An Executive Summary of The Philippine Interim Clinical Practice Guidelines for the Diagnosis and Management of Well Differentiated Thyroid Cancer 2021

The Philippine CPG on Differentiated Thyroid Cancer Working Group

ABSTRACT

Objectives. Thyroid cancer is the most common endocrine cancer in the Philippines affecting primarily women in the reproductive age group. Considering the burden of thyroid cancer in the country, the Department of Health (DOH) called for the development of a national clinical practice guideline that would address patient needs, and aid physicians in clinical decision-making while considering therapeutic cost and availability in the local setting. The 2021 guidelines are aimed at providing optimal care to Filipino patients by assisting clinicians in the evaluation of thyroid nodules and management of well differentiated thyroid cancer.

Methods. A steering committee convened to formulate clinical questions pertaining to the screening and evaluation of thyroid nodules, surgical and post operative management of thyroid cancer, and palliative care for unresectable disease. A technical working group reviewed existing clinical guidelines, retrieved through a systematic literature search, synthesized clinical evidence, and drafted recommendations based on the ADAPTE process of clinical practice guideline development. The consensus panel reviewed evidence summaries and voted on recommendations for the final statements of the clinical practice guidelines.

Results. The guidelines consist of clinical questions and recommendations grouped into six key areas of management of well differentiated thyroid cancer: screening, diagnosis, surgical treatment, post operative management, surveillance, and palliative care.

Conclusion. The 2021 guidelines for well differentiated cancer could direct physicians in clinical decision making, and create better outcomes for Filipino patients afflicted with the disease. However, patient management should still be governed by sound clinical judgement and open physician-patient communication.

Keywords: guidelines, consensus, medical standards, carcinoma, thyroid neoplasms, thyroid nodule, thyroidectomy

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INTRODUCTION

Thyroid cancer is considered the most common endocrine cancer in the Philippines.[1] Recent data show that thyroid cancer is the 9th most common cancer in the world for both sexes, with an incidence of 586,202 cases in 2020 alone.[2] In the Philippines, thyroid cancer is the 6th most common cancer with a 5-year prevalence of 19,260 cases, and it ranks 21st in terms of mortality as of 2020.[3] Thyroid cancer affects more women of reproductive age than other population groups. There are several local and international guidelines available; however, the recommendations stated in these guidelines may not be applicable in the local setting due to cost or availability. Considering the burden of thyroid cancer in the Philippines, the Department of Health (DOH) called for the development of a national practice guideline

that could address the needs of patients afflicted with this malignancy and aid the physician in his/her clinical decision-making for these patients. This CPG aims to present recommendations on (a) the screening, diagnosis, surgical and postoperative management, surveillance, and palliative care of well-differentiated thyroid cancer (WDTC); and (b) the postoperative management and palliative care of poorly differentiated or anaplastic thyroid cancer (ATC) based on existing local and international CPGs from 2012 to the present.

METHODS

Guideline preparation

A steering committee (SC) was formed, composed of specialists from Jose Reyes Memorial Medical Center (JRRMMC), the Philippine College of Surgeons, Philippine Society of General Surgeons, Philippine Society of Otolaryngology-Head and Neck Surgery, Philippine Academy for Head and Neck Surgery, Inc., Philippine Society of Endocrinology Diabetes and Metabolism, Philippine Thyroid Association, Philippine Society of Nuclear Medicine, and Philippine Radiation Oncology Society who are involved in the management of thyroid cancer. The SC was responsible for determining the scope and the target users of the CPG, developing clinical questions, deciding on the process of CPG development to be pursued, and drafting the recommendation statements.

The technical working group (TWG) was composed of physicians from different specialties of medicine involved in the management of thyroid cancer. These individuals were recommended by their respective organizations based on their expertise, training, and experience in the preparation of CPGs. Members of the TWG reviewed existing CPGs and drafted recommendations based on the gathered evidence. To prepare for evidence synthesis, a clinical epidemiologist was invited to an orientation workshop to discuss the ADAPTE process of CPG development.

The consensus panel (CP) included representatives of the different specialties involved in the management of thyroid cancer; a representative from DOH to provide the public health point of view; and a lay person and a thyroid cancer survivor to provide a patient's perspective. The panel reviewed the evidence summaries and voted on recommendations. Members of the CP were recommended by their respective organizations based on their expertise, training, and experience in the management of thyroid cancer.

All individuals involved in the development of the CPG were required to disclose potential conflicts of interest that have existed in the past 12 months. None of the members of the TWG nor the CP have primary conflicts of interest. Those with secondary conflicts of interest (i.e., authorship in reviews and sponsorships from pharmaceutical companies) declared their conflict of interest during the CP meetings.

The protocol for this CPG development was reviewed and given approval by the Single Joint Ethics Review.

Search and retrieval of guidelines

At least three members of the TWG performed a systematic search for existing thyroid cancer CPGs in MEDLINE, Google Scholar, and HERDIN Plus. The inclusion criteria were the following: published in text or online, guidelines about adult WDTC and ATC, written or translated in English, published in the last 10 years (2012 onwards), and guidelines that included a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence. Guidelines about pregnant, pediatric, and medullary thyroid cancer patients were excluded from the systematic search.

A total of 424 articles were retrieved from the three databases. Two hundred and thirty articles were retrieved from MEDLINE; of these 230 articles, 20 remained after reviewing their titles and abstracts. Only eight articles remained after review of the full-text documents. For Google Scholar, one hundred and ninety articles were retrieved. Thirty-one of these remained after reviewing their titles and abstracts, and seven articles remained after reviewing the full-text documents. Lastly, only four articles were retrieved from HERDIN Plus. Two articles remained after review of title and abstracts, and of their corresponding full-text versions. Search results were eventually merged to eliminate duplicate publications. Subsequently, only nine guidelines were left. The remaining guidelines were assessed using the AGREE II tool for critical appraisal, then the level of evidence was classified according to the modified GRADE system.[4]

Formulation of Recommendation Statements

The SC and the TWG drafted recommendations answering the clinical questions based on the evidence collected from the CPGs. When no evidence was found to answer a clinical question, a consensus statement was prepared. Local publications were used as evidence even though they were not obtained through the initial literature searches. The evidence base and the draft recommendations were sent to the CP members a week prior the en banc meetings.

Consensus panel meeting process

Recommendation statements were presented and panelists were given the opportunity to voice their opinions or concerns about the recommendation. Panelists then voted on the recommendations, and consensus was reached when there was 75% agreement from the CP for both the direction and strength of the recommendations. The Delphi method was employed. The voting was repeated for a maximum of three times until consensus was reached.

Technical and ethical review

The guidelines were given to the DOH for technical review and Single Joint Review Ethics Board for ethics review. Funding was shouldered by the DOH.

External review process

The manuscript underwent review by a panel of external reviewers who were not part of the TWG or the CP. The panel included content and methods experts representing both specialty and non-specialty organizations involved in thyroid cancer management. Experts coming from different areas and types of practice were selected in order to obtain feedback on the applicability and feasibility of the recommendations in different areas in the country and in different healthcare settings. The overall evaluation by the external reviews using the AGREE II tool showed that the guideline was considered to be of high quality and that it was also recommended for use.

The guideline underwent a series of external reviews by the DOH National Guidelines Clearing House and later, by its quality review panel using the AGREE-II instrument.

It was then eventually approved and endorsed by the DOH as the national practice guideline on thyroid cancer last October 2022.

Updating of the guidelines

This CPG will be updated every three years. The SC and TWG will do quarterly reviews of available evidence that may affect the initial recommendations stated in the guideline. If new, high-certainty evidence on thyroid cancer diagnosis and management would become available before the scheduled update, the TWG will evaluate the evidence and the SC may convene the CP if there would be a need to issue amendments to the recommendations. Feedback from the target users of the CPG will also be reviewed annually to guide implementors and policymakers on matters pertaining to the CPG.

Steps involved in the Updating of the Thyroid Cancer CPG

	Process	Responsible Unit/ Organization	Frequency	Timeline
1.	***Review of current evidence relevant to thyroid cancer management***	SC and TWG	Quarterly	2022-2024
2.	***Review of feedback on the 2021 Thyroid cancer CPG by end users***	SC	Annual	2022-2024
3.	***Amendment to the recommendations if new strong evidence becomes available***	SC, TWG, and CP	N/A	2022-2024
4.	***Major update of the 2021 Thyroid cancer CPG based on recent evidence and feedback obtained using the questionnaire***	SC, TWG, and CP DOH	N/A	2024-2025

THE 2021 INTERIM CLINICAL PRACTICE GUIDELINES

Screening

Clinical Question 1.1

Among asymptomatic apparently healthy adults, should screening for thyroid cancer be done?

Recommendation

We do not recommend screening asymptomatic apparently healthy adults for thyroid cancer. (Strength of recommendation: Strong, Certainty of evidence: Moderate)

For screening to be effective, there should be a substantial proportion of undiagnosed disease in the target population, which may not be assured if the prevalence of disease is low. This may be the case for the Philippines where only 3.9% of non-pregnant and nonlactating Filipino adults aged 20 years and older had nodular goiter, based on a national survey conducted in 2008.[5] Aside from low prevalence, evidence on the small benefit of screening showed that outcomes were similar between patients treated for the disease and patients with common tumor types who were only monitored. Data from observational studies also showed a lack of difference in trends of deaths due to thyroid cancer after a population-based screening program was introduced. In addition, the harms of screening thyroid cancer outweighed the potential benefits. Overall harm was judged to be moderate, due to findings of serious adverse events related to treatment of thyroid cancer, as well as the likelihood of overdiagnosis and overtreatment, which could result from screening.[6]

Clinical Question 1.2

Who should be screened for thyroid cancer?

Recommendation

We recommend screening for thyroid cancer in individuals at high risk, defined as having any one of the following: a history of significant exposure to ionizing radiation to the head and neck area, especially in childhood; an inherited genetic syndromes associated with thyroid cancer (e.g., familial adenomatous polyposis); or one or more first-degree relatives with a history of thyroid cancer. (Strength of recommendation: Strong, Certainty of evidence: Moderate)

Although the USPSTF recommended against screening in the general asymptomatic adult population, it did list specific patient characteristics which would elevate their risk in developing thyroid cancer. In this patient population, there is benefit in performing screening procedures.[6]

Clinical Question 1.3

Among individuals at high risk, how should screening for thyroid cancer be done?

Recommendations

- **We recommend systematic neck palpation and neck US in individuals at high risk to screen for thyroid cancer. (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **In low-resource settings, we recommend systematic neck palpation at each outpatient visit to screen for thyroid cancer. (Strength of recommendation: Strong, Certainty of evidence: Moderate)**

Neck palpation and US could be used as screening tools for thyroid cancer. While neck US has a high degree of accuracy in detecting thyroid nodules (sensitivity 95 –100%, specificity 95–100%),[7] current evidence does not support the implementation of an US-based screening program in high-risk populations. US screening was only found to be associated with increased detection of one tumor histology, based on the 2010 Korea Community Health Survey.[8] This method could also detect a large number of benign nodules, which could lead to a substantial number of unnecessary fine-needle aspirations (FNAB) and surgeries with associated risks and harms.[7] Although not found to be associated with mortality,[8] such screening would result in harms that outweighed any potential benefits. Systematic neck palpation (sensitivity 17–43%, specificity 96–100%) might represent a balanced compromise between potentially overly sensitive neck US and no screening at all, despite poor diagnostic performance.[7]

Diagnosis

Clinical Question 2.1

What are the clinical data which support an impression of thyroid malignancy?

Recommendations

- **Clinical features suggestive of increased risk for thyroid malignancy include age <14 years old or >70 years old, male sex, family history of thyroid cancer, previous history of head or neck irradiation, rapid neck mass growth, and recent onset hoarseness, dysphagia, or dyspnea (Strength of recommendation: Strong, Certainty of evidence: Low to Moderate)**
- **Physical exam findings suggestive of higher risk for thyroid malignancy include firm or hard thyroid nodule consistency, fixed nodule, and cervical adenopathy (Strength of recommendation: Strong, Certainty of evidence: Low to Moderate)**

The American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi (AACE/ACE/AME) 2016, the American Association of Endocrine Surgeons (AAES), the American Thyroid Association (ATA) 2015, and the African Head and Neck Society (AfHNS) 2020 guidelines listed clinical features suggestive of higher risk for thyroid malignancy.[9-12] There are studies which show an increased malignancy risk in male patients, and patients within the extremes of age.[13-15] In a meta-analysis of 41 studies,[16] clinical features found to be significantly associated with thyroid cancer were male sex (OR 1.22; 95% CI 1.01–1.47), family history of thyroid cancer (for nodule size ≥4 cm: OR 1.63; 95% CI 1.04–2.55; for a single nodule[17,18]: OR 1.43 95% CI 1.09–1.88), and prior head or neck irradiation (OR 1.29; 95% CI 1.02–1.64). In a retrospective review among adult patients who underwent thyroid surgery at a tertiary center in the Philippines, male sex (OR 2.4), a rapidly enlarging thyroid nodule (OR 2.6), the presence of a hard (OR 103.7), firm (OR 12.8) or fixed nodule (OR 5.0), and the presence of cervical lymphadenopathies (OR 4.4) were found to increase the likelihood of thyroid malignancy.[19]

Clinical Question 2.2

Among patients suspected to have malignant thyroid nodules, what are the essential diagnostic and preoperative work-up that should be requested?

Recommendations

- **We recommend serum TSH ± T4 (free or total) measurement in the initial evaluation of patients suspected to have malignant thyroid nodules. (Strength of recommendation: Strong, Certainty of evidence: Moderate to High)**
- **If the serum TSH is subnormal, we recommend a radionuclide thyroid scan to determine whether the nodule is hyperfunctioning or not. (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend a diagnostic neck US for all patients with thyroid nodule. (Strength of recommendation: Strong, Certainty of evidence: High)**
- **We recommend that US evaluation of the neck must include assessment of the status of the cervical lymph nodes whenever a thyroid nodule is detected. (Strength of recommendation: Strong, Certainty of evidence: High)**

Serum thyroid-stimulating hormone (TSH) should be obtained upon discovery of a thyroid nodule greater than 1 cm in diameter. For subnormal serum TSH, a radionuclide thyroid scan should be obtained to determine whether the nodule is hyperfunctioning or "hot," isofunctioning or "warm," or nonfunctioning or "cold."[17] The prevalence of malignancy is low in hot nodules so no cytologic evaluation is necessary unless suspicious clinical findings are present.[17,20-23] A warm nodule has the same risk of malignancy as cold nodules so both cold and warm nodules necessitate FNAB.[24,25]

Thyroid sonography with assessment of the cervical lymph nodes in all patients having clinically suspected or

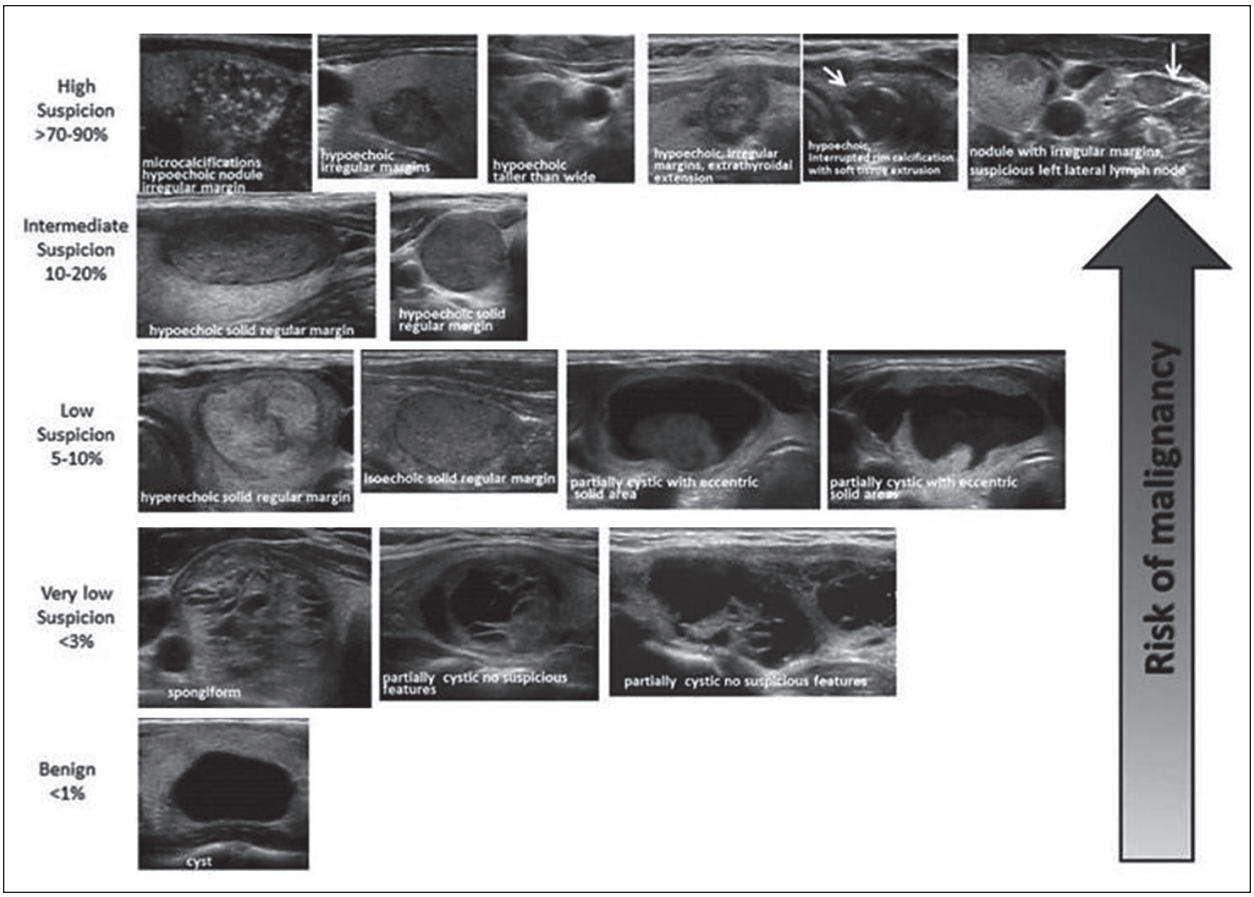

Figure 1. ATA nodule sonographic patterns and risk of malignancy. *Source: Haugen et al.*[11]

known thyroid nodule was strongly recommended by ATA 2015, the AACE/ACE/AME 2016, the Korean Thyroid Association (KTA) 2016 and the AAES 2020 based on high quality evidence.[9-11,26] Sonographic features highly suspicious for thyroid cancer have been shown in many studies to include microcalcifications, hypoechogenicity, irregular margins, and a taller-than-wide shape measured on transverse view (Figure 1).[27-36] US features of lymph nodes suspicious for malignant involvement include loss of fatty hilum;[37,38] microcalcifications; cystic, peripheral vascularity; hyperechogenecity; and round shape.[39] The sensitivity of US in detecting abnormal lymph nodes varies between 25–60% in the central neck and between 70–95% in the lateral neck.[40,41]

Clinical Question 2.3

What are the indications for doing thyroid biopsy?

Recommendations

- **We recommend that FNAB should be performed on all nodules suspected of being malignant based on clinical or US findings. (Strength of recommendation: Strong, Certainty of evidence: High)**
- **For thyroid glands with multiple nodules, we recommend that each nodule be evaluated separately and the decision to perform a FNAB be individualized. (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We do not recommend FNB for nodules that are purely cystic or hyperfunctioning on thyroid scintigraphy. (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We recommend FNAB for cervical lymph nodes with suspicious clinical and US findings. (Strength of recommendation: Moderate, Certainty of evidence: Moderate)**

FNAB is the diagnostic procedure of choice in confirming thyroid malignancy due to its accuracy and cost-effectiveness.[10,11,42] Some guidelines agree that FNAB should be performed on lesions with high suspicion of malignancy based on US, and those greater than 1 cm.[9,11] Evaluation of each nodule should be made independent of the others, and the recommendation on whether to biopsy or not should be based on the clinical and US findings of each particular nodule. The members of the CP emphasized the need to choose the most suspicious nodule for sampling. As for the lymph nodes, biopsy is performed on any cervical lymph node with suspicious findings on physical examination

and US evaluation.[9,10] In areas where FNAB could not be adequately performed, clinical and US findings may be used to stratify risk wherein those classified as high-risk were advised to undergo surgery.[12]

Clinical Question 2.4

When should ultrasound-guided fine-needle aspiration biopsy be done?

Recommendation

We recommend US-guided FNAB in the following: multi nodular goiter, complex nodules with more than 25% cystic component, posteriorly located nodules, nodules >1 cm with indeterminate US findings, nodules <1 cm with indeterminate US findings, which increased in size after 6 months, subcapsular or paratracheal lesions, and an inadequate initial FNAB result (Strength of recommendation: Strong, Certainty of evidence: Moderate)

The ATA 2015, the AAES 2020, and the Philippine College of Surgeons (PCS) 2013 listed down several indications for the use of US-guided FNAB, all of which were strongly recommended. Evidence showed that this strategy makes the procedure safer, more reliable, and more accurate.[10] In addition, utilizing this technique lowered the rates of both non-diagnostic and false-negative reports.[10,11] Both guidelines also stated that, for clinically palpable nodules, free hand or US-guided FNAB can be done.

Clinical Question 2.5

How should the fine-needle aspiration biopsy/fine-needle aspiration cytology/aspiration biopsy (FNAB) result be reported?

Recommendation

We recommend reporting of thyroid cytopathology using the TBSRTC for FNAB cytodiagnosis (Strength of recommendation: Strong, Certainty of evidence: High)

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) established a standardized reporting system with a limited number of diagnostic categories for thyroid FNAB specimens.[43-46] Each category has an implied cancer risk that ranges from 0–3% for the "benign" category to virtually 100% for the "malignant" category. In the 2017 revision, the malignancy risks were updated based on new data. Recommendation of treatment and options are provided per category.

Clinical Question 2.6

Among patients who underwent fine needle aspiration cytology of a thyroid nodule, when is molecular testing warranted and most helpful in diagnostic and therapeutic applications?

Recommendation

We can consider molecular testing, for indeterminate FNAB diagnosis, in particular, Bethesda Category III and IV to further stratify thyroid lesions into molecular/behavioral subsets of lesions (Strength of recommendation: Strong, Certainty of evidence: Moderate)

PTC most commonly contains the following genetic alterations: RET (13–43%), BRAF mutation (29–69%), NTRK1 rearrangement (5–13%), Ras mutation (0–21%).[47] In follicular thyroid cancer (FTC), the most common genetic alterations found are Ras mutation (4053%) and PPARG rearrangement (25–63%).[47] About 25% of cases lack the common driver mutations.[48] Non-invasive FTC with papillary-like nuclear features and invasive encapsulated follicular variant of PTC possess molecular profiles similar to follicular adenomas or carcinomas, such as higher rates of Ras than BRAF mutations.[49] Conversely, the infiltrative follicular variant of PTC has a molecular profile more similar to that of classic PTC (i.e., higher rates of BRAF than Ras mutations). The molecular profiles of encapsulated and infiltrative follicular variant parallel their biological behavior. Hence, FNAB-indeterminate diagnoses may suggest the need for molecular testing to further prognosticate thyroid lesions into these molecular/behavioral subsets of lesions.

Clinical Question 2.7

Among patients suspected to have differentiated thyroid cancer, what are the indications for additional diagnostic imaging?

Recommendations

- **We do not recommend the routine use of CT scan, MRI, thyroid scintigraphy, and PET/CT (Strength of recommendation: Strong, Certainty of evidence: High)**
- **Use of CT scan and/or MRI with intravenous contrast may be considered in clinically advanced cases like bulky and fixed tumors (Strength of recommendation: Strong, Certainty of evidence: Moderate)**

The AACE/ACE/AME 2016 and ATA 2015 guidelines do not recommend the routine use of contrast-enhanced CT scan and/or MRI for evaluation of all patients suspected with thyroid malignancy. However, these imaging tests may be used in more advanced cases to better assess the size of the mass, degree of airway compression, possible substernal extension, presence of nodal involvement, and extent of local or distant metastases after initial physical examination and neck US.[9,11]

Clinical Question 2.8

Among patients suspected to have thyroid cancer, what are the indications for evaluating vocal cord function preoperatively?

Recommendation

We recommend visualization of vocal folds for the following patients with notable voice changes based on physical examination; pre-existing laryngeal disorder; prior neck, mediastinal, cardiac, or upper thoracic surgery; known thyroid cancer with extrathyroidal extension; large substernal goiter; extensive central nodal metastasis; and/or history of long-standing hoarseness which resolves spontaneously (Strength of recommendation: Strong, Certainty of evidence: Low to Moderate)

AAES 2020 and the ATA 2015 enumerated the aforementioned indications for evaluating vocal fold function preoperatively with low to moderate qualities of evidences.[10,11] Vocal cord paresis or paralysis at preoperative laryngoscopy has incidence rates that could range from 0–3.5% among patients where thyroid disease is benign, and could reach up to 8% for patients with more advanced cancer.[11] Extrathyroidal extension could be found in about 10–15% of thyroid cancers, with the following structures being most commonly involved: strap muscle (53%), the RLN (47%), trachea (30%), esophagus (21%), and larynx (12%).[50] Anatomic assessment of vocal fold function can be performed by indirect mirror examination, by transcutaneous laryngeal ultrasound (TLUS), or by indirect flexible laryngoscopy and videolaryngostroboscopy.[10]

Treatment

Clinical Question 3.1

What is the appropriate operation for patients with proven malignant thyroid nodules (Category V and VI)?

Recommendations

- **We recommend total thyroidectomy for all Category V and VI unifocal nodules measuring >1 cm (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend total thyroidectomy for Category V and VI nodules with clinical or radiographic evidence of the following regardless of the size: bilateral thyroid disease, extrathyroidal invasion, lymph node metastases, and distant metastases (Strength of recommendation: Strong, Certainty of evidence: Moderate)**

Leaving more than 1 gram of tissue with the posterior capsule on the uninvolved side is also inappropriate for possible thyroid cancer. Completeness of surgical resection is a very important determinant of outcome.[10] Recommendations in international literature state that nodules should be at least 4 cm in size to be considered for total thyroidectomy of Category V and VI nodules.[10-12] However, Filipinos are at higher risk of aggressive disease since local data suggest that a lower cutoff of 2 cm for total thyroidectomy is sufficient.[51] In a local study by Jauculan et al., the recurrence rate among persons with low-risk PTC (n=145) who underwent total/near total thyroidectomy was 35.17%.[52] The significant predictors for recurrence in this study were found to be a tumor diameter ≥2 cm (OR 9.17; 95% CI 1.62–51.88; p=0.012) and a family history of PTC (OR 67.27; 95% CI 2.03 –2,228.96; p=0.018), while RAI therapy and low initial titers of Tg and TgAb were shown to be significant protective factors against disease recurrence among the low-risk patients.[52]

Clinical Question 3.2

What is the appropriate operation for patients with thyroid nodules cytologically suspicious for follicular neoplasm (Category IV)?

Recommendation

We recommend lobectomy with isthmusectomy as the initial and minimum surgery for solitary Category IV nodules (Strength of recommendation: Strong, Certainty of evidence: Low to Moderate)

The primary goal of thyroid surgery for a thyroid nodule that is cytologically indeterminate (i.e., AUS/FLUS or FN/SFN) is to establish a histological diagnosis and definitive removal, while reducing the risks associated with remedial surgery in the previously operated field if the nodule proves to be malignant.[10,11] The extent of surgery may be modified or converted to total thyroidectomy based on aggressive sonographic characteristics, high clinical risks for malignancies, a nodule size greater than 4 cm, patient preference, and/or molecular testing, if performed.

Clinical Question 3.3

What is the appropriate neck dissection for patients diagnosed with thyroid malignancy with gross metastatic nodal disease?

Recommendations

- **We recommend therapeutic neck dissection for patients with gross metastatic nodal disease (Strength of recommendation: Strong, Certainty of evidence: High)**
- **We recommend therapeutic central neck dissection (Level VI) if there are lymph node metastases in the central compartment (Strength of recommendation: Strong, Certainty of evidence: High)**
- **We recommend therapeutic central (Level VI) and posterolateral neck dissection (Level II–V) if there are lymph node metastases in the ipsilateral lateral compartment (Strength of recommendation: Strong, Certainty of evidence: High)**

In a retrospective cohort study among WDTC patients (n=723) at a government-university hospital, LNM at presentation was a strong predictor of recurrence for PTC

(OR 4; 95% CI 2.99 –5.34; p<0.001).[53-57] "Berry picking" or "plucking" (which refers to the removal only of the clinically involved node) is not acceptable and is not synonymous with selective "compartment-oriented" dissection. Neck dissection should follow proper anatomical borders to lessen the risk of recurrence.[58,59] Thyroid cancer LNM in Level I is rare (<10%), and recurrence is also rare (<1%) if not dissected at initial neck dissection.[60] Clearance of Levels II–V is associated with a lower risk of recurrence.[61] The role of therapeutic lymph node dissection for treatment of thyroid cancer nodal metastases is well-accepted for the clinically positive or cN1 disease, but the value of routine prophylactic Level VI (central) neck dissection and lateral neck dissection for cN0 disease remains unclear.[10,11,42,53-55] There are limited data to prove that prophylactic dissection of microscopic PTC LNM improves disease-specific outcomes.[11,57]

Clinical Question 3.4

What is the role of surgery for patients presenting with distant metastasis of well-differentiated thyroid cancer?

Recommendations

- **We recommend total thyroidectomy ± neck dissection for patients with DTC even with distant metastasis (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend surgical excision for resectable metastatic disease without adverse functional outcome in selected patients (Strength of recommendation: Strong, Certainty of evidence: Moderate)**

The preferred hierarchy of treatment for metastatic disease still starts with surgical excision of locoregional disease in potentially curable patients before other systemic and/or adjuvant treatment modalities.[11] Since most metastatic WDTC are considered as oligomestasis, the purpose of local treatment remains to be curative. Individualized course or decision may be applied based on functional performance status and life expectancy.

Clinical Question 3.5

How should we manage perioperative complications after thyroidectomy?

Recommendations

- **We recommend at least an overnight observation for patients at high risk for postoperative hematoma, when clinically appropriate (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend oral calcium as first-line therapy for postoperative hypocalcemia. If hypocalcemia is persistent or refractory, calcitriol may be added. If hypocalcemia is severe, persistent, or refractory, intravenous calcium should be used (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **For patients at high risk for hypocalcemia, determination of ionized calcium or serum calcium and albumin should be requested post-operatively (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We recommend preoperative assessment and supplementation of calcium and 25 hydroxy vitamin D when appropriate, such as in patients post Roux-en-Y gastric bypass, those with Graves' disease, and other conditions known to be at risk for postoperative hypocalcemia (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend formal laryngeal evaluation for patients with dyspnea and/or stridor, aspiration, dysphagia, and hoarseness (Strength of recommendation: Strong, Certainty of evidence: Low)**

Although outpatient thyroid surgery has been proven to be safe, patients undergoing a total thyroidectomy have a higher complication rate than those who undergo partial thyroid surgery. Complications include hypocalcemia, vocal cord paralysis, and hematoma formation.[11] Voice assessment should be based on the patient's subjective report and the physician's objective assessment of voice. This assessment can be performed at 2 weeks to 2 months after surgery, except in the presence of absolute functional limitations (e.g., dysphagia, aspiration, dyspnea, etc.). Early detection of vocal cord motion abnormalities after thyroidectomy is important for facilitating prompt intervention (typically through early injection vocal cord medialization), which is associated with better long -term outcome, including a lower rate of formal open thyroplasty repair.[10,11,61-63]

Clinical Question 3.6.

What is the role of surgery for pregnant patients with thyroid nodules?

Recommendation

We recommend to defer surgery until after delivery for patients with nodules that remain stable clinically and on USG, or if it is diagnosed beyond 24–26 weeks of gestation or the second half of pregnancy (Strength of recommendation: Moderate, Certainty of evidence: Low)

It is currently unknown if the likelihood of malignancy is higher for thyroid nodules discovered in pregnant women than in nonpregnant women as current evidence has not explicitly demonstrated this phenomenon.[11] The recommendation by the ATA 2015 on evaluating clinically relevant nodules is the same for pregnant and non-pregnant patients, however a radionuclide scan is contraindicated for the former.[11] Patients in the early stages of pregnancy who were found to have PTC by cytology should be monitored sonographically. Surgery among these patients is usually delayed to minimize risk from surgery after the second trimester. However, surgical intervention may be necessary for progressively enlarging

biopsy-proven Category V and VI nodules and/or biopsy-proven LNM in pregnant patients before 24–26 weeks of gestation, or if there are other risks.[11]

Clinical Question 3.7

What is the role of frozen section in the management of thyroid nodules suspicious for malignancy?

Recommendation

Frozen section is not routinely used, but may be considered in the following: confirmation of extrathyroidal extension, confirmation of PTC if the diagnosis will alter the extent of the surgical plan, and confirmation of the nature of equivocal structure (e.g., parathyroid glands, lymph nodes) (Strength of recommendation: Strong, Certainty of evidence: Moderate)

Intraoperative evaluation could be performed during a lobectomy to determine whether completion thyroidectomy would be recommended. A frozen section could be used for this purpose and would provide the most utility for a diagnosis of classic PTC, but not for the follicular variant of PTC and in FTC.[10,11] The patient should be informed of the advantages and disadvantages of these procedures (i.e., having a thyroidectomy from the start versus thyroid lobectomy with isthmusectomy that may proceed to thyroidectomy) that must be considered.

Clinical Question 3.8

What are the indications for completion thyroidectomy?

Recommendation

We recommend completion thyroidectomy in any of the following: unanticipated malignancy with a tumor diameter >1 cm, confirmed contralateral malignancy, confirmed nodal metastasis, and aggressive histologic type (Strength of recommendation: Moderate, Certainty of evidence: Moderate)

Completion thyroidectomy in general, should be offered to patients for whom a total thyroidectomy would have been recommended had the diagnosis been available before the initial surgery.[10,11,42,54]

Post-operative management

Clinical Question 4.1

What is the role of postoperative staging systems in the management of well-differentiated thyroid cancer?

Recommendation

We recommend the use of the AJCC/UICC staging for all patients with DTC to standardize encoding in the cancer registry and for its utility in predicting disease mortality (Strength of recommendation: Moderate, Certainty of evidence: Moderate)

Evidence from multiple studies have shown that the AJCC/UICC system had the highest proportion of variance explained relative to other staging systems, and was consistently able to better predict mortality among various patient cohorts.[11,42,51,54] The system has also been validated in clinical practice through prospective and retrospective studies. However, similar to other staging systems for the prediction of mortality, the AJCC/UICC system was only able to account for a small proportion of eventual deaths due to thyroid cancer.

Clinical Question 4.2

What is the role of initial risk stratification in the management of well-differentiated thyroid cancer?

Recommendation

We recommend the use of the 2015 ATA risk stratification system for patients with DTC to serve as a guide for further treatment and for surveillance (Strength of recommendation: Moderate, Certainty of evidence: Moderate)

On stratifying risk of recurrent disease, some guidelines recommended the use of the 2015 ATA risk stratification system.[11,42] In a Canadian study on thyroid cancer outcomes among Filipino patients, the odds of recurrence in Filipinos was 6.99 (95% CI 2.31–21.07; p<0.001) times higher compared to non-Filipinos.[64,65] This highlights the need for a specific risk stratification system for Filipinos in the future. No local study is available for reference; hence, further observational study is recommended.

Clinical Question 4.3

Should postoperative disease status be considered in decision making for radioiodine therapy for patients with well differentiated thyroid cancer?

Recommendations

- **We recommend that postoperative disease status (i.e., the presence or absence of residual disease) should be considered in deciding whether additional treatment (e.g., RAI, surgery, or other treatment) may be needed (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **Postoperative serum Tg, ideally 3-4 weeks post-operatively, can help in assessing the persistence of disease or thyroid remnant and predicting potential future disease recurrence (Strength of recommendation: Strong, Certainty of evidence: Moderate)**

Tg measurement should be done 3–4 weeks postoperatively, which is when postoperative Tg is at its

lowest for nearly all patients.[11] TgAb should be measured at least once to ascertain the reliability of the measured serum Tg.[56] A retrospective study found that the presence of TgAb may interfere in the detection of Tg and significant residual/recurrent tumors.[66]

Routine postoperative diagnostic whole-body scan (WBS) with ^{131}I is not recommended as problems with detection sensitivity and post-imaging stunning may arise.[51] However, these may be prevented by the use of low-activity ^{131}I (about 1–3 mCi) or alternative isotopes such as ^{123}I.

Clinical Question 4.4.1

What is the role of radioiodine (including remnant ablation, adjuvant therapy, or therapy for persistent disease) after thyroidectomy in the primary management of well-differentiated thyroid cancer?

Recommendations

- **We recommend routine RAI adjuvant therapy after total thyroidectomy for ATA high risk DTC patients (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend RAI adjuvant therapy after total thyroidectomy in ATA intermediate-risk level DTC patients (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We do not recommend routine RAI remnant ablation after thyroidectomy for ATA low-risk DTC patients (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We do not recommend routine RAI remnant ablation after lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma, in the absence of other adverse features (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We do not recommend routine RAI remnant ablation after thyroidectomy for patients with multifocal papillary microcarcinoma, in absence of other adverse features (Strength of recommendation: Moderate, Certainty of evidence: Low)**

Patients without nodal extension, perithyroidal extension, or distant metastasis may be given an ^{131}I activity of 30–100 mCi (or 1,110–3,700 MBq). In patients with nodal metastasis or distant metastasis on their RAI therapy, an activity of 150 mCi (5,550 MBq) will be delivered. An activity of 200 mCi (7,300 MBq) will be used in succeeding RAI ablation (RAIA) among patients with distant metastases, except if diffuse lung metastases are present as the recommended activity would then be 150 mCi (5,550 MBq).[51,67-70]

Clinical Question 4.4.2

How should post-thyroidectomy patients be prepared for radioiodine remnant ablation/treatment or diagnostic scanning?

Recommendation

We recommend that RAI should be given after TSH stimulation, ideally, until serum TSH levels reach at least 30 mIU/ml or alternatively, rhTSH can be given (Strength of recommendation: Strong, Certainty of evidence: Moderate)

Prior to RAIA, TSH stimulation must be done until serum TSH levels reach a minimum of 30 μIU/ml.[11,42,51] TSH stimulation could be facilitated through prescription of a low iodine diet, withdrawal of levothyroxine (LT4), or through administration of recombinant human TSH (rhTSH). LT4 may be withdrawn for 4–5 weeks, and is recommended especially for patients with distant metastases. rhTSH could be administered as a daily injection of 0.9 mg of rhTSH for two days, immediately followed by RAI on the third day. The use of rhTSH has also shown positive short-term effects on quality of life.[71] A cheaper alternative to rhTSH is the use of T3 (Tertoxine or Cytomel) which can be given 2 weeks before therapy thus shortening the period of hypothyroidism.

Clinical Question 4.4.3

Should a posttherapy scan be performed following remnant ablation or adjuvant therapy?

Recommendation

We recommend that RAI administration must be followed by WBS to stage the disease and document the 131 I avidity of any structural lesion (Strength of recommendation: Strong, Certainty of evidence: High)

All patients who had RAIA should have a post-therapy WBS with ^{131}I within 3–7 days of RAIA.[51] Routine diagnostic WBS is not required during follow-up among patients with negative stimulated Tg levels, TgAb levels and cervical US.

Clinical Question 4.5

Among patients with differentiated thyroid cancer post-surgery, what is the role of thyroid hormone suppression?

Recommendations

- **We recommend initial TSH suppression to below 0.1 mU/L for high-risk DTC patients (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We suggest initial TSH suppression to 0.1–0.5 mU/L for intermediate-risk DTC patients (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We suggest that TSH may be maintained at the lower end of the reference range (0.5–2 mU/L) for low-risk DTC patients who have undergone remnant ablation and have undetectable serum thyroglobulin levels while continuing surveillance for recurrence (Strength of recommendation: Strong, Certainty of evidence: Low)**

- **We suggest that TSH may be maintained at or slightly below the lower limit of normal (0.1–0.5 mU/L) for low-risk DTC patients who have undergone remnant ablation and have low-level serum thyroglobulin levels while continuing surveillance for recurrence (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We suggest that TSH may be maintained in the mid to lower reference range (0.5–2 mU/L) for low-risk DTC patients who have undergone lobectomy while continuing surveillance for recurrence. Thyroid hormone therapy may not be needed if patients can maintain their serum TSH in this target range (Strength of recommendation: Moderate, Certainty of evidence: Low)**

Thyroid hormone suppression therapy (THST) has been used to improve health outcomes in the management of DTC. In a systematic review of 10 observational studies (n=4,174) with follow-up that ranged from 4.5–19.5 years, there was decreased risk of any of the following outcomes for those who received THST in patients who underwent total thyroidectomy.[72,73] Observational studies provided evidence of improved long-term outcomes from TSH suppression to <0.1 mU/L, such as longer relapse-free survival with consistent TSH suppression (≤0.05 mU/L),[73] and decreased likelihood of disease progression compared to patients with lesser degree of TSH suppression (p=0.03).[74-76] In the analysis of registry (n=4,941, median follow-up up 6 years) of DTC, TSH score 2.0–2.9 (subnormal) was related with lower risk of recurrence and mortality compared to TSH score 3.0–4.0 (normal elevated).[77,78] At different stages of thyroid cancer, there was an improvement in OS (RR stages I-IV: 0.13, 0.09, 0.13, 0.33) and DFS (RR stages I-III: 0.52, 0.40, 0.18).

On the other hand, there is paucity of data to guide the recommendation of TSH suppression among those who had undergone lobectomy. Studies investigating the extent of surgery comparing lobectomy to total thyroidectomy did not analyze TSH suppression therapy[76,79-81] or even excluded[82]. In a retrospective study of patients with DTC who underwent lobectomy (n=466) comparing those with and without TSH suppression (less than 2 mIU/L), no significant difference was noted on DFS regardless of TSH levels (p=0.63).[83] In addition, subclinical thyrotoxicosis resulting from TSH suppression could include worsening angina, increased the risk of atrial fibrillation for elderly patients, and increased risk of postmenopausal women's osteoporosis.[80] Thus, the ATA 2015 suggested relaxing TSH targets may be considered for those with tachycardia, osteopenia, age older than 60, osteoporosis, and atrial fibrillation.[11]

Clinical Question 4.6.1

Among patients with differentiated thyroid cancer post-surgery, is there a role for adjunctive external beam radiation therapy?

Recommendations

- **We do not recommend routine adjuvant EBRT to the neck in patients with DTC after initial complete surgical removal of the tumor (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We suggest that EBRT may however be very selectively considered within the context of a multidisciplinary team for DTC patients with high-risk features such as, but not limited to, the following: surgically unresectable gross residual disease, inadequate RAI uptake, extranodal extension or involvement of soft tissues, tumors threatening vital structures, rapid progression, locally advanced disease, older age with extrathyroidal extension, and tumors undergoing multiples and frequent serial reoperations for locoregionally recurrent disease (Strength of recommendation: Strong, Certainty of evidence: Low)**

The use of adjuvant EBRT for DTC is controversial with lack of prospective data and conflicting reports on its benefit after surgical resection. In some guidelines, EBRT was very selectively considered in patients with high-risk features such as, but not limited to the following: surgically unresectable gross residual disease[11,53,54,84], inadequate RAI uptake[11,53,84], extranodal extension or involvement of soft tissues[11,84], tumors threatening vital structures[10,84], rapid progression[84], locally advanced disease[11,53], older patients with extensive extrathyroidal extension[11,53], tumors undergoing multiple and frequent serial reoperations for locoregionally recurrent disease[11].

Clinical Question 4.6.2

Among patients with anaplastic thyroid cancer diagnosed postoperatively, what is the role of external beam radiation therapy?

Recommendations

- **We recommend post-operative EBRT with systemic therapy for resectable, nonmetastatic, good performance status patients desirous of aggressive treatment (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We recommend EBRT with systemic therapy for unresectable, nonmetastatic, good performance status patients desirous of aggressive treatment. Surgery can be reconsidered after neoadjuvant therapy depending on response (Strength of recommendation: Strong, Certainty of evidence: Low)**

The ATA 2021 and NCCN guidelines recommend post-operative EBRT with systemic therapy for resectable, non-metastatic, good performance status patients desirous of aggressive treatment.[84-86] EBRT can improve local control and increase short-term survival in IVA/IVB ATC patients who are able to undergo complete (R0) or near-complete

(R1) surgical resection followed by radiation therapy. The ATA 2021 in particular recommends that adjuvant radiation therapy should begin no later than 6 weeks after surgery.[86] Even for patients with unresectable or gross residual (R2) regionally confined disease, radiation therapy and/or systemic therapy has been recommended to increase local control for symptom prevention or palliation (e.g., to prevent asphyxiation). Intensity modulated radiation therapy as an available EBRT technique is recommended by the ATA 2021 in both the post-operative and unresectable settings to decrease the dose to surrounding normal structures and to reduce possible treatment-related toxicity.[86] The decision however to undergo aggressive bi- or tri-modality therapy must be weighed with the patient's goals of care, medical and psychosocial fitness for therapy, availability of social support, and expected impacts on quality of life.

Clinical Question 4.7.1

Among patients with differentiated thyroid cancer post-surgery, is there a role for chemotherapy in the adjuvant setting?

Recommendation

We do not recommend the use of chemotherapy in patients with DTC (beyond RAI and/or TSH suppressive therapy) in the adjuvant setting (Strength of recommendation: Strong, Certainty of evidence: Very low)

There are no clinical trial data to indicate that any adjuvant therapy beyond RAI and/or TSH suppressive therapy using LT4 provides net benefit to patients with DTC.[11,42,51,84] The prognosis of these patients in complete remission is very good, especially if they are without any indication of active systemic disease. As toxicities, and even the risk of death, from use of kinase inhibitor therapies are appreciable, these risks have strong potential to exceed expected therapeutic benefit in the adjuvant context in most patients with DTC.

Clinical Question 4.7.2

Among patients with anaplastic thyroid cancer diagnosed postoperatively, is there a role for chemotherapy in the adjuvant setting?

Recommendation

We recommend the use of cytotoxic chemotherapy with or without RT in patients with ATC when clinically appropriate in the adjuvant setting (Strength of recommendation: Strong, Certainty of evidence: Low)

For patients who present with resectable tumors, we suggest complete resection followed by combined chemotherapy and RT.[11,42,84,86] There are very little data about the optimal chemotherapy to be used with RT for ATC. Randomized controlled trials are not available to definitively prove benefit for combined modality therapy. Thus, there are no standard regimens. However, the use of weekly doxorubicin (10 mg/m^2) concurrently with RT is both reasonable and commonly applied, while more aggressive regimens have combined docetaxel and doxorubicin or cisplatin and doxorubicin with radiation. Given the overall poor prognosis of current treatment modalities, consideration should always be given to referring a patient with ATC for participation in a clinical trial.

Clinical Question 4.8.1

Among patients with differentiated thyroid cancer post-surgery, what is the role of targeted therapy and immunotherapy in the adjuvant setting?

Recommendation

We do not recommend the use of targeted treatment such as kinase inhibitors and immunotherapy in the adjuvant setting (Strength of recommendation: Strong, Certainty of evidence: Low)

Kinase inhibitors are reserved for RAI Refractory (RR)-DTC patients with metastatic (e.g., lung, liver, muscle), rapidly progressive, and symptomatic disease not amenable to other local therapies (e.g., resection of distant metastases – metastasectomy and/or RT). Immunotherapy is also only limited to RR-DTC with advanced, progressive, or threatening disease. Immunotherapy such as pembrolizumab is indicated after doing genomic testing (tumor mutational burden or TMB) and if the result is high (≥10 mut/Mb).[11,42,51,84]

Clinical Question 4.8.2

Among patients with anaplastic thyroid cancer, what is the role of targeted therapy and immunotherapy in the adjuvant setting?

Recommendation

We can consider the use of targeted agents in the presence of druggable mutations and genetic aberrations in the adjuvant setting, if accessible (Strength of recommendation: Strong, Certainty of evidence: Low)

Dabrafenib plus trametinib combination or larotrectinib are options for BRAF V600E mutation-positive tumors or for NTRK gene fusion-positive tumors, respectively. Other druggable genetic aberrations are ALK fusion (crizotinib, ceritinib, alectinib) and RET mutation (pralsetinib, selpercatinib). All these data are supported by phase II clinical trials with PFS benefit.[11,42,84,86,87]

Molecular testing is recommended to help inform decisions regarding systemic therapy and eligibility for clinical trials. If a BRAF V600E mutation is present, most guidelines suggest neoadjuvant dabrafenib (150 mg twice daily) plus trametinib (2 mg daily) to improve the chance of complete tumor resection. In resectable disease and favorable response to dabrafenib plus trametinib, complete resection

should be attempted as long as gross resection could be achieved with minimal morbidity. This would be followed by chemoradiation (CRT) as described for Stage IVA (Figure 2). Evidence shows prolonged survival (i.e., more than 2 years) in some patients when surgery is combined with post-operative adjuvant CRT. In unresectable disease, dabrafenib plus trametinib can be continued if associated with disease stability or improvement. Alternative management options include CRT, clinical trials, or best supportive care if the response is not favorable.

Surveillance

Clinical Question 5.1

Which criteria should be utilized to classify response to therapy of a patient with well-differentiated thyroid cancer?

Recommendation

We recommend to utilize the response to treatment categories based on the modified ATA dynamic or ongoing risk stratification system. Response to treatment is classified as any of the following: excellent, biochemical incomplete, structural incomplete or indeterminate response. (Strength of recommendation: Strong, Certainty of evidence: Moderate)

Monitoring strategies are based upon the patient's risk of recurrence.[11,88,89] The original dynamic risk stratification described the best response to initial therapy during the first 2 years of follow-up. But as the classification became more acceptable, it is now being used to describe the patient's status at any point during follow-up.[89] The precise definition of type of response is dependent on the extent of initial therapy (Table 1). The best evidence and cut-off values are most consistent with those patients who underwent total thyroidectomy and RAIA. The patient's response to therapy is reclassified at each follow-up visit. Aside from thorough clinical history and physical examination, the response to therapy is assessed primarily with measurements of serum Tg and neck US. The interpretation of the serum Tg level depends upon the initial therapy.

Clinical Question 5.2

How should a patient's response to therapy in the first year of treatment be followed up?

Recommendations

- **We recommend that the initial dynamic risk stratification should be determined within 6 months after treatment (Strength of recommendation: Strong, Certainty of evidence: Moderate)**

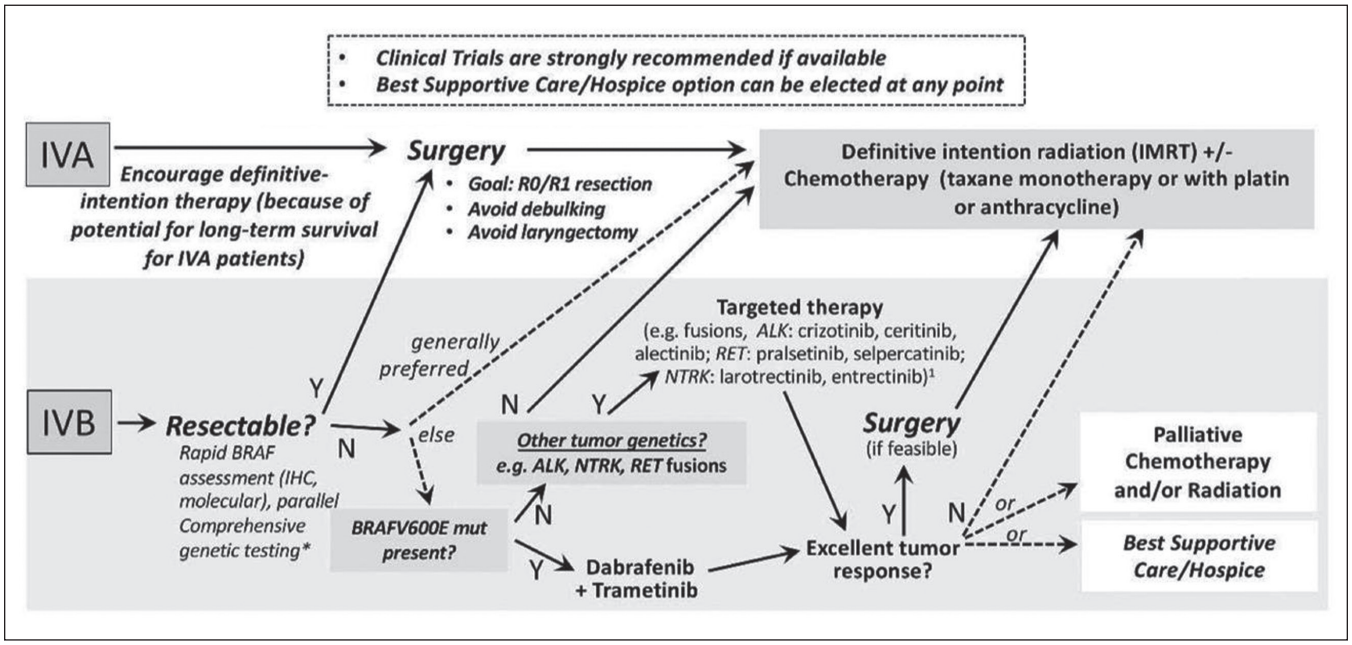

Figure 2. Initial treatment of stages IVA and IVB anaplastic thyroid cancer. *Source: Bible et al.*[86]

[1] Additional 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).*

Dashed arrows depict circumstances where competing therapeutic options may be of consideration.

ATC – anaplastic thyroid cancer

- **We recommend using Tg and TgAb assays that are calibrated with a reference standard (Strength of recommendation: Strong, Certainty of evidence: High)**
- **We recommend that serum Tg and TgAb levels be checked every 3–6 months in the first year after treatment (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend measurement of unstimulated or stimulated Tg and TgAb for patients who have undergone total thyroidectomy and radioactive remnant ablation therapy (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend measurement of unstimulated Tg and TgAb for patients who have undergone total thyroidectomy but do not require radioactive remnant ablation, and who are at low risk of recurrence (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We do not recommend routine measurement of serum Tg and TgAb for patients who have not undergone total thyroidectomy and with low risk of recurrence (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend that neck US should be performed at a 6- to 12-month interval depending on risk assessment (Strength of recommendation: Strong, Certainty of evidence: Moderate)**

The publications of Tuttle et al. were adapted by most international societies and guidelines. Response to initial therapy is defined at 6 to 12 months after therapy (surgery with or without RAI).[90-93] Sensitivity and specificity of Tg differs depending if it is stimulated or unstimulated. Stimulated Tg through thyroid hormone withdrawal has a sensitivity of 96% and specificity of 95%. Stimulated Tg through recombinant thyroid stimulating hormone (rTSH) has a sensitivity of. 93% and specificity of 88%. Unstimulated Tg has a sensitivity of 78% and specificity of 98%. The same assay should be used when doing serial Tg measurements since inter-assay variability can be substantial.[94] To improve the serum Tg sensitivity in the detection of persistent/recurrent thyroid cancer, serum Tg levels can be measured during TSH stimulation (either thyroid hormone withdrawal or with rhTSH).[95-99] Among patients who underwent lobectomy, specific criteria for distinguishing normal residual thyroid tissue from persistent or recurrent thyroid cancer have not been defined. Serum Tg used independently is of limited value for predicting or detecting disease recurrence following thyroid lobectomy.[100-103]

TgAb is detectable in as much as 10% of the general population, and is present initially in about 25% of patients with thyroid cancer. It can interfere with all assays for Tg so TgAb should be measured using the same assay. Serum Tg and TgAb should be measured because disease recurrence can be heralded by a rise in TgAb with or without corresponding rise in serum Tg. On the other hand, a significant fall in these titers suggests future recurrence is unlikely.[96-99] There is normally no need to measure serum Tg more frequently than every 3 months.

Table 1. Response to different treatment categories of well differentiated thyroid cancer

Responses to treatment	Total thyroidectomy + radioactive iodine remnant ablation	Total thyroidectomy alone	Lobectomy
Excellent response (no clinical, biochemical or structural evidence of disease)	No clinical evidence of tumor and Negative imaging and Undetectable Tg antibody and Unstimulated Tg <0.2 ng/mL or stimulated Tg <1 ng/mL	No clinical evidence of tumor and Negative imaging and Undetectable Tg antibody and Unstimulated Tg <0.2 ng/mL or stimulated Tg <2 ng/mL	No clinical evidence of tumor and Negative imaging and Stable Tg levels and Undetectable TgAb
Biochemical incomplete response (abnormal Tg or rising TgAb values in the absence of localizable disease)	No clinical evidence of tumor and Negative imaging and Undetectable TgAb and Unstimulated Tg >1 ng/mL or stimulated Tg >10 ng/mL	No clinical evidence of tumor and Negative imaging and Undetectable TgAb and Unstimulated Tg >5 ng/mL or stimulated Tg >10 ng/mL or rising TgAb levels	No clinical evidence of tumor and Negative imaging and Undetectable TgAb and Unstimulated Tg >30 ng/mL or Rising Tg values with similar TSH levels or rising TgAb
Structural incomplete response (persistent or newly identified locoregional or distant metastases)	Clinical or imaging evidence of disease (regardless of Tg and TgAb levels)	Clinical or imaging evidence of disease (regardless of Tg and TgAb levels)	Clinical or imaging evidence of disease (regardless of Tg and TgAb levels)
Indeterminate response (nonspecific biochemical or structural findings that cannot be classified as either benign or malignant)	Nonspecific imaging findings or Faint uptake in thyroid bed on RAI scanning or Tg 0.2-1 ng/mL or Stimulated Tg 1-10 ng/mL or TgAb levels stable or declining in the absence of structural or functional disease	Nonspecific imaging findings or Faint uptake in thyroid bed on RAI scanning or Tg 0.2-5 ng/mL or Stimulated Tg 2-10 ng/mL or TgAb levels stable or declining in patients with no imaging evidence of disease	Nonspecific imaging findings or TgAb levels stable or declining in the absence of structural or functional disease

Adapted from Momesso DP & Tuttle RM[90]; Haugen BR, Alexander EK, Bible KC, et al.[11]; and Filetti S, Durante C, Hartl D, et al.[42]

RAI – radioiodine, Tg – thyroglobulin, TgAb – anti-thyroglobulin

Clinical Question 5.3

How should a patient's response to therapy after the first year of treatment be followed up?

Recommendations

- **We recommend increasing the time interval between repeat measurements of unstimulated Tg and TgAb for patients who achieve excellent response (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend measuring stimulated or unstimulated Tg at least every 6–12 months for high-risk and all patients with biochemical incomplete, structural incomplete or indeterminate response (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We do not recommend using stimulated Tg and TgAb in the follow-up of these subsets of patients: those with excellent response, and those with incomplete structural response (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We recommend increasing the time interval between repeat neck US for patients who achieve excellent response (Strength of recommendation: Strong, Certainty of evidence: Moderate)**

Ongoing follow-up is guided by assessment by individual patient's response to therapy (Table 2). Most recurrences of DTC occur within the first 5 years after initial treatment, but recurrences may occur many years or even decades later. Monitoring interval may be increased to every 1–2 years for patients who achieve excellent response.

Clinical Question 5.4

What are the roles of radiologic and nuclear imaging studies in the follow-up of well-differentiated thyroid cancer?

Recommendations

- **We recommend periodic neck US depending on the patient's risk for recurrent disease and Tg status (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend US-guided FNAB for ultrasonographically suspicious lymph nodes >10 mm in widest dimension (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We do not recommend routine diagnostic WBS using low-dose131 I in low-risk patients who have negative serum Tg, TgAb, and neck US during follow-up. WBS may be considered if persistent disease is suspected, despite a negative finding in the other tests (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We recommend FDG-PET scanning in high-risk DTC patients with elevated serum Tg and with negative RAI imaging (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend neck and/or chest CT or MRI in the following settings: bulky and recurrent nodal disease where US may not completely delineate disease; possible invasive recurrent disease involving aerodigestive tract; inadequacy of neck US in visualizing nodal disease (high Tg, negative neck US); and possible involvement of lung parenchyma and/or mediastinum (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend imaging of other organs including brain MRI, skeletal MRI, and/or CT or MRI of the abdomen in high-risk DTC patients with elevated serum Tg and negative neck and chest imaging who have symptoms referable to those organs (Strength of recommendation: Strong, Certainty of evidence: Moderate)**

Table 2. Monitoring after first year of treatment [a,b]

Diagnostic Test	Response to therapy			
	Excellent	Biochemical incomplete	Structural incomplete	Indeterminate
Unstimulated Tg (with TgAb)	Every 1-2 years	Every 6 months	Every 6 months	Every 6-12 months
Stimulated Tg (with TgAb)	Not indicated	May be repeated 2- to 3-year intervals if needed to establish excellent response to therapy	Not indicated	May be repeated 2- to 3-year intervals if needed to establish excellent response to therapy
Neck US	Consider 3- to 5-year interval	1- to 5-year interval	1- to 5-year interval	Consider 6-12-month intervals for 5 years
CT or MRI	Not indicated	Not indicated	6-12-month intervals depending on rate of progression	Not indicated
FDG-PET	Not indicated	Not indicated	To identify additional sites of disease and prognostic purpose	Not indicated

Data from Haugen BR, Alexander EK, Bible KC, et al.[11]; Filetti S, Durante C, Hartl D, et al.[42]; and Tuttle RM[103]

CT – computed tomography, FDG-PET – fluorodeoxyglucose-positron emission topography, MRI – magnetic resonance imaging, Tg – thyroglobulin; TgAb – anti-thyroglobulin, US – ultrasound

[a] Monitoring should still be individualized; [b] Consider if unstimulated Tg is greater than 10 ng/mL or Tg is rising

Serum Tg measurements may fail to identify patients with relatively small amounts of residual tumor. These minimal amounts of residual disease are often located in the neck, and performing neck US offers the best opportunity to recognize or exclude neoplastic disease even when the serum Tg is undetectable. When neck foci the thyroid bed or the lymph nodes suspicious for malignant recurrence are present, ultrasound-guided biopsy is advised. [38,100-105]

A WBS with ^{131}I will be done within 3–7 days post-therapy among all patients who underwent RAIA. Diagnostic WBS may be considered in patients with abnormal uptake outside the thyroid bed on posttherapy WBS; in patients with poorly informative post-ablation WBS; and in patients with TgAb at risk of false-negative Tg even without suspicious neck US finding. In these rare indications, ^{123}I is preferred, but it is not readily available locally. 18F-FDG PET/CT is complementary to ^{131}I WBS (in the presence of detectable ^{131}I uptake), because F-18 uptake may be present in neoplastic foci with no ^{131}I uptake. It is recommended in high-risk patients with elevated serum Tg (generally greater than 10 ng/mL) and negative RAI imaging. It has a median sensitivity and specificity of 83% and 84%, respectively, in non-^{131}I-avid DTC, and is said to be more sensitive in patients with aggressive histologic subtype (e.g., poorly differentiated, tall cell, and Hurthle cell thyroid cancer). 18F-FDG PET/CT is correlated with poor survival and is a negative predictor for response to RAI treatment.

CT or MRI may be used in patients with elevated Tg (generally greater than 10 ng/mL) or TgAb without evidence of disease.[11] This is most useful for bulky and invasive disease where anatomic delineation will affect treatment, especially surgery. RAI can be administered after 4–8 weeks following injection of contrast medium. Iodine contamination would have disappeared in most patients after this period. Although MRI does not use iodine contrast and may better delineate the aerodigestive tract, it is less sensitive than CT for detection of lung micronodules.

Palliative care

Clinical Question 6.1

What services/interventions can be provided for palliation?

Recommendation

We recommend consult with a multidisciplinary team that includes a pain medicine/ palliative care practitioner to address the needs of a thyroid cancer patient in the advanced stage of the disease (Strength of recommendation: Strong, Consensus statement)

Thyroid cancer — specifically, the follicular cell-derived papillary and follicular cancers — generally has good prognosis. However, aggressive types such as the tall cell variant of PTC, and the poorly differentiated to undifferentiated type of cancer have bad prognosis and poor survival. There are patients that have undergone primary surgery but cannot be resected totally; and with recurrent symptomatic tumors wherein surgery and RAIA have previously been given (including tumors considered to be RAI-refractory). Patients who are symptomatic may have airway obstruction, bleeding, difficulty swallowing, intractable pain. These patients afflicted with advanced and complicated thyroid cancer may benefit from various palliative measures which can be discussed through a multidisciplinary approach as agreed upon by the consensus panel.

Clinical Questions 6.2

How do we treat advanced radioiodine-refractory thyroid cancer?

Recommendations

- **We do not recommend further RAI when a patient with DTC is classified as refractory to RAI (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We recommend kinase inhibitors or immunotherapy for patients with RR-DTC (Strength of recommendation: Strong, Certainty of evidence: High)**
- **We recommend multidisciplinary discussion and enrollment in clinical trials for patients with RR-DTC (Strength of recommendation: Strong, Certainty of evidence: Low)**

The European Society of Medical Oncologists (ESMO) defines RAI-refractory thyroid cancer as (a) the absence of initial RAI uptake in metastases, (b) the absence of RAI uptake in metastases after treatment with RAI, (c) the presence of RAI uptake in some metastases, but absence in others, and (d) RECIST progression (i.e., an increase of 20% in the sum of target lesions or the appearance of new lesions) despite RAI uptake in all metastases.[42] In the setting of overall poor anticipated outcome of patients with radiographically evident or symptomatic metastases that do not respond to RAI, the complexity of multidisciplinary treatment considerations and the availability of prospective clinical trials should encourage the clinician to refer such patients to tertiary centers with particular expertise.

Clinical Question 6.3

What is the role of radiotherapy in the palliative setting?

Recommendation

We recommend EBRT to patients who develop metastasis that can cause symptoms that affect function and quality of life (Strength of recommendation: Strong, Certainty of evidence: Moderate)

EBRT may be given to patients with metastasis (i.e., brain, bone, lung, liver) to alleviate symptoms like pain, bleeding,

obstruction, and symptoms that cause neurologic compromise or compression. Most of the studies on the use of EBRT on thyroid cancer metastasis are limited to retrospective reviews of cases.[11,26,42,51,54] The use of stereotactic radiotherapy (SRT) has also been incorporated in the management of patients presenting with metastasis because it allows the delivery of precise, highly conformal, intense dose radiation in one to five fractions using specialized equipment. However, the available data on the use of this approach in thyroid cancer is limited, and the evidence that support its use is currently based on solid tumors.

Clinical Question 6.3.1

What is the role of radiotherapy in spinal cord compression due to bone metastasis?

Recommendation

We recommend EBRT to patients who develop spinal cord compression secondary to bone metastasis (Strength of recommendation: Strong, Certainty of evidence: Moderate)

Surgery followed by RT is recommended for patients with fair to excellent performance status, good life expectancy, controlled or stable systemic disease, and available effective systemic therapy options.[106-108] However, hypofractionated stereotactic radiotherapy (HFSRT) can be offered as definitive treatment among those with grade 2 epidural spinal cord compression, with intermediate spinal stability, with low rates of functional disability, and who are not candidates for surgery. It has been reported that HFSRT alone without surgery only had a 10.4% cumulative incidence of locoregional failure among patients who met these criteria. Best supportive care may be offered to patients with poor prognosis or poor performance status.[11]

Clinical Question 6.3.2

What is the role of radiotherapy in bleeding tumors?

Recommendation

We can consider palliative RT to patients with bleeding tumors not amenable to surgery or other treatments (Strength of recommendation: Strong, Certainty of evidence: Moderate)

Multiple observational studies among patients with various head and neck malignancies have shown that RT is an effective treatment option for the palliation of bleeding, compression, or obstruction. The choice of fractionation regimen will depend on the prognosis and performance status of the patient. Short-course, cyclic, hypofractionated courses are preferred for patients with poor performance status and worse prognosis, while more protracted courses that deliver higher doses may be preferred for patients with good performance status and greater life expectancy.[85,109,110]

Clinical Question 6.3.3

What is the role of radiotherapy in brain metastasis?

Recommendation

We recommend EBRT to patients who develop brain metastasis (Strength of recommendation: Strong, Certainty of evidence: Moderate)

The main management for brain metastasis from thyroid cancers is neurological resection and EBRT.[111-113] Published experience with brain metastasis from DTC have shown that surgical management is reasonable for patients with solitary or oligometastatic disease, and/or patients with symptomatic metastasis.[111-113] RT is given either upfront or postoperatively. Historically, whole brain radiotherapy (WBRT) with/without surgery has been standard of care. However, the toxicities associated with traditional WBRT, which include neurocognitive decline, have prompted the development and increased utilization of other radiotherapeutic modalities such as hippocampal avoidance whole brain radiation (HAWBRT), and focal radiation in the form of stereotactic radiosurgery (SRS) and HFSRT. The choice between SRS, HFSRT, HA-WBRT, and conventional WBRT will depend on patient characteristics and preferences, and on the number, volume, size, and location of the lesions.[114-122] The decision may also vary depending on individual institutional protocols. Best supportive care alone may be considered in older patients with short life expectancy and poor performance status.[123]

Clinical Question 6.4.1

What is the role of systemic therapy in lung/visceral metastases?

Recommendations

- **In high-resource settings, we recommend the use of kinase inhibitors or immunotherapy for RR-DTC patients with lung and/or other visceral metastases not otherwise amenable to local therapies (Strength of recommendation: Strong, Certainty of evidence: High)**
- **In low-resource settings, we can consider the use of cytotoxic chemotherapy in RR-DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease when kinase inhibitors or immunotherapy are not available (Strength of recommendation: Strong, Certainty of evidence: Low)**

Kinase inhibitors (lenvatinib, sorafenib, vandetanib, pazopanib, sunitinib, axitinib or cabozantinib) should be considered in RR-DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches. Of these kinase inhibitors, only sorafenib and lenvatinib have phase III trials that showed prolongation of progression-free survival. There is no clinical trial directly comparing lenvatinib versus sorafenib for DTC. At the time

this guideline was written, other kinase inhibitors had phase II trial evidence of survival benefit. Phase II trials for the median progression free survival and overall response rate for Vandetanib[124], Pazopanib[125], Sunitinib[126] and Axitinib[127] are 11.1 months, 11.7 months and 49%, 13.1 months and 22%, 16.1 months and 35%, and 16.1 months and 18%, respectively. Phase III trials namely SELECT, DECISION and COSMIC-311 have demonstrated a median PFS and ORR of 18.3 months (HR 0.21; 99% CI 0.15-0.31) and 64.8% for Lenvatinib, 10.8 months (HR 0.59; 95% CIn 0.45-0.76) and 12.2% for Sorafenib, and 11.0 months (after progression on Lenvatinib or Sorafenib) and 18% for Cabozantinib[128]. If mutational studies have been performed and a targetable mutation is present, a mutation-specific kinase inhibitor may be considered.

Cytotoxic chemotherapy (e.g., doxorubicin ± cisplatin) may be considered in RR-DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to control through other approaches (including kinase inhibitors or immunotherapy) or with contraindications to these treatment options. In a review of published series, 38% of patients had response to doxorubicin, and patients with pulmonary metastases seemed to benefit more from chemotherapy.[85] It is important to note that studies supporting the use of chemotherapy are small, underpowered, and only showed minimal efficacy. Long-term responses are uncommon.

Clinical Question 6.4.2

What is the role of systemic therapy in brain metastases?

Recommendations

- **In high-resource settings, we may consider the use of kinase inhibitors or immunotherapy for brain metastases in RR-DTC patients not otherwise amenable to local therapies (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **In low-resource settings, we do not recommend the use of cytotoxic chemotherapy for brain metastases (Strength of recommendation: Strong, Certainty of evidence: Low)**

Evidence on responses of patients with brain metastases given kinase inhibitors are limited to those found in case reports and case series, which showed stable or partial responses to kinase inhibitors.[84,129-131] Initial phase III trials found had excluded patients with brain metastases. Immunotherapy such as pembrolizumab may also be considered in these patients if the result is high (≥10 mut/Mb) after doing genomic testing (TMB). Case reports have shown that chemotherapy did not show any objective responses in patients with brain metastases.

Clinical Question 6.4.3

What is the role of systemic therapy in bone metastases?

Recommendations

- **In high-resource settings, we recommend the use of denosumab in RR-DTC patients with diffuse and/or symptomatic bone metastases, either alone or concomitantly with other therapies (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **In low-resource settings, we recommend the use of bisphosphonates in RR-DTC patients with diffuse and/or symptomatic bone metastases, either alone or concomitantly with other therapies (Strength of recommendation: Strong, Certainty of evidence: Moderate)**

In solid tumors, bone-directed therapeutics such as bisphosphonates (especially zoledronic acid) and the RANK ligand–directed agent, denosumab, have been shown to delay time to occurrence of subsequent skeletal-related adverse events (fracture, pain, neurologic complications), to improve symptoms, and to provide benefits for patients with diffuse bone metastases. The determination of benefits across several tumor types suggests that they may be broadly generalizable, prompting FDA approval for their general use in patients with solid tumor bone metastases. Two small studies have suggested benefit from bisphosphonates specifically within the context of DTC bone metastases.[132-133]

Prior to starting therapy, renal function (bisphosphonates) and calcium levels (both bisphosphonates and denosumab) should be determined. A dental evaluation before initial use is also needed.

Clinical Question 6.5

What is the role of systemic therapy in the palliative setting in anaplastic thyroid cancer?

Recommendation

We recommend chemotherapy, targeted therapy or immunotherapy used alone or sequentially, when clinically appropriate (Strength of recommendation: Strong, Certainty of evidence: Moderate)

There is no curative therapy for metastatic ATC, and the disease is uniformly fatal. It is considered the most lethal of all thyroid cancers, and median survival is poor (3–10 months), likely due to rapid growth (20–24 hours doubling time in cell culture).[87,134-136] In patients who desire active therapy rather than palliative care, are fit, and are awaiting molecular or genetic studies, chemotherapy should be offered as treatment and should not be delayed given the aggressive nature of this disease (Figure 3). Enrollment in clinical trials of BRAF-targeted therapy (based on molecular testing) is strongly encouraged. In the absence of clinical trials, multiple guidelines suggest the use of dabrafenib plus trametinib.

Surgical resection for residual tumors can then be considered if the disease is responsive. If these tumors are resectable, surgery should then be followed by re-initiation of dabrafenib plus trametinib, provided that the distant metastases are stable or improved during prior therapy. However, if not resectable, dabrafenib plus trametinib may be continued if a favorable response to therapy is seen. Furthermore, other options include CRT best supportive care in cases where there is poor response to dabrafenib plus trametinib.

In patients with adequate performance status, consider using targeted agents for druggable genetic aberrations such as larotrectinib or entrectinib for NTRK gene fusion positive tumors; crizotinib, ceritinib, or alectinib for ALK fusion; pralsetinib or selpercatinib for RET mutation; and everolimus for TSC1/TSC2. For non-druggable mutations, targeting the tumor microenvironment or common cancer signaling pathways is an alternative approach. Immunotherapy may be considered after doing genomic testing.

Clinical Question 6.6

How should pain be managed among patients with thyroid cancer?

Recommendations

- **We recommend the use of the WHO 3-Step Ladder Approach to pain management across stages of thyroid cancer (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **We recommend a non-opioid analgesic combined with adjuvant drugs for thyroid cancer patients with mild cancer-related pain (Strength of recommendation: Strong, Certainty of evidence: Moderate)**
- **For patients with moderate to severe pain, we recommend a trial of a strong opioid (Strength of recommendation: Moderate, Certainty of evidence: Moderate)**
- **For cancer-related pain that is non-responsive to conventional analgesic drugs, we recommend a multi-modal approach to include any of the following pain management strategies: interventional pain procedures such as epidural block, rehabilitation, and complementary/integrative therapies) (Strength of recommen-dation: Strong, Certainty of evidence: Moderate)**
- **We recommend pain management using the alternative routes when the conventional (oral and intravenous) routes are not tolerated or possible. These alternative routes include subcutaneous administration, transdermal opioid delivery system, morphine elixir by gastrostomy or jejunostomy tube or sublingual route when indicated (Strength of recommendation: Strong, Certainty of evidence: Low)**
- **We recommend the use of non-pharmacologic modalities such as but not limited to cognitive behavioral therapy, support groups, acupuncture as part of the holistic approach to a patient with cancer-related pain (Strength of recommendation: Strong, Certainty of evidence: Low)**

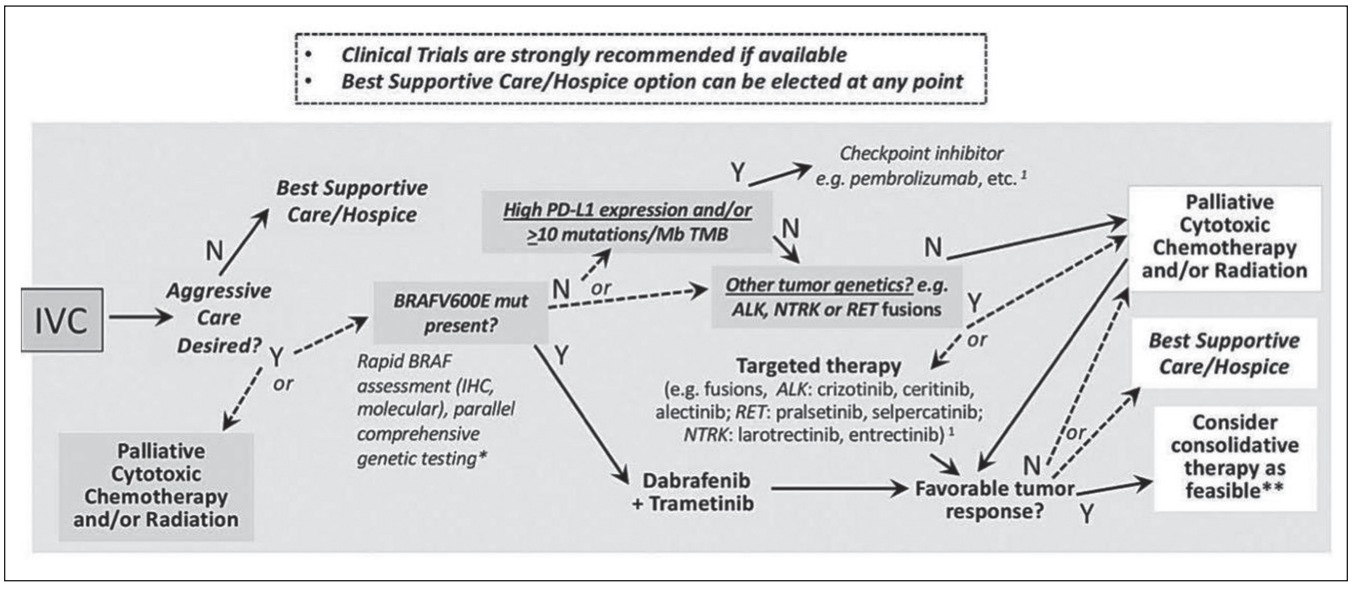

Figure 3. Initial treatment of stage IVC anaplastic thyroid cancer. *Source: Bible et al.*[86]

[1] *Additional 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

The use of analgesic medications is the mainstay of cancer pain management.[137-140] When combined with appropriate dosing guidelines, the World Health Organization three-step ladder approach is capable of providing adequate relief to 70–90% of patients.[137,140] Emphasizing that the intensity of pain and the type/s of pain mechanisms involved, rather than its specific etiology, should be the prime consideration in analgesic selection, the approach advocates three basic steps. This strategy should be integrated with non-pharmacological methods of cancer pain control, including RT, chemotherapy, hormone therapy, surgery, anesthetic interventions, physiotherapy, and psychological/cognitive approaches.

CONCLUSION

Thyroid nodule evaluation begins with targeted history and physical examination. Classification of thyroid nodules based on ultrasound appearance dictate the need for fine needle aspiration biopsy. In turn, the resulting Bethesda classification would influence operative management. Postoperatively, adjuvant treatment and surveillance methods should be based on risk of recurrence. In cases of palliative care, a multidisciplinary approach should be undertaken to address the needs and symptoms of the patient.

The 2021 CPG for well differentiated cancer was made to assist physicians in clinical decision making, and create better prognosis for Filipino patients afflicted with the disease. However, patient management should still be governed by sound clinical judgement and open physician-patient communication.

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APPENDIX

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