NCCN Guidelines® Insights
Thyroid Carcinoma, Version 2.2018
Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Thyroid Carcinoma provide recommendations for the management of different types of thyroid carcinoma, including papillary, follicular, Hürthle cell, medullary, and anaplastic carcinomas. These NCCN Guidelines Insights summarize the panel discussion behind recent updates to the guidelines, including the expanding role of molecular testing for differentiated thyroid carcinoma, implications of the new pathologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features, and the addition of a new targeted therapy option for *BRAF* V600E–mutated anaplastic thyroid carcinoma.

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Release date: December 10, 2018; Expiration date: December 10, 2019

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Thyroid Carcinoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Thyroid Carcinoma

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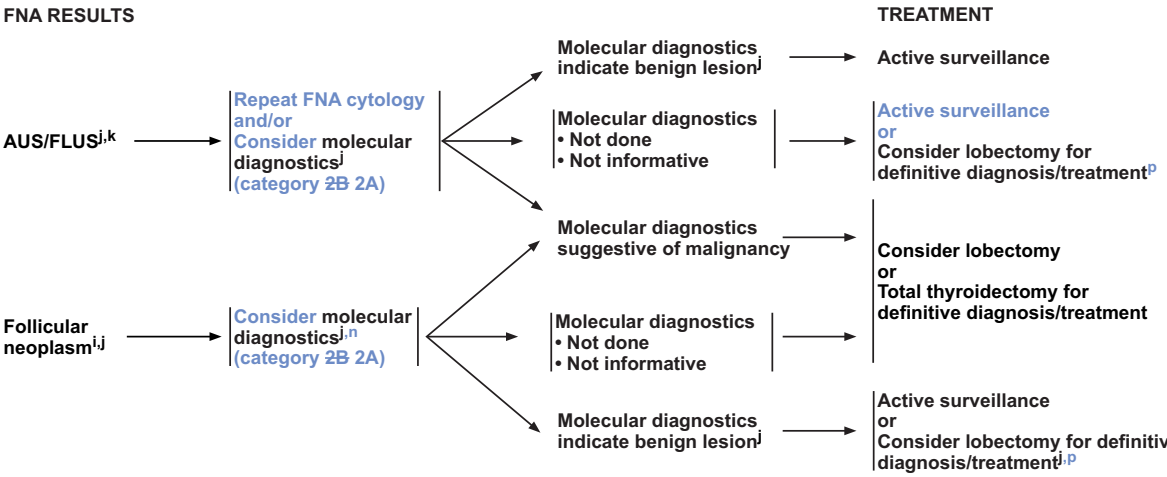

Diagnostic categories for FNA results reflect NCI state of the science conference, the Bethesda Classification. Cibas ES and Ali SZ. Thyroid 2017;27(11):1341-1346. https://www.ncbi.nlm.nih.gov/pubmed/29091573. Cytology reports should be interpreted in light of terminology used by local cytopathologists.

[i]Alternative term: Suspicious for follicular neoplasm. Estimated risk of malignancy is 15%–40%. Numbers may vary by institution or cytopathologist.
[j]The diagnosis of follicular carcinoma or Hürthle cell carcinoma requires evidence of either vascular or capsular invasion, which cannot be determined by FNA. Molecular diagnostics may be useful to allow reclassification of follicular lesions (ie, follicular neoplasm, atypia of undetermined significance (AUS), follicular lesions of undetermined significance (FLUS)) as either more or less likely to be benign or malignant based on the genetic profile. If molecular testing suggests papillary thyroid carcinoma, especially in the case of BRAF V600E, see (PAP-1). If molecular testing, in conjunction with clinical and ultrasound features, predicts a risk of malignancy comparable to the risk of malignancy seen with a benign FNA cytology (approximately 5% or less), consider active surveillance. Molecular markers should be interpreted with caution and in the context of clinical, radiographic, and cytologic features of each individual patient.
[k]Alternative terms include: rule out neoplasm, atypical follicular lesion, and cellular follicular lesion. Estimated risk of malignancy is 5%–15%.
[n]~~Molecular diagnostics are not recommended for Hürthle cell neoplasm.~~ Molecular diagnostics may not perform well for Hürthle cell neoplasms.
[p]Clinical risk factors, sonographic patterns, and patient preference can help determine whether active surveillance or lobectomy is appropriate.

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NCCN Categories of Evidence and Consensus

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

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

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

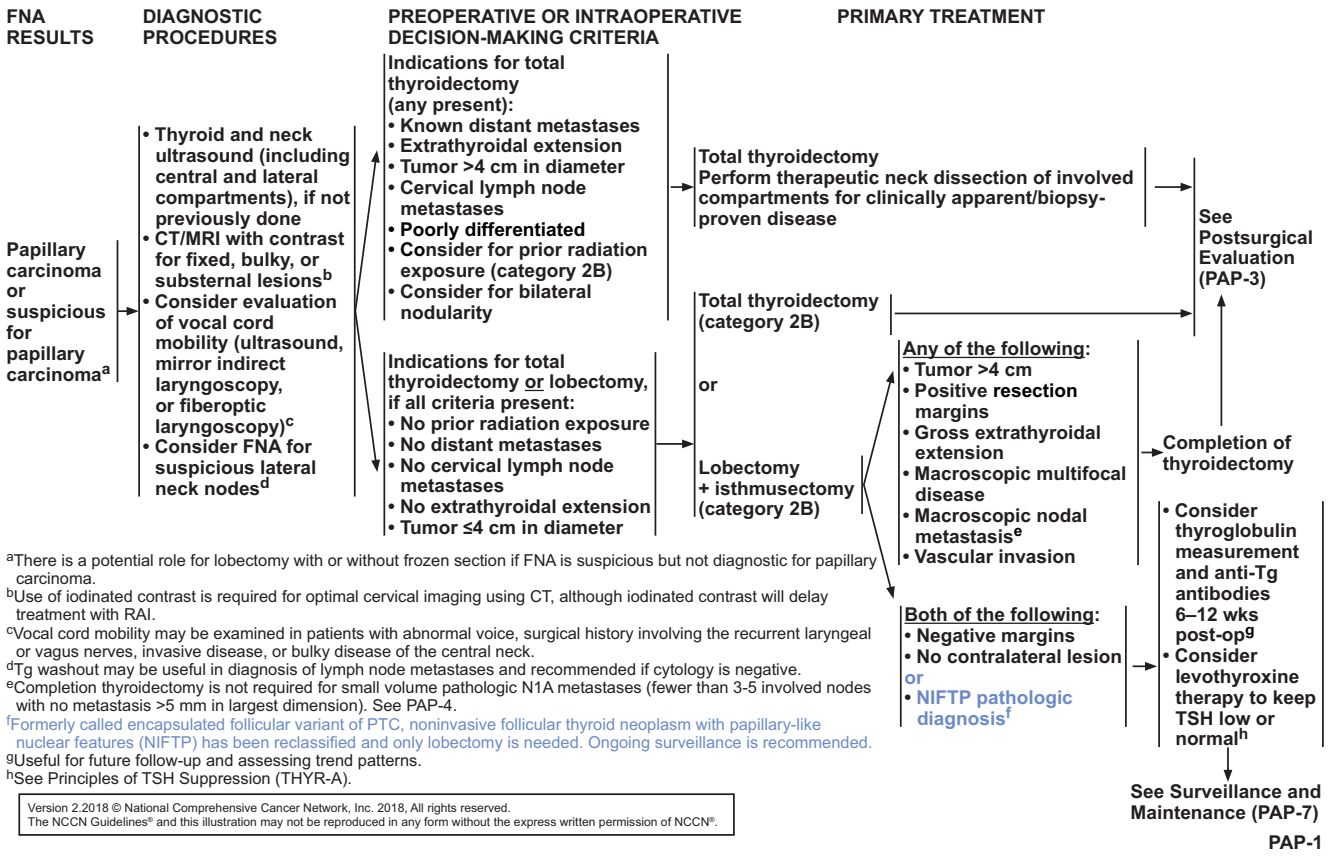
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Overview

Thyroid nodules, often palpated during routine physical examination, are relatively common and increase in frequency throughout life, reaching a prevalence of approximately 5% of US individuals aged ≥50 years having palpable thyroid nodules.[1–3] Nodules are even more prevalent when the thyroid gland is examined at autopsy or surgery, or when using ultrasonography; 50% of the thyroids studied have nodules, which are almost always benign.[2,4] By contrast, thyroid carcinoma is uncommon. For the US population, the lifetime risk of being diagnosed with thyroid carcinoma is 1.2%,[5] with an estimated 53,990 new cases of thyroid carcinoma being diagnosed in 2018.[6] As with thyroid nodules, thyroid carcinoma occurs 2 to 3 times more often in women than in men and is currently the fifth most common malignancy diagnosed in women.[6] The main histologic types of thyroid carcinoma are (1) differentiated thyroid carcinoma (DTC; including papillary, follicular, and Hürthle cell); (2) medullary thyroid carcinoma (MTC); and (3) anaplastic thyroid carcinoma (ATC). Of 63,324



[a]There is a potential role for lobectomy with or without frozen section if FNA is suspicious but not diagnostic for papillary carcinoma.
[b]Use of iodinated contrast is required for optimal cervical imaging using CT, although iodinated contrast will delay treatment with RAI.
[c]Vocal cord mobility may be examined in patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.
[d]Tg washout may be useful in diagnosis of lymph node metastases and recommended if cytology is negative.
[e]Completion thyroidectomy is not required for small volume pathologic N1A metastases (fewer than 3-5 involved nodes with no metastasis >5 mm in largest dimension). See PAP-4.
[f]Formerly called encapsulated follicular variant of PTC, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has been reclassified and only lobectomy is needed. Ongoing surveillance is recommended.
[g]Useful for future follow-up and assessing trend patterns.
[h]See Principles of TSH Suppression (THYR-A).

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PAP-1

patients diagnosed with thyroid carcinoma from 2011 to 2015, 89.8% had papillary carcinoma, 4.5% had follicular carcinoma, 1.8% had Hürthle cell carcinoma, 1.6% had MTC, and 0.8% had ATC.[5]

Mortality rates for thyroid carcinoma are, in general, very low. DTC usually has an excellent prognosis, with 10-year survival rates exceeding 90% to 95%.[7] In contrast, ATC, an aggressive undifferentiated tumor, is almost uniformly lethal. However, because DTCs represent >95% of all cases, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas. In 2018, it is estimated that approximately 2,060 cancer deaths will occur among persons with thyroid carcinoma in the United States.[6] The stable age- and sex-adjusted mortality rate for thyroid carcinoma contrasts distinctly with the declining rates for other solid tumors in adults, and highlights the need for new treatment options for advanced thyroid cancers.[5,8,9]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Thyroid Carcinoma provide recommendations for management of the different types of thyroid carcinoma, including papillary, follicular, Hürthle cell, MTC, and ATC. These NCCN Guidelines Insights summarize the panel discussion behind recent updates to the guidelines, including the expanding role of molecular testing for DTC, implications of the new pathologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), and the addition of a new targeted therapy option for *BRAF* V600E–mutated ATC.

Molecular Testing for DTC

Molecular testing for DTC may be conducted for diagnostic, prognostic, and/or predictive purposes. Because many thyroid cancers have an excellent prognosis and benign nodules are common, diagnostic or prognostic markers can be useful for evaluating suspicious thyroid nodules so that appropriate treatment options can be determined.[1,10,11] Predictive markers,

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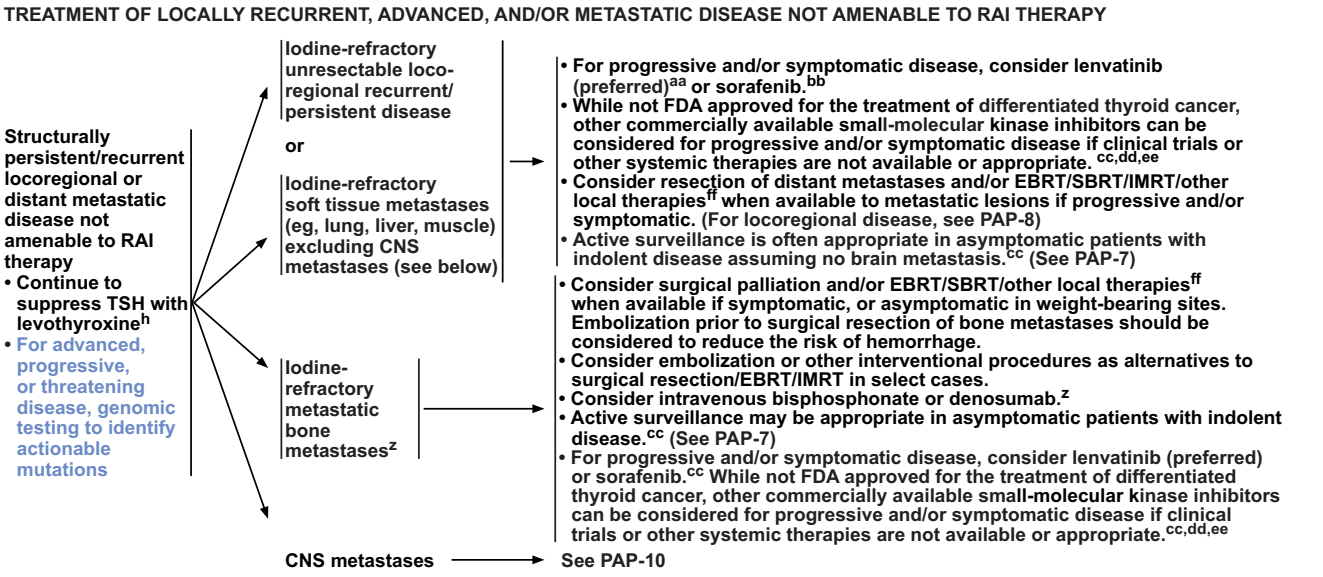

[h]See Principles of TSH Suppression (THYR-A).
[z]Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.
[aa]In a subset of patients (older than 65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, Worden FP, Newbold KL, et al. Effect of age on the efficacy and safety of lenvatinib in radioiodine-refractory differentiated thyroid cancer in the phase III SELECT trial. J Clin Oncol 2017;35:2692-2699.
[bb]The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[cc]Kinase inhibitor therapy may not be approriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[dd]While not FDA approved for treatment of differentiated thyroid cancer, commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF-positive], dabrafenib [BRAF-positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ee]Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[ff]Ethanol ablation, cryoablation, RFA, etc.

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PAP-9

used to guide treatment with specific targeted therapies, are increasingly being used (particularly within clinical trials) for advanced thyroid cancers. The following sections detail the NCCN panel's discussions on the use of molecular markers for the diagnosis and treatment of thyroid cancer.

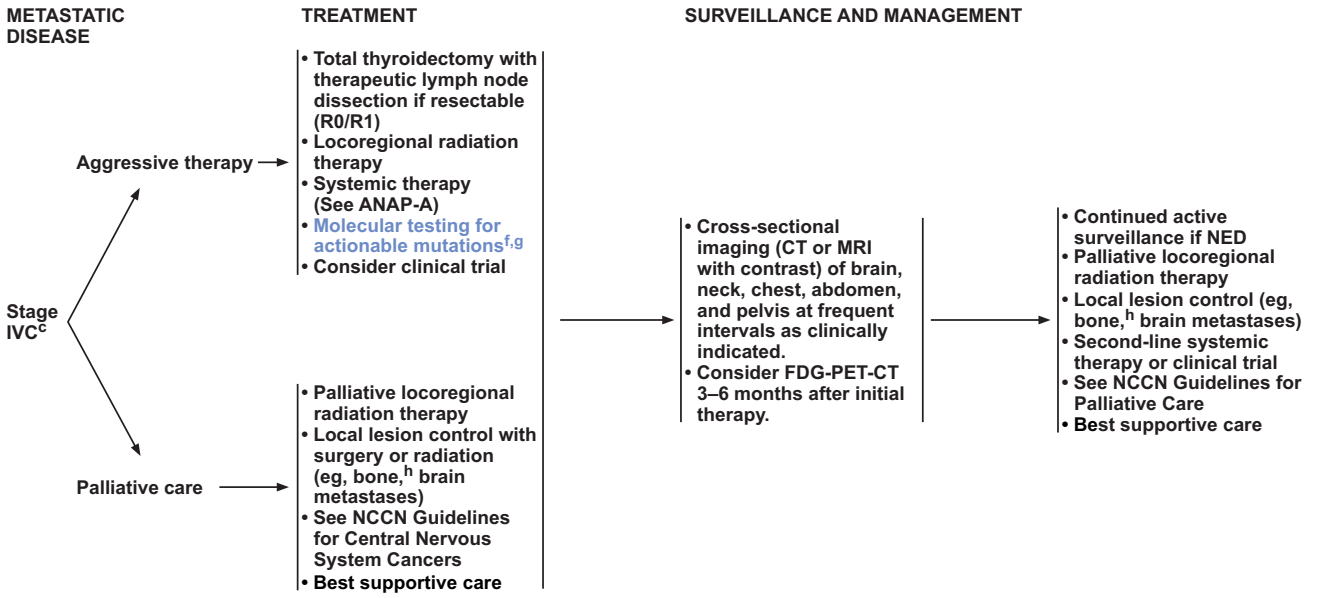
Diagnostic/Prognostic Markers

Fine-needle aspiration (FNA) with ultrasound guidance is the preferred procedure for evaluating suspicious thyroid nodules.[3,11,12] FNA of clinically significant or suspicious cervical lymph nodes should also be considered if identified in the ultrasonographic evaluation of the thyroid and neck. Cytologic examination of an FNA specimen is typically categorized as:

- Category I: nondiagnostic or unsatisfactory biopsy;
- Category II: benign (ie, nodular goiter, colloid goiter, hyperplastic/adenomatoid nodule, Hashimoto's thyroiditis);
- Category III: atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS);
- Category IV: follicular neoplasm or suspicious for follicular neoplasm (includes Hürthle cell neoplasm);
- Category V: suspicious for malignancy; or
- Category VI: malignancy (includes papillary, MTC, ATC or lymphoma).

These diagnostic categories for FNA results reflect the 2017 Bethesda System for Reporting Thyroid Cytopathology.[13]

Molecular diagnostic testing to detect individual mutations (eg, *BRAF* V600E, *RET/PTC*, *RAS*, *PAX8/PPARγ*) or pattern recognition approaches using molecular classifiers may be useful in evaluating FNA samples that are indeterminate to assist in management decisions.[14–22] The *BRAF* V600E mutation occurs in approximately 45% of papillary carcinomas



[c]See Staging (ST-1).
[f]Consider dabrafenib/trametinib combination therapy if *BRAF* V600E mutation is positive.
[g]Subbiah V, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600–mutant anaplastic thyroid cancer. J Clin Oncol 2018;36(1):7-13.
[h]Consider use of intravenous bisphosphonates or denosumab. Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

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ANAP-2

and is the most common mutation.[23] Some studies have linked the *BRAF* V600E mutation to poor prognosis, especially when occurring with a *TERT* promoter mutation.[24–26] Choice of the precise molecular test depends on the cytology and the clinical question being asked.[27–30] Molecular diagnostic testing may include multigene assays (eg, a gene expression classifier [GEC]) or individual mutational analysis.

Rather than proceeding to immediate surgical resection to obtain a definitive diagnosis for these indeterminate FNA cytology groups (follicular neoplasm or AUS/FLUS), patients can be followed with active surveillance if the application of a specific molecular diagnostic test (in conjunction with clinical and ultrasound features) results in a predicted risk of malignancy that is comparable to the rate seen in cytologically benign thyroid FNAs (approximately ≤5%). It is important to note that the predictive value of molecular diagnostics may be significantly influenced by the pretest probability of disease associated with the various FNA cytology groups. Furthermore, in the cytologically indeterminate groups, risk of malignancy from FNA can vary widely between institutions.[13,31] Therefore, proper implementation of molecular diagnostics into clinical care requires an understanding of both the performance characteristics of the specific molecular test and its clinical meaning across a range of pretest disease probabilities.[32,33]

The NCCN panel discussed the use of molecular diagnostic testing for evaluating FNA results of follicular neoplasm/suspicious for follicular neoplasm or AUS/FLUS. Although most of the panel members agreed that they are using molecular diagnostics for this purpose, they expressed uncertainty regarding whether the testing was helpful in guiding treatment. Some panel members voiced concern that the structure of THYR-4 placed too much emphasis on the role of molecular diagnostics. Therefore, the algorithm on THYR-4 was restructured to deemphasize molecular diagnostic testing and to allow an option for active surveillance when molecular diagnostics are not performed for AUS/FLUS (page 1431). In addition, the

panel softened the recommendation for molecular diagnostic testing by adding the word "consider" to emphasize that implementation of molecular diagnostics is not mandatory in these cases. With these changes, a re-vote on molecular diagnostics changed the recommendation from category 2B to category 2A, reflecting the increasing number of institutions that consider molecular diagnostic testing to be an appropriate intervention, albeit not standard of care.

Historically, studies have shown that molecular diagnostics do not perform well for Hürthle cell neoplasms.[34–36] A 2015 publication of 134 patients looked at the performance of the Afirma GEC (Veracyte, Inc.) in guiding management of FNA diagnoses of suspicious for Hürthle cell neoplasm or AUS concerning for Hürthle cell neoplasm. This study found that 86% of patients with suspicious findings on Afirma GEC had unnecessary surgery.[36] However, results presented at the 2017 American Thyroid Association Annual Meeting described improved results using the Afirma Genomic Sequencing Classifier (Veracyte, Inc.) with 2 dedicated classifiers to (1) differentiate Hürthle cell–containing specimens from non-Hürthle specimens, and (2) differentiate neoplastic Hürthle specimens from nonneoplastic. By applying this process to 186 specimens, this study reported an 88.9% sensitivity for detection of Hürthle cell malignancies and a 58.8% specificity for identification of benign Hürthle lesions, representing a marked improvement over previous results.[37] Another molecular test, the ThyroSeq v3 Genomic Classifier (CBLPath, Inc.), has also shown promise for the diagnosis of Hürthle cell–containing specimens. This test analyzes 112 genes for a variety of genetic alterations and was validated in 238 tissue samples and 174 FNA samples with known surgical follow-up. A 2018 publication on the ThyroSeq v3 Genomic Classifier reported a sensitivity of 92.9% (95% CI, 80.52%–98.50%) and a specificity of 69.3% (95% CI, 48.21%–85.67%) for detecting Hürthle cell cancers.[38]

The NCCN panel discussed the limitations of molecular testing for Hürthle cell lesions at the panel meetings for both the 2017 and 2018 updates. Panel members' experiences agreed with the published literature on this subject—several commented that they did not use molecular testing for Hürthle cell lesions because the false-positive rates for malignancy were unacceptably high. In response, the panel added a footnote in the 2017 version to clarify that molecular diagnostic testing was not recommended for Hürthle cell neoplasms. For the 2018 update, the panel discussed recent data showing that the Afirma Genomic Sequencing Classifier and the ThyroSeq v3 Genomic Classifier may perform better with Hürthle cell neoplasms. The panel agreed that although the data were encouraging, they were not yet mature enough to make a recommendation for molecular testing in Hürthle cell lesions; however, they did soften the language of the footnote to read "molecular diagnostics may not perform well for Hürthle cell neoplasms" to account for these emerging data (see THYR-4, page 1431).

Predictive Markers

In addition to their utility in diagnostics, molecular markers may drive decisions related to targeted therapy for advanced disease. Systemic therapy can be considered for locally recurrent, advanced, and/or metastatic DTCs that are not surgically resectable, are not amenable to radioactive iodine (RAI), and are progressing and/or symptomatic. Overall, traditional cytotoxic systemic chemotherapy, such as doxorubicin, has minimal efficacy in patients with metastatic DTC.[39] Therefore, novel treatments for patients with metastatic DTC have been evaluated. Agents with documented efficacy in this setting include lenvatinib,[40,41] sorafenib,[42] sunitinib,[43,44] axitinib,[45–47] everolimus,[48] vandetanib,[49] cabozantinib,[50,51] and pazopanib among others.[52] Severe or fatal side effects from kinase inhibitors include bleeding, hypertension, stroke, and liver toxicity; however, most side effects can be managed and are reversible with discontinuation of the drug.[40–42,53] Dose modifications of kinase inhibitors may be required.

Although the clinical use of predictive markers is currently limited for advanced thyroid cancers, recent data have shown that the BRAF inhibitors vemurafenib and dabrafenib can be effective treatment options for DTC harboring the *BRAF* V600E mutation.[54–56] Because this mutation is common in papillary thyroid cancers, these therapies may be especially promising for this tumor type. An open-label nonrandomized phase II trial of 51 patients with *BRAF* V600E mutation–positive recurrent or metastatic papillary thyroid cancer that was refractory to RAI investigated the safety and efficacy of vemurafenib.[56] Of these 51 patients, 26 had never received a VEGFR-targeted therapy (cohort 1) and 25 had previously received this class of therapy (cohort 2). The primary end point, best overall response rate

for cohort 1, was 38.5% (95% CI, 20.2–59.4). Grade ≥3 adverse events were reported in 65% of patients in cohort 1 and 68% in cohort 2.[56] In a subset of 14 patients with *BRAF* V600E–mutant thyroid carcinoma from a phase I study of dabrafenib, 29% showed partial responses and 64% showed at least a 10% decrease.[54] In addition, another study of 10 patients with *BRAF* V600E–mutant, RAI-refractory papillary thyroid cancer showed that dabrafenib stimulated radioiodine uptake in 60% of patients, suggesting that dabrafenib may sensitize these tumors to RAI therapy.[55] Both of these studies reported that dabrafenib was well tolerated.[54,55] Additionally, emerging data suggest that anaplastic lymphoma kinase (ALK) inhibitors may be effective in patients with papillary carcinoma who have *ALK* gene fusion.[57–60]

In response to these emerging data, the panel added a recommendation for genomic testing to identify actionable mutations for patients with advanced, progressive, or threatening DTC (see PAP-9, page 1433). Panel members commented that molecular testing is particularly important to inform eligibility for clinical trial participation. The panel also voted to add vemurafenib and dabrafenib as treatment options for patients with *BRAF* mutation–positive DTCs that are locally recurrent, advanced, and/or metastatic, are not surgically resectable, are not amenable to RAI, and are progressing and/or symptomatic (see PAP-9, page 1433). The decision was made to not specify *BRAF* V600E mutation, because data show that these inhibitors can work for *BRAF*-activating mutations other than V600E.[61] The panel discussed whether to add the dabrafenib/trametinib combination (discussed for ATC in the following section) as an option for *BRAF*-mutated DTC, but decided to not add this regimen due to preliminary results from a phase II clinical trial for DTC presented at the 2017 ASCO Annual Meeting that did not show clear improvements compared with dabrafenib alone.[62]

NIFTP Pathologic Diagnosis

NIFTP, formerly known as noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), is characterized by its follicular growth pattern, encapsulation or clear demarcation of the tumor from adjacent tissue with no invasion, and nuclear features of papillary carcinoma.[63,64] NIFTP has a low risk for adverse outcomes and, therefore, requires less aggressive treatment.[64–67] NIFTP was reclassified in 2016 to prevent overtreatment of this indolent tumor type and the psychological consequences of a cancer diagnosis on patients.[63,64] The College of American Pathologists updated its protocols with NIFTP in the June 2017 version. Per their protocol, reporting is optional because NIFTP is not overtly malignant and only size, laterality, and margin status are reported.[68]

Although molecular diagnostic testing may be useful for diagnosing NIFTP in the future, currently available tests were not validated using NIFTP samples. Studies have shown that NIFTP specimens frequently carry characteristic mutations/alterations, including *RAS*, *PAX8/PPARγ*, and/or *BRAF* (with the exception of the aggressive *BRAF* V600 mutations), differentiating it from papillary subtypes that more frequently show *BRAF* V600E and *RET/PTC* alterations.[18,69,70] However, multiple studies investigating the performance of molecular diagnostics for this subtype have reported that most thyroid nodules histologically diagnosed as NIFTP are classified as "suspicious" by GEC, possibly leading to more aggressive surgical treatment than is necessary.[71,72] Therefore, the validation of molecular diagnostics with NIFTP samples will be necessary to ensure that the tests are accurately classifying these.

The panel members agreed that although NIFTP is still considered a subset of papillary carcinoma, these tumors have low malignant potential and therefore do not require completion thyroidectomy after lobectomy. Based on this, the panel consensus was to conduct no further treatment after lobectomy and histologic diagnosis of NIFTP, and rather to proceed to active surveillance with consideration of thyroglobulin measurement and anti-Tg antibodies 6 to 12 weeks after lobectomy. Levothyroxine therapy may be considered to keep thyroid-stimulating hormone levels low to normal (see PAP-1, page 1432). At the time of the panel meeting, some panel members mentioned that the NIFTP terminology was still in the process of being accepted within practice patterns and that some institutions may still be classifying these tumors as EFVPTC. To address this, they decided to add a footnote clarifying that noninvasive EFVPTC had been reclassified as NIFTP.

Systemic Therapy for ATC

ATC is an aggressive undifferentiated tumor, with a disease-specific mortality approaching 100%.[73] Treatment of ATC should be planned in consultation with a multidisciplinary team and ideally performed at a high-volume center with expertise in treating ATC. Therapy is often multimodal, consisting of surgery, systemic therapy, and/or radiation therapy, because ATC often responds poorly to single-modality therapy.[74,75] Given the poor outcome with current standard therapy, all patients—regardless of surgical resection—should be considered for clinical trials.

Panel members commented that few therapies have emerged for treating ATC over the years. Given the limited available treatments and a very poor prognosis, clinicians are grasping for options for these patients. With this in mind, the panel decided to add a recommendation to conduct molecular testing for actionable mutations in all patients with ATC who are considering systemic therapy (see ANAP-2, page 1434). Panel members agreed that molecular testing is part of the global approach to managing patients with ATC and is strongly recommended. Although there is now an FDA-approved therapy for ATC with the *BRAF* V600E mutation (discussed in the following paragraph), the panel does not intend for the recommendation regarding molecular testing to only apply to *BRAF* mutations; any targeted therapies that are effective against an identified mutation/alteration may be considered (eg, crizotinib for *ALK* mutations).

BRAF mutations have been reported in patients with ATC, supporting the utility of BRAF inhibitors for treatment.[76–80] An open-label, nonrandomized, multicenter phase II trial evaluated the efficacy and safety of dabrafenib in combination with trametinib for treatment of *BRAF* V600E–mutated rare cancers (including in a cohort of 16 patients with ATC).[80] The primary end point, confirmed overall response rate, was 69% (95% CI, 41%–89%), with 7 responses ongoing. Although duration of response, progression-free survival, and overall survival were not yet reached, the 12-month estimates were 90%, 79%, and 80%, respectively. The combination was found to be well tolerated as evaluated in 100 patients across 7 rare tumor types; common adverse events included fatigue (38%), pyrexia (37%), and nausea (35%).[80] Based on these data, the FDA approved dabrafenib/trametinib for patients with ATC and *BRAF* V600E mutations on May 4, 2018.[81]

The panel commented that the survival and response rate reported in this trial were very encouraging, especially for a disease with such a poor prognosis. However, they cautioned that the small size of the ATC cohort (N=16) limited their ability to make a strong recommendation for this regimen. Therefore, the panel drafted a footnote suggesting consideration of dabrafenib/trametinib combination therapy in *BRAF* V600E mutation–positive ATC (see ANAP-2, page 1434). Several panel members mentioned that their institutions have adopted testing for *BRAF* mutations and are treating patients with dabrafenib/trametinib when *BRAF* V600E mutations are detected. Anecdotally, they have noted impressive responses in patients with disease that responds to the therapy. The panel also discussed whether the dabrafenib/trametinib recommendation should be limited to only *BRAF* V600E, because deep sequencing will often yield multiple actionable mutations in this tumor type. The decision was to specify V600E mutation because there are currently no data to guide how to treat ATC with other mutations. The panel looks forward to additional data with larger numbers of patients showing benefit from this regimen in *BRAF*-mutated ATC, at which time they may consider strengthening their recommendation. In the meantime, the panel stressed that clinical trial participation should still be the preferred treatment option for patients with ATC who qualify.

Conclusions

Recent medical advances have improved treatment for patients with thyroid cancers through better identification of indolent subtypes that require less aggressive treatment and the development of new targeted therapy options for advanced or metastatic disease. Although the data are not yet strong enough to be considered a standard of care, use of molecular diagnostics for indeterminate FNA results may help some patients with indolent nodules avoid surgery. Likewise, the recent reclassification of the NIFTP subtype allows patients with this low-risk tumor to avoid total thyroidectomy and its associated side effects. However, molecular markers can also inform the use of targeted therapies and/or clinical trial eligibility for advanced or metastatic thyroid carcinoma. This approach is especially promising for ATC, a subtype with poor prognosis and few treatment options.

References

1. Mazzaferri EL. Thyroid carcinoma: papillary and follicular. In: Mazzaferri EL, Samaan N, eds. Endocrine Tumors. Cambridge, England: Blackwell Scientific Publications; 1993:278–333.
2. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med 2004;351:1764–771.
3. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–1214.
4. Ezzat S, Sarti DA, Cain DR, Braunstein GD. Thyroid incidentalomas. Prevalence by palpation and ultrasonography. Arch Intern Med 1994;154:1838–1840.
5. Noone AM, Howlader N, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2015, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. Bethesda, MD: National Cancer Institute; 2018. Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed November 20, 2018.
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
7. Amin MB, Edge SB, Greene F, et al, eds. AJCC Cancer Staging Manual, 8th ed. New York, NY: Springer International Publishing; 2017.
8. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212–236.
9. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–249.
10. Kaplan MM. Clinical evaluation and management of solitary thyroid nodules. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:996–1010.
11. Layfield LJ, Cibas ES, Gharib H, Mandel SJ. Thyroid aspiration cytology: current status. CA Cancer J Clin 2009;59:99–110.
12. Yang J, Schnadig V, Logrono R, Wasserman PG. Fine-needle aspiration of thyroid nodules: a study of 4703 patients with histologic and clinical correlations. Cancer 2007;111:306–315.
13. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2017;27:1341–1346.
14. Giordano TJ, Beaudenon-Huibregtse S, Shinde R, et al. Molecular testing for oncogenic gene mutations in thyroid lesions: a case-control validation study in 413 postsurgical specimens. Hum Pathol 2014;45:1339–1347.
15. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med 2012;367:705–715.
16. Nikiforov YE, Ohori NP, Hodak SP, et al. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. J Clin Endocrinol Metab 2011;96:3390–3397.
17. Ohori NP, Nikiforova MN, Schoedel KE, et al. Contribution of molecular testing to thyroid fine-needle aspiration cytology of "follicular lesion of undetermined significance/atypia of undetermined significance". Cancer Cytopathol 2010;118:17–23.
18. Rivera M, Ricarte-Filho J, Knauf J, et al. Molecular genotyping of papillary thyroid carcinoma follicular variant according to its histological subtypes (encapsulated vs infiltrative) reveals distinct BRAF and RAS mutation patterns. Mod Pathol 2010;23:1191–1200.
19. Nikiforov YE, Steward DL, Robinson-Smith TM, et al. Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules. J Clin Endocrinol Metab 2009;94:2092–2098.
20. Musholt TJ, Fottner C, Weber MM, et al. Detection of papillary thyroid carcinoma by analysis of BRAF and RET/PTC1 mutations in fine-needle aspiration biopsies of thyroid nodules. World J Surg 2010;34:2595–2603.
21. Lassalle S, Hofman V, Ilie M, et al. Clinical impact of the detection of BRAF mutations in thyroid pathology: potential usefulness as diagnostic, prognostic and theragnostic applications. Curr Med Chem 2010;17:1839–1850.
22. Chudova D, Wilde JI, Wang ET, et al. Molecular classification of thyroid nodules using high-dimensionality genomic data. J Clin Endocrinol Metab 2010;95:5296–5304.
23. Yarchoan M, LiVolsi VA, Brose MS. BRAF mutation and thyroid cancer recurrence. J Clin Oncol 2015;33:7–8.
24. Li C, Lee KC, Schneider EB, Zeiger MA. BRAF V600E mutation and its association with clinicopathological features of papillary thyroid cancer: a meta-analysis. J Clin Endocrinol Metab 2012;97:4559–4570.
25. Basolo F, Torregrossa L, Giannini R, et al. Correlation between the BRAF V600E mutation and tumor invasiveness in papillary thyroid carcinomas smaller than 20 millimeters: analysis of 1060 cases. J Clin Endocrinol Metab 2010;95:4197–4205.
26. Liu R, Bishop J, Zhu G, et al. Mortality risk stratification by combining BRAF V600E and TERT promoter mutations in papillary thyroid cancer: genetic duet of BRAF and TERT promoter mutations in thyroid cancer mortality [published online September 1, 2016]. JAMA Oncol. doi: 10.1001/jamaoncol.2016.3288.
27. Sadow PM, Heinrich MC, Corless CL, et al. Absence of BRAF, NRAS, KRAS, HRAS mutations, and RET/PTC gene rearrangements distinguishes dominant nodules in Hashimoto thyroiditis from papillary thyroid carcinomas. Endocr Pathol 2010;21:73–79.
28. Rodrigues HG, De Pontes AA, Adan LF. Contribution of the BRAF oncogene in the pre-operative phase of thyroid carcinoma. Oncol Lett 2013;6:191–196.
29. Canadas-Garre M, Becerra-Massare P, Lopez de la Torre-Casares M, et al. Reduction of false-negative papillary thyroid carcinomas by the routine analysis of BRAF(T1799A) mutation on fine-needle aspiration biopsy specimens: a prospective study of 814 thyroid FNAB patients. Ann Surg 2012;255:986–992.
30. Lee ST, Kim SW, Ki CS, et al. Clinical implication of highly sensitive detection of the BRAF V600E mutation in fine-needle aspirations of thyroid nodules: a comparative analysis of three molecular assays in 4585 consecutive cases in a BRAF V600E mutation-prevalent area. J Clin Endocrinol Metab 2012;97:2299–2306.
31. Wang CC, Friedman L, Kennedy GC, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. Thyroid 2011;21:243–251.
32. Albarel F, Conte-Devolx B, Oliver C. From nodule to differentiated thyroid carcinoma: contributions of molecular analysis in 2012. Ann Endocrinol (Paris) 2012;73:155–164.
33. Hodak SP, Rosenthal DS, American Thyroid Association Clinical Affairs Committee. Information for clinicians: commercially available molecular diagnosis testing in the evaluation of thyroid nodule fine-needle aspiration specimens. Thyroid 2013;23:131–134.
34. McIver B, Castro MR, Morris JC, et al. An independent study of a gene expression classifier (Afirma) in the evaluation of cytologically indeterminate thyroid nodules. J Clin Endocrinol Metab 2014;99:4069–4077.
35. Celik B, Whetsell CR, Nassar A. Afirma GEC and thyroid lesions: an institutional experience. Diagn Cytopathol 2015;43:966–970.
36. Brauner E, Holmes BJ, Krane JF, et al. Performance of the Afirma Gene Expression Classifier in Hurthle cell thyroid nodules differs from other indeterminate thyroid nodules. Thyroid 2015;25:789–796.
37. Duh QY, Angell TE, Babiarz J, et al. Development and validation of classifiers to enhance the Afirma genomic sequencing classifier performance among Hürhtle cell specimens. Presented at the 87th Annual Meeting of the American Thryoid Association; October 18–22, 2017; Victoria, BC, Canada.
38. Nikiforova MN, Mercurio S, Wald AI, et al. Analytical performance of the ThyroSeq v3 genomic classifier for cancer diagnosis in thyroid nodules. Cancer 2018;124:1682–1690.
39. Sherman SI. Cytotoxic chemotherapy for differentiated thyroid carcinoma. Clin Oncol (R Coll Radiol) 2010;22:464–468.
40. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015;372:621–630.
41. Brose MS, Worden FP, Newbold KL, et al. Effect of age on the efficacy and safety of lenvatinib in radioiodine-refractory differentiated thyroid cancer in the phase III SELECT trial. J Clin Oncol 2017;35:2692–2699.
42. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014;384:319–328.
43. Carr LL, Mankoff DA, Goulart BH, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. Clin Cancer Res 2010;16:5260–5268.
44. Cabanillas ME, Waguespack SG, Bronstein Y, et al. Treatment with tyrosine kinase inhibitors for patients with differentiated thyroid cancer: the M. D. Anderson experience. J Clin Endocrinol Metab 2010;95:2588–2595.
45. Locati LD, Licitra L, Agate L, et al. Treatment of advanced thyroid cancer with axitinib: phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments. Cancer 2014;120:2694–2703.

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46. Cohen EE, Rosen LS, Vokes EE, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. J Clin Oncol 2008;26:4708–4713.
47. Cohen EE, Tortorici M, Kim S, et al. A phase II trial of axitinib in patients with various histologic subtypes of advanced thyroid cancer: long-term outcomes and pharmacokinetic/pharmacodynamic analyses. Cancer Chemother Pharmacol 2014;74:1261–1270.
48. Lim SM, Chang H, Yoon MJ, et al. A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes. Ann Oncol 2013;24:3089–3094.
49. Leboulleux S, Bastholt L, Krause T, et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. Lancet Oncol 2012;13:897–905.
50. Shah MH, De Souza J, Wirth L, et al. Cabozantinib in patients with radioiodine-refractory differentiated thryoid cancer who progressed on prior VEGFR-targeted therapy: results of NCI- and ITOG-sponsored multicenter phase II clinical trial [abstract]. Presented at the 15th International Thyroid Congress; October 18–23, 2015; Orlando, Florida. Abstract 73.
51. Cabanillas ME, Brose MS, Holland J, et al. A phase I study of cabozantinib (XL184) in patients with differentiated thyroid cancer. Thyroid 2014;24:1508–1514.
52. Bible KC, Suman VJ, Molina JR, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. Lancet Oncol 2010;11:962–972.
53. Klein Hesselink EN, Steenvoorden D, Kapiteijn E, et al. Therapy of endocrine disease: response and toxicity of small-molecule tyrosine kinase inhibitors in patients with thyroid carcinoma: a systematic review and meta-analysis. Eur J Endocrinol 2015;172:R215–225.
54. Falchook GS, Millward M, Hong D, et al. BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer. Thyroid 2015;25:71–77.
55. Rothenberg SM, McFadden DG, Palmer EL, et al. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. Clin Cancer Res 2015;21:1028–1035.
56. Brose MS, Cabanillas ME, Cohen EE, et al. Vemurafenib in patients with BRAF(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17:1272–1282.
57. Chou A, Fraser S, Toon CW, et al. A detailed clinicopathologic study of ALK-translocated papillary thyroid carcinoma. Am J Surg Pathol 2015;39:652–659.
58. Park G, Kim TH, Lee HO, et al. Standard immunohistochemistry efficiently screens for anaplastic lymphoma kinase rearrangements in differentiated thyroid cancer. Endocr Relat Cancer 2015;22:55–63.
59. Perot G, Soubeyran I, Ribeiro A, et al. Identification of a recurrent STRN/ALK fusion in thyroid carcinomas. PLoS One 2014;9:e87170.
60. Kelly LM, Barila G, Liu P, et al. Identification of the transforming STRN-ALK fusion as a potential therapeutic target in the aggressive forms of thyroid cancer. Proc Natl Acad Sci U S A 2014;111:4233–4238.
61. Turski ML, Vidwans SJ, Janku F, et al. Genomically driven tumors and actionability across histologies: BRAF-mutant cancers as a paradigm. Mol Cancer Ther 2016;15:533–547.
62. Shah MH, Wei L, Wirth LJ, et al. Results of randomized phase II trial of dabrafenib versus dabrafenib plus trametinib in BRAF-mutated papillary thyroid carcinoma [abstract]. J Clin Oncol 2017;35(Suppl):Abstract 6022.
63. Patel KN. Noninvasive encapsulated follicular variant of papillary thyroid "cancer" (or not): time for a name change. JAMA Oncol 2016;2:1005–1006.
64. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2016;2:1023–1029.
65. Vivero M, Kraft S, Barletta JA. Risk stratification of follicular variant of papillary thyroid carcinoma. Thyroid 2013;23:273–279.
66. Piana S, Frasoldati A, Di Felice E, et al. Encapsulated well-differentiated follicular-patterned thyroid carcinomas do not play a significant role in the fatality rates from thyroid carcinoma. Am J Surg Pathol 2010;34:868–872.
67. Liu J, Singh B, Tallini G, et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. Cancer 2006;107:1255–1264.
68. Seethala RR, Asa SL, Bullock MJ, et al. Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland 2017. Available at: https://cap.objects.frb.io/protocols/cp-thyroid-17protocol-4000.pdf. Accessed March 22, 2018.
69. Paulson VA, Shivdasani P, Angell TE, et al. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features accounts for over half of "carcinomas" harboring RAS mutations. Thyroid 2017;27:506–511.
70. Brandler TC, Liu CZ, Cho M, et al. Does noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) have a unique molecular profile? Am J Clin Pathol 2018;150:451–460.
71. Jiang XS, Harrison GP, Datto MB. Young investigator challenge: molecular testing in noninvasive follicular thyroid neoplasm with papillary-like nuclear features. Cancer Cytopathol 2016;124:893–900.
72. Song SJ, LiVolsi VA, Montone K, Baloch Z. Pre-operative features of non-invasive follicular thyroid neoplasms with papillary-like nuclear features: an analysis of their cytological, Gene Expression Classifier and sonographic findings. Cytopathology 2017;28:488–494.
73. Are C, Shaha AR. Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors, and treatment approaches. Ann Surg Oncol 2006;13:453–464.
74. Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1104–1139.
75. Nachalon Y, Stern-Shavit S, Bachar G, et al. Aggressive palliation and survival in anaplastic thyroid carcinoma. JAMA Otolaryngol Head Neck Surg 2015;141:1128–1132.
76. Kunstman JW, Juhlin CC, Goh G, et al. Characterization of the mutational landscape of anaplastic thyroid cancer via whole-exome sequencing. Hum Mol Genet 2015;24:2318–2329.
77. Rosove MH, Peddi PF, Glaspy JA. BRAF V600E inhibition in anaplastic thyroid cancer. N Engl J Med 2013;368:684–685.
78. Takano T, Ito Y, Hirokawa M, et al. BRAF V600E mutation in anaplastic thyroid carcinomas and their accompanying differentiated carcinomas. Br J Cancer 2007;96:1549–1553.
79. Keutgen XM, Sadowski SM, Kebebew E. Management of anaplastic thyroid cancer. Gland Surg 2015;4:44–51.
80. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. J Clin Oncol 2018;36:7–13.
81. U.S. Food & Drug Administration. FDA approves dabrafenib plus trametinib for anaplastic thyroid cancer with BRAF V600E mutation. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm606708.htm. Accessed August 24, 2018.

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Posttest Questions

1. Consideration of molecular diagnostic testing is currently recommended in the NCCN Guidelines for Thyroid Carcinoma for which of the following FNA results?
   a. Carcinoma (malignancy)
   b. Follicular neoplasm or suspicious for follicular neoplasm
   c. AUS or FLUS
   d. A, B, and C
   e. B and C

2. True or False: Based on its low potential for malignancy, noninvasive EFVPTC has been reclassified as NIFTP, and completion thyroidectomy is not recommended for this pathologic diagnosis.

3. Which of the following therapies is recommended in the NCCN Guidelines for treatment of locally advanced or metastatic ATC with BRAF V600E mutation and no satisfactory locoregional treatment options?
   a. Vemurafenib
   b. Encorafenib + binimetinib
   c. Dabrafenib + trametinib
   d. All of the above