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2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer

American Thyroid Association Anaplastic Thyroid Cancer Guidelines Task Force

Keith C. Bible,[1] Electron Kebebew,[2] James Brierley,[3] Juan P. Brito,[4] Maria E. Cabanillas,[5] Thomas J. Clark Jr.,[6] Antonio Di Cristofano,[7] Robert Foote,[8] Thomas Giordano,[9] Jan Kasperbauer,[10] Kate Newbold,[11] Yuri E. Nikiforov,[12] Gregory Randolph,[13] M. Sara Rosenthal,[14] Anna M. Sawka,[15] Manisha Shah,[16] Ashok Shaha,[17] Robert Smallridge,[18] and Carol K. Wong-Clark*

Background: Anaplastic thyroid cancer (ATC) is a rare but highly lethal form of thyroid cancer. Since the guidelines for the management of ATC by the American Thyroid Association were first published in 2012, significant clinical and scientific advances have occurred in the field. The aim of these guidelines is to inform clinicians, patients, and researchers on published evidence relating to the diagnosis and management of ATC.
Methods: The specific clinical questions and topics addressed in these guidelines were based on prior versions of the guidelines, stakeholder input, and input of the Task Force members (authors of the guideline). Relevant literature was reviewed, including serial PubMed searches supplemented with additional articles. The American College of Physicians Guideline Grading System was used for critical appraisal of evidence and grading strength of recommendations.
Results: The guidelines include the diagnosis, initial evaluation, establishment of treatment goals, approaches to locoregional disease (surgery, radiotherapy, targeted/systemic therapy, supportive care during active therapy), approaches to advanced/metastatic disease, palliative care options, surveillance and long-term monitoring, and ethical issues, including end of life. The guidelines include 31 recommendations and 16 good practice statements.
Conclusions: We have developed evidence-based recommendations to inform clinical decision-making in the management of ATC. While all care must be individualized, such recommendations provide, in our opinion, optimal care paradigms for patients with ATC.

Keywords: BRAF, chemoradiation, chemotherapy, chemotherapy, ethics, IMRT (intensity-modulated radiotherapy), multimodality therapy, palliative care, radiation therapy, SBRT (stereotactic body radiation therapy), squamous cell cancer of the thyroid, surgery, targeted therapy, undifferentiated thyroid cancer

[1]Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA.
[2]Stanford University, School of Medicine, Stanford, California, USA.
[3]Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada.
[4]Division of Diabetes, Endocrinology, Metabolism, and Nutrition, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA.
[5]Department of Endocrine Neoplasia & Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.
[6]Thermo Fisher Scientific, Carlsbad, California, USA.
[7]Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, New York, USA.
[8]Department of Radiation Oncology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA.
[9]Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan, USA.
[10]Department of Otolaryngology, Head and Neck Surgery, Mayo Clinic, Rochester, Minnesota, USA.
[11]The Royal Marsden NHS Foundation Trust, Fulham Road, London, United Kingdom.
[12]Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[13]Division of Thyroid and Parathyroid Endocrine Surgery, Massachusetts Eye and Ear, Boston, Massachusetts, USA.
[14]Program for Bioethics and Markey Cancer Center Oncology Ethics Program, Departments Internal Medicine, Pediatrics and Behavioral Science, University of Kentucky, Lexington, Kentucky, USA.
[15]Division of Endocrinology, Department of Medicine, University Health Network and University of Toronto, Toronto, Canada.
[16]The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA.
[17]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York, USA.
[18]Mayo Clinic, Jacksonville, Florida, USA.
*Unaffiliated with an institution.
Authors listed in alphabetical order including the cochairs (K.C.B. and E.K.).

INTRODUCTION

American Thyroid Association (ATA) guidelines for management of patients with anaplastic thyroid cancer (ATC) by Smallridge *et al.* (1) were published in 2012, being the first major original work on this subject. In view of the advances in the field of thyroid and other cancers and emerging concepts since that publication, we sought to craft comprehensive new guidelines for ATC based on sound methodology, evidence-based concepts, expert opinion, ethical principles, and sensitivity to the key importance of the wishes and concerns of patients, guided by their families and close loved ones, as they relate to the medical and professional care they receive. The ATA guidelines Task Force (the authors of the guideline) for ATC was the impetus for the development of these guidelines as they had a major influence on the authorship and provided administrative support. We were granted independence, however, in the creation of this work by the ATA. Moreover, as authors of an original work, we have assumed independence and accountability for its content. The organization of these guidelines is summarized in the Table of Contents, directing readers to content-specific text, recommendations, and good practice statements developed from the literature, reviewed and synthesized considering also expert opinion and input from patient advocates. Table 1 provides the key steps in the management of ATC, including guidance in attaining accurate diagnosis, evaluation, and staging, followed promptly by establishing goals of care desired by the patient; ATC management strategies are thereafter indicated in Figure 1 (stage IVA and IVB) and in Figure 2 (stage IVC). These flow diagrams are introduced early as a reference, with supporting evidence and nuances appearing in the pertinent corresponding text sections, and a summary of all the recommendations, and good practice statements.

Thyroid cancer incidence has increased in the United States (2). ATC is derived from follicular thyroid cells (''thyrocytes'') and is associated with the highest mortality risk of any thyroid-arising tumor, but accounts for only a small percentage of thyroid cancer cases overall (2). In the United States, ATC is responsible for 1.7% of all thyroid cancers, while geographically, ATC accounts for 1.3% to 9.8% (median = 3.6%) of all thyroid cancers (3). In several countries, the incidence of ATC has decreased (4,5). The increasing diagnosis of papillary thyroid cancer (PTC) has increased the denominator of all detected thyroid cancers especially in developed countries, having the potential to decrease the percentage of all thyroid cancers accounted for by ATC.

ATC patients have a historical median survival of about 5 months and a 1-year overall survival of 20% (3). All patients with ATC are classified by the American Joint Committee on Cancer (AJCC) TNM system as stage IV (A, B, or C) because of this universally poor historical prognosis; accordingly, counseling, defining goals of care, and establishing a management plan must be accomplished quickly. While all thyroid cancer patients require a multidisciplinary team of specialists, the sudden onset and aggressive course of ATC necessitate the immediate and coordinated involvement of surgeons, radiation and medical oncologists/oncologic endocrinologists, and palliative care teams.

METHODS

General aims of the guidelines, target audiences, and stakeholder representation

The overarching goal of these guidelines is to improve patient care with respect to the diagnosis and management of ATC predicated upon an ethical and patient-centered approach, evidence-informed and encompassing structured literature reviews. We strived to achieve this goal by applying the highest standards of evidence and ethical practice achievable, informed by expert clinician and patient stakeholder panelists (i.e., the authors of the guideline) with the

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Table 1. Key Steps in the Management of Anaplastic Thyroid Cancer

1. Rapidly and definitively establish the diagnosis

Because ATC is a highly dedifferentiated cancer that retains few characteristics of noncancerous thyroid cells, attaining a definitive diagnosis can be challenging, yet critical. Time is also of the essence because of the very rapid growth rate of ATC and due to the importance of early intervention in minimizing catastrophic airway compromise.

- Differential considerations/mimics can include primary thyroid lymphoma, SCC of the head and neck, and metastatic cancer (especially from lung).
- Early assessment of tumor mutations is key in expanding therapeutic options.

2. Attain multidisciplinary team engagement and coordination

Coordinate early multidisciplinary involvement of surgeons, radiation and medical oncologists, endocrinologists, and palliative care teams to arrive at options for best care as outlined below.

3. Determine extent of disease

- Staging with imaging is required to classify as stage IVA, IVB, IVC; this is best done with FDG PET/CT and/or alternatively with dedicated body CT or MRI.
- Extent of local invasion must also be evaluated in parallel to assist in surgical decision-making, and requires laryngoscopy.

4. Undertake patient counseling to establish individualized patient goals of care

Counseling must be provided by a team/individuals skilled in the surgical, medical, and palliative management of complex thyroid malignancies in which trade-offs counterbalancing risks and benefits with goals of care are completely discussed. This counseling should best involve not only the patient but also involve supportive individuals/family members.

5. Evaluate Surgical Options

- The primary goals in stages IVA and IVB ATC patients within an aggressive approach to their care are complete resection and prompt transition to adjuvant definitive-intention therapy, as long-term survival may be attainable. Thus, surgical procedures should not generate a wound or result in complications that would prevent chemotherapy and radiation onset due to the risk of wound breakdown given the lack of data supporting an association between increased extent of surgery and improved survival outcomes.
- In IVC ATC, the limited benefit resulting from surgery must be carefully tempered in consideration of other available palliative approaches, including radiation and systemic therapy.

6. Surgical decision-making

Rapidly assess resectability determining tumor invasion of the larynx, trachea, esophagus, and status of the major vessels of the neck. Consider the need for tracheotomy, extent of thyroidectomy, neck dissection, and the need to avoid laryngectomy, esophageal resection, and major vessel reconstruction.

Balancing morbidity from surgery with expected benefits within the context of patient-anticipated prognosis and individualized goals of care is paramount.

Considerations:

- Performance score/status.
- Presence of distant metastasis.
- Extent of local invasion of trachea and esophagus.
- Need for urgent tracheostomy, understanding that placement of a tracheostomy results in immediate improvement in upper airway obstruction but requires significant education for care and understanding that tumor location and growth may make management of the tracheotomy complex.
- Patient goals of care and willingness to accept anticipated morbidity of planned surgery.

7. Nonsurgical management decision-making

Other than surgery, options may include postoperative or primary chemoradiation versus palliative radiotherapy, systemic therapy, or best supportive care considered within the context of:

- Patient goals of care and willingness to accept anticipated toxicities of presented options.
- Patient performance status and comorbidities and their impacts on feasibility of planned care.
- Trade-offs from one approach to care versus alternatives.

8. Keep hospice/end-of-life care discussions in the foreground

- Given the historically dire prognosis of ATC, especially if stage IVC, hospice should always be presented among care options.
- Truth telling and realistic presentation of anticipated prognosis are critical in allowing sound patient decisions within their individual goals of care.
- For some patients, hospice may be preferrable—even from the outset—in comparison with other alternative care options.

ATC, anaplastic thyroid cancer; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; SCC, squamous cell carcinoma.

resulting draft document revised in accord with input from the ATA Board of Directors, Committees, and Membership. The target audiences of these guidelines are physicians caring for patients with ATC, health policy makers, and ATC patients and their families/partners. Contributors to these guidelines include physicians who specialize in oncologic endocrinology, endocrine surgery, head/neck surgery, nuclear medicine, radiation oncology, medical oncology, pathology, the basic science of thyroid cancers, bioethics, guideline methodology, and patient advocate stakeholders.

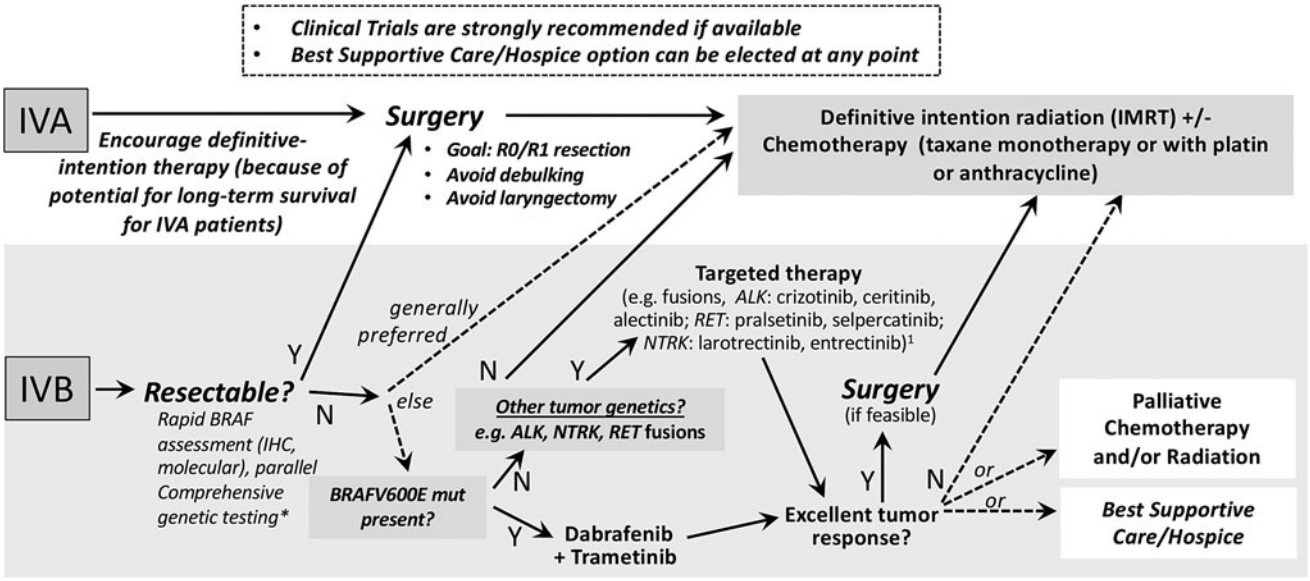

FIG. 1. Initial treatment of stages IVA and IVB ATC. [1]Additonal agents exist and are in development, listing not meant to be comprehensive; clinical trials preferred if available; see text. *Cytotoxic chemotherapy may be started as a ''bridge'' while awaiting genomic information or while awaiting targeted therapy (e.g., dabrafenib and trametinib). Dashed arrows depict circumstances where competing therapeutic options may be of consideration. ATC, anaplastic thyroid cancer.

The role of patient advocate stakeholders (T.J.C. and C.K.W.-C.) was to provide input on the clinical content and recommendations from a patient perspective, participating actively in the consensus process along with the other panel members, with specific involvement in developing ethics sections of the guidelines along with an expert bioethicist (M.S.R.). The medical opinions expressed in these guidelines reflect author consensus, with consideration of extensive expert experience and patient stakeholder input. This publication was approved by the ATA Board of Directors after a period of comment from its members.

The formulation of the Task Force (the authors of the guideline) membership roster was directed by the ATA Board of Directors to be constituted by about 50% prior, and the remainder new, members; the number of members was also considerably expanded. Attention to gender equity and diversity of specialty, race/ethnicity, and regionality was requested by the Board within the context of suitable ATC ''experts,'' with the Board also helping to shape Task Force membership. An initial slate of Task Force candidates was accordingly proposed to the ATA Board by the Task Force cochairs (E.K. and K.C.B.), and

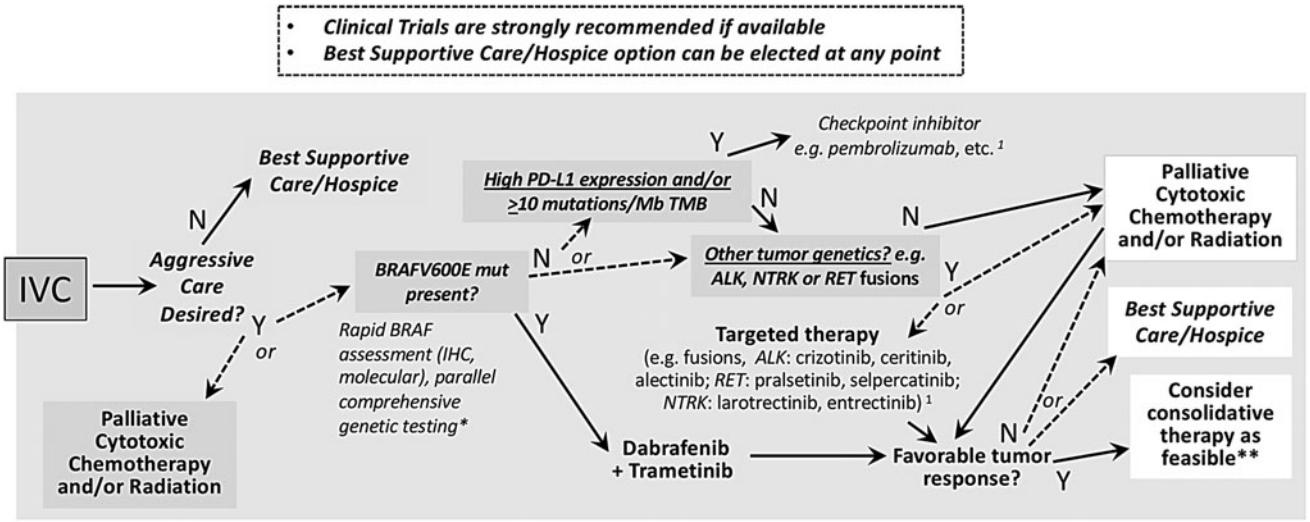

FIG. 2. Initial treatment of stage IVC ATC. [1]Additonal agents exist and are in development, listings not meant to be comprehensive; clinical trials preferred if available; see text. *Cytotoxic chemotherapy may be started as a ''bridge'' while awaiting genomic information or while awaiting targeted therapy (e.g., dabrafenib and trametinib). **Consolidate Rx refers to focal therapy intended to control residual macrometastatic disease among those electing aggressive therapy. Dashed arrows depict circumstances where competing therapeutic options may be of consideration. TMB, tumor mutational burden.

iterated and modified based upon Board directives. Two methodologists with experience in clinical practice guidelines (J.P.B. and A.M.S.) were designated to assist.

Management of potential competing interests. In efforts to minimize to the very greatest extent possible any potential influences of conflicts of interest on the opinions herein expressed, no personal financial conflicts of interest were permitted of the Task Force chairs and of all Task Force members from the outset. At inception, competing interests of the authors were reviewed by the Guideline Chairs as well as the ATA Guidelines and Statements Committee. Authors were also approved by the ATA Guidelines and Statements Committee. Potential competing interests acquired during the development of the guidelines were revisited periodically and again upon completion of the article, striving to assure continued compliance. All later acquired identified potential financial competing interests are declared in the article (Supplementary Data S1), which was reviewed by the ATA Guidelines and Statements Committee and the Board of Directors. As a technical note, conflicts of authors' institutions of employment were deemed nonexclusionary. No external funding from industry was received by the ATA or by authors for guideline development.

Scope of the guideline and search for relevant literature. In preparing these guidelines, we developed a consensus comprehensive list of questions covering the areas of ATC evaluation and diagnosis, ethics of ATC care, and establishing patient goals of care, approaches to locoregional disease as well as to advanced/metastatic disease, palliative care/hospice, and surveillance and long-term monitoring. To maximize our deliberations, we developed consensus draft recommendations and solicited input from the ATA Board of Directors, ATA Guidelines and Statements Committee, and members of the ATA by posting them on the members-only section of the ATA website www.thyroid.org. Input of all authors, including expert clinicians and patient advocates, ATC researchers, and methodologists—as well as from the ATA Board of Directors and ATA members—was vetted and discussed and a set of questions were drafted by the cochairs (E.K. and K.C.B.). The list of questions was circulated electronically to all authors, revised as needed, and all authors agreed on the list of seminal questions. For any questions for which systematic reviews were planned, methodologists (J.P.B. and A.M.S.) provided input on structuring of questions using the PICO format (''patient, intervention, comparator, outcome''), or other formats as applicable.

To identify relevant literature that might assist in preparing this document as comprehensively as possible, a medical reference librarian consulted with a panel members and designed and executed a search of several databases, including the following: Ovid Medline In-Process and Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. Databases were searched from inception to the date of the search (February 15, 2017, initially and updated in May 11, 2020), without restriction of publication date or language (search strategy in Supplementary Data S2). The search was supplemented by handsearching the resulting reference lists from eligible included studies, and based upon additional references forwarded by Task Force members. A total of 3064 articles were identified, of which 205 studies were deemed as the most relevant literature, but none of these articles included a randomized clinical trial. Expert panelists also provided additional studies for consideration, from respective personal records and from publications emerging during guideline development.

Review and grading of the evidence. Systematic reviews on the topics of surgery, external beam radiation therapy, and systemic therapies for management of ATC were commissioned by the ATA from the Mayo Evidence-Based Practice group (J.P.B.). In addition, expert panelists reviewed relevant literature from the search and from personal records. The authors of respective sections drafted recommendations and explained the rationale for the recommendations in accompanying supporting text, enhanced by input from the entire panel.

The quality and strength of the authors' recommendations based on the body of evidence were reported using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Group, GRADE workgroup system; a detailed description of the grading scheme has been published elsewhere (6). In this system, recommendations are classified as strong or conditional. Strong recommendations (''we recommend'') are those in which the panel is confident that the anticipated desirable effects of following a recommendation clearly outweigh undesirable effects and that the recommendation should be implemented into practice. Conditional recommendations (''we suggest'') are those in which the panel concludes that the anticipated desirable effects of following these recommendations probably outweigh undesirable effects, but is not confident about this conclusion and there may be reasonable alternative options for consideration in clinical practice. Importantly, however, these are guidelines, indicating that nuances of individual patients must shape implementation.

One factor that influences the strength of recommendations is the quality of the body of supportive evidence. In the GRADE system, there are four categories of quality of evidence: high quality, moderate quality, low quality, and very low quality (6,7). High-quality evidence on therapeutic interventions requires one or more studies at low risk of bias (e.g., randomized-controlled trials [RCTs] without important limitations), that have consistent results and precise estimates. Very low-quality evidence derives from studies at high risk of bias (e.g., observational), or inconsistent and imprecise results across studies. Along with the quality of the body of evidence, the authors considered a balance between benefits, risks, and burdens of interventions as an important factor in deciding the strength of the recommendation. The strength of the recommendation is correlated with the quality of evidence. For instance, strong recommendations are usually supported by moderate- or high-quality evidence. Nevertheless, we were frequently able to make strong recommendations based on low-quality evidence. The GRADE system offers five distinct situations where these types of recommendations are appropriate. The adherence to these paradigmatic situations by these guidelines is shown in Supplementary Data S3. When the authors deemed that there was a large body of indirect evidence to support the benefit of a recommendation, and in which the evaluation of

alternatives in clinical trials would be unproductive and unnecessary, the authors provided good practice statements (7,8). These good practice recommendations are developed based on the authors' expert opinion, without a formal literature search, that there is sufficient indirect evidence to provide high certainty that the recommendation will result in more desirable than undesirable effects. As such, good practice recommendations are actionable statements that the authors feel are necessary, but are not appropriate for rating the quality of evidence. Good practice recommendations are different than strong recommendations with low-quality evidence, as the latter are recommendations that panelists judge to be applicable to the majority of patients despite warranting low or very low certainty. To identify good practice statements, the authors applied the following criteria: (i) the message was necessary, (ii) after consideration of all relevant outcomes and potential downstream consequences, implementing the good practice statement will result in large net positive consequences, (iii) collecting and summarizing the evidence was poor use of a guideline panel's limited time and energy, and (iv) there was a well-documented, clear, and explicit rationale connecting the indirect evidence (9). An experienced GRADE methodologist (J.P.B.) oversaw the grading of all recommendations and the quality of evidence.

Consensus procedure. Recommendations, good practice statements, and supporting text were electronically distributed to all authors, and thereafter discussed as a group on monthly or bimonthly conference calls as well as during several in-person meetings. During or shortly after conference calls/meetings, a revised document was circulated to all authors for additional input, comment, and suggestions for further revisions. Any additional necessary revisions were incorporated and discussed, and, if no further changes were requested, a consensus of the group was assumed. Many sections of this document were reviewed iteratively during calls two to three times, and any author could at any point ask to revisit any section. Upon completion of all sections of the guidelines, a list of all of the recommendations and good practice statements, as well as the entire guideline document, was circulated to all authors, with further opportunity for revision or rewording, as needed. Once no further revisions were requested or deemed necessary by the guideline co-chairs, consensus on the entire document was achieved. The experienced GRADE methodologist (J.P.B.) checked all recommendations and good practice statements to ensure they were consistent with the GRADE approach. Uniform (100%) consensus was obtained among the group on the wording and strength of all recommendations, however, given the technicalities involved in critically appraising evidence and operationalizing the GRADE system, the final decisions on the quality of evidence or the appropriate application of the good practice statement category were deferred to the GRADE methodologist (J.P.B.).

Patient representative advisor involvement in the guideline development process. Patient representative advisors (T.J.C. and C.K.W.-C.) were fully involved in the guideline development process, including contributing input on questions, text, and recommendations and formally voting on recommendations. However, patient representative advisors were able to defer to other expert authors on specific technical scientific aspects of any recommendation that was beyond their comfort level. An important role of patient representative advisors was providing input on Values Statements. In the process of discussing recommendations, if the patient representative advisors believed there were important considerations regarding values that should be communicated (beyond that described in the recommendation and the text describing the evidence basis for the recommendation), Values Statements were proposed. Values Statements were intended to complement the presentation of accompanying recommendations and descriptions of the evidence and were not graded themselves. All panel members had the opportunity to contribute to the wording of Values Statements, and consensus was reached among the group (in a similar process to that of recommendations) on the final Values Statements.

Staging system used in the guidelines. The AJCC Cancer Staging Manual (8th Edition) Residual Tumor (R) Classification was used to assess surgical effects on outcomes across the studies reviewed.

Terms and definitions

TNM staging. All ATCs are stage 4 (AJCC 8th Edition). Stage IVA lesions **(T1-T3a, N0, M0)** are still localized within the thyroid gland and have not definitely spread to lymph nodes (N0) or to distant sites (M0). In Stage IVB ATC, the primary tumor has grown outside/through the thyroid capsule **(T3b, T4)** and/or is involving locoregional lymph nodes **(≥N1)**, but it has not spread to distant sites (M0). In Stage IVC **(Any T, Any N, M1)**, the tumor has spread to distant site(s).

Extent of resection. R0 designates complete resection with negative microscopic margins, R1 designates complete resection of all grossly visible tumors but with involved surgical resection margins (microscopically involved resection margins), and R2 designates resection in which gross cancer was left in place (macroscopically involved resection margins).

Adjuvant therapy and neoadjuvant therapy. Radiation, systemic therapy, or the combination given *after* surgery with curative intention is referred to as *adjuvant therapy*; and when given *before* surgery, *neoadjuvant therapy*.

Oligometastatic disease. Some cancers are associated with only a small number of macrometastases (termed oligometastatic cancer). In general, most studies of oligometastatic cancer have included patients with one to five distinct metastases. With a limited number of metastases, it becomes theoretically possible to treat detectable tumors with curative intention using surgery and/or locally ablative therapies, realizing that occult metastatic disease may nevertheless exist.

Definition of therapeutic terms

Standard radiation prescription. The unit dose of radiation is the Gray, abbreviated to Gy. Some prescriptions are given in centiGray or cGy (1 Gy = 100 cGy). A radiation prescription describes the total dose of radiation to be

delivered, the number of fractions (number of daily treatments), the dose of each daily treatment, and the overall length of the treatment course. The usual daily fraction size is 1.8 or 2 Gy. A standard prescription in the setting of neck irradiation in ATC would be, for instance: 66 Gy over 61/2 weeks, given as 33 daily fractions of 2 Gy per day, 5 days a week for definitive treatment, but this is adjusted depending on the clinical setting as discussed later in the document.

Altered fractionation. Altered fractionation implies a larger number of fractions (*hyperfractionated*), or a smaller number of fractions (*hypofractionated*), or a shorter overall treatment time (*accelerated*). By using hyperfractionated treatment with more than one daily fraction given, it enables the prescription to be given over a shorter treatment time (*accelerated hyperfractionated radiotherapy*). In a rapidly growing tumor such as ATC, accelerating the treatment has the potential to minimize tumor growth that may occur over the radiotherapy treatment course. By giving multiple small fractions, the toxicity may also be reduced. An example of an accelerated hyperfractionated prescription would be: 60 Gy over 4 weeks given as 40 twice-daily fractions of 1.5 Gy, 5 days a week.

Radiotherapy dose. There are many different potential radiation prescription doses; for the purpose of this report they have been grouped as definitive-intention or palliative-intention.

Definitive-intention radiotherapy is high-dose radiation given with or without concurrent chemotherapy with the intent of maximizing the chance of long-term local control. Examples range from 50 Gy in 20 fractions, 2.5 Gy per fraction over 4 weeks at the low end, to 70 Gy in 35 fractions, 2 Gy per fraction over 7 weeks at the high end. *Palliative-intention Radiotherapy* is lower dose radiotherapy given over a shorter time period with the primary aim of improving local symptoms and achieving initial disease control while minimizing hospital/clinic visits. This may be directed to the primary tumor or to metastases. Typical examples could be 20 Gy in 5 fractions, 4 Gy per fraction over 1 week and 30 Gy in 10 fractions, 3 Gy per fraction over 2 weeks.

Conformal radiation. In conformal radiotherapy, the volume treated is tailored to and ''conforms'' to the shape of the tumor. The toxicity of radiation to the surrounding normal tissues is thereby reduced.

Intensity-modulated radiotherapy. By modulating the intensity of the radiation fields as well as shape of the fields, the radiation can be made more conformal (tailored), thereby reducing toxicity to the adjacent normal structures and potentially enabling a higher radiation dose to be given to the tumor areas.

Radiosurgery and stereotactic body radiotherapy (stereotactic radiosurgeries). Radiosurgery and stereotactic body radiotherapy (SBRT) are highly conformal/focused radiation that allows a single large fraction of radiation to be given. *Stereotactic radiosurgery* usually refers to radiosurgery to the brain (e.g., Gamma Knife®). *Stereotactic body radiosurgery* usually refers to radiosurgery to parts of the body other than to the brain (e.g., CyberKnife®, X-Knife®) and SBRT usually refers to highly conformal radiotherapy given in 3 to 10 fractions.

Concurrent chemoradiation. Some chemotherapeutic agents when given concurrently with radiation can potentiate the antitumor effects of radiation and thereby act as ''radiation sensitizers.'' This therapeutic advantage may be at the cost of increased toxicity, and in some regimens may require a reduction of the radiation dose. The principal aim of chemotherapy given concurrently with radiation is to increase the chance of local control of the tumor, and also with the intentions to affect more rapid tumor cytoreduction (assuming that the systemic therapy involved may be active in ATC) and, aspirationally, in parallel to control systemic micrometastatic disease if present.

Chemotherapy. Chemotherapy, for the purposes of these guidelines, denotes cytotoxic agents that target basic cellular components and processes that are commonly altered in cancers. Examples include agents targeted toward cell division machinery (e.g., antimicrotubule inhibitors, paclitaxel and docetaxel), DNA repair pathways (e.g., topoisomerase inhibitors and poly-adenosine diphosphate ribose polymerase inhibitors), or DNA structure (e.g., platins).

Genomic tumor assessment. Genomic tumor assessment denotes rigorous analysis of tumor DNA for the purposes of defining altered genes of potential or actual relevance to cancer growth and/or survival. Various platforms are available for this assessment, each with their own strengths and weakness as discussed in the Diagnosis of ATC section.

Genetically informed targeted therapy. ''Targeted therapy'' denotes systemic treatment intended to be specifically directed toward an actually or presumed altered molecule or pathway relevant to cancer growth or survival. In general, an agent or agents are selected to target a specifically identified ''driver'' mutation.

Bridging therapy. ''Bridging therapy'' is used to denote interim approaches to the treatment of general applicability in ATC intended to contain disease while information is being attained that may better inform subsequent individualization of systemic therapy such as via targeted approaches.

Response evaluation criteria in solid tumor response. Response Evaluation Criteria in Solid Tumors (RECIST) are used to assess objectively the effects of systemic therapy on tumor dimensions/size (10). After determining the baseline diameters of index lesions (must be >1 cm for visceral lesions, >1.5 cm short axis for nodal metastases; only two measured lesions per disease site/organ allowed, generally the largest) with cross-sectional imaging (computed tomography [CT], magnetic resonance imaging [MRI]), follow-up measurements of the same lesions are determined at defined intervals and compared with baseline as a percentage of the sum of all index lesions. A complete response (CR) means disappearance of all lesions; a partial response (PR) is at least a 30% reduction in the lesional sum, confirmed at least once at a ≥4-week interval once observed; progressive disease (PD) is a 20% or greater increase in lesional sum from baseline or nadir; and stable disease (SD) refers to tumors not reaching criteria for either PR or PD. Of note is that these criteria require the absence of new locations of disease and the absence of growth of any nontarget lesions.

DISCLAIMERS AND GENERAL GUIDANCE

In line with, and echoing the official policies of the ATA, our recommendations and good practice statements cannot be ''all things to all people'' from the methodological standpoint. It is not possible to use and reconcile all proper methodological approaches due to inherent and irreconcilable differences in various utilized and acceptable competing guideline methodologies. These guidelines do not establish a standard of care, replace sound clinical judgment, or capture all nuances likely to be present in any particular patient, and specific outcomes are not guaranteed. We recommend that treatment decisions be based on independent judgments of health care providers carefully considering each *patient's* individual circumstances and the goals of care (established at the outset and revisited frequently), as well as feasibility considerations (including regional access to specific health care resources). Our guideline recommendations are not intended to take the place of best physician judgment in diagnosing and treating particular patients, or to supplant patient directives. We expect that those who use these guidelines will consider them as an aid in, not a replacement for, sound and thoughtful clinical decision-making, with full consideration of each patient's individuality in terms of history and physical traits, comorbidities, functional status, and goals of care.

REVIEW AND RECOMMENDATIONS

ATC risk factors

ATC is an aggressive tumor with a poor prognosis (3,11–14); median survival is 5–6 months and the 1-year survival is ~20% (3,13). Patients with ATC rarely survive more than 2 years after diagnosis. Reports suggest that between 3% and 10% survive more than 10 years. For example, Lam *et al.* reported a 10-year survival rate of ATC in China of ~3% (15), while another case series reported that ~10% of patients with ATC remained free of disease at 10, 12, and 13 years after treatment (16). Given its poor prognosis, identifying any potential risk factors for ATC has the potential to inform strategies to prevent this malignancy or allow early detection.

Case/control studies are the most effective approach used to identify risk factors for different conditions, but are scarce in ATC. In one case/control study of 126 patients with ATC and 252 controls individually matched by sex, age, and place of residence found in multivariate logistic regression analysis that low education level (odds ratio [OR] 1.42, 95% confidence interval [CI 1.09–1.86]), type B blood group (OR 2.41, [CI 1.03–5.66]), or goiter (OR 25–33, [CI 5.66–126.65]) was associated with higher ATC risk (17). In a similar study, but using in the control group patients operated for goiter, they noticed that a lower level of education (OR 1.85, [CI 1.21–2.82]) and type B blood group (OR 3.69, [CI 1.10–12.49]) continued to be risk factors for ATC (18). Association between education and ATC might be explained by confounding variables such as access to care and lower health awareness triggering neglected thyroid conditions with potential to link to increased chances of ATC pathogenesis; however, the biological explanation for the association between ATC and blood type remains unclear.

The reason for the observed association of goiter with ATC is uncertain, but could reflect at least two possible contributory factors. First, there are some data that iodine deficiency, a known predisposing condition for goiter, may also be a risk factor for ATC—based, in part, upon data indicating decreasing ATC incidence associated with public health effort to introduce food iodination in European and South America nations (19,20). Such data are, however, confounded of course by many factors also drifting over the time of such public health efforts. Second, one might alternatively speculate that neglected goiters among medically underserved communities might have the potential to lead to higher ATC risk, potentially thereby also linking lower socioeconomic status and goiter to each other and to ATC.

Two systematic reviews and meta-analyses (21,22) and one pooled analysis of prospective studies (23) have reported a positive association between measures of adiposity and risk of thyroid cancer, including small subgroup analyses in ATC. Schmid *et al.* reported, based on data from three studies, that the relative risk of ATC (with CI) was 1.93 [CI 1.23–3.02] relative to lean patients according to the World Health Organization (WHO) obesity body mass index (BMI) classification (21). Ma *et al.* similarly reported that, based on data from three studies, the relative risk of ATC in obese patients was 1.93 ([CI 1.23–3.03], $p = 0.004$) relative to lean patients (22). Kitahara *et al.* reported that the hazard ratio (HR) for ATC in obesity was 1.43 [CI 1.09–1.89], restricted to BMI values between 15.0 and 59.9 kg/m^2, including data from 19 ATC cases (23). More and larger studies are needed to confirm these findings, incorporating adjustments for relevant confounders.

A very small subset of differentiated thyroid cancer (DTC) transforms to ATC, supporting the view that DTC is a risk factor for ATC. Oishi *et al.* recently retrospectively compared the clinicopathological and molecular features in histopathology specimens from 27 ATC cases that contained antecedent PTC with that of 92 archived PTC cases (without ATC) (24). The rarity of anaplastic transformation of PTC is reflected by the fact that these authors had to screen 11,480 cases of PTC and 228 cases of ATC, to identify 27 cases of anaplastic transformation of PTC. In a multivariable analysis, the *TERT* promoter mutation (C228T) was the only factor independently implicated as potentially associated with anaplastic transformation of PTC (OR 68.18, [CI 13.97–332], $p < 0.001$, adjusted for age, sex, and $BRAF^{V600E}$ mutation) (24). Furthermore, Oishi *et al.* validated their findings using publicly available data from the Cancer Genome Atlas study, and in this data set found that in multivariate analysis, age >60 years (OR 4.87; [CI 1.17–20.37]) and *TERT* promoter mutation (OR 39.48; [CI 7.93–196.56]) were independently associated with anaplastic transformation of PTC (but not $BRAF^{V600E}$, $p = 0.066$) (24). Genomic studies of poorly differentiated thyroid cancer (PDTC) and ATC provide evidence for a model of tumorigenesis in which ATCs arise from preexisting DTC, via the accumulation of additional somatic genetic alterations (25), including *TP53* and *TERT* promoter mutations.

DIAGNOSIS OF ATC: CYTOLOGY AND CORE BIOPSY, HISTOPATHOLOGY, AND DIFFERENTIAL DIAGNOSIS

Cytology and pathology procedures

Fine needle aspiration and core biopsy. Fine needle aspiration (FNA) is generally the first type of biopsy attempted

(26–29). However, the cytological diagnosis of aggressive types of thyroid cancer, especially ATC, can be challenging (30) and is often associated with interobserver variability (31). The diagnostic yield of FNA is highly variable, but the diagnosis of ATC can be obtained in the majority of cases (>60%) (31,32), especially when the aspirate is highly cellular and immunohistochemistry (IHC) can be performed using a ''cell block'' using the IHC markers discussed below (33,34). In those cases in which the cellular yield is insufficient, core biopsy may be diagnostic (35). However, such biopsies may also be nondiagnostic due to sampling issues related to the presence of tumor necrosis and reactive and inflammatory changes; hence, ultrasound guidance is helpful to identify solid areas or nodal disease that may be more suitable for biopsy. FNA of the paucicellular variant of ATC has been technically infeasible due to the inability to obtain sufficient cells (36). Molecular analysis can be performed on FNA materials (37), but core biopsy often permits a broader range of genomic testing. Rarely, some cases of ATC are only diagnosed after surgical/open biopsy or surgical resection despite undergoing FNA and/or core biopsy.

Histopathology

The diagnosis of many thyroid tumors, especially ATC, includes clinical, biochemical, radiographic, and histomorphologic evaluations. While the diagnosis of ATC is often suspected in older patients with large, symptomatic, and rapidly growing neck masses, the diagnosis of ATC ultimately rests on tissue-based pathological assessment to confirm the diagnosis and exclude other treatable entities that may have significantly better prognoses and other treatments.

The WHO defines ATC as ''a highly aggressive thyroid malignancy composed of undifferentiated follicular thyroid cells'' (WHO Classification of Tumours of Endocrine Organs, IARC 2017, Lyon, France). Several synonyms are recognized, including undifferentiated thyroid carcinoma, plus several others that reflect specific morphological features (e.g., sarcomatoid carcinoma). The histopathological spectrum of ATC is highly variable (38,39), which creates diagnostic challenges and reflects the marked degree of underlying genetic and genomic complexity that has recently been illuminated. Despite this wide variation, several morphological subtypes have been recognized, including sarcomatoid or spindle cell, giant cell, and squamoid or epithelial (40,41). Many tumors display mixed morphologies with the combination of spindle cell and giant cell being a common presentation. Significant mixed chronic inflammation is usually present in ATCs (42,43). Rare subtypes have also been recognized, including the paucicellular variant (44), which is characterized by abundant hypocellular fibrous tissue, and the rhabdoid (45–47), angiomatoid (48,49), and lymphoepithelial variants. Recognizing the wide spectrum of histological variation is diagnostically useful, but is generally not prognostically nor otherwise clinically significant and can add confusion in diagnosis.

ATCs are highly invasive tumors characterized by tumor cell infiltration of adjacent thyroid and other tissues, as well as lymphatic and blood vessel invasion and of high potential for distant metastases. All ATCs are characterized by a high degree of cellular proliferation regardless of the specific morphological subtype observed. Accordingly, high mitotic rates (>1 mitoses per hpf) and high Ki-67 proliferation indices (generally >30% but usually higher) are expected (50,51), and the absence of proliferation suggests an alternative diagnosis. Atypical mitoses are also very common, which reflects ATC's underlying genomic instability. Confluent areas of tumor necrosis are common, best observed in resection specimens and large biopsies, and may confound the diagnostic process. Heterologous elements, such as malignant bone and cartilage, have been described; hence, the use of the term carcinosarcoma by some authors. ATCs uniformly represent high-grade undifferentiated neoplasms; accordingly there is no established grading scheme.

The diagnosis of ATC is straightforward when a coexistent differentiated carcinoma, commonly a tall cell variant or other high-grade variant of PTC (52), is identified and intimately admixed with an undifferentiated component (53). Thus, extensive tissue sampling of resection specimens is recommended to increase the likelihood of sampling the often minority differentiated component. Recent genomic studies of such mixed cases demonstrate common molecular alterations (24,25,54,55), reflecting their shared lineage and supporting a model in which ATC often arises from preexiting differentiated carcinomas.

Immunohistochemistry

The use of IHC is essential in the diagnostic evaluation of ATC, with the only possible exception being unequivocal cases that contain a form of coexistent differentiated carcinoma as mentioned above. As a general rule, thyroid-specific proteins such as thyroglobulin (TG) and thyroid-lineage markers such as thyroid-transcription factor 1 (TTF-1) are expected to be absent, reflecting the undifferentiated nature of ATC (41,50,56,57). Significant expression of TG or TTF-1 indicates higher levels of thyroid differentiation than predicted based on morphology alone and suggests other diagnoses may be more appropriate. However, expression of another thyroid-lineage marker, PAX8, is retained in 40–60% of ATCs, at least focally (50,58–60). Thus, immunohistochemical detection of PAX8 can provide essential affirmative evidence of follicular cell origin and supports a diagnosis of ATC in the proper morphological context of an otherwise undifferentiated high-grade neoplasm. However, PAX8 expression is not restricted to thyroid and occurs in the kidney and Müllerian system (61). Thus, renal cell and ovarian carcinomas must be entertained in the differential diagnosis, but neither prominently or commonly involve the thyroid gland. Furthermore, some PAX8 antibodies can cross-react with PAX5 (62,63), a B cell lineage marker that is expressed in some large B cell lymphomas (64). Thus, PAX8 IHC must be interpreted in the proper morphological context and as part of a broad panel of IHC markers.

IHC for cytokeratins can be useful in many cases, especially those in the epithelial nature of the neoplasm are not readily apparent by morphology, such as the spindle cell and giant cell variants (41,65,66). However, the complete absence of cytokeratin expression does not eliminate a diagnosis of ATC.

In some cases, especially where it may be difficult to assess proliferation by mitotic activity (e.g., small biopsies), cellular proliferation can be assessed by Ki-67 IHC. In general, ATCs

should display a high Ki-67 proliferation index (percent positive tumor nuclei) of at least 30% but most often significantly higher (50).

Loss of p53 tumor suppressor function via somatic mutation of *TP53* is a molecular hallmark of ATC (25,67–70). Accordingly, immunohistochemical analysis of p53 protein expression can predict somatic mutation of TP53, either by showing complete loss of p53 protein or markedly increased p53 protein abundance due to increased protein half-life (50,71). While *TP53* mutations are not specific to ATC as they occur in many high-grade neoplasms, abnormal p53 immunoreactivity can support a diagnosis of ATC in the proper histological and immunohistochemical context.

Similar to PTC, somatic alterations of *BRAF* are common in ATC, 40–70% depending on the series (25,50,71–77). Immunohistochemical detection of the most common *BRAF* mutation ($BRAF^{V600E}$) is specific and sensitive (33,78). Positive immunoreactivity for $BRAF^{V600E}$ can support the diagnosis of ATC, although these mutations are also present in a variety of other tumor types (79). IHC for $BRAF^{V600E}$ can also serve as a surrogate for molecular testing preoperatively and in the immediate postdiagnostic period and thus can be used theranostically for targeted BRAF inhibition (33,80). However, the correlation between immunoreactivity and mutation is not complete and confirmatory molecular diagnostics should be performed.

A routine panel of IHC markers for the evaluation of suspected ATC and results compared with other tumors is suggested in Table 2.

Differential diagnosis

ATC should be prominently suspected in any patient presenting with a rapidly growing thyroid gland mass; most such tumors will turn out to reflect ATC or primary thyroid lymphoma. However, not all ATCs are found stemming from this presentation, and in such instances, the differential diagnosis can be considerably broader as outlined below.

Poorly differentiated thyroid cancer. Among other thyroid carcinomas, the most frequent and difficult differential diagnostic consideration is PDTC. Thyroid cancers display a full range of follicular cell differentiation, which simplistically yet effectively serves as the scaffold for their classification. PDTC occupies an intermediate position between highly differentiated carcinomas (e.g., PTC) and ATC and may be a transitional form (81). Accordingly, the distinction between PDTC and ATC can be difficult and can result in diagnostic discrepancies in some cases. The prototypical type of PDTC, termed insular carcinoma (82), is characterized by large nests and trabeculae of relatively small and uniform cells. Other essential diagnostic features include significant mitotic activity (>3 mitoses per 10 hpfs) and *bona fide* tumor necrosis, generally single cell or focal patches. Compared with insular PDTC, which is usually composed of sheets of monotonous-appearing cells, ATCs have much higher degrees of cellular atypia and nuclear pleomorphism, a significantly higher mitotic activity, and confluent areas of tumor necrosis (50). The majority of PDTC retain expression of TG in contrast to ATC. Distinguishing PDTC and ATC is clinically important due to their significantly different prognoses and often differing therapies.

Squamous cell carcinoma of the thyroid. Primary squamous cell carcinoma (SCC) of the thyroid is exceptionally rare, representing far less than 1% of thyroid cancers (83). Primary SCC of the head and neck and metastasis from a distant SCC should be excluded whenever feasible. The distinction between primary SCC and the squamoid variant of ATC is difficult, yet the morphological and molecular context can provide useful diagnostic information (83). For example, a coexistent differentiated carcinoma supports a diagnosis of ATC, whereas chronic lymphocytic thyroiditis with squamous metaplasia can lend support to a diagnosis of primary SCC. A similar challenge is presented by primary SCC of the head and neck, which can clinically mimic ATC and be morphologically indistinguishable from primary SCC of the thyroid (84). IHC for TTF-1 and PAX8 can be informative for this differential diagnosis (85). Finally, it should be noted that although SCC is considered a separate entity from anaplastic carcinoma by the current WHO classification, it shares with ATC the presence of $BRAF^{V600E}$ mutations and a similar outcome prompting some to suggest that it represents another morphologic variant of ATC (77,86).

Table 2. Panel of Routine Immunohistochemical Markers for the Evaluation of Suspected Anaplastic Thyroid Cancer and Expected Results Compared with Other Tumor Types

IHC marker	*DTC*	*PDTC*	*ATC*	*MTC*	*SCC*	*Lymphoma*
Pan-cytokeratins	+++	+++	+++/–	+++	+++	–
Thyroglobulin	+++	+/–	–	–	–	–
Thyroid-transcription factor 1	+++	+/–	–/+	+/–	–	–
$BRAF^{V600E}$	+/–	–/+	–/+	–	–	–
PAX8	+++	+++	+/–	+/–	–	+/–[a]
Ki-67[b]	<5%	5–30%	>30%	<20%	>30%	variable
Chromogranin	–	–	–	+++	–	–
Calcitonin	–	–	–	+++/–	–	–
Carcinoembryonic antigen	–	–	–	+++	–	–
p53	– (rare +)	–/+	+/–	–	+/–	+/–
CD45, other lymphoid markers	–	–	–	–	–	+++

+ indicates relative positive staining, – indicates negative staining, +/– indicates variable positivity.
[a]PAX8 antibodies can cross-react with PAX5, which is expressed in lymphoid cells.
[b]Percentage of nuclei positive for Ki-67.
DTC, differentiated thyroid cancer; IHC, immunohistochemistry; MTC, medullary thyroid cancer; PDTC, poorly differentiated thyroid cancer.

Medullary thyroid cancer. Anaplastic forms of medullary thyroid cancer (MTC) consisting of spindle cells or cells with marked nuclear pleomorphism have been described (87–89). IHC for routine markers for MTC (i.e., calcitonin, chromogranin, synaptophysin, and carcinoembryonic antigen) can usually differentiate cases of MTC with anaplastic features from true ATC.

Lymphoma. Large B cell lymphoma and anaplastic large cell lymphoma of the thyroid can arise in the thyroid. Once the diagnosis of lymphoma is entertained based on a population of smaller and more uniform cells, a panel of lymphoid (CD45, CD20, and other markers depending on the specific lymphoma type) and epithelial markers (ctyokeratins) can often assist in the differential diagnosis (40,90). As noted above, antibodies against PAX8 can cross-react with PAX5 (63). Such knowledge can help prevent an erroneous diagnosis of B cell lymphoma.

Miscellaneous tumors. The differential diagnosis of ATC includes a large group of nonthyroid tumors (38). True sarcomas of the thyroid and head and neck occur and can be notoriously difficult to distinguish from sarcomatoid types of ATC. Spindle cell forms of melanoma exist and can be differentiated from ATC with a variety of melanocytic markers (e.g., SOX10). Metastases from other solid tumors can present as a neck mass that simulates ATC. Such cases can often be diagnosed using the IHC markers discussed herein plus other relevant markers depending on the origin of the metastatic tumor. Monoclonal PAX8 antibodies may provide additional help in identifying primary thyroid tumors (91).

Squamous metaplasia. Squamous metaplasia can be present in differentiated thyroid tumors and chronic thyroiditis and can be confused with ATC. The presence of nuclear pleomorphism, mitosis, tumor necrosis, and large invasive islands of squamous cells helps diagnose ATC instead of squamous metaplasia.

■ **RECOMMENDATION 1**

FNA cytology can play an important diagnostic role in the initial evaluation of ATC, but parallel core biopsy may be necessary for definitive diagnosis and to obtain sufficient material for molecular interrogation.

Strength of Recommendation: Strong
Quality of Evidence: Low

■ **RECOMMENDATION 2**

Every effort should be made to establish a diagnosis via biopsy before proceeding with surgical resection, as surgical resection may be inappropriate.

Strength of Recommendation: Strong
Quality of Evidence: Low

Intraoperative frozen section

The use of intraoperative frozen section should be focused on the determination of whether the specimen contains diagnostic material and to guide assessment of margin and tumor extent. If the frozen tissue consists of largely necrotic and/or inflammatory tissue, additional tissue can be obtained when feasible. Should lymphoma be suspected on frozen section based on morphology, additional tissue can be requested for a ''lymphoma workup'' that includes sending fresh tissue for flow cytometry analysis. Final diagnoses of ATC should not be made on frozen section, with the possible exception of those cases in which an unequivocal DTC, such as PTC, is present in addition to an anaplastic component. Frozen section can also be used during surgery for DTC in which an anaplastic component is suspected by the surgeon.

Surgical pathology

The histopathological assessment of thyroidectomy specimens should be primarily focused on confirmation of an ATC diagnosis, extent of disease, and the identification of any coexistent DTC. Generous sampling of the tumor, including its advancing edge, is indicated and necessary to fully characterize the neoplasm and increase the probability of finding any coexistent carcinoma and/or other pathologic findings. Additional or repeat immunohistochemical analysis should be performed as needed.

Many cases of ATC arise in patients with a history of resected differentiated carcinoma or PDTC. As noted above, cases of ATC often contain coexisting differentiated carcinoma. Collectively, these observations plus emerging genetic data strongly support the view that the majority of ATCs arise via dedifferentiation of preexisting well-differentiated or poorly differentiated carcinomas (24,25,54,55). The preexisting differentiated carcinoma is most often a high-grade form of PTC such as the tall cell variant (52), however, ATCs have been observed to be associated with follicular (92), Hürthle cell carcinomas (93), and PDTC. As expected, the better differentiated components of such carcinomas display intact expression of thyroid markers (TG, TTF-1, and PAX8). The finding of an associated thyroid carcinoma rules out the possibility of a metastatic tumor and thus strongly supports the diagnosis of ATC. ATCs in which the anaplastic component represents a minority may be associated with an improved outcome and the percentage of ATC within a tumor should be reported when appropriate (94–97).

■ **RECOMMENDATION 3**

Routine surgical pathology evaluation of resection specimens should focus on confirming a definitive diagnosis of ATC, documenting the extent of disease, and defining the presence of any coexisting DTC and/or other pathologies. The proportion of tumor that represents ATC should also be documented.

Strength of Recommendation: Strong
Quality of Evidence: Low

■ **RECOMMENDATION 4**

Once ATC diagnosis is considered, assessment of $BRAF^{V600E}$ mutation should be expeditiously performed by IHC and confirmed/expeditiously assessed by molecular testing.

Strength of Recommendation: Strong
Quality of Evidence: Moderate

Role of molecular testing

Although ATCs have an approximately sixfold higher tumor mutational burden (TMB) than that observed in well-

differentiated PTC, most ATCs do not meet the formal criterion for high TMB (>10 mutations/Mb) (25). Main driver mutations can be classified as early and late mutations. Early mutations, such as those of *BRAF* and *RAS*, are common in well-DTCs, a precursor of ATC. The late mutations include *TP53* and *TERT* mutations; they are frequently found in ATC but not in well-DTCs. These mutations are likely to occur late in carcinogenesis and be essential for anaplastic transformation. Mutations affecting the PI3K/AKT pathway are also likely to belong to the late mutation group (24).

Point mutations in one of the *RAS* genes (*NRAS*, *HRAS*, or *KRAS*) are characteristic of the well-differentiated follicular-patterned thyroid tumors and ATC developing from these tumors. *RAS* mutations are found in 15–40% of ATC (25,76,98–101). *EIF1AX* mutations are found in ~10% of these tumors, frequently coexisting with *RAS* mutations.

The $BRAF^{V600E}$ mutation is common in classic PTC and tall cell variant PTC, and can be seen in 40–70% of ATCs (74–77). Many *BRAF*-mutated ATCs contain a well-differentiated PTC component, frequently the tall cell variant. *BRAF* mutations are found in both PTC and ATC areas, indicating that they occur early in carcinogenesis (74,102,103).

Mutations in the promoter region of the *TERT* gene are found with increasing frequency from well-differentiated to poorly differentiated and to ATC. Approximately 65–75% of ATCs carry *TERT* promoter mutation (25,98–101). Similar to *TERT* mutations, *TP53* mutations are much more frequent in ATCs than in DTCs, being found in 50–70% of ATCs (25,76,98–101). Loss of the *TP53* gene locus is another mechanism of inactivation of this gene. A multistep process of tumor dedifferentiation has been suggested in a tumor in which a well-differentiated component showed an *RAS*+/*TP53*- genotype, whereas the adjacent ATC was *RAS*+/*TP53*+ altered (104).

Mutations in the effectors of the PI3K/AKT signaling pathway occur in 30–40% of ATCs (76,99). Among those, *PIK3CA* mutations are found in 10–18% of tumors, *PTEN* mutations are found in 10–15%, and *AKT1* and *AKT2* mutations in <5%. An increased copy number of the *PIK3CA* locus may also be found in ATC (75,105). *PIK3CA* and other mutations are frequently seen in ATC coexisting with *BRAF* or *RAS* mutations, suggesting that they may be a late event.

Some ATCs carry mutations and copy number alterations in the cell cycle genes *CDKN2A* and *CDKN2B*. A significant proportion of those tumors have no *BRAF* or *RAS* mutations, and they may represent a biologically distinct group of ATCs (76). Mutations in the *ATM*, *NF1*, and *RB1* genes can be found in ~10% of ATCs (25,76,100). Five percent to 10% of ATCs carry mutations in the DNA mismatch repair genes such as *MSH*, *MLH1*, among others (25,76,101). These tumors may exhibit a ''hypermutator'' phenotype with an accumulation of a very high number of mutations. Mutations in genes coding for components of the SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin remodeling complex and for histone methyltransferases (HMTs) are found in 10–20% of ATCs (25,76).

In rare cases, ATCs harbor *ALK* fusions, typically *STRN-ALK* (100,106). The fusion results in strong expression and activation of anaplastic lymphoma kinase (ALK) (106), and treatment with ALK inhibitor results in arresting tumor growth.

ATC has a highly unstable genome and typically shows multiple losses and gains of whole chromosomes, chromosome arms, and smaller interstitial chromosomal regions. Cytogenetically, these tumors have a complex karyotype with multiple and diverse numerical and structural chromosomal abnormalities (107,108). Progressive accumulation of chromosomal alterations from well-differentiated carcinomas to poorly differentiated carcinomas and to ATCs has been observed, supporting the multistep dedifferentiation process (109,110). In one study, copy number alterations were found to be more frequent in anaplastic carcinomas that lacked *BRAF* and *RAS* driver mutations (25), possibly pointing to a distinct pathway of ATC development.

Standard clinical approaches to tumor (''somatic'') genotyping involve targeted next-generation sequencing performed using large pan-cancer gene panels (25,76,99,111) or thyroid cancer-specific panels (111–113), as well as whole-genome sequencing. Genotyping using circulating tumor DNA, so-called liquid biopsy, is a newer tool that can be used to assess ATC patients for $BRAF^{V600E}$, and sometimes other mutations and fusions, and it may be potentially helpful to obtain information on mutational profiles of ATCs in a primary diagnostic setting or as a tool to monitor response to targeted therapy (113–115). However, at the present time, further work is required to create robust and clinical-grade assays that can use tumor DNA shed to patient blood for routine genotyping of ATC.

Is it necessary or helpful in the diagnostic realm to perform genetic analysis to look for molecular alterations?. None of the genetic alterations found in ATC is specific for ATC, although in some situations molecular testing may help the histopathologic diagnosis, which remains the gold standard. While *TERT* and *TP53* mutations are common in ATCs, they can occasionally be seen in poorly differentiated and some well-differentiated carcinomas. $BRAF^{V600E}$ and *RAS* mutations are not specific for thyroid carcinomas and would not differentiate ATCs from other high-grade epithelial tumors, although they are very rare in sarcomas. Moreover, typical hotspots for *RAS* mutations (*NRAS* codon 61 and *HRAS* codon 61) are rare in other tumors except melanomas and lymphomas. Therefore, if a particular site of origin or tumor type is suspected upon encountering an undifferentiated tumor, *BRAF* and *RAS* mutational status in conjunction with the gene alterations typically seen at that putative site may provide additional evidence for or against ATC. Combinations of $BRAF^{V600E}$ and *TERT* promoter or/and *TP53* mutations—or *RAS, TERT* promoter, or/and *TP53* mutations are more common in ATCs and PDTCs than in DTCs. Although genomic profiling of tumor tissue is not sufficient to allow the diagnosis of ATC, such results can at times be useful in differential diagnosis.

Is it helpful to do genetic testing to inform initial or later targeted therapy? If so, when and in what settings should this testing be done?. Molecular profiling of ATCs is increasingly used to search for therapeutic targets that may inform individualized targeted therapy. A phase 2 clinical trial with dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor) showed a significant response rate (RR) in ATC patients with the $BRAF^{V600E}$ mutation. This combination is now approved by the U.S. Food and Drug Administration (FDA) for this indication (116–119). Other examples include *ALK* fusions paired with ALK inhibitors such as crizotinib (120) and *TSC2* mutations for the mammalian target of rapamycin (mTOR) inhibitor everolimus, which can be effective therapeutics (116,121). A subset (~11–28%) of ATCs also

express programmed death ligand-1 (PD-L1) in either the inflammatory background or the tumor cells themselves making this tumor a potential candidate for immunotherapies (122,123). Tumor agnostic therapies are also approved for cancers with *NTRK* fusions, and may be relevant also in ATCs with *RET* fusions.

Molecular profiling of ATCs may be achieved by analyzing several of the most common mutations using conventional sequencing techniques, or by broad genotyping using next-generation sequencing. Although the large-scale whole-exome and whole-transcriptome analyses could provide the most comprehensive assessment of genetic alterations in these tumors, they require a significant amount of DNA/RNA and results usually become available in several weeks, which restrict their clinically utility for this rapidly progressive cancer. Targeted next-generation sequencing panels either pan-cancer or thyroid-specific contain the vast majority of genes of interest, require less DNA/RNA, and usually offer results in 1–2 weeks and therefore are preferable for the initial molecular profiling of ATCs.

■ RECOMMENDATION 5

Molecular profiling should be performed at the time of ATC diagnosis to inform decisions related to the use of targeted therapies, especially as there are now FDA-approved mutation-specific therapies in this context.

Strength of Recommendation: Strong
Quality of Evidence: Moderate

INITIAL EVALUATIONS

Laboratory, biopsy, and imaging procedures

There are a number of preoperative staging procedures of importance in ATC (Table 3). These consist of laboratory studies to appropriately characterize the physiological status of the patient and provide baseline parameters for further medical care, as well as radiological studies to determine the extent/stage of disease and to determine the best initial medical and/or surgical therapies. Molecular testing or IHC for $BRAF^{V600E}$ mutation should also be done at the time of diagnosis.

Table 3. Initial Evaluation for Staging, Tests, and Procedures

Laboratory tests
- CBC with differential
- Comprehensive chemistry panel (electrolytes, calcium, blood urea nitrogen, creatinine, glucose, and liver tests)
- Thyroid function tests (TSH, free thyroxine), TG/TG antibody
Imaging
- ^{18}F FDG PET/CT (preferred, whole body)[a]
- CT of neck, chest, abdomen, and pelvis with contrast *or* MRI (acceptable if PET unavailable—and as needed for surgical decision-making)
Recommended and if clinically indicated[b]
- MRI of brain with and without contrast
Procedures
- Laryngoscopy, also esophagoscopy as indicated
- BRAF assessment by IHC and NGS testing of tumor[c]

[a]If PET/CT unavailable, bone scan may be useful to identify bone metastases.
[b]Clinically indicated if the patient has symptoms suggestive of brain metastases (i.e., neurologic deficit, headache).
[c]BRAF IHC provides a rapid result and if positive NGS testing may not be necessary. If BRAF IHC is negative, NGS should be performed as it is more sensitive.
CBC, complete blood count; NGS, next generation sequencing; TG, thyroglobulin; TSH, thyrotropin.

Requisite laboratory studies include a complete blood count and differential to evaluate for anemia, assess adequacy of platelets, and to discern any underlying leukocytosis suggestive of active infection (124) or diminished white blood cell components suggesting immunodeficiency. Interestingly, 16–30% of ATC patients present with marked leukocytosis apparently consequent to tumor secretion of lymphokines such as granulocyte colony-stimulating factor (43,125–127); thus, leukocytosis may not indicate infection. Blood chemistry evaluation could include the following: electrolytes, serum urea nitrogen, creatinine, glucose, and liver function tests. Free thyroxine and thyrotropin should be assessed because large tumor masses may have compromised thyroid function, and rare cases of ATC are associated with significant thyrotoxicosis (128,129). TG can be produced in DTC coexisting with ATC, but is not a marker in ATC. The absence of TG production can also be helpful to give further credence of the diagnosis of ATC. Calcium and phosphorus should be measured because tumor invasion may compromise parathyroid function, as can surgical intervention, and unusual ATC cases can present with humoral hypercalcemia of malignancy (130). Coagulation studies, prothrombin time, and activated partial thrombin time should also be obtained. Considering the technical difficulties of surgical resection for invasive ATC and the likely need for blood transfusion, it is reasonable to provide a preoperative blood sample for type and crossmatch rather than just utilizing a type-and-hold approach if surgical resection is being planned.

Preoperative radiological studies should not delay urgent therapeutic intervention and any required radiologic tests should be performed expeditiously. Cross-sectional imaging of the neck with contrast should be done to assess the extent of disease and to plan any subsequent surgery and/or radiation therapy (131). A high-resolution ultrasound of the neck may be helpful in providing rapid evaluation of the primary thyroid tumor and assessing involvement of the central and lateral lymph nodal basins. CT with contrast of the chest, abdomen, and pelvis is a critical preoperative study; alternatively, an MRI using gadolinium contrast can be substituted (132). If accessible, positron emission tomography (PET), utilizing ^{18}F-fluorodeoxyglucose (FDG) and fused to a coincident CT scan (whole body), is particularly valuable in evaluating metastatic sites that are sometimes not appreciated on cross-sectional imaging (133–136). If PET/CT is not available, a bone scan to identify metastatic lesions to the bones can be obtained. MRI or CT of the brain with contrast should also be performed in ATC patients to identify brain metastases, if clinically indicated.

■ RECOMMENDATION 6

Initial radiological tumor staging should include cross-sectional imaging, in particular, CT neck, chest, abdomen, and pelvis with contrast (or MRI), and, if available,

FDG PET/CT. Contrast-enhanced imaging of the brain (MRI preferred) should also be performed, if clinically indicated.

Strength of Recommendation: Strong
Quality of Evidence: Moderate

Biopsy of distant masses. Biopsy of distant lesions is often unnecessary if primary tumor material is sufficient to make a diagnosis and sufficient for molecular testing. It is common for ATC and DTC to coexist in the same patient (137,138) because it is believed that ATC arises by dedifferentiation of preexisting DTC. Thus, one must consider that metastases can arise from either ATC or DTC. However, these DTC lesions often behave less aggressively and therefore would rarely change the management of the patient. Likewise, ATC may be diagnosed in patients with separate cancers (previously diagnosed or not) such as primary lung carcinomas, metastatic prostate cancers, or metastatic breast cancers. Under such circumstances, therapeutic modalities vary considerably depending upon the proper tumor diagnosis. Infections, such as those in the lung, may mimic metastatic disease, and therefore, if this is suspected, image-guided biopsy may be useful.

Although it is important to properly characterize the etiology of metastatic tumor sites, it must be considered whether this knowledge would have a significant effect upon the planning or implementation of primary surgery for ATC. For this reason, in most circumstances, primary surgery should not be delayed to biopsy distant metastases.

GOOD PRACTICE STATEMENT 1

In the event that biopsy of a suspected metastatic disease site is clinically indicated, primary management of ATC should not be delayed until biopsy is obtained.

Timing and nature of evaluations

In the assessment of a rapidly growing neck mass (Figs. 1 and 2), necessary preoperative evaluations must be completed quickly. All initial staging procedures should be expedited by the treating physician and should not be relegated to any schedule that delays treatment. It is critical that preoperative medical and anesthesia assessments be accomplished in the briefest time possible.

GOOD PRACTICE STATEMENT 2

All critical appointments and assessments that are required before primary treatment of ATC should be prioritized and completed as rapidly as possible.

Airway and vocal cord assessment

Vocal cord paralysis is quite common in patients with ATC, compared with those with DTC. Because of laryngeal nerve involvement by tumor, the patient may present with obvious hoarseness, raising the question of vocal cord mobility. The best way to evaluate vocal cord mobility is laryngeal evaluation, which can easily be performed in the office with mirror or fiberoptic laryngoscopy (1,139,140). Patients may present with one paralyzed vocal cord and an adequate airway. The fiberoptic laryngoscopy will also help to evaluate whether there is direct involvement of the tumor in the larynx and the upper trachea.

■ RECOMMENDATION 7

Every patient with ATC should undergo evaluation of the vocal cords at initial presentation, and thereafter based upon changing symptoms.

Strength of Recommendation: Strong
Quality of Evidence: Low

ESTABLISHING GOALS OF CARE

In ATC, goals of care may be therapeutic and/or palliative depending on staging and prognosis when considered in the context of available therapies, comorbidities, and patient's wishes. This section outlines the multiple steps involved in establishing realistic and ethically sound goals of care for ATC patients. We herein consider: (a) patients in whom aggressive therapies are medically appropriate; and (b) patients in whom aggressive therapies are not medically appropriate.

Advanced multidisciplinary care planning

A multidisciplinary team discussion with subspecialists who may be involved in the patient's care (141–144), including palliative care expertise (145), should be convened in the case of every ATC patient. Given the rarity and generally dire prognosis of ATC, consultation with outside specialists highly experienced in treating ATC should be undertaken in the absence of local expert ATC providers.

A multidisciplinary team discussion should precede a discussion of the treatment options, risks and benefits, and outcomes with the patient to reach consensus about realistic treatment options and reduce internal disagreement over what to offer the patient, how to frame goals of care, and how to optimize truthful prognostication. Overly optimistic messages to patients, as well as overly pessimistic messages, can dramatically and unduly affect advanced care planning discussions (146–149), patient decision-making, well-being, and beneficent care (150).

■ RECOMMENDATION 8

Comprehensive disease-specific multidisciplinary input should be attained before defining ''goals of care'' or undertaking therapeutic discussions with patients. Those involved in management decisions should include specialists highly experienced in treating ATC.

Strength of Recommendation: Strong
Quality of evidence: Low

Patient competency and decision-making capacity

Competency and decision-making capacity are frequently confused as synonyms, but they are distinct. ''Competency'' is a legal determination; decision-making capacity is a medical determination any physician can make. All emancipated adults and all emancipated minors are presumed competent unless the courts have determined otherwise, and also presumed to have decision-making capacity. Patients without adequate decision-making capacity cannot provide valid consent to treatment. Decision-making capacity is

Table 4. Informed Consent Checklist

The three components of informed consent involve disclosure, decision-making capacity, and voluntariness

Disclosure
- Truthful prognostication
  - Treatment options available and all associated side-effects, ranging from aggressive treatment to palliative care and hospice, including the option of medical assistance in dying.
- Consent for treatment
  - Discuss advance directives, code status, and naming a surrogate decision maker.
    - *Surgical management*
      - Surgical candidacy and expected benefits and risks
      - Discussion of intubation and tracheostomy
    - *Drug therapies*
      - Candidacy and contraindications
      - Costs and expected benefit ratio
      - Expected side-effects and rare side-effects
      - When to stop the drug if risks outweigh benefits
    - *External beam radiation*
      - Candidacy and contraindications
      - All side-effects and palliation of side-effects
      - When to stop radiation if risks outweigh benefits

Decision-making capacity[a]
- After the disclosure discussion, do a ''teach back'' with the following questions to assess U-ARE
  - *What do you understand about your situation?*
  - *What are your treatment options?*
  - *What will happen when you take/do not take this treatment?*
  - *Why do you want/not want it?*
  - *What other choices do you have?*
  - *How did you arrive at your choice?*
  - *What questions do you have?*
  - *What are you worried about?*

Voluntariness
- Discuss with patient a decision-making model that works best, which can include shared decision-making or nondirective counseling about options. If there are concerns that the patient is being coerced into an option, consider speaking to patient alone or having a family meeting, or request a clinical ethics consultation to help assess patient's preferred options.
- Consent for comfort care/hospice
  - For patients who opt for comfort care and hospice, all discussions should include a palliative care service or expert, as well as pastoral care to plan an appropriate regimen for the patient. Discussions surrounding palliative surgery and palliative radiation must disclose all risks, benefits, and costs.

[a]If you have concerns that your patient does not have decision-making capacity, request a formal capacity assessment with a mental health provider, or request a clinical ethics consultation at your institution. If the patient requires a surrogate decision maker and does not have an advance directive or a court-appointed guardian, consult your state surrogacy laws, which may involve family hierarchy laws, or consult your institutional legal office.

U-ARE, Understanding (U), Appreciation (A), Rationality (R) and ability to Express a choice (E).

Understanding (U), Appreciation (A), Rationality (R), and ability to Express a choice (E) (U-ARE) criteria (Table 4). Input from psychiatry and neuropsychology services can offer a formal opinion about decision-making capacity.

For incompetent patients. If a patient diagnosed with ATC has been declared incompetent by the courts for some reason, the guiding ethical Principle of Respect for Persons obligates practitioners to ensure such patients have an authentic surrogate decision maker. In these cases, patients should participate in decision-making to the extent that they can; patient preferences should still guide surrogate decisions for incompetent patients, when possible. Not all incompetent patients lack decision-making capacity, but in the United States, incompetent patients lack decision-making *authority*, which means that guardians have the legal authority to make decisions against the patient's wishes. Treatment teams should request an Ethics Consultation under such circumstances, while an institution's Office of Legal Counsel can also assist. In patients without decision-making authority, the most common conflict over goals of care involves a guardian's decision for aggressive care and an incompetent patient's refusal. In such cases, refusals must be taken seriously, as the psychosocial consequences of forced medical treatment typically do not meet the standard required under the Principle of Beneficence (maximizing benefits; minimizing harms). Forced cancer treatment is a common ethical dilemma in the oncology context, but in the ATC context, forced treatment cannot be ethically justified.

GOOD PRACTICE STATEMENT 3

Patients must have understanding and decision-making capacity to consent to treatment or to make particular

medical decisions. Concerns about diminished or impaired capacity should prompt mental health and/or clinical ethics consultation to assess barriers to capacity.

"Goals-of-care" discussion with patient: truth telling, patient autonomy, and beneficent care

Once the prognosis and management options are clear, consultation with the patient and family should occur rapidly to address truthful prognostication, combined with proactive communication and early involvement of expert consultants (151). The care team should refer to ''breaking bad news'' models in the literature, such as the SPIKES model, the six-step protocol for delivering bad news (152). Delaying breaking bad news can introduce unintended psychosocial harms; it can also cause care team ''moral distress'' should they identify the best moral action but are constrained from acting on it (153–156). The most common clinical ethics consultation in hospitals surrounds moral distress from nursing professionals explicitly caused by primary teams who delay breaking bad news.

Beneficent care refers to care in which clinical benefits are maximized, and potential harms minimized (157–159). What may constitute clinical harms may be highly variable and depend upon patient's age, comorbid conditions, tumor status, overall health, and psychosocial support system. Thus, clinical management must be guided by patient preferences with respect to quality of life, in which there is full disclosure of the diagnosis, realistic prognosis, and treatment options available for either prolonging life (160–164) or hastening death, so that patients can control their dying process (165,166). In this discussion, all relevant potential risks and benefits of available therapies must be disclosed (163), which include the financial costs or burdens of various treatments, mental health consequences (e.g., fatigue, depression, loss of appetite, anhedonia), and what the patient will need in terms of psychosocial support. For the ATC Informed Consent Checklist, see Table 4.

If applicable, the concept of ''innovative therapy'' should be fully explained to the patient for any treatment plan developed in the absence of an accepted standard therapy. The goal is always beneficent care and the optimization of treatment, not the collection of data for future analysis (167,168). If the patient is being considered for or is enrolling in a clinical trial, this must be fully disclosed, and the informed consent procedures for the trial must be followed.

All ATC patients should be counseled about the full range of treatment options that include palliative care and aggressive pain management, intensive care unit (ICU)-related options, as well as the option to make end-of-life decisions, with the support of psychosocial experts, including pastoral care (145,169,170). The early introduction of psychosocial support and pastoral care can help to reduce ''existential suffering'' in patients who may need to have closure about their life events or life relationships (171). Advance directives must be discussed, as well as patient preferences (Physician Orders for Life Sustaining Treatment [POLST] or Medical Orders for Scope of Treatment [MOST] form).

Once initial treatment goals have been established and active therapy has been initiated, interval developments (e.g., tumor response, progression, adverse events) will necessarily shape therapy. Hence, additional careful discussions with the patient will be required throughout the course of care to review therapeutic options and reestablish goals in the best interest of the patient, including palliative care.

Traveling medical orders: POLST/MOST

Advance directives are frequently not followed because they may be inapparent in a patient's chart due to care across centers (172), even with electronic medical records. ATC patients frequently travel, making ATC patients ideal candidates for ''traveling orders.'' POLST is a declaration that travels with the patient documenting three levels of treatment: Full Treatment; Limited Interventions; and Comfort Measures Only. In the United States, some states have a POLST registry (172). The second type of traveling medical order is called MOST, which is a newer version of the POLST. MOST forms also have ''Full Scope of Treatment'' (173); Limited Scope of Treatment; and Comfort Measures (173). Because patients have very particular preferences about what they perceive as ''limited,'' ''full,'' or ''comfort'' scopes of care, POLST/MOST forms can optimize patient-centered care options. POLST or MOST forms can be specifically adapted using an online guide (https://www.health.ny.gov/forms/doh-5003.pdf).

Advance directives, feeding, intubation, and code status

All ATC patients with decision-making capacity should be encouraged to draft an advance directive or fill out a POLST/MOST form. In many countries, advance directives are a requirement. For example, in the United States, *The Patient Self-Determination Act* (174,175) requires hospitals, nursing homes, and other health care facilities to ask about advance directives or to record patient preferences regarding certain treatments should they lose the decision-making capacity.

Although advance directive forms vary from state to state, they specify code status such as do not resuscitate (DNR), do not intubate, or allow natural death (AND) (176,177). Advance directive documents can be highly problematic at times, however, because they do not account for many of the nuances (177–179), which is why in some hospitals, the code status ''AND'' was introduced when discussing end-of-life preferences with patients (177). Clinical ethicists recommend that naming a surrogate decision maker is the most important feature of advance directives (180,181). In states with ''family hierarchy'' laws, patients without a designated surrogate could have decisions being made by estranged spouses or other relatives (182).

Patients should be asked about code status preferences, nutrition, and hydration at an appropriate juncture, guided by a values history (183,184). Patients who have indicated they wish to be DNR or AND should be asked about suspension of such orders during surgery (185,186) or during other palliative procedures (186).

GOOD PRACTICE STATEMENT 4

Patients should be encouraged to draft both an advance directive in which they name a surrogate decision maker and list code status and other end-of-life preferences including POLST or MOST document. Circumstances

where suspension of DNR may occur must be discussed with the patient as well.

Cultural competence, values history, and health disparities

ATC patients are as diverse as any other group of cancer patients and will have moral and cultural diversity. Cultural competence entails taking a ''values history'' of all patients (184), which can be done by using documents such as the Five Wishes document, now used by many hospitals. Not all patients wish to be in charge of their medical decisions; in some cultures, deference to elders or spiritual leaders may be the patient's preference, and deferral to another decision maker is the patient's option.

Health disparities in ATC patients may leave them without insurance, and/or they may not have legal status in the country of treatment. In such cases, treatment should be provided on a compassionate basis, in consultation with the institution's administrative policy guidance.

Medical assistance in dying

Although controversial, several countries now have laws that allow medical assistance in dying (MAID) (see https://www.deathwithdignity.org/learn/access/or https://lop.parl.ca/sites/PublicWebsite/default/en_CA/ResearchPublications/2015116E) in the United States; for Canada see https://www.canada.ca/en/health-canada/services/medical-assistance-dying.html). In ATC, a delayed diagnosis can limit how patients can take advantage of such laws. However, in jurisdictions that have MAID laws, or in any patient who asks about MAID, ATC treatment teams have a clear ethical obligation to either discuss this option as part of the end-of-life discussion, or to have someone in the institution discuss this option if the practitioner is not comfortable (187).

GOOD PRACTICE STATEMENT 5

A ''goals-of-care'' discussion should be initiated with the patient as soon as possible. In consultation with a multidisciplinary team, a candid session should be conducted in which there is full disclosure of the potential risks and benefits of various treatment options, updated frequently, including how such options will impact the patient's life. Treatment options discussed should include all end-of-life options, such as hospice and palliative care. Patient preferences should guide clinical management.

Ethical issues with feeding

A common clinical ethics consultation involves feeding and feeding tubes. The typical dilemma revolves around patients who have indicated they want aggressive treatment and are full code, but who have stopped eating or drinking. Such patients should be evaluated for depression, or other physiologic barriers to comfortable eating, including swallowing problems. Ultimately, voluntary stopping of eating and drinking can be offered and honored. Another common clinical ethics consultation surrounds the conflict between the care team and patient/surrogate about the medical appropriateness of feeding tubes. We endorse the ''7 Step'' process for resolution over ICU-related care developed by the American Thoracic Society (151) with respect to potentially inappropriate treatments in ICU settings, as well as the Society of Critical Care Medicine Ethics Committee recommendations (188).

Ethical issues with tracheostomy

When there are conflicts between patient/surrogate decision makers and the care team surrounding tracheostomy decisions, we endorse the ''7 Step'' process for resolution over ICU-related care developed by the American Thoracic Society (151) with respect to potentially inappropriate treatments in ICU settings, as well as the Society of Critical Care Medicine Ethics Committee recommendations (188).

When to involve palliative care services or hospice care services

The WHO currently defines palliative care as: ''an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual'' (189). As such, palliative care is an integral part of all aspects of ATC patient care.

There is a distinction between ''palliative care'' and ''hospice care.'' Although it is common for these terms to be used interchangeably, they are not the same services. Palliative care consultation can be useful at any stage. On the contrary, hospice care focuses on pain and symptom management for patients who are no longer receiving life-prolonging therapies (190). Some jurisdictions mandate that physicians involve palliative care expertise and discuss palliative care options when patients are diagnosed with terminal illnesses. For example, within the United States, in 2009, The Terminal Patients' Right to Know End-of-Life Options Act took effect in California (CALIFORNIA CODES, HEALTH AND SAFETY CODE SECTIONS 442–442.7), while in 2011, The Palliative Care Information Act (Public Health Law section 2997-c) was passed in New York State. Such laws mean that failure to discuss palliative care options with terminally ill patients now violate state law. Although some critics (191) have pointed out that legally mandating such discussions is difficult in cases where a terminal diagnosis is ambiguous, terminal illness is not ambiguous in ATC. Physicians practicing in states with palliative care laws would be required to involve palliative care expertise for their ATC patients.

Definition of a palliative care service. In an academic medical setting, a palliative care service is a multidisciplinary service that addresses the physical, intellectual, emotional, social, and spiritual needs of the patient and family. Such services typically include one or more of the following: a medical practitioner specifically trained in palliative medicine; a nurse practitioner; and trained counselors to deal with patients and families coping with serious illness, life-limiting illnesses with no predictable endpoint, complications of therapies, or end-or-life situations. Palliative care is inclusive of life-prolonging therapies.

In the U.S. private practice setting, or a nonacademic setting, palliative care services are quite likely to be available in local hospitals, even in remote settings. In most private

practices—even in remote areas—it is usually possible to find a hospital close to the patient providing such services (145,192,193).

When to involve palliative care in ATC. Palliative care is useful at any point during the patient's treatment, and expertise from palliative care services may help the patient remain more active and comfortable in resuming daily activities. In addition, physicians who may have difficulty addressing the patient's emotional, psychosocial, or spiritual anxieties about ATC can call upon palliative care experts to assist with these issues. In reference to specific patient management issues, such as pain control, nutrition, and airway preservation, see the appropriate sections in this document.

When to involve hospice care in ATC. When patients decline therapies intending to prolong life, yet desire dignity and quality of life for end-of-life care spanning the remainder of their illness, hospice cCare is appropriate. In such cases, the same palliative care teams or services may remain involved but are specifically provided with a ''hospice'' goal. In such cases, pastoral expertise or support may also be provided to patients and families if desired, as well as hospice options. Hospice care is frequently undertaken within the patient's home; however, in some cases, a hospice facility may provide the best setting.

Working effectively with a palliative care or hospice care team. Practitioners managing ATC patients should not ''abandon'' their patients to palliative care or hospice care teams. Rather, one of the patient's physicians should serve to coordinate this care. The patient might still require a multiteam level of care or may choose to utilize the expertise of a single physician.

Support systems, palliative care and hospice care. Palliative or hospice care should involve those individuals close to the patients; it is as much about quality of life for the dying as it is quality of life for the caregivers and those who are left behind. As Mehta *et al.* note: ''To deliver the best care, we need to understand that the patient is immersed in a context called family, an interactive system. Death and dying should be perceived as a family event that likely throws the family out of balance and requires adjustment of all family members to the new family reality.'' Ultimately, ''the experience of death and dying cannot be addressed in isolation, restricted to the patient alone. Palliative patients often face crises in symptom management, recurrent visits to the emergency room, and changes of roles within the family'' (194). ATC care teams should be familiar with Family Systems Theory, a framework for delivering health care in which the patient is *part* of the family unit (195). Even in cases with the unbefriended or unrepresented patient, the absence of family can be mitigated by ensuring that a psychosocial support structure is part of the care plan (195,196). This theoretical model focuses on the family as a dynamic, interactive system where illness in one family member affects all the family members because the family unit is interdependent (197). Often, family meetings surrounding goals of care will deviate into complex discussions about family finances, and many other psychosocial issues that health care providers may think are extraneous to the patient's medical needs (197). In this framework, we believe that practitioners should view the patient as part of an interactive family unit in which illness and decisions affect all the family members.

■ **RECOMMENDATION 9**

The treatment team should include palliative care expertise at every stage of patient management to help with pain and symptom control, as well as addressing psychosocial and spiritual issues.

Strength of Recommendation: Strong
Quality of evidence: Low

■ **RECOMMENDATION 10**

The treatment team should engage hospice care for ATC patients who decline therapies against their tumor intending to prolong life, yet who still require symptom and pain relief spanning the remainder of their illness.

Strength of Recommendation: Strong
Quality of evidence: Low

■ **RECOMMENDATION 11**

At all stages of palliative care and hospice care in ATC patients, practitioners should be aware of family systems, and how they affect patient decision-making.

Strength of Recommendation: Strong
Quality of evidence: Low

SURGICAL MANAGEMENT OF ATC

Initial surgical approach to patients with ATC depends on multiple factors that should be discussed expeditiously with the patient and in a multidisciplinary care team with close attention to the patient's goals of care. What is the extent of disease based on accurate and rapid staging of the disease? What is the patient's airway status? Is the tumor resectable to the best advantage of the patient (avoiding laryngectomy or partial resection)? What is the functional status of the patient and the patient's goals for care? Has neoadjuvant therapy been given or is it an option? Is adjuvant therapy planned postoperatively? Is the surgical treatment going to be palliative, preventive of future complications, or for curative intent? In some circumstances, surgical intervention, even if possible, may be foregone.

Evaluation of extent of disease for surgical intervention

Patients with ATC should have rapid and accurate staging, as this will determine whether the patient is a surgical candidate and what type of surgical intervention is needed or possible. Patients with stage IVA or IVB ATC may be surgical candidates. A subset of patients with stage IVC ATC may be considered for surgical treatment for locoregional disease control for palliation or to prevent future complications (e.g., prevent impending airway invasion/obstruction, esophageal invasion/obstruction, laryngeal invasion/obstruction). It is extremely important that the extent of disease evaluation is defined immediately before surgical intervention as ATC is rapidly progressive and the clinical stage of disease can change rapidly.

Table 5. Airway Evaluation, Inclusion and Exclusion Criteria for Resectability Before or During Surgical Intervention

***Immediate* Airway Evaluation**
Does the patient have stridor?
Is immediate tracheostomy required?

Prerequisites/Inclusion Criteria for Surgery

Detailed surgical aerodigestive evaluation:
Fiberoptic evaluation including vocal cord status: laryngeal, subglottic, and upper tracheal regions need to be examined
Contrast-enhanced imaging of neck and upper mediastinum (CT or MRI preferred over ultrasound)
Consider: Endoscopic visualization of esophagus to assess invasion
Consider: Bronchoscopic visualization to assess tracheal invasion

Is R0/R1[a] resection expected?
R0/R1 resection anticipated without extensive visceral/vascular resection (laryngectomy, arterial/tracheal resection, permanent tracheostomy not anticipated)
Assembled surgical team optimally poised for the planned surgery

Undertake systematic evaluation (experienced surgeon, endocrinologist, pathologist, radiation oncology, medical oncology, radiology, nuclear medicine, and palliative care and ethics consultations)
- Assure correct pathologic diagnosis
  FNA and core, negative calcitonin, expert pathology review including immunohistochemical marker assessment; send sample for genomic interrogation (especially $BRAF^{V600E}$ mutation assessment)
- Completed radiographic evaluation/clinical staging (Table 3):
  Define global clinical stage (IVA, IVB, IVC)
  Brain imaging (MR preferred, else contrast-enhanced CT)
- Patient comorbidities and psychosocial fitness for surgery assessed—and acceptable to proceed based upon global patient condition
- Patient competent in terms of decision-making capacity and meeting the U-ARE criteria and with sufficient understanding to make thoughtful decisions (see Table 4 and consider involvement of surrogate decision makers as needed)
- Patient goals of care, preferences, code (DNR/DNI) status, advanced directives, and surrogate/proxy decision makers defined
- Consensus achieved with patient and team on initial therapeutic plan and go/no-go for surgery

Exclusionary Conditions Before or at Time of ATC Surgery
Patient condition, goals of care, or decision-making capacity unsuitable for surgery
High-volume ATC metastases[b]

Anticipated prohibitive morbidity from required surgical procedure?
Unacceptably high risk of extensive laryngeal, tracheal, bilateral nerve, esophageal, and/or vascular resection required to achieve R0/R1 resection
Anticipated time of postoperative recovery prohibitive in the context of anticipated need for additional superimposed therapies (e.g., chemoradiotherapy)

[a]R0, negative microscopic and gross margin resection; R1, negative gross margin resection.
[b]High-volume metastatic disease should preclude surgery, but coexistent metastatic DTC or oligometastatic/low-volume metastatic ATC should not necessarily preclude surgery.
DNI, do not intubate; DNR, do not resuscitate; FNA, fine needle aspiration.

Airway assessment

Airway assessment is an important element in the care of any patient with thyroid cancer; but in the setting of ATC, airway assessment is critical and must necessarily be expeditious as well as thorough (Table 5). Key findings in the airway assessment of ATC include the following. (i) The presence of altered vocal fold mobility (this indicates nerve invasion and is impactful in the surgical management of the contralateral recurrent nerve), (ii) tumor mass affecting the position of pharyngeal, laryngeal, tracheal, and esophageal structures, and extent of any luminal narrowing, and (iii) transluminal invasion of the pharynx, larynx, or trachea, which significantly escalates surgical complexity. Examinations required are endoscopic evaluation and anatomical imaging with CT or MRI with contrast. CT may be preferable due to decreased time of scanning. Neck ultrasonography may also help to evaluate neck soft tissue invasion, anatomical relations of the tumor, the presence of lymph node metastasis, or jugular vein invasion or thrombosis. Endoscopic evaluation should adequately assess the mucosal surfaces adjacent to the thyroid gland, inspection should extend from the pharynx, through the larynx and subglottis and into the trachea. Symptoms of dysphagia or imaging findings suggesting esophageal invasion should also prompt esophagoscopy, and the use of endoscopic ultrasonography may be valuable in estimating proximity of the cancer to the lumen. Office endoscopy is a standard examination in most surgical practice, most often using topical anesthesia. Extending the endoscopy examination to the trachea via fiberoptic assessment is necessary.

Resectability of ATC

We believe that two important criteria should be used to determine whether the tumor is resectable with curative

intention: (i) distinguishing between locoregionally confined disease and those with distant metastatic disease, and (ii) defining the extent of local invasion and the structures involved (Table 5). In patients with only locoregional disease (stage IVA/IVB), the determination of whether the tumor is resectable should be based on what structures are involved, whether a satisfactory resection could be achieved (R0/R1), and whether resection of the involved structure results in significant morbidity or mortality in the context of the patient's goals of care. Complete visible tumor resection (R0 or R1), not debulking (R2 resection), is the goal of surgery and should be used to define what constitutes a resectable tumor.

ATC can invade structures in the central and lateral neck and mediastinum by direct tumor invasion or by lymphatic invasion. Locoregional invasion into the internal jugular vein, carotid artery, nerves (e.g., recurrent laryngeal, vagus, spinal accessory, and phrenic), sternocleidomastoid muscle, esophagus, trachea, larynx, and/or superior vena cava is frequent and needs to be evaluated to determine resectability on an individualized basis. Therefore, routine preoperative imaging in all patients should be performed to evaluate the extent of disease locally and to exclude the presence of distant metastasis as mentioned above. A high-resolution ultrasound of the neck should be obtained to evaluate the primary thyroid tumor and to assess for involvement of the central and lateral lymph node basins. Cross-sectional imaging of the neck and chest with MRI and/or CT scan with contrast is also necessary to determine the presence of regional disease, invasion of great vessels and viscera, and exclude distant metastasis. All ATC patients should also be subject to direct laryngoscopy; the subglottis and upper cervical trachea should be assessed. There should also be a low threshold for undertaking an additional bronchoscopy and/or esophagoscopy if there is any question of tracheal and/or esophageal invasion anatomically or symptomatically. Patients with locoregional disease should be offered a resection if complete tumor resection can be achieved with minimal morbidity. This is because most studies suggest that complete resection (R0/R1) is associated with prolonged disease-free survival and/or overall survival with or without combination chemotherapy and radiotherapy (4,95,198–207). However, in a recent systematic review based on limited data, no differences in disease-free or overall survival rates were found comparing patients who had R0 versus R1 versus R2 resections (208). Hence, in patients with systemic disease, resection of locoregional disease for palliation may be considered if there is imminent airway or esophageal obstruction. Also, some patients may require exploration to establish surgical resectability.

Whether resection of ATC involving visceral and vascular structures in patients with stage IVB ATC provides a survival advantage is unclear. Due consideration should be given to quality of life and patient wishes while considering radical resection. Impact on time frame of further therapies must also be considered. This is because most patients develop locoregional recurrence and/or distant metastases, and no association with a survival advantage has been shown with such surgical intervention.

In summary, resectability of ATC should be determined by routine preoperative imaging (ultrasound, CT, MRI, and/or PET scan) as well as laryngoscopy and often also esophagostomy and bronchoscopy. If locoregional disease is present and a negative margin (R0/R1 resection) can be achieved, surgical resection should be considered and is independently associated with longer overall survival (4,95,198–208). In patients with systemic disease, resection of the primary tumor for palliation or prevention of future complication can be considered to avoid current or eventual airway, esophageal obstruction, or major bleeding complications.

Optimal extent of surgery

Approximately 10% of patients with ATC present with only an intrathyroidal tumor, whereas 40% have extrathyroidal invasion and/or lymph node metastasis, with the remainder of patients presenting with widely metastatic disease (198,209). Patients who have surgical intervention for ATC have a significantly longer median overall survival (8 months) compared with patients who did not have a surgical intervention (median overall survival of 3 months) (208). This may be due to patient selection (patients with less advanced disease having surgical intervention) as the distribution of extent of disease in these patients was 48.1% stage IVA, 44.4% stage IVB, and 7.5% stage IVC.

The type and extent of surgical intervention used in ATC were most commonly a total thyroidectomy (48.6%) with lymph node dissection (59%%) with 1.7% of patients having a larygectomy/pharyngectomy as part of the procedure. Total or near-total thyroidectomy with therapeutic lymph node dissection of the central and lateral neck lymph node compartments should be considered the most optimal surgical treatment in patients with resectable disease. The rationale for a total or near-total thyroidectomy is that $\sim$20% of patients with ATC have coexisting DTC, and a complete resection (R0/R1) may be associated with improved disease-free survival and overall survival with or without combination chemotherapy and radiotherapy (4,95,198–207,210,211).

Although there are insufficient data regarding the outcome from thyroid lobectomy in patients with localized and resectable ATC (normal contralateral lobe on preoperative ultrasound), it is reasonable to consider when there is concern of or documented injury to the ipsilateral recurrent laryngeal nerve, or no identification of the ipsilateral parathyroid glands. In the setting of generally poor prognosis and high rates of systemic relapse, ATC extensively involving the upper aerodigestive tract is generally considered surgically incurable. However, individualized decisions should be made based upon disease extent in view of surgical radicality, appropriate reconstruction, and expected impacts on intended postoperative therapies such as chemoradiation. Prophylactic central or lateral neck node dissection in patients with ATC is not indicated, but every attempt should be made to remove clinically apparent disease.

■ RECOMMENDATION 12

For patients with confined (stage IVA/IVB) ATC in whom R0/R1 resection is anticipated, we strongly recommend surgical resection.

Strength of Recommendation: Strong
Quality of Evidence: Low
Values Statement regarding Recommendation 12—The authors for this recommendation placed a higher value for the benefit (longer overall survival) of surgical resection and placed a lower value for potential morbidity and subsequent delay in chemotherapy and/or radiation therapy.

■ **RECOMMENDATION 13**

Radical resection (including laryngectomy, tracheal resections, esophageal resections, and/or major vascular or mediastinal resections) is generally not recommended given the poor prognosis of ATC and should be considered only very selectively after thorough discussion by the multidisciplinary team, also considered in light of new information based upon mutations present and the availability of targeted therapies.

Strength of Recommendation: Strong
Quality of Evidence: Low

GOOD PRACTICE STATEMENT 6

If surgery is undertaken, intraoperative frozen section and pathology consultation may be a helpful adjunct to inform surgical decision-making.

Surgery and survival

As indicated in our systemic review undertaken for the guideline document, the majority of studies that evaluate the role of surgery in ATC reveal an improvement in outcomes when surgery is undertaken (Supplementary Data). This is confirmed whether the interventions include radiation administered postoperatively or whether adjuvant treatment includes chemoradiation. Multiple factors contribute to limiting the conclusions drawn from available data. These include definition of resectability, definition of debulking versus biopsy, retrospective nature of most studies, as well as patient selection bias.

The retrospective review of the National Cancer Database (NCDB) identified ATC's used inverse probability weighted propensity score to adjust for selection bias and the conditional landmark method with a cutoff of 3 months (the estimated time period in which patients should have completed multimodal therapy) to account for potential immortal time bias (212). In this study, 50% of patients did not undergo surgery, 59% were treated with external beam radiotherapy, 42% received chemotherapy, and 33% received both chemotherapy and radiation therapy. When surgery was completed, thyroidectomy was performed in 50%. Importantly, survival was significantly improved by the following: (i) total thyroidectomy versus no surgery or less than total thyroidectomy, (ii) negative margins, and (iii) treatment at higher volume centers. High-dose radiation therapy was also associated with improved survival, notably the combination of high-dose radiation therapy with surgery provided greater improvement in survival outcomes than surgery or radiation alone. Chemotherapy was associated with improved survival on multivariable analysis but lost significance when immortal time bias and indication were adjusted. The lack of improved survival with chemotherapy is likely due to multiple factors, including the inability to identify whether the intention of treatment was palliative, whether chemotherapy was primary or concurrent with radiation therapy, and due to the small numbers of treated patients among the available studies.

A recent systematic review of the role of surgery in ATC provided additional insight with a tighter link to stage of disease as the selection of articles included a requirement for staging information (208). Statistical analysis was completed on a subset of articles, but several factors prevented a meta-analysis and calculation of effect sizes. The distribution of patient by stage was noted to be IVA 10%, IVB 48%, and IVC 36%. Similar to the above retrospective review, the median overall survival was 4.6 months. Patients treated with surgery experienced a median overall survival of 6.6 months, which increased to a median of 9.6 months with adjuvant therapy. Patients treated without surgery survived a median of 2.1 months. Those treated with primary radiation therapy, chemotherapy only, palliative therapy, and without treatment survived a median of 3 months. Although there were 1683 patients in the studies reviewed and included, only 314 had data on staging, and outcomes with the Kaplan–Meier analysis were limited to a subgroup of 203 patients with data available on individual outcomes. In this analysis, the overall survival at 6 months was 47.8% with a fall to 6.6% at 2 years. Statistically significant differences were noted in survival according to clinical stage. Patients undergoing surgery had a significantly better survival than those not treated by surgery. In contrast to the review of the NCDB, the extent of surgery (perhaps margin status) did not have a significant impact on survival.

Resection extent and capability of adjuvant therapies to prevent local progression and death from head and neck complications

Given ATC's characteristic rapid progression, including distant metastasis and mortality, the onset of therapy must be timely. In addition, ATC frequently has distant metastasis develop early in the course of disease and often causing patient death. Therefore, adjuvant therapy should preferentially be started within 2–3 weeks of the surgical date. Rationale for this approach can be supported by the following. (i) Corollary data from other aggressive malignancies. (ii) Supporting data in the literature. (iii) Prevention of local progression with radiation and possibly chemotherapy. To have a surgical wound that will tolerate chemotherapy and radiation in a 2- to 3-week time window, tracheal or esophageal resections and reconstruction would pose risks of significant morbidity. Most surgeons would thus likely recommend a delay of 4–6 weeks before the onset of adjuvant chemotherapy and radiation therapy in the setting of tracheal or esophageal resection and reconstruction, a factor that needs to be considered when undertaking these procedures.

Tumor margin and survival

The goal for any cancer operation is to achieve negative (R0) or microscopic (R1) surgical tumor margins, as an R2 resection (grossly positive margins or debulking operations) usually does not result in a survival advantage or durable local control. Although most, but not all, studies suggested that patients with ATC undergoing R0/R1 surgical resection have improved survival with or without adjuvant chemotherapy and radiotherapy, a recent systematic review of studies from 2000 to 2016 observed no difference by tumor margin status (208).

Frozen section analysis at the time of surgical intervention may be used to determine tumor margin status especially when trying to determine the extent of resection needed to achieve negative tumor margins. Most ATCs can be distinguished from normal tissue on frozen section analysis (213). There are no data on whether routine frozen section analysis undertaken in-operation to determine tumor status affects improved patient outcomes.

Palliative surgery

Palliative surgery in patients with ATC could be under some conditions a preventive procedure (e.g., securing the airway because of impending airway compromise, resection of locoregional disease in a patient with distant metastases) or palliative for symptoms associated with the disease (pain from bulky locally invasive disease, airway obstruction, esophageal obstruction). Surgical resection of locoregional disease may alternatively be strongly considered in patients with low-volume distant metastases if it can be done with minimal morbidity so that it would not affect the initiation of systemic therapy, if such an intervention is planned. In some circumstances, the presence of distant metastasis may be clinically ambiguous and such patients should be considered for surgical exploration if their disease is resectable/borderline resectable.

Debulking surgery

There are limited data on the impact on overall survival in patients who undergo debulking surgery with nebulously defined threshold for tumor volume reduction reported in the literature. Although some studies suggest that such intervention may improve patient survival, most ATCs progress rapidly. Furthermore, such intervention may delay external beam radiation or systemic chemotherapy because of wound complications.

Indications for neoadjuvant therapy

Between 85% and 95% of ATC patients present with extensively invasive primary tumors (209,214). Careful radiological assessment of tumor involvement in the visceral compartment, nearby vascular structures, and posterior paraspinous structures may reveal significant obstacles to a complete primary surgery. This is because 32–69% of patients have tracheal invasion, 37–55% have esophageal invasion, and 24–39% have carotid artery involvement (215,216). Endoscopic evaluation of the hypopharynx, esophagus, larynx, and trachea may be needed to supplement radiographic studies.

The aggressiveness of the operative resection should be considered in the context of morbidities that may occur from resecting adjacent involved structures. Extensive tumor involvement in the thoracic inlet and upper mediastinum may presage involvement of mediastinal vascular structures that warrant emergent sternotomy to control hemorrhage. Approximately 38% of primary thyroidectomies for ATC require extended resections (4). Ultimately, preoperative staging and assessment of local tumor extent are balanced against the experience, judgment, and technical expertise of the surgeon to determine whether a primary tumor resection should be attempted with acceptable morbidity and risk. Thus, the definition of ''unresectable'' can vary among different surgeons.

If a primary tumor is deemed unresectable, then there are alternative neoadjuvant approaches that may be appropriate in carefully selected patients. Full or partial course external beam radiotherapy may be followed by primary surgical resection, and then completion of radiotherapy if there had been a partial course. This can be as efficacious as initial primary resection (217). Likewise, neoadjuvant chemotherapy (218,219) or a combination of chemo- and radiotherapy (220) may prove effective in permitting delayed primary resection in similar circumstances.

In $BRAF^{V600E}$-mutated ATC patients, the successful use of neoadjuvant dabrafenib plus trametinib with or without immunotherapy has been described in a series of six patients (221,222). In these patients, the BRAF-directed therapy required continuation after completion of surgery, to maintain control of the disease. All but one patient received adjuvant chemoradiation after surgery. The one patient who did not receive adjuvant chemoradiation had stage IVC disease and was alive 19 months after the initial diagnosis. Overall survival at 6 and 12 months was 100% and 83%, respectively, but the locoregional control rate was 100%. It is unclear at this time whether adjuvant chemoradiation should be administered after complete surgical resection, particularly in stage IVC patients, as continuation of the BRAF/MEK inhibitor therapy is needed.

Some patients with ATC who receive initial radiotherapy with or without chemotherapy will have a PR—or rarely a CR to treatment (200,201,205,220,223). In such cases, the tumor may become resectable even if initially unresectable. Although external beam radiation may result in significant scarring making surgical resection difficult, patients who have a durable response and who have residual disease may be considered operative candidates if there is no other disease outside the neck. There are, however, no data in the literature to determine if such an approach results in improved disease-free survival and overall survival. One of the main rationales for such an approach is that the relapse rate after PR/CR to radiotherapy is high, and operative resection may reduce the risk of local relapse (205).

Surgical management of incidental ATC

At the time of diagnosis, ATC is confined to the thyroid in 2–15% of patients (198,202,209,224–226). Even more uncommonly (2–6% of cases), ATC is identified as a small, incidental finding after surgical resection of a predominantly non-ATC tumor (97,200,227). Completely resected intrathyroidal ATC is associated with a better prognosis (224,228). Whether completion thyroidectomy might thus be considered if only an initial lobectomy was performed is based more upon the characteristics of the non-ATC component of the malignancy than on the incidental finding of ATC, including the findings of preoperative imaging studies evaluating the contralateral lobe for the initial lobectomy. There are no data that demonstrate a difference in disease-free survival or survival based on the extent of thyroidectomy for an incidental ATC. Although there are also no data on whether adjuvant chemotherapy with or without radiotherapy is indicated in intrathyroidal incidentally detected ATC, it is important to remember that most patients with stage IVA ATC previously succumb to their cancer, but that few do if instead treated with modern multimodal therapy (229,230). For the role of adjuvant chemotherapy and radiation treatment for incidental ATC, see Recommendation 14.

Airway assessment

Airway assessment is of central importance initially and throughout the care of ATC patients. The airway may be altered at the level of the larynx by unilateral or bilateral

recurrent laryngeal nerve dysfunction, laryngeal edema from tumor or radiotherapy, tracheal compression, tracheal or laryngeal invasion with intraluminal airway disease. Airway patency is very likely to change during the course of treatment such that a low threshold for repeat airway examination (endoscopy and imaging) must be maintained, primarily driven by the patient's airway symptoms. As in the initial evaluation of ATC, interval evaluations should include inspection of the larynx, subglottis, and upper trachea.

Tracheostomy and ATC

Airway symptomatology and consideration for tracheostomy are very common in patients with ATC. One series noted that 19% of patients presented with stridor, an additional 23% developed significant airway symptoms during radiotherapy, with 36% of patients ultimately dying of airway obstruction (231). Another recent series reported that tracheostomy was necessary in 40% of their patients and that patients presenting with dyspnea had a significantly lower overall survival (232). However, while tracheostomy offers airway control, it has been associated with decreased survival perhaps due to more advanced/aggressive disease or by delaying the onset of radiotherapy (233).

Individualized patient-centered tracheostomy decision-making

The role of tracheostomy both in planned curative treatment and in the palliative settings is complex, as is its timing. Tracheostomy is considered with equipoise; on one hand, tracheostomy is seen as a tool to prevent death by asphyxiation counterbalanced by the overall grave ATC prognosis, and consideration of the fact that tracheostomy triggers significant alterations in quality of life. Many experienced surgeons who typically manage ATC patients have trained in an era where tracheostomy was a standard offering both in the acute and elective settings in many patients with ATC. In 2020, the pendulum has swung toward a more individualized patient-centered tracheostomy decision-making algorithm.

The decision to perform tracheostomy requires laryngeal examination and axial imaging (perhaps with endoscopy), and expert multidisciplinary input folded into the patient's goals of care.

In the decision-making process, the patient must be fully informed as to the nature of tracheostomy, what it can provide, and what functions it alters. There must be a clear discussion of the expected time frame of tracheostomy and the high likelihood that it may be permanent. The patient's cognitive and manual functioning should be considered, as should the patient's overall resources and support so as to enable tracheostomy care. Tracheostomy may delay subsequent therapy with radiation and targeted chemotherapy for up to 2 weeks or longer depending on wound healing issues.

Elective or prophylactic tracheostomy

Tracheostomy may occasionally be felt necessary as part of the initial surgical offering either planned from the onset, or felt necessary depending on the degree of bilateral dissection with resulting edema or perhaps bilateral cord paralysis. This is not an uncommon scenario and therefore tracheostomy should be part of the standard consent form in most patients undergoing any significant resection for ATC. Tracheotomy also may occasionally be considered necessary before a course of radiotherapy in anticipation of laryngeal or tracheal edema in the setting of a marginal airway at the onset of treatment.

Many patients with ATC will not require surgical airway intervention unless the patient has stridor or acute airway distress. The presence of a tracheostomy tube and secretions will lead to considerable discomfort on the part of the patient, and there is generally no need for creation of a surgical airway, even in patients with unresectable ATC.

GOOD PRACTICE STATEMENT 7

In patients without impending airway compromise, we advise against preemptive tracheostomy placement.

Acute obstruction and tracheostomy

ATC patients presenting with acute airway obstruction is unfortunately common. This couples the airway medical emergency with a nascent patient/physician relationship. In this circumstance, there should be a low threshold for tracheostomy to allow time for the patient and family to obtain a greater understanding of the disease, treatment options, and outcomes with an understanding that the patient's long-term goals and informed consent may not be fully developed, but airway stabilization through tracheostomy allows for ongoing conversations over time after the airway is secured. It is difficult if not impossible for treatment reduction or palliative options to be offered immediately upon entering a treatment relationship in the setting of active significant airway symptomatology.

Tracheostomy in this setting can be very high risk, as intubation may be difficult or impossible, and access to the trachea, which may be displaced and deformed, may involve significant and difficult overlying tumor dissection. The seriousness of the procedure should not be underestimated, and thoughtful discussion with the patient and family is necessary as is careful review of the axial CT with anesthesia who need to be prepared mentally and with the necessary equipment, and need to be armed with backup plans if initial attempts fail.

The tumor may be extensive and overlying the trachea, and its bleeding may prevent tracheostomy in the typical upper cervical trachea. Intubation in the OR by experienced anesthesia and surgery personnel is best performed before tracheostomy but may not always be possible. Placing a tracheostomy under local anesthesia is often difficult given the typical extensive tumor distribution. In such circumstances, a higher tracheostomy through the cricothyroid membrane (i.e., a cricothyroidotomy) may be the best option if the tracheotomy tube placed at this level will bypass the obstruction. In this setting, there is less concern with endolaryngeal or vocal cord alteration given the graveness of the prognosis and extreme risk and consequence of losing the airway during the procedure.

Airway management and indications for tracheostomy

Tracheostomy in patients with ATC is performed in extreme circumstances to support an airway that is causing life-threatening asphyxia. Most patients who require a tracheostomy in ATC have an extremely guarded prognosis

and progression of disease. Tracheostomy is best avoided if possible. However, if the patient is in severe airway distress, the patient should be brought to the operating room since tracheostomy is best performed under anesthesia with preoperative intubation, if possible. Patients often require isthmusectomy or debulking of the pretracheal tumor to obtain adequate access for a tracheostomy, highlighting the importance of having a highly experienced surgeon involved. An attempt to perform the tracheostomy either in the ward or in the emergency room under local anesthesia should be avoided.

The precarious ATC airway prompts diligence in optimizing placement of the tracheotomy tube. To determine that the luminal positioning is appropriate, fiberoptic examination of the position of the distal end of the tracheotomy tube should confirm a patent airway distally. To reduce the potential for the tracheotomy tube to become dislodged, the tracheotomy tube can be secured with standard ties and also secured with transcutaneous sutures passed through the faceplate of the tracheotomy tube. Careful observation of airway status while recovering in the operating room and while in the recovery room is necessary.

After the surgical procedure, the patient should remain intubated for a short period of time and extubated either in the operating room itself or in the recovery room with close observation. If the airway was secure preoperatively, most patients will not have postoperative airway-related issues. However, if there is an airway-related issue, the patient should have direct laryngoscopy evaluation and be reintubated and extubated under optimal circumstances with close observation. If there is any continued major concern about stridor or shortness of breath, the patient will require revaluation and possible semielective tracheostomy, which should be performed in the operating room. The patient's airway should be closely monitored in the recovery room during the postoperative period.

Benefits of tracheostomy

Tracheostomy can prolong life, as it overcomes acute airway distress and impending mortality. Tracheostomy can also maintain airway patency to facilitate other therapies. However, patients with ATC who require tracheostomy likely have advanced local disease, and the chances of long-term survival are low. Under these circumstances, tracheostomy may prolong suffering. Tracheostomy in particular tends to increase secretions, coughing, speech and swallowing alterations (at least in the short term), need for frequent suctioning, and overall discomfort that the patient may experience.

Tracheostomy has also been found to negatively affect patient well-being and body image perception (234). The impact of tracheostomy on caregivers has been reviewed in the pediatric population with less than 50% of families feeling prepared adequately at discharge, 11% lacking emergency preparedness training, and 14% seeking emergency care within the first week of discharge (235). Tracheostomy has been found to affect the caregivers' stress level with reduction in their quality of life (236).

Also, placing a tracheostomy may provide only transient airway security. Since tumor often needs to be entered as a tracheostomy is placed, there may be ongoing tumor growth around the tracheostomy stoma. This causes bleeding and ultimately tracheostomy tube displacement. However, it does overcome acute airway distress with some prolongation of life. Whether that is meaningful or not remains controversial.

Tracheostomy during active treatment

ATC itself poses imminent risk to patients both in terms of the threat to airway and esophagus due to local disease in the neck, and potentially also consequent to risk of metastatic disease. Moreover, during active treatment, some existing patient risks increase, while other new risks arise. The patient, family, and involved health care providers must be fully informed about these risks. It is critical that all involved be aware of the potential risks that need to be identified and act on any emerging problems as they arise. Patients should be educated to be proactive in bringing emerging issues to the attention of their caregivers, and caregivers should be educated as to how to respond in the best interests of the patient given the unusual context of ATC under active therapy.

Patients with ATC undergoing radiation therapy require especially close airway monitoring. The airway may become narrowed from the effect of ATC, vocal cord paralysis, or endolaryngeal edema due to radiation therapy. In the absence of impending airway compromise, minor airway-related issues are best overcome with humidity, rest, and occasional use of short-term corticosteroids.

RADIOTHERAPY AND SYSTEMIC CHEMOTHERAPY IN LOCOREGIONALLY CONFINED (STAGES IVA AND IVB) ATC: PRINCIPLES AND APPROACHES

The emphasis of this section is upon the advisability of the early use of radiotherapy in patients with IVA/IVB ATC. After expeditiously (i) establishing a correct diagnosis of ATC, (ii) assembling a team and base of care for the patient, (iii) defining patient goals of care, and (iv) establishing whether surgery to resect the primary tumor should be undertaken, the next question generally to arise in patients with IVA/IVB ATC is how best to limit the threat from residual macro- or microscopic ATC in the neck, which is otherwise expected to lead to terminal airway and/or esophageal compromise. Regardless of whether surgery is performed, radiotherapy to the tumor bed should be considered a next step. This section addresses this important topic, and also considers the parallel question of whether there should additionally be a role for superimposed systemic therapy intended to increase efficacy to radiation therapy and also control any occult systemic micrometastatic disease.

The application of radiotherapy and/or systemic chemotherapy in locoregionally confined (IVA/IVB) ATC should be tailored to the capabilities and directives of the patient in coordination with the treatment team in accord with the patient's goals of care. Critical in defining approaches to be used are the following: (i) the wishes/directives of the patients developed in accord with their goals of care, (ii) the fitness of the patient (performance status, comorbidities) to undergo candidate therapeutic approaches, (iii) the availability of treatment approaches at intended treatment site(s) and the existence of a team of providers capable of expertly coordinating the patient's care in the setting of a complex and toxic combined modality therapeutic plan, and (iv) detailed and balanced discussions of the patient's willingness to

accept the risks, toxicities, and logistical demands of candidate therapeutic approaches in light of uncertain outcomes in the setting of an aggressive cancer with a very high risk of mortality.

In general, initial treatment goals (as elected by the patient, devised in consultation with the treating team) first need to be established as either palliative or potentially curative in intention, realizing that interval developments in terms of tumor response and progression and also in terms of interval adverse events will necessarily shape therapy once underway. Typically, the mainstays of therapy in addition to surgery can involve: (i) locoregional approaches, most commonly radiotherapy plus or minus concurrent chemotherapy, and (ii) systemic approaches, conventionally cytotoxic chemotherapy but now also potentially targeted therapies. In particular, context-dependent targeted therapeutics personalized to specific somatic ATC mutations may also be of consideration, especially dabrafenib plus trametinib in $BRAF^{V600E}$-mutated ATC.

Radiotherapy after complete/near-complete (R0 or R1) resection

The best outcomes in terms of both local control and survival in IVA/IVB ATC based upon consistent results from multiple studies appear to be associated with complete/near-complete surgical resection followed by radiotherapy, often administered in combination with chemotherapy; studies are summarized in Supplemental Data S4. Unfortunately, there is inconsistency in outcomes measured, reporting of effectiveness of local control, and in terminology used; multimodality often is also sometimes used to describe surgery and postoperative radiotherapy without chemotherapy. In published reports, there is furthermore always an element of case selection bias; invariably, patients with better performance status, younger age, and less extensive disease receive more aggressive combination therapy. Nevertheless, unselected Surveillance, Epidemiology, and End Results (SEER) data detailing 516 patients revealed in a multivariate analysis that, along with age, only the combined use of surgical resection and radiotherapy was identified as an independent predictor of survival (224). Given large patient numbers and the fact that this was a population-based study, these data provide the strongest and least biased evidence presently available. That the combination of surgery and radiotherapy is important is also supported in the form of another smaller population-based study from British Columbia analyzing 75 patients; survival was better in patients who had more extensive surgery and had high-dose radiotherapy with or without chemotherapy (203). Moreover, a meta-analysis of 17 retrospective studies that included 1147 patients also concluded that postoperative radiotherapy reduces the risk of death compared with surgery alone (237).

More recently, although not population based, there have been three analyses of NCDB data obtained from U.S. cancer centers. In one study, longer survival was associated with doses of radiotherapy >59.4Gy—but not with lower doses. There was a survival of 38% at 2 years (median 16 months) in patients who received high-dose radiotherapy after a thyroidectomy—but these accounted for only 5% of the study population, suggesting selection bias (212). In another analysis of patients who had unresected disease, again, a higher radiotherapy dose was associated with greater survival, but so was an ''intermediate dose'' (defined as 45–59.9 Gy) in patients with unresectable ATC (238). In a third analysis of NCDB data (239), a small survival benefit was found from trimodality treatment.

In general, most single-institution studies also report improved results due to the combination of surgery and radiotherapy (4,66,95,97,200–202,204,206,207,218,240–244). In a multicenter study from Korea (245) involving 329 patients, median survival was 15 months (84 patients) with a 1-year survival of 50% among patients undergoing surgery and radiotherapy compared with 5 months without surgery (50 patients) but with radiotherapy or chemoradiotherapy alone—and only 2 months with no treatment (81 patients).

Assessing the incremental additional contribution of systemic therapy to that of radiotherapy and surgery has been less well studied, but available retrospective data suggest benefit. In patients with stage IVA disease, trimodality treatment was associated with a longer median survival than surgery and radiotherapy without chemotherapy (11.2 months vs. 9.3 months, $p < 0.001$) The difference was maintained in stage IVB patients (9.9 months vs. 5.9 months, $p < 0.001$) and even in patients with metastatic disease (4.9 months vs. 3.5 months, $p < 0.001$).

Most studies report survival only, but those reporting local control generally show improvement with multimodality treatment. For instance, Liu *et al.* reported a 2-year local control rate of 43% with postoperative radiotherapy compared with 7% in surgery alone in patients without distant metastases (201,206,207,240,246,247). In a recent series from Prasongsook *et al.*, local control was 90% for the lifetime of patients treated with combination chemotherapy and concurrent radiotherapy (248).

In the majority of series, radiotherapy is given after surgery; however, in a few, preoperative radiotherapy has been given. In some series, radiotherapy is ''sandwiched'' pre- and postoperatively (95,97). For instance, Tennvall *et al.* initially used a ''sandwich'' approach with preoperative chemoradiotherapy followed by surgery then further chemoradiotherapy—but subsequently instead administered preoperative chemoradiation then surgery, then adjuvant chemotherapy without radiation (220). In their latest series, 17 out of 23 patients were able to undergo some form of surgery, 2 with gross residual disease. Despite this approach, the median survival was only 2 months (220); this approach has not been adopted by other centers, although some have utilized preoperative chemotherapy alone (219,221).

In a recent series comparing outcomes from an intensive combined modality approach (surgery, when feasible, followed by chemo-intensity-modulated radiotherapy [IMRT] using taxanes) versus historical pre-IMRT approaches combined with doxorubicin, all-stage overall survival at 1 year improved from 10% to 43% (248). In comparing stage-specific outcomes, however, differences in overall survival among patients receiving the most intensive trimodal therapy were only statistically significant among stages IVA and IVB patients.

In patients with initially resectable disease, there does not appear to be any substantive evidence that preoperative radiotherapy is preferable to postoperative radiotherapy. Surgical resection may therefore reasonably be performed first, with

postoperative chemoradiotherapy given subsequently. However, in patients with initially unresectable disease, chemoradiotherapy may rarely enable subsequent resection and should be considered in patients with good performance status and without significant metastatic disease. However, the potential benefit in a few must be weighed against the risk of toxicity in a population of patients, the majority of whom still have poor survival. It is unclear if patients with incidentally detected ATC after thyroidectomy benefit from radiotherapy (249).

Toxicities from radiotherapy and chemoradiotherapy, risks versus benefits

The reported benefits from aggressive bi- or trimodal therapy, however, must be carefully balanced with patient goals of care and expected negative impacts on short- and long-term quality of life. Quality-of-life data are completely lacking. However, historical data reporting toxicities from prior approaches exist, but must also be viewed in light of current use of IMRT, which reduces toxicities to normal adjacent structures. It is nevertheless clear that short-term toxicities from multimodal therapy in the setting of ATC are extreme, but confounded by issues arising from the cancer itself. For example, Prasongsook *et al.* reported a 60% hospitalization rate and a temporary requirement for feeding tube placement in 60% among ATC patients undergoing trimodal therapy (248). Prasongsook *et al.* also reported a 3% mortality rate during multimodal therapy in ATC (248). Chronic problems such as lymphedema, limited neck range of motion, and chronic dry mouth are also common and irreversible. Hence, it is imperative to discuss such complications with patients so as to insure their informed decision-making.

There are few specific data on radiation toxicity in patients being treated for ATC. The available data are outlined above. In general, it can be assumed that toxicity is similar to that seen in the treatment of other head and neck cancers but is dependent on the volume being treated and the radiation dose prescribed and if concurrent chemoradiation is given. Serious complications are rare following well-planned external beam radiation therapy. Acute toxicity at the end of a course of radiation therapy includes skin erythema and moist desquamation and mucositis of the esophagus, trachea, and larynx and also xerostomia. Late toxicity includes skin telangiectasias, skin pigmentation, soft tissue fibrosis, and mild lymphedema, usually appearing just below the chin. Esophageal stenosis can usually be treated by dilatation, but gastric tube (G-tube) dependency. Tracheal stenosis is rare.

Two large series on the use of external beam radiation therapy without concurrent chemotherapy in DTC reported no Radiation Therapy Oncology Group grade IV toxic effects (250,251). However, in a series of 12 ATC patients, 23% experienced acute or chronic morbidity requiring hospitalization, and 2 out of 5 long-term survivors who were treated with concurrent chemoradiation had esophageal stenosis (one required a permanent G-tube) (244).

■ RECOMMENDATION 14

Following R0 or R1 resection, we recommend that good performance status patients with no evidence of metastatic disease who wish an aggressive approach should be offered standard fractionation IMRT with concurrent systemic therapy.

Strength of Recommendation: Strong
Quality of Evidence: Low

GOOD PRACTICE STATEMENT 8

Radiation therapy should begin no later than 6 weeks after surgery.

GOOD PRACTICE STATEMENT 9

Patient goals of care, medical and psychosocial fitness for therapy, potential toxicities, financial considerations, and robustness of social support must be prominently considered in the decision to proceed with aggressive multimodal therapy.

Timing and sequencing of perioperative radiotherapy and/or systemic chemotherapy

There are no definitive data to indicate when radiotherapy and chemotherapy should start or how they should be sequenced. Some physicians may prefer sequential therapy. However, given that ATC grows very rapidly, it is probably prudent to start therapy as soon as feasible. Radiotherapy can generally begin after postoperative healing has transpired and when the patient has recovered sufficiently to lie supine and tolerate immobilization. In particular, radiation treatment planning should begin expeditiously when postoperative swelling has diminished, $\sim$2 to 3 weeks after surgery. Depending on the time required for treatment planning, treatment may start with a parallel opposed pair beam arrangement until the final treatment plan is available, which should be less than 5 business days. In terms of time of initiation of systemic therapy if elected, this too should begin expeditiously. However, systemic chemotherapy can often be initiated more quickly after surgery than can radiotherapy, as less postoperative healing is required for its safe administration. In a single-institution series, Prasongsook *et al.* reported a median time from surgery to chemotherapy of 19 days, and median time from surgery to radiotherapy initiation of 27 days (248).

GOOD PRACTICE STATEMENT 10

Cytotoxic chemotherapy can be initiated within 1 week of surgery, providing sufficient healing, in anticipation of subsequent chemoradiation.

Radiotherapy and/or chemotherapy in patients with unresectable or gross residual locoregionally confined disease

Even among patients who do not have resectable disease, or who have an R2 resection, radiotherapy can achieve local control; several series, however, show a radiation dose/response relationship with outcomes. These data must be interpreted with caution as all such studies are retrospective with selection bias; patients with less extensive disease and better performance status and better expected outcomes are more likely to be given high-dose radiotherapy. Levendag *et al.* reported that patients who received <30 Gy had a median survival of 1 month compared with 3.3 months if >30 Gy was given (225). Pierie *et al.* reported that ATC patients who had ≥45 Gy had better survival (200). Swaak-Kragten *et al.* reported that median survival was 5.4 months if given >40 Gy but only 1.7 months if less <40 Gy was given (201). Wang *et al.* reported a median survival was 3 months if <40 Gy and 11 months if >40

Gy was administered (226). In a recent report on the experience with radiotherapy and weekly doxorubicin, a median survival of 6 months was reported, but a radiotherapy dose ≥50 Gy was associated with a median survival of 8.4 months, and, if >60 Gy was given, the median survival was highest at 14 months (252). These studies collectively suggest that higher dose radiotherapy is associated with longer survival and moreover that IMRT should be used to deliver these doses safely and effectively.

How to most appropriately select patients for aggressive multimodal therapy remains uncertain, but patients with good performance status and no metastases should probably be offered high-dose tumor bed radiotherapy. There is, however, also the suggestion that patients with limited metastatic disease may benefit from an aggressive approach to the local and regional disease to ensure local tumor control. Levendag *et al.* reported that median survival in patients with metastatic disease was improved if local control was achieved (8 months vs. 2 months) (225).

In the analysis of data from the NCDB discussed above, patients with stage IVC disease had slightly better survival after trimodality treatment than after bimodal therapy (surgery and radiotherapy, IVC 4.9 months vs. 3.5 months, $p < 0.001$). In contrast, both Liu *et al.* and Prasongsook *et al.* reported no survival benefit from multimodality treatment in patients with clearly metastatic disease at diagnosis. Thus, enthusiasm for aggressive therapies must be tempered in consideration of the overall poor survival of patients with metastatic disease and in light of patient wishes.

■ RECOMMENDATION 15

We recommend that patients who have undergone R2 resection or have unresectable but nonmetastatic disease with good performance status and who wish an aggressive approach be offered standard fractionation IMRT with systemic therapy. Alternatively, in *BRAF*^{V600E}-mutated ATC, combined BRAF/MEK inhibitors can be considered in this context.

Strength of Recommendation: Strong
Quality of Evidence: Low

■ RECOMMENDATION 16

In patients with unresectable disease during initial evaluation in whom radiotherapy and/or systemic (chemotherapy or combined BRAF/MEK inhibitors) therapy render the tumor potentially resectable, we recommend reconsideration of surgical resection.

Strength of Recommendation: Strong
Quality of Evidence: Low

For patients with poor performance status who decline—or who would not be expected to tolerate—high-dose radiotherapy, low-dose radiotherapy may be of palliative benefit with respect to control of local disease/symptoms, but there are few supporting data. Juror and associates reported a 40% CR rate from radiotherapy, and a 42% PR rate for an overall RR of 82%, and a trend to increased survival with higher doses. Higher doses of radiotherapy, however, were not associated with improved RRs (doses of less than 20 Gy were excluded) (205). Thus, there is probably a reasonable chance of transient response to palliative radiotherapy using modest doses. However, in the analysis of NCDB data, by Glaser *et al.*, a survival benefit was only seen in patients who received greater than 59.4 Gy (212). In contrast, in the series of patients with unresected ATC from the NCDB, Pezzi *et al.* showed no survival benefit from <45 Gy compared with no radiotherapy; however, there was improved survival associated with 45–59.9 Gy compared with less or no radiotherapy (238). Importantly, outcome measures included survival and not symptom or local control, and so, a palliative effect of low-dose radiation (often given in large fractions such as 3 Gy times 10 (30 Gy) or 4 Gy times 5 (20 Gy) is uncertain. There are few data on quality-of-life impacts in these patients. Lessened toxicity in response to a palliative radiotherapy program could therefore prompt consideration of such an approach in symptomatic patients not considered appropriate for high-dose radiotherapy because of considerations such as performance status, widespread metastatic disease, or patient wishes.

GOOD PRACTICE STATEMENT 11

In patients of poor performance status, palliative or preventative (no residual disease present) locoregional radiotherapy over high-dose radiotherapy is suggested.

Radiotherapy treatment volume and techniques (conventional, altered fractionation, IMRT, adaptive radiotherapy, proton therapy)

The radiotherapy treatment volume required to optimally treat either unresected or postoperative ATC is generally very large (thyroid gland or operative bed, bilateral level II–V cervical nodes, level VI central neck nodes, and upper mediastinal nodes to the carina), with an element of compromise therefore required in efforts to achieve acceptable toxicity. A variety of conventional two-dimensional and three-dimensional planning techniques have been used over the years; however, with IMRT, it is possible to generate concave dose distributions and dose gradients with narrow margins so as to enable treatment of complex treatment volumes minimizing dose to adjacent normal structures such as spinal cord, larynx, esophagus, brachial plexus, and salivary glands. In the rare instance that chemoradiotherapy produces a rapid reduction in the tumor volume, there may also be a role for adaptive radiotherapy and replanning radiotherapy to ensure adequate treatment of the tumor volume while avoiding higher doses to organs at risk and to treat a smaller high-dose tumor volume and potentially reduce toxicities.

There is strong evidence of the benefit of IMRT in improving outcomes and reducing toxicity in other head and neck cancers (253,254). Although there is insufficient evidence in a systematic review to propose evidence-based recommendations for ATC, given the dosimetric advantages and potential reduction in toxicity, IMRT should be offered to patients with ATC as an alternative to conventional treatment planning (255). The availability of intensity-modulated proton therapy may offer an advantage over IMRT in reducing radiotherapy dose to normal structures such as the larynx, esophagus, and salivary glands—but evidence of incremental clinical benefit over IMRT is presently lacking.

Using hyperfractionation may also increase radiotherapy RRs, at the cost of increased physical toxicity and financial burden—but with the advantage of shorter overall treatment time compared with conventional radiotherapy (which theoretically can reduce the risk of tumor cell repopulation).

This latter effect may be important in rapidly growing ATC, and has been used in combination with chemotherapy in several studies. In a study of radiotherapy alone, Wang *et al.* found that hyperfractionated radiotherapy resulted in longer median survival compared with conventional fractionation (13.6 months vs. 10.3 months), although the difference was not statistically significant (226). In a small number of patients, Kobayashi *et al.* reported better local control with postoperative hyperfractionated radiotherapy than conventional radiotherapy (242). In contrast, Dandekar *et al.* reported that a hyperfractionated accelerated protocol with larger fraction sizes than usually given conferred significant toxicity but no survival advantage (256). One study used high-dose, short-course hypofractionated radiotherapy to complete radiotherapy in a shorter time and reported it to be effective with comparable local control and toxicity compared with conventional fractionation (257).

■ **RECOMMENDATION 17**

Among patients who are to receive radiotherapy for unresectable thyroid cancer or in the postoperative setting, IMRT is recommended.

Strength of Recommendation: Strong
Quality of Evidence: Low

Role of chemotherapy combined with radiotherapy as neo/adjuvant therapy in locoregionally confined (stages IVA or IVB) ATC

In the past, when chemoradiotherapy was given for thyroid cancer, radiotherapy was most often combined with doxorubicin, reported in a series of single-institutional studies. Although these reports have not shown consistent benefit, there is increasing evidence that taxanes, which are also radiosensitizing agents, may be more effective chemotherapeutic agents than those traditionally used in ATC (218,244,258). Kawada *et al.* (259) alternatively reported a discouraging RR of only 14% to docetaxel monotherapy in advanced ATC. Encouraging results, however, have been reported when taxanes are combined with radiotherapy. Troch *et al.* reported four CR and two PR among six patients treated with combined docetaxel and IMRT, with five of six patients surviving >21 months (260). Similarly, among 10 consecutively treated IVA and IVB ATC patients with locoregional disease, Foote *et al.* (230) reported that five patients were alive and cancer-free having been followed >32 months with a median overall survival of 60 months (overall survival at 1 and 2 years was 70% and 60%, respectively) in response to IMRT combined with adjuvant and radiosensitizing chemotherapy, including docetaxel plus doxorubicin. In an updated report examining 30 patients receiving multimodal therapy and 18 treated with palliative intention, median overall survival was 21 months compared with 3.9 months in the pooled multimodal therapy versus palliative intention groups (HR, 0.32; $p=0.0006$). Among patients with stage IVB disease, median overall survival was 22.4 months among multimodal therapy, versus 4 months among palliative intention patients (OR 0.12; [CI 0.03–0.44]; $p=0.0001$), with 68% multimodal therapy versus 0% palliative intention patients alive at 1 year; however, the cohort size was small, all multimodal therapy patients received both chemotherapy and IMRT, and the study was historical and not randomized. Hence, although this study suggests improved outcomes in response to multimodal therapy in IVA/IVB ATC, it does not specifically clarify the incremental value of the addition of chemotherapy to IMRT. Among patients with stage IVC cancer, overall survival did not differ by therapy in the same study (248), suggesting also that improved outcomes are concentrated in patients without distant metastases. In a small series of 18 patients from Egypt, debulking surgery followed by concurrent chemoradiotherapy with docetaxel and further chemotherapy was shown to be feasible and effective (261).

Altered fractionation can be combined with chemotherapy (referred to as concurrent chemotherapy), but with the risk of increased toxicity. Altered fractionation does not prevent the initiation of chemotherapy after completion, and, as overall treatment time is reduced with altered fractionation schedules, chemotherapy may be started sooner than after conventional radiotherapy.

To date, there has been no comparison of altered fractionation radiotherapy alone or combined with chemotherapy compared with conventional chemoradiotherapy, and either may be considered depending on institutional preferences.

■ **RECOMMENDATION 18**

The use of cytotoxic chemotherapy involving a taxane (paclitaxel or docetaxel), administered with or without anthracyclines (doxorubicin) or platin (cisplatin or carboplatin), is recommended in patients treated with definitive-intention radiation.

Strength of Recommendation: Strong
Quality of Evidence: Low

SYSTEMIC THERAPEUTIC APPROACHES TO LOCALLY ADVANCED UNRESECTABLE AND/OR METASTATIC DISEASE

Defining therapeutic goals, expected/possible adverse events, appropriate expectations, and limits of care

Most patients with stage IVC, and many with stage IVB, ATC have short survival, measured in weeks or months, excepting those who prove to be exceptional responders to personalized approaches such as patients with tumors harboring a $BRAF^{V600E}$ mutation who are treated with—and who respond to—BRAF-directed therapy. It is therefore imperative that the formulation of treatment plans in patients with ATC be undertaken expeditiously—but only after detailed discussions of options and expected outcomes with careful considering for the patient's goals of care in this extreme context. In particular, resuscitation/code status and advance directives including assessment of patient goals of care (a values history) should be rapidly established (262). Refer to the section on Establishing Treatment Goals above for additional discussion of these important topics. POLST/MOLST is also advisable for patients who may be visiting multiple hospitals or institutions for their care.

Systemic therapy for unresectable stage IVB and stage IVC patients

In advanced disease, decisions related to the timing and administration of systemic therapies relative to palliative local therapies depend greatly on the following: the patient's goals of care, the burden of distant metastatic disease and

Table 6. Examples of Concurrent (in Combination with Radiation Therapy) Chemotherapy Regimens in Patients with Anaplastic Thyroid Cancer

Regimen	*Agents/dosages*	*Frequency*
Paclitaxel/carboplatin	Paclitaxel 50 mg/m^2, carboplatin AUC2 IV	Weekly
Docetaxel/doxorubicin	Docetaxel 20 mg/m^2 IV, doxorubicin 20 mg/m^2 IV	Weekly
Paclitaxel	Paclitaxel 30–60 mg/m^2 IV	Weekly
Docetaxel	Docetaxel 20 mg/m^2 IV	Weekly

AUC, area under the curve.

threat(s) imposed by said disease, the patency and stability of the airway, prior therapies, the availability of attractive therapeutic options including clinical trials, patient clinical condition and comorbidities, and whether the patient's tumor harbors a targetable mutation in which personalized targeted therapy is readily available and affordable. Figures 1 and 2 illustrate in broad strokes approaches to patients with locally advanced or metastatic disease taking these factors into account. Because of the paucity of data indicating comparative efficacies of various candidate systemic therapies in this context, and the critical need for better data in this context, clinical trials should be prominently considered if available and feasible. Inclusion criteria for clinical trials can be rigid; thus, if a clinical trial is an option for the patient, this should be considered early on and be expeditious. Critically, many clinical trials require good performance status and commonly also the ability of patients to swallow intact tablets/capsules, thus excluding the sickest ATC patients from studies and from potentially life-extending therapies, and in the process having the potential to bias study results to have uncertain relevance to many ATC patients.

Expeditious therapy initiation. Given the very aggressive nature of ATC and imminent threat from disease progression, expeditious treatment initiation is critical among patients wishing an aggressive approach. As described below, anthracyclines (doxorubicin) and taxanes (paclitaxel, docetaxel) have modest and often disappointing and only transient clinical activity in advanced ATC. While awaiting molecular information or targeted drug approval, radiotherapy and/or the expeditious initial use of these cytotoxic chemotherapy drugs as ''bridging'' chemotherapy are prudent among patients wishing aggressive treatment (Table 6). Furthermore, productively targetable alterations may not exist in a particular tumor, or targeted therapy may not be available, making cytotoxic chemotherapy the only viable systemic therapeutic option. Consequently, the early application of ''bridging'' cytotoxic chemotherapy has been used in clinical practice, reported in the literature (263), and is being used in at least one first-line ATC therapeutic clinical trial (NCT03181100), so as to ensure that a potentially effective therapy is not withheld or delayed. This is a strategy of strong consideration in clinical practice and in other trial designs.

Use of RAI. Radioactive iodine (RAI) is ineffective in ATC and should not be used. Rarely, however, in patients with coexistent DTC and ATC, in which the ATC component is in complete remission yet the DTC component is progressing and threatening, RAI may have a role—but only in treating the DTC component.

■ **RECOMMENDATION 19**

Among ATC patients with unresectable or advanced disease wishing aggressive therapy, we suggest early initiation of cytotoxic chemotherapy as an initial and potentially bridging approach until mutational interrogation results and/or mutationally specified therapies might be available, and if appropriate.

Strength of Recommendation: Conditional
Quality of Evidence: Low

Systemic therapy: targeted approaches

Mutation-guided individualized targeted therapeutic strategies are now increasingly finding application, especially in advanced or initially unresectable ATC. Retrospective assessments of outcomes observed from using this strategy are now being published, with emerging evidence to support a potential survival advantage to the use of targeted therapy in ATC in one recent study (HR in response to use versus nonuse of targeted therapy, 0.49; [CI 0.39–0.63]; $p < 0.001$) (264).

BRAF^{V600E}*-mutated ATC*

Because targetable somatic mutations in ATC may suggest potentially efficacious personalized therapeutics, most centers with ATC expertise interrogate tumors for mutations early on so as to define later candidate opportunities that may exist in this space. Among ATCs, *BRAF^{V600E}* is the most commonly encountered productively actionable mutation, seen in 50–70% of cases (74–76). When PTC coexists in the pathology specimen with ATC, over 90% may harbor a *BRAF^{V600E}* mutation (126).

In May 2018, the BRAF/MEK inhibitor combination, dabrafenib plus trametinib, was approved by the U.S. FDA for ATC patients harboring a *BRAF^{V600E}* (but not other) mutation. BRAF-directed therapy can induce prompt and impressive tumor regression in these patients, and therefore, use of these drugs in stage IVC patients is recommended in *BRAF^{V600E}*-mutated patients. In *BRAF^{V600E}*-mutated ATC patients with unresectable stage IVB disease, however, consideration of upfront chemoradiation is the current standard. Alternatively, when upfront chemoradiation may be contraindicated or not desired by the patient, systemic therapy with BRAF-directed therapy can be considered. Neoadjuvant use of dabrafenib plus trametinib is also being explored as a way to convert an unresectable primary tumor to resectable (221,222). Moreover, there are now emerging data to suggest that surgical resection following favorable response to neoadjuvant BRAF inhibitory therapy can lead to prolonged survival (94% 1-year overall survival, $n = 20$) (264).

In particular, dabrafenib (150 mg twice daily) combined with trametinib (2 mg daily) was studied in a prospective, nonrandomized clinical trial of patients with *BRAF*^{V600E}-mutated ATC (116). Data presented to the FDA on 23 evaluable patients showed an overall RR of 61% [CI 39–80%]; CR was seen in 4% and PR in 57%. Response duration was ≥6 months in 64% of responding patients and overall survival was 80% at 1 year. In this clinical trial, all patients had an Eastern Cooperative Oncology Group performance status of 0–1 and patients who were unable to swallow pills were excluded; thus, patients enrolled in this trial may have had a lessor tumor burden and could have biased results. Recently updated results presented at the European Society of Medical Oncology 2018 (265) indicated that that median overall survival was 86 weeks [CI 35 weeks–not estimable], and median progression-free survival was 60 weeks by investigator assessment [CI 20 weeks–not estimable]; the study, however, included some IVA and IVB patients.

Single-agent BRAF inhibitor therapy alternatively using vemurafenib was studied in seven BRAF-mutated ATC patients, with two responses noted (266). Vemurafenib/cobimetinib (MEK inhibitor) in combination with immunotherapy is currently also being studied in a prospective clinical trial (NCT03181100).

There is consensus that at least *BRAF*^{V600E} mutational analysis should be undertaken early-on and urgently in ATCs. Rapid BRAF testing can be performed by IHC (33) if there is available and viable tissue, or potentially by cfDNA blood-based ''liquid biopsy'' testing of peripheral blood (113) as alternatives to more comprehensive and definitive, but time-consuming, mutational interrogation.

■ RECOMMENDATION 20

In *BRAF*^{V600E}-mutated IVC and in unresectable IVB ATC patients who decline radiation therapy, initiation of BRAF/MEK inhibitors (dabrafenib plus trametinib) is recommended over other systemic therapies if available.

Strength of Recommendation: Strong
Quality of Evidence: Low
Values Statement regarding Recommendation 20

The authors—including patient advocates—for this recommendation placed a high value on available and emerging data indicating the potential for profound benefit from using this approach in a setting where little hope had previously existed, supporting the strong recommendation made in the presence of low-quality evidence.

■ RECOMMENDATION 21

In *BRAF*^{V600E}-mutated unresectable stage IVB ATC in which radiation therapy is feasible, chemoradiotherapy or neoadjuvant dabrafenib/trametinib represents alternatives to initial therapy.

Strength of Recommendation: Conditional
Quality of Evidence: Low

BRAF-*nonmutated ATC*

In patients whose tumors do not harbor a *BRAF*^{V600E} therapeutically targetable mutation or where mutational status is unknown, patient goals of care, disease extent, and threats imposed by disease should together especially inform the election and timing of the application of systemic therapy. In cases in which the patient is stage IVB or stage IVC with a low burden of distant metastatic disease and/or symptomatic or imminently threatening locoregional disease that can be treated with radiation therapy to the neck, external beam radiation therapy +/– concomitant chemotherapy should be a priority to reduce risk of asphyxiation. If radiation is intended, a more definitive IMRT course is preferable, best with coadministration of cytotoxic chemotherapy such as a taxane with or without cis- or carboplatinum or with doxorubicin (e.g., docetaxel plus doxorubicin), with restaging scans performed midway through any longer IMRT course so as to assess for early distant disease progression. If there is rapid progression of distant metastatic disease, immediate change of systemic therapy should be offered.

Clinical trials, particularly those that are mutation targeted, should be considered in patients who are healthy enough to participate, given some success in targeting the *BRAF*^{V600E} oncogene in ATC. Molecular testing, to include fusion testing, and referral to trials should be made very early on in the diagnosis so as to minimize delay in initiation of systemic therapy, also realizing that other potentially productively targetable mutations may present therapeutic opportunities beyond those involving cytotoxic chemotherapy, as discussed in the following sections.

■ RECOMMENDATION 22

In *BRAF* nonmutated patients, radiation therapy with concurrent chemotherapy should be considered in an effort to maintain the airway in patients with low burden of metastatic disease.

Strength of Recommendation: Strong
Quality of Evidence: Low

NTRK, RET, *and* ALK *fusions in ATC*

NTRK and *RET* fusions are rare events found in solid tumors—including in PTC, PDTC, and ATC—and are almost always mutually exclusive of other oncogenic driver mutations. Thus, in a patient without another candidate oncogenic driver, fusion testing should be performed.

The TRK inhibitors, larotrectinib and entrectinib, are FDA approved for pediatric and adult patients with *NTRK* fusion, but not *NTRK*-mutated, solid tumors. While trials did enroll thyroid cancer patients, specific histologies were not teased out in initial reports. Thus, we recommend that patients who are able to participate in clinical trials with these drugs continue to do so until more data specifically relevant to response and progression-free survival in ATC patients with *NTRK* fusions are available. If a trial is not available, consideration of commercial use of the drug is recommended if available, with parallel close monitoring for PD. Currently, clinical trials with selective NTRK inhibitors are ongoing (e.g., NCT02576431, NCT02122913, NCT02568267, NCT02650401).

Larotrectinib is an inhibitor of TRK 1–3 and was studied in 55 patients with *NTRK* fusion solid tumors, of whom 5 had thyroid cancer (histologies not specified) (267). All thyroid cancer patients achieved a response (four PR and one CR), but it is unclear whether any of these were ATCs. Entrectinib also inhibits TRK 1–3 but in addition also inhibits the ALK and ROS1 tyrosine kinases, and is also approved for *NTRK* fusion

solid tumors. Five thyroid cancer patients were included in the clinical trial that led to the FDA approval, however, histologies were not specified (268). One of five thyroid cancer patients achieved a PR to therapy. *ROS1* fusions, which are exceedingly rare in PTC, are likely also seen in ATC, in very rare instances. A case of a patient with PTC successfully treated with entrectinib has been reported (269). Clinical trials for *ROS1* fusion thyroid cancers should be sought, if available.

The selective RET inhibitor, selpercatinib, is also now FDA approved as of May 2020 for patients with *RET* fusion thyroid and lung cancer, as well as for patients with *RET*-mutated MTC. This approval was based on the results of a phase 1/2 trial that enrolled 170 thyroid cancer patients, of whom 19 had RET fusion thyroid cancer (270). Only two ATC patients were enrolled in the trial and one of these patients responded for 18 months to selpercatinib. Given the sparse data in ATC with respect to selective RET inhibitors, we recommend their use in ATC in the clinical trial setting.

ALK fusions are very rare in ATC and there is only case report of patients with *ALK* fusion who were successfully treated with ALK inhibitors (120,271). Again, given limited information, ALK inhibitors are preferably used in a clinical trial setting.

■ RECOMMENDATION 23

In *NTRK* or *RET* fusion ATC patients with stage IVC disease, we suggest initiation of a TRK inhibitor (either larotrectinib or entrectinib) or RET inhibitor (either selpercatinib or pralsetinib), preferably in a clinical trial, if available.

Strength of Recommendation: Conditional
Quality of Evidence: Very Low

Antiangiogenic drugs

In patients without a $BRAF^{V600E}$ mutation, or in the setting of patients who do not respond to—or who progress through—personalized targeted therapy, there are few data to support the use of any one class of drug. Historically, cytotoxic chemotherapy has been used, but responses to these are often very short-lived. Thus, interest in targeted molecular therapy with antiangiogenic drugs in ATC has resulted in several clinical trials (272–274). Only one antiangiogenic drug, lenvatinib, a multikinase inhibitor of VEGFR 1–3, FGFR 1–4, PDGFR, RET, and kit (FDA approved for DTC) has shown efficacy in a prospective clinical trial done in Japan, and on this basis is approved for use in Japan (245). Of 17 ATC patients, 4 (24%) responded, with a median overall survival of 10.6 months. Other retrospective studies have shown some efficacy in ATC (263,275). However, an intended confirmatory phase 2 trial of lenvatinib undertaken in ATC through the International Thyroid Oncology Group was closed at interim analysis due to lack of efficacy. Sorafenib, axitinib, gefinitnib, and pazopanib used as a single agent have not shown promising results, suggesting that kinase inhibitors may collectively have little activity in ATC (276–279).

One of the major limitations of using antiangiogenic drugs in ATC patients is the risk of bleeding in this patient population where disease often invades the trachea, esophagus, and great vessels. Rapid tumor shrinkage could alternatively lead to bleeding and/or fistula when these structures are invaded with tumor (280–283). Patients who are being treated with potent antiangiogenic drugs should be warned about these potential risks.

Immunotherapy

Immunotherapy for patients with ATC is also currently under investigation. Small studies have shown that ATC tumors express immune markers such as PD-L1 and immune infiltration is a hallmark of this disease (284,285). While checkpoint inhibitors are approved across a variety of solid tumors, none is FDA approved specifically for ATC.

Spartalizumab, an anti-PD-1/PD-2 immunotherapy drug, has been studied in ATC (286). The primary objective of the phase 2 portion of this trial was to determine the overall RR by RECIST v1.1. The RR was 19% (five PR and three CR observed). Twelve $BRAF^{V600E}$-mutated ATC patients participated in this trial and the RR in this group was only 8% (1 of 12 $BRAF^{V600E}$-mutated patients obtained a PR). The median overall survival in the entire cohort was 5.9 months, with 40% of patients alive at 1 year. The median progression-free survival was 1.7 months. Interestingly, those patients with PD-L1 expression of <1% had a median overall survival of 1.6 months and there were no responses in this group; however, those with PD-L1 expression of 1–49% and ≥50% had a median overall survival that had not been reached and an overall RR of 18% (2/11) and 35% (6/17). It should be noted that at the time of the writing of these guidelines, spartalizumab is not FDA approved and is not commercially available.

Several clinical trials using immunotherapy in combination with other systemic agents or with radiation are underway (NCT03181100; NCT03122496; NCT02239900; NCT02404441). There are anecdotal reports of combination therapy involving immunotherapy showing responses in ATC (287). In addition, there are now retrospective data to also indicate apparently improved ATC outcomes when immunotherapy is added to targeted therapy in ATC (OR 0.58, [CI 0.36–0.94], $p = 0.03$) (264).

■ RECOMMENDATION 24

In IVC ATC patients with high PD-L1 expression, checkpoint (PD-L1, PD1) inhibitors can be considered first-line therapy in the absence of other targetable alterations or as later line therapy, preferably in the context of a clinical trial.

Strength of Recommendation: Conditional
Quality of Evidence: Low

mTOR inhibitors

Everolimus is a rapamycin analogue that inhibits mTOR. Three clinical trials with everolimus have included patients with ATC (288–290). All three of these trials included fewer than 10 ATC patients and none had more than one responder. However, in two of these studies, one patient in each trial had a dramatic response to everolimus. The trial by Hanna *et al.* included molecular analysis of thyroid cancer patient tumors. It was noted that although the median progression-free survival was short in the ATC group, in the larger cohort of thyroid cancer, those with a mutation in the PI3K/mTOR/AKT pathway had a median progression-free survival of 15.2

months. One patient had a *TSC2* mutation and had a PR that lasted nearly 18 months. Wagle *et al.* (121) describe this case in great detail in a separate publication. Another ATC patient had an *NF1* mutation and had SD that lasted for 26 months. Thus, patient selection for PI3K/mTOR/AKT pathway mutations may be important in ATC, although a larger trial with selected patients is needed. A second-generation mTOR inhibitor trial was recently completed with results currently unavailable (NCT02244463).

Vascular disrupting agents

Fosbretabulin, a prodrug of the investigational antimicrotuble disrupting agent combretastatin, was assessed in a phase 2 trial in ATC, producing no PR or CR in ATC patients. However, SD was seen in 7 of 26 patients with a median survival of 4.7 months and 23% of patients surviving 1 year (291). This drug is not presently commercially available.

Systemic therapy: cytotoxic chemotherapy

Taxanes. A nonrandomized multicenter clinical trial conducted by Ain *et al.* demonstrated that the taxane paclitaxel administered weekly or every 3 weeks resulted in transient disease regression in 53% of 19 evaluable patients, with anecdotal evidence suggestive that weekly therapy may be superior to every 3-week 96-hour infusional therapy (258). However, reported dosages of paclitaxel (225 mg/m^2 IV weekly) were incorrect (Kenneth Ain, pers. comm.), as paclitaxel dosages should instead be 60–90 mg/m^2 IV weekly to assure safety. The WHO criteria were used to determine response, but maintenance of response was required for only 2, rather than the typical 4 weeks utilized in the RECIST criteria, making study results difficult to interpret in the context of studies using RECIST response criteria. The median overall survival was 24 weeks.

Anecdotal experience, however, suggests that single-agent paclitaxel can have disease-modifying effects in some patients and may impact survival in a subset of treated patients. Furthermore, a recent report indicated also that docetaxel at a dosage of 60 mg/m^2 IV administered as a single agent every 3 weeks can occasionally also even produce CR—but more commonly stabilize disease for a period of time (259). In this study, one of seven patients had a CR lasting 50 weeks, but median time to progression was only 6 weeks.

Anthracyclines and platins. Published studies of the application of doxorubicin in ATC generally discuss its use in combination with surgery and radiotherapy, making assessment of RRs and impact on survival uncertain in advanced disease (220,292). However, in a trial conducted by the Eastern Cooperative Oncology Group (293) from 1976 to 1982, 84 patients with advanced progressive thyroid cancer of all histotypes (not specifically ATC) were randomized to receive doxorubicin alone (60 mg/m^2 IV every 3 weeks) or doxorubicin plus cisplatin (60 mg/m^2 IV doxorubicin, 40 mg/m^2 cisplatin IV every 3 weeks). In 37 patients with ATC on this study, doxorubicin alone produced no CR and 1 PR in 21 treated ATC patients, while doxorubicin plus cisplatin yielded 3 each CR and PR of 18 treated ATC patients (PR+CR: 5% vs. 33%; $p < 0.03$). Median survival in ATC was only 2.7 months, but two responses to doxorubicin plus cisplatin were durable at 41.3 and 34.7 months, suggesting a possible impact on survival in select patients with ATC. Doxorubicin, 20 mg/m^2 IV weekly or 60–75 mg/m^2 IV every 3 weeks, is the only cytotoxic chemotherapy specifically approved by the FDA for use in ATC.

GOOD PRACTICE STATEMENT 12

Patients with *BRAF* wild-type (*BRAF* "negative" or unknown mutation status) IVB unresectable or metastatic ATC wishing an aggressive approach and not receiving chemoradiation should be encouraged to participate in clinical trials given the rarity of ATC, the paucity of data in support of improved survival or quality of life from any systemic therapeutics, and the need to develop evidence-based safe and effective therapeutic approaches in advanced ATC.

■ **RECOMMENDATION 25**

In metastatic ATC patients lacking other therapeutic options including clinical trials, we suggest cytotoxic chemotherapy including a taxane and/or an anthracycline or taxane with or without cis- or carbo-platin.

Strength of Recommendation: Conditional
Quality of Evidence: Low

GOOD PRACTICE STATEMENT 13

Therapeutic decision-making in the setting of PD after initial therapy regardless of somatic mutational status or therapy is very complex and not easily defined by an algorithmic approach. In this setting, care guided by an expert in ATC therapeutics is best pursued.

GOOD PRACTICE STATEMENT 14

As prognosis is dire in metastatic and progressive ATC, best supportive care (hospice) should also be discussed as an option.

APPROACHES TO BRAIN METASTASES

Clinically apparent brain metastases at presentation are relatively unusual in ATC, occurring in ~1–5% of patients, but they are associated with worse prognosis (41,66,199,294,295). Chiu *et al.* (295) studied 47 cases of all types of thyroid cancer that had metastatic disease to the brain. Brain metastases were most commonly detected during the monitoring of the patient after the original diagnosis of thyroid cancer, but were the initial manifestation of thyroid cancer in 15%. Patients with brain metastases tended to be older and had more aggressive disease; 11 of the 47 (23%) had ATC. In ATC patients with brain metastases, 56% had locoregional invasion, and 89% had locoregional cervical node involvement. The median time interval from ATC diagnosis to brain metastases diagnosis was 0.7 years, with median time from diagnosis of brain lesions to death being 1.3 months; disease-specific mortality was 100%. Salvati *et al.* (294) reported solitary brain metastases in 12 patients with thyroid cancer, 5 of whom had ATC; median size of brain metastases in the ATC patients was 4 cm. All patients were treated with surgical removal and radiotherapy. The median survival of the five patients with ATC was 9 months (individual survival in months: 7, 8, 9, 10, 10).

Brain MRI and CT scans are more sensitive in detecting brain lesions than FDG PET scans, with evidence suggesting that brain MRI is more sensitive than CT (294,296); therefore, MRI should ideally be performed before initiating systemic therapy as a part of initial ATC staging.

■ **RECOMMENDATION 26**

In ATC patients considering therapy, we recommend brain MRI assessing the presence of brain metastases at time of diagnosis as a part of initial staging and when symptoms otherwise prompt concern.

Strength of Recommendation: Strong
Quality of Evidence: Low

Salvati *et al.* (294) found a statistically significant improvement in survival ($p = 0.03$) among ATC patients undergoing gross total removal of brain metastases compared with patients undergoing subtotal removal. Surgical treatment resulted in improvement in quality of life and improvement in neurological symptoms. However, the number of patients studied was small, being three for total removal (survival 9, 10, and 10 months) and two for subtotal removal (survival 7 and 8 months), and selection bias may be a significant issue in this study.

There are insufficient data to make a recommendation for or against stereotactic radiotherapy in patients with ATC and brain metastases versus resection (295), but the poor prognosis of ATC and the logistical advantages of stereotactic radiotherapy make it preferable to surgery in most patients. Carefully to be considered in the decision-making process, however, is whether other systemic diseases are imminently threatening, coupled with consideration of the patient goals of care. Multiple lesions not amenable to stereotactic radiotherapy should instead be treated with whole-brain radiation therapy, else the patient should be referred to hospice care.

There is no published evidence that systemic therapy is effective in treating brain metastases from ATC, however, dabrafenib does cross the blood/brain barrier. Although VEGF-R-directed kinase inhibitors penetrate the central nervous system, it should be noted that they may be detrimental by increasing risk of bleeding into brain metastases in the case of untreated brain metastases (297,298).

Ryken *et al.* (299) published guidelines for patients with brain metastases from a variety of different tumors, recommending that patients with brain metastases with mass effect be treated with 4–8 mg/day of dexamethasone as the initial dose. Patients with moderate to severe cranial symptoms should be considered to receive 16 mg/day (generally 4 mg, four times daily) (299). It is recommended that there be discussion of the long-term issues regarding corticosteroid administration, and pneumocystis carinii pneumonia prophylaxis may be a consideration.

■ **RECOMMENDATION 27**

In ATC patients with neurologic brain compressive symptoms or signs, we recommend dexamethasone (4–16 mg/day).

Strength of Recommendation: Strong
Quality of Evidence: Low

■ **RECOMMENDATION 28**

In ATC patients with brain metastases, referral to neurosurgery/radiation oncology should be made.

Strength of Recommendation: Strong
Quality of Evidence: Low

Mikkelsen *et al.* (300) provided guidelines that did not recommend routine prophylactic use of antiseizure medications for adult patients with brain metastases who have not yet had a seizure. There is a paucity of relevant controlled studies. A single underpowered RCT did not detect a statistically significant difference in seizure activity in patients who prophylactically received antiseizure medication and those who did not (301), but further clarity is needed on this issue.

GOOD PRACTICE STATEMENT 15

Patients with brain metastases may be expected to be at increased risk if operating motor vehicles or if placed in a situation in which they may jeopardize themselves or others and therefore should be appropriately counseled.

APPROACHES TO BONE METASTASES

ATC metastasizes to bone in 5–15% of cases, usually in the presence of multiple other sites of distant metastases (41,66,199,302). With regard to therapy for symptomatic or threatening bony metastases, surgery or radiotherapy should be considered and tailored to the situation. Radiation therapy is preferred unless surgery is required either to preserve, or to treat loss of function (e.g., actual or imminent spinal cord compression, pathological long bone fracture). Interventional radiology palliation, such as via cryoablation, may also have a role, especially in patients in whom surgery and radiotherapy are contraindicated (303). Other approaches such as vertebroplasty may also be appropriate in selected cases, and consultation with the local expert spinal and orthopedic teams should be considered.

Once bone metastases are noted, assessment for additional metastases should be undertaken. Since ^{99m}Tc methylene diphosphonate bone scan mainly detects osteoblastic lesions, this technique has less sensitivity and specificity than ^{18}F FDG PET scan (304). MRI and CT scans are excellent for identifying bone lesions in a specific site of concern, but are less useful for general skeletal screening, but whole-body MRI may be used for this purpose (305). Although a skeletal survey with plain radiographs to also include long bones may also be used to screen the skeleton, it is time-consuming and it may be distressing and trigger pain among patients with symptomatic metastases (305). As an alternative to general skeletal screening and/or FDG PET imaging, an expectant approach with symptomatic monitoring triggering therapy directed to symptomatic disease may be preferable in patients electing a less aggressive approach or best supportive care.

In addition to pharmacological pain palliation, bone pain from metastases can be effectively alleviated with a course of palliative radiotherapy, typically performed over 1–2 weeks with 5–10 equal daily fractions of 300–400 cGy to a total dose of 2000–3000 cGy. A single fractionation of 800 cGy may also be an appropriate alternative fractionation. In the setting of metastases involving weight-bearing bones causing structural weakness, orthopedic fixation should be considered

(306). Palliative radiotherapy can be administered usually after orthopedic fixation to further promote pain relief and also after surgical decompression of spinal cord compression is existent. A randomized trial has shown that direct decompressive surgery plus postoperative radiotherapy is superior to radiotherapy alone in the treatment of spinal cord compression secondary to metastatic disease (307,308).

For patients experiencing progression of bone metastases despite systemic therapy, there may be a role for bisphosphonates (e.g., zoledronic acid/Zometa, 4 mg IV every 3 months in patients with normal renal function), as bisphosphonates have been shown to be effective in preventing, inhibiting, and delaying cancer-associated skeletal complications. Denosumab, an inhibitor of receptor activator of nuclear factor B ligand (RANK ligand), is also effective in decreasing skeletal events in patients with metastatic cancer to the bones, and in some settings is more effective than IV bisphosphonates (309). In parallel with administration of antiresorptive agents, calcium and vitamin D supplementation is essential, and calcium levels must be assessed before each cycle of antiresorptive therapy to assure safe administration; in the case of zoledronic acid, dosage is also reduced proportionate to reductions in renal function.

■ **RECOMMENDATION 29**

In patients with ATC with symptomatic or threatening bone metastases—but without structural compromise or threatened spinal cord compression in need of surgical remediation—we recommend palliative radiotherapy.

Strength of Recommendation: Strong
Quality of Evidence: Low

■ **RECOMMENDATION 30**

In patients with ATC with bone metastasis causing structural compromise in a weight-bearing region or threatening spinal cord compression, we recommend orthopedic fixation before initiation of palliative radiotherapy.

Strength of Recommendation: Strong
Quality of Evidence: Low

■ **RECOMMENDATION 31**

In patients with ATC with bone metastasis, we suggest periodic intravenous bisphosphonate infusions or subcutaneous RANK ligand inhibitor.

Strength of Recommendation: Conditional
Quality of Evidence: Low

APPROACHES TO OTHER SITES OF METASTASES

Thyroid cancers including ATCs can metastasize to any site. Systemic therapy as described above is the first line of treatment, but if a particular metastasis is symptomatic or has progressed despite systemic therapy, treatment may be individualized to metastatic locations, much as would be the case for other malignancies.

For example, lung metastases are quite common in advanced ATC; in patients who develop symptomatic metastases to pleura/chest wall, these can be palliated using radiotherapy. Occasionally, central mediastinal nodal metastases arise that compress bronchi and threaten postobstructive pneumonia. Under such circumstances, palliative radiotherapy should be considered. Endobronchial lesions causing hemoptysis can be palliated using endobronchial therapy such as laser or by radiotherapy. Hence, the approach to other metastatic disease sites must be thoughtfully individualized in the context of the threat posed by individual lesions relative to that posed by other and more diffuse multicentric metastatic diseases, also considered in the context of patient goals of care.

APPROACHES TO OLIGOPROGRESSIVE METASTATIC DISEASE

In patients on systemic therapy who are fortunate to have a good response, resistant clones develop, resulting in progression of metastatic disease. This usually results in a change in systemic therapy or, if there are no alternative systemic therapies, cessation of treatment. If, however, progression occurs in a small number of metastases (conventionally 5 or less), then the disease is said to be oligoprogressive (310). Local therapy such as SBRT or radiofrequency ablation (RFA) directed to the oligo-progressive disease sites may control this disease, allowing the patient to stay on otherwise effective therapy, delaying the need to change systemic management for a time. Hypothetically, such therapy may also initiate an immunological cascade and a potential abscopal effect on other disease sites. Surgery, however, is usually not appropriate in ATC patients with multiple known other sites of metastatic disease, but can be considered on a case-by-case basis, depending on the morbidity of the involved surgery. The addition of pembrolizumab at the time of progression has been described anecdotally.

There is currently little prospective evidence available to definitively support the application of ablative therapy in oligo-progressive cancer patients (311,312), but there is evidence that treatment of oligo-metastatic disease can be curative in some malignancies (such as colorectal cancer and soft tissue sarcoma (313,314). Thus, it seems reasonable to consider local therapy such as SBRT or RFA for oligo-progressive metastases in ATC patients who have otherwise had a good response to systemic therapies and who wish a continued aggressive approach. Additional prospective data are needed to prove that therapy directed at oligoprogressive disease is of benefit to patients in terms of survival or quality of life in ATC; realizing that such data are challenging to generate in ATC, data available for more common cancers may serve as a guide in ATC.

GOOD PRACTICE STATEMENT 16

In patients on systemic therapy who develop oligoprogressive disease, local tumor-directed therapy may be considered to postpone the need to change otherwise beneficial systemic therapy.

ATC PROGNOSTIC FACTORS

It is important to ascertain prognostic factors for ATC to help risk-stratify patients, understand the natural history of disease, and guide treatment and diagnostic decision-making. Many studies have evaluated potential prognostic factors in ATC and how these factors influence treatment

outcomes. Estimates from these studies are, however, inconsistent and limited by selection bias and other study design limitations such as the presence of confounders (e.g., exposure to different treatment modalities), which offer an alternative explanation for the relationship between the prognostic factor and disease-specific outcomes such as cancer-specific mortality. Despite these limitations, several prognostic factors have been consistently linked with outcomes in ATC such as age, tumor extension, and presence of metastasis.

In a large series of patients with ATC, nontreatment factors associated with improved survival at 2 years in a multivariate model were younger age (≤65 years), lower comorbidity score (Charlson/Deyo comorbidity score of 0), no known nodal disease, no known metastasis, primary tumor confined to the thyroid, and smaller tumor size (≤6 cm) (212). Year of diagnosis, sex, race/ethnicity, insurance status, income, education, and facility volume (more than five cases) were not predictive of survival after 2 years (239). These findings are consistent with two previously published population-based studies using the SEER database. One study consisted of 516 patients with ATC diagnosed between 1973 and 2000 and found that poor prognostic characteristics included age older than 60 years and the presence of extrathyroidal involvement (224). The other study consisted of 261 patients with ATC diagnosed between 1983 and 2002 and found that both metastatic disease and tumor size >7 cm were negatively associated with survival (209). Retrospective studies in other data sets identified similar prognostic factors. In a retrospective review of 121 patients with ATC, age younger than 60 years, tumor size less than 7 cm, and less extensive disease at presentation were independent predictors of decreased disease-related mortality (228). In a separate study of 47 patients with ATC, the presence of acute symptoms, tumor size larger than 5 cm, and distant metastases were each independent risk factors predicting a poor outcome and increased risk of death (127). In a study by Akaishi *et al.* of 100 patients with ATC (315), only 6 patients were noted to have a small ATC within a DTC. Survival rates at 1 year were 72.7%, 24.8%, and 8.2% for patients with disease stage IVA, IVB, and IVC, respectively. Several characteristics, such as age equal to or older than 70 years, extrathyroidal invasion, and distant metastases at presentation, were associated with poorer outcomes.

A common prognostic factor across the reviewed studies is that prognosis was superior in patients with intrathyroidal ATC (with no evidence of extrathyroidal extension or distal metastasis), who were treated with complete tumor removal followed by radiotherapy and other chemotherapies.

ATC contains several recurrent genetic mutations. In patients with ATC, concomitant *BRAF/RAS* and *TERT* mutations are associated with worse prognosis than mutation in only one of the genes (77). Also, recent studies suggest that certain genetic mutations may be associated with better clinical outcomes when treated with targeted therapies. For example, in a multicenter, open-label, nonrandomized phase 2, Subbiah *et al.* (116) reported the efficacy of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) combination therapy in 16 patients with $BRAF^{V600E}$-mutated ATC never treated with BRAF and/or MEK inhibitors, but who previously received surgery, radiotherapy, or chemotherapy. They found that after a follow-up of 47 weeks (range 4–120 weeks) and with a median duration of exposure to dabrafenib and trametinib of ~10 months, 69% overall RRs (CR [$n = 1$], PRs [$n = 10$]), and at 12 months, estimated overall survival was 80% compared with the historical survival rate of 20–40%. In addition, Iyer *et al.* reported on the efficacy and safety of targeted therapy in 16 ATC patients excluded from trial participation. From these 16 patients, 6 patients had a $BRAF^{V600E}$ mutation and were treated with the combination of dabrafenib plus trametinib. Three patients had PR, with a median progression-free survival and overall survival of 3.7 months and 9.3 months, respectively.

ATC HEALTH CARE DISPARITIES

There are considerable data to suggest that lower socioeconomic status and reduced health care access significantly and negatively impact health care provision and outcomes among patients afflicted with many cancers, and recently, ATC-specific data have become available. Glaser *et al.* performed a retrospective analysis of 3552 patients with ATC using the NCDB during the time period of 1998 to 2012 (212). In this study, 49.5% of patients had surgery, 58.7% had external beam radiation therapy, and 41.6% had chemotherapy. In multivariable logistic regression analyses adjusted for demographic, clinical, and treatment variables, private health care insurance status (compared with other insurance status) was significantly associated with an improved chance of undergoing surgery or of receiving external beam radiation therapy. Similarly, Roche *et al.* reported on data from 719 ATC patients identified in the SEER program registries between 1998 and 2011 (316). In the SEER study, 80.1% of patients received either surgery or external beam radiotherapy, while 58.3% had external beam radiation therapy alone. Data on systemic therapies were not collected. In this study, 69.5% of patients were reported to be non-Hispanic white. In multivariable logistic regression analysis adjusted for demographic characteristics, tumor size, time period of diagnosis, disease stage, and residing in a high-poverty federal-designated county (≥15% of adults with income below the federal poverty level) all impacted on outcome. The OR of nonwhite ATC patients receiving any treatment compared with non-Hispanic whites was significantly reduced (OR 0.29, [CI 0.16–0.54]) and the OR of receiving any external beam radiation therapy was also significantly reduced (OR 0.55, [CI 0.35–0.88]). Recent analysis of bankruptcy filings in Washington State indicated that bankruptcy was 2.65 times greater among cancer patients than among those without cancer and that bankruptcy was especially more common among thyroid cancer patients (317). Moreover, bankruptcy filing was associated with a statistically significantly higher probability of death (OR 1.79, [CI 1.64–1.96]), with thyroid cancer patients having among the highest HRs. These data collectively suggest that socioeconomic and demographic factors significantly influence the likelihood of treatment and some outcomes in ATC. Providers must therefore be mindful of the effects of patient socioeconomic, educational, cultural, and insurance status on access to therapy and work toward optimization of access for all patients. Furthermore, providers must be cognizant of the financial impact of ATC care on individual patients so as to fully support them, triggering social work consultation and other resources in order that we optimally support our ATC patients. Health disparities may also be a factor in higher

Table 7. List of Recommendations and Good Practice Statements

Recommendations

RECOMMENDATION 1

FNA cytology can play an important diagnostic role in the initial evaluation of ATC, but parallel core biopsy may be necessary for definitive diagnosis and to obtain sufficient material for molecular interrogation.

Strength of recommendation: strong

Quality of evidence: low

RECOMMENDATION 2

Every effort should be made to establish a diagnosis via biopsy before proceeding with surgical resection, as surgical resection may be inappropriate.

Strength of recommendation: strong

Quality of evidence: low

RECOMMENDATION 3

Routine surgical pathology evaluation of resection specimens should focus on confirming a definitive diagnosis of ATC, documenting extent of disease, and defining the presence of any coexisting DTC and/or other pathologies. The proportion of tumor that represents ATC should also be documented.

Strength of recommendation: strong

Quality of evidence: low

RECOMMENDATION 4

Once ATC diagnosis is considered, assessment of *BRAF*^{V600E} mutation should be expeditiously performed by IHC and confirmed/expeditiously assessed by molecular testing.

Strength of recommendation: strong

Quality of evidence: moderate

RECOMMENDATION 5

Molecular profiling should be performed at the time of ATC diagnosis to inform decisions related to the use of targeted therapies, especially as there are now Food and Drug Administration-approved mutation-specific therapies in this context.

Strength of recommendation: strong

Quality of evidence: moderate

RECOMMENDATION 6

Initial radiological tumor staging should include cross-sectional imaging, in particular, CT neck, chest, abdomen, and pelvis with contrast (or MRI), and, if available, FDG PET/CT. Contrast-enhanced imaging of the brain (MRI preferred) should also be performed, if clinically indicated.

Strength of recommendation: strong

Quality of evidence: moderate

RECOMMENDATION 7

Every patient with ATC should undergo evaluation of the vocal cords at initial presentation, and thereafter based upon changing symptoms.

Strength of recommendation: strong

Quality of evidence: low

RECOMMENDATION 8

Comprehensive disease-specific multidisciplinary input should be attained before defining ''goals of care'' or undertaking therapeutic discussions with patients. Those involved in management decisions should include specialists highly experienced in treating ATC.

Strength of recommendation: strong

Quality of evidence: low

RECOMMENDATION 9

The treatment team should include palliative care expertise at every stage of patient management to help with pain and symptom control, as well as addressing psychosocial and spiritual issues.

Strength of recommendation: strong

Quality of evidence: low

RECOMMENDATION 10

The treatment team should engage hospice care for ATC patients who decline therapies against their tumor intending to prolong life, yet who still require symptom and pain relief spanning the remainder of their illness.

Strength of recommendation: strong

Quality of evidence: low

RECOMMENDATION 11

At all stages of palliative care and hospice care in ATC patients, practitioners should be aware of family systems, and how they affect patient decision-making.

Strength of recommendation: strong

Quality of evidence: low

RECOMMENDATION 12

For patients with confined (stage IVA/IVB) ATC in whom R0/R1 resection is anticipated, we strongly recommend surgical resection.

Strength of recommendation: strong

Quality of evidence: low

Value Statement regarding Recommendation 12—The authors for this recommendation placed a higher value for the benefit (longer overall survival) of surgical resection and placed a lower value in potential morbidity and subsequent delay in chemotherapy and/or radiation therapy.

(*continued*)

TABLE 7. (CONTINUED)

Recommendations

RECOMMENDATION 13

Radical resection (including laryngectomy, tracheal resections, esophageal resections, and/or major vascular or mediastinal resections) is generally not recommended given the poor prognosis of ATC and should be considered only very selectively after thorough discussion by the multidisciplinary team also considered in light of new information based upon mutations present and the availability of targeted therapies.

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 14

Following R0 or R1 resection, we recommend that good performance status patients with no evidence of metastatic disease who wish an aggressive approach should be offered standard fractionation IMRT with concurrent systemic therapy.

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 15

We recommend that patients who have undergone R2 resection or have unresectable but nonmetastatic disease with good performance status and who wish an aggressive approach be offered standard fractionation IMRT with systemic therapy. Alternatively, in *BRAF*^{V600E}-mutated ATC, combined BRAF/MEK inhibitors can be considered in this context.

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 16

In patients with unresectable disease during initial evaluation in whom radiotherapy and/or systemic (chemotherapy or combined BRAF/MEK inhibitors) therapy render the tumor potentially resectable, we recommend reconsideration of surgical resection.

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 17

Among patients who are to receive radiotherapy for unresectable thyroid cancer or in the postoperative setting, IMRT is recommended.

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 18

The use of cytotoxic chemotherapy involving a taxane (paclitaxel or docetaxel), administered with or without anthracyclines (doxorubicin) or platin (cisplatin or carboplatin), is recommended in patients treated with definitive-intention radiation.

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 19

Among ATC patients with unresectable or advanced disease wishing aggressive therapy, we suggest early initiation of cytotoxic chemotherapy as an initial and potentially bridging approach until mutational interrogation results and/or mutationally specified therapies might be available, and if appropriate.

Strength of recommendation: conditional
Quality of Evidence: low

RECOMMENDATION 20

In *BRAF*^{V600E}-mutated IVC and in unresectable IVB ATC patients who decline radiation therapy, initiation of BRAF/MEK inhibitors (dabrafenib plus trametinib) is recommended over other systemic therapies if available.

Strength of recommendation: strong
Quality of evidence: low

Value Statement regarding Recommendation 20

The authors—including patient advocates—for this recommendation placed a high value on available and emerging data indicating the potential for profound benefit from using this approach in a setting where little hope had previously existed, supporting the strong recommendation made in the presence of low-quality evidence.

RECOMMENDATION 21

In *BRAF*^{V600E}-mutated unresectable stage IVB ATC in which radiation therapy is feasible, chemoradiotherapy or neoadjuvant dabrafenib/trametinib represents alternatives to initial therapy.

Strength of recommendation: conditional
Quality of evidence: low

RECOMMENDATION 22

In *BRAF* nonmutated patients, radiation therapy with concurrent chemotherapy should be considered in an effort to maintain the airway in patients with low burden of metastatic disease.

Strength of recommendation: strong
Quality of evidence: low

(*continued*)

TABLE 7. (CONTINUED)

Recommendations

RECOMMENDATION 23

In *NTRK* or *RET* fusion ATC patients with stage IVC disease, we suggest initiation of a TRK inhibitor (either larotrectinib or entrectinib) or RET inhibitor (selpercatinib or pralsetinib), preferably in a clinical trial, if available.

Strength of recommendation: conditional
Quality of Evidence: very low

RECOMMENDATION 24

In IVC ATC patients with high PD-L1 expression, checkpoint (PD-L1, PD1) inhibitors can be considered first-line therapy in the absence of other targetable alterations or as later line therapy, preferably in the context of a clinical trial.

Strength of recommendation: conditional
Quality of evidence: low

RECOMMENDATION 25

In metastatic ATC patients lacking other therapeutic options including clinical trials, we suggest cytotoxic chemotherapy including a taxane and/or an anthracycline or taxane with or without cis- or carbo-platin.

Strength of recommendation: conditional
Quality of evidence: low

RECOMMENDATION 26

In ATC patients considering therapy, we recommend brain MRI assessing the presence of brain metastases at time of diagnosis as a part of initial staging and when symptoms otherwise prompt concern.

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 27

In ATC patients with neurologic brain compressive symptoms or signs, we recommend dexamethasone (4–16 mg/day).

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 28

In ATC patients with brain metastases, referral to neurosurgery/radiation oncology should be made.

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 29

In patients with ATC with symptomatic or threatening bone metastases—but without structural compromise or threatened spinal cord compression in need of surgical remediation—we recommend palliative radiotherapy.

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 30

In patients with ATC with bone metastasis causing structural compromise in a weight-bearing region or threatening spinal cord compression, we recommend orthopedic fixation before initiation of palliative radiotherapy.

Strength of recommendation: strong
Quality of evidence: low

RECOMMENDATION 31

In patients with ATC with bone metastasis, we suggest periodic intravenous bisphosphonate infusions or subcutaneous RANK ligand inhibitor.

Strength of recommendation: conditional
Quality of evidence: low

Good practice statements

GOOD PRACTICE STATEMENT 1

In the event that biopsy of a suspected metastatic disease site is clinically indicated, primary management of ATC should not be delayed until biopsy is obtained.

GOOD PRACTICE STATEMENT 2

All critical appointments and assessments that are required before primary treatment of ATC should be prioritized and completed as rapidly as possible.

GOOD PRACTICE STATEMENT 3

Patients must have understanding and decision-making capacity to consent to treatment or to make particular medical decisions. Concerns about diminished or impaired capacity should prompt mental health and/or clinical ethics consultation to assess barriers to capacity.

GOOD PRACTICE STATEMENT 4

Patients should be encouraged to draft both an advance directive in which they name a surrogate decision maker and list code status and other end-of-life preferences including POLST or MOST document. Circumstances where suspension of DNR may occur must be discussed with the patient as well.

(*continued*)

TABLE 7. (CONTINUED)

Good practice statements

GOOD PRACTICE STATEMENT 5
A ''goals-of-care'' discussion should be initiated with the patient as soon as possible. In consultation with a multidisciplinary team, a candid session should be conducted in which there is full disclosure of the potential risks and benefits of various treatment options, updated frequently, including how such options will impact the patient's life. Treatment options discussed should include all end-of-life options, such as hospice and palliative care. Patient preferences should guide clinical management.

GOOD PRACTICE STATEMENT 6
If surgery is undertaken, intraoperative frozen section and pathology consultation may be a helpful adjunct to inform surgical decision-making.

GOOD PRACTICE STATEMENT 7
In patients without impending airway compromise, we advise against preemptive tracheostomy placement.

GOOD PRACTICE STATEMENT 8
Radiation therapy should begin no later than 6 weeks after surgery.

GOOD PRACTICE STATEMENT 9
Patient goals of care, medical and psychosocial fitness for therapy, potential toxicities, financial considerations, and robustness of social support must be prominently considered in the decision to proceed with aggressive multimodal therapy.

GOOD PRACTICE STATEMENT 10
Cytotoxic chemotherapy can be initiated within 1 week of surgery, providing sufficient healing, in anticipation of subsequent chemoradiation.

GOOD PRACTICE STATEMENT 11
In patients of poor performance status, palliative or preventative (no residual disease present) locoregional radiotherapy over high-dose radiotherapy is suggested.

GOOD PRACTICE STATEMENT 12
Patients with *BRAF* wild-type (*BRAF* ''negative'' or unknown mutation status) IVB unresectable or metastatic ATC wishing an aggressive approach and not receiving chemoradiation should be encouraged to participate in clinical trials given the rarity of ATC, the paucity of data in support of improved survival or quality of life from any systemic therapeutics, and the need to develop evidence-based safe and effective therapeutic approaches in advanced ATC.

GOOD PRACTICE STATEMENT 13
Therapeutic decision-making in the setting of progressive disease after initial therapy regardless of somatic mutational status or therapy is very complex and not easily defined by an algorithmic approach. In this setting, care guided by an expert in ATC therapeutics is best pursued.

GOOD PRACTICE STATEMENT 14
As prognosis is dire in metastatic and progressive ATC, best supportive care (hospice) should also be discussed as an option.

GOOD PRACTICE STATEMENT 15
Patients with brain metastases may be expected to be at increased risk if operating motor vehicles or if placed in a situation in which they may jeopardize themselves or others and therefore should be appropriately counseled.

GOOD PRACTICE STATEMENT 16
In patients on systemic therapy who develop oligo-progressive disease, local tumor-directed therapy may be considered to postpone the need to change otherwise beneficial systemic therapy.

IMRT, intensity-modulated radiotherapy; PD-L1, programmed death ligand-1; MOST, Medical Orders for Scope of Treatment; POLST, Physician Orders for Life Sustaining Treatment; RANK ligand, receptor activator of nuclear factor B ligand.

incidence of ATC in vulnerable populations that have no access to primary care, screening for thyroid nodules, or treatment for DTC. As shown in a recent study on Alaskan natives that raises ethical questions about access to treatment specifically in the context of thyroid disease and cancers (318).

ATC centers of excellence and clinical trials

Unfortunately, due to the rarity and frequently rapidly progressive natural history of ATC, there are limited data to inform the management of patients, particularly in the setting of advanced disease. Patients frequently present to centers with minimal experience with ATC, and investigations leading to the diagnosis are often protracted—thereby leading to detrimental delay in initiating management. This context provides a strong argument for the centralization of care of ATC in centers with a high volume of patients and where discussions regarding management can take place within multidisciplinary teams. This will increase the access to timely, state-of-the-art care and in parallel to clinical trials.

There is a historical, and not entirely unjustified, nihilism in the approach to ATC by many nonsubspecialist providers that can impede active management or onward referral. To make progress in treating this rare disease, it is therefore critical to continue to strive to open, and to make readily

available, informative ATC clinical trials with the ultimate aim of improving ATC patient outcomes. At each point during the care pathway of a patient with a diagnosis of ATC, the availability of clinical trials should be assessed and, if appropriate and feasible, offered to the patient.

Clinical trials in ATC must be designed so that the time interval between identification of an eligible patient, consent, and starting trial interventions is as short as possible so that active management is not delayed and that participation is optimized. Similarly, inclusion and exclusion trial criteria should be streamlined to facilitate patient participation. As discussed throughout these guidelines, the rapidity of decision-making and quality of care in ATC from presentation, to diagnosis, to treatment initiation are critical to optimize ATC patient outcomes. A rapid diagnostic pathway (''FAST'') implemented by the MD Anderson Cancer Center to improve access to multidisciplinary care is yet to show improved outcomes, but referral rates have increased, and clinical trial enrollment is at an impressive 34% (264,319). Moreover, data from California indicate that clinical trial participation was independently associated with lower mortality in a population-based analysis across multiple cancer types (321).

Keys to enabling streamlined ATC care include dissemination of national guidelines and knowledge of regional referral centers to those clinicians who will diagnose or suspect ATC in the community, and availability of clinical trials at distributed sites across nations and the world through cooperative groups (e.g., ITOG, RTOG, ACCRU, ALLIANCE). National bodies such as the U.S. National Cancer Institute, ATA, and patient support groups (e.g., ThyCa) are critical to disseminating this information. Resources readily available for defining clinical trial availability include www.clinicaltrials.gov and the International Thyroid Oncology Group website (www.ITOG.org), but direct contact with an ATC referral center will assure access to the most recent trial information—as web resources are commonly out-of-date. All authors of the guideline can be contacted for assistance also in defining trial opportunities.

FUTURE DIRECTIONS

Despite significant advances in the diagnosis and treatment of patients with ATC, there remains a critical need for more effective therapies. Ongoing research efforts, starting from basic studies on the biology of ATC in both cell lines and genetically modified mouse models, and culminating with the preclinical implementation of the new knowledge thus gathered, are required to generate improved and rationally designed novel therapeutic approaches. It is critical that awareness of the importance of this pipeline is maintained.

Below, we highlight a few paradigmatic examples of very recent studies that have provided actionable preclinical evidence supporting either novel uses of approved inhibitors or the potential efficacy of novel inhibitor combinations.

Radiation sensitization

A recent study (322) has provided strong evidence supporting the notion that $BRAF^{V600E}$ induces radiation resistance by upregulating nonhomologous end joining and thus double-strand DNA break repair. Accordingly, $BRAF^{V600E}$ inhibition dramatically abrogated radioresistance in a relevant xenograft ATC model. Along the same line, a phase 1 clinical trial of the MEK inhibitor, Trametinib, combined with neoadjuvant chemoradiation in colorectal cancer patients resulted in 50% pathologic complete response (pCR) or near-pCR rate, a promising increase compared with a historical 10–15% pCR in these patients (323).

Genetically informed targeted therapy

Based on the notion that loss or mutation of the *RB1* tumor suppressor are rare events in ATC (25,76), which suggests that therapies directed at inhibiting the cyclin D/CDK4 complexes, responsible for retinablastoma phosphorylation and inactivation, might be effective in ATC, a recent study has shown that the CDK4/6 inhibitor, palbociclib, strongly inhibited proliferation in a xenograft ATC model. Furthermore, combination of palbociclib with a PI3K/mTOR dual inhibitor was dramatically effective in inhibiting both tumor growth and the development of resistance to palbociclib (324).

Resistance to $BRAF^{V600E}$ inhibition unfortunately commonly develops rapidly after an initial therapeutic response. Recent data obtained in a relevant genetically engineered mouse model show that resistance is often associated with activation of an HGF/MET (hepatocyte growth factor/tyrosineprotein kinase Met) signaling axis (325). In fact, an MET inhibitor induced significant regression of *Met*-amplified recurrent mouse ATCs. Also, preclinical studies of combination therapy with BRAF and multitargeting tyrosine kinase inhibitors have been shown be more effective in $BRAF^{V600E}$ mutant ATC than single-agent or BRAF and MEK inhibitors and in overcoming resistance to $BRAF^{V600E}$ inhibition (326).

Recently also, significant attention has been devoted to ERK1/2 inhibition as a potential strategy to overcome resistance to upstream MAPK inhibitors (BRAF, MEK). A recent phase 1 clinical trial (327), in patients with BRAF mutant tumors, showed PR or SD in 9 of 19 patients with *BRAF* mutant melanoma previously treated with MAPK inhibitor therapy, warranting similar studies in the context of ATC patients.

Other actionable targets

In addition to the novel therapeutic approaches described above, which may be closer to translation to the clinical setting, recent studies have identified novel potentially actionable targets that deserve full attention from the ATC research community.

Other actionable targets: chromatin modifiers

Genome-wide DNA sequencing of ATC samples has recently revealed (25) a high prevalence of mutations of genes encoding components of the SWI/SNF chromatin remodeling complex (36%) and of HMTs (24%), pointing at these groups as likely key players in the biology of ATC. Current efforts at elucidating the pathogenetic role of these mutations and at developing pharmacological approaches countering their alterations will eventually result in novel tools to treat ATC patients.

Other actionable targets: apoptosis modulation

One key problem is the fact that the effect of both current chemoradiation regimens and of investigative targeted therapies is at best cytostatic, as shown by the systematic lack of durable responses and the rarity even of achieving SD. Direct

and efficient induction of apoptosis would be the ideal and definitive therapeutic approach to ATC. Increased understanding of the structure and function of BCL2 proteins has led to the development of BH3 mimetics, small molecules that bind to antiapoptotic BCL2 proteins in the docking site for the BH3 domains of the death-promoting members of the family, thus releasing the latter from sequestration to induce apoptosis.

ATC cells frequently overexpress antiapoptotic BCL2 family members (328,329). Although ATCs are generally refractory to single BH3-targeting approaches, several research groups are currently developing combinatorial inhibition strategies that will ultimately allow effective apoptosis induction with curative intent.

Other actionable targets: cell cycle

The first fully accrued randomized therapeutic clinical trial in ATC has recently completed (NCT01236547) testing the hypothesis that synergistic benefit may result from the addition of pazopanib to paclitaxel therapy when combined with radiation therapy. This trial was based upon synergy data from *in vitro* and *in vivo* in ATC models suggesting that pazopanib targets the cell cycle kinase Aurora A and thereby induces increased cell death through augmented mitotic catastrophe upon combination with paclitaxel and other antimicrotubule cytotoxic agents (330). The results of this trial are expected to be mature and released within the next 12 months.

SUMMARY

The present document represents the second ATA ATC guidelines (the first published in 2012) and the culmination of 4 years of multidisciplinary international effort, with strict attention to the published evidence, and inclusive of varied stakeholders in the formulation of clinical recommendations and good practice statements. Summarized in Table 7 is the list of recommendations and good practice statements.

AUTHORS' CONTRIBUTIONS

All of the listed authors (also referred to as panelist and Task Force members) equally contributed to the conception and design of the work; acquisition, analysis, and interpretation of the data; drafting the work and revising it for critically important intellectual content; and provided final approval of the current article version. All of the listed authors also have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ENDORSEMENTS

The final document was officially endorsed by the American Association of Endocrine Surgeons, American Head and Neck Society, European Society for Endocrinology, International Association of Endocrine Surgeons, Korean Society of Head and Neck Surgery, Latin American Thyroid Society, Society of Nuclear Medicine and Molecular Imaging and the Society of Surgical Oncology.*

***Correction on** May 10, 2021 after after first online publication of March 11, 2021: The Society of Surgical Oncology has been added to the list of endorsing societies.

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No competing financial interests exist.

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SUPPLEMENTARY MATERIAL

Supplementary Data S1
Supplementary Data S2
Supplementary Data S3
Supplementary Data S4
Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4

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Address correspondence to:
Electron Kebebew, MD
Stanford University
School of Medicine
300 Pasteur Drive, H3642
Stanford, CA 94305
USA

E-mail: kebebew@stanford.edu

Keith C. Bible, MD, PhD
Division of Medical Oncology
Mayo Clinic
200 First Street Southwest
Rochester, MN 55905
USA

E-mail: bible.keith@mayo.edu