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Anaplastic Thyroid Carcinoma, Version 2.2015

Clinical Practice Guidelines in Oncology

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Overview

The main histologic types of thyroid carcinoma include 1) differentiated, which includes papillary, follicular, and Hürthle cell carcinoma; 2) medullary carcinoma; and 3) anaplastic carcinoma (which is an aggressive undifferentiated tumor). An average of 58,629 patients per year were diagnosed with thyroid carcinoma between 2008 to 2012.[1] Of these patients, 89% had papillary carcinoma, 5.1% had follicular

Abstract

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma focuses on anaplastic carcinoma because substantial changes were made to the systemic therapy recommendations for the 2015 update. Dosages and frequency of administration are now provided, docetaxel/doxorubicin regimens were added, and single-agent cisplatin was deleted because it is not recommended for patients with advanced or metastatic anaplastic thyroid cancer. (J Natl Compr Canc Netw 2015;13:1140–1150)

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 for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Thyroid Carcinoma are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

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 1150. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

carcinoma, 2.2% had Hürthle cell, 1.7% had medullary carcinoma, and 0.8% had anaplastic thyroid carcinoma (ATC).[1] The 5-year relative survival rates for patients with papillary and follicular carcinomas (stages I–III) were 98% and 90%, respectively.[2] In contrast, the 5-year relative survival rate for ATC is about 7%.[2]

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma focuses on ATC, because substantial changes were made to the systemic therapy recommendations for the 2015 update (available online, in these guidelines, at NCCN.org [ANAP-A]). The complete version of the NCCN Guidelines for Thyroid Carcinoma addresses all aspects of management for the different types of thyroid carcinoma, including papillary, follicular, Hürthle cell, medullary, and anaplastic carcinoma. Additional sections are included in the complete version of these guidelines, such as Nodule Evaluation, Principles of Thyroid Stimulating Hormone (TSH) Suppression, Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma, and the AJCC staging tables.[2] The complete version of the NCCN Guidelines for Thyroid Carcinoma is updated at least once a year (to view the most recent version of these guidelines, visit the NCCN Web site at NCCN.org).

The summary of the guidelines updates briefly describes the new changes for the NCCN Guidelines for 2015 (see the complete version of the NCCN Guidelines for Thyroid Carcinoma at NCCN.org). A brief introduction to thyroid carcinoma is provided

Text cont. on page 1144.

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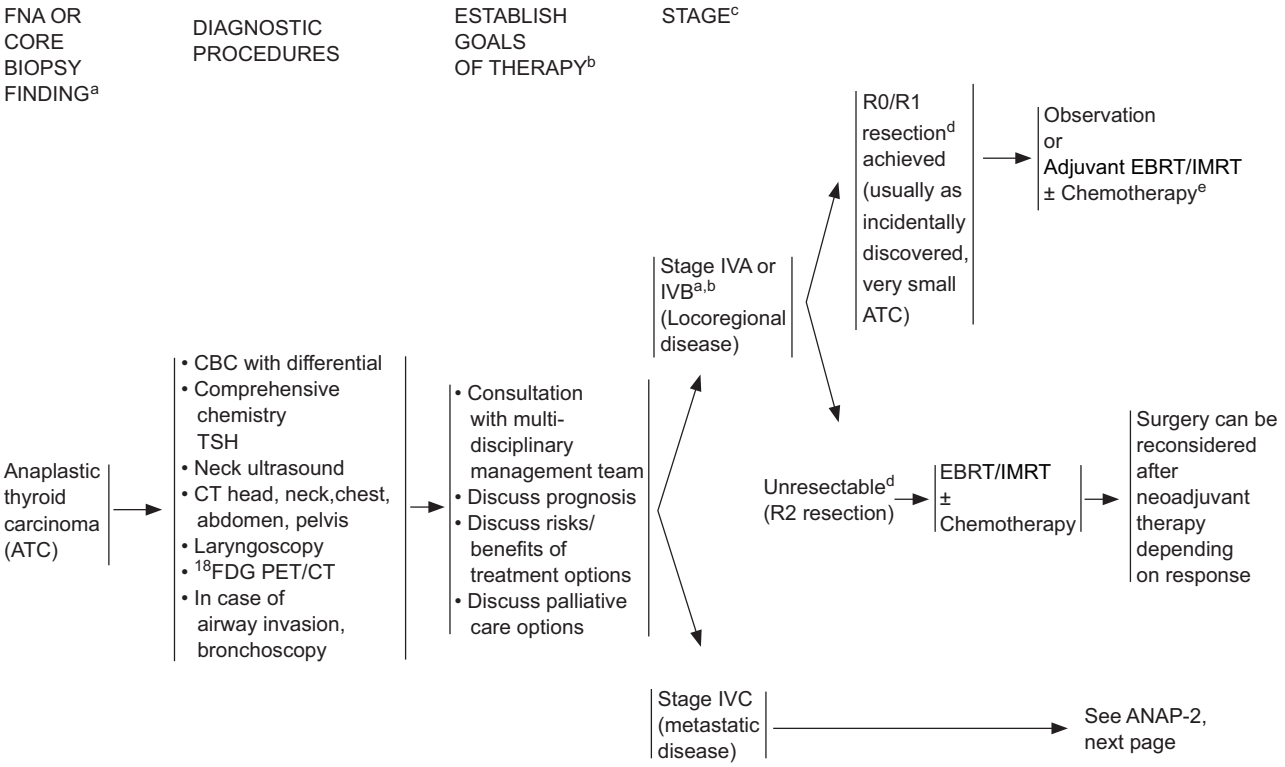

[a]Consider core or open biopsy if FNA is "suspicious" for ATC or is not definitive. Morphologic diagnosis combined with immunohistochemistry is necessary in order to exclude other entities such as poorly differentiated thyroid cancer, medullary thyroid cancer, squamous cell carcinoma, and lymphoma.

[b]Preoperative evaluations need to be completed as quickly as possible and involve integrated decision making in a multidisciplinary team and with the patient. Consider referral to multidisciplinary high-volume center with expertise in treating ATC.

[c]See Staging (ST-1; available online, in these guidelines, at NCCN.org).

[d]Resectability for locoregional disease depends on extent of involved structures, potential morbidity, and mortality associated with resection. In most cases, there is no indication for a debulking surgery. See Staging (ST-1; available online, in these guidelines, at NCCN.org) for definitions of R0/R1/R2.

[e]See Systemic Therapy for Anaplastic Thyroid Carcinoma (ANAP-A, next page).

ANAP-1

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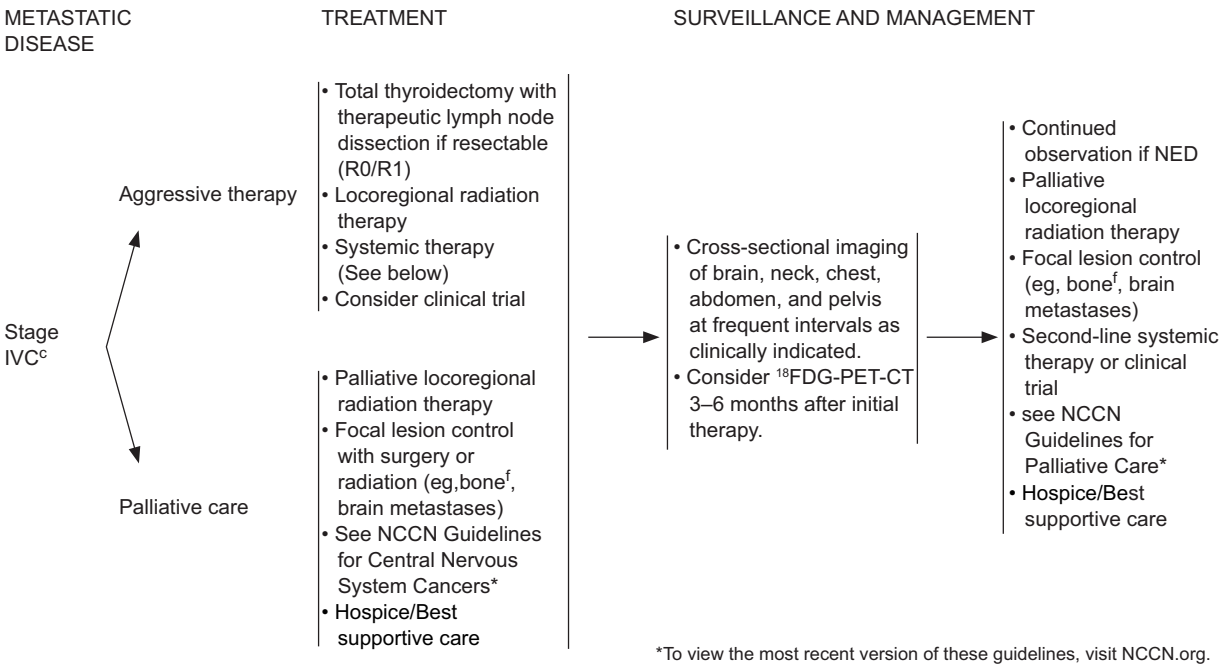

*To view the most recent version of these guidelines, visit NCCN.org.

[c]See Staging (ST-1; available online, in these guidelines, at NCCN.org).

[f]Consider use of intravenous bisphosphonates or denosumab. Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

SYSTEMIC THERAPY[1]

Regimen	Agents/Dosages	Frequency
Paclitaxel/carboplatin	Paclitaxel 60–100 mg/m^2, carboplatin AUC 2 mg/m^2 IV	Weekly
Paclitaxel/carboplatin	Paclitaxel 135–175 mg/m^2, carboplatin AUC 5–6 mg/m^2 IV	Every 3–4 weeks
Docetaxel/doxorubicin	Docetaxel 60 mg/m^2 IV, doxorubicin 60 mg/m^2 IV (with pegfilgrastim) or Docetaxel 20 mg/m^2 IV, doxorubicin 20 mg/m^2 IV	Every 3-4 weeks Weekly
Paclitaxel	60–90 mg/m^2 IV	Weekly
Paclitaxel	135–200 mg/m^2 IV	Every 3–4 weeks
Doxorubicin	60–75 mg/m^2 IV	Every 3 weeks
Doxorubicin	20 mg/m^2 IV	Weekly

[1]Reprinted with permission from Mary Ann Liebert, Inc.,Smallridge RC, et al. American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer. Thyroid 2012;22:1124.

ANAP-2, ANAP-A

Text cont. from page 1141.

in the following section. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the panel members while developing these guidelines.

Epidemiology

Thyroid nodules are approximately 4 times more common in women than in men. Palpable nodules increase in frequency throughout life, reaching a prevalence of about 5% in the United States population for individuals ages 50 years and older.[3–5] Nodules are even more prevalent when the thyroid gland is examined at autopsy or surgery or when ultrasonography is used; 50% of the thyroids studied have nodules, which are almost always benign.[4,6] New nodules develop at a rate of about 0.1% per year, beginning in early life, but nodules develop at a much higher rate (approximately 2% per year) after exposure to head and neck irradiation.[7,8]

By contrast, thyroid carcinoma is uncommon. For the United States population, the lifetime risk of being diagnosed with thyroid carcinoma is 1.1%.[1] Experts estimate that approximately 62,450 new cases of thyroid carcinoma will be diagnosed in the United States in 2015.[9] As with thyroid nodules, thyroid carcinoma occurs 2 to 3 times more often in women than in men. Thyroid carcinoma is currently the fourth most common malignancy diagnosed in women.[9] Among persons aged 20 to 34 years, thyroid carcinoma accounts for 15.1% of all thyroid malignancies.[1] The disease is also diagnosed more often in white North Americans than in African Americans. Although thyroid carcinoma can occur at any age, the peak incidence is age 50 years.[1]

Incidence and Mortality Rates

Experts estimated that approximately 1950 cancer deaths will occur in 2015 among persons with thyroid carcinoma in the United States.[9–15] ATC is almost uniformly lethal; however, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas, because they account for nearly 95% of all thyroid carcinoma cases. Although thyroid carcinoma occurs more often in women, mortality rates are lower for younger women.[10–14] The incidence of thyroid carcinoma increased almost 310% between 1950 and 2004, but mortality rates decreased more than 44%.[13] From 1975 to 2004, thyroid cancer rates doubled in the United States.[15] From 1975 to 2009, thyroid cancer rates tripled, mainly because of small papillary thyroid cancers.[16] Although the estimated incidence of thyroid carcinoma increased between 2013 and 2014 (60,220 vs 62,980, respectively), the estimated incidence did not increase between 2014 and 2015 (62,980 vs 62,450, respectively).[9,17] Because overall mortality has not dramatically increased since 1975 (1150 vs 1950 deaths), the increasing incidence may reflect, at least in part, earlier detection of subclinical disease (ie, small papillary cancers).[15,16,18–20] However, recent data show the incidence has increased by varying degrees across all tumor sizes.[21–25] The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.[26,27]

ATC

ATCs are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.[28] Patients with anaplastic carcinoma are often older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.[29] Fewer than 10% of patients are younger than age 50 years, and 60% to 70% of patients are women.[29,30] The incidence of ATC is decreasing because of better management of differentiated thyroid cancer and because of increased iodine in the diet.[28,31] As previously mentioned, anaplastic carcinoma is the least common type of thyroid carcinoma. An average of 58,629 patients per year were diagnosed with thyroid carcinoma between 2008 and 2012, but only 499 patients per year had ATC.[1]

Approximately 50% of patients with ATC have either a prior or coexisting differentiated carcinoma. Anaplastic carcinoma develops from more differentiated tumors as a result of one or more dedifferentiating steps, particularly loss of the p53 tumor suppressor protein.[32] No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain. Iodine deficiency is associated with ATC. More than 80% of patients with ATC have a history of goiter.[31,33,34] Differentiated thyroid carcinomas can

concentrate iodine, express TSH receptor, and produce thyroglobulin (Tg), whereas poorly differentiated or undifferentiated carcinomas typically do not. Therefore, 131I imaging and Tg measurement cannot be used in patients with ATC; radioactive iodine treatment is not effective.[31]

ATC is typically diagnosed based on clinical symptoms, unlike differentiated thyroid carcinoma, which is typically diagnosed after fine-needle aspiration (FNA) on a suspicious thyroid nodule. Patients with ATC may present with symptoms such as rapidly enlarging neck mass, dyspnea, dysphagia, neck pain, Horner's syndrome, stroke, and hoarseness due to vocal cord paralysis.[35] Patients with ATC present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.[36,37] The lungs and pleura are the most common site of distant metastases (≤90% of patients with distant disease). About 5% to 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

Cytologic examination of an FNA specimen from a neck mass or nodule is categorized as 1) carcinoma (papillary, medullary, or anaplastic) or suspicious for carcinoma; 2) follicular or Hürthle cell neoplasm; 3) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); 4) thyroid lymphoma; 5) benign (ie, nodular goiter, colloid goiter, hyperplastic/adenomatoid nodule, Hashimoto's thyroiditis); or 6) insufficient biopsy (nondiagnostic) (see Nodule Evaluation in the complete version of these guidelines, available online at NCCN.org). These diagnostic categories for FNA results reflect the NCI's State of the Science Conference held in 2007.[38,39]

Pathology and cytopathology slides should be reviewed at the treating institution by a pathologist with expertise in the diagnosis of thyroid disorders. Although FNA is a very sensitive test—particularly for papillary thyroid carcinoma—false-negative results are sometimes obtained; therefore, a reassuring FNA should not override worrisome clinical findings.[40,41]

If FNA results are suspicious or not definitive, core or surgical biopsy should be performed to establish the diagnosis of ATC.[31] Discriminating between ATC and other primary thyroid malignancies (ie, medullary thyroid carcinoma [MTC], thyroid lymphoma, sarcoma) or poorly differentiated cancers that metastasize to the thyroid, such as melanoma, is sometimes difficult.[31,39,42] The appearance of ATCs varies widely; many have mixed morphologies. The most common morphology is biphasic spindle and giant cell tumor. Molecular techniques are not recommended for diagnosis of ATC.[31] Additional immunohistochemical studies (eg, calcitonin) may occasionally be required to confirm the diagnosis of MTC.[39] Hürthle cell neoplasms can sometimes mimic MTC cytologically and on frozen section. Metastatic renal carcinoma can mimic a follicular neoplasm, melanoma can mimic MTC, and metastatic lung cancer can mimic ATC.[39] Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens, such as those from the College of American Pathologists (CAP). The CAP protocol template may be useful; the protocol was updated in August 2014 and reflects the 2010 staging (7th edition) from the AJCC (see Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland on the CAP website).[2,43]

Diagnostic procedures include CBC, comprehensive chemistry, TSH level, and imaging studies. Neck ultrasound can rapidly assess tumor extension and invasion.[35] CT scans of the neck can accurately determine the extent of the thyroid tumor and identify tumor invasion of the great vessels and upper aerodigestive tract structures.[44] PET/CT scans are recommended to accurately stage the disease. Bone metastases are usually lytic. All ATCs are considered stage IV (A, B, or C) (see Table 1 in the complete version of the NCCN Guidelines for Thyroid Carcinoma, available at NCCN.org). The T4 category includes 1) T4a tumors that are intrathyroidal; and 2) T4b tumors that are extrathyroidal. Clinically apparent anaplastic tumors are usually unresectable.

Prognosis

No curative therapy exists for ATC; it is almost uniformly fatal.[45,46] The median survival from diagnosis is about 5 months.[31,47] The 1-year relative survival rate is about 18%.[2] Death is attributable to upper airway obstruction and suffocation (often despite tracheostomy) in 50% of these patients; in the remaining patients, death is attributable to complications of local and distant disease or therapy.[48] Patients with disease confined to the neck at diagnosis have a mean

survival of 8 months compared with 3 months if the disease extends beyond the neck.[49] Other variables that may predict a worse prognosis include older age at diagnosis, distant metastases, WBC of 10,000 mm^3 or more, and dyspnea as a presenting symptom.[50,51]

Treatment

Surgery: After the diagnosis of ATC is confirmed, rapidly determining whether local resection is an option is essential.[28] The surgeon should be experienced in accurately assessing the extent of disease and capable of performing extensive neck dissections 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.[48] If the patient appears to have resectable disease, an attempt at total thyroidectomy with complete gross tumor resection should be made, with selective resection of all involved local or regional structures and nodes. 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.[47,49,52,53] Patients need to receive levothyroxine if total thyroidectomy is performed.

The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur more frequently after total thyroidectomy. Transient clinical hypoparathyroidism after surgery is common in adults undergoing total thyroidectomy.[54] The rates of long-term recurrent laryngeal nerve injury and hypoparathyroidism, respectively, were 3% and 2.6% after total thyroidectomy and were 1.9% and 0.2% after subtotal thyroidectomy.[55] One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.[56] Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia.[57]

When experienced surgeons perform thyroidectomies, complications occur at a lower rate. A study of 5860 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.[58]

ATC has a very poor prognosis and responds poorly to conventional therapy. The role of palliative and supportive care is paramount and should be initiated early in the disease. It is important that the surgeon be very experienced in evaluating the extent of disease—particularly in the larynx, trachea, and neck—before attempting resection. 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.

Radiation Therapy: External-beam radiation therapy (EBRT)/intensity-modulated radiation therapy (IMRT) can increase short-term survival in some patients; EBRT can also improve local control and can also be used for palliation (eg, to prevent asphyxiation).[28,31,51,59–62] Surgical excision or external irradiation should be considered for isolated skeletal metastases. For solitary brain lesions, neurosurgical resection, radiation therapy, or both are recommended.[31,63] After brain metastases are diagnosed, disease-specific mortality is very high, with a reported median survival of 1.3 months.[63] 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).[31] If enteral feeding is considered, a careful conversation should occur with the patient about their wishes.

Systemic Therapy: Treatment with single-drug chemotherapy is not very effective, although some patients may respond or have stable disease.[31] Hyperfractionated EBRT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with subsequent median survival of 1 year.[64] Distant metastases then become the leading cause of death.[65] Similar improvement in local disease control has been reported with a combination of hyperfractionated RT and doxorubicin-based regimens, followed by surgery in patients who respond or other multimodality approaches.[66–68] IMRT may be useful to reduce toxicity.[31,60,69–73] However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or with improved survival.

Systemic therapy recommendations are described in the algorithm (see ANAP-A; page 1143).[31,74] For

the 2015 update, the recommended systemic therapy regimens for ATC were revised based on the guidelines from the American Thyroid Association (ATA) guidelines.[31] Docetaxel/doxorubicin regimens were added, which can be used with or without radiation therapy.[31,75,76] Single-agent cisplatin was deleted, because it is not recommended for patients with advanced/metastatic ATC or those with impaired renal function. In addition, the dosage and frequency of administration of all the recommended systemic therapy agents are now provided. 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.[31]

Chemotherapy alone can be considered for patients with unresectable or metastatic disease. Single-agent doxorubicin is the only agent that is approved by the FDA for ATC.[31] Single-agent paclitaxel may benefit some newly diagnosed patients; increased survival has been reported in patients with stage IVB disease.[77–79] If weekly paclitaxel is used, the ATA guidelines recommend using paclitaxel at 60 to 90 mg/m^2 intravenously weekly and not the dose previously reported.[31,79] Note that carboplatin is dosed using the following: 1) Calvert formula with the Cockroft & Gault equation; 2) actual body weight; and 3) a minimum serum creatinine value of 0.7 mg/dL (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm).

Given the poor outcome with current standard therapy, all patients—regardless of surgical resection—should be considered for clinical trials. Clinical trials include fosbretabulin (and its parent drug, combretastatin A4 phosphate [CA4P], and crolibulin [EPC2407], which are vascular disrupting agents), efatutazone (an oral PPAR gamma agonist), and novel multitargeted therapies including bevacizumab with doxorubicin, sorafenib, sunitinib, imatinib, and pazopanib.[74,80–89] Outside of clinical trials, targeted therapies are not currently recommended for patients with ATC in the NCCN Guidelines, although some are recommended for patients with papillary, follicular, Hürthle cell, or medullary carcinoma.

A trial in 80 patients (FACT) reported that the addition of fosbretabulin—to a carboplatin/paclitaxel regimen—resulted in a nonsignificant increase in median survival (5.2 vs 4.0 months).[74,90] Multimodality therapy is recommended in patients with locally resectable disease (see ANAP-1; page 1142).[31,69,74,91–95] Although optimal results have been reported with hyperfractionated EBRT combined with chemotherapy, the NCCN panel acknowledged that considerable toxicity is associated with such treatment and that prolonged remission is uncommon.[96] Preliminary data suggest that anaplastic lymphoma kinase (ALK) inhibitors may be effective in a subset of patients with papillary thyroid cancer who have *ALK* gene fusions; however, these *ALK* gene fusions are rarely reported in patients with ATC.[97–100] *BRAF* mutations have been reported in patients with ATC.[35,101–103]

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Individual Disclosures of the NCCN Anaplastic Thyroid Carcinoma Panel				
Panel Member	**Clinical Research Support/ Data Safety Monitoring Board**	**Scientific Advisory Boards, Consultant, or Expert Witness**	**Promotional Advisory Boards, Consultant, or Speakers Bureau**	**Date Completed**
Douglas W. Ball, MD	Eisai Inc.; Exelixis Inc.; and Roche USA	Exelixis Inc.	None	12/7/11
Naifa Lamki Busaidy, MD	Bayer HealthCare	Bayer HealthCare	None	11/12/14
David Byrd, MD	None	None	None	11/10/14
Glenda Callender, MD	None	None	None	9/20/14
Paxton Dickson, MD	None	None	None	3/1/15
Quan-Yang Duh, MD	None	None	None	9/23/14
Hormoz Ehya, MD	None	Eli Lilly and Company	None	10/29/14
Robert I. Haddad, MD	Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Celgene Corporation; Merck & Co., Inc.; and VentiRx Pharmaceuticals, Inc.	Bristol-Myers Squibb Company; Celgene Corporation; Eisai Inc.; and Merck & Co., Inc.	None	2/27/15
Megan Haymart, MD	National Cancer Institute	None	None	8/10/15
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Judith C. McCaffrey, MD	None	None	None	2/26/15
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[a]The following of disclosed that they have an Employment/Governing Board, Patent, Equity, or Royalty conflict:
Peter Kopp, MD: American Thyroid Association; Editor in Chief of *Thyroid. Official Journal American Thyroid Association*
Matthew Ringel, MD: International Thyroid Oncology Group; The Endocrine Society
Robert C. Smallridge, MD: American Thyroid Association

The NCCN Guidelines Staff have no conflicts to disclose.