Thyroid Carcinoma, Version 2.2022

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ABSTRACT

Differentiated thyroid carcinomas is associated with an excellent prognosis. The treatment of choice for differentiated thyroid carcinoma is surgery, followed by radioactive iodine ablation (iodine-131) in select patients and thyroxine therapy in most patients. Surgery is also the main treatment for medullary thyroid carcinoma, and kinase inhibitors may be appropriate for select patients with recurrent or persistent disease that is not resectable. Anaplastic thyroid carcinoma is almost uniformly lethal, and iodine-131 imaging and radioactive iodine cannot be used. When systemic therapy is indicated, targeted therapy options are preferred. This article describes NCCN recommendations regarding management of medullary thyroid carcinoma and anaplastic thyroid carcinoma, and surgical management of differentiated thyroid carcinoma (papillary, follicular, Hurthle cell carcinoma).


NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

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The complete NCCN Guidelines for Thyroid Carcinoma are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Thyroid Carcinoma Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Thyroid Carcinoma Panel members can be found on page 951. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
Overview

For the United States population, the lifetime risk of being diagnosed with thyroid carcinoma is 1.2%. It is estimated that approximately 43,800 new cases of thyroid carcinoma will be diagnosed in the United States in 2022. The main histologic types of thyroid carcinoma are (1) differentiated (including papillary, follicular, and Hürthle cell); (2) medullary; and (3) anaplastic, which is an aggressive undifferentiated tumor. Mortality rates for thyroid carcinoma are, in general, very low. Differentiated thyroid carcinomas usually have an excellent prognosis, with 10-year survival rates exceeding 90%-95%. In contrast, anaplastic thyroid carcinoma (ATC) is almost uniformly lethal. However, since differentiated thyroid carcinomas represent more than 95% of all cases, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas. In 2022, it is estimated that approximately 2,230 cancer deaths will occur among persons with thyroid carcinoma in the United States. Thyroid carcinoma occurs more often in women; however, mortality rates are lower for younger women.

Although the estimated incidence of thyroid carcinoma previously increased by an average of approximately 5% annually between 2004 and 2013, the incidence rate has more recently stabilized, likely due to more conservative indications for thyroid biopsy and the reclassification of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Because overall mortality has not dramatically increased since 1975 (1,150 vs 2,060 deaths), the previous increase in incidence may reflect, at least in part, earlier detection of subclinical disease (ie, small papillary carcinomas). However, data show the incidence has increased by varying degrees across all tumor sizes and age groups. The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma address management for the different types of thyroid carcinomas including papillary, follicular, Hürthle cell, medullary, and anaplastic carcinoma. This section of the guidelines describes medullary carcinoma, anaplastic carcinoma, and surgical management of papillary, follicular, Hürthle cell carcinoma.

Surgical Management of Differentiated Thyroid Cancer

Managing differentiated (ie, papillary, follicular, Hürthle cell) thyroid carcinoma can be a challenge, because until...
recently, few prospective randomized trials of treatment have been done. Most of the information about treatment comes from studies of large cohorts of patients for whom therapy has not been randomly assigned. This accounts for much of the disagreement about managing differentiated carcinoma. Nonetheless, most patients can be cured of this disease when properly treated by experienced physicians and surgeons. The treatment of choice is surgery, followed by radioactive iodine (RAI) ablation (iodine-131) in selected patients and thyroxine therapy in most patients.

Imaging is performed before surgery to ascertain the extent of disease and to aid in the surgical decision-making process. A cervical ultrasound, including the thyroid and the central and lateral compartments, is recommended. Biopsy suspicious lymph nodes or contralateral lesions should be interrogated with fine needle aspiration (FNA) biopsy before surgery. Thyroglobulin (Tg) washout assay can be a useful adjunct to FNA biopsy. Molecular diagnostics may also be a useful adjunct when cytology is not definitive. Cross-sectional imaging (CT or MRI) should be performed for locally advanced disease (eg, if the thyroid lesion is fixed, bulky, or substernal) or for vocal cord paresis. Iodinated contrast is required for optimal cervical imaging with CT, although iodinated contrast will delay treatment with RAI (delaying RAI treatment is not harmful). Assessment of vocal cord mobility is recommended, particularly for patients with abnormal voice, prior neck surgery (eg, thyroid or parathyroidectomy, anterior cervical disc fusion), locally invasive disease, or bulky disease of the central neck. Evaluation is essential in patients with voice changes. Vocal cord mobility may be evaluated by ultrasound, mirror indirect laryngoscopy, or fiber-optic laryngoscopy.

**Ipsilateral Lobectomy Versus Total Thyroidectomy**

Decisions about the extent of thyroidectomy should be individualized and made in consultation with the patient. Circumstances in which lobectomy include T3 or T4 tumor, N1b disease, M1 disease, and poorly differentiated subtypes. Family history, exposure history, and coexistent bilateral thyroid disease may also be considered when making decisions about the extent of surgery. Lobectomy is often chosen because most studies have found that the extent of surgery is not associated with

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**Primary Treatment**

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**TSH Suppression (THYR-A*)**

*Available online, in these guidelines, at NCCN.org.

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**CLINICAL PRESENTATION**

**Primary Treatment**

- **Completion of thyroidectomy**
  - Perform therapeutic neck dissection of involved compartments for clinically apparent/biopsy-proven disease if not previously done.
  - Consider levothyroxine therapy to keep TSH low or normal.

- **Postsurgical Evaluation (PAP-3)**

- **Completion of thyroidectomy or Disease Monitoring (category 2B)**
  - Consider levothyroxine therapy to keep thyroid stimulating hormone (TSH) low or normal.

- **Disease Monitoring and Maintenance (PAP-7)**

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**Completion of thyroidectomy is not required for incidental small volume pathologic N1A metastases (<5 involved nodes with no metastasis >2 mm in largest dimension) PAP-4**.

**Formerly called encapsulated follicular variant of PTC, NIFTP has been reclassified and only lobectomy is needed. Ongoing surveillance is recommended.**

Measurement of thyroglobulin and anti-thyroglobulin antibodies may be useful for obtaining a postoperative baseline; however, data to interpret Tg and TgAb in the setting of an intact thyroid lobe are lacking.

Principles of TSH Suppression (THYR-A*).

Available online, in these guidelines, at NCCN.org.
Panel Members recommend total thyroidectomy for patients with biopsy-proven PTC under the following circumstances: T3 or larger, clinical N1 disease, M1 disease, aggressive subtype, significant radiation exposure, significant family history, or coexistent thyroid disease. Of all of these clinical features, tumor size is the most debated and is the feature in which there is not uniform agreement.

Many prominent thyroid cancer specialists (including those at NCCN Member Institutions) advocate for unilateral lobectomy as appropriate management for most patients with papillary and follicular carcinoma based on (1) the low mortality and low recurrence rates among most patients (ie, those patients categorized as low risk by the AMES and other prognostic classification schemes); and (2) the high complication rates reported with more extensive thyroidectomy. The large thyroid remnant remaining after unilateral lobectomy, however, may complicate long-term follow-up with serum Tg determinations and whole body iodine-131 imaging. Panel members recommend lobectomy (without RAI ablation) for patients with PTC who have incidental small-volume pathologic N1A metastases (<5 involved nodes with no metastasis >2 mm, in largest dimension). Because most patients with follicular neoplasia on FNA actually overall survival for unifocal, cN0, cM0 tumors up to 4 cm in size. A study of more than 5,000 patients found that survival of patients after partial thyroidectomy was similar to the survival after total thyroidectomy for patients at low and high risk. An observational study (SEER database) in more than 35,000 patients with papillary thyroid carcinoma (PTC) limited to the thyroid gland suggests that survival is similar whether (or not) patients are treated in the first year after diagnosis and whether they undergo lobectomy or total thyroidectomy. Another study of 2,784 patients with differentiated thyroid carcinoma (DTC) limited to the thyroid gland suggests that survival is similar whether (or not) patients are treated in the first year after diagnosis and whether they undergo lobectomy or total thyroidectomy. A National Cancer Database study of 52,173 patients with PTC found that tumor size was related to recurrence and survival and that total thyroidectomy reduced recurrence rates and improved survival in patients with PTC of 1 cm or larger when compared with lobectomy. In contrast, in a more recent National Cancer Database examination of 61,775 patients with PTC, the researchers were able to risk-adjust for more variables and concluded that extent of surgery did not correlate with better overall survival (OS) for tumors 1–4 cm. This study did not, however, examine recurrence rate or tumors larger than 4 cm.
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have benign disease, total thyroidectomy is recommended only if radiographic evidence or interoperative findings of extrathyroidal extension or nodal metastases are apparent at the time of surgery, or if the patient opts for total thyroidectomy to avoid a second surgery (ie, completion thyroidectomy) if cancer is found at pathologic review.39–40 Otherwise, lobectomy plus isthmusectomy is advised as the initial surgery for follicular neoplasia on FNA (see FOLL-1, page 930). The surgical management of Hürthle cell carcinoma is almost identical to follicular thyroid carcinoma, except that (1) locoregional nodal metastases may be more common, and therefore therapeutic lymph node dissections of the affected compartment is needed for clinically apparent biopsy-proven disease; and (2) metastatic Hürthle cell tumors are less likely to concentrate iodine-131 (see HURT-1, page 931).41

The appropriate extent of thyroid resection—ipsilateral lobectomy versus total thyroidectomy—is very controversial for lower-risk PTC. This debate reflects the limitations of prognostic scoring42 and the morbidity often associated with total thyroidectomy performed outside of major cancer centers. Cancer-specific mortality and recurrence rates after unilateral or bilateral lobectomy were assessed in patients with PTC considered to be low risk by AMES criteria.43 No significant differences were found in cancer-specific mortality or distant metastasis rates between the two groups. However, the 20-year frequencies of local recurrence and nodal metastasis after unilateral lobectomy were 14% and 19%, respectively, which were significantly higher ($P=.0001$) than the frequencies of 2% and 6% seen after bilateral thyroid lobe resection. Hay et al44 concluded that bilateral thyroid resection is the preferable initial surgical approach for patients with AMES low-risk PTC. A more recent retrospective multicenter study from Spain that evaluated the 2015 American Thyroid Association (ATA) recommendation that low-risk PTC between 1 cm and 4 cm could receive lobectomy as clinically indicated found that 57.5% of patients who underwent total thyroidectomy between 2000 and 2017 would have needed thyroidectomy between 2000 and 2017 would have needed thyroxine, and 57.5% of patients who underwent total thyroidectomy between 2000 and 2017 would have needed thyroxine, and 57.5% of patients who underwent total thyroidectomy between 2000 and 2017 would have needed thyroxine.

NCCN Panel Members believe that lobectomy alone is adequate treatment of papillary microcarcinomas provided the patient has not been exposed to radiation, has no other risk factors, and has a tumor 1 cm or smaller that is unifocal and confined to the thyroid without
vascular invasion (see PAP-1, page 926). Lobectomy alone is also adequate treatment for NIFTP pathologies and minimally invasive follicular thyroid carcinomas (see FOLL-1, page 930). Lobectomy plus isthmusectomy is recommended for patients who cannot (or refuse to) take thyroid hormone replacement therapy for the remainder of their lives. Note that some patients prefer to have total thyroidectomy to avoid having a second surgery (ie, completion thyroidectomy). Other patients prefer to have a lobectomy in an attempt to avoid thyroid hormone replacement therapy. Most guidelines (eg, NCCN, ATA) do not recommend active surveillance for patients with PTC. However, for PTC 1 cm or smaller and no concerning lymph node involvement or risk features (eg, posterior location, abutting the trachea, or apparent invasion), surgery may not be warranted, and active surveillance with ultrasound may be sufficient.

Clinically positive and/or biopsy-proven nodal metastases should be treated with a formal compartmental resection. In the central neck, this is achieved through a unilateral or bilateral level VI dissection. Based on the results of 2 randomized controlled trials, the panel does not recommend prophylactic central neck dissection if the central compartment lymph nodes are clinically negative. Two trials of patients with cN0 PTC randomized to receive either total thyroidectomy alone or total thyroidectomy plus central neck dissection showed no difference in outcomes between the 2 groups.

Completion Thyroidectomy
Completion thyroidectomy is recommended when remnant ablation is anticipated or if long-term follow-up is planned with serum Tg determinations and with (or without) whole body iodine-131 imaging. Completion thyroidectomy has a complication rate similar to that of total thyroidectomy. Completion thyroidectomy is recommended for any of the following: tumor larger than 4 cm in diameter, positive resection margins, gross extrathyroidal extension, macroscopic multifocal disease (ie, >1 cm), macroscopic nodal metastases, confirmed contralateral disease, or vascular invasion (see PAP-2, page 927). Note that “gross extrathyroidal extension” refers
to spread of the primary tumor outside of the thyroid capsule with invasion into the surrounding structures such as strap muscles, trachea, larynx, vasculature, esophagus, and/or recurrent laryngeal nerve. In patients with local or distant tumor recurrence after lobectomy, cancer is found in more than 60% of the resected contralateral lobes.

If invasive follicular thyroid carcinoma (widely invasive or encapsulated angioinvasive with ≥4 vessels) is found on the final histologic sections after lobectomy plus isthmusectomy, prompt completion of thyroidectomy is recommended (see FOLL-1, page 930). Minimally invasive cancer is characterized as an encapsulated tumor with microscopic capsular invasion and without vascular invasion. Lobectomy is preferred for minimally invasive cancers, as well as NIFTP tumors, followed by surveillance, because minimally invasive follicular carcinomas and NIFTP usually have an excellent prognosis. Although deaths attributed to minimally invasive follicular carcinoma do occasionally occur, the panel believes that the benefit of completion thyroidectomy for small minimally invasive follicular cancers may not justify the additional morbidity.

**Surgical Complications**

The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur more frequently after total thyroidectomy. Transient clinical hypoparathyroidism postoperatively is common in adults and children undergoing total thyroidectomy. One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later. Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia. Superior laryngeal nerve injury is under reported and negatively impacts voice projection and high pitch range. When experienced surgeons perform thyroidectomies, complications occur at a lower rate. A study of 5,860 patients found that surgeons who performed more than 100 thyroidectomies a year had the lowest overall complication rate (4.3%), whereas surgeons who performed fewer than 10 thyroidectomies a year had 4 times as many complications.

**Postoperative Radioactive Iodine**

Clinicopathologic factors should be used to guide decisions about whether to administer postoperative RAI (see...
“Clinicopathologic Factors” in the NCCN Guidelines for Thyroid Carcinoma; available at NCCN.org). The NCCN Guidelines provide algorithms to assist in decision-making about use of RAI in different settings: (1) RAI for removal of postsurgical gland remnant is referred to as iodine-131 thyroid remnant ablation and is typically not indicated for patients classified as having a low risk of recurrence/disease-specific mortality; (2) adjuvant therapy with RAI may be considered for patients with intermediate-risk disease without gross residual disease, but data are conflicting regarding the benefit of RAI in this setting; and (3) RAI treatment is often used for patients with known postoperative residual disease or inoperable distant metastasis based on whether the persistent tumor is shown to be iodine-131–avid. Iodine-131 pre- and post-treatment imaging (with consideration of dosimetry for distant metastasis) is recommended for suspected or proven iodine-131–avid metastatic foci (see “RAI Being Considered Based on Clinicopathologic Features” in the NCCN Guidelines for Thyroid Carcinoma; available at NCCN.org). In patients with known or suspected distant metastatic disease, radioiodine diagnostic imaging (iodine-123 or iodine-131) with adequate thyroid-stimulating hormone (TSH) stimulation (thyroid withdrawal or thyrotropin alfa) should be considered before iodine-131 therapy is administered, with attention to dosing recommendations (see “Principles of Radiation and Radioactive Iodine Therapy” in the NCCN Guidelines for Thyroid Carcinoma; available at NCCN.org) to avoid the problem of stunning, which may limit treatment effect.

See the full Discussion section in the NCCN Guidelines for Thyroid Carcinoma (available at NCCN.org) for more detail on postoperative RAI.

### Surveillance and Maintenance

The recommendations for postsurgical evaluation and surveillance and maintenance of surgically treated differentiated thyroid cancer are described in the algorithm (see PAP-3, page 928, and PAP-7, page 929). About 85% of patients are considered to be low risk after surgery for PTC.55 In patients treated with lobectomy, disease monitoring after surgery includes physical examination, TSH assessment, and periodic neck ultrasound. If abnormal contralateral nodule or lymph nodes are found, then FNA biopsy should be performed.

In patients who have had total (or near total) thyroidectomy and thyroid remnant ablation using iodine-131,
the ATA Guidelines define the absence of persistent tumor (also known as no evidence of disease) as: (1) absence of clinical evidence of tumor; (2) absence of imaging evidence of tumor; and (3) undetectable Tg levels (during either TSH suppression or TSH stimulation) and absence of anti-Tg antibodies.47 Patients treated with total thyroidectomy should be followed with physical examination and measurement of TSH, Tg, and Tg antibody. RAI imaging (TSH-stimulated [during either TSH suppression or TSH stimulation]) can be considered in patients at high risk for persistent or recurrent disease, distant metastases, or disease-specific mortality; patients with previous RAI-avid metastases; or patients with abnormal Tg levels, stable or increasing Tg ab, or abnormal ultrasound results. Iodine-avid disease that has been treated with radioisotope and is no longer evident, or significant biochemical response, or is dramatically reduced in prominence on follow-up imaging beyond 6 months posttherapy may be considered as having responded to treatment. Favorable response to iodine-131 treatment is also assessed through change in volume of known iodine-concentrated lesions by CT or MRI, as well as by decreasing unstimulated or stimulated Tg levels.47

A subgroup of patients at low risk (eg, micropapillary carcinomas entirely confined to the thyroid gland) may only require periodic neck ultrasound follow-up (without stimulated Tg or follow-up whole body imaging) as long as their basal Tg remains low. Otherwise, long-term ultrasound follow-up is not required. Note that Tg should be measured using the same laboratory and the same assay, because Tg levels vary widely between laboratories.47 Patients with clinically significant residual disease can typically be identified by the trend in Tg levels over time.47

Non-RAI imaging—such as ultrasound of the central and lateral neck compartments, neck CT, chest CT, or FDG-PET/CT—may be considered if RAI imaging is negative and stimulated Tg is greater than 2 to 5 ng/mL. High-risk factors include incomplete tumor resection, macroscopic tumor invasion, and distant metastases in patients at high risk for persistent or recurrent disease, distant metastases, or disease-specific mortality.47 Since Hürthle cell carcinoma tends to be non-iodine-avid, negative scans that were done without single-photon emission CT may fail to detect distant structural disease. Therefore, if Tg is high and/or pathology is high-risk, FDG-PET is indicated.

**Medullary Thyroid Carcinoma**

Medullary thyroid carcinoma (MTC) arises from the neuroendocrine parafollicular C cells of the thyroid.66–69

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<td>Medullary thyroid carcinoma diagnosed after initial thyroid surgery&lt;sup&gt;6&lt;/sup&gt;</td>
<td>• Basal serum calcitonin level&lt;br&gt;• CEA&lt;br&gt;• Screen for germline RET proto-oncogene mutations&lt;sup&gt;6,7&lt;/sup&gt; (exons 10, 11, 13–16); genetic counseling may be indicated&lt;br&gt;• Central and lateral neck compartments ultrasound, if not previously done</td>
<td>Additional Workup and Primary Treatment (MEDU-3)</td>
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<sup>6</sup>Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling. See Principles of Cancer Risk Assessment and Counseling (THYR-E<sup>6</sup>).

<sup>7</sup>If initial thyroid surgery was less than a total thyroidectomy, additional surgical intervention (eg, completion thyroidectomy ± central neck dissection) may be necessary unless there is a positive germline RET mutation or radiographic evidence of disease (ie, biopsy-proven residual neck disease).

<sup>6</sup>Prior to germline testing, all patients should be offered genetic counseling either by their physician or a genetic counselor.

<sup>4</sup>Available online, in these guidelines, at NCCN.org.
Sporadic MTC accounts for about 80% of all cases of the disease. The remaining cases consist of inherited tumor syndromes, such as (1) multiple endocrine neoplasia (MEN) type 2A (MEN2A), which is the most common type; and (2) MEN2B. RET mutations are generally considered pathogenic in MEN2A and FMTC. Sporadic disease typically presents in the fifth or sixth decade of life. Inherited forms of MTC often present at a younger age. 

Nodule Evaluation and Diagnosis

Patients with MTC can be identified by using pathologic diagnosis or by prospective genetic screening. Separate pathways are included in the algorithm (see MEDU-1, page 932) depending on the method of identification.

Sporadic MTC

Sporadic MTC is usually suspected after FNA of a solitary nodule. Reports suggest that about 3% of patients with nodular thyroid disease will have an increased serum calcitonin level when measured by a sensitive immunometric assay; 40% of these patients will have MTC at 5%–10% of patients at initial presentation. Many patients with advanced MTC have diarrhea and flushing, because the tumor can secrete calcitonin and sometimes other hormonally active peptides (ie, adrenocorticotropic hormone, calcitonin gene-related peptide). Rarely, Cushing syndrome occurs due to tumor adrenocorticotropic hormone production. Treatment with somatostatin analogs (eg, octreotide, lanreotide) may be useful in patients with these symptoms. Patients with unresectable or metastatic disease may have either slowly progressive or rapidly progressive disease. Rapid calcitonin and CEA doubling times are predictive of more aggressive disease.
Inherited MTC

All familial forms of MTC and MEN2 are inherited in an autosomal-dominant fashion. Mutations in the RET proto-oncogene are found in at least 95% of kindreds with MEN2A. The RET proto-oncogene codes for a cell membrane-associated tyrosine kinase receptor whose ligand is glial cell line-derived neurotrophic factor. Mutations associated with MEN2A have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13; nearly all patients with MEN2B harbor the RET M918T mutation found within the intracellular exon 16. Somatic mutations in exons 11, 13, and 16 have also been found in at least 25% of sporadic MTC tumors—particularly the codon 918 mutation that activates the tyrosine kinase function of the receptor—and are associated with poorer prognosis of the patient.

Compared with sporadic disease, the typical age of presentation for MEN2A is the third or fourth decade of life, without gender preference. In patients with MEN2A, signs or symptoms of hyperparathyroidism or pheochromocytoma rarely present before those of MTC, even in the absence of screening. Controlling for the effect of age at diagnosis, the prognosis of patients with inherited disease (who typically are diagnosed at an earlier age) is probably similar to those with sporadic disease. Despite an even younger typical age at diagnosis, however, patients with MEN2B who have MTC are more likely than those with MEN2A (or familial MTC) to have locally aggressive disease.

For patients from known kindreds with inherited MTC, prospective family screening with testing for mutant RET genes can identify disease carriers long before clinical symptoms or signs are noted. About 6% of patients with clinically sporadic MTC carry a germline RET mutation, leading to identification of new kindreds with multiple (previously undiagnosed) affected individuals. Germline testing for RET proto-oncogene mutations with genetic counseling by a physician or genetic counselor is recommended for all patients with newly diagnosed MTC, including patients with clinically suspected sporadic MTC. If a germline RET mutation is found, then mutation testing should also be done for family members. MTC can involve difficult ethical decisions.
for clinicians if parents or guardians refuse screening and/or treatment of children with possible MTC. Principles regarding genetic risk assessment can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at NCCN.org).

The generally accepted preoperative workup includes measurement of serum markers (basal serum calcitonin and serum CEA), screening for hyperparathyroidism, and urinary and/or plasma fractionated metanephrines and catecholamines to rule out pheochromocytoma. Preoperative thyroid and neck ultrasound (including central and lateral neck compartments) is recommended. Contrast-enhanced CT of neck/chest and liver MRI or 3-phase CT of liver can be considered as clinically indicated, such as in cases of high burden of disease, preoperative calcitonin greater than 400 pg/mL, or elevated CEA levels. Distant metastasis is not, however, a contraindication to surgery. Liver imaging is rarely needed if calcitonin is less than 400 pg/mL. Evaluation of vocal cord mobility should be performed for patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.

Before surgery for MTC, it is necessary to diagnose coexisting pheochromocytoma. When present, pheochromocytoma should be resected before the MTC to avoid hypertensive crisis during surgery (see the NCCN Guidelines for Neuroendocrine Tumors, available at NCCN.org). Pheochromocytoma should be removed using laparoscopic adrenalectomy.

Surgical Management

Surgery is the main treatment for MTC. MTC cells do not concentrate iodine. Therefore, there is no role for iodine-131 in MTC. Postoperative levotyroxine is indicated for all patients; however, TSH suppression is not appropriate because C cells lack TSH receptors. Thus, TSH should be kept in the normal range by adjusting the levotyroxine dose. Patients should be assessed for hyperparathyroidism and pheochromocytoma preoperatively, even in patients who have apparently sporadic disease. Testing for a germline RET proto-oncogene mutation is indicated for all patients with MTC.

Total thyroidectomy and bilateral central neck dissection (level VI) are indicated in all patients with MTC whose tumor is ≥1 cm or who have bilateral thyroid disease; total thyroidectomy is recommended and neck dissection is a standard practice.
dissection can be considered for those whose tumor is <1 cm and for unilateral thyroid disease (see MEDU-1, page 932).89,90

If a patient with MEN2A is diagnosed early enough, the recommendation is to perform a prophylactic total thyroidectomy when the mutation is identified, especially in patients with codon 609, 611, 618, 620, 630, or 634 RET mutations.66,67,91 Appropriate age of thyroidectomy in children is an evolving field. If the mutation is identified during childhood, then thyroidectomy may be considered. Note that C634 mutations are the most common mutations.66,67 Total thyroidectomy is recommended in the first year of life or at diagnosis for patients with MEN2B who have codon 883 RET mutations, 918 RET mutations, or compound heterozygous (V804M + E805K, V804M + Y806C, or V804M + S904C) RET mutations (see MEDU-3, page 934), because these RET mutations carry the highest risk for MTC (ie, level D).66,67,92

However, for patients with codon 768, 790, 791, 804, and 891 RET (risk level A) mutations, the lethality of MTC may be lower than with other RET mutations.66,67,92,93 In patients with these less high-risk (ie, lower-risk level A) RET mutations and no structural evidence of disease, annual basal calcitonin testing and annual ultrasound are recommended; total thyroidectomy and central node dissection may be deferred if results of these tests are normal, there is no family history of aggressive MTC, and the family agrees to defer surgery (see MEDU-4, page 935).66,67,94,95 Delaying thyroidectomy may also be appropriate for children with lower-risk mutations (ie, level A) because of the late onset of MTC development.66,67,93,94,96

A study found no evidence of persistent or recurrent MTC 5 years or more after prophylactic total thyroidectomy in young patients with RET mutations for MEN2A; longer follow-up is necessary to determine if these patients are cured.97

Variations in surgical strategy for MTC depend on the risk for locoregional node metastases and on whether simultaneous parathyroid resection for hyperparathyroidism is necessary.66,67 A bilateral central neck dissection (level VI) can be considered for all patients with MEN2B. For those patients with MEN2A who undergo prophylactic thyroidectomy, therapeutic ipsilateral or bilateral central neck dissection (level VI) is recommended if patients have an increased calcitonin or CEA test or if ultrasound shows a thyroid or nodal abnormality. Similarly, more extensive lymph node dissection (levels II–V) is considered for these patients with primary tumor(s) ≥1 cm in diameter (>0.5 cm for patients with MEN2B) or for patients with central compartment lymph node
metastases (see MEDU-3 and MEDU-4, pages 934 and 935).

With a concurrent diagnosis of hyperparathyroidism in MEN2A, the surgeon should leave or autotransplant the equivalent mass of one normal parathyroid gland if multinodular hyperplasia is present. Cryopreservation of resected parathyroid tissue should be considered to allow equivalent mass of one normal parathyroid gland if multiple resections are performed. Principles of Inhibitor Therapy in Advanced Thyroid Carcinomas (THYR-B) treatment with systemic therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Principles of Inhibitor Therapy in Advanced Thyroid Carcinomas (THYR-B). Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone. Only health-care professionals and pharmacies certified through the Vanderbilt Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, will be able to prescribe and dispense the drug.

Consider resection (if possible), ablation (e.g., RFA, embolization, other regional therapy), or other regional treatment.

Consider palliative resection, ablation (e.g., RFA, embolization, other regional therapy), or other regional treatment.

Best supportive care, see the NCCN Guidelines for Palliative Care.

**RECURRENT OR PERSISTENT DISEASE**

**DISTANT METASTASES**

**Asymptomatic disease**

- Disease monitoring
- Consider resection (if possible), ablation (e.g., RFA, embolization, other regional therapy)
- Systemic therapy if not resectable and progressing by RECIST criteria

**Preferred Regimens**

- Vandetanib (category 1)
- Cabozantinib (category 1)
- Selpercatinib (RET mutation-positive)
- Pralsetinib (RET mutation-positive)
- Pembrolizumab (TMH-H [210 mut/Mb])
- Systemic therapy or clinical trial

**Other Recommended Regimens**

- Consider other small-molecule kinase inhibitors
- Dacarbazine (DTIC)-based chemotherapy
- Pembrolizumab (TMH-H [210 mut/Mb])
- EBRT/IMRT for local symptoms
- Consider intravenous bisphosphonate or denosumab therapy for bone metastases
- Consider palliative resection, ablation (e.g., RFA, embolization, other regional therapy), or other regional treatment
- Best supportive care, see the NCCN Guidelines for Palliative Care

**Symptomatic disease or Progression**

- Pembrolizumab (TMH-H [210 mut/Mb])
- Systemic therapy or clinical trial

**Preferred Regimens**

- Vandetanib (category 1)
- Cabozantinib (category 1)
- Selpercatinib (RET mutation-positive)
- Pralsetinib (RET mutation-positive)
- Pembrolizumab (TMH-H [210 mut/Mb])
- Systemic therapy or clinical trial

**Other Recommended Regimens**

- Consider other small-molecule kinase inhibitors
- Dacarbazine (DTIC)-based chemotherapy
- Pembrolizumab (TMH-H [210 mut/Mb])
- EBRT/IMRT for local symptoms
- Consider intravenous bisphosphonate or denosumab therapy for bone metastases
- Consider palliative resection, ablation (e.g., RFA, embolization, other regional therapy), or other regional treatment
- Best supportive care, see the NCCN Guidelines for Palliative Care

**Progressive disease, see pathway below**

**Recurrent or Persistent Disease**

- Disease monitoring
- Consider resection (if possible), ablation (e.g., RFA, embolization, other regional therapy)
- Systemic therapy if not resectable and progressing by RECIST criteria

**Preferred Regimens**

- Vandetanib (category 1)
- Cabozantinib (category 1)
- Selpercatinib (RET mutation-positive)
- Pralsetinib (RET mutation-positive)
- Pembrolizumab (TMH-H [210 mut/Mb])
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**Other Recommended Regimens**

- Consider other small-molecule kinase inhibitors
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- Consider intravenous bisphosphonate or denosumab therapy for bone metastases
- Consider palliative resection, ablation (e.g., RFA, embolization, other regional therapy), or other regional treatment
- Best supportive care, see the NCCN Guidelines for Palliative Care

**Persistent Evolution of CEA**

- Baseline CEA concentration is obtained at the time of thyroidectomy.
- CEA levels are measured at 2 to 3 months postoperatively.
- If CEA levels are elevated, consider CT scanning of the neck, chest, and abdomen.
- Persistent elevation of CEA indicates the need for continued clinical follow-up.

**Adjuvant RT**

External beam radiation therapy (EBRT) has not been adequately studied as adjuvant therapy in MTC. Slight improvements in local disease-free survival have been reported after EBRT for selected patients, such as those with extrathyroidal invasion or extensive locoregional node involvement. However, most centers do not have extensive experience with adjuvant EBRT for this disease. Although therapeutic EBRT may be considered for grossly incomplete resection when additional attempts at surgical resection have been ruled out, adjuvant EBRT is rarely recommended (see MEDU-1, page 932). EBRT can also be given to palliate painful or progressing bone metastases. There is little evidence regarding appropriate treatment volumes for use of RT for MTC, but intensity-modulated RT (IMRT) technique is encouraged, and guidance regarding EBRT dose and fractionation is provided in the “Principles of Radiation and Radioactive Iodine Therapy: External Beam Radiation Therapy” in the full NCCN Guidelines for Thyroid Carcinoma (available at NCCN.org).
indicative of residual disease. Those patients with residual disease may benefit from further evaluation to detect either residual resectable disease in the neck or the presence of distant metastases. Patients with detectable basal calcitonin or elevated CEA who have negative imaging and who are asymptomatic may be followed (see MEDU-5, page 936). Patients with a basal serum calcitonin value greater than 1,000 pg/mL—and with no obvious MTC in the neck and upper mediastinum—probably have distant metastases, most likely in the liver. However, occasionally patients have relatively low serum CEA and calcitonin levels but have extensive metastatic disease; initial postoperative imaging is therefore reasonable despite the absence of very high serum markers.

The prognosis for patients with postoperative hypercalcitoninemia depends primarily on the extent of disease at the time of initial surgery. Routine lymphadenectomy or excision of palpable tumor generally fails to normalize the serum calcitonin concentrations in such patients; therefore, some have focused on detection and eradication of microscopic tumor deposits with a curative intent in patients without distant metastases. When repeat surgery is planned for curative intent, preoperative assessment should include locoregional imaging (ie, ultrasonography of the neck and upper mediastinum) and attempts to exclude patients with distant metastases, which may include contrast-enhanced CT or MRI of the neck, chest, and abdomen.

Postoperative Management and Surveillance
Calcitonin is very useful for surveillance, because this hormone is only produced in the parafollicular cells. Thus, measurements of serum calcitonin and CEA levels are the cornerstone of postoperative assessment for residual disease (see MEDU-5, page 936). For patients with a detectable basal calcitonin or elevated CEA level, neck ultrasound is recommended. Patients with undetectable calcitonin levels and normal CEA levels can subsequently be followed with annual measurements of serum markers. Additional studies or more frequent testing can be done for those with significantly rising calcitonin or CEA. Nonetheless, the likelihood of significant residual disease is very low in patients with an undetectable basal calcitonin level in a sensitive assay. If the patient has MEN, annual screening for pheochromocytoma (MEN2B or MEN2A) and hyperparathyroidism (MEN2A) should also be performed. For some low-risk RET mutations (eg, codons 768, 790, 804, or 891), less frequent screening may be appropriate.
Patients with detectable serum markers should have CT or MRI of the neck, chest, and liver. Bone scan and MRI of axial skeleton should be considered in select patients such as those with elevated calcitonin levels. The NCCN Thyroid Carcinoma Panel recognizes that many different imaging modalities may be used to examine for residual or metastatic tumor, but there is insufficient evidence to recommend any particular choice or combination of tests.

For patients with asymptomatic disease and detectable markers in whom imaging fails to identify foci of disease, the panel recommends conservative surveillance with repeat measurement of the serum markers every 6 to 12 months. Additional imaging studies (eg, FDG PET/CT, Ga-68 DOTATATE, or MRI with contrast of the neck, chest, and abdomen with liver protocol) may be indicated depending on calcitonin/CEA doubling time. For patients who are asymptomatic with abnormal markers and repeated negative imaging, continued disease monitoring or consideration of cervical reoperation is recommended if primary surgery was incomplete. For the patient with increasing serum markers, more frequent imaging may be considered. Outside of clinical trials, no therapeutic intervention is recommended on the basis of abnormal markers alone.

Recurrent or Persistent Disease

Kinase inhibitors may be appropriate for select patients with recurrent or persistent MTC that is not resectable (see MEDU-6 and MEDU-7, pages 937 and 938). Although kinase inhibitors may be recommended for patients with MTC, it is important to note that kinase inhibitors may not be appropriate for patients with stable or slowly progressing indolent disease.

Vandetanib and cabozantinib are oral receptor kinase inhibitors that improve progression-free survival (PFS) in patients with metastatic MTC. Vandetanib inhibits RET, VEGFR, and EGFR. In a phase III randomized ZETA trial in patients with unresectable, locally advanced, or metastatic MTC (n=331), vandetanib improved PFS when compared with placebo (hazard ratio [HR], 0.46; 95% CI, 0.31–0.69; P<.001); OS data are not yet available. A posthoc subgroup analysis including 184 patients with symptomatic and progressive disease at baseline also showed improved PFS (HR, 0.43; 95% CI, 0.28–0.64; P<.001) in patients who received vandetanib, compared with the placebo, although time to worsening pain was not significantly different between the 2 groups (HR, 0.67; 95% CI, 0.43–1.04; P=.07). In this subgroup,
the overall response rate (ORR) was 37% in the patients who received vandetanib and 2% in patients who received the placebo ($P < .001$). The FDA approved the use of vandetanib for patients with locally advanced or metastatic MTC who are not eligible for surgery and whose disease is causing symptoms or growing. However, access is restricted through a vandetanib REMS (Risk Evaluation and Mitigation Strategy) program because of potential cardiac toxicity involving prolongation of the QTc interval. The panel recommends vandetanib (category 1) as a preferred option for patients with recurrent or persistent MTC (see MEDU-6 and MEDU-7, pages 937 and 938).

Cabozantinib is a multitargeted kinase inhibitor that inhibits RET, VEGFR2, and MET. In a phase 3 randomized trial (EXAM) in patients with locally advanced or metastatic MTC ($n = 330$), cabozantinib improved median PFS when compared with placebo (11.2 vs 4.0 months; HR, 0.28; 95% CI, 0.19–0.40; $P < .001$). The median OS for patients treated with cabozantinib was 26.6 months compared with 21.1 months for placebo, although this difference was not statistically significant (stratified HR, 0.85; 95% CI, 0.64–1.12, $P = .24$).

Exploratory analyses have suggested that cabozantinib may have a greater clinical benefit for medullary thyroid cancers harboring RET M918T or RAS mutations, although prospective trials are needed to confirm these findings. In 2012, the FDA approved the use of cabozantinib for patients with progressive, metastatic MTC. The panel also recommends cabozantinib (category 1) as a preferred option based on the phase III randomized trial and FDA approval (see MEDU-6 and MEDU-7, pages 937 and 938). Rare adverse events with cabozantinib include severe bleeding and gastrointestinal perforations or fistulas; severe hemorrhage is a contraindication for cabozantinib.

RET mutations account for a significant percentage of MTC cases, supporting investigation into the impact of recently developed RET-specific inhibitors on RET-mutated MTC. The phase I–II LIBRETT-001 study evaluated the efficacy of the RET-specific inhibitor selpercatinib in 143 patients with RET-mutant MTC. In patients previously treated with vandetanib and/or cabozantinib ($n = 55$), the ORR and 1-year PFS rates were 69% (95% CI, 55%–81%) and 82% (95% CI, 69%–90%), respectively. In patients with no previous vandetanib or cabozantinib treatment ($n = 88$), the ORR and 1-year PFS rates were 73% (95% CI, 62%–82%) and 92% (95% CI, 82%–97%), respectively. The most commonly reported toxicities (grade 3 and 4) were hypertension (21%), increased alanine aminotransferase (11%), increased aspartate aminotransferase (12%), and proteinuria (21%).

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aminotransferase (9%), hyponatremia (8%), and diarrhea (6%). Dose reductions due to treatment-related adverse events were reported in 30% of patients. Pralsetinib, another RET-specific inhibitor, was evaluated in the phase I–II ARROW study, which included 92 patients with RET-mutant MTC.\textsuperscript{122} The ORR was 60% (95% CI, 46%–74%) in patients previously treated with vandetanib and/or cabozantinib (n=61) and 74% (95% CI, 49%–91%) in patients with no previous vandetanib or cabozantinib treatment (n=22). Pralsetinib was generally well-tolerated, with the most commonly reported grade 3–4 treatment-related adverse events being hypertension (11%) and neutropenia (10%). These results are currently reported in abstract form, and the ARROW study is ongoing and continuing to enroll patients. In 2020, the FDA approved both of these RET inhibitors for RET-mutated MTC requiring systemic therapy. Based on the data and the FDA approvals, the NCCN Panel recommends selpercatinib and pralsetinib as preferred options for patients with RET-mutation positive disease. Pembrolizumab is also an option for patients with high tumor mutation burden (TMB-H; ≥10 mut/Mb) disease, based on results of the phase II KEYNOTE-158 trial, which included 2 patients with thyroid cancer.\textsuperscript{124} TMB is rarely high in MTC. The panel does not recommend treatment with systemic therapy for increasing calcitonin or CEA alone in the absence of radiographically evident structural disease.

For unresectable locoregional disease that is symptomatic or progressing by RECIST (Response Evaluation Criteria in Solid Tumors) criteria,\textsuperscript{123} the following options can be considered: (1) EBRT; or (2) systemic therapy. Treatment can be considered for symptomatic distant metastases (eg, those in bone); recommended options include palliative resection, ablation (eg, radiofrequency, embolization) or other regional treatment, and systemic therapy (see MEDU-6 and MEDU-7, pages 937 and 938). These interventions may be considered for asymptomatic distant metastases (especially for progressive disease), but disease monitoring is acceptable given the lack of data regarding alteration in outcome. If systemic therapy is indicated, then vandetanib and cabozantinib are category 1 preferred options. Selpercatinib or pralsetinib are preferred options for patients with RET-mutation positive disease. Pembrolizumab is also an option for patients with high tumor mutation burden (TMB-H; ≥10 mut/Mb) disease, based on results of the phase II KEYNOTE-158 trial, which included 2 patients with thyroid cancer.\textsuperscript{124} TMB is rarely high in MTC. The panel does not recommend treatment with systemic therapy for increasing calcitonin or CEA alone in the absence of radiographically evident structural disease.
In the setting of symptomatic disease or progression, the NCCN Thyroid Carcinoma Panel recommends systemic therapy or enrollment in a clinical trial. As stated previously for locoregional disease, preferred systemic therapy options include vandetanib (category 1), cabozantinib (category 1), and selpercatinib or pralsetinib for patients with RET mutation–positive disease. Other small-molecule kinase inhibitors (ie, sorafenib, sunitinib, lenvatinib, pazopanib) may be considered if clinical trials or the NCCN-preferred systemic therapy options are not available or are not appropriate.125–131 If the patient progresses on a preferred option, then systemic chemotherapy can be administered using dacarbazine or combinations including dacarbazine.66,132–134 Pembrolizumab is also an option for patients with TMB-H (≥10 mut/Mb) disease (useful in certain circumstances).124 EBRT can be used for local symptoms. Intravenous bisphosphonate therapy or denosumab can be considered for bone metastases.135–137 Best supportive care is also recommended.

Results from clinical trials have shown the effectiveness of novel multitargeted therapies including sunitinib,128,138 sorafenib,126,139 lenvatinib,128 and pazopanib120 in MTC. Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, and liver toxicity; however, many side effects can be managed.140–143 Because some patients may have indolent and asymptomatic disease, potentially toxic therapy may not be appropriate.140

Novel therapies and the management of aggressive MTC have been reviewed.66,144–148 Of interest, calcitonin levels decreased dramatically after vandetanib therapy, which did not directly correlate with changes in tumor volume; thus, calcitonin may not be a reliable marker of tumor response in patients receiving RET inhibitor therapy.149 A phase II trial in patients with progressive metastatic MTC assessed treatment using pretargeted anti–CEA radioimmunotherapy with iodine-131.150 OS was improved in the subset of patients with increased calcitonin doubling times.151

### Anaplastic Thyroid Carcinoma

ATCs are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.152 Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.153 Fewer than 10% of patients are younger than 50 years, and 60%–70% of patients are women.153,154 The incidence of ATC is decreasing because of better management of differentiated thyroid cancer and because of increased iodine in the diet.152,155 ATC is
the least common type of thyroid carcinoma.23 Approximately 50% of patients with ATC have either a prior or coexistent differentiated carcinoma. ATC develops from more differentiated tumors as a result of one or more dedifferentiating steps, particularly loss of the p53 tumor suppressor protein. No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain. Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas undifferentiated carcinomas typically do not. Therefore, iodine-131 imaging and therapy cannot be used.

Patients with ATC may present with symptoms such as rapidly enlarging neck mass, dyspnea, dysphagia, neck pain, Horner syndrome, stroke, and hoarseness due to vocal cord paralysis.156 Patients with ATC present with extensive local invasion, and distant metastases are found at initial disease presentation in 15%–50% of patients.157,158 The lungs and pleura are the most common sites of distant metastases (≈90% of patients with distant disease). About 5%–15% of patients have bone metastases; 5% have brain metastases; and a few have metastases to the skin, liver, kidneys, pancreas, heart, and adrenal glands.

Diagnosis
Sometimes it is difficult to discriminate between ATC and other primary thyroid malignancies (ie, MTC, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid on FNA, and thus, core or surgical biopsy is preferred when the diagnosis of ATC is suspected.159–160 Diagnostic procedures include a complete blood count with differential, comprehensive metabolic panel, TSH level, direct exam of larynx with evaluation of vocal cord mobility, and imaging studies (see ANAP-1, page 939). Neck ultrasound can rapidly assess tumor extension and invasion.156 CT scans of the head, neck, chest, abdomen, and pelvis can accurately determine the extent of the thyroid tumor and identify tumor invasion of the great vessels and upper aerodigestive tract structures.161 PET/CT or MRI scans are recommended to accurately stage the patient. Bone metastases are usually lytic. All ATCs are considered stage IV (A, B, or C).3 Clinically apparent anaplastic tumors are often unresectable. Given the increasing number of therapeutic targets for ATC, tumor testing for actionable mutations (BRAF, NTRK, ALK, RET, MSI, dMMR, and TMB) is recommended (see “Systemic Therapy,” page 945).160

Treatment
ATC has a very poor prognosis and responds poorly to conventional therapy. RAI treatment is not effective in these patients.160 The role of palliative and supportive care is paramount and should be started early in the disease.160 At the outset of the diagnosis, it is critical that conversations about end-of-life care be initiated so that a clear understanding of how to manage the airway is undertaken, which is clear to the family and all providers. Tracheostomy is often a morbid and temporary treatment of the airway and may not be the option a patient would choose.162,163 See ANAP-2 (page 940) for locoregional disease and ANAP-3 (page 941) for metastatic disease.

Surgery
Once the diagnosis of ATC is confirmed, it is essential to rapidly determine whether local resection is an option.152 Before resection is attempted, the extent of disease—particularly with disease potentially involving the larynx, trachea, esophagus, pharynx, carotid artery, and other neck structures—should be accurately assessed by an experienced surgeon who is capable of performing complex neck surgery, if necessary. However, most patients with ATC have unresectable or metastatic disease. The patency of the airway should be assessed throughout the patient's course of treatment.163 If the patient appears to have resectable disease, an attempt at total thyroidectomy with complete gross tumor resection should be made, with resection of all involved local or regional structures and nodes.160 Total thyroidectomy with attempted complete tumor resection has not been shown to prolong survival except for the few patients whose tumors are small and confined entirely to the thyroid or readily excised structures.164–165 Patients need to receive levothyroxine if total thyroidectomy is done. Tracheostomy may be considered in patients with stage IV C disease.

Radiation Therapy
EBRT can increase survival in some patients; EBRT can also improve local control and can be used for palliation (eg, to prevent asphyxiation).99,160,166–170 Adjuvant RT, especially when combined with concurrent chemotherapy, is associated with improved survival (see ANAP-A 1 of 3, page 942).171 Higher RT dose is associated with OS in patients with unresected ATC.172 For solitary brain lesions, either neurosurgical resection or RT is recommended. Once brain metastases are diagnosed, disease-specific mortality is very high, with a reported median survival of 1.3 months. For unresected or incompletely resected disease, RT, usually with concurrent chemotherapy, should commence as quickly as possible. For R0 or R1 resection, adjuvant RT, usually with concurrent chemotherapy, should begin as soon as the patient has sufficiently recovered from surgery, ideally 2 to 3 weeks postoperatively. IMRT technique is encouraged. Enteral nutrition may be useful for some patients who have difficulty swallowing (see “Principles of Nutrition: Management and Supportive
Care,” in the NCCN Guidelines for Head and Neck Cancer, available at NCCN.org). If enteral feeding is considered, a careful conversation should occur with the patient about their wishes. For guidance regarding appropriate treatment volumes for use of RT for ATC, see Principles of Radiation and Radioactive Iodine Therapy: External Beam Radiation Therapy in the full NCCN Guidelines for Thyroid Carcinoma (available at NCCN.org).

**Systemic Therapy**

Systemic therapy recommendations are described in the algorithm (see ANAP-A 2 of 3, page 943). When systemic therapy is indicated, targeted therapy options are preferred. Dabrafenib plus trametinib combination is an option for BRAF V600E mutation-positive tumors. Larotrectinib or entrectinib are options for NTRK gene fusion-positive tumors. Selpercatinib or pralsetinib are options for RET fusion-positive disease, and pembrolizumab is an option for TMB-H (≥10 mut/Mb) disease. Other recommended regimens include paclitaxel and doxorubicin monotherapies. Doxorubicin combined with cisplatin is an option based on a small randomized trial. Paclitaxel combined with carboplatin and docetaxel combined with doxorubicin are also systemic therapy options for patients with metastatic ATC, but these are category 2B options based on low-quality evidence and less panel consensus.

The NCCN Thyroid Carcinoma Panel recommends molecular testing to help inform decisions regarding systemic therapy and to determine eligibility for clinical trials. The dosage and frequency of administration of all the recommended systemic therapy agents are provided in the algorithm. Either concurrent chemoradiation or chemotherapy alone regimens may be used depending on the clinical setting; however, chemoradiation is generally more toxic. If using chemoradiation, the ATA Guidelines recommend using weekly chemotherapy regimens.

A phase II, open-label trial of 16 patients with BRAF V600E-mutated ATC evaluated the efficacy and safety of dabrafenib 150 mg, twice daily, in combination with trametinib 2 mg, once daily. The confirmed ORR was 69% (95% CI, 41%–89%), with 7 responses ongoing. Although duration of response, PFS, and OS were not yet reached, the 12-month estimates were 90%, 79%, and 80%, respectively. The combination was found to be well-tolerated as evaluated in 100 patients across 7 rare tumor types. Common adverse events included fatigue (38%), pyrexia (37%), and nausea (35%). Based on these data, the FDA approved dabrafenib/trametinib for ATC with BRAF V600E mutation in 2018.

A pooled analysis of 3 studies (a phase 1 including adults, a phase 1/2 involving children, and a phase 2 involving adolescents and adults) studied the safety and efficacy of larotrectinib in patients with NTRK gene fusion-positive tumors, including in 7 patients with thyroid cancer of whom one patient had ATC. For the whole population, the ORR was 75% (95% CI, 61%–85%) by independent review and 80% (95% CI, 67%–90%) by investigator assessment. One hundred percent of the thyroid cancers in this study responded to larotrectinib, with one complete response and 4 partial responses. Larotrectinib was found to be well-tolerated, because the majority (93%) of adverse events were grades 1 or 2 and no treatment-related adverse events of grades 3 or 4 occurred in more than 5% of patients. A pooled analysis from a phase II trial and two phase I trials including 54 patients with NTRK gene fusion-positive cancer (9% having thyroid cancer) showed an objective response rate of 57.4% for entrectinib, another TRK inhibitor. Based on these data, the FDA approved larotrectinib and entrectinib for treatment of patients with NTRK gene fusion-positive tumors, and the panel also recommends NTRK therapy options such as larotrectinib or entrectinib for patients with NTRK gene fusion-positive metastatic ATC.

The phase I-II LIBRETTO-001 study evaluated the efficacy of the RET inhibitor selpercatinib in 19 patients with previously treated RET fusion-positive thyroid cancer (2 patients with anaplastic disease). The ORR was 79% (95% CI, 54%–94%), and 1-year PFS was 64% (95% CI, 37%–82%). In the ongoing phase I-II ARROW study, pralsetinib, another RET inhibitor, is being evaluated in patients with RET fusion-positive disease (NCT03037385). In an analysis including 9 patients with RET fusion-positive thyroid cancer, the ORR was 89% (95% CI, 52%–100%) with durable responses (100% disease control rate). In 2020, the FDA approved both of these RET inhibitors for RAI-refractory RET fusion-positive thyroid cancer requiring systemic therapy.

The FDA approved the anti-PD-1 antibody pembrolizumab for treatment of previously treated TMB-H (≥10 mut/Mb) solid tumors in 2020 based on results of the phase II KEYNOTE-158 trial, which included 2 patients with thyroid cancer. For the whole sample, the ORR was 29% (95% CI, 21%–39%). Grade 3–5 treatment-related adverse events were reported in 15% of the patients. A phase II study evaluated another anti-PD-1 antibody, spartalizumab, in 42 patients with locally advanced or metastatic ATC. The ORR was 19% (95% CI, 8.6%–34.1%), but was higher for patients with PD-L1–positive disease (29%; 95% CI, 13.2%–48.7%) and highest in patients with PD-L1 greater than 50% (35%; 95% CI, 14.2%–61.7%).

Treatment with anthracyclines and taxanes is generally not very effective for advanced anaplastic disease, although some patients may show disease response or
have stable disease. Single-agent doxorubicin is approved by the FDA for ATC. A randomized trial including 84 patients with advanced thyroid cancer (not limited to ATC) showed an 11.6% complete response rate in patients who received doxorubicin combined with cisplatin, compared with a complete response in 0 patients who received single-agent doxorubicin. ORR did not differ significantly between the study arms (26% vs 17%, respectively). Single-agent paclitaxel may benefit some patients with newly diagnosed ATC; increased survival has been reported in patients with stage IVB disease. If weekly paclitaxel is used, the ATA Guidelines recommend using paclitaxel at 60 to 90 mg/m² intravenously weekly and not the dose previously reported in the study by Ain et al.

Given the poor outcomes with current standard therapy, all patients—regardless of surgical resection—should be considered for clinical trials. Previous clinical trials for ATC have tested therapies including fosfotubulin (and its parent drug, combretastatin A4 phosphate [CA4P], and crolibulin [EPC2407], which are vascular disrupting agents), efatutase (an oral PPAR gamma agonist), and novel multitargeted therapies including bevacizumab with doxorubicin, sorafenib, sunitinib, imatinib, and pazopanib. A trial in 80 patients (FACT) reported that the addition of fosfotubulin—to a carboplatin/paclitaxel regimen—resulted in a nonsignificant increase in median survival (5.2 vs 4.0 months). Preliminary data suggest that ALK inhibitors may be effective in a subset of patients with PTC who have ALK gene fusions; however, these ALK gene fusions are rarely reported in patients with ATC.

Hyperfractionated EBRT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with a subsequent median survival of 1 year. Distant metastases then become the leading cause of death. Similar improvement in local disease control has been reported with a combination of hyperfractionated RT and doxorubicin-based regimens, followed by debulking surgery in responsive patients or other multimodality approaches. IMRT may be useful to reduce toxicity. However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or with improved survival. Other radiosensitizing agents that may be considered include docetaxel and paclitaxel with or without carboplatin. Although optimal results have been reported with hyperfractionated EBRT combined with chemotherapy, the NCCN Thyroid Carcinoma Panel acknowledges that considerable toxicity is associated with such treatment and that prolonged remission is uncommonly reported.

Multimodality therapy is recommended in patients with locally resectable disease (see ANAP-2, page 940). Small retrospective studies have reported that patients with ATC who receive trimodal therapy including surgery, radiation, and systemic therapy demonstrate improved survival compared with those who undergo less aggressive treatment approaches. In a case series, complete surgical resection without tracheostomy or radical resection was achieved in 6 patients with initially unresectable BRAF V600E-mutated ATC who received neoadjuvant dabrafenib/trametinib. One-year OS was 83%, and the local control rate was 100%. Two patients eventually died of distant metastasis, but the treatment response continued to be durable in the remaining 4 patients.

References

32. Jonklaas J, Sarlis NJ, Litofsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 2006;16:1229–1242.


### Individual Disclosures for the NCCN Thyroid Carcinoma Panel

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<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support/Data Safety Monitoring Board</th>
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<td>Lori J. Wirth, MD</td>
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The NCCN Guidelines Staff have no conflicts to disclose.

*The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:

- Rod Rezaee, MD: Biomet, Inc.
- Cord Sturgeon, MD: American Association of Endocrine Surgeons

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