

Thyroid Nodules and Cancer in Older Adults

Melissa G. Lechner, MD, PhD, Division of Endocrinology, Diabetes and Metabolism, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, and Endocrinology and Diabetes Division, West Los Angeles Veterans Affairs Medical Center, Los Angeles, CA.

Jerome M. Hershman, MD, Division of Endocrinology, Diabetes and Metabolism, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, and Endocrinology and Diabetes Division, West Los Angeles Veterans Affairs Medical Center, Los Angeles, CA.
jhershmn@mednet.ucla.edu

Updated December 2, 2018

ABSTRACT

Thyroid nodules and cancer are common in elderly patients and demonstrate age-specific prevalence, malignancy risk, and clinical behavior. Improved risk stratification by ultrasound characteristics and molecular testing of thyroid nodules has reduced the need for diagnostic surgery. Surgery, radioactive iodine ablation, and thyroid hormone suppression remain the cornerstones of differentiated thyroid cancer treatment. Co-morbid conditions and patient preference should inform management of these entities in the elderly, with particular attention to the risks of surgery and medication adverse effects. The mechanisms underlying the distinct clinical behavior of thyroid cancer found in older patients, including the drivers of more advanced stage at presentation, higher recurrence risk, and greater mortality, remain poorly understood. Patients with advanced thyroid cancer may benefit from recently developed chemotherapy and immunotherapy.

THYROID NODULES IN THE ELDERLY

Thyroid nodules are common in clinical practice and present unique management issues in elderly patients. The reported prevalence of thyroid nodules in iodine sufficient regions is 1-6 % as detected by palpation, or as high as 19-68% when detected by ultrasound imaging (1-5). Evaluation of thyroid nodules is increasingly a concern for general internists and endocrinologists due to several factors, including an aging population, increased use of imaging in clinical practice, and rising obesity.

Thyroid nodules are more frequent in elderly patients, with a linear increase with age in both the presence of nodules and the absolute number of nodules per patient (6). Approximately 50% of individuals aged 65 years have thyroid nodules detected by ultrasonography (7). A cross-sectional survey of asymptomatic adults in Germany using ultrasonography to detect thyroid nodules demonstrated an even higher prevalence of 80% in women and 74% in men over 60 years old (4). In a prospective study of 6,391 patients referred for thyroid nodules at a large academic center, Kwong *et al.* showed a linear increase in the number of thyroid nodules per patient with age, rising from an average of 1.55 nodules ≥ 1 cm in patients age 20–29 years old

to a mean of 2.21 nodules ≥ 1 cm in patients ≥ 70 years old, demonstrating a 1.6% annual increased risk for multinodularity (6).

Another potential contributor to this rising prevalence of thyroid nodules is the increased use of high-frequency ultrasound, CT, and MR imaging in routine clinical care, leading to the detection of asymptomatic, or incidental, thyroid nodules (4,5,7,8). Lastly, changes in population demographics over time, specifically increased rates of obesity, may contribute. Data from several ethnically diverse cohorts has identified parameters independently associated with the development of thyroid nodules, including obesity, female sex, radiation exposure, iodine deficiency, and smoking. These should be noted when evaluating elderly patients for potential thyroid nodules (9).

Once identified, thyroid nodules should be evaluated to determine appropriate management. The differential diagnosis of thyroid nodularity includes benign and malignant solitary nodules, multinodular goiter, autonomous functioning nodules, cysts, and inflammation or thyroiditis (10). Nodules causing thyroid dysfunction, compressive symptoms, or harboring malignancy require attention.

In the presence of biochemical or clinical signs of hyperthyroidism, a radioiodine uptake and scan should be pursued to distinguish autonomous nodules. Adjunctive data to support a diagnosis of inflammation or autoimmune destruction may include thyroid autoantibodies [anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg)]; the presence of thyroid stimulating immunoglobulins can suggest a diagnosis of Graves' disease in the presence of goiter (11).

Nodules without associated thyroid function abnormalities should be further evaluated to determine or exclude the presence of cancer. Guidelines from the American Thyroid Association were recently updated and summarize the management of non-functional thyroid nodules based upon imaging and patient characteristics (12). A general approach to evaluation of thyroid nodules is shown in Figure 1.

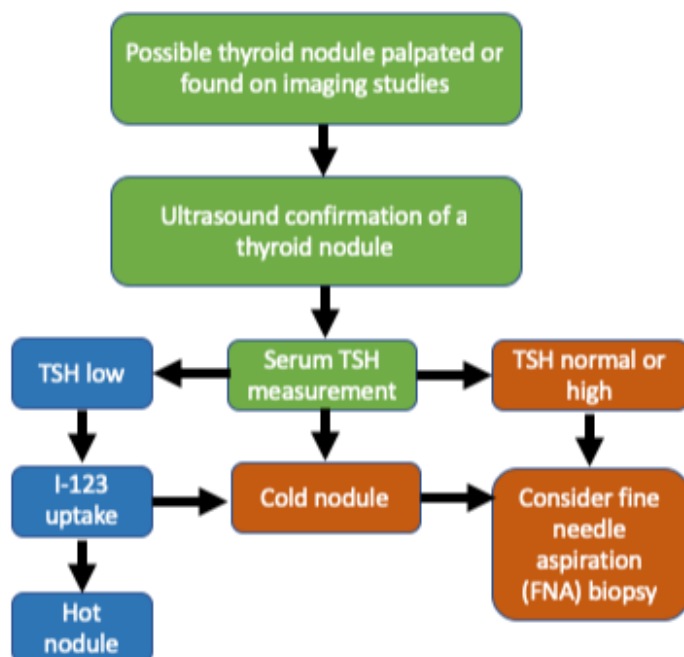


Figure 1. Evaluation of a Thyroid Nodule. Hot nodules refer to autonomous, hyperfunctioning thyroid follicular tissue producing thyroid hormone excess. Cold nodules refer to nodules without autonomous production of thyroid hormone.

Briefly, solid, hypoechoic thyroid nodules with suspicious ultrasound features (*i.e.* irregular margins, microcalcifications, taller than wide shape, rim calcifications, or evidence of extrathyroidal extension) have a high risk of malignancy (70-90%) and should be biopsied when ≥ 1 cm in largest diameter. Solid, hypoechoic nodules without high risk features on imaging, still portend a 10-20% risk of malignancy and should similarly be biopsied when size ≥ 1 cm. Isoechoic or hyperechoic, solid nodules without microcalcification, irregular margin, extrathyroidal extension or taller than wide shape are recommended to biopsy when ≥ 1.5 cm, with a 5-10% risk of malignancy. Spongiform or partially cystic nodules absent the above suspicious features, may be followed by imaging surveillance or biopsied if ≥ 2 cm. The associated risk of malignancy with such lesions is low ($<3\%$). Purely cystic nodules seen on ultrasound do not warrant biopsy given the exceedingly low risk of malignancy ($<1\%$) (12). A summary of thyroid nodule ultrasound characteristics and their relation to malignancy risk is shown in Table 1.

Table 1. Ultrasound Features of Thyroid Nodules and Associated Malignancy Risk				
Ultrasound Imaging Features				
- Cyst	- Spongiform - Partially cystic - No suspicious features	- Hyperechoic and isoechoic solid nodule	- Hypoechoic solid and regular margins - Macro-calcifications	- Micro-calcifications or Interrupted rim calcifications - Lobulated or irregular margins

		- Partially cystic with eccentric solid area - No calcifications or comet tail artifact		- Extrathyroidal extension/invasion - Taller than wide shape
Estimated Risk of Nodule Malignancy				
<1%	<3%	5-10%	10-20%	>70-90%
Benign	Very low suspicion	Low suspicion	Intermediate suspicion	High suspicion

Fine needle aspiration (FNA) biopsy is the recommended modality for sampling thyroid nodules. Cytology specimens collected by FNA are classified traditionally by the Bethesda System for Reporting Thyroid Cytopathology (13) across six categories: (i) non-diagnostic or unsatisfactory; (ii) benign; (iii) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); (iv) follicular neoplasm or suspicious for a follicular neoplasm; (v) suspicious for malignancy; and (vi) malignant. The risk of malignancy determined by surgical pathology is estimated across each category and used to guide decisions about continued clinical observation or treatment with surgical resection (13), summarized in Table 2.

Table 2. Bethesda System for Reporting Thyroid Cytopathology and Associated Estimated Risk of Malignancy.

Bethesda category	Cytopathology	Cytologic descriptions	Malignancy risk - Cancer = NIFTP - Cancer ≠ NIFTP	Typical management
I	Non-diagnostic	Acellular specimen Cyst fluid only Obscuring factors	- 5-10% - 5-10%	Repeat FNA
II	Benign	Benign follicular nodule Chronic lymphocytic thyroiditis Granulomatous thyroiditis	- 0-3% - 0-3%	Clinical and ultrasound follow-up
III	Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)	Atypia: Cytologic (focal nuclear changes, extensive but mild nuclear changes, atypical cyst lining cells, or “histiocytoid” cells) and/or architectural (predominantly microfollicles, sparsely cellular); Hurthle cells	- 6-18% - 10-30%	Repeat FNA, molecular testing, or lobectomy
IV	Follicular neoplasm or suspicious for a	Follicular-patterned cases with mild nuclear changes (increased nuclear size, nuclear contour irregularity,	- 10-40% - 25-40%	Repeat FNA, molecular testing, lobectomy

	follicular neoplasm	and/or chromatin clearing), and lacking true papillae and intranuclear pseudo-inclusions		
V	Suspicious for malignancy	Features <i>suspicious</i> for PTC, MTC, lymphoma, or other malignancy	- 45-60% - 50-75%	Total thyroidectomy or lobectomy
VI	Malignant	Features <i>conclusive</i> for malignancy: - PTC (true papillae, psammoma bodies, nuclear pseudo-inclusions) - MTC - Poorly differentiated / ATC - Non-endocrine malignancy (squamous cell, lymphoma, metastatic)	- 94-96% - 97-99%	Total thyroidectomy or lobectomy for thyroid cancers

PTC, papillary thyroid carcinoma. MTC, medullary thyroid cancer. ATC, anaplastic thyroid cancer. NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

In situations of non-diagnostic FNA results or indeterminate cytology (*i.e.*, Bethesda iii or iv), repeat FNA biopsy is recommended. Additionally, three molecular tests for cancer risk stratification are presently available. The ThyroSeq assay (University of Pittsburgh Medical Center and CBL PATH, Pittsburgh, PA) detects the presence of high-risk cancer mutations and was developed as a rule-in test for thyroid cancer (14). An independent evaluation of ThyroSeq v2 performance in a series of indeterminate nodules calculated a sensitivity of 70% and a specificity of 77%, somewhat decreased from the originally reported 90% and 93%, with a positive predictive value (PPV) of 42% and a negative predictive value (NPV) of 91% (14,15). Performance data for ThyroSeq v3, a revised version of the molecular test incorporating 112 genes associated with thyroid cancer, was recently published by Nikiforov *et al.* with a reported sensitivity of 98% and specificity of 81% for detection of thyroid cancer from FNA samples (16). The Afirma gene expression classifier (GEC) assay (Veracyte, San Francisco, CA, USA) analyzed the expression pattern of mRNA in cytology specimens to classify them as benign or suspicious and was designed as a rule-out test for cancer. The original Afirma GEC had a reported NPV of 94–95% and a PPV of 37–38% (17,18). The next iteration of this test was approved in 2018 as the Afirma gene sequence classifier (GSC) and includes detection of thyroid cancer-associated mutations with a reportedly improved specificity for thyroid cancer (NPV 95%, PPV 47%) (19). Lastly, the combined ThyraMIR microRNA Classifier and ThyGenX Oncogene Panel (Interpace Diagnostics, Parsippany, NJ) is a cancer rule-in test that uses multiplex PCR to identify cancer-associated gene mutations and translocations, done in tandem with evaluation of microRNA expression. The test estimated NPV and PPV are 94% and 74%, respectively (20). As molecular testing continues to evolve, clinicians and patients will have additional tools to aid in treatment decisions.

Judicious use of FNA biopsy, improved stratification of nodule cancer risk by ultrasound characteristics, and molecular testing have improved pre-operative determination of malignancy

risk in patients with thyroid nodules and reduced the need for diagnostic surgery. However, a significant number of patients who undergo thyroid nodule resection for suspicious nodules are still ultimately found to have benign lesions on surgical histopathology. Particularly in elderly patients with a greater burden of co-morbid medical disease, the risk of unnecessary thyroid surgery is an important consideration.

Several recent studies have specifically addressed thyroid cancer risk and nodule management across the age spectrum. Kwong *et al.* (6) reported the rate of malignancy in a cohort of 6,391 patients referred to a large academic center who underwent thyroid ultrasound and FNA of 12,115 nodules (all ≥ 1 cm). With advancing age, the prevalence of clinically relevant (>1 cm) thyroid nodules increased, whereas the risk that such nodules were malignant decreased. For patients ages 20–29, 30–39, 40–49, 50–59, 60–69, and >70 years, the cancer prevalence was 22.9, 21.8, 17.1, 13.0, 13.7, and 12.6%, respectively ($p < 0.001$). When the malignancy rate was analyzed “per-nodule,” the youngest cohort (20–29 years) demonstrated a 14.8% malignant risk per nodule at diagnosis in comparison to 5.6% in the oldest cohort (>70 y; $p < 0.01$). Between the ages of 20 and 60 years, each advancing year was associated with a 2.2% reduction in the relative risk that any newly evaluated thyroid nodule was malignant (OR 0.972; $p < 0.001$), and this risk of malignancy stabilized after age 60 years. However, this study also found that despite a lower likelihood of malignancy for nodules in elderly patients, these cancers were more likely to have aggressive phenotypes (6).

Further addressing the burden and risk of thyroid nodule evaluation in older patients, Angell and colleagues recently analyzed a large cohort of elderly patients (age 70 years and older) who underwent thyroid nodule evaluation over a 20-year period (21). In this study, 1,129 patients over the age of 70 years with 2,527 nodules ≥ 1 cm were evaluated. Thyroid cancer-specific mortality was observed in 8% of thyroid cancer patients. All such patients could be recognized during initial evaluation based on the presence of invasive tumor, extensive lymph node metastases, or distant metastases. While FNA was a safe procedure in this age-group and a benign result was obtained in two-thirds of samples, FNA led to surgery in 208 patients, of whom 93 (44.7%) had benign histopathology. These data suggest that while an identifiable group of older patients are at risk for mortality from thyroid cancer warranting aggressive treatment, many patients ≥ 70 years old derive little benefit or are even harmed by thyroid nodule therapy.

DIFFERENTIATED THYROID CANCER IN THE ELDERLY

While thyroid nodules are relatively common in elderly patients and the vast majority are benign (21), thyroid cancer is identified in a subset. Patients and their families are often concerned about the implications of this diagnosis and disease outcomes. Several subtypes of thyroid cancer are frequently encountered and increasing information about the underlying biology of these malignancies is now available. Most thyroid cancers are identified incidentally on imaging rather than by palpation on physical examination. Rarely, symptoms of thyroid cancer can include lymphadenopathy, hoarseness from laryngeal nerve involvement, dysphagia, airway compression from mass effect, or pain; when present, these symptoms portend more advanced

disease and worse clinical prognosis (22,23). When thyroid cancer is identified, a combination of surgical, radioactive iodine and surveillance strategies are employed and tailored to the individual patient and disease characteristics.

Incidence and Prevalence of Thyroid Cancer

Thyroid cancer accounts for 3.1% of all new cancers, but only 0.3% of cancer deaths, in the United States annually (24). In 2018, there were an estimated 53,990 new cases of thyroid cancer and over 750,000 people living with thyroid cancer (24). In the general population, the peak occurrence is between ages 51 and 60 years (25). Thyroid cancer is more common in women than men and among those with a family history of thyroid disease (24).

The incidence of thyroid cancer has risen over time, with an approximately two-fold increase between 1973 and 2002. Notably, small (<2 cm) papillary thyroid cancers account for the majority of this increase (26), and despite a much higher incidence, thyroid cancer mortality has only increased slightly (27), likely reflecting greater detection of early disease associated with a good prognosis. Debate exists whether the increased detection by high resolution imaging alone has simply identified more incidental thyroid cancers or whether a true increase in the incidence in these cancers is occurring over the past several decades (26-28).

With more thyroid cancers being diagnosed, particularly when they may be of limited mortality significance, clinicians must be well-versed in the management options and the particular risks and benefits anticipated for elderly patients.

Classification of Thyroid Cancer

Thyroid follicular cell-derived cancer is subdivided into several histopathologic types: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), Hurthle cell carcinoma (HCC), and poorly differentiated or anaplastic thyroid cancer (29-31). Other malignancies encountered in the thyroid include medullary thyroid cancer arising from thyroid gland C-cells, lymphoma, and secondary metastasis of other primary cancers.

Papillary thyroid cancer (PTC) is the most common type of differentiated thyroid cancer (DTC) accounting for approximately 80 to 85% of all cases (24,29-31). It has a bimodal frequency, with the peak incidence being in the third and sixth decades, and it affects women three times more often than men. These carcinomas arise from the thyroid follicular cells and frequently harbor *BRAF* V600E mutations, produce thyroglobulin, and express the sodium-iodide symporter (NIS) with resultant radio-iodine avidity (29). A history of radiation exposure increases the risk of PTC (32-34). PTC frequently spreads via the lymphatics to the regional lymph nodes, and bilateral involvement is present in approximately one-third of the cases at diagnosis. In rare cases, metastatic disease occurs in the lungs, brain, and bone (29).

Micropapillary thyroid cancer, defined as a PTC less than 1 cm in diameter and confined to the thyroid, is likely to be of minimal clinical significance (35). A prospective, observation study of

papillary thyroid microcarcinoma in Japan, found that patients less than age 40 progressed to clinical disease, (defined as significant growth, size >1.2 cm, or lymph node metastases), in contrast to those over age 60, whose disease remained static (36), suggesting that in most elderly patients these lesions can be safely observed.

Follicular thyroid cancer (FTC) is the second most common type of DTC and constitutes approximately 10 to 15% of all thyroid cancers (24,29,30). Risk factors include iodine deficiency and female sex (24,37,38). Compared to PTC, FTC less often has cervical lymph node spread but shows a predilection for vascular invasion and distant metastasis (39). Mutations of RAS, an activator of the mitogen-activated protein kinase and PI3K-AKT pathways, and rearrangements of *PPAR-γ* (e.g. *PAX8-PPAR-γ* translocation) have been implicated in the tumorigenesis of follicular adenomas and FTC (39,40).

Hurthle cell carcinomas (HCCs) account for 5% of DTC and are characterized by an abundance of dysfunctional mitochondria (>75% of cell volume) and tendency for vascular invasion (41,42). These malignancies are more often radio-iodine refractory and aggressive in clinical behavior. Unique genetic drivers of HCC have recently been reported, namely widespread loss of heterozygosity, a high burden of disruptive mutations to protein-coding and tRNA-encoding regions of the mitochondrial genome, and recurrent mutations in *DAXX*, *TP53*, *NF1*, *CDKN1A*, *ARHGAP35*, *TERT* promoter, and the RTK/RAS/AKT/ mTOR pathway (43,44).

Anaplastic thyroid cancer and medullary thyroid cancer are discussed separately.

Variation in Histopathology and Tumor Extent by Age

Several studies have shown variance in histopathology distribution with rising age. Lin *et al.* (45) conducted a retrospective analysis of 204 thyroid cancer patients aged 60 years and older; 142 (70%) thyroid cancers were well differentiated and of those 68% were PTC, 30% FTC, and 2% Hurthle cell carcinoma. Fifty-nine (29%) of the thyroid cancers were poorly differentiated (39 anaplastic thyroid, 9 metastatic cancers to the thyroid, 7 lymphoma, 4 squamous cell carcinomas, and 4 without enough cells for interpretation) and 3 (2%) were medullary thyroid cancer. This pattern is significant for fewer PTC and more FTC in elderly patients, as well as more poorly-differentiated tumors.

Girardi *et al.* conducted a retrospective study of thyroid cancer in 596 adults from 2000-2010; their results similarly showed a lower frequency of PTC among elderly patients, with a complementary increase in the frequency of FTC, poorly differentiated and anaplastic thyroid carcinoma (25). This study also demonstrated variability in other presenting features of thyroid cancer in elderly patients (age ≥ 65 years) compared to middle-aged cohorts (25-44 years or 45-64 years); specifically, there was larger primary tumor size (median 2.1 cm for elderly versus 1.5 cm in 25-44 years and 1.1 cm in 45-64 years) and higher rates of extra-thyroidal disease (mean 43% for elderly versus 25.3% in 25-44 years and 28.6% in 45-64 years) (25). Lymph node metastasis was greatest at the extremes of age (<24 and >70 years).

Another retrospective analysis of 1,022 patients undergoing thyroidectomy reported by Payne *et al.* showed that well-differentiated thyroid cancer (*i.e.*, PTC and FTC), and lymph node metastasis occurred more often in patients younger than 50 years, whereas micropapillary carcinoma was more common in patients 50 years or older (46). Chereau *et al.* evaluated histopathology and extent of disease at diagnosis in elderly (65-75 years old) and very elderly (>75 years old) patients compared to younger patients in 3,835 patients treated at an academic center from 1978 to 2014 (47). These data were notable for significantly increased primary tumor size, tumor number, extra-capsular invasion, advanced TNM stage, and lymph node and distant metastasis in the very old group (47). Collectively these studies show a pattern of more widespread disease at presentation in elderly patients and a relative increase in the frequency of more aggressive histologic subtypes.

Relation of Age to Mortality and Risk of Recurrence

Numerous studies have demonstrated increased recurrence and mortality in thyroid cancer with rising age (48-53). Indeed, age is incorporated into current clinical staging systems for differentiated thyroid cancer, including the American Joint Committee on Cancer (AJCC) 8th edition (54); Metastasis, Age, Completeness of resection, Invasion, Size (MACIS) model (55); Age, Grade, Extent, Size (AGES) score; and the Age, Metastasis, Extent, Size (AMES) score (56). In all of these staging systems, advanced age is included as a risk factor predicting worse prognosis.

Historic studies by Halnan (57) and Cady *et al.* (58) established a positive correlation between advanced age and worse prognosis in patients with DTC, later corroborated by Ito *et al.* (59) in a study of 1,740 patients with PTC and by Sugino *et al.* (60) in 134 patients with FTC. In many of these studies, worse prognosis has been defined variably as recurrence, decreased disease- or metastasis-free survival, cause-specific mortality, and/or overall mortality. Other reports have shown that the presence of lymph node involvement and extrathyroidal extension may portend a more ominous outcome in older compared to younger patients (58,61-63). Extrathyroidal disease in older patients increased recurrence to 67% and death rates to 60% compared to those with intrathyroidal disease, while in younger patients the relative increases were 12% and 4%, respectively (58). Additionally, the risk of death with distant metastasis is greater in older compared to younger patients (96% versus 63%) (58).

Recently, this well-accepted tenet of thyroid cancer has been modified in two important ways, namely that age likely modifies prognosis in a continuous rather than dichotomous manner and that age itself may not be as relevant to thyroid cancer behavior as the accompanying changes in accumulated cell mutations, immune senescence, and hormone changes that accompany it (64).

With the 8th edition of AJCC staging for differentiated thyroid cancer, the age threshold for increased risk was raised from 45 to 55 years, based upon several reports suggesting that this increased validity for staging (65,66). More recent data suggest that thyroid cancer mortality and

recurrence prediction is more robust when age is modeled as a continuous variable, leading some to suggest the elimination of a specific age cutoff from staging completely (64).

In a study of 3,664 patients with differentiated thyroid cancer, Ganly *et al.* found that disease-specific mortality increased progressively with advancing age, without a threshold age (53). Similarly, evaluation of over 30,000 patients in the Surveillance, Epidemiology, and End Result (SEER) database by Orosco *et al.* demonstrated a linear association with age and thyroid cancer death (52).

A recent review by Haymart *et al.* summarizes possible biologic mechanisms underlying the clinical observations of worse thyroid cancer prognosis in the elderly (50). Briefly, mortality findings may be confounded by greater comorbid nonthyroidal diseases with older age. Higher baseline levels of thyroid-stimulating hormone (TSH) may accelerate tumor cell growth via stimulation of the TSH-receptor. If one presumes that thyroid cancers detected in elderly patients have had a longer time of subclinical growth and evolution compared to cancers detected in younger patients, then such tumors might have had greater opportunity to acquire genetic mutations facilitating cell cycle escape, loss of differentiated features (e.g. loss of sodium-iodine symporter and radioiodine avidity), and metastasis. In summary, there is significant observational evidence that older patients with thyroid cancer have worse clinical outcomes, though the precise effect of increasing age and the etiology of this distinct clinical behavior remain incompletely understood.

Treatment of Differentiated Thyroid Cancer

The cornerstones of therapy for differentiated thyroid cancer are surgical resection, radioactive iodine ablation, and thyroid hormone suppression of TSH. Serum thyroglobulin trends and follow-up neck ultrasound imaging are used for monitoring patients over time. Patients with progressive or metastatic disease may benefit from repeat surgery, radioactive iodine ablation (RAIA), or chemotherapy (12). A general approach to the treatment of differentiated thyroid cancers is presented in Figure 2. Management will be influenced by patient characteristics, such as age and comorbid conditions, as noted in the figure.

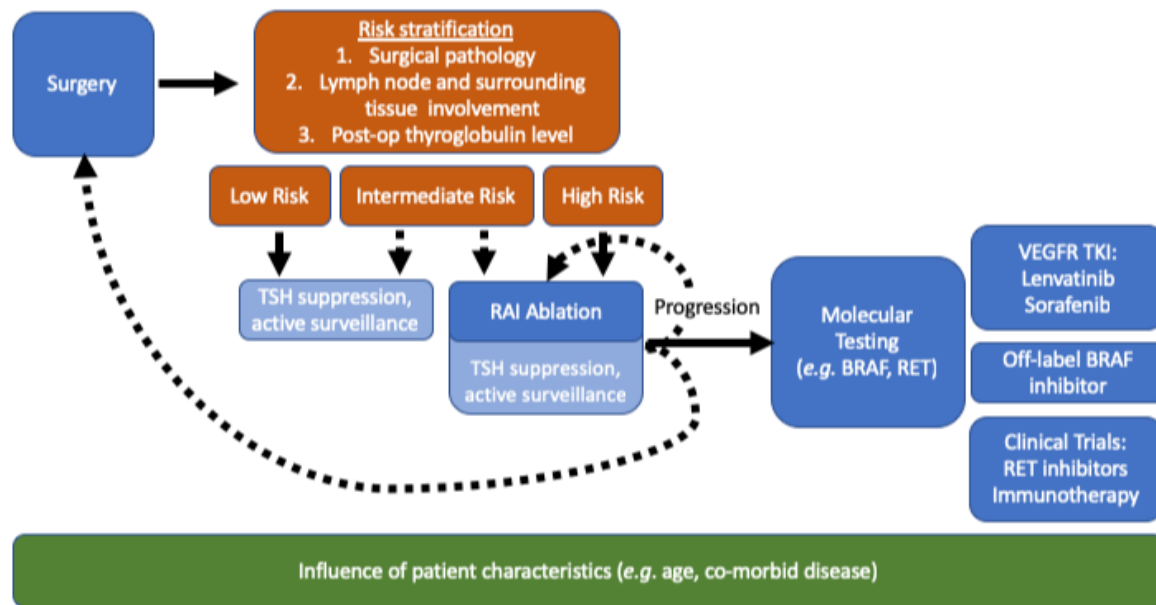


Figure 2. Treatment of Differentiated Thyroid Cancers. RAI, radioactive iodine. TSH, thyroid stimulating hormone. VEGFR, vascular endothelial growth factor receptor. TKI, tyrosine kinase inhibitor

SURGERY

Patients diagnosed with DTC by FNA, should be referred to a surgeon for thyroid resection. The decisions to pursue surgery and the extent of surgery (*i.e.* total thyroidectomy versus lobectomy) in an elderly patient require individual evaluation of co-morbid illnesses and life expectancy.

The most common complications of thyroidectomy include hypoparathyroidism, recurrent laryngeal nerve injury, hematoma, and wound infection; high-volume thyroid surgeons have minimal to no increase in the risk of surgical complications with increasing age (67,68-72). However, elderly patients are more likely to receive thyroidectomy at community and low-volume sites (73) where the rate of surgical complications may be higher. In population-based studies of thyroidectomy, which may reflect more accurately the experience of many elderly patients, increasing age is associated with longer hospital length of stay (73) and readmissions after thyroidectomy (74).

In the cohort of elderly and very elderly patients studied by Chereau *et al.* (47), the authors found no increase in thyroidectomy-specific complications (*i.e.* permanent hypocalcemia and recurrent laryngeal nerve palsy) with increasing age, but did find an increase in medical complications surrounding surgery, 2.3-2.7% in those over 65 years of age compared to 0.6% in those under 65 years old.

Lobectomy, a more limited surgery, may be considered in select patients with multiple co-morbid conditions and low-risk disease (tumors <2 cm) (12,67). On the other hand, elderly patients more often have aggressive disease features on surgical pathology and higher rates of local recurrence requiring re-operation, potentially arguing for a total thyroidectomy (70).

RADIOACTIVE IODINE ABLATION

Based upon the extent of primary disease noted on surgical pathology (*i.e.* tumor size, histologic subtype, extrathyroidal extension, lymph node and vascular spread, and the presence of distant metastasis), a risk of recurrence and recommendation for RAIA with I¹³¹ can be made.

Generally, patients with ATA high and intermediate risk should be considered for RAIA therapy (12) to ablate residual disease and remnant thyroid tissue.

Two multicenter studies showed that an ablative dose of 30 mCi (1.1 MBq) I¹³¹ was as effective as 100 mCi (3.7 MBq); both doses were 90% effective for ablation of residual thyroid tissue (75,76). A long-term follow-up of one of these studies (median 4.5 years) showed that the radioiodine dose did not affect recurrence rate (77). A recent analysis of 21,870 patients with intermediate-risk PTC found that adjuvant radioiodine therapy was associated with a 29% reduced risk of death overall with clear benefit in those over 65 years of age (78). The adverse effects observed following RAIA, transient neck pain and swelling, dry mouth and eyes, and secondary malignancy, correlate positively to higher doses (79).

THYROID-STIMULATING HORMONE (TSH) SUPPRESSION

Following surgery, and RAIA if indicated, patients are treated with thyroid hormone, usually with a dose of levothyroxine that suppresses serum TSH to subnormal levels. Several special considerations for the goals of thyroid hormone therapy following thyroid cancer arise in elderly patients.

Thyroid hormone replacement is titrated to levels sufficient to suppress pituitary secretion of TSH, which is considered a growth-promoting factor for follicular cell-derived thyroid cancers. Revised guidelines from the American Thyroid Association (12) suggest individualized targets for TSH suppression in thyroid cancer, generally targeting a low to low-normal range TSH. Greater TSH suppression in more aggressive disease is balanced with greater cardiac and bone complications in elderly patients.

Older patients are more likely to have co-morbid cardiac disease, including arrhythmias, coronary artery disease, and heart failure, which can place them at increased risk for complications from thyroid hormone excess. A population-based study of patients taking levothyroxine for any cause, found a significantly higher risk of cardiac arrhythmias [HR 1.6 (1.10–2.33)] and cardiovascular admission or death [1.37 (1.17–1.60)] in those with a suppressed serum TSH (≤ 0.03 mU/L) compared to those with TSH in the normal reference interval (80). Notably, increased cardiovascular risk was not observed in patients with a low but not fully suppressed TSH (TSH 0.04 – 0.4 mU/L). Specifically, in thyroid cancer patients treated

with levothyroxine with modestly suppressed TSH (mean TSH <0.35 mU/L), atrial fibrillation was common (17.5% prevalence) in those patients ≥60 years old (80).

Longstanding hyperthyroidism is associated with osteoporotic fractures and loss of bone mineral density. Specifically, post-menopausal women (≥65yo) with suppressed TSH levels (0.1 mU/L) due to endogenous or exogenous thyroid hormone had significantly higher rates of new hip (OR 3.6, 95% CI 1.0-12.9) and vertebral fractures (OR 4.5, 95% CI 1.3 -15.6) compared to comparable women with normal TSH levels over a 3.7 years follow-up (81). In adult patients on levothyroxine therapy, a suppressed TSH (≤0.03 mU/L) was associated with a two-fold increase in risk [HR 2.02 (1.55–2.62)] of new osteoporotic fracture compared to similar patients treated with levothyroxine with a TSH maintained in the normal reference interval (80). Studies evaluating thyroid cancer patients are limited in outcome evaluation of bone mineral density (BMD) rather than fracture incidence, but generally support similar conclusions regarding lower BMD with suppressive-dose levothyroxine therapy (82-84). In elderly patients receiving TSH-suppression therapy, dual-emission X-ray absorptiometry (DEXA) monitoring of BMD should be considered based upon age and other risk factors for osteoporosis. There are no guidelines to suggest the optimal interval for DEXA screening; osteoporosis once identified should be treated using standard therapies (such as bisphosphonates or RANKL inhibitor) unless otherwise contraindicated (85).

Peripheral metabolism of thyroid hormone and clearance decreases with advanced age so that a lower medication dose is needed to achieve comparable serum levels (86,87). Levothyroxine therapy is complicated further by polypharmacy in elderly patients, where commonly prescribed medications (e.g. calcium, iron) can decrease gut absorption of levothyroxine (88) or change drug metabolism (e.g. rifampicin, phenytoin, carbamazepine, amiodarone) (89).

In summary, as suggested by society guidelines (12), TSH goals in thyroid cancer should be individualized and re-evaluated over time. Patients with co-morbid cardiac disease and/or osteoporosis with intermediate risk disease recurrence, might best be managed with TSH targets in the low but not fully suppressed range to minimize adverse effects of therapy.

THYROGLOBULIN MONITORING

Follow-up by measurement of serum thyroglobulin (Tg) at intervals of 4 to 6 months on thyroxine suppression therapy is recommended (12). At one-year post treatment completion, a stimulated Tg measurement may provide a more sensitive evaluation for persistent or recurrent disease (90). A Tg level >0.2 ng/mL, a stimulated Tg level >2- 5 ng/mL, a rising Tg level, or the persistence of Tg antibodies, warrant further evaluation (12, 91). Diagnostic imaging studies such as neck ultrasound, whole body radioiodine uptake, and PET imaging should be performed to locate the residual thyroid tissue. Identification of abnormal lymph nodes or tumor mass can then be further evaluated for possible further treatment with radioactive iodine, surgery, or targeted therapy.

TARGETED THERAPY

Older cytotoxic drugs have shown little benefit for progressive, advanced, or metastatic papillary or follicular thyroid cancer while causing significant side effects. Improved understanding of the pathogenesis of these cancers is leading to the development of new agents aimed at specific oncogenic mechanisms (e.g. RET, BRAF). Currently two tyrosine kinase inhibitors are approved for therapy of metastatic, radio-resistant differentiated thyroid cancer: sorafenib and lenvatinib.

Sorafenib, an oral multi-kinase inhibitor, inhibits vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3), RET kinase (including RET/PTC), *BRAF* V600E, and platelet-derived growth factor receptor (PDGFR) beta. In the DECISION phase 3 multicenter placebo-controlled trial of 416 patients, 409 had distant metastases: 86% in the lungs, 51% in lymph nodes, and 27% in bone (92). The group treated with sorafenib had longer progression-free survival (10.8 months) compared to the placebo group (5.8 months). At disease progression, 71% of patients in the placebo group crossed over to receive open-label sorafenib; as a consequence, overall survival did not differ between the two groups. Twenty percent of patients in the sorafenib group received other cancer therapy after the trial. The most frequent adverse events in the active drug group were palmar-plantar erythrodysesthesia, diarrhea, alopecia, rash, weight loss, hypertension, anorexia, oral mucositis and pruritus. Side effects were relieved by dose reduction.

Lenvatinib is a tyrosine kinase inhibitor of the VEGFRs 1, 2, and 3; fibroblast derived growth factor receptor (FGFR)s 1 through 4; PDGFR α ; RET; and KIT signaling pathways. The SELECT phase 3 trial randomly assigned 261 patients to receive lenvatinib and 131 patients to receive placebo; the median age of patients in the trial was over 60 years (93). The median duration of follow-up was 17 months; 114 patients assigned placebo had progression, and 109 of them elected to receive lenvatinib. Disease progression occurred in 36% in the lenvatinib group compared to 83% in the placebo group. Median progression free survival was 18.3 months with lenvatinib versus 3.6 months with placebo. Disease response rate was 66% with lenvatinib compared with 1.5% with placebo. The benefit appeared in all subgroups, including all histologic types of tumor. Adverse events occurred in 97% of patients taking lenvatinib and in 60% taking placebo; the main adverse events were hypertension, diarrhea, fatigue, decreased appetite, palmar-plantar erythrodysesthesia, proteinuria, renal failure, and thromboembolic events. While not without side effects, lenvatinib and sorafenib demonstrated efficacy in patients with metastatic, radioiodine-refractory differentiated thyroid cancer and should be considered in elderly patients with sufficient performance status and potential benefit.

For differentiated thyroid cancer that progresses despite these therapies, additional treatment with external beam radiation, off label use of BRAF inhibitors, and clinical trials of immunotherapy are sometimes utilized. These modalities are discussed below in the context of anaplastic thyroid cancer.

ANAPLASTIC THYROID CANCER

Anaplastic thyroid carcinoma (ATC) is a rare and aggressive subtype of thyroid cancer that accounts for <1% of all thyroid cancers (24,29). It more commonly affects the elderly, with a mean age at diagnosis of 65 years and more than 90% patients with ATC are over age 50 (29). Despite recent advances, the median overall survival remains poor, around 3–5 months, with a 1-year survival of approximately 20% (94). Aldinger *et al.* reported a five-year survival rate of only 7.1% with a mean survival period of 6.2 months from the time of tissue diagnosis and 11.8 months from the time of onset of symptoms (95).

The most frequent presenting complaint in patients with ATC is a rapidly growing mass with tightness in the neck (95). Patients may also complain of dysphagia, hoarseness, dyspnea, neck pain, sore throat, and cough. Examination of the neck usually reveals a fixed, large, firm mass, which may impair the ability to detect lymphadenopathy on clinical examination. Hemorrhage and necrosis within the tumor may result in soft, fluctuant masses. Rarely, patients with massive tumor extension into the mediastinum or lungs may present with superior vena cava syndrome or dyspnea.

Unfortunately, most patients with ATC present with advanced stage disease. In a retrospective study of thyroid cancers in 204 elderly (age >60 years) patients by Lin *et al.* (45), 75% of patients diagnosed with ATC had distant metastases to the lung, bone, mediastinum, and peritoneum at presentation. Similarly, in the cohort reported by Aldinger *et al.*, 78 of 84 (93%) patients with ATC presented with advanced stage III and stage IV disease (95). Additional patient factors associated with worse prognosis in ATC include advanced age (>60–70 years), male gender, presence of leukocytosis (>10,000), and symptoms related to tumor mass effect, such as neck pain, dysphagia, rapidly growing neck mass. Regarding older age as a poor prognostic factor, in a cohort of 516 patients with ATC, Kebebew *et al.* reported a 28% greater mortality in patients over 60 years of age compared to those less than 60 years determined by multivariate analysis (94).

ATC often, but not always, arises from pre-existing differentiated thyroid cancer, with 20% of patients with antecedent DTC and another 20-30% with concurrent DTC (co-existent on histopathology). There is also a higher incidence of ATC in patients with endemic goiter. These associations are relevant for the treatment of ATC because driver mutations such as BRAF and RAS may be retained in the anaplastic tumor cells and can be targeted with therapy (29,95).

Treatment of Anaplastic Thyroid Cancer

While the prognosis of ATC remains poor, treatment options to slow the progression of disease, palliate symptoms, and, in rare cases, attempt cure, are available as approved therapies and in clinical trials.

EXTERNAL RADIATION

External radiation to the neck region is appropriate for patients with aggressive cancers that cannot be completely resected surgically (12). Schwartz *et al.* reported limited success in the

treatment of I^{131} -refractory patients with extrathyroidal spread, positive surgical margins, or gross residual disease with a mean of 60 Gy (38-72 Gy); survival was less in patients with high-risk pathology, metastases, and gross residual disease (96). In the context of ATC, disease is often assumed to be radioiodine refractory, and external beam radiation may be used for preservation of vital neck structures.

TARGETED THERAPY AND IMMUNOTHERAPY

Most patients with ATC have rapidly progressive disease and should be evaluated for clinical trials when feasible as new treatments continue to be developed. Targeted therapy with inhibitors to specific gene mutations and fusions has shown some success and is the focus of numerous ongoing clinical trials. Therapies include inhibitors of RET (discussed below under medullary thyroid cancer treatment), BRAF, MEK, NTRK, and ALK. Combination treatment with BRAF inhibitor dabrafenib and MEK inhibitor trametinib was recently approved for the treatment of *BRAF* V600E mutated, unresectable/locally advanced ATC, following a 69% overall response rate in a phase II open label trial of 16 patients with ATC (97).

Immunotherapy reagents target the impaired immune responses and immune suppression that arise in cancer allowing malignant cells to grow and spread. Checkpoint inhibitors are a kind of immunotherapy that block immune regulatory pathways with the goal of increasing anti-tumor immune responses and producing tumor killing by host leukocytes. Two primary classes of immunotherapy being evaluated for advanced thyroid cancer are inhibitors of cytotoxic T lymphocyte A (CTLA)-4 (such as ipilimumab) and inhibitors of programmed cell death (PD) receptor/ligand interactions (nivolumab, pembrolizumab, atezolizumab). Currently, immune checkpoint inhibitors are being evaluated alone and in combination with targeted therapies for ATC (97).

MEDULLARY THYROID CANCER

Medullary thyroid cancer (MTC) constitutes approximately 2-5% of all thyroid malignancies, but it is responsible for up to 13.4% of all deaths from thyroid cancer (27,98). It is a well-differentiated type of tumor that arises from the parafollicular C cells of the thyroid gland, and therefore it is categorized as a neuroendocrine tumor. In 80% of patients, medullary thyroid cancer occurs sporadically, but in about 20% of patients there is a family history of medullary carcinoma. Familial MTC is inherited in an autosomal dominant pattern with nearly complete penetrance. A germline mutation in the *RET* proto-oncogene, which encodes a transmembrane tyrosine kinase receptor, predisposes individuals to develop hereditary MTC. In the sporadic form, the tumor occurs as a result of a mutation involving only the somatic cells. Sporadic forms of MTC are more common in older patients (mean age at presentation 47 years), while the hereditary forms of MTC are more common in younger patients (98). The prevalence of MTC is nearly equal in males and females.

Parafollicular cells secrete calcitonin, and in MTC this protein is greatly elevated and serum level correlates directly with the burden of disease (99). Other neuroendocrine cell products,

including histamine, serotonin, prolactin, vasoactive intestinal polypeptide, and prostaglandin, can be elevated in patients with MTC and lead to systemic symptoms such as diarrhea or flushing (99). In some cases, Cushing's syndrome may develop as a result of ectopic adrenocorticotrophic hormone (ACTH) secretion from the tumor. The typical presentation of MTC is a palpable nodule in the upper part of the thyroid lobe, and the presence of systemic symptoms is almost universally associated with distant metastases (37). In the retrospective report of 104 patients with MTC by Kebebew *et al.*, 74% of the patients in the sporadic group presented with a thyroid mass, 16% had local symptoms (dysphagia, dyspnea, or hoarseness), and 10% had systemic symptoms (bone pain, flushing, and/or diarrhea) attributable to the cancer (98).

Within MTC, older age at diagnosis has been associated with a worse prognosis. Kebebew *et al.* followed patients with MTC for a mean time of 8.6 years and found that advanced age and stage at diagnosis were independent predictors of worse survival (98). The 5-year survival rates by stage were 100% (stage I), 90% (stage II), 86 % (stage III), and 55% (stage IV). The highest survival was seen in female patients under age 45 with MTC confined to the thyroid (98). Saad *et al.* similarly reported that patients younger than 40 years old at diagnosis had a significantly better survival rate in MTC (99). Scopsi *et al.* reported a worse prognosis in patients with sporadic MTC who had extrathyroidal tumor invasion, distant metastases, or age greater than 60 years at the time of diagnosis (100). Interestingly, a more recent study that adjusted for baseline age-related mortality in the general population found no significant association with age and prognosis in MTC (101). This raises similar questions to those posed recently for differentiated thyroid cancer as to whether age truly has an independent role in prognosis for these thyroid cancers apart from the general increase in morbidity and mortality with aging.

Treatment of Medullary Thyroid Cancer

The standard treatment for MTC is surgical resection (total thyroidectomy) with regional lymph node dissection, with routine bilateral central neck dissection and consideration of lateral neck dissection in patients with large primary tumors (>1 cm) or pre-operative imaging with involved nodes. Successful complete surgical resection is associated with improved prognosis. In patients with disease restricted to the thyroid gland and without nodal involvement, the risk of recurrence and mortality is very low, compared to those with nodal disease at presentation (102).

Serum calcitonin and CEA levels are trended post-operatively to monitor for residual or recurrent disease, beginning around 2-3 months after surgery. A rise in either tumor marker should prompt imaging to look for recurrent disease. Radioactive iodine is not indicated in the treatment of MTC as parafollicular cells do not express NIS or concentrate iodine. Additionally, thyroid hormone replacement is required following thyroidectomy, with TSH targeted to the normal range rather than suppression (103). TSH does not stimulate the growth of parafollicular cells.

In patients with progressive or metastatic disease not amenable to surgery, two tyrosine kinase inhibitors are currently approved for the treatment of MTC: vandetanib and cabozantinib. Vandetanib is an oral inhibitor that targets VEGFR, RET, and epidermal growth factor receptor (EGFR). In the international, randomized controlled phase III ZETA trial of vandetanib 300 mg per day that included over 300 patients with unresectable, locally advanced or metastatic sporadic or hereditary MTC, progression-free survival was significantly greater for patients treated with vandetanib (hazard ratio 0.46, 95% CI 0.31-0.69 versus placebo) (104). Adverse events occurred more commonly with vandetanib compared to placebo, including diarrhea, nausea, palmar-plantar erythrodysesthesia, hypertension, and headache.

Cabozantinib (105) is another oral tyrosine kinase inhibitor targeting MET, VEGFR2, and RET signaling pathways. The phase III international, randomized controlled EXAM trial evaluated cabozantinib versus placebo in the treatment of 330 patients with progressive, metastatic MTC, with a primary outcome of progression free survival (PFS). Median PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (hazard ratio, 0.28; 95% CI, 0.19 to 0.40; $P < 0.001$), with benefit seen across all subgroups including age, prior TKI treatment, and RET mutation status (hereditary or sporadic). Response rate was 28% for cabozantinib and 0% for placebo. Common cabozantinib-associated adverse events noted in the trial included diarrhea, palmar-plantar erythrodysesthesia, decreased weight, nausea, and fatigue.

Lastly, two ongoing clinical trials of oral RET inhibitors, LOXO-292 and BLU-667, have shown promise in open label phase I clinical trials, with phase II trials currently underway. LOXO-292 was evaluated in the LIBRETTO phase I trial in patients with RET-altered cancers, including RET fusion-positive MTC (29 patients) and DTC (9 patients). Interim results showed an overall response rate of 77% (95% CI 61-89%), with the MTC subset showing a 45% (95% CI 24-68%) response rate, by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Additionally, the treatment was well tolerated with diarrhea, constipation, dry mouth, and fatigue as common treatment-emergent side effects and rare grade 3 or 4 toxicities (106,107).

In the phase I ARROW trial, RET inhibitor BLU-667 was evaluated for the treatment of 69 patients with RET fusion-positive malignancies, including MTC (35 patients) and PTC (4 patients). The most recent interim analysis from 2018 showed 90% of patients had a radiographic response by RECIST 1.1 criteria, with the overall response rate somewhat lower in the MTC subset of patients (49%). Regarding adverse effects, the most common treatment-emergent events were constipation, increased aspartate aminotransferase, hypertension, anemia, neutropenia, fatigue, and headache; most adverse events were Grade 1 and only 2 of 69 patients discontinued treatment due to treatment-related toxicities (108). Given the poor prognosis of MTC, continued development of new treatment strategies is needed and management at a center experienced with this type of cancer is recommended.

CONCLUSION

In summary, thyroid nodules and cancer are common in elderly patients and demonstrate age-specific prevalence, malignancy risk, and clinical behavior. Co-morbid conditions and patient

preference should inform management of these entities in the elderly, with particular attention to the risks of surgery and medication adverse effects. More research is needed to understand the mechanisms underlying the distinct clinical behavior of thyroid cancer found in older patients, including the drivers of more advanced stage at presentation, higher recurrence risk, and greater mortality.

REFERENCES

1. Vander JB, Gaston EA, Dawber TR 1968 The significance of nontoxic thyroid nodules. Final report of a 15- year study of the incidence of thyroid malignancy. *Ann Intern Med* 69:537–540.
2. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T, Smith PA 1977 The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf)* 7:481–493.
3. Tan GH, Gharib H 1997 Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. *Ann Intern Med* 126: 226–231.
4. Guth S, Theune U, Aberle J, Galach A, Bamberger CM 2009 Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. *Eur J Clin Invest* 39:699–706.
5. Dean DS, Gharib H. Epidemiology of thyroid nodules. *Best Pract Res Clin Endocrinol Metab* 22:901-911, 2008.
6. Kwong N, Medici M, Angell TE, Liu X, Marqusee E, Cibas ES, Krane JF, Barletta JA, Kim MI, Larsen PR, Alexander EK. The Influence of Patient Age on Thyroid Nodule Formation, Multinodularity, and Thyroid Cancer Risk. *J Clin Endocrinol Metab*. 2015 Dec;100(12):4434-40.
7. Mazzaferri E. Management of a solitary thyroid nodule. *N Engl J Med* 328:553-559, 1993.
8. Ezzat S, Sarti DA, Cain DR, et al. Thyroid incidentalomas prevalence by palpation and ultrasonography. *Arch Intern Med* 154:1838-1840, 1994.
9. Dauksiene D, Petkeviciene J, Klumbiene J, Verkauskiene R, Vainikonyte-Kristapone J, Seibokaite A, Ceponis J, Sidlauskas V, Daugintyte-Petrusiene L, Norkus A, Zilaitiene B. Factors Associated with the Prevalence of Thyroid Nodules and Goiter in Middle-Aged Euthyroid Subjects. *Int J Endocrinol*. 2017;2017:8401518.
10. Diez JL. Goiter in adult patients aged 55 years and older: etiology and clinical features in 634 patients. *J Gerontol A Biol Sci Med Sci* 60:920-923, 2005.
11. Schlumberger M, Filetti S, Hay I. Nontoxic Diffuse and Nodular Goiter and Thyroid Neoplasia. In: Melmed S, Williams RH, editors. *Williams Textbook of Endocrinology*. 12th ed. Philadelphia: Elsevier/Saunders; 2011. p 440-449.
12. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016 Jan;26(1):1-133.

13. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*. 2017 Nov;27(11):1341-1346.
14. Nikiforov YE, Carty SE, Chiosea SI, et al. Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay. *Cancer* 2014; **120**: 3627–34.
15. Valderrabano P, Khazai L, Leon ME, et al. Evaluation of ThyroSeq v2 performance in thyroid nodules with indeterminate cytology. *Endocr Relat Cancer* 2017; **24**: 127–36.
16. Nikiforova MN, Mercurio S, Wald AI, Barbi de Moura M, Callenberg K, Santana-Santos L, Gooding WE, Yip L, Ferris RL, Nikiforov YE. Analytical performance of the ThyroSeq v3 genomic classifier for cancer diagnosis in thyroid nodules. *Cancer*. 2018 Apr 15;124(8):1682-1690.
17. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med* 2012; **367**: 705–15.
18. Alexander EK, Schorr M, Klopper J, et al. Multicenter clinical experience with the Afirma gene expression classifier. *J Clin Endocrinol Metab* 2014; **99**: 119–25.
19. Patel KN, Angell TE, Babiarz J, Barth NM, Blevins T, Duh QY, Ghossein RA, Harrell RM, Huang J, Kennedy GC, Kim SY, Kloos RT, LiVolsi VA, Randolph GW, Sadow PM, Shanik MH, Sosa JA, Traweek ST, Walsh PS, Whitney D, Yeh MW, Ladenson PW. Performance of a Genomic Sequencing Classifier for the Preoperative Diagnosis of Cytologically Indeterminate Thyroid Nodules. *JAMA Surg*. 2018 Sep 1;153(9):817-824.
20. Labourier E, Shifrin A, Busseniers AE, Lupo MA, Manganeli ML, Andruss B, Wylie D, Beaudenon-Huibregtse S. Molecular Testing for miRNA, mRNA, and DNA on Fine-Needle Aspiration Improves the Preoperative Diagnosis of Thyroid Nodules With Indeterminate Cytology. *J Clin Endocrinol Metab*. 2015 Jul;100(7):2743-50.
21. Wang Z, Vyas CM, Van Benschooten O, Nehs MA, Moore FD Jr, Marqusee E, Krane JF, Kim MI, Heller HT, Gawande AA, Frates MC, Doubilet PM, Doherty GM, Cho NL, Cibas ES, Benson CB, Barletta JA, Zavacki AM, Larsen PR, Alexander EK, Angell TE. Quantitative Analysis of the Benefits and Risk of Thyroid Nodule Evaluation in Patients ≥70 Years Old. *Thyroid*. 2018 Apr;28(4):465-471.
22. Smith SA, Hay ID, Goellner JR, et al. Mortality from papillary thyroid carcinoma: a case-control study of 56 lethal cases. *Cancer* 62:1381-1388, 1988.
23. Tollefsen HR, DeCosse JJ, Hutter RVP. Papillary carcinoma of the thyroid: a clinical and pathological study of 70 fatal cases. *Cancer* 17:1035-1044, 1964.
24. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.
25. Girardi FM. Thyroid Carcinoma Pattern Presentation According to Age. *Int Arch Otorhinolaryngol*. 2017 Jan;21(1):38-41.
26. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA* 295:2164-2167, 2006.
27. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *JAMA*. 2017 Apr 4;317(13):1338-1348.

28. Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM. Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results national cancer data registry. *Surgery* 148:1147-1152, 2010.
29. Lebastchi AH, Callender GG. Thyroid cancer. *Curr Probl Cancer*. 2014 Mar-Apr;38(2):48-74.
30. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. *Lancet*. 2016 Dec 3;388(10061):2783-2795.
31. Gupta KL. Neoplasm of the thyroid gland. *Clin Geriatr Med* 11:271-290, 1995.
32. Sarne D, Schneider AB. External radiation and thyroid neoplasia. *Endocrinol Metab Clin North Am* 1996;25(1): 181–195.
33. Ron E, Kleinerman RA, Boice JD Jr, LiVolsi VA, Flannery JT, Fraumeni JF Jr. A population-based case-control study of thyroid cancer. *J Natl Cancer Inst* 1987;79(1):1–12.
34. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. 1995. *Radiat Res* 2012;178(2):AV43–AV60.
35. Lee YS, Lim H, Chang HS, Park CS. Papillary thyroid microcarcinomas are different from latent papillary thyroid carcinomas at autopsy. *J Korean Med Sci* 29:676-679, 2014.
36. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid*. 24:27-34, 2014.
37. Grebe SK, Hay ID. Follicular thyroid cancer. *Endocrinol Metab Clin North Am* 24:761, 1995.
38. Brennan MD, Bergstralh, EJ, Van Heerden JA, et al. Follicular thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. *Mayo Clin Proc* 66:11-22, 1991.
39. Grani G, Lamartina L, Durante C, Filetti S, Cooper DS. Follicular thyroid cancer and Hürthle cell carcinoma: challenges in diagnosis, treatment, and clinical management. *Lancet Diabetes Endocrinol*. 2018 Jun;6(6):500-514.
40. Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nat Rev Cancer*. 2013 Mar;13(3):184-99.
41. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. *Cancer*. 1998 Dec 15;83(12):2638-48.
42. Máximo V, Lima J, Prazeres H, Soares P, Sobrinho-Simões M. The biology and the genetics of Hürthle cell tumors of the thyroid. *Endocr Relat Cancer*. 2016 Dec;23(12):X2.
43. Ganly I, Makarov V, Deraje S, Dong Y, Reznik E, Seshan V, Nanjangud G, Eng S, Bose P, Kuo F, Morris LGT, Landa I, Carrillo Alborno PB, Riaz N, Nikiforov YE, Patel K, Umbricht C, Zeiger M, Kebebew E, Sherman E, Ghossein R, Fagin JA, Chan TA. Integrated Genomic Analysis of Hürthle Cell Cancer Reveals Oncogenic Drivers, Recurrent Mitochondrial Mutations, and Unique Chromosomal Landscapes. *Cancer Cell*. 2018 Aug 13;34(2):256-270.e5.
44. Gopal RK, Kübler K, Calvo SE, Polak P, Livitz D, Rosebrock D, Sadow PM, Campbell B, Donovan SE, Amin S, Gigliotti BJ, Grabarek Z, Hess JM, Stewart C, Braunstein LZ, Arndt PF, Mordecai S, Shih AR, Chaves F, Zhan T, Lubitz CC, Kim J, Iafrate AJ, Wirth L, Parangi S, Leshchiner I, Daniels GH, Mootha VK, Dias-Santagata D, Getz G, McFadden DG. Widespread Chromosomal Losses and Mitochondrial DNA Alterations as Genetic Drivers in Hürthle Cell Carcinoma. *Cancer Cell*. 2018 Aug 13;34(2):242-255.e5.

45. Lin JD, Chao TC, Chen ST, et al. Characteristics of thyroid carcinomas in aging patients. *Eur J Clin Invest* 30:147-153, 2000.
46. Payne RJ, Bastianelli M, Mlynarek AM, et al. Is age associated with risk of malignancy in thyroid cancer? *Otolaryngol Head Neck Surg* 746-750, 2014.\
47. Chereau N, Trésallet C, Noullet S, Godiris-Petit G, Tissier F, Leenhardt L, Menegaux F. Prognosis of papillary thyroid carcinoma in elderly patients after thyroid resection: A retrospective cohort analysis. *Medicine (Baltimore)*. 2016 Nov;95(47):e5450.
48. Lerch H, Schober O, Kuwert T, et al. Survival of differentiated thyroid carcinoma studied in 500 patients. *J Clin Onc* 15:2067-2075, 1997.
49. Shi LY, Liu J, Yu LJ, Lei YM, Leng SX, Zhang HY. Clinic-pathologic Features and Prognostic Analysis of Thyroid Cancer in the Older Adult: A SEER Based Study. *J Cancer*. 2018 Jul 1;9(15):2744-2750.
50. Haymart MR. Understanding the relationship between age and thyroid cancer. *Oncologist*. 2009 Mar;14(3):216-21.
51. Adam MA, Pura J, Goffredo P, Dinan MA, Reed SD, Scheri RP, Hyslop T, Roman SA, Sosa JA. Presence and Number of Lymph Node Metastases Are Associated With Compromised Survival for Patients Younger Than Age 45 Years With Papillary Thyroid Cancer. *J Clin Oncol*. 2015 Jul 20;33(21):2370-5.
52. Orosco RK, Hussain T, Brumund KT, Oh DK, Chang DC, Bouvet M. Analysis of age and disease status as predictors of thyroid cancer-specific mortality using the Surveillance, Epidemiology, and End Results database. *Thyroid*. 2015 Jan;25(1):125-32.
53. Ganly I, Nixon IJ, Wang LY, Palmer FL, Migliacci JC, Aniss A, Sywak M, Eskander AE, Freeman JL, Campbell MJ, Shen WT, Vaisman F, Momesso D, Corbo R, Vaisman M, Shaha A, Tuttle RM, Shah JP, Patel SG. Survival from Differentiated Thyroid Cancer: What Has Age Got to Do with It? *Thyroid*. 2015 Oct;25(10):1106-14.
54. Brierley, J.D.; Gospodarowicz, M.K.; Wittekind, C. *TNM Classification of Malignant Tumours*, 8th ed.; John Wiley & Sons: Weinheim, Germany, 2017; pp. 69–71.
55. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery*. 1993 Dec;114(6):1050-7.
56. Davis NL, Bugis SP, McGregor GI, Germann E. An evaluation of prognostic scoring systems in patients with follicular thyroid cancer. *Am J Surg*. 1995 Nov;170(5):476-80.
57. Halnan KE. Influence of age and sex on incidence and prognosis of thyroid cancer. *Cancer* 19:1534-1536, 1966.
58. Cady B, Sedgwick CE, Meissner WA, et al. Risk factor analysis in differentiated thyroid cancer. *Cancer* 43:810-820, 1979.
59. Ito Y, Miyauchi A, Jikuzono T, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Ichihara K, Kuma K. Risk factors contributing to a poor prognosis of papillary thyroid carcinoma: validity of UICC/AJCC TNM classification and stage grouping. *World J Surg*. 2007 Apr;31(4):838-48.
60. Sugino K, Ito K, Nagahama M, Kitagawa W, Shibuya H, Ohkuwa K, Yano Y, Uruno T, Akaishi J, Kameyama K, Ito K. Prognosis and prognostic factors for distant metastases and tumor mortality in follicular thyroid carcinoma. *Thyroid*. 2011 Jul;21(7):751-7.

61. Voutilainen PE, Multanen MM, Leppaniemi AK, et al. Prognosis after lymph node recurrence in papillary thyroid carcinoma depends on age. *Thyroid* 11:953, 2001.
62. Zaydfundim V, Feurer ID, Griffin MR, et al. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. *Surgery* 144:1070-1077, 2008.
63. Ito Y, Kudo T, Takamura Y, Kobayashi K, Miya A, Miyauchi A. Prognostic factors of papillary thyroid carcinoma vary according to sex and patient age. *World J Surg* 35:2684-2690, 2011.
64. Ylli D, Burman KD, Van Nostrand D, Wartofsky L. Eliminating the Age Cutoff in Staging of Differentiated Thyroid Cancer: The Safest Road? *J Clin Endocrinol Metab*. 2018 May 1;103(5):1813-1817.
65. Nixon IJ, Wang LY, Migliacci JC, Eskander A, Campbell MJ, Aniss A, Morris L, Vaisman F, Corbo R, Momesso D, Vaisman M, Carvalho A, Learoyd D, Leslie WD, Nason RW, Kuk D, Wreesmann V, Morris L, Palmer FL, Ganly I, Patel SG, Singh B, Tuttle RM, Shaha AR, Gönen M, Pathak KA, Shen WT, Sywak M, Kowalski L, Freeman J, Perrier N, Shah JP. An International Multi-Institutional Validation of Age 55 Years as a Cutoff for Risk Stratification in the AJCC/UICC Staging System for Well-Differentiated Thyroid Cancer. *Thyroid*. 2016 Mar;26(3):373-80.
66. Nixon IJ, Kuk D, Wreesmann V, Morris L, Palmer FL, Ganly I, Patel SG, Singh B, Tuttle RM, Shaha AR, Gönen M, Shah JP. Defining a Valid Age Cutoff in Staging of Well-Differentiated Thyroid Cancer. *Ann Surg Oncol*. 2016 Feb;23(2):410-5.
67. McLeod DS, Carruthers K, Kevat DA. Optimal differentiated thyroid cancer management in the elderly. *Drugs Aging*. 2015 Apr;32(4):283-94.
68. Randolph GW, Doherty GM. Carcinoma of the follicular thyroid: surgical therapy. In: Braverman LE, Cooper DS, editors. *Werner & Ingbar's the thyroid: a fundamental and clinical text*. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. p. 702–11.
69. Bliss R, Patel N, Guinea A, et al. Age is no contraindication to thyroid surgery. *Age Ageing*. 1999;28:363–6.
70. Passler C, Avanesian R, Kaczirek K, et al. Thyroid surgery in the geriatric patient. *Arch Surg*. 2002;137:1243–8.
71. Seybt MW, Khichi S, Terris DJ. Geriatric thyroidectomy: safety of thyroid surgery in an aging population. *Arch Otolaryngol Head Neck Surg*. 2009;135:1041–4.
72. Raffaelli M, Bellantone R, Princi P, et al. Surgical treatment of thyroid diseases in elderly patients. *Am J Surg*. 2010;200: 467–72.
73. Sosa JA, Mehta PJ, Wang TS, et al. A population-based study of outcomes from thyroidectomy in aging Americans: at what cost? *J Am Coll Surg*. 2008;206:1097–105.
74. Tuggle CT, Park LS, Roman S, et al. Rehospitalization among elderly patients with thyroid cancer after thyroidectomy are prevalent and costly. *Ann Surg Oncol*. 2010;17:2816–23.
75. Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med* 366:1663-1673, 2012.
76. Mallick U, Harmer C, Yap B, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med* 366:1674-1685, 2012.

77. Schlumberger M, Leboulleux S, Catargi B, et al. Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial. *Lancet Diabetes Endocrinol* 6:618–626, 2018.
78. Ruel E, Thomas S, Dinan M, Perkins JM, Roman SA, Sosa JA. Adjuvant radioactive iodine therapy is associated with improved survival for patients with intermediate-risk papillary thyroid cancer. *J Clin Endocrinol Metab* 100:1529-1536, 2015.
79. Andresen NS, Buatti JM, Tewfik HH, Pagedar NA, Anderson CM, Watkins JM. Radioiodine Ablation following Thyroidectomy for Differentiated Thyroid Cancer: Literature Review of Utility, Dose, and Toxicity. *Eur Thyroid J*. 2017 Jul;6(4):187-196
80. Flynn RW, Bonellie SR, Jung RT, et al. Serum thyroid stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *J Clin Endocrinol Metab*. 2010;95:186–93.
81. Bauer DC, Ettinger B, Nevitt MC, et al. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. *Ann Intern Med*. 2001;134:561–8.
82. Kung AW, Yeung SS. Prevention of bone loss induced by thyroxine suppressive therapy in postmenopausal women: the effect of calcium and calcitonin. *J Clin Endocrinol Metab*. 1996;81:1232–6.
83. Sugitani I, Fujimoto Y. Effect of postoperative thyrotropin suppressive therapy on bone mineral density in patients with papillary thyroid carcinoma: a prospective controlled study. *Surgery*. 2011;150:1250–7.
84. Wang LY, Smith AW, Palmer FL, Tuttle RM, Mahrous A, Nixon IJ, Patel SG, Ganly I, Fagin JA, Boucai L. Thyrotropin suppression increases the risk of osteoporosis without decreasing recurrence in ATA low- and intermediate-risk patients with differentiated thyroid carcinoma. *Thyroid*. 2015 Mar;25(3):300-7.
85. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R; National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int*. 2014 Oct;25(10):2359-81.
86. Gregerman RI, Gaffney GW, Shock NW, et al. Thyroxine turnover in euthyroid man with special reference to changes with age. *J Clin Invest*. 1962;41:2065–74.
87. Rosenbaum RL, Barzel US. Levothyroxine replacement dose for primary hypothyroidism decreases with age. *Ann Intern Med*. 1982;96:53–5.
88. Singh N, Weisler SL, Hershman JM. The acute effect of calcium carbonate on the intestinal absorption of levothyroxine. *Thyroid*. 2001 Oct;11(10):967-71.
89. Kim M, Ladenson P. Thyroid. In: Goldman L, Schafer AI, editors. *Goldman's Cecil medicine*. 24th ed. Philadelphia: Elsevier Saunders; 2012. p 1450–63.
90. Soroushyari A, Do D, Langton J, et al. Partial withdrawal of levothyroxine to stimulate serum thyroglobulin for thyroid cancer monitoring. *Thyroid* 14:1105-1107, 2004.
91. Spencer C, Fatemi S. Thyroglobulin antibody (TgAb) methods - Strengths, pitfalls and clinical utility for monitoring TgAb-positive patients with differentiated thyroid cancer. *Best Pract Res Clin Endocrinol Metab*. 2013 Oct;27(5):701-12.
92. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014;384:319-328.

93. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 372:621-30, 2015.
94. Kebebew E, Greenspan FS, Clark OH, et al. Anaplastic thyroid carcinoma treatment outcome and prognostic factors. *Cancer* 103:1330-1335, 2005.
95. Aldinger KA, Samaan NA, Ibanez M, et al. Anaplastic carcinoma of the thyroid a review of 84 cases of spindle and giant cell carcinoma of the thyroid. *Cancer* 41:2267-2275, 1978.
96. Schwartz DL, Lobo ML, Ang KK, et al. Postoperative external beam radiotherapy for differentiated thyroid cancer: outcomes and morbidity with conformal treatment. *Int J Radiat Oncol Biol Phys* 75:1-9, 2009.
97. Rao SN, Cabanillas ME. Navigating systemic therapy in advanced thyroid carcinoma: From standard care to personalized therapy and beyond. *J Endocr Soc.* 2018 Oct 1; 2(10): 1109–1130.
98. Kebebew E, Ituarte PHG, Siperstein AE, et al. Medullary thyroid carcinoma clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. *Cancer* 88:1139-1147, 2000.
99. Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid: a study of the clinical features and prognostic factors in 161 patients. *Medicine (Baltimore)* 63:319, 1984.
100. Scopsi L, Sampietro G, Boracchi P, et al. Multivariate analysis of prognostic factors in sporadic medullary carcinoma of the thyroid: a retrospective study of 109 consecutive patients. *Cancer* 78:2173-2183, 1996.
101. deGroot JW, Plukker JT, Wolffenbuttel BH, et al. Determinants of life expectancy in medullary thyroid cancer: age does not matter. *Clin Endocrinol (Oxf)* 65:729, 2006.
102. Machens A, Hauptmann S, Dralle H. Increased risk of lymph node metastasis in multifocal hereditary and sporadic medullary thyroid cancer. *World J Surg* 2007;31:1960 –1965
103. Roy M, Chen H, Sippel RS. Current understanding and management of medullary thyroid cancer. *The Oncologist*, 2013;18:1093–1100.)
104. Wells SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double blind phase III trial. *J Clin Oncol* 30:134, 2012.
105. Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC, Niederle B, Cohen EE, Wirth LJ, Ali H, Hessel C, Yaron Y, Ball D, Nelkin B, Sherman SI. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol.* 2013 Oct 10;31(29):3639-46.
106. Drilon AE, Subbiah V, Oxnard GR, et al. A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers [abstract]. Annual meeting of the American Society of Clinical Oncology; 2018 June 1-5; Chicago, IL.
107. Wirth L, et al. Clinical activity of LOXO-292, a highly selective RET inhibitor, in patients with RET-altered thyroid cancers [abstract]. 88th Annual meeting of the American Thyroid Association; 2018 Oct 3-7; Washington, D.C.
108. Hu M, et al. Clinical activity of selective RET inhibitor, BLU-667, in advanced RET-altered thyroid cancers: updated results from the phase I ARROW study [abstract]. 88th Annual meeting of the American Thyroid Association; 2018 Oct 3-7; Washington, D.C.

