NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-.

Thyroid Cancer

Authors

Kenny Lee; Catherine Anastasopoulou[1]; Chandriya Chandran[2]; Sebastiano Cassaro[3].

Affiliations

[1] Jefferson Einstein Medical Center
[2] Ascension St. Vincent Hospital
[3] UN California Irvine / Kaweah Delta

Last Update: May 1, 2023.

Continuing Education Activity

Thyroid cancer is a malignancy arising from the thyroid parenchymal cells. Its incidence is steadily increasing worldwide, while the mortality rate has remained stable over the past several years. The clinical behavior of thyroid cancer is highly variable, from indolent, slowly progressing tumors to highly aggressive tumors with high mortality rates. There are various new cutting-edge treatment options for advanced thyroid cancer, while there is also evidence against the overtreatment of low-risk thyroid cancers. Hence, a thorough understanding of the types of thyroid cancer and its management is of paramount importance in providing the appropriate treatment to the patient. This activity reviews the incidence, etiology, pathophysiology, diagnosis, and treatment of thyroid cancer and highlights the role of interprofessional communication in optimizing the care of these patients.

Objectives:

- Outline the epidemiology and risk factors of thyroid cancer.
- Describe the clinical presentation and detailed histopathology of the different types of thyroid cancer.
- Explain the different treatment options for patients with thyroid cancer.
- Highlight the importance of interprofessional teams in coordinating care to optimize outcomes for patients with thyroid cancer.

Access free multiple choice questions on this topic.

Introduction

Thyroid cancer is a malignancy of the thyroid parenchymal cells. The thyroid parenchyma consists of two major cell types, the thyroid follicular cells that give rise to differentiated thyroid cancer(DTC) and the parafollicular or C-cells that give rise to medullary thyroid carcinoma (MTC). DTC comprises papillary thyroid cancer(PTC), follicular thyroid cancer(FTC), and Hurthle cell cancer which account for 90-95% of all thyroid malignancies. MTC accounts for around 1 to 2%, and anaplastic thyroid carcinoma accounts for less than 1% of all thyroid cancers[1]

Etiology

Familial occurrence of thyroid cancer is approximately 5% for PTC and FTC and 15 to 30% for MTC.[2] Over the last

decades, the incidence of papillary thyroid cancer has increased worldwide, mostly due to early detection and advanced imaging technology with the risk of overdetection.[3] Mutations and translocations in the genes coding the mitogen-activated protein kinase (MAPK) cellular signaling pathway have been implicated in the genetic basis of most thyroid cancers.[4]

Some of the common mutations are as follows:

PTC - Point mutation in the BRAF gene leading to BRAF V600E mutant kinase is the most common mutation leading to PTC (29 to 69%) and PTC-associated anaplastic thyroid cancer (0 to 12%).[5] Translocation of the RET-papillary thyroid cancer(RET/PTC) occurs in about 7% of PTC.[6] Mutations in RAS proto-oncogene occur in 10-20% of follicular variant PTC (FVPTC).[2]

FTC - Mutations in RAS proto-oncogene are most common in FTC (40 to 50%). Translocation in PAX8–peroxisome proliferator-activated receptor γ (PPARγ) has been identified in around 30 to 35% of FTC.[7]

Anaplastic - Inactivating mutation of the *p53* tumor suppressor gene has been identified in addition to early inactivating mutations in about 50 to 80% of the cases with anaplastic thyroid cancer.[8][9][10] Also, 66% of anaplastic thyroid cancers have been identified to harbor mutations in the CTNNB1 gene.[5] RAS mutations are also associated with 20 to 40% of anaplastic thyroid cancers.

MTC - Germline mutations of RET proto-oncogene in inherited forms of MTC (approximately 25% of MTC) and RAS mutations in 25% of MTC.[11]

Several other uncommon gene mutations have been associated with the development of thyroid cancer, such as TERT mutations, especially highly aggressive PTC.[12] DTC can be inherited by autosomal dominant inheritance or appear as a part of tumor-susceptibility syndromes.[13]

Risk factors: Female sex, a family history of thyroid cancer, and radiation exposure of the thyroid gland during childhood are the major risk factors associated with DTC.[14][15][16][15][14] A recent study showed that thyroid cancer affects both genders equally, as seen in autopsy reports, but it might be detected in women more frequently than men. The difference could be explained by access to medical care.[17]

Epidemiology

Thyroid cancer represents 1% to 4% of all malignancies and is the fifth most common cancer in women in the United States.[14] It has a female preponderance of around 3:1.[18] There has been a steady rise in the incidence of thyroid cancer globally; particularly, PTC detection has risen by 240% in the last three decades.[19] This increase in the incidence has been observed in both genders and among all races and is thought to be primarily due to an increasing trend in the rate of diagnostic imaging.[20][21]

PTC is the most common endocrine cancer, responsible for 96% of all new and 66.8% of deaths due to endocrine cancers.[22] As was mentioned earlier, most thyroid cancers derive from the follicular epithelium, with PTC and FTC being far more common than anaplastic thyroid cancer.[23][24]

Histopathology

PTC: Microscopically, the unique characteristic feature of PTC is papillae formation. A papilla consists of layers of tumor cells surrounding a fibrovascular core. Follicles are typically absent in classic PTC. Typical cellular histomorphology includes cells with large and clear nuclei with finely granular chromatin, often described as ground-glass or "Orphan Annie-eyed" nuclei with nuclear grooving and intranuclear inclusion bodies. Psammoma bodies,

which are calcified clumps of cells likely derived from necrosed papillae, are also common.[25]

Some variants of PTC do not form papillae and are termed follicular variants of PTC, provided they still have the nuclear features of PTC. Variants of PTC such as tall cell variant, columnar variant, insular carcinoma, and diffuse sclerosing variant are more aggressive than classic PTC and are termed thyroid cancers with intermediate differentiation.[26]

FTC: The histological features of FTC can be highly variable, from a well-differentiated follicular pattern to a poorly differentiated pattern with marked nuclear atypia, absence of follicles, extensive capsular or vascular invasion, and solid growth. The latter changes are associated with a poor prognosis.[27] As described above, features that are characteristic of PTC should be absent. Differentiating a follicular carcinoma from a benign follicular adenoma can only be made based on extracapsular and/or vascular invasion. FTC is further classified as minimally invasive, encapsulated, angioinvasive, and widely invasive, depending on the extent of invasion.

Hurthle cell carcinoma: This is characterized by the occurrence of eosinophilic oxyphilic cells with abundant cytoplasm (oncocytes) and prominent nucleoli.[28]

MTC: Given its origin from the parafollicular C cells, its histological features are the presence of spindle-shaped cells with no follicle formation. Amyloid deposition and calcitonin immunoreactivity are typically present.

Anaplastic thyroid carcinoma: The usual histologic variants are spindle-cell, pleomorphic giant cell, and squamoid variants.[29] Most of these cancers can consist of a mixed morphology of 2 or 3 variants. Atypical mitosis and numerous mitotic figures are very common. These cancers are less likely to stain for thyroid transcription factor 1 (TTF1), PAX 8, or thyroglobulin.

History and Physical

The most common presenting feature in DTC is either neck swelling (detected by the patient or a clinician) or incidentally detected thyroid nodules on neck imaging. The risk of malignancy of a thyroid nodule in the general population is around 5 to 10%, with the risk being higher in men and extremes of age.[30]

A careful history and physical examination will help to differentiate low-risk vs. high-risk nodules, although these signs and symptoms lack specificity. Aspects in the patient's history that could be concerning for malignancy include a sudden increase in the size of the nodule with pressure symptoms such as hoarseness of voice, dysphagia, dyspnea, or Horner's Syndrome, as well as a family history of thyroid cancer, childhood irradiation to the head and neck region, or the occurrence of systemic effects such as weight loss and fatigue. On physical examination of the neck, firmness of the nodule, immobility, and the presence of neck lymph nodes should trigger suspicion for malignancy and lead to further evaluation.

On the other hand, anaplastic thyroid cancer can present as a rapidly enlarging neck mass and rapid occurrence of compressive symptoms of the aerodigestive tract. Some patients can present with constitutional symptoms such as fever, weight loss, and anorexia.[31][32]

Evaluation

A thyroid function panel is the most appropriate initial evaluation in a patient with a thyroid nodule. A hyperthyroid state often correlates with a lower risk of malignancy; in such patients, a radionuclide uptake scan is indicated. If the nodule/nodules are identified as hyperfunctioning, fine-needle aspiration biopsy (FNAB) should generally be avoided. This is because these nodules are rarely malignant, and the FNAB results for hyperfunctioning nodules are often inaccurate.[30]

Evaluation of the thyroid nodule when biochemically euthyroid or hypothyroid should begin with a high-resolution diagnostic thyroid ultrasound. This can help assess the nodules for high-risk features, detect additional nodules not felt on physical examination, evaluate for neck lymph nodes, and guide FNAB if warranted. High-risk features on ultrasound include a significant increase in size from prior imaging, hypoechogenicity, irregular margins, size taller than wide, microcalcifications, a solid internal structure, extra-thyroidal extension, and central vascularity. The features associated with a lower risk of malignancy are a purely cystic nodule, spongiform appearance, comet tail shadowing, and peripheral vascularity. The decision to subject a nodule for FNAB should be based on these radiological criteria with guidance from Thyroid Imaging Reporting and Data System (TIRADS) or American Thyroid Association (ATA) criteria, but importance should be given to clinical indications irrespective of imaging criteria.[33][34][35]

Limitations of FNAB

Of note, the diagnostic accuracy of FNAB depends on the skill of the person performing the procedure as well as the pathologist interpreting the results, and it ranges between 70 to 97%. Approximately 17 to 20% of FNAB are classified as insufficient samples.[36] Also, since FNAB allows for the analysis of individual cellular features and not the overall architecture of the nodule, it is excellent for diagnosing PTC, but it cannot detect capsular or vascular invasions by FTC. As a result, while FNA can categorize certain findings as suspicious for FTC, a diagnosis of FTC can only be made from the final pathology after surgical resection.[37] The same applies to Hurthle cell neoplasms.

Bethesda System for Reporting Thyroid Cytopathology

The FNAB result is usually reported by the Bethesda Criteria for Reporting Thyroid Cytology, which stratifies the biopsy results based on the cytology, and recommends a further course of action.[38]

Bethesda Category 1 is indicative of non-diagnostic FNAB; re-aspiration is indicated.

Bethesda Category 2 is suggestive of a benign nodule that can be followed clinically with periodic thyroid ultrasound as warranted.

Bethesda Categories 3 (Atypia of undetermined significance, AUS or Follicular lesion of undetermined significance, FLUS) and 4 (follicular neoplasm, FN or suspicious for follicular neoplasm) suggests that the inclusion or exclusion of thyroid cancer is not clear, and these patients may benefit from repeat FNAB (Category 3), molecular testing, or lobectomy (Categories 3 and 4).

Bethesda Categories 5 (Suspicious for malignancy) and 6 (Malignant) usually require surgery.

Role of Molecular Testing in Thyroid Cancer

Molecular testing is generally used in Bethesda categories 3 and 4, where cytology is indeterminate.[34] Recently, testing for single mutations such as BRAF V600E or RET/PTC translocations was performed. While these tests yield good specificity (100%), their sensitivity is usually poor (50 to 60%).[39][40]

Molecular Diagnostic Approaches [41]

1. Gene mutation profiling panel- such as the 7-gene panel that detects multiple genes including BRAF V600E, HRAS codon 61, KRAS codons 12/13, and NRAS codon 61 point mutations, and RET/PTC1, PAX8/PPARγ, and RET/PTC3 translocations which account for approximately 70% of thyroid cancer.[41] This panel has improved the sensitivity and the negative predictive of these tests to >90%. [42] Therefore, mutation tests are good rule-in tests for thyroid cancer.[43]
2. A 167-Gene expression classifier provides a strong negative predictive value, while its positive predictive value

is only around 50%.[41] Hence, gene expression classifier testing is a good rule-out test for thyroid cancer.

However, recently a large multi-gene panel of mutation markers has been introduced, further improving sensitivity and specificity.[43][44]

While CT and MRI scans are not routine modalities in evaluating thyroid nodules for malignancies, their use may be appropriate in assessing local spread in more advanced diseases or those with enlarged cervical nodes in association with a suspicious mass.[45] A CT scan should be advised for patients with thyroid mass with extension into the substernal region confirmed by ultrasound or plain radiographs.

Treatment / Management

Papillary and Follicular Thyroid Cancers

Surgical Treatment

Surgical resection remains the main treatment modality of both PTC and FTC, followed by radioiodine ablation (RAI ablation) when indicated and suppression therapy with thyroid hormone.[34][46] Systemic radiation and chemotherapy seldom play a significant role in treatment, although they may be used in advanced cases refractory to conventional methods.

To minimize the risk of complications, specifically recurrent laryngeal nerve injury and hypoparathyroidism, surgery is recommended, performed by experienced, "high-volume" thyroid surgeons.[47]

Pre-operative neck ultrasound is pivotal in deciding the appropriate surgical procedure. Surgical resection can be hemithyroidectomy or total thyroidectomy, with or without lymph node dissection. The choice of surgery depends on tumor size, presence of lymph node metastasis, extra-thyroidal extension, age of the patient, and the presence or absence of co-morbid conditions. In patients with locally advanced disease, additional imaging of the neck is advised.

A thyroid lobectomy is preferred for unilateral DTC < 1 cm, without any extra-thyroidal or lymph node invasion, unless there are clear indications for total thyroidectomy, such as childhood head and neck irradiation or a strong family history of thyroid cancer. Lately, there is also a trend for just active surveillance without immediate surgery, but more studies are needed to show the difference, if any, in the outcomes and prognosis.[48]

For tumor sizes between 1 and 4 cm with no extrathyroidal or lymphatic invasion, the procedure of choice can either be a total thyroidectomy or lobectomy, depending on patient preferences and risk factors, as described above. This decision should be made with the patient aware that a completion thyroidectomy may be necessary depending on pathology results.

For tumors > 4 cm or tumors with extra-thyroidal or lymph node invasion, a total thyroidectomy is the preferred surgical procedure as there is a high risk of multifocal carcinoma in such cancers. It is also intended to facilitate RAI ablation and future surveillance with thyroglobulin as a tumor marker.

The decision for lymph node dissection should be made on a patient-by-patient basis, and there is still a lot of controversy about the proven survival benefit of prophylactic node dissection. Regardless, all patients with proven or suspected PTC should undergo a thorough examination of both the central and lateral neck for possible nodal metastasis. The lateral neck compartments are not routinely entered in thyroidectomy and should be assessed preoperatively with ultrasound and subsequent FNAB if there is a concern for lymphatic spread. If pathologic nodes are confirmed, an ipsilateral neck dissection should be carried out, with a formal clearance of defined lymph node compartments as opposed to isolated "berry-picking" of diseased nodes. The central neck lymph nodes are difficult to

assess preoperatively due to their location. A careful inspection and palpation of the central neck should be performed at the time of surgery, with subsequent compartmental neck dissection if abnormal nodes are found.

Postsurgical Risk Stratification

Postsurgical risk stratification must be performed to determine the need for additional treatment, especially with RAI ablation. The TNM (Tumor, Node, Metastasis) risk stratification by the American Joint Commission on Cancer(AJCC) predicts disease-specific mortality, while the American Thyroid Association (ATA) risk stratification system, which is widely used, helps predict the persistence or recurrence of residual cancer.[49]

The ATA system classifies patients as low, intermediate, or high risk based on clinicopathologic findings, including but not limited to tumor size, histologic type, vascular or lymph node involvement, local invasion, distant metastasis, the extent of tumor resection, post-operative thyroglobulin levels, and post-operative radioiodine uptake outside of the thyroid gland.[34][50][34]

The TNM-AJCC system accounts for factors such as the tumor size, the presence and extent of extra-thyroidal invasion, the number of nodal metastases, and whether there is the presence of distal metastasis. Age is a significant factor in predicting mortality in thyroid cancer patients, and its role is also significant in staging the disease. Patients under 55 years old at the time of diagnosis will receive a stage II diagnosis at the most.[51]

Radioiodine (RAI) Ablation Therapy

RAI therapy after thyroidectomy is used for remnant ablation of normal residual thyroid tissue, as adjuvant therapy for subclinical micrometastases, or as treatment of apparent local or distant metastasis.[52] High-risk and some selected intermediate-risk patients, per the ATA risk stratification system, will benefit from RAI ablation. Patients who are candidates for RAI therapy should maintain a low iodine diet for 1 to 2 weeks before the treatment to ensure iodine depletion of the cells; they should also be cautioned against large iodine administrations such as through iodinated contrast or amiodarone to improve the avidity of the thyroid follicular cells to iodine. RAI ablation works best when thyroid hormone has been withdrawn, with a goal thyroid-stimulating hormone (TSH) of 30mIU/liter or higher. This level of TSH can be achieved either through the withdrawal of thyroid hormones or the administration of exogenous recombinant human TSH.

Thyroid Hormone Suppression Therapy

Thyroid hormone suppression therapy to suppress TSH and thereby potentially minimize its stimulation of thyroid cancer growth is recommended in most patients after surgery. For patients with ATA high-risk, the goal TSH should be no more than 0.1m IU/liter, and for patients in the intermediate-risk category, the goal TSH should be between 0.1 and 0.5 mIU/liter. For the ATA low-risk category, a goal TSH between 0.5 and 2.0 mIU/liter is acceptable.[53][54][53]

Persistent or Recurrent Disease

For recurrent minimal iodine-avid disease, RAI ablation is the preferred therapy. For invasive neck disease, surgical resection is recommended. Percutaneous ethanol injection[55] has been tried for cervical lymph node metastasis. For small distant metastasis to bones or lungs, radiofrequency ablation has been used. Other treatment options are external beam radiation and systemic chemotherapy.

Systemic Chemotherapy

Systemic chemotherapy is usually only considered in a group of carefully selected patients with a high metastatic disease burden or rapidly progressive metastatic disease despite the above treatment (Iodide-refractory). Because of the significant adverse effects associated with such therapy, it should be considered only when the associated benefits

exceed the risks.[34]

Systemic chemotherapy for DTC is preferably administered through a clinical trial. The common agents of choice are the kinase inhibitor class of drugs such as anti-angiogenic multi-targeted kinase inhibitors (aaMKI- lenvatinib, sorafenib), BRAF kinase inhibitors (vemurafenib, dabrafenib), MEK inhibitors (trametinib, cobimetinib), NTR kinase inhibitors (larotrectinib), and RET inhibitor (selpercatinib).[56] The choice of agent depends on the occurrence of specific gene mutations or signaling irregularities such as those described above. For patients with no identifiable mutations, aaMKIs are the recommended first-line therapy.

Dynamic Risk Stratification

After the initial postsurgical risk stratification and appropriate treatment as above, patients should be re-stratified during each follow-up visit depending on their response to therapy into one of the following clinical outcomes: 1. Excellent response, 2. Biochemical incomplete response, 3. Structural incomplete response, 4. Indeterminate response.[57][58][59]

Monitoring in the first postsurgical year primarily involves a thyroid ultrasound scan every 6 to 12 months and TSH and thyroglobulin levels every 3 to 6 months, depending on risk. For higher-risk patients, additional imaging such as CT scan, MRI, FDG-PET, or whole-body radioiodine scanning is required.

After one year, the frequency of monitoring depends on the dynamic risk stratification.

Medullary Thyroid Cancer

Surgical therapy that includes total thyroidectomy with resection of local and regional metastases is the mainstay of treatment for MTC. In most patients with confirmed MTC and no evidence of pre-operative cervical lymph node metastasis on ultrasound, prophylactic central lymph node dissection should be performed at the time of the total thyroidectomy. Patients with confirmed lateral zone nodal metastases should receive lateral compartment dissection, central neck dissection, and total thyroidectomy. Serum calcitonin, carcinoembryonic antigen, and biochemical testing for coexisting hyperparathyroidism and pheochromocytoma should be performed. Patients should be monitored long-term with serial calcitonin levels, neck ultrasound, and physical examination. Of note, as MTC is not of follicular origin, there is no role for radioiodine ablation or TSH suppression in its management.[60] For refractory MTC, systemic chemotherapy with kinase inhibitors has been shown to be beneficial. RET-specific kinase inhibitors are preferred in patients with RET mutation, while in patients negative for RET mutation, aaMKIs are the preferred drugs.

Anaplastic Thyroid Cancer

In patients diagnosed with anaplastic thyroid cancer, BRAF V600E mutation testing and staging are performed. Resectable disease is surgically removed, followed by specific BRAF kinase inhibitors in patients with BRAF V600E mutations. Other patients received targeted radiation treatment and cytotoxic chemotherapy after surgery. However, distant metastases are common in patients even at initial diagnosis due to their rapidly progressive course, and local invasion into the trachea or vasculature may occur, making it unresectable. Mortality is near 100% for these cancers, and a conservative surgical approach for palliation can be considered in such high-risk patients.

Differential Diagnosis

- Benign thyroid nodule
- Toxic nodular goiter
- Primary thyroid lymphoma

- Cervical lymphadenopathy

Prognosis

The prognosis of thyroid cancer varies greatly, depending on its type, tumor size, the extent of metastasis, patient's age, and amenability to resection. The prognosis is generally good, with up to 95% 5-year survival rate for patients of all ages and races. Poor prognostic factors include large tumor size, the presence of extra-thyroidal extensions or metastases, older age, or unfavorable tumor types such as undifferentiated cancer.[61]

Complications

Untreated thyroid cancer can be locally invasive into the airway, esophagus, or other nearby neurovascular structures. Distant metastasis most commonly involves the lung, bone, and other soft tissue structures.

Both thyroid lobectomy and total thyroidectomy carry the potential for neurovascular injuries, with the most common involving the recurrent laryngeal nerve, leading to hoarseness of voice and potentially respiratory failure with bilateral injuries.

Treatment of thyroid cancer during pregnancy, mostly with thyroidectomy, did not show any significant increase in the complications of pregnancy.[62]

Consultations

- Thyroid surgeon
- Endocrinologist
- Radiologist
- Pathologist

Deterrence and Patient Education

As previously discussed, patients with risk factors, such as prior irradiation to the head and neck area and a family history of thyroid cancer, should be screened for thyroid cancer, especially when such a patient presents with thyroid nodules with or without pressure symptoms.

Enhancing Healthcare Team Outcomes

Thyroid cancer, as discussed, can have highly varied manifestations, from a clinically indolent low-risk disease that can be managed with only active surveillance to a highly aggressive metastatic disease that needs extensive surgical resection with or without systemic chemotherapy.

Hence, managing a patient with thyroid cancer is a highly individualized process taking into account the patient's risk of recurrence and preferences (after being educated about the different treatment strategies and risks vs. benefits of each). A close collaboration between all interprofessional team members, including but not limited to the thyroid surgeon, the endocrinologist, the pathologist, the radiologist, and possibly the oncologist, plays a vital role in providing the most appropriate treatment for the patient while avoiding overtreatment at the same time. Nursing staff should ensure the patient is involved and comfortable every step of the way, from pre-operative planning to treatment and postoperative monitoring. When pursuing chemotherapy, a specialized oncology pharmacist is also a valuable addition to the interprofessional team. Interprofessional teamwork relies on open communication channels between all team

members, and the maintaining of meticulous records so that all professionals involved in the case have access to the same updated patient information and can reach out to other team members if they see anything that requires their attention. This type of interprofessional care coordination combined with open information sharing will yield the best patient outcomes. [Level 5]

Review Questions

- Access free multiple choice questions on this topic.
- Click here for a simplified version.
- Comment on this article.

References

1. Noone AM, Cronin KA, Altekruse SF, Howlader N, Lewis DR, Petkov VI, Penberthy L. Cancer Incidence and Survival Trends by Subtype Using Data from the Surveillance Epidemiology and End Results Program, 1992-2013. Cancer Epidemiol Biomarkers Prev. 2017 Apr;26(4):632-641. [PMC free article: PMC5380602] [PubMed: 27956436]
2. Nikiforov YE, Nikiforova MN. Molecular genetics and diagnosis of thyroid cancer. Nat Rev Endocrinol. 2011 Aug 30;7(10):569-80. [PubMed: 21878896]
3. Miranda-Filho A, Lortet-Tieulent J, Bray F, Cao B, Franceschi S, Vaccarella S, Dal Maso L. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. Lancet Diabetes Endocrinol. 2021 Apr;9(4):225-234. [PubMed: 33662333]
4. Fagin JA. How thyroid tumors start and why it matters: kinase mutants as targets for solid cancer pharmacotherapy. J Endocrinol. 2004 Nov;183(2):249-56. [PubMed: 15531713]
5. Carling T, Udelsman R. Thyroid cancer. Annu Rev Med. 2014;65:125-37. [PubMed: 24274180]
6. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014 Oct 23;159(3):676-90. [PMC free article: PMC4243044] [PubMed: 25417114]
7. Raman P, Koenig RJ. Pax-8-PPAR-γ fusion protein in thyroid carcinoma. Nat Rev Endocrinol. 2014 Oct;10(10):616-23. [PMC free article: PMC4290886] [PubMed: 25069464]
8. Nikiforova MN, Wald AI, Roy S, Durso MB, Nikiforov YE. Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. J Clin Endocrinol Metab. 2013 Nov;98(11):E1852-60. [PMC free article: PMC3816258] [PubMed: 23979959]
9. Santarpia L, El-Naggar AK, Cote GJ, Myers JN, Sherman SI. Phosphatidylinositol 3-kinase/akt and ras/raf-mitogen-activated protein kinase pathway mutations in anaplastic thyroid cancer. J Clin Endocrinol Metab. 2008 Jan;93(1):278-84. [PubMed: 17989125]
10. Hou P, Liu D, Shan Y, Hu S, Studeman K, Condouris S, Wang Y, Trink A, El-Naggar AK, Tallini G, Vasko V, Xing M. Genetic alterations and their relationship in the phosphatidylinositol 3-kinase/Akt pathway in thyroid cancer. Clin Cancer Res. 2007 Feb 15;13(4):1161-70. [PubMed: 17317825]
11. Leboulleux S, Baudin E, Travagli JP, Schlumberger M. Medullary thyroid carcinoma. Clin Endocrinol (Oxf). 2004 Sep;61(3):299-310. [PubMed: 15355445]
12. Landa I, Ganly I, Chan TA, Mitsutake N, Matsuse M, Ibrahimpasic T, Ghossein RA, Fagin JA. Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. J Clin Endocrinol Metab. 2013 Sep;98(9):E1562-6. [PMC free article: PMC3763971] [PubMed: 23833040]
13. Malchoff CD, Malchoff DM. Familial nonmedullary thyroid carcinoma. Cancer Control. 2006 Apr;13(2):106-10. [PubMed: 16735984]

14. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015 Jan-Feb;65(1):5-29. [PubMed: 25559415]
15. Galanti MR, Ekbom A, Grimelius L, Yuen J. Parental cancer and risk of papillary and follicular thyroid carcinoma. Br J Cancer. 1997;75(3):451-6. [PMC free article: PMC2063376] [PubMed: 9020497]
16. Robbins J, Schneider AB. Thyroid cancer following exposure to radioactive iodine. Rev Endocr Metab Disord. 2000 Apr;1(3):197-203. [PubMed: 11705004]
17. LeClair K, Bell KJL, Furuya-Kanamori L, Doi SA, Francis DO, Davies L. Evaluation of Gender Inequity in Thyroid Cancer Diagnosis: Differences by Sex in US Thyroid Cancer Incidence Compared With a Meta-analysis of Subclinical Thyroid Cancer Rates at Autopsy. JAMA Intern Med. 2021 Oct 01;181(10):1351-1358. [PMC free article: PMC8406211] [PubMed: 34459841]
18. Franceschi S, Boyle P, Maisonneuve P, La Vecchia C, Burt AD, Kerr DJ, MacFarlane GJ. The epidemiology of thyroid carcinoma. Crit Rev Oncog. 1993;4(1):25-52. [PubMed: 8416150]
19. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA. 2006 May 10;295(18):2164-7. [PubMed: 16684987]
20. Zhu C, Zheng T, Kilfoy BA, Han X, Ma S, Ba Y, Bai Y, Wang R, Zhu Y, Zhang Y. A birth cohort analysis of the incidence of papillary thyroid cancer in the United States, 1973-2004. Thyroid. 2009 Oct;19(10):1061-6. [PMC free article: PMC2833179] [PubMed: 19732011]
21. Davies L, Ouellette M, Hunter M, Welch HG. The increasing incidence of small thyroid cancers: where are the cases coming from? Laryngoscope. 2010 Dec;120(12):2446-51. [PubMed: 21108428]
22. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013 Jan;63(1):11-30. [PubMed: 23335087]
23. Pancer J, Mitmaker E, Ajise O, Tabah R, How J. A thyroid gland with over 30 foci of papillary thyroid carcinoma with activating BRAF V600E mutation. Endocrinol Diabetes Metab Case Rep. 2019 Mar 18;2019 [PMC free article: PMC6432975] [PubMed: 30884463]
24. Echanique KA, Govindan A, Mohamed OM, Sylvester M, Baredes S, Yu-Lan Ying M, Kalyoussef E. Age-Related Trends of Patients Undergoing Thyroidectomy: Analysis of US Inpatient Data from 2005 to 2013. Otolaryngol Head Neck Surg. 2019 Mar;160(3):457-464. [PubMed: 30829140]
25. Means C, Clayburgh DR, Maloney L, Sauer D, Taylor MH, Shindo ML, Coussens LM, Tsujikawa T. Tumor immune microenvironment characteristics of papillary thyroid carcinoma are associated with histopathological aggressiveness and BRAF mutation status. Head Neck. 2019 Aug;41(8):2636-2646. [PubMed: 30896061]
26. Carling T, Ocal IT, Udelsman R. Special variants of differentiated thyroid cancer: does it alter the extent of surgery versus well-differentiated thyroid cancer? World J Surg. 2007 May;31(5):916-23. [PubMed: 17345120]
27. Collini P, Sampietro G, Rosai J, Pilotti S. Minimally invasive (encapsulated) follicular carcinoma of the thyroid gland is the low-risk counterpart of widely invasive follicular carcinoma but not of insular carcinoma. Virchows Arch. 2003 Jan;442(1):71-6. [PubMed: 12536317]
28. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2009 Nov;19(11):1159-65. [PubMed: 19888858]
29. Carcangiu ML, Steeper T, Zampi G, Rosai J. Anaplastic thyroid carcinoma. A study of 70 cases. Am J Clin Pathol. 1985 Feb;83(2):135-58. [PubMed: 2578727]
30. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009 Nov;19(11):1167-214. [PubMed: 19860577]
31. Glikson M, Feigin RD, Libson E, Rubinow A. Anaplastic thyroid carcinoma in a retrosternal goiter presenting as

fever of unknown origin. Am J Med. 1990 Jan;88(1):81-2. [PubMed: 2294770]
32. Chang TC, Liaw KY, Kuo SH, Chang CC, Chen FW. Anaplastic thyroid carcinoma: review of 24 cases, with emphasis on cytodiagnosis and leukocytosis. Taiwan Yi Xue Hui Za Zhi. 1989 Jun;88(6):551-6. [PubMed: 2794956]
33. Horvath E, Silva CF, Majlis S, Rodriguez I, Skoknic V, Castro A, Rojas H, Niedmann JP, Madrid A, Capdeville F, Whittle C, Rossi R, Domínguez M, Tala H. Prospective validation of the ultrasound based TIRADS (Thyroid Imaging Reporting And Data System) classification: results in surgically resected thyroid nodules. Eur Radiol. 2017 Jun;27(6):2619-2628. [PubMed: 27718080]
34. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016 Jan;26(1):1-133. [PMC free article: PMC4739132] [PubMed: 26462967]
35. Shonka DC, Ho A, Chintakuntlawar AV, Geiger JL, Park JC, Seetharamu N, Jasim S, Abdelhamid Ahmed AH, Bible KC, Brose MS, Cabanillas ME, Dabekaussen K, Davies L, Dias-Santagata D, Fagin JA, Faquin WC, Ghossein RA, Gopal RK, Miyauchi A, Nikiforov YE, Ringel MD, Robinson B, Ryder MM, Sherman EJ, Sadow PM, Shin JJ, Stack BC, Tuttle RM, Wirth LJ, Zafereo ME, Randolph GW. American Head and Neck Society Endocrine Surgery Section and International Thyroid Oncology Group consensus statement on mutational testing in thyroid cancer: Defining advanced thyroid cancer and its targeted treatment. Head Neck. 2022 Jun;44(6):1277-1300. [PMC free article: PMC9332138] [PubMed: 35274388]
36. Theoharis CG, Schofield KM, Hammers L, Udelsman R, Chhieng DC. The Bethesda thyroid fine-needle aspiration classification system: year 1 at an academic institution. Thyroid. 2009 Nov;19(11):1215-23. [PubMed: 19888859]
37. Wang TX, Song YT, Xu GH, Yu WB, Wei W, Zhang B. [Fine-needle aspiration for the diagnosis of lymph node metastasis in papillary thyroid carcinoma]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2019 Jan 07;54(1):23-27. [PubMed: 30704165]
38. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2017 Nov;27(11):1341-1346. [PubMed: 29091573]
39. Adeniran AJ, Hui P, Chhieng DC, Prasad ML, Schofield K, Theoharis C. BRAF mutation testing of thyroid fine-needle aspiration specimens enhances the predictability of malignancy in thyroid follicular lesions of undetermined significance. Acta Cytol. 2011;55(6):570-5. [PubMed: 22156468]
40. Kim SK, Hwang TS, Yoo YB, Han HS, Kim DL, Song KH, Lim SD, Kim WS, Paik NS. Surgical results of thyroid nodules according to a management guideline based on the BRAF(V600E) mutation status. J Clin Endocrinol Metab. 2011 Mar;96(3):658-64. [PubMed: 21239517]
41. Alexander EK, Kennedy GC, Baloch ZW, Cibas ES, Chudova D, Diggans J, Friedman L, Kloos RT, LiVolsi VA, Mandel SJ, Raab SS, Rosai J, Steward DL, Walsh PS, Wilde JI, Zeiger MA, Lanman RB, Haugen BR. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. N Engl J Med. 2012 Aug 23;367(8):705-15. [PubMed: 22731672]
42. Nikiforov YE, Ohori NP, Hodak SP, Carty SE, LeBeau SO, Ferris RL, Yip L, Seethala RR, Tublin ME, Stang MT, Coyne C, Johnson JT, Stewart AF, Nikiforova MN. 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 Nov;96(11):3390-7. [PMC free article: PMC3205883] [PubMed: 21880806]
43. Nikiforov YE, Carty SE, Chiosea SI, Coyne C, Duvvuri U, Ferris RL, Gooding WE, LeBeau SO, Ohori NP, Seethala RR, Tublin ME, Yip L, Nikiforova MN. Impact of the Multi-Gene ThyroSeq Next-Generation

Sequencing Assay on Cancer Diagnosis in Thyroid Nodules with Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance Cytology. Thyroid. 2015 Nov;25(11):1217-23. [PMC free article: PMC4652198] [PubMed: 26356635]
44. Valderrabano P, Khazai L, Leon ME, Thompson ZJ, Ma Z, Chung CH, Hallanger-Johnson JE, Otto KJ, Rogers KD, Centeno BA, McIver B. Evaluation of ThyroSeq v2 performance in thyroid nodules with indeterminate cytology. Endocr Relat Cancer. 2017 Mar;24(3):127-136. [PMC free article: PMC7771306] [PubMed: 28104680]
45. Nieto HR, Thornton CEM, Brookes K, Nobre de Menezes A, Fletcher A, Alshahrani M, Kocbiyik M, Sharma N, Boelaert K, Cazier JB, Mehanna H, Smith VE, Read ML, McCabe CJ. Recurrence of Papillary Thyroid Cancer: A Systematic Appraisal of Risk Factors. J Clin Endocrinol Metab. 2022 Apr 19;107(5):1392-1406. [PMC free article: PMC9016467] [PubMed: 34791326]
46. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W., European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol. 2006 Jun;154(6):787-803. [PubMed: 16728537]
47. Adam MA, Thomas S, Youngwirth L, Hyslop T, Reed SD, Scheri RP, Roman SA, Sosa JA. Is There a Minimum Number of Thyroidectomies a Surgeon Should Perform to Optimize Patient Outcomes? Ann Surg. 2017 Feb;265(2):402-407. [PubMed: 28059969]
48. Chou R, Dana T, Haymart M, Leung AM, Tufano RP, Sosa JA, Ringel MD. Active Surveillance Versus Thyroid Surgery for Differentiated Thyroid Cancer: A Systematic Review. Thyroid. 2022 Apr;32(4):351-367. [PMC free article: PMC11265616] [PubMed: 35081743]
49. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017 Mar;67(2):93-99. [PubMed: 28094848]
50. Leboulleux S, Bournaud C, Chougnet CN, Zerdoud S, Al Ghuzlan A, Catargi B, Do Cao C, Kelly A, Barge ML, Lacroix L, Dygai I, Vera P, Rusu D, Schneegans O, Benisvy D, Klein M, Roux J, Eberle MC, Bastie D, Nascimento C, Giraudet AL, Le Moullec N, Bardet S, Drui D, Roudaut N, Godbert Y, Morel O, Drutel A, Lamartina L, Schvartz C, Velayoudom FL, Schlumberger MJ, Leenhardt L, Borget I. Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer. N Engl J Med. 2022 Mar 10;386(10):923-932. [PubMed: 35263518]
51. Tuttle RM, Alzahrani AS. Risk Stratification in Differentiated Thyroid Cancer: From Detection to Final Follow-Up. J Clin Endocrinol Metab. 2019 Sep 01;104(9):4087-4100. [PMC free article: PMC6684308] [PubMed: 30874735]
52. Avram AM, Zukotynski K, Nadel HR, Giovanella L. Management of Differentiated Thyroid Cancer: The Standard of Care. J Nucl Med. 2022 Feb;63(2):189-195. [PubMed: 34413146]
53. Yoon BH, Lee Y, Oh HJ, Kim SH, Lee YK. Influence of Thyroid-stimulating Hormone Suppression Therapy on Bone Mineral Density in Patients with Differentiated Thyroid Cancer: A Meta-analysis. J Bone Metab. 2019 Feb;26(1):51-60. [PMC free article: PMC6416150] [PubMed: 30899725]
54. Papaleontiou M, Chen DW, Banerjee M, Reyes-Gastelum D, Hamilton AS, Ward KC, Haymart MR. Thyrotropin Suppression for Papillary Thyroid Cancer: A Physician Survey Study. Thyroid. 2021 Sep;31(9):1383-1390. [PMC free article: PMC8558057] [PubMed: 33779292]
55. Hay ID, Charboneau JW. The coming of age of ultrasound-guided percutaneous ethanol ablation of selected neck nodal metastases in well-differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2011 Sep;96(9):2717-20. [PubMed: 21896899]
56. Weitzman SP, Sherman SI. Novel Drug Treatments of Progressive Radioiodine-Refractory Differentiated Thyroid Cancer. Endocrinol Metab Clin North Am. 2019 Mar;48(1):253-268. [PubMed: 30717907]

57. Schumm MA, Shu ML, Kim J, Tseng CH, Zanocco K, Livhits MJ, Leung AM, Yeh MW, Sacks GD, Wu JX. Perception of risk and treatment decisions in the management of differentiated thyroid cancer. J Surg Oncol. 2022 Aug;126(2):247-256. [PubMed: 35316538]
58. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, Brokhin M, Omry G, Fagin JA, Shaha A. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid. 2010 Dec;20(12):1341-9. [PMC free article: PMC4845674] [PubMed: 21034228]
59. Tuttle RM, Leboeuf R. Follow up approaches in thyroid cancer: a risk adapted paradigm. Endocrinol Metab Clin North Am. 2008 Jun;37(2):419-35, ix-x. [PubMed: 18502335]
60. Rosario PW, Mourão G, Calsolari MR. Risk of recurrence in patients with papillary thyroid carcinoma and minimal extrathyroidal extension not treated with radioiodine. J Endocrinol Invest. 2019 Jun;42(6):687-692. [PubMed: 30353424]
61. Park SY, Kim HI, Kim JH, Kim JS, Oh YL, Kim SW, Chung JH, Jang HW, Kim TH. Prognostic significance of gross extrathyroidal extension invading only strap muscles in differentiated thyroid carcinoma. Br J Surg. 2018 Aug;105(9):1155-1162. [PubMed: 29663333]
62. Moon S, Yi KH, Park YJ. Risk of Adverse Pregnancy Outcomes in Young Women with Thyroid Cancer: A Systematic Review and Meta-Analysis. Cancers (Basel). 2022 May 12;14(10) [PMC free article: PMC9139607] [PubMed: 35625995]

Disclosure: Kenny Lee declares no relevant financial relationships with ineligible companies.

Disclosure: Catherine Anastasopoulou declares no relevant financial relationships with ineligible companies.

Disclosure: Chandriya Chandran declares no relevant financial relationships with ineligible companies.

Disclosure: Sebastiano Cassaro declares no relevant financial relationships with ineligible companies.

Bookshelf ID: NBK459299 PMID: 29083690