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Thyroid Cancer
A Review

Laura Boucai, MD; Mark Zafereo, MD; Maria E. Cabanillas, MD

IMPORTANCE Approximately 43 720 new cases of thyroid carcinoma are expected to be diagnosed in 2023 in the US. Five-year relative survival is approximately 98.5%. This review summarizes current evidence regarding pathophysiology, diagnosis, and management of early-stage and advanced thyroid cancer.

OBSERVATIONS Papillary thyroid cancer accounts for approximately 84% of all thyroid cancers. Papillary, follicular (≈4%), and oncocytic (≈2%) forms arise from thyroid follicular cells and are termed well-differentiated thyroid cancer. Aggressive forms of follicular cell-derived thyroid cancer are poorly differentiated thyroid cancer (≈5%) and anaplastic thyroid cancer (≈1%). Medullary thyroid cancer (≈4%) arises from parafollicular C cells. Most cases of well-differentiated thyroid cancer are asymptomatic and detected during physical examination or incidentally found on diagnostic imaging studies. For microcarcinomas (≤1 cm), observation without surgical resection can be considered. For tumors larger than 1 cm with or without lymph node metastases, surgery with or without radioactive iodine is curative in most cases. Surgical resection is the preferred approach for patients with recurrent locoregional disease. For metastatic disease, surgical resection or stereotactic body irradiation is favored over systemic therapy (eg, lenvatinib, dabrafenib). Antiangiogenic multikinase inhibitors (eg, sorafenib, lenvatinib, cabozantinib) are approved for thyroid cancer that does not respond to radioactive iodine, with response rates 12% to 65%. Targeted therapies such as dabrafenib and selpercatinib are directed to genetic mutations (*BRAF*, *RET*, *NTRK*, *MEK*) that give rise to thyroid cancer and are used in patients with advanced thyroid carcinoma.

CONCLUSIONS Approximately 44 000 new cases of thyroid cancer are diagnosed each year in the US, with a 5-year relative survival of 98.5%. Surgery is curative in most cases of well-differentiated thyroid cancer. Radioactive iodine treatment after surgery improves overall survival in patients at high risk of recurrence. Antiangiogenic multikinase inhibitors and targeted therapies to genetic mutations that give rise to thyroid cancer are increasingly used in the treatment of metastatic disease.

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Author Affiliations: Department of Medicine, Division of Endocrinology, Memorial Sloan Kettering Cancer Center, New York, New York (Boucai); Department of Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, Texas (Zafereo); Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas MD Anderson Cancer Center, Houston, Texas (Cabanillas).

Corresponding Author: Laura Boucai, MD, Memorial Sloan Kettering Cancer Center, Koch Building, 530 E 74th St, Ste 22244, New York, NY 10021 (boucail@mskcc.org).

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Approximately 1.2% of people in the United States will be diagnosed with thyroid cancer at some point during their lifetime and about 43 720 new cases of thyroid carcinoma are anticipated in 2023.[1] The incidence of thyroid cancer has increased by 313% in the past 4 decades, mainly due to increased detection from the widespread use of imaging studies and the introduction of fine-needle aspiration biopsies. A change in tumor biology with increased incidence of advanced-stage thyroid cancer (3.5% increase per year since 1981) may also partially explain this trend.[2] Although thyroid cancer is common, the 5-year relative survival, a weighted average of all stages of the disease, is high (98.5%) with approximately 2100 thyroid cancer deaths estimated per year in the US.[1,3] The recognition of the indolent course with an excellent prognosis in most cases has resulted in recommendations against screening, thereby mitigating overdetection.

Papillary thyroid carcinoma accounts for approximately 84% of all thyroid cancers. Papillary, follicular (≈4%), and oncocytic (≈2%) are termed well-differentiated thyroid cancer. Less common and more aggressive subtypes include poorly differentiated and anaplastic thyroid carcinoma that arise from well-differentiated thyroid cancer after accumulation of genetic mutations in the tumor (**Figure 1**). Medullary thyroid cancer (≈4%) arises from parafollicular C cells (Figure 1). Total thyroidectomy with or without radioactive iodine therapy has been typically recommended for the treatment of most forms of thyroid cancer. Molecular profile testing has allowed for more personalized treatment. Specific genetic mutations define unique pathologic phenotypes, with distinct clinical presentations and susceptibility to radioactive iodine and targeted therapies that can be used to tailor treatment. This review summarizes current evidence regarding pathophysiology, diagnosis, and management of early-stage and advanced thyroid cancer (**Box**).

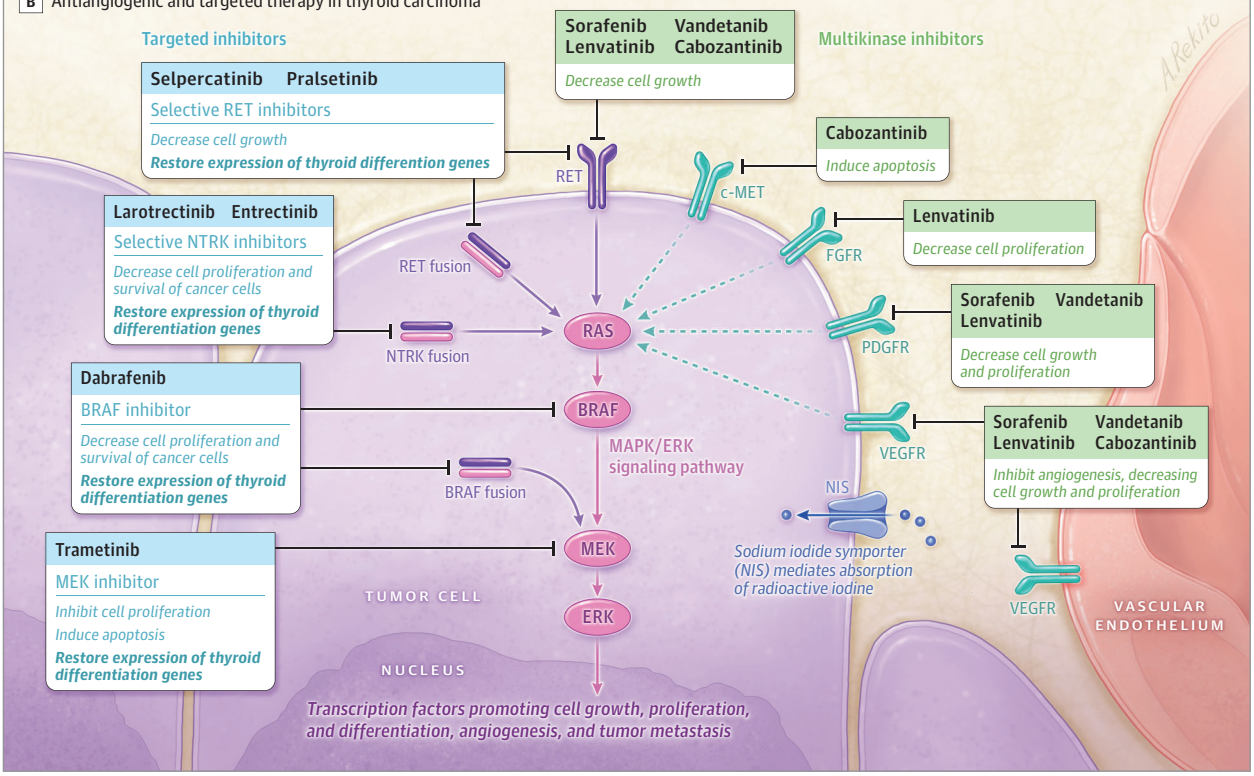
Figure 1. Histologic Subtypes and Molecular Profiling of Thyroid Carcinoma

A Thyroid carcinoma classification and FDA-approved systemic agents

Thyroid carcinoma types, frequency, and FDA-approved systemic treatments

Systemic treatments and their targets	EPITHELIAL FOLLICULAR CELLS: Differentiated thyroid carcinoma (DTC)	EPITHELIAL FOLLICULAR CELLS: Undifferentiated thyroid carcinoma	C CELLS: Medullary thyroid carcinoma (MTC)
	Papillary, ≈84%; Follicular, ≈4%; Oncocytic, ≈2%; *More aggressive subtypes, ≈5%*: High-grade differentiated, Poorly differentiated	Anaplastic thyroid carcinoma (ATC), ≈1%	MTC, ≈4%
Antiangiogenic multikinase inhibitors			
Sorafenib - targets VEGFR, PDGFR, RET	▶ Radioactive iodine refractory (RAIR) DTC		
Lenvatinib - targets VEGFR, PDGFR, FGFR, RET	▶ RAIR DTC		
Vandetanib - targets VEGFR, PDGFR, RET			▶ MTC
Cabozantinib - targets VEGFR, RET, MET	▶ RAIR DTC (second line)		▶ MTC
Targeted inhibitors			
Dabrafenib/trametinib - targets BRAF/MEK		▶ BRAF mutation ATC	
Dabrafenib - targets BRAF	▶ BRAF mutation RAIR DTC		
Larotrectinib - targets NTRK	▶ NTRK fusion DTC	▶ NTRK fusion ATC	
Entrectinib - targets NTRK	▶ NTRK fusion DTC	▶ NTRK fusion ATC	
Selpercatinib - targets RET	▶ RET fusion DTC	▶ RET fusion ATC	▶ RET mutation MTC
Pralsetinib - targets RET	▶ RET fusion DTC	▶ RET fusion ATC	

B Antiangiogenic and targeted therapy in thyroid carcinoma



A. Papillary, follicular, and oncocytic carcinoma derive from epithelial follicular cells and are classified as differentiated thyroid cancers. High-grade differentiated thyroid carcinoma, poorly differentiated thyroid carcinoma, and poorly differentiated thyroid carcinoma, oncocytic subtype are advanced forms of thyroid cancer. Anaplastic thyroid carcinoma is an undifferentiated and the most lethal form of thyroid cancer. Medullary thyroid carcinoma derives from parafollicular C cells. B. Drugs in green are antiangiogenic multikinase inhibitors. Drugs in blue are targeted inhibitors. Proteins derived from gene fusions are in pink and purple. c-MET indicates mesenchymal epithelial transition factor; FGFR, fibroblast growth factor receptor; PDGFR, platelet derived growth factor receptor; RET, rearranged during transfection, and VEGFR, vascular endothelial growth factor receptor.

Methods

A PubMed search was performed for English-language randomized clinical trials, meta-analyses, and systematic reviews of thyroid cancer published between January 1, 2010, and November 16, 2023. A total of 1255 studies were identified. We prioritized the inclusion of recent, high-quality articles based on relevance, topics covered, randomized clinical trials when available, rigor of study design, adequate sample size, and long-term follow-up. A total of 96 studies were included, consisting of 17 clinical trials, 2 meta-analyses, 9 systematic reviews, 11 guidelines, 29 cohort studies, 26 cross-sectional studies, 1 Surveillance Research Program NCI website, and 1 staging manual including publications prior to 2010.

Epidemiology and Screening

Thyroid cancer is the ninth most common cancer worldwide, the seventh most common cancer in US women, and the most common cancer in adolescents and adults younger than 40 years.[1,4] Data from the Surveillance, Epidemiology, and End Results 9 (SEER-9) cancer registry program shows that the incidence of thyroid cancer has increased from 1974-1977 to 2010-2013, from 4.6 to 14.4 cases per 100 000 US person-years,[2] largely due to detection of small asymptomatic cancers[2] with a higher incidence in women than in men. Mortality rates for thyroid cancer have remained low at 0.5 per 100 000 US persons per year,[3] with a 5-year relative survival rate of 98.5% that varies widely by histology and disease stage.[1,3] Although anaplastic thyroid cancer represents only 1% of all thyroid cancers, it contributes to 19.9% of annual thyroid cancer–related mortality[2] with a median overall survival of 6.5 months (95% CI, 4.3-10).[5] Attempts have been made to develop thyroid cancer screening strategies, but based on current evidence on accuracy of screening using neck palpation or ultrasound, and benefits and harms of early detection and treatment, the US Preventive Services Task Force recommends against screening for thyroid cancer in asymptomatic adults.[6]

Modifiable and Inherited Risk Factors

Exposure to ionizing radiation in childhood has the strongest association with papillary thyroid cancer (1.3-35.1 cases per 10 000 person-years).[7-9] A cohort study of 13 127 individuals younger than 18 years living in Ukraine after the 1986 Chernobyl nuclear accident screened individuals for thyroid cancer between 1998 and 2000. There were 45 cases of thyroid cancer detected, with an excess relative risk of thyroid cancer of 5.25 (95% CI, 1.70-27.5) per gray (Gy) of radiation exposure.[10] The study found a dose-response relationship between radiation exposure and thyroid cancer. Younger age at exposure was also associated with increased risk of radiation-related thyroid cancer, and this risk persisted nearly 30 years after exposure.[11]

Most thyroid cancer risk factors are nonmodifiable: age, sex, race or ethnicity, and family history of thyroid cancer are the strongest predictors of risk. Older age is associated with increased incidence and worse survival. In the SEER-9 cancer registry, the incidence rate of thyroid cancer and the incidence-based mortality rate between 1974-2013 were 13.15 cases (95% CI, 12.95-13.35) and 0.22 deaths (95% CI, 0.21-0.24) per 100 000 person-years among 60- to 79-year-old patients compared with 8.00 cases (95% CI, 7.89-8.09) and 0.02 deaths (95% CI, 0.02-0.02) per 100 000 person-years in the group aged 20 to 39 years.[2] Women have a 3-fold higher incidence of thyroid cancer than men (17.7 cases per 100 000 person-years in women versus 6.0 cases per 100 000 person-years in men), a ratio consistently observed across the world, which has remained constant over time.[2]

Twenty-five percent of patients with medullary thyroid carcinoma have germline sequence variants associated with hereditary multiple endocrine neoplasia types 2A and 2B syndromes.[12] Hereditary forms of well-differentiated thyroid cancer occur in 3% to 9% of the cases.[13]

In the Danish National Patient registry, with more than 8 million residents followed up between 1978-2013, nontoxic nodular goiter was associated with increased risk of thyroid cancer (standardized incidence ratio [SIR], 4.91 [95% CI, 3.91-6.09]).[14] Higher preoperative serum thyrotropin level was also associated with thyroid cancer in a retrospective cohort study of 843 patients undergoing thyroid surgery for unilateral or bilateral thyroid nodules, large thyroid glands, or autoimmune thyroid disease. In that study, 16% of patients (9/55) with a thyrotropin level less than 0.06 mIU/L had thyroid cancer vs 52% (15/29) with a thyrotropin level of 5mIU/L or greater (adjusted odds ratio [OR], 4.56 [95% CI, 1.35-15.45]; analyses adjusted for preoperative serum thyrotropin concentration in patients not receiving levothyroxine).[15]

Diagnosis

Thyroid nodules may be detected on physical examination or diagnosed incidentally on diagnostic imaging studies. The prevalence of palpable thyroid nodules has been reported to be approximately 5%

Box. Three Questions Commonly Asked by Generalists About Thyroid Cancer

When Should an Incidentally Found Thyroid Nodule Be Biopsied?
Certain ultrasonographic characteristics (eg, hypoechogenicity, irregular borders, hypervascularity, taller than wide, microcalcifications) and size of thyroid nodules (1 cm or greater) are indications for a fine-needle aspiration biopsy. In the case of indeterminate cytology (Bethesda III or IV), the use of molecular testing refines the risk of malignancy.

What Is the Initial Treatment and Surveillance of Well-Differentiated Thyroid Cancer?
Selected unilateral thyroid cancers with a diameter less than 1.5 cm can be observed without surgical resection; surgery with or without radioactive iodine is curative in most cases. After surgery, surveillance is performed by measuring serum thyroglobulin and thyroglobulin antibody levels, thyrotropin levels, and ultrasonography every 6 to 12 months.

How Does Molecular Testing Help in the Treatment of Advanced Thyroid Cancer?
Molecular testing helps to guide treatment decisions; for example, tumors with *BRAF* V600E mutations respond less well to radioactive iodine therapy, whereas tumors with *RAS* mutations typically respond to repeated doses of radioactive iodine. Targeted therapies are selected based on specific genetic mutations and fusions in advanced differentiated thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, and medullary thyroid cancer.

in women and 1% in men who live in iodine-sufficient areas of the world.[16] Studies have reported detection of thyroid nodules with high-resolution thyroid ultrasound in 19% to 68% of randomly selected individuals, and they are more common in women (40.6%-44.7%) than in men (27.0%-29.9%).[16] Current guidelines suggest that between 7% and 15% of thyroid nodules are malignant. Determination of malignancy is based on ultrasound characteristics and cytology.[16] However, in a recent prospective cohort of 17 592 patients with thyroid nodules larger than 1 cm, of whom 7776 underwent fine needle aspiration for cytology and 9816 were evaluated by sonography alone, thyroid cancer was histologically confirmed in 189 patients (1.1%) with up to 23 years of follow-up (median, 5 years).[17] Of the 189 cases of thyroid cancer, 155 were diagnosed during the first year of management, 25 in years 2 through 5 of follow-up, 9 in years 6 through 10, and none in 1165 patients followed up beyond 10 years.

The American Thyroid Association guidelines recommend avoiding biopsy of nodules smaller than 1 cm.[16] Thyroid ultrasound characteristics help determine when a fine needle aspiration is needed. A meta-analysis of 39 studies with 49 661 patients comparing 6 ultrasound classification systems showed that sonographic characteristics including nodule size, echogenicity, borders, vascularity, and presence of calcifications are 64% to 77% sensitive and 82% to 90% specific for detecting malignancy.[18] The American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS) ultrasound classification system had the best diagnostic performance.[19]

Nodules 1 cm or larger should only be biopsied when ultrasound characteristics are concerning for malignant disease.[19] Ultrasound features that suggest malignancy include irregular borders, hypoechogenicity, increased vascularity, microcalcifications, and taller than wide on transverse view. The recently updated Bethesda classification system provides a framework for the evaluation of thyroid cytopathology.[20] In the case of indeterminate cytology (Bethesda III and IV), which can occur in up to 30% of cases, molecular testing has helped refine the diagnosis. Benign (Bethesda II) or malignant (Bethesda V or VI) cytology does not require molecular testing. A comprehensive genomic analysis of 50 734 indeterminate nodules found that 65.3% tested negative for malignancy, 33.9% tested positive, 0.6% were positive for parathyroid tissue, and 0.2% were positive for medullary thyroid cancer[21] (Box).

Patients with thyroid cancer are generally asymptomatic. A retrospective study of 1328 patients, 613 with thyroid cancer, who underwent thyroid-directed surgery in 16 centers in 4 countries showed that only 30% of patients (183/613) had symptoms at the time of diagnosis.[22] Patients presenting with a neck mass, dysphagia, globus sensation, and hoarseness typically have more advanced disease (**Table 1**).[16,23-25]

Histologic Subtypes and Molecular Profiling

The molecular characterization of thyroid cancer has helped refine interpretation of indeterminate cytology, and define distinct subtypes of thyroid carcinoma, each with specific clinical behavior, susceptibility to radioactive iodine, and targeted therapies (Figure 1). In advanced thyroid cancer (when the disease is metastatic and does not respond to radioactive iodine), molecular testing is performed to identify therapies specifically targeted to the genetic mutation that gives rise to these tumors. The most common genetic variants that are associated with and promote growth of thyroid cancer occur in proteins of the intracellular mitogen-activated protein kinase (MAPK) pathway (Figure 1).[26,27] The most common gene variant is *BRAF* V600E, which is found in approximately 60% of patients with papillary thyroid cancer.[26] The *BRAF* V600E mutation occurs most frequently in classical and tall-cell variant papillary thyroid carcinomas, which have a high frequency of cervical lymph node metastases, locoregional recurrences, and are less responsive to radioactive iodine.[28] *RAS* mutations occur in about 13% of papillary thyroid cancers[26] and in 25% to 50% of follicular thyroid cancers.[26,29,30] Thyroid cancers with *RAS* mutations are prone to vascular invasion and retain the ability to respond to radioactive iodine. Chromosomal fusions occur in 15.3% of adults and 60% to 70% of children with papillary thyroid cancer[31,32] who do not have *BRAF* and *RAS* mutations. *RET* fusions are the most common chromosomal fusion (6.8%).[26] In the pediatric population, chromosomal fusions are associated with increased invasive behavior and decreased response to therapy.[33,34] Oncocytic thyroid carcinomas (formerly Hurthle cell carcinomas) (Figure 1) are genetically distinct, with loss of 1 arm of most chromosomes (haploidy) and duplication of chromosomes 5 and 7.[35-37] High-grade differentiated thyroid cancer,[38] poorly differentiated thyroid carcinomas, and anaplastic thyroid cancers[39,40] derive from thyroid follicular cells, are rare (≈6%), have a higher burden of mutations, are less responsive to radioactive iodine, and have the highest thyroid cancer mortality (Figure 1).

Medullary thyroid carcinoma is hereditary in 25% of patients (*RET* mutations) and occurs sporadically in 75%[41-43] (Figure 1). Clinicians should check for germline *RET* mutations in all patients with medullary thyroid cancer to determine if it is hereditary.

Active Surveillance

Despite ongoing educational efforts within the medical community, overdiagnosis and overtreatment of thyroid cancers remains a concern. A recent survey of 439 thyroidologists reported that 64% recommended management that would result in overdiagnosis of small thyroid nodules, while 40% would overtreat low-risk papillary thyroid cancer with total thyroidectomy and/or radioactive iodine.[44] In general, thyroid nodules smaller than 1 cm and thyroid nodules smaller than 1.5 cm without ultrasound features suspicious for malignancy should be monitored with ultrasound rather than biopsied.[16] Observation without surgery may be appropriate for selected patients with small papillary thyroid cancers. A prospective cohort of 340 Japanese patients with biopsy-proven well-differentiated thyroid cancer (smaller than ≈1 cm) were followed up without surgical resection for a median of 6 years and up to 15 years; 15.9% of microcarcinomas grew by 3 mm or more, 3.4% of patients developed cervical lymph node metastases at 10 years, and none developed distant metastases at 10 years. This active surveillance strategy was replicated in the US in a prospective cohort of 291 patients with well-differentiated thyroid cancer smaller than 1.5 cm and had similar results.[45,46]

Surgery

Most well-differentiated thyroid cancers (54%) are at low risk of recurrence and can be cured with surgery alone[16,47] (**Figure 2**).

Table 1. Overview of Diagnosis, Treatment, and Surveillance of Different Types of Thyroid Cancer

Thyroid cancer type	Tumor markers	Initial workup	Initial treatment	Surveillance	Treatment of advanced disease
DTC[16] (≈85%)	Thyroglobulin and thyroglobulin antibodies	Ultrasound (to include lateral neck) and FNA For locally advanced tumors, CT of neck with contrast or MRI of neck	Surgery; thyrotropin suppression and RAI reserved for intermediate and high-risk thyroid cancer (Figure 2)	Ultrasound (to include lateral neck), thyroglobulin and thyroglobulin antibodies, thyroid function tests to ensure thyrotropin suppression for intermediate- to high-risk patients, every 6 mo initially; annually if no evidence of disease	For recurrent disease in metastatic lymph nodes or distant metastases that grow on cross-sectional imaging despite RAI, additional surgery, radiation, targeted therapy (Figure 1)
ATC[23,24] (≈1%)	None	Ultrasound with FNA cell block or core biopsy; rapid *BRAF* V600E testing (IHC or PCR); cross-sectional imaging of brain, neck, chest, abdomen, pelvis Airway assessment	Localized to neck: If resectable, surgery then radiation with/without chemotherapy If unresectable and with *BRAF* V600E mutation, consider neoadjuvant dabrafenib + trametinib If unresectable and no *BRAF* V600E mutation, radiation with/without chemotherapy Metastatic outside neck: Anaplastic thyroid cancer with *BRAF* V600E mutation: dabrafenib/trametinib Anaplastic thyroid cancer without *BRAF* V600E mutation: clinical trials when available and consideration of palliative radiation to the neck	Cross-sectional imaging of neck, chest, abdomen every 3 mo; brain MRI yearly	All patients with anaplastic thyroid cancer are considered to have advanced disease Refer to "initial treatment" in this row
MTC[25] (≈4%)	Calcitonin and CEA	Tumor markers; germline testing for RET mutations Ultrasound (to include lateral neck) and FNA Cross-sectional neck imaging for advanced disease If calcitonin >500 pg/mL, cross-sectional imaging to rule out metastatic disease (neck, chest, liver, axial skeleton)	Surgery when resectable For hereditary disease, evaluation for pheochromocytoma and primary hyperparathyroidism prior to surgical resection	Ultrasound (to include lateral neck), calcitonin, CEA If calcitonin >150 pg/mL, consider cross-sectional imaging to evaluate for metastatic disease every 6 mo	For locally advanced persistent disease, surgery should be considered. If inoperable, targeted therapy (see Figure 1)
			Metastatic disease outside neck: initial observation to determine need for systemic therapy	Ultrasound (to include lateral neck), cross-sectional imaging of metastatic disease sites, calcitonin, CEA every 6 mo or more frequently if disease shows growth or calcitonin increases (calcitonin doubling time <1 y)	For metastatic disease that grows on cross-sectional imaging studies, targeted therapy (see Figure 1)

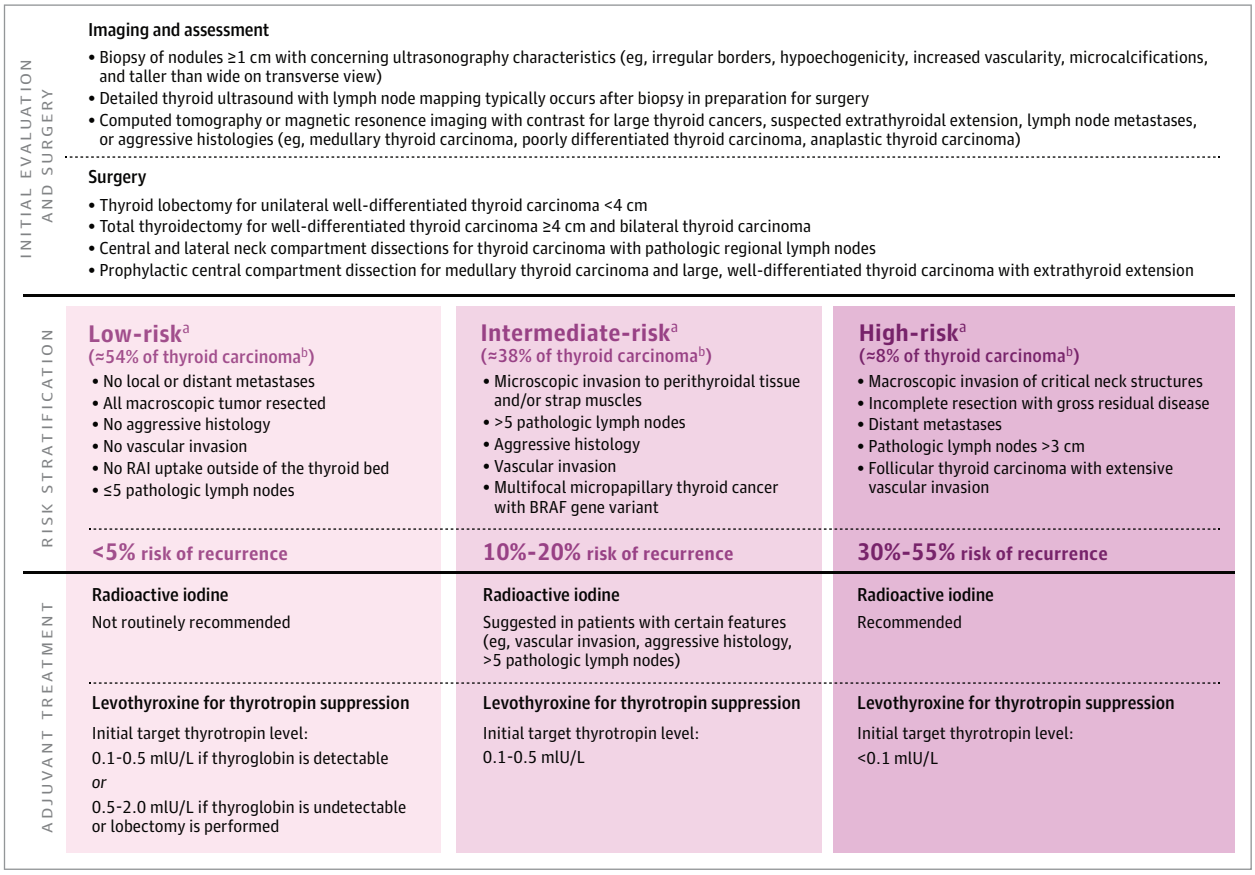
Abbreviations: DTC, well-differentiated thyroid cancer; ATC, anaplastic thyroid cancer; MTC, medullary thyroid cancer; RAI, radioactive iodine; FNA, fine-needle aspiration; CT, computed tomography; MRI, magnetic resonance imaging; IHC, immunohistochemistry; CEA, Carcinoembrionic antigen, RET gene, rearranged during transfection gene.

Preoperative high-definition neck ultrasound to evaluate the thyroid and central and lateral neck compartments is mandatory. Computed tomography (CT) of the neck with contrast or magnetic resonance imaging (MRI) are reserved for patients with large tumors, suspected extrathyroidal extension, lymph node metastases, or aggressive histologies (ie, medullary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer) (Table 1).

Patients undergoing surgery should have a preoperative assessment of the vocal cords to ensure bilateral mobility. For unilateral well-differentiated thyroid cancer smaller than 4 cm, thyroid lobectomy is often preferred as survival is equivalent to that with total thyroidectomy, and complications such as hypoparathyroidism are less frequent. A retrospective cohort study with propensity score matching evaluated the 10-year overall survival of 22 806 patients undergoing thyroid lobectomy compared with 61 494 patients undergoing total thyroidectomy and found overall survival to be equivalent [91.2% [95% CI, 89.6%-92.6%] vs 91.3% [95% CI, 89.7%-92.7%], respectively).[48] Total thyroidectomy is generally recommended for well-differentiated thyroid cancer 4 cm or larger and for bilateral thyroid cancer.

Central and lateral neck compartment dissections are performed for patients with disease that has spread to regional lymph nodes.[16] Prophylactic central compartment dissections are only performed for patients with medullary thyroid cancer and some well-differentiated thyroid cancers that are large and have extrathyroidal extension. Prophylactic lateral neck dissections may be considered for patients with medullary thyroid cancer. Plasma metanephrines, calcium, and parathyroid hormone (PTH) levels should be evaluated preoperatively in patients with suspected hereditary medullary thyroid cancer to rule out concomitant pheochromocytoma and hyperparathyroidism as part of MEN2A syndrome.

Figure 2. American Thyroid Association Risk Stratification System and Initial Treatment Recommendations



American Thyroid Association risk stratification system of well differentiated thyroid carcinoma, risk of recurrence, surgery, indications for radioactive iodine treatment, and levothyroxine suppressive therapy. RAI indicates radioactive iodine.

[a] Haugen et al,[16] 2016.

[b] Grani et al,[47] 2021.

For all types of thyroid cancer, oncologic outcomes are best, and complications are lowest, when care is managed by high-volume thyroid surgeons (>50 thyroidectomies per year). In a retrospective cohort of 72 594 patients undergoing elective thyroid surgery, high-volume thyroid surgeons had a lower rate of medical complications (OR, 0.57 [95% CI, 0.45-0.71]), surgical complications (OR, 0.67 [95% CI, 0.51-0.87]), and death or life-threatening complications [OR, 0.21 [95% CI, 0.08-0.52]) (absolute rates not available) than lower-volume thyroid surgeons.[49,50]

Clinical Staging and Risk Stratification

The American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system predicts disease-specific survival based on patient age, tumor size, presence of nodal metastases, macroscopic locoregional invasion, and distant metastases.[51] The American Thyroid Association (ATA)[16] and European Thyroid Association (ETA)[52] risk stratification systems predict disease recurrence because they include relevant histopathologic features and some molecular markers. These staging systems are implemented immediately after surgery and approximately 6 months later and guide the initial treatment and intensity of surveillance (Figure 2).[16,47]

Adjuvant Therapy for Thyroid Cancer

The goals of postoperative radioactive iodine (RAI) administration to patients with well-differentiated thyroid cancer after total thyroidectomy include destruction of normal thyroid tissue to facilitate follow-up with thyroglobulin levels; destruction of suspected limited persistent disease to decrease recurrence; or treatment of patients with persistent disease who are at high risk for progression.[16] Retrospective observational studies[53-55] and a recent randomized trial[56] showed that RAI does not reduce recurrence rates among patients with low-risk thyroid cancer at 3 years. In the trial, the recurrence rate was 4.1% with RAI vs 4.4% without RAI (difference, −0.3 [90% CI, −2.7 to 2.2]) among 730 patients with low-risk thyroid cancer.[56] In patients at high risk of recurrence, a prospective multicenter study of 2936 patients (30% of these at high risk) showed improved overall survival (risk ratio [RR], 1.43 [95% CI, 1.17-1.72]; $P < .001$) and decreased recurrence rates (RR, 1.32 [95% CI, 1.02-1.68]; $P = .04$) after RAI administration (risk ratio >1 indicates a better outcome associated with RAI; absolute risk data for

Table 2. Systemic Therapy, Targets, Indications, Efficacy, and Common Adverse Events From Clinical Trials

Drugs	Targets	Approved indication	No. of patients	Efficacy	Common adverse events (% of patients)
Sorafenib[a]	VEGFR, PDGFR, RET	RAI-R DTC	417[76]	Response rate: 12.2% (24/196) for sorafenib and 0.5% (1/201) for placebo, $P < .001$ mPFS: 10.8 mo for sorafenib vs 5.8 mo for placebo, $P < .001$	Hand-foot skin reaction (redness, swelling, and pain of palms and/or soles) (76), diarrhea (69), alopecia (67), rash (50)
Lenvatinib[a]	VEGFR, PDGFR, FGFR, RET	RAI-R DTC	392[77]	Response rate: 64.8% for lenvatinib and 1.5% for placebo, $P < .001$ mPFS: 18.3 mo for lenvatinib vs 3.6 mo for placebo, $P < .001$	Hypertension (68), diarrhea (59), fatigue (59), decreased appetite (50), decreased weight (46), nausea (41)
Vandetanib[a]	VEGFR, PDGFR, RET	MTC	331[78]	Response rate: 45% (104/231) for vandetanib and 13% (13/100) for placebo, $P < .001$ mPFS: NR for vandetanib vs 19.3 mo for placebo, $P < .001$	Diarrhea (56), rash (45), nausea (33), hypertension (32), headache (26)
Cabozantinib[a]	VEGFR, RET, MET	MTC	330[79]	Response rate: 28% for cabozantinib and 0% for placebo, $P < .001$ mPFS: 11.2 mo for cabozantinib vs 4 mo for placebo, $P < .001$	Diarrhea (70), weight loss (58), hand-foot skin reaction (53), nausea (47), fatigue (43), hypertension (33)
		Second-line RAI-R DTC	164[80]	Response rate: 15% (10/67) for cabozantinib and 0% (0/33) for placebo, $P = .028$ mPFS: NR for cabozantinib vs 1.9 mo for placebo, $P < .001$	
Dabrafenib + trametinib	BRAF + MEK BRAF ± MEK	*BRAF*-mutated ATC	36[81]	Response rate: 56% (95% CI, 38.1%-78.1%) mPFS 6.7 mo mOS: 14.5 mo	Fever (47), anemia (36), decreased appetite (33), fatigue (33), nausea (33), rash (28)
Dabrafenib with/without trametinib[b]		RAI-R DTC with *BRAF* mutation	53[82]	Single agent: Response rate: 35% (9/26) mPFS: 10.7 mo mOS: 37.9 mo Dual therapy: Response rate: 30% (8/27) mPFS: 15.1 mo mOS: 47.5 mo	
Larotrectinib	NTRK	NTRK-fusion thyroid cancer	29[83]	DTC: Response rate: 86% (95% CI, 64%-97%) mPFS and mOS: NR ATC: Response rate: 29% (95% CI, 4%-71%) mPFS 2.2 mo mOS: 8.8 mo	Myalgia (41), fatigue (34), nausea (34), constipation (31), cough (31), dizziness (31), peripheral edema (31), ALT and AST increased (28), arthralgia (24), anemia (28)
Entrectinib	NTRK	NTRK-fusion thyroid cancer	13[84]	Response rate: 53.8% (7/13) mPFS: 19.9 mo mOS: 19.9 mo	Dysgeusia (35), weight gain (28), diarrhea (31), fatigue (28).
Selpercatinib	RET	MTC (treatment naive) with *RET* variant	291[87]	Response rate: 69.4% (95% CI, 62.4%-75.8%) mPFS: not reached One-year PFS: 86.8% (95% CI, 79.8%-91.6%)	Dry mouth (46), hypertension (43), diarrhea (38), fatigue (38), increased ALT and AST levels (35), nausea (35), constipation (35), headache (31), peripheral edema (30)
		RET-fusion non-MTC thyroid cancer	19[85]	Response rate: 79% (95% CI, 54%-94%) mPFS: 20.1 mo 1-y PFS: 64% (95% CI, 37%-82%)	
Pralsetinib	RET	RET-fusion non-MTC thyroid cancer	20[86]	Response rate: 89% (8/9 patients with thyroid cancer) (95% CI, 52%-100%) mPFS: NR 1-y PFS: 81% 1-y OS: 91% (95% CI: 74%-100%)	Increased AST and ALT levels (34), constipation (28), decreased WBC count (34), hypertension (33), hyperphosphatemia (22), asthenia (26), neutropenia (34), anemia (29)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DTC, well-differentiated thyroid cancer; MTC, medullary thyroid cancer; ATC, anaplastic thyroid cancer; mPFS, median progression-free survival; mOS, median overall survival; OS, overall survival; NR, not reached; RAI-R, radioactive iodine refractory.

[a] Antiangiogenic drugs, multikinase inhibitors.

[b] Single agent dabrafenib and dual therapy with dabrafenib + trametinib were studied in 1 trial.

the high risk cohort not available)[57] and therefore RAI is recommended for patients at high risk of recurrence[16] (Figure 2). In patients with intermediate risk of recurrence, the use of RAI is considered selective (Figure 2).[58] Tumors with *RAS* variants, typically follicular carcinomas or follicular-variant papillary thyroid carcinoma, retain expression of the sodium-iodine transporter on the cellular membrane and typically respond to repeated doses of radioactive iodine. In contrast, thyroid cancers with *BRAF* variants (classical type and tall-cell variants) downregulate the expression of this transporter and typically become refractory to radioiodine in patients who develop persistent disease.[59] Thus, repeated administration of RAI should be limited to patients who continue to demonstrate a therapeutic response.

Thyrotropin suppression with supraphysiologic doses of levothyroxine (Figure 2) is used to prevent thyroid cancer cell growth and production of thyroglobulin. The benefit of suppressing thyrotropin must outweigh the risk of a patient developing atrial fibrillation (8.5%) or osteoporosis (9.6%).[60] Initial thyrotropin suppres-

sion to below 0.1 mU/L improves overall survival (RR, 1.9 [95% CI, 1.07-3.44]; *P* = .03, absolute risk not reported) among patients with high-risk thyroid cancer[57,61] but not among patients at intermediate or low risk of recurrence. Thyrotropin suppression is not recommended for medullary thyroid cancer because parafollicular C cells do not express the thyrotropin receptor.

Long-Term Monitoring After Thyroid Cancer Treatment

After hemithyroidectomy, patients are followed up with thyroid ultrasonography annually for 5 years. Thyroid hormones are also monitored annually because 29% of patients can develop hypothyroidism after hemithyroidectomy.[62] Following total thyroidectomy, annual thyroid ultrasonography, thyroglobulin levels, thyroglobulin antibody levels, and thyrotropin levels are used to detect persistent/recurrent disease in patients with low-risk thyroid cancer[63] (Table 1). Thyrotropin suppression is not recommended for patients with low-risk thyroid cancer due to its excellent prognosis, and less frequent thyroid ultrasounds (approximately yearly or every 2 years depending on response to therapy) are encouraged.[16] A thyroglobulin level obtained with a thyrotropin level greater than 10 mIU/L[64] or the use of a whole body radioiodine scan[65] do not improve the sensitivity to detect recurrent thyroid cancer during follow-up. Computed tomography of the neck and chest with contrast after surgery are reserved for the evaluation of the neck, retropharyngeal space, mediastinum, or lungs when thyroid cancer is suspected based on persistently elevated thyroglobulin levels but is not detected on ultrasonography, or when there is potential invasion of the aerodigestive tract.[66] ^{18}Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is more sensitive (83% [range, 50%-100%]) and specific (84% [range, 42%-100%]) in patients with aggressive histological subtypes such as tall-cell variant, poorly differentiated thyroid cancer, and widely invasive oncocytic thyroid carcinoma.[67] Gadolinium-enhanced magnetic resonance imaging can delineate disease in the central compartment of the neck and mediastinum and detect osseous lesions in the spine.[68] Patients with medullary thyroid carcinoma should be followed up with measurement of calcitonin and carcinoembryonic antigen (CEA) levels and thyroid ultrasound twice a year or annually. Chest CT and liver MRI should be obtained for patients with persistently elevated CEA and calcitonin levels greater than 150 pg/mL, and contrast-enhanced cross-sectional imaging should be performed for patients with known sites of metastatic disease (Table 1).

Standard Therapy for Recurrent Differentiated Thyroid Cancer

Locoregional Disease

Most persistent or recurrent well-differentiated thyroid cancer is detected in the neck in the first 5 years after initial thyroidectomy (median time to recurrence, 3.6 years).[69] Surgical management is the preferred approach for locoregional disease, and RAI is unlikely to provide benefit in patients who have gross residual disease. External beam radiation to unresectable thyroid cancer or suspected microscopic persistent disease, as determined by an experienced thyroid surgeon, is rarely indicated[70] and is reserved for patients at very high risk of local recurrence. In young patients with differentiated thyroid cancer for whom the potential for long-term sequela such as esophageal strictures and dental caries may negatively affect quality of life, external beam radiation is rarely indicated.

Distant Metastatic Disease

A small percentage of patients (5%) have distant metastatic disease either at presentation or during the course of their disease. The histology and genomics of the tumor predict the location of distant metastases, as papillary thyroid carcinoma (mostly with *BRAF* variants) spreads via the lymphatic system and metastasizes to cervical lymph nodes and lung, whereas follicular thyroid carcinoma and oncocytic thyroid carcinoma (mostly with *RAS* variants) spread hematogenously and bone metastases are more frequent.[71] Mortality differs by organ site affected: the 5-year survival is 77% in patients whose only site of metastasis is the lung, whereas those with bone and liver metastases have a 5-year survival of 25% and 21%,[72] respectively. Mutational profile has gained prognostic value, and guidelines regarding the selection of patients in whom genetic testing is appropriate have been published.[73]

Treatment of Advanced Thyroid Cancer

Most patients with radioiodine refractory well-differentiated thyroid cancer and those with recurrent/metastatic medullary thyroid cancer have indolent disease and do not need immediate treatment with systemic therapy. Criteria for starting systemic therapy[74,75] include progression of disease (growth of metastatic lesions) on cross-sectional imaging in the prior 14 months, symptomatic disease, tumor affecting an organ or limb function (ie, bone fracture), or tumors 1.5 cm or larger. For some patients, it may be more appropriate to irradiate or surgically remove a thyroid cancer metastasis that is compromising organ or limb function or causing symptoms.

There are 9 drugs or drug combinations approved by the US Food and Drug Administration (FDA) for thyroid cancer.[76-87] The antiangiogenic drugs are multikinase inhibitors and include sorafenib, lenvatinib, vandetinib, and cabozantinib. Targeted agents include the selective RET inhibitors (selpercatinib) for tumors harboring *RET* fusions or *RET* mutations, NTRK inhibitors (entrectinib, larotrectinib) for tumors with NTRK fusions, and the *BRAF*/*MEK* inhibitor combination (dabrafenib/trametinib) for tumors with *BRAF* V600E mutations. The targets of these drugs (Figure 1), indications, efficacy, and adverse events are listed in **Table 2**. None of these agents are curative and their toxicities limit their use in some patients[88]; therefore, delaying their initiation is preferable.

Emerging/Novel Therapies

Two emerging strategies that benefit from the temporary use of targeted therapies are currently under investigation—neoadjuvant kinase inhibitors and redifferentiation therapy for differentiated thyroid cancer. The neoadjuvant strategy has been reported as a retrospective study in anaplastic thyroid carcinoma with *BRAF* V600E mutations.[24] The study evaluated overall survival among 57 patients who were treated with *BRAF*-directed therapy prior to surgery (neoadjuvant therapy) or after surgery (adjuvant therapy), or among those who never had surgery. All patients received a BRAF inhibitor with a MEK inhibitor and in most cases with a checkpoint inhibitor (immunotherapy). The overall survival for the neoadjuvant group at 1 year was 93.6% (95% CI, 84.9%-100%), compared with 74.1% (95% CI, 48.7%-99.5%) for patients in the adjuvant group and 38.5% (95% CI, 12.1%-64.9%) for patients who did not have surgery.[24] Prospective multicenter trials to evaluate neoadjuvant targeted therapy

followed by surgery in anaplastic thyroid cancer with *BRAF* variation, *RET*-altered thyroid cancer, and well-differentiated thyroid cancer are underway.

Redifferentiation therapy uses the selective kinase inhibitors in conjunction with RAI to restore the ability of radioiodine refractory cells to concentrate I-131. There are currently 8 published redifferentiation trials or case series.[89-96] The addition of targeted therapies to RAI has the potential to reduce the size of the tumor (if it concentrates I-131) and allow the patient to discontinue the selective kinase inhibitor drug. Prospective redifferentiation clinical trials with the selective MEK and RET inhibitors are underway.

Limitations

This review has several limitations. First, it is not a systematic review and the quality of included literature was not formally evaluated. Second, some relevant studies may have been missed. Third, it does not cover all aspects of the epidemiology, diagnosis, and management of thyroid cancer.

Conclusions

Approximately 44 000 new cases of thyroid cancer are diagnosed each year in the US, with a 5-year relative survival of 98.5%. Surgery is curative in most cases of well-differentiated thyroid cancer. Radioactive iodine treatment after surgery improves overall survival in patients at high risk of recurrence. Antiangiogenic multikinase inhibitors and targeted therapies to genetic mutations that give rise to thyroid cancer are increasingly used in the treatment of metastatic disease.

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