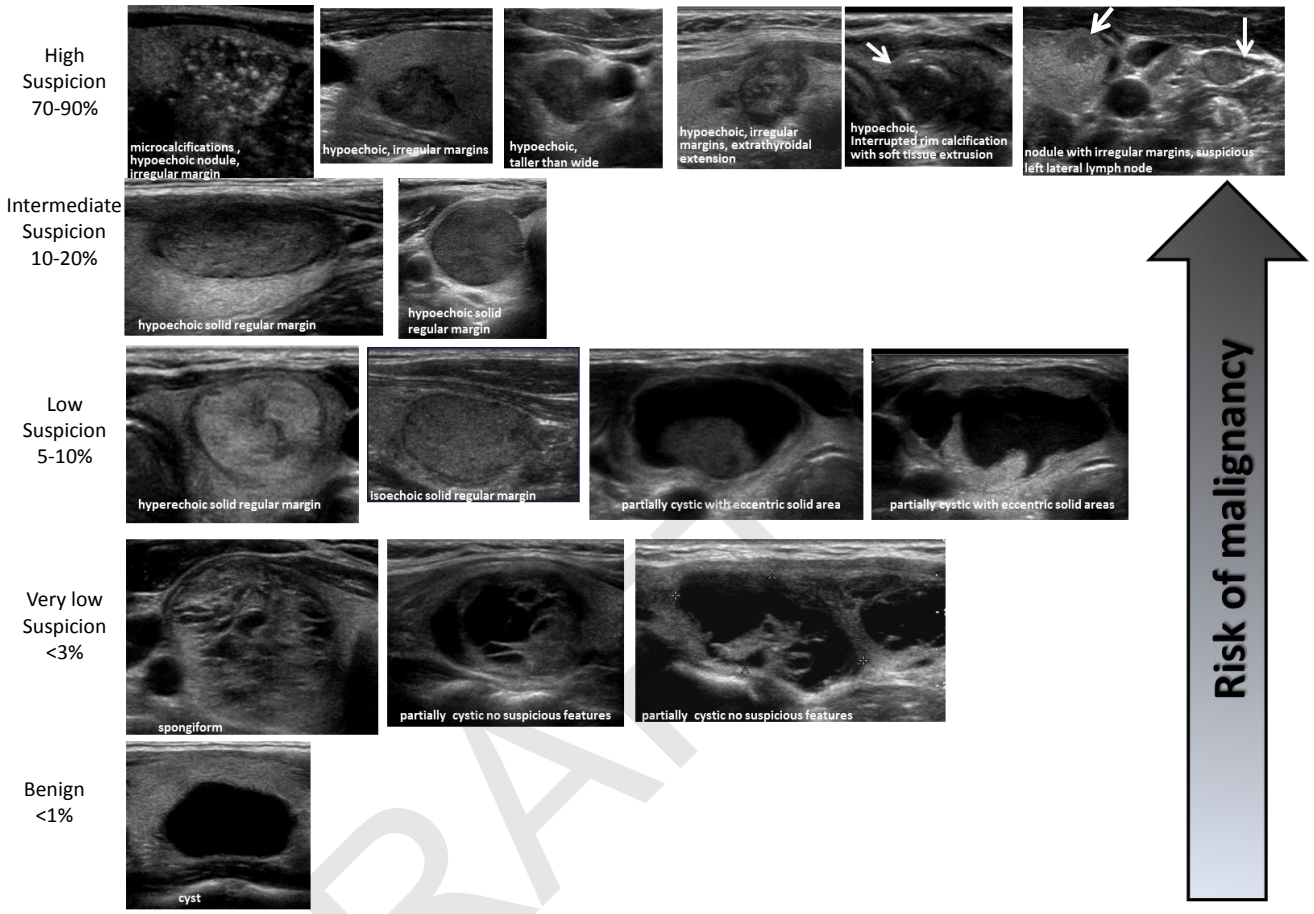
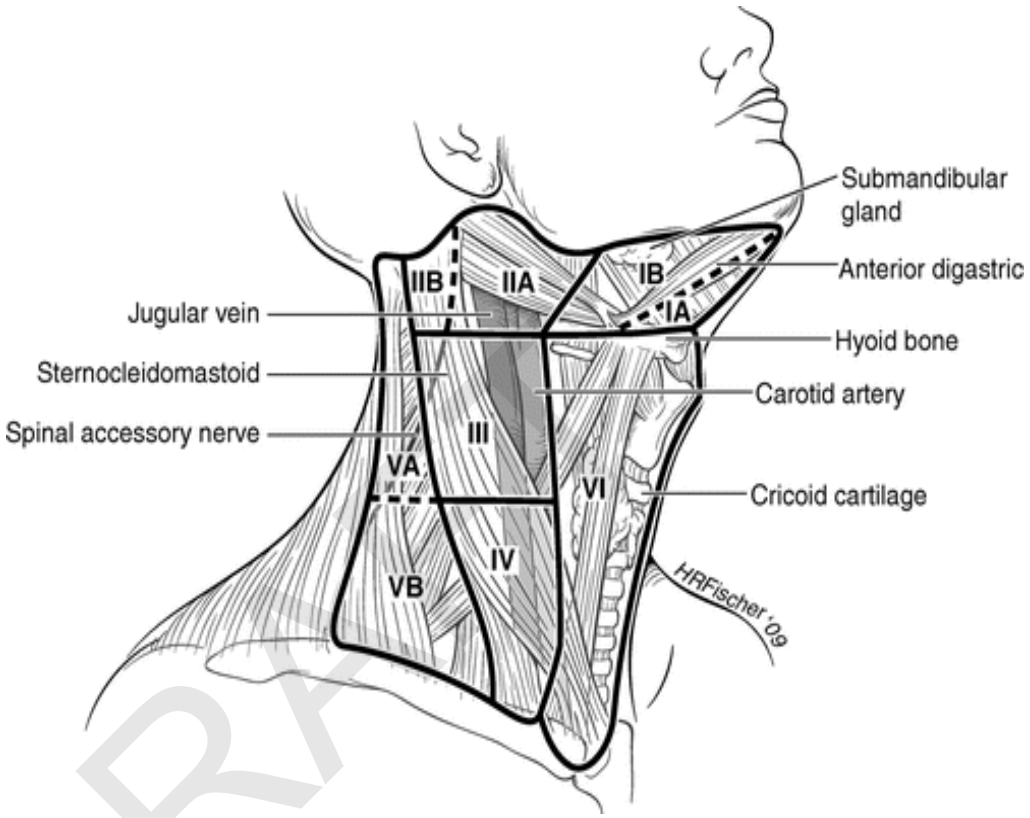


Figure 3



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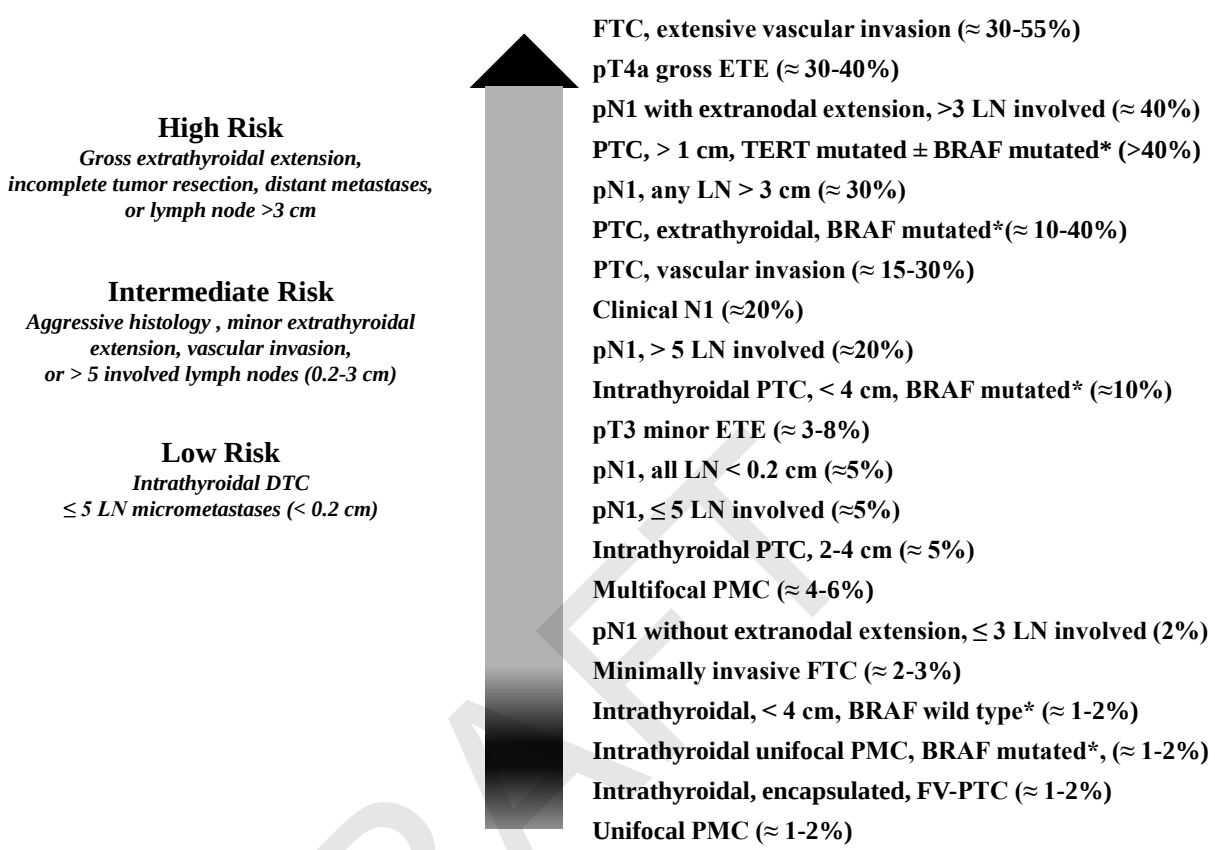


Figure 5

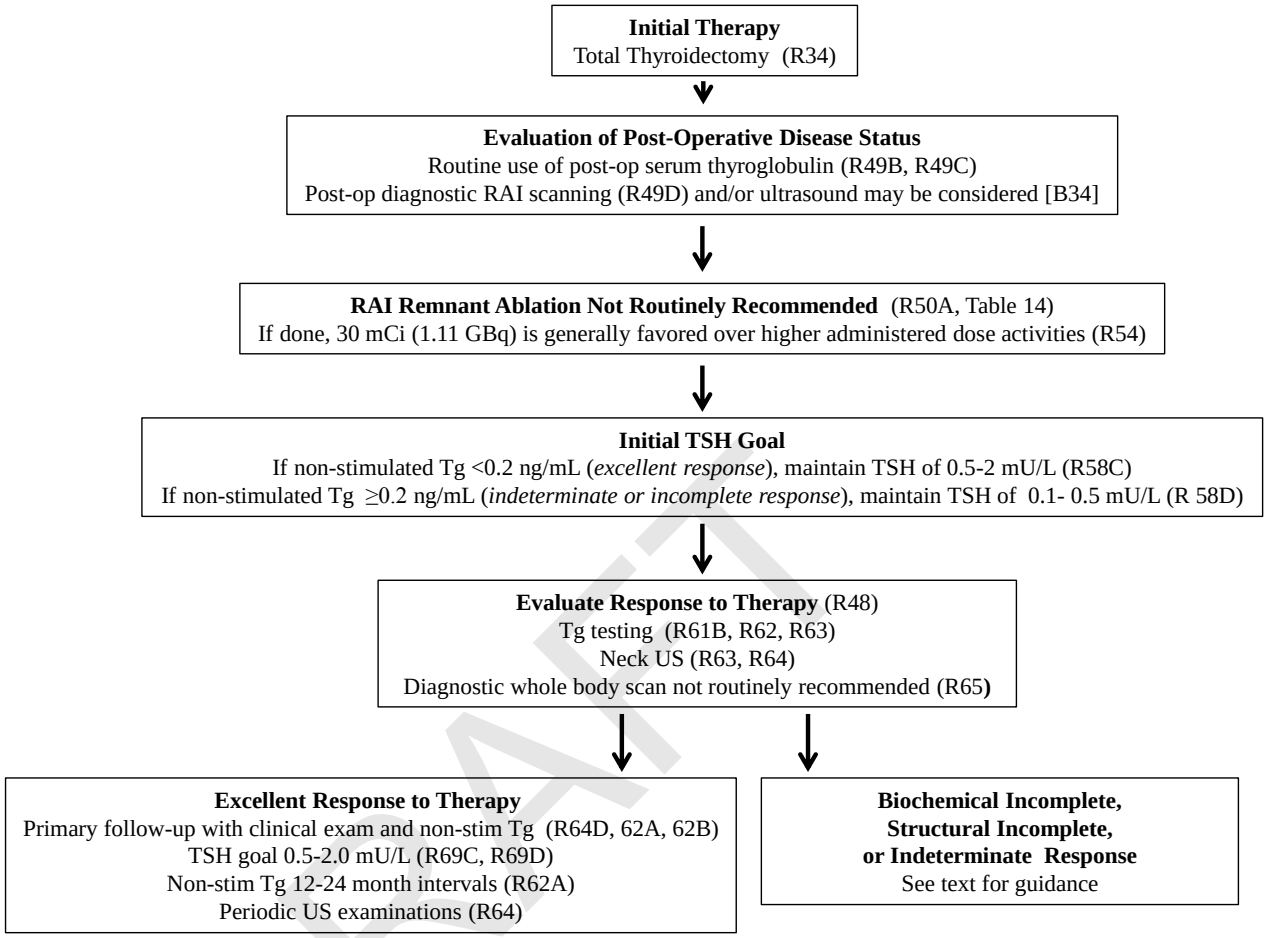


Figure 6

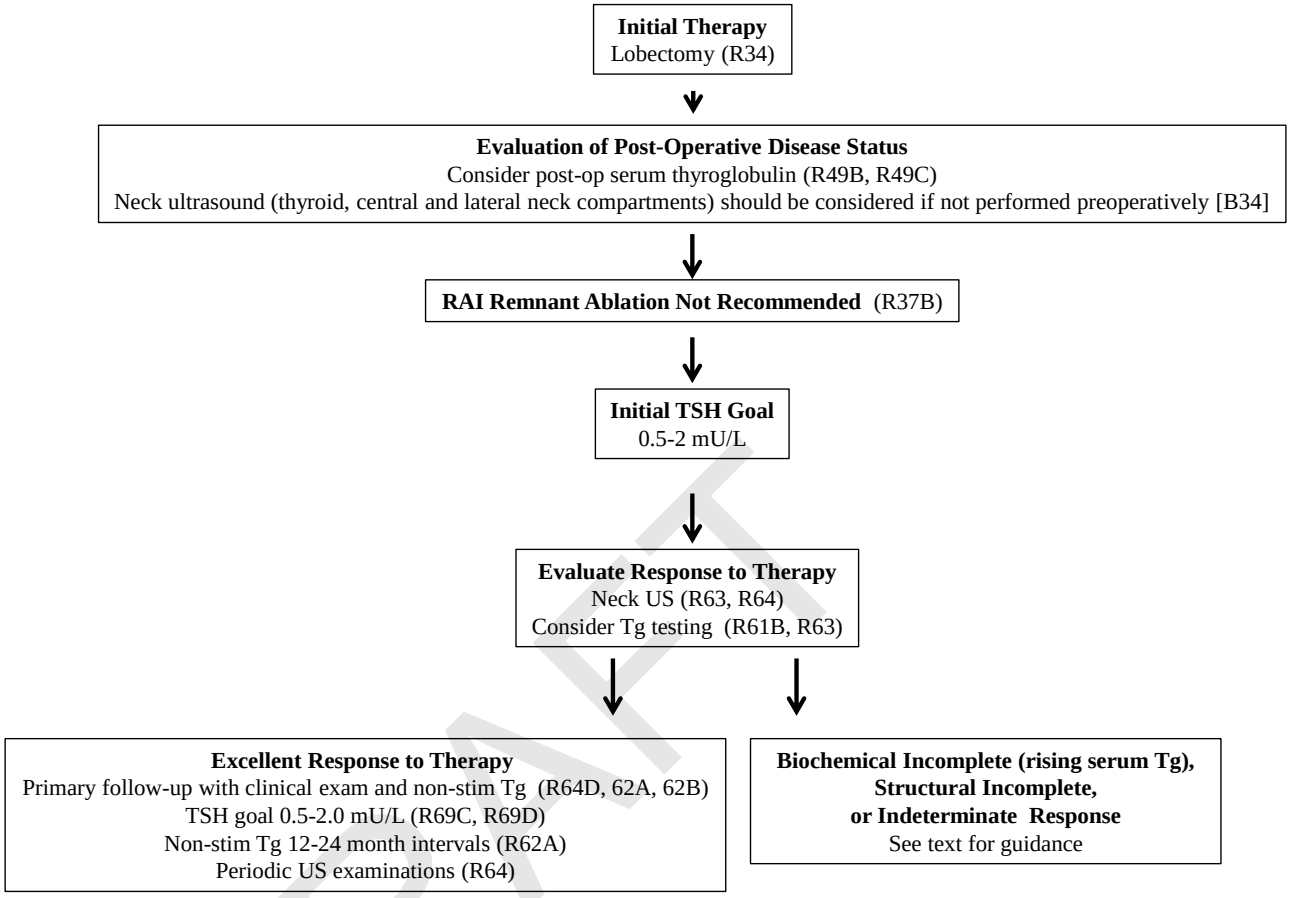


Figure 7

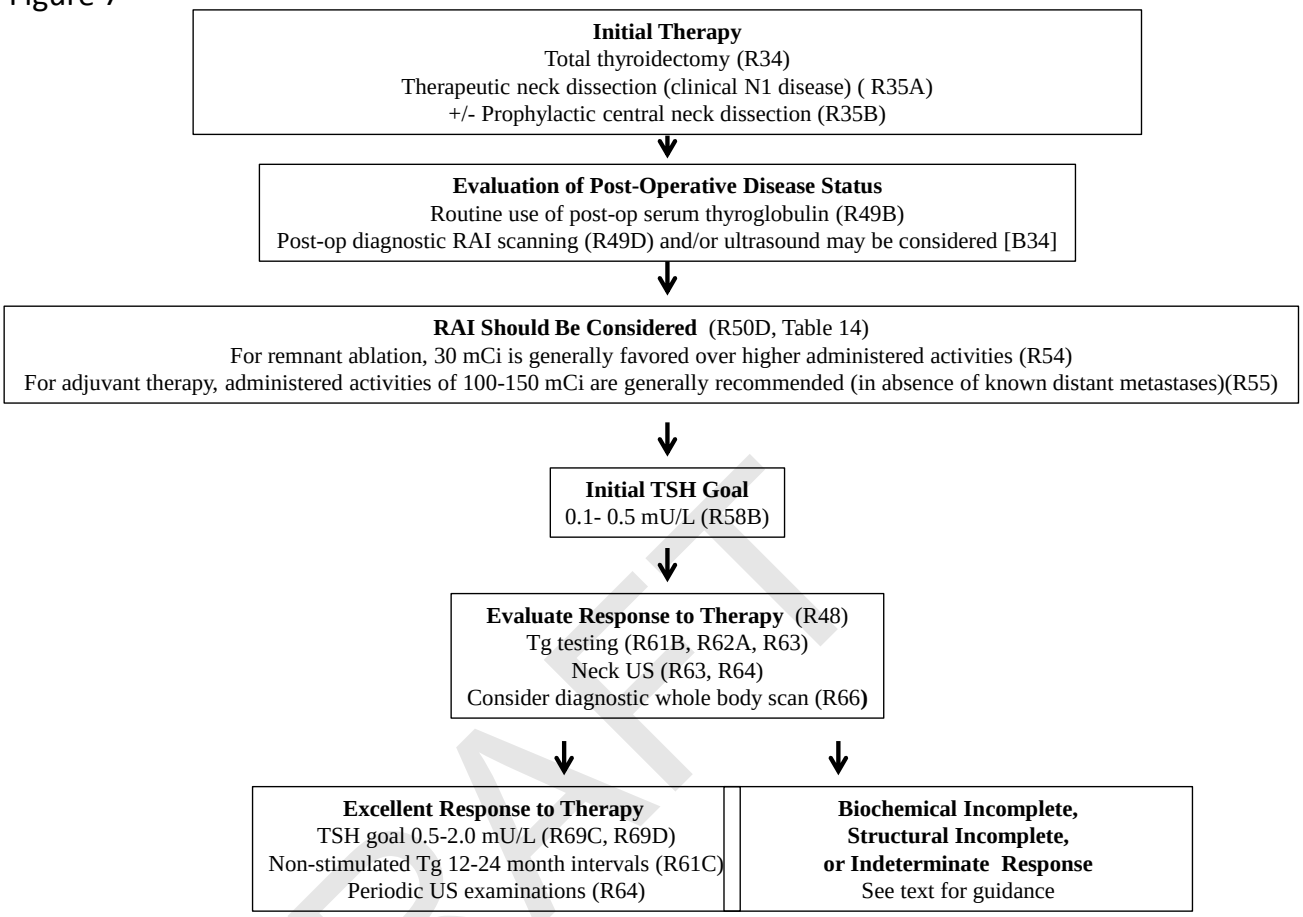
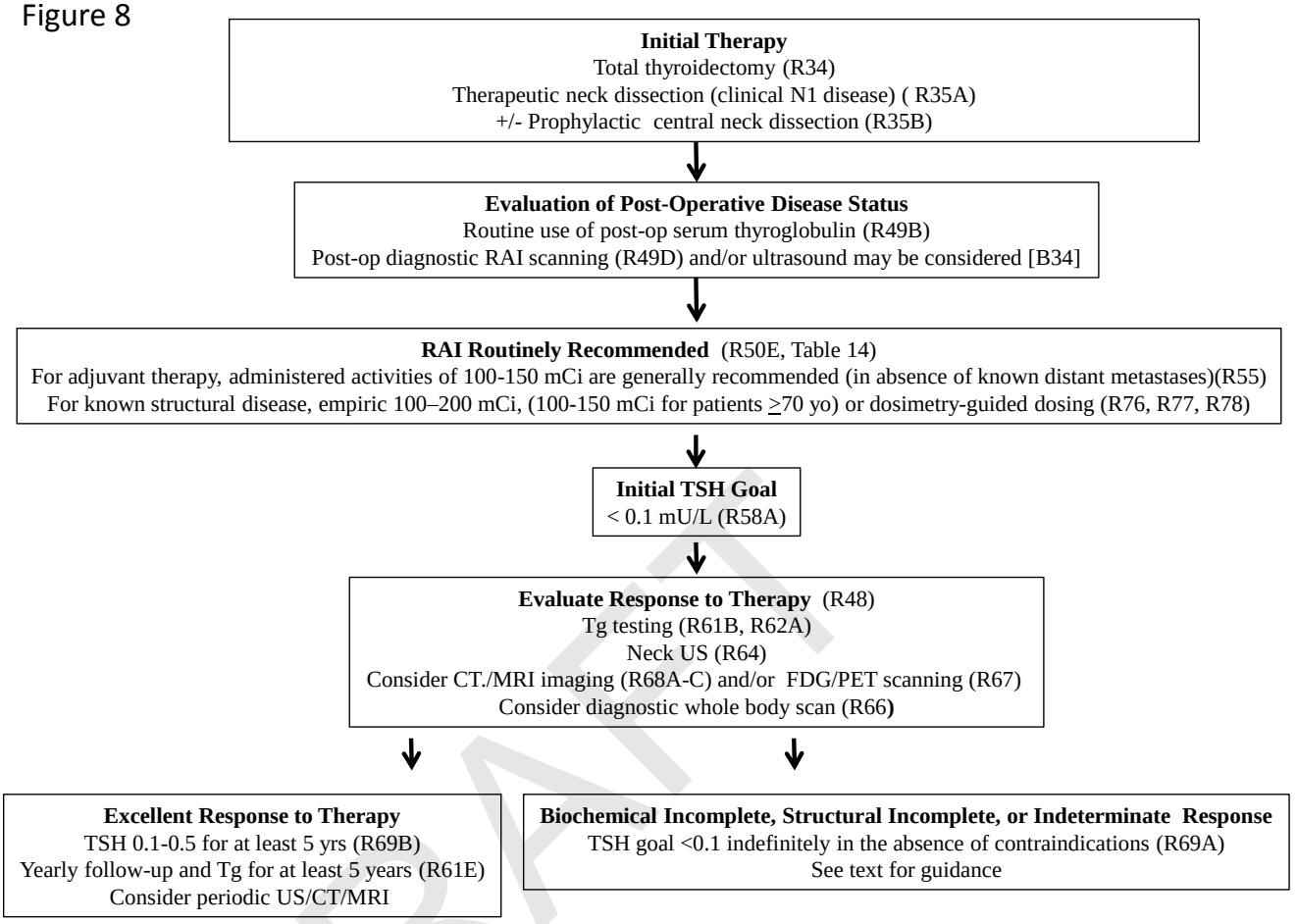


Figure 8



Abbreviations

mCi – millicurie (1 mCi = 37 MBq, megabecquerels)

LT4 – levothyroxine