



Published in final edited form as:

*J Natl Compr Canc Netw*. 2015 September ; 13(9): 1140–1150.

## **Anaplastic Thyroid Carcinoma, Version 2.2015:**

### **Clinical Practice Guidelines in Oncology**

Robert I. Haddad, MD, William M. Lydiatt, MD, Douglas W. Ball, MD, Naifa Lamki Busaidy, MD, David Byrd, MD, Glenda Callender, MD, Paxton Dickson, MD, Quan-Yang Duh, MD, Hormoz Ehya, MD, Megan Haymart, MD, Carl Hoh, MD, Jason P. Hunt, MD, Andrei Iagaru, MD, Fouad Kandeel, MD, PhD, Peter Kopp, MD, Dominick M. Lamonica, MD, Judith C. McCaffrey, MD, Jeffrey F. Moley, MD, Lee Parks, MD, Christopher D. Raeburn, MD, John A. Ridge, MD, PhD, Matthew D. Ringel, MD, Randall P. Scheri, MD, Jatin P. Shah, MD, PhD, Robert C. Smallridge, MD, Cord Sturgeon, MD, Thomas N. Wang, MD, PhD, Lori J. Wirth, MD, Karin G. Hoffmann, RN, CCM, and Miranda Hughes, PhD

### **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.

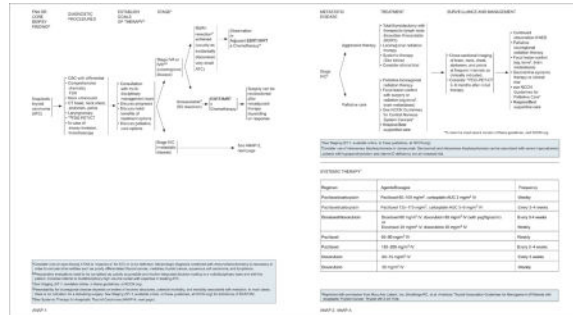
### **Overview**

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.<sup>1</sup> Of these patients, 89% had papillary carcinoma, 5.1% had follicular carcinoma, 2.2% had Hürthle cell, 1.7% had medullary carcinoma, and 0.8% had anaplastic thyroid carcinoma (ATC).<sup>1</sup> The 5-year relative survival rates for patients with papillary and follicular carcinomas (stages I–III) were 98% and 90%, respectively.<sup>2</sup> In contrast, the 5-year relative survival rate for ATC is about 7%.<sup>2</sup>

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](http://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.<sup>2</sup> 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](http://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](http://NCCN.org)). A brief introduction to thyroid carcinoma is provided 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.<sup>3–5</sup> 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.<sup>4,6</sup> 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.<sup>7,8</sup>

By contrast, thyroid carcinoma is uncommon. For the United States population, the lifetime risk of being diagnosed with thyroid carcinoma is 1.1%.<sup>1</sup> Experts estimate that approximately 62,450 new cases of thyroid carcinoma will be diagnosed in the United States in 2015.<sup>9</sup> 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.<sup>9</sup> Among persons aged 20 to 34 years, thyroid carcinoma accounts for 15.1% of all thyroid malignancies.<sup>1</sup> 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.<sup>1</sup>

## Incidence and Mortality Rates

Experts estimated that approximately 1950 cancer deaths will occur in 2015 among persons with thyroid carcinoma in the United States.<sup>9–15</sup> 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.<sup>10–14</sup> The incidence of thyroid carcinoma increased almost 310% between 1950 and 2004, but mortality rates decreased more than 44%.<sup>13</sup> From 1975 to 2004, thyroid cancer rates doubled in the United States.<sup>15</sup> From 1975 to 2009, thyroid cancer rates tripled, mainly because of small papillary thyroid cancers.<sup>16</sup> 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).<sup>9,17</sup> 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).<sup>15,16,18–20</sup> However, recent data show the incidence has increased by varying degrees across all tumor sizes.<sup>21–25</sup> The stable age- and gender-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults.<sup>26,27</sup>

## ATC

ATCs are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.<sup>28</sup> Patients with anaplastic carcinoma are often older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.<sup>29</sup> Fewer than 10% of patients are younger than age 50 years, and 60% to 70% of patients are women.<sup>29,30</sup> The incidence of ATC is decreasing because of better management of differentiated thyroid cancer and because of increased iodine in the diet.<sup>28,31</sup> 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.<sup>1</sup>

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.<sup>32</sup> 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.<sup>31,33,34</sup> 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.<sup>31</sup>

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.<sup>35</sup> Patients with ATC present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.<sup>36,37</sup> 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](http://NCCN.org)). These diagnostic categories for FNA results reflect the NCI's State of the Science Conference held in 2007.<sup>38,39</sup>

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.<sup>40,41</sup>

If FNA results are suspicious or not definitive, core or surgical biopsy should be performed to establish the diagnosis of ATC.<sup>31</sup> 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.<sup>31,39,42</sup> 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.<sup>31</sup> Additional immunohistochemical studies (eg, calcitonin) may occasionally be required to confirm the diagnosis of MTC.<sup>39</sup> 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.<sup>39</sup> 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).<sup>2,43</sup>

Diagnostic procedures include CBC, comprehensive chemistry, TSH level, and imaging studies. Neck ultrasound can rapidly assess tumor extension and invasion.<sup>35</sup> 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.<sup>44</sup> 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](http://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.<sup>45,46</sup> The median survival from diagnosis is about 5 months.<sup>31,47</sup> The 1-year relative survival rate is about 18%.<sup>2</sup> 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.<sup>48</sup> 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.<sup>49</sup> Other variables that may predict a worse prognosis include older age at diagnosis, distant metastases, WBC of 10,000 mm<sup>3</sup> or more, and dyspnea as a presenting symptom.<sup>50,51</sup>

## Treatment

**Surgery**—After the diagnosis of ATC is confirmed, rapidly determining whether local resection is an option is essential.<sup>28</sup> 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.<sup>48</sup> 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.<sup>47,49,52,53</sup> 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.<sup>54</sup> 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.<sup>55</sup> One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.<sup>56</sup> Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia.<sup>57</sup>

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.<sup>58</sup>

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).<sup>28,31,51,59–62</sup> Surgical excision or external irradiation should be considered for isolated skeletal metastases. For solitary brain lesions, neurosurgical resection, radiation therapy, or both are recommended.<sup>31,63</sup> After brain metastases are diagnosed, disease-specific mortality is very high, with a reported median survival of 1.3 months.<sup>63</sup> 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).<sup>31</sup> 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.<sup>31</sup> Hyperfractionated EBRT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with subsequent median survival of 1 year.<sup>64</sup> Distant metastases then become the leading cause of death.<sup>65</sup> 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.<sup>66–68</sup> IMRT may be useful to reduce toxicity.<sup>31,60,69–73</sup> 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).<sup>31,74</sup> For the 2015 update, the recommended systemic therapy regimens for ATC were revised based on the guidelines from the American Thyroid Association (ATA) guidelines.<sup>31</sup> Docetaxel/doxorubicin regimens were added, which can be used with or without radiation therapy.<sup>31,75,76</sup> 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.<sup>31</sup>

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.<sup>31</sup> Single-agent paclitaxel may benefit some newly diagnosed patients; increased survival has been reported in patients with stage IVB disease.<sup>77–79</sup> If weekly paclitaxel is used, the ATA guidelines recommend using paclitaxel at 60 to 90 mg/m<sup>2</sup> intravenously weekly and not the dose previously reported.<sup>31,79</sup> Note that carboplatin is dosed using the following: 1) Calvert formula with the Cockcroft & 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.<sup>74,80–89</sup> 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).<sup>74,90</sup> Multimodality therapy is recommended in patients with locally resectable disease (see ANAP-1; page 1142).<sup>31,69,74,91–95</sup> 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.<sup>96</sup> 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.<sup>97–100</sup> *BRAF* mutations have been reported in patients with ATC.<sup>35,101–103</sup>

## 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<sup>®</sup>) 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<sup>®</sup> 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<sup>®</sup> (NCCN<sup>®</sup>) 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](http://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](http://NCCN.org).)

These guidelines are also available on the Internet. For the latest update, visit [NCCN.org](http://NCCN.org).

### NCCN Thyroid Carcinoma Panel Members

\*Robert I. Haddad, MD/Chair<sup>†</sup>

Dana-Farber/Brigham and Women's Cancer Center

William M. Lydiatt, MD/Vice-Chair<sup>¶§</sup>

Fred & Pamela Buffett Cancer Center

Douglas W. Ball, MD

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Naifa Lamki Busaidy, MD

The University of Texas MD Anderson Cancer Center

David Byrd, MD<sup>¶</sup>

Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Glenda Callender, MD<sup>¶</sup>

Yale Cancer Center/Smilow Cancer Hospital

Paxton Dickson, MD<sup>¶</sup>

St. Jude Children's Research Hospital/University of Tennessee Health Science Center

Quan-Yang Duh, MD<sup>¶</sup>

UCSF Helen Diller Family Comprehensive Cancer Center



Hormoz Ehya, MD  
Fox Chase Cancer Center

Megan Haymart, MD<sup>P</sup>  
University of Michigan Comprehensive Cancer Center

Carl Hoh, MD<sup>ϕ</sup>  
UC San Diego Moores Cancer Center

Jason P. Hunt, MD<sup>¶</sup>  
Huntsman Cancer Institute at the University of Utah

Andrei Iagaru, MD<sup>ϕ</sup>  
Stanford Cancer Institute

Fouad Kandeel, MD, PhD  
City of Hope Comprehensive Cancer Center

Peter Kopp, MD <sup>P</sup>  
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Dominick M. Lamonica, MD<sup>Pϕ</sup>  
Roswell Park Cancer Institute

Judith C. McCaffrey, MD<sup>Ⓢ</sup>  
Moffitt Cancer Center

Jeffrey F. Moley, MD<sup>¶</sup>  
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of  
Medicine

Lee Parks, MD  
Vanderbilt-Ingram Cancer Center

Christopher D. Raeburn, MD<sup>¶</sup>  
University of Colorado Cancer Center

John A. Ridge, MD, PhD<sup>¶</sup>  
Fox Chase Cancer Center

Matthew D. Ringel, MD

The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute

Randall P. Scheri, MD<sup>¶</sup>

Duke Cancer Institute

Jatin P. Shah, MD, PhD<sup>¶</sup>

Memorial Sloan Kettering Cancer Center

Robert C. Smallridge, MD

Mayo Clinic Cancer Center

Cord Sturgeon, MD<sup>¶</sup>

Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Thomas N. Wang, MD, PhD<sup>¶</sup>

University of Alabama at Birmingham Comprehensive Cancer Center

Lori J. Wirth, MD<sup>†</sup>

Massachusetts General Hospital Cancer Center

NCCN Staff: Karin G. Hoffmann, RN, CCM, and Miranda Hughes, PhD

KEY:

\*Writing Committee Member

Specialties: <sup>†</sup>Medical Oncology; <sup>¶</sup>Surgery/Surgical Oncology; <sup>§</sup>Otolaryngology; Endocrinology; Pathology; <sup>♯</sup>Inte

### 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

<b>Panel Member</b>	<b>Clinical Research Support/ Data Safety Monitoring Board</b>	<b>Scientific Advisory Boards, Consultant, or Expert Witness</b>	<b>Promotional Advisory Boards, Consultant, or Speakers Bureau</b>	<b>Date Completed</b>
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
Carl Hoh, MD	None	None	None	10/3/13
Jason P. Hunt, MD	None	None	None	11/5/14
Andrei Iagaru, MD	General Electric	Bayer HealthCare	None	10/28/14
Fouad Kandeel, MD, PhD	None	None	None	2/25/15
Peter Kopp, MD <sup>a</sup>	None	None	None	5/8/14
Dominick M. Lamonica, MD	None	None	None	2/23/15
William M. Lydiatt, MD	None	None	None	2/26/15
Judith C. McCaffrey, MD	None	None	None	2/26/15
Jeffrey F. Moley, MD	AstraZeneca Pharmaceuticals LP; and Exelixis Inc.	Exelixis Inc.	None	4/6/15
Lee Parks, MD	AstraZeneca Pharmaceuticals LP	None	None	2/24/15
Christopher D. Raeburn, MD	None	None	None	10/14/14
John A. Ridge, MD, PhD	None	None	None	2/26/15
Matthew D. Ringel, MD <sup>a</sup>	National Cancer Institute	None	None	9/30/14
Randall P. Scheri, MD	None	None	None	10/23/14
Jatin P. Shah, MD, PhD	None	None	None	7/1/15
Robert C. Smallridge, MD <sup>a</sup>	AstraZeneca Pharmaceuticals LP; and GlaxoSmithKline	None	None	10/27/14
Cord Sturgeon, MD	None	None	None	2/25/15
Thomas N. Wang, MD, PhD	None	None	None	11/6/14
Lori J. Wirth, MD	AstraZeneca Pharmaceuticals LP; Eisai Inc.; Exelixis Inc.; Genentech, Inc.; and Novartis Pharmaceuticals Corporation	AstraZeneca Pharmaceuticals LP; and Eisai Inc.	AstraZeneca Pharmaceuticals LP; and Eisai Inc.	12/4/14

<sup>a</sup>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.

## References

- Howlader, N.; Noone, A.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975–2012 based on November 2014 SEER data submission, posted to the SEER web site, April 2015. Bethesda, MD: National Cancer Institute; 2015. Available at: [http://seer.cancer.gov/csr/1975\\_2012/](http://seer.cancer.gov/csr/1975_2012/).
- Edge, SB.; Byrd, DR.; Compton, CC., et al. AJCC Cancer Staging Manual. 7th. New York: Springer; 2010. p. 1-646.
- Mazzaferri, EL. Thyroid carcinoma: papillary and follicular. In: Mazzaferri, EL.; Samaan, N., editors. *Endocrine Tumors*. Cambridge: Blackwell Scientific Publications; 1993. p. 278-333.
- Hegedus L. Clinical practice: the thyroid nodule. *N Engl J Med*. 2004; 351:1764–1771. [PubMed: 15496625]
- Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009; 19:1167–1214. [PubMed: 19860577]
- Ezzat S, Sarti DA, Cain DR, Braunstein GD. Thyroid incidentalomas: prevalence by palpation and ultrasonography. *Arch Intern Med*. 1994; 154:1838–1840. [PubMed: 8053752]
- Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res*. 1995; 141:259–277. [PubMed: 7871153]
- Schneider AB, Bekerman C, Leland J, et al. Thyroid nodules in the follow-up of irradiated individuals: comparison of thyroid ultrasound with scanning and palpation. *J Clin Endocrinol Metab*. 1997; 82:4020–4027. [PubMed: 9398706]
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015; 65:5–29. [PubMed: 25559415]
- Jonklaas J, Noguera-Gonzalez G, Munsell M, et al. The impact of age and gender on papillary thyroid cancer survival. *J Clin Endocrinol Metab*. 2012; 97:E878–887. [PubMed: 22496497]
- Stroup AM, Harrell CJ, Herget KA. Long-term survival in young women: hazards and competing risks after thyroid cancer. *J Cancer Epidemiol*. 2012; 2012:641372. [PubMed: 23091489]
- Altekruse, S.; Kosary, C.; Krapcho, M., et al. SEER Cancer Statistics Review. Bethesda, MD: National Cancer Institute; 2010. p. 1975-2007.
- SEER Cancer Statistics Review, 1975–2006. Bethesda, MD: National Cancer Institute; 2009.
- Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med*. 1994; 97:418–428. [PubMed: 7977430]
- Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA*. 2006; 295:2164–2167. [PubMed: 16684987]
- Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngol Head Neck Surg*. 2014; 140:317–322. [PubMed: 24557566]
- Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014; 64:9–29. [PubMed: 24399786]
- Li N, Du XL, Reitzel LR, et al. Impact of enhanced detection on the increase in thyroid cancer incidence in the United States: review of incidence trends by socioeconomic status within the surveillance, epidemiology, and end results registry, 1980–2008. *Thyroid*. 2013; 23:103–110. [PubMed: 23043274]
- Wilhelm S. Evaluation of thyroid incidentaloma. *Surg Clin North Am*. 2014; 94:485–497. [PubMed: 24857572]
- Ito Y, Tomoda C, Uruno T, et al. Papillary microcarcinoma of the thyroid: how should it be treated? *World J Surg*. 2004; 28:1115–1121. [PubMed: 15490053]

21. Aschebrook-Kilfoy B, Grogan RH, Ward MH, et al. Follicular thyroid cancer incidence patterns in the United States, 1980–2009. *Thyroid*. 2013; 23:1015–1021. [PubMed: 23360496]
22. Aschebrook-Kilfoy B, Ward MH, Sabra MM, Devesa SS. Thyroid cancer incidence patterns in the United States by histologic type, 1992–2006. *Thyroid*. 2011; 21:125–134. [PubMed: 21186939]
23. Yu GP, Li JC, Branovan D, et al. Thyroid cancer incidence and survival in the national cancer institute surveillance, epidemiology, and end results race/ethnicity groups. *Thyroid*. 2010; 20:465–473. [PubMed: 20384488]
24. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. *Cancer*. 2009; 115:3801–3807. [PubMed: 19598221]
25. Enewold L, Zhu K, Ron E, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. *Cancer Epidemiol Biomarkers Prev*. 2009; 18:784–791. [PubMed: 19240234]
26. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin*. 2011; 61:212–236. [PubMed: 21685461]
27. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin*. 2009; 59:225–249. [PubMed: 19474385]
28. Are C, Shaha AR. Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors, and treatment approaches. *Ann Surg Oncol*. 2006; 13:453–464. [PubMed: 16474910]
29. Kebebew E, Greenspan FS, Clark OH, et al. Anaplastic thyroid carcinoma: treatment outcome and prognostic factors. *Cancer*. 2005; 103:1330–1335. [PubMed: 15739211]
30. Gilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma: a population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) program 1973–1991. *Cancer*. 1997; 79:564–573. [PubMed: 9028369]
31. Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*. 2012; 22:1104–1139. [PubMed: 23130564]
32. Moretti F, Farsetti A, Soddu S, et al. p53 re-expression inhibits proliferation and restores differentiation of human thyroid anaplastic carcinoma cells. *Oncogene*. 1997; 14:729–740. [PubMed: 9038381]
33. Maatouk J, Barklow TA, Zakaria W, Al-Abbadi MA. Anaplastic thyroid carcinoma arising in long-standing multinodular goiter following radioactive iodine therapy: report of a case diagnosed by fine needle aspiration. *Acta Cytol*. 2009; 53:581–583. [PubMed: 19798888]
34. Aldinger KA, Samaan NA, Ibanez M, Hill CS Jr. Anaplastic carcinoma of the thyroid: a review of 84 cases of spindle and giant cell carcinoma of the thyroid. *Cancer*. 1978; 41:2267–2275. [PubMed: 657091]
35. Keutgen XM, Sadowski SM, Kebebew E. Management of anaplastic thyroid cancer. *Gland Surg*. 2015; 4:44–51. [PubMed: 25713779]
36. Thompson LD, Wieneke JA, Paal E, et al. A clinicopathologic study of minimally invasive follicular carcinoma of the thyroid gland with a review of the English literature. *Cancer*. 2001; 91:505–524. [PubMed: 11169933]
37. Sherman, SI. Anaplastic carcinoma: Clinical aspects. In: Wartofsky, L.; Van Nostrand, D., editors. *Thyroid Cancer: A Comprehensive Guide to Clinical Management*. 2nd. Totowa, NJ: Humana Press; 2006. p. 629–632.
38. Layfield LJ, Cibas ES, Gharib H, Mandel SJ. Thyroid aspiration cytology: current status. *CA Cancer J Clin*. 2009; 59:99–110. [PubMed: 19278960]
39. Baloch ZW, Cibas ES, Clark DP, et al. The National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference: a summation. *Cytojournal*. 2008; 5:6. [PubMed: 18394201]
40. Eilers SG, LaPolice P, Mukunyadzi P, et al. Thyroid fine-needle aspiration cytology: performance data of neoplastic and malignant cases as identified from 1558 responses in the ASCP Non-GYN Assessment program thyroid fine-needle performance data. *Cancer Cytopathol*. 2014; 122:745–750. [PubMed: 24913410]

41. Yeh MW, Demircan O, Ituarte P, Clark OH. False-negative fine-needle aspiration cytology results delay treatment and adversely affect outcome in patients with thyroid carcinoma. *Thyroid*. 2004; 14:207–215. [PubMed: 15072703]
42. Asa, SL.; Bedard, YC. Fine-needle aspiration cytology and histopathology. In: Clark, OH.; Noguchi, S., editors. *Thyroid Cancer: Diagnosis and Treatment*. St Louis: Quality Medical Publishing; 2000. p. 105-126.
43. Seethala, RR.; Asa, SL.; Carty, SE., et al. Protocol for the examination of specimens from patients with carcinomas of the thyroid gland: based on AJCC/UICC TNM. 7th. College of American Pathologists; 2014. Protocol web posting date: August 2014 Available at: <http://www.cap.org/web/home/resources/cancer-reporting-tools/cancer-protocol-templates>.
44. Takashima S, Morimoto S, Ikezoe J, et al. CT evaluation of anaplastic thyroid carcinoma. *AJR Am J Roentgenol*. 1990; 154:1079–1085. [PubMed: 2108546]
45. Neff RL, Farrar WB, Kloos RT, Burman KD. Anaplastic thyroid cancer. *Endocrinol Metab Clin North Am*. 2008; 37:525–538, xi. [PubMed: 18502341]
46. Wein RO, Weber RS. Anaplastic thyroid carcinoma: palliation or treatment? *Curr Opin Otolaryngol Head Neck Surg*. 2011; 19:113–118. [PubMed: 21252667]
47. Untch BR, Olson JA Jr. Anaplastic thyroid carcinoma, thyroid lymphoma, and metastasis to thyroid. *Surg Oncol Clin N Am*. 2006; 15:661–679, x. [PubMed: 16882503]
48. Shaha AR. Airway management in anaplastic thyroid carcinoma. *Laryngoscope*. 2008; 118:1195–1198. [PubMed: 18438260]
49. Venkatesh YS, Ordonez NG, Schultz PN, et al. Anaplastic carcinoma of the thyroid: a clinicopathologic study of 121 cases. *Cancer*. 1990; 66:321–330. [PubMed: 1695118]
50. Sugitani I, Miyauchi A, Sugino K, et al. Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. *World J Surg*. 2012; 36:1247–1254. [PubMed: 22311136]
51. Akaishi J, Sugino K, Kitagawa W, et al. Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. *Thyroid*. 2011; 21:1183–1189. [PubMed: 21936674]
52. Junor EJ, Paul J, Reed NS. Anaplastic thyroid carcinoma: 91 patients treated by surgery and radiotherapy. *Eur J Surg Oncol*. 1992; 18:83–88. [PubMed: 1582515]
53. McIver B, Hay ID, Giuffrida DF, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. *Surgery*. 2001; 130:1028–1034. [PubMed: 11742333]
54. Burge MR, Zeise TM, Johnsen MW, et al. Risks of complication following thyroidectomy. *J Gen Intern Med*. 1998; 13:24–31. [PubMed: 9462491]
55. Udelsman R, Lakatos E, Ladenson P. Optimal surgery for papillary thyroid carcinoma. *World J Surg*. 1996; 20:88–93. [PubMed: 8588420]
56. Pattou F, Combemale F, Fabre S, et al. Hypocalcemia following thyroid surgery: incidence and prediction of outcome. *World J Surg*. 1998; 22:718–724. [PubMed: 9606288]
57. Hassanain M, Wexler M. Conservative management of well-differentiated thyroid cancer. *Can J Surg*. 2010; 53:109–118. [PubMed: 20334743]
58. Sosa JA, Bowman HM, Tielsch JM, et al. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. *Ann Surg*. 1998; 228:320–330. [PubMed: 9742915]
59. Dumke AK, Pelz T, Vordermark D. Long-term results of radiotherapy in anaplastic thyroid cancer. *Radiat Oncol*. 2014; 9:90. [PubMed: 24685141]
60. Brierley J, Sherman E. The role of external beam radiation and targeted therapy in thyroid cancer. *Semin Radiat Oncol*. 2012; 22:254–262. [PubMed: 22687950]
61. Burnison CM, Lim S. Multimodal approach to anaplastic thyroid cancer. *Oncology (Williston Park)*. 2012; 26:378–384, 390. [PubMed: 22655531]
62. Wang Y, Tsang R, Asa S, et al. Clinical outcome of anaplastic thyroid carcinoma treated with radiotherapy of once- and twice-daily fractionation regimens. *Cancer*. 2006; 107:1786–1792. [PubMed: 16967442]
63. Chiu AC, Delpassand ES, Sherman SI. Prognosis and treatment of brain metastases in thyroid carcinoma. *J Clin Endocrinol Metab*. 1997; 82:3637–3642. [PubMed: 9360519]

64. De Crevoisier R, Baudin E, Bachelot A, et al. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy. *Int J Radiat Oncol Biol Phys.* 2004; 60:1137–1143. [PubMed: 15519785]
65. Kim JH, Leeper RD. Treatment of locally advanced thyroid carcinoma with combination doxorubicin and radiation therapy. *Cancer.* 1987; 60:2372–2375. [PubMed: 3664425]
66. Mohebati A, Dilonzo M, Palmer F, et al. Anaplastic thyroid carcinoma: a 25-year single-institution experience. *Ann Surg Oncol.* 2014; 21:1665–1670. [PubMed: 24554064]
67. Derbel O, Limem S, Segura-Ferlay C, et al. Results of combined treatment of anaplastic thyroid carcinoma (ATC). *BMC Cancer.* 2011; 11:469. [PubMed: 22044775]
68. Wallin G, Lundell G, Tennvall J. Anaplastic giant cell thyroid carcinoma. *Scand J Surg.* 2004; 93:272–277. [PubMed: 15658667]
69. Smallridge RC. Approach to the patient with anaplastic thyroid carcinoma. *J Clin Endocrinol Metab.* 2012; 97:2566–2572. [PubMed: 22869844]
70. Bhatia A, Rao A, Ang KK, et al. Anaplastic thyroid cancer: Clinical outcomes with conformal radiotherapy. *Head Neck.* 2010; 32:829–836. [PubMed: 19885924]
71. Sun XS, Sun SR, Guevara N, et al. Chemoradiation in anaplastic thyroid carcinomas. *Crit Rev Oncol Hematol.* 2013; 86:290–301. [PubMed: 23218594]
72. Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). *Cancer Radiother.* 2011; 15:555–559. [PubMed: 21802333]
73. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT): Contents. *J ICRU.* 2010; 10 NP.
74. Sosa JA, Balkissoon J, Lu SP, et al. Thyroidectomy followed by fosbretabulin (CA4P) combination regimen appears to suggest improvement in patient survival in anaplastic thyroid cancer. *Surgery.* 2012; 152:1078–1087. [PubMed: 23158178]
75. Swaak-Kragten AT, de Wilt JH, Schmitz PI, et al. Multimodality treatment for anaplastic thyroid carcinoma—treatment outcome in 75 patients. *Radiother Oncol.* 2009; 92:100–104. [PubMed: 19328572]
76. Lowe NM, Loughran S, Slevin NJ, Yap BK. Anaplastic thyroid cancer: the addition of systemic chemotherapy to radiotherapy led to an observed improvement in survival: a single centre experience and review of the literature. *Scientific World J.* 2014; 2014:674583.
77. Higashiyama T, Ito Y, Hirokawa M, et al. Induction chemotherapy with weekly paclitaxel administration for anaplastic thyroid carcinoma. *Thyroid.* 2010; 20:7–14. [PubMed: 20025538]
78. Ain KB. Anaplastic thyroid carcinoma: behavior, biology, and therapeutic approaches. *Thyroid.* 1998; 8:715–726. [PubMed: 9737368]
79. Ain KB, Egorin MJ, DeSimone PA. Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group. *Thyroid.* 2000; 10:587–594. [PubMed: 10958311]
80. Bible KC, Suman VJ, Menefee ME, et al. A multiinstitutional phase 2 trial of pazopanib monotherapy in advanced anaplastic thyroid cancer. *J Clin Endocrinol Metab.* 2012; 97:3179–3184. [PubMed: 22774206]
81. Ha HT, Lee JS, Urba S, et al. A phase II study of imatinib in patients with advanced anaplastic thyroid cancer. *Thyroid.* 2010; 20:975–980. [PubMed: 20718683]
82. Savvides P, Nagaiah G, Lavertu P, et al. Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid. *Thyroid.* 2013; 23:600–604. [PubMed: 23113752]
83. Keefe SM, Troxel AB, Rhee S, et al. Phase II trial of sorafenib in patients with advanced thyroid cancer [abstract]. *J Clin Oncol.* 2011; 29(Suppl 15) Abstract 5562.
84. Brose MS, Nutting CM, Sherman SI, et al. Rationale and design of decision: a double-blind, randomized, placebo-controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory, differentiated thyroid cancer. *BMC Cancer.* 2011; 11:349. [PubMed: 21834960]
85. Antonelli A, Fallahi P, Ulisse S, et al. New targeted therapies for anaplastic thyroid cancer. *Anticancer Agents Med Chem.* 2012; 12:87–93. [PubMed: 22043992]

86. Perri F, Lorenzo GD, Scarpati GD, Buonerba C. Anaplastic thyroid carcinoma: a comprehensive review of current and future therapeutic options. *World J Clin Oncol*. 2011; 2:150–157. [PubMed: 21611089]
87. Deshpande HA, Gettinger SN, Sosa JA. Novel chemotherapy options for advanced thyroid tumors: small molecules offer great hope. *Curr Opin Oncol*. 2008; 20:19–24. [PubMed: 18043252]
88. Mooney CJ, Nagaiah G, Fu P, et al. A phase II trial of fosbretabulin in advanced anaplastic thyroid carcinoma and correlation of baseline serum-soluble intracellular adhesion molecule-1 with outcome. *Thyroid*. 2009; 19:233–240. [PubMed: 19265494]
89. Smallridge RC, Marlow LA, Copland JA. Anaplastic thyroid cancer: molecular pathogenesis and emerging therapies. *Endocr Relat Cancer*. 2009; 16:17–44. [PubMed: 18987168]
90. Sosa JA, Elisei R, Jarzab B, et al. Randomized safety and efficacy study of fosbretabulin with paclitaxel/carboplatin against anaplastic thyroid carcinoma. *Thyroid*. 2014; 24:232–240. [PubMed: 23721245]
91. Foote RL, Molina JR, Kasperbauer JL, et al. Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy. *Thyroid*. 2011; 21:25–30. [PubMed: 21162687]
92. Nagaiah G, Hossain A, Mooney CJ, et al. Anaplastic thyroid cancer: a review of epidemiology, pathogenesis, and treatment. *J Oncol*. 2011; 2011:542358. [PubMed: 21772843]
93. Siironen P, Hagstrom J, Maenpaa HO, et al. Anaplastic and poorly differentiated thyroid carcinoma: therapeutic strategies and treatment outcome of 52 consecutive patients. *Oncology*. 2010; 79:400–408. [PubMed: 21455012]
94. Brignardello E, Gallo M, Baldi I, et al. Anaplastic thyroid carcinoma: clinical outcome of 30 consecutive patients referred to a single institution in the past 5 years. *Eur J Endocrinol*. 2007; 156:425–430. [PubMed: 17389456]
95. Yau T, Lo CY, Epstein RJ, et al. Treatment outcomes in anaplastic thyroid carcinoma: survival improvement in young patients with localized disease treated by combination of surgery and radiotherapy. *Ann Surg Oncol*. 2008; 15:2500–2505. [PubMed: 18581185]
96. Heron DE, Karimpour S, Grigsby PW. Anaplastic thyroid carcinoma: comparison of conventional radiotherapy and hyperfractionation chemoradiotherapy in two groups. *Am J Clin Oncol*. 2002; 25:442–446. [PubMed: 12393980]
97. Chou A, Fraser S, Toon CW, et al. A detailed clinicopathologic study of ALK-translocated papillary thyroid carcinoma. *Am J Surg Pathol*. 2015; 39:652–659. [PubMed: 25501013]
98. Park G, Kim TH, Lee HO, et al. Standard immunohistochemistry efficiently screens for anaplastic lymphoma kinase rearrangements in differentiated thyroid cancer. *Endocr Relat Cancer*. 2015; 22:55–63. [PubMed: 25527510]
99. Perot G, Soubeyran I, Ribeiro A, et al. Identification of a recurrent STRN/ALK fusion in thyroid carcinomas. *PLoS One*. 2014; 9:e87170. [PubMed: 24475247]
100. Kelly LM, Barila G, Liu P, et al. Identification of the transforming STRN-ALK fusion as a potential therapeutic target in the aggressive forms of thyroid cancer. *Proc Natl Acad Sci U S A*. 2014; 111:4233–4238. [PubMed: 24613930]
101. Kunstman JW, Juhlin CC, Goh G, et al. Characterization of the mutational landscape of anaplastic thyroid cancer via whole-exome sequencing. *Hum Mol Genet*. 2015; 24:2318–2329. [PubMed: 25576899]
102. Rosove MH, Peddi PF, Glaspy JA. BRAF V600E inhibition in anaplastic thyroid cancer. *N Engl J Med*. 2013; 368:684–685. [PubMed: 23406047]
103. Takano T, Ito Y, Hirokawa M, et al. BRAF V600E mutation in anaplastic thyroid carcinomas and their accompanying differentiated carcinomas. *Br J Cancer*. 2007; 96:1549–1553. [PubMed: 17453004]