PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

ENDOCRINE

THYROID

Differentiated Thyroid Cancer

Endocrine Site Group – Thyroid
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Differentiated Thyroid Cancer

1. Introduction:

- Differentiated thyroid cancer (DTC) includes papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), poorly differentiated thyroid cancer (PDTC), and anaplastic thyroid cancer (ATC).
  - PDTC and ATC represent a continuum of dedifferentiation of thyroid cancer cells up to terminal dedifferentiation (ATC).
  - Medullary thyroid cancer (MTC) originates from parafollicular C-cells which are embryologically distinct from thyrocytes, and thus not considered a part of differentiated thyroid cancer.
  - In addition to thyroid cancer, the thyroid gland can be the site of other malignancies, including lymphoma and metastatic cancer from distant sites.
- DTC makes up over 90% of all thyroid malignancies diagnosed annually. [1, 2]
  - 80% of all thyroid cancers are of PTC origin, named for their papillary histologic architecture.
  - 15% of all thyroid cancers are of FTC origin, making it the second most commonly diagnosed DTC.
  - PDTC and ATC represent a small subset of thyroid cancers diagnosed annually (<5%), but are responsible for significant portion of the morbidity and mortality associated with thyroid cancer.
- In general, patients diagnosed and treated for DTC have an excellent cure rate with 5-year overall survival over 95% and long-term 20-year survival rates of approximately 90%. [3]
  - Certain high-risk populations and histologic subtypes of PTC and FTC have more aggressive clinical courses with higher rates of local recurrences as well as regional and distant metastases:
    - older age (≥55 years old), male sex, local invasion or distant metastasis at presentation, large size (≥4cm), multicentricity, tall cell, columnar, or diffuse sclerosing variants and angioinvasion.
  - PDTC and ATC are some of the most aggressive solid tumour cancers overall, with mortality rates of 38%-57% in PDTC to nearly 100% in ATC, with a mean survival time of 3-6 months in patients with ATC. [4]
- The Princess Margaret Cancer Center Clinical Practice Guidelines for Differentiated Thyroid Cancer represents an amalgamation of several national and international guidelines and serves as a general template for the management of patients with DTC treated at our institution.
- As appropriate, references for the recommendations will be given throughout the text.
  1. 2015 ATA Guidelines
  2. The Bethesda System Reporting for Thyroid Cancer Criteria
  3. Cancer Care Ontario: Differentiated Thyroid Cancer Pathway Maps
- Physicians treating patients for thyroid cancer should be intimately familiar with these guidelines and treatment algorithms.

2. Prevention, Screening, and Risk Factors

- The incidence of thyroid cancer has increased 3-fold over the past 30 years, with approximately 63,000 new cases diagnosed in the United States each year. [2, 5]
  - The large increase in the diagnosis of DTC is at least partially due to an increase the use of ultrasound imaging (U/S) and increased detection and workup of thyroid nodules.
  - Because of the likely over-diagnosis of DTC, the United States Preventative Task Force (USPTF) has recommended against screening for thyroid cancer in asymptomatic adults, which includes the use of thyroid ultrasound. [6]
- DTC is three-times more common in females compared to males. It is the sixth most common cancer in women, and the most commonly diagnosed cancer in women aged 20 to 34. [7]

- Thyroid nodules are a common finding in the general population.
  - The prevalence of *palpable* nodules is estimated to be 5% of women and 1% of men.
  - However, high-resolution U/S can detect thyroid nodules in 19-68% of randomly selected individuals, with even higher rates in females and the elderly. [5]
- Approximately 7%-15% of patients with thyroid nodules may have DTC.
  - Thyroid nodules are less common in male patients and young patients (children, teenagers, and young adults). Furthermore, nodules diagnosed in these patients have an increased risk of malignancy (ROM) when compared to females with nodules.
- General risk factors for thyroid cancer include female gender, a history of prior radiation exposure (growing up in an endemic region with ionizing radiation fallout, a history of radiotherapy treatment, or occupational exposure to ionizing radiation), and an extensive family history of thyroid cancer. [5]
  - Most thyroid cancers are sporadic (not inheritable) genetic mutations leading to cancer. There are a few heritable genetic syndromes that are associated with DTC, including familial adenomatous polyposis (FAP), and PTEN-associated hamartomas (Cowden's disease).
  - Having a single first-degree family member with a history of DTC only slightly increases the risk of thyroid cancer, and in the absence of other genetic syndromes or multiple family members with thyroid cancer, it is not recommended that patients undergo routine screening for thyroid cancer. (ATA Recommendation 1)
- Certain clinical findings also increase the suspicion for thyroid cancer. These include rapid nodule growth, new-onset of hoarseness, and cervical lymphadenopathy in patients with known thyroid nodules.
- It is important to recognize risk factors for thyroid cancer because they can increase the pre-test probability of malignancy during the workup of nodules, and may modify the recurrence risk after treatment.

3. Screening and Early Detection

3.1 Work up of Thyroid Nodules
- In 2015, the American Thyroid Association (ATA) published their management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. [5]
- The Cancer Care Ontario (CCO) Thyroid Working Group developed the Differentiated Thyroid Cancer Diagnosis Pathway Map based on 2015 ATA guidelines and modified for the care of patients within Ontario. These modifications have been highlighted where appropriate. [8-10]
- Any patient with a thyroid nodule ≥1cm in any dimension should have their serum thyrotropin (TSH) level evaluated prior to any cytologic investigations. (ATA Recommendation 2)
  - A suppressed TSH level (low TSH) indicates a hyperfunctioning thyroid gland and a radionuclide thyroid scan should be obtained (preferably with ^{123}I, which produces no beta radiation). (ATA Recommendation 2B)
    - "Hot nodules" rarely harbor malignancy and in the absence of other significant concerning findings, no further workup of the nodule is necessary (although further evaluation and treatment for overt or subclinical hyperthyroidism may be needed).
    - Patients with cold nodules on radionuclide iodine scan and patients with high TSH levels should have their nodules investigated based on U/S characteristics. (See "Imaging")
- Patients with thyroid nodules should have a complete diagnostic neck U/S to investigate for additional thyroid nodules or the presence of cervical lymphadenopathy. (ATA Recommendation 6)
- Incidental thyroid nodules detected by other imaging modalities (CT, MRI, PET) should be further evaluated with a diagnostic U/S of the thyroid and bilateral lateral neck compartments. [5]

- Incidental FDG-avid nodules on PET/CT scans obtained in the workup of other malignancies have ~50% risk of malignancy which warrant further workup (FNA recommended for size >1cm), depending on the patient's overall health status and prognosis related to the malignancy for which the PET was ordered. (ATA Recommendation 5)

3.2   Imaging

3.2.1   Ultrasonography
- Ultrasonography (U/S) is the imaging modality of choice for the workup of thyroid nodules.
  - Limitations to ultrasonography include being operator-dependent, the need for advanced training, difficulty with detecting nodules within the central neck and mediastinum, as well as poor sensitivity in detecting invasion of the aerodigestive tract.
- U/S reports of nodules and lymph nodes (LN) should include the size (in 3 dimension), echogenicity, margins, presence of calcifications, eccentricity of solid components in a mixed nodule, as well as the position of the nodule within the thyroid.
  - High-risk ultrasonographic features include nodule hypoechogenicity, the presence and type of calcifications (microcalcifications, macrocalcifications, rim/peripheral calcification), irregular or infiltrative margins, shape taller than wide, evidence of extrathyroidal extension, and suspicious cervical lymphadenopathy. [5, 11, 12]
- Various organizations have developed standardized criteria to help guide management of nodules based on ultrasonographic findings. [13]
  - The American College of Radiology (ACR) reports nodules on the 5-tiered point-based TI-RADS™ system, which stratifies nodules based on composition, echogenicity, shape, margin, and echogenic foci. [14]
  - The ATA uses a 5-tiered pattern-based categorization system which associates a constellation of ultrasonographic findings with a nodule's risk of malignancy (benign, very low-, low-, intermediate-, and high-suspicion nodules). [5]
  - The ATA guidelines recommend FNA biopsy of nodules at various sizes based on the sonographic pattern and its associated risk of malignancy. (ATA Recommendation 7, 12; See "Fine Needle Aspiration" and Table 1)
- Cancer Care Ontario (CCO) generally endorses the ATA guidelines for FNA biopsy of suspicious nodules, with only a minor modifications in size criteria for biopsy, as noted in Table 1. [8, 9]
  - In patients with suspicious nodules by ultrasound, the Cancer Care Ontario (CCO) guidelines for DTC diagnosis pathway recommend referral to a thyroid surgeon or an endocrinologist for further risk evaluation prior to FNA biopsy.

3.2.2   Computed Tomography (CT) with IV contrast
- Computed Tomography (CT) with IV contrast plays a limited role in the initial workup of thyroid nodules, but has several key advantages over U/S and is indicated in select patients.
- Contrast-enhanced CT imaging provides highly-detailed and reproducible anatomic images of the neck and upper mediastinum, including nodal regions typically inaccessible to ultrasonography.
  - Although it had previously been advocated to avoid iodinated contrast because it delays adjuvant radioactive iodine (RAI) ablation by 8 weeks, several studies have demonstrated a clear benefit that contrast-enhancement provides in detecting metastatic disease and potential involvement of critical structures in aggressive thyroid cancer. [15]
  - Furthermore, RAI ablation is typically not given until 6-8 weeks after surgery, and several studies have shown that even significant delays in starting RAI therapy have minimal to no effect on its efficacy. [5, 15, 16] (See "Adjuvant Therapy")

- Indications for contrast-enhanced CT include concerning clinical findings which raise the risk of aerodigestive tract invasion (e.g. RLN paresis, dyspnea, hemoptysis, stridor), concerning features on ultrasonography (invasion of strap muscles, mediastinal extension, suspicious lateral neck lymphadenopathy), as well as in the workup of revision surgery cases. [5, 15, 17]
- CT imaging of the chest provides the best sensitivity in detecting small pulmonary metastases, which can often be missed by PET/CT and whole-body scintigraphy (WBS). [5]
  - Pulmonary micrometastases have a significantly better prognosis than pulmonary macrometastatic lesions, and can usually be treated with RAI with complete response. (See "RAI Therapy") [5]
- If CT imaging of the neck is performed in the workup of thyroid cancer, it should be contrast-enhanced unless the patient has significant contraindications to IV contrast. [15]

3.3   Fine Needle Aspiration (FNA)

- Fine needle aspiration (FNA) is the procedure of choice for patients with suspicious thyroid nodules.
  - Ultrasound-guided FNA (USGFNA) provides more accurate diagnostic sampling of suspicious nodules[5, 18] (ATA Recommendation 7, 8)
- The Cancer Care Ontario diagnostic pathway outlines criteria for FNA biopsy of suspicious nodules. The sonographic suspicion categories remain the same as outlined in the ATA guidelines, however the size criteria for biopsy differ. [5, 8, 9] (See Table 1)

Sonographic Pattern	ROM	ATA Recommendations	CCO Recommendations
Benign	<1%	No biopsy	FNA at >4 cm
Very low risk	<3%	Consider at >2 cm	FNA at >4 cm
Low risk	5-10%	FNA at >1.5 cm	FNA at >2 cm
Intermediate	10-20%	FNA at >1 cm	FNA at >2 cm
High risk	70-90%	FNA at >1 cm	FNA at >1 cm

Table 1: Comparison of Size Criteria for FNA biopsy (ROM= Risk of Malignancy)

- Any nodule that is less than 1cm in size, regardless of characteristics, should not be biopsied.
  - Nodules with high-suspicion that do not meet size criteria for biopsy at initial evaluation should be closely followed with repeat U/S in 6-12 months. [9]
    - Nodules with low to intermediate suspicion can be followed with repeat imaging in 12-24 months.
    - Select "very low suspicion" nodules and purely cystic nodules may not need follow up imaging, although there was insufficient data for the 2015 ATA guidelines to recommend for or against this recommendation. (ATA Recommendation 24)
- Growth in nodules (defined as 20% growth in at least two dimensions, or 50% change in volume), or a change and the level of suspicion on ultrasonography should prompt for reevaluation and possible biopsy. [9]
- The addition of thyroglobulin levels from the aspirate of a lymph node is associated with increased rates of diagnosis of metastatic lymphadenopathy compared to cytopathologic assessment alone.

3.3.1   Thyroid Cytopathology

- In 2009, The Bethesda System for Reporting Thyroid Cytology (TBSRTC) was created to standardize the communication of thyroid FNA cytopathology between pathologists and clinicians. [19]

- The 6 diagnostic categories are associated with an implied risk of malignancy (ROM) and the recommended clinical management. In 2017, the Bethesda criteria were updated, with revised ROM based on several pooled data sets indicating increased ROM in the AUS/FLUS category and allowing pathologists to include their institutional-specific ROM. [20-22]
- When discussing the ROM within the indeterminate nodules categories, it is important to consider the pre-test probability of malignancy within each individual patient (clinical presentation, risk factors, imaging characteristics) as well as patient preferences and goals when deciding on the appropriate treatment option. [21]

I. Non-diagnostic (ND) or Unsatisfactory (UDS)
  o To be satisfactory for evaluation, at least 6 groups of benign follicular cells are required, with each group composed of at least 10 cells. FNA specimens containing abundant colloid may also be called 'benign', as this implies macrofollicular nodules, which are almost always benign.
  o The ROM for ND/UDS is approximately 5-10% and repeat USGFNA is recommended.
  o Fewer than 10% of specimens should include this definition. [19]

II. Benign
  o This group makes up the majority of FNA cytology cases and has very low rates of malignancy, between 0-3%.
    - In the absence of significant concerns for malignancy, patients with benign cytopathology results can be clinically followed with surveillance ultrasounds without the need for further FNA biopsies without significant changes in U/S characteristics or sizes.
  o A repeat USGFNA biopsy may be indicated in patients with high-risk features on ultrasound or clinical exam.

III. Atypia of Undetermined Significance (AUS) or Follicular Lesion of Undetermined Significance (FLUS)
  o This is the first of 3 "indeterminate nodules" categories. The two terms (AUS and FLUS) are synonymous and should not be used to denote two distinct categories. However, the 2017 TBSRTC guidelines recommends that pathologists subclassify the atypia into one of 5 categories, based on the nature of the atypia.
    - These subgroups can better estimate the ROM within AUS/FLUS, but generally will not affect patient management.
  o The risk of malignancy (ROM) within this group varies widely among institutions, but is generally estimated to be between 10-30%. [20, 22-25]
  o The ATA and TBSRTC provides general guidelines for the management of these indeterminate findings, which includes (1) Repeat FNA testing, (2) Molecular testing (See "Molecular Cytopathology"), or (3) Diagnostic lobectomy.
  o This category is ideally used <10% of the time and should only be used as a diagnostic "category of last resort." [20]

IV. Follicular Neoplasm (FN) or Suspicious for Follicular Neoplasm (SFN)
  o The malignancy rate of this indeterminate category is generally between 10-40%.
  o This category is used for follicular aspirates with cellular crowding or microfollicular patterns with limited nuclear atypia, without nuclear findings of papillary thyroid cancer, or aspirates comprised of nearly entirely Hürthle cells.
    - Many of these nodules represent follicular adenomas, which are benign hyperplastic neoplasms. However, follicular adenomas cannot be differentiated from follicular thyroid carcinomas based on cytopathology because the diagnosis of FTC requires the evaluation of the entire nodule's capsule for evidence of capsular or vascular invasion.
  o Because of the increased risk for a malignancy possibly more aggressive disease (widely invasive or angioinvasive FTC), the ATA and TBSRTC recommends patients either (a) undergo a diagnostic

lobectomy or (b) have molecular testing of the thyroid nodule for improved risk stratification (See "Molecular Cytopathology").

V. Suspicious for Malignancy (SUSP)
- o SUSP is considered an indeterminate nodule as the associated ROM as estimated by the NCI is 60%-75%. However, the ROM of this group can vary significantly between institutions with rates as high as 91%. Therefore, SUSP nodules are generally treated as if they were "malignant" with surgical management (thyroid lobectomy or total thyroidectomy) as the primary treatment options. [21, 30] (ATA Recommendation 17)

VI. Malignant
- o Nodules diagnosed as malignant have a risk of malignancy ranging from 97-99%.
- o Although the ATA and TBSRTC recommend surgical treatment (thyroid lobectomy or total thyroidectomy), there is evidence that small, intrathyroidal, well-circumscribed nodules without posterior extension may be closely followed with routine ultrasound, in the context of clinical trials. [31-33] (ATA Recommendation 12)

3.3.2 Molecular Cytopathology

- Thyroid cancer is characterized by common occurrences of various genetic alterations within the thyroid nodule (somatic mutations). Outside of medullary thyroid cancer, there is no role for testing germline mutations.
- Approximately 15-30% of FNA biopsies will be diagnosed as "Indeterminate" with overall rates of malignancy ranging from 5-30% or more. [35, 36]
  - o The main goal of molecular testing of indeterminate thyroid nodules is to correctly identify benign nodules and reduce the need for unnecessary diagnostic surgery, while not missing malignant nodules.
  - o If molecular testing is being considered, patients should be counseled regarding the benefits and limitations of molecular testing. (ATA Recommendation 13)
- As of July 2019, three companies offer commercially-available molecular tests for profiling AUS/FLUS and FN/SFN nodules. Although the subtleties between these tests are beyond the scope of these guidelines, a brief discussion of each test is described below. [37-39]

1. Afirma Gene Expression Classifier – Microarray technology analyzing mRNA expression levels of 167 genes, based on gene profiling from surgically-proven benign and malignant nodules. [37, 38]
   - o The current algorithm categorizes nodules into binary "Low-risk" or "High-risk" groups.
     - The low-risk group has a ROM of 4%, comparable to Bethesda II: Benign. Approximately 80% of their tests fall into this category.
     - The high-risk group has a ROM of >50%, comparable to Bethesda V: Suspicious for malignancy. Approximately 20% of patients will fall into this category.
   - o This test is considered a good "Rule out" test with high NPV (94%), but low PPV (38%).
     - Subsequent studies showed that this test provides the most useful information in a setting where the malignancy rates in indeterminate nodules is between 15%-21%[37].

2. ThyGeNEXT – Next-generation sequencing (NGS) platform to identify more than 150 genetic alterations across genes associated with thyroid malignancy. A second molecular test (ThyraMIR) may be added in conjunction with ThyGeNEXT, when lower-risk genetic markers are present. ThyraMIR analyzes 10 microRNAs (miRNAs) that are associated with thyroid malignancy. [37, 39, 40]
   - o High-risk mutations (BRAF, TERT, ALK, and RET/PTC) are categorized as "Strong mutations" and recommended for surgery.
     - The clinical sensitivity and specificity of the updated ThyGeNEXT compared to the previous version (ThyGenX) are similar (89% and 85%, respectively), but the company claims the

newest algorithms can aid in the detection of aggressive forms of DTC (like $BRAF^{V600E}$ + $TERT^{mut}$ tumours).

- o ThyGeNEXT + ThyraMIR testing has a reported NPV of 94% (good "Rule out test") and a higher PPV of 74%, compared to Afirma GEC. [37, 39]

3. <u>ThyroSeq v3</u> – 112-gene classifier panel utilizing NGS platform evaluating >12,000 mutation hotspots and detecting 5 classes of genetic alterations, including copy number alterations. [36, 37]
   - o Risk-stratifies patients with AUS/FLUS and FN/SFN into one of 5 categories based on the mutational profile of the nodule and its associated ROM (3-4%, 5-10%, 70-90%, 95-99%, and 98-100%).
     - This test also claims to aid in the detection of aggressive forms of DTC with the report indicating when multiple high-risk mutations are present, and recommending more aggressive surgical treatment.
   - o Testing performance in AUS/FLUS and FN/SFN indicates a NPV of 97% and PPV of 66% (with malignancy rates of 28% in indeterminate nodules). [36]

- Although the ATA does not recommend routinely testing for somatic mutations in thyroid cancer, the additional data provided by these molecular tests for indeterminate nodules may assist beyond diagnosis and aid in treatment planning.
  - o The field of molecular testing is a rapidly evolving field and there is a lack of long-term outcome data on the use of molecular testing to guide the extent of surgical treatment. [36]

4. Diagnosis and Pathology

4.1 Molecular Genetics of PTC

- In 2014, The Cancer Genome Atlas (TCGA) published the results of the most comprehensive multiplatform analysis of 496 PTCs. [35]
  - o Prior to the TCGA study, 25% of PTC nodules did not have an identifiable driver mutation. With the extensive multiplatform testing, they were able to identify all but 4% of driver mutations, which has the potential to significantly improve the diagnosis of cancer preoperatively, guide surgical management, and expand the role of targeted therapy in cases of metastatic disease.
  - o The results of this multi-institutional study demonstrate that the mutational landscape for PTC is relatively bland in comparison to other solid-tumour malignancies. The large majority of genetic alterations involve the MAPK and PI3K pathways with relatively low levels of somatic mutations, likely representing the indolent nature of PTC.
  - o In the TCGA series, age correlated with mutation density. This finding underscored the importance of age as a continuous variable in the dynamic risk stratification.
- In general, DTC is a MAPK-driven cancer with two *mutually exclusive* driver mutations, either in *BRAF* or *RAS*, each with distinct signaling consequences and resultant *BRAF*-like, *RAS*-like, and non-*BRAF/RAS*-like tumour phenotypes. [28, 35, 41, 42]
- ***BRAF* mutation** is the most frequent genetic alteration found in PTC. Virtually all point mutations are $BRAF^{V600E}$ mutations, which constitutively activates the MAPK pathway and disrupts the autoregulatory mechanism of the MAPK pathway.
  - o In general, 40-60% of PTCs have $BRAF^{V600E}$, which is usually associated with classic and tall cell variants, but seen in a comparable percentage of microPTCs. [35]
    - $BRAF^{V600E}$ mutations are also seen in 20-40% of poorly differentiated thyroid carcinomas and 25-40% of anaplastic thyroid carcinomas, but are not identified in FTC, encapsulated follicular variant PTC, or benign nodules. [41, 43]
  - o The presence of $BRAF^{V600E}$ predicts increased risk of lymph node involvement as well as extranodal extension.

- Although a $BRAF^{V600E}$ mutation alone may not predict adverse biology, a small fraction of $BRAF^{V600E}$-harboring tumours tend to show more aggressive biology via multiple mechanisms, including genetic instability, epigenetic modifications, and activation of TGFβ and NF-κB pathways involving invasion and angiogenesis.
        - Mortality is increased when $BRAF^{V600E}$ mutations are present in patients with lymph node metastasis (11.1% vs 2.6%), distant metastatic disease (51.5% vs 18.2%), Stage IV disease (31.4% vs 13%) and age $\geq$45 yo at diagnosis (8% vs 1.9%). [43, 44]
- **RAS genes** are GTPases associated with MAPK and PI3K/AKT pathways. *RAS* mutations lock RAS into a constitutively active state.
    - *RAS* mutations are present in tumours that are associated with follicular growth patterns and can be seen in benign follicular adenomas as well as in FTCs, follicular variant papillary thyroid carcinomas, and NIFTP (noninvasive follicular thyroid neoplasm with papillary-like nuclear features, formerly known as noninvasive follicular variant papillary thyroid carcinomas). [26, 28, 29]
        - Additionally, other *RAS*-like mutations, including *PAX-PPARγ* oncogenes, are frequently found in both FTC and encapsulated follicular variant PTC, leading some thyroid experts to recommend reclassifying these tumours under FTC, rather than PTC. [26, 45]
- **TERT-promoter mutations** activate telomerase activity, which allows cells that have critically short telomers to bypass the normal cellular mechanisms which would lead to cell death. [43, 46, 47]
    - This can immortalize cells which already have deficient DNA damage response mechanisms.
    - Approximately 10% of tumours in the TCGA cohort had activating *TERT* mutations, and were associated with older age, less-differentiated cancers, and higher recurrence rates.
- A *TERT*-promoter mutation coexistent with $BRAF^{V600E}$ (*TERT* + $BRAF^{V600E}$) is synergistic with a significant decrease in recurrence-free survival compared to either mutation alone. [46]
    - The 2015 ATA risk stratification places patients with both *TERT* + $BRAF^{V600E}$ at high-risk for disease recurrence, with an estimate of 40% recurrence risk, equivalent to a pT4a with gross extrathyroidal extension or pN1 with extranodal extension and >3 nodes involved.
    - This data forms the basis for the incorporation of prognostic features seen in two of the commercially available molecular tests, as noted in "Molecular Cytopathology".
- Although the ATA does not recommend routinely testing for somatic mutations in thyroid cancer, the additional data provided by these molecular tests for indeterminate nodules may assist beyond diagnosis and aid in treatment planning.

4.2   Histologic Subtypes of DTC
- **Papillary Thyroid Carcinoma**
    - There are approximately 15 subtypes of PTC, with some subtypes linked to an increased biologic aggressiveness including diffuse sclerosing, tall cell, hobnail, and columnar cell variants. [48-50]
- **Diffuse sclerosing variant**: rare, 1-2% of PTC, but often in younger female patients and children who present with a diffuse goiter.
    - Common nodal and lung metastases with historically poor prognosis. However, when treated with total thyroidectomy and comprehensive central neck dissection followed by adjuvant radiotherapy, this subtype has similar prognosis as a classic variant of PTC.
- **Tall cell variant**: 4-10% of PTC, usually harbor $BRAF^{V600E}$ mutations.
    - Frequently seen in large nodules with extrathyroidal extension, distant metastases are common.
    - Tall cell variant designation requires the identification of tall cell change that accounts for $\geq$30% of the tumour volume.
- **Hobnail variant**: newly described, rare (<1%) variant, usually associated with older patients.
    - Moderately differentiated PTC with frequent $BRAF^{V600E}$ mutations and higher rates of concurrent *TERT* promoter mutations.

- o Hobnail variants of PTC display aggressive behavior with frequent extrathyroidal extension, however further research is needed in terms of determining prognosis as it relates to this variant and the percentage of the tumor exhibiting hobnail change.
  - o Lymph node metastasis is present in up to 75% of patients and distant metastasis in 40% of patients, with 5- and 10-year overall survival rates of 69% and 64%.
- **Columnar cell variant:** Rare, can express CDX-2, more common in older males.
  - o Associated with locally infiltrative growth and tend to be aggressive.
- **Papillary microcarcinoma**: described as PTCs ≤1cm in the 2017 WHO classification.
  - o Common incidental finding, up to 21%-36% of carefully sectioned thyroids at autopsy.
  - o Frequently multifocal, often with some degree of capsular invasion (both of which are poor prognostic features).
  - o Infrequent nodal involvement (but up to 12%-31% in some studies).
  - o Although excellent prognosis in general, there is no consensus on treatment of incidentally detected nodules.
- **Follicular variant (fvPTC):** By definition, follicular variant PTCs are invasive tumours. They are divided into two distinct subgroups: (i) encapsulated follicular variant (efvPTC) with tumour capsular and/or vascular invasion, and (ii) infiltrative follicular variant (ifvPTC). A separate noninvasive subtype of efvPTC has been proposed, but is not formally recognized by the WHO.
  - I. **Encapsulated follicular variant (efvPTC):** This is the more common variant of fvPTC, with follicular architecture and a capsule surrounding the carcinoma, which may or may not be invaded.
    - efvPTCs rarely metastasizes to regional lymph nodes when angioinvasion is not identified.
    - Molecular profiling of efvPTC demonstrates high numbers of *RAS*-like mutations, and in general, do not display *BRAF^V600E* mutations.
      - The molecular profile and clinical characteristics place efvPTC closer to FTC rather than PTC, though this reclassification remains contentious. [41]
  - II. **Infiltrative follicular variant (ifvPTC):** In comparison to efvPTC with invasive growth, ifvPTC has no capsule and diffusely infiltrates the thyroid tissue.
    - These tumours have higher rate of lymph node metastasis (65%-72%) at presentation.
    - These tumours are enriched with *BRAF^V600E* mutations with a *BRAF*-like phenotype similar to the classic variant of PTC. [41]
  - III. **Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)**: This is the newest diagnostic category applied for follicular neoplasms formerly known as noninvasive follicular variant papillary thyroid carcinomas that is made on histopathologic assessment of surgical specimens and not FNA.
    - By definition, NIFTP should not have cytomorphologic features associated with more aggressive PTC, including high mitotic activity or *BRAF*-like mutations. [8, 27-29]
    - Initially described as a separate benign entity in 2016, several follow up studies have demonstrated the potential for a less benign clinical course, including regional lymph node metastasis.
    - To answer these criticisms, the criteria for diagnosis were strengthened to reduce the risk of mis-diagnosis of efvPTC, and the potential for under-treatment of a malignant condition.
      - This diagnostic category may be rare in practices where rigid criteria and exhaustive tumour sampling are performed.
    - The 2015 ATA guidelines predate the description and diagnostic criteria for NIFTP, and there is currently insufficient data for changing the management of patients diagnosed with NIFTP.
- **<u>Follicular Thyroid Carcinoma</u>**

- o FTC makes up 6-10% of all DTC diagnosed in iodine-sufficient regions (iodine deficiency is a risk-factor). The diagnosis of FTC requires extensive evaluation of the capsule to prevent mis-diagnosis as a benign follicular adenoma. [5, 51]
- o The 2017 WHO classification introduced three clinically relevant histologic subtypes of FTCs, which underscores the importance of vascular invasion as a risk modifier in the classification of these tumours.

I. **Minimally invasive FTC:** A follicular neoplasm that has only tumour capsular invasion but no evidence of vascular invasion.
- Minimally invasive FTCs are considered to have an excellent prognosis.

II. **Encapsulated angioinvasive FTC**: Encapsulated FTCs showing even a single focus of vascular invasion are termed as encapsulated angioinvasive FTC.
- These neoplasms may also have minimal tumour capsular invasion.
- Unlike the 2015 ATA risk stratification, even a single focus of angioinvasion is now recognized to predict biologic aggressiveness in the 2017 WHO classification of thyroid cancers.

III. **Widely invasive FTCs** are defined based on their extent of tumour invasiveness, frequently with extensive invasion of the thyroid gland and extrathyroidal soft tissues.
- This diagnostic category may also show angioinvasion.
- FTCs demonstrate low lymphatic metastatic potential (<5% with ipsilateral lymphadenopathy, thus usually not requiring lymph node dissection), but frequent hematogenous spread to distant sites.
- Up to 69% of patients develop distant metastasis, most frequently to lung and bone. Associated with poor long-term survival (<50%).

- **Oncocytic (Hürthle cell) thyroid carcinoma (HCC)**
  - o Follicular neoplasm with >75% of oncocytic tumour cells due to accumulation of dysfunctional mitochondria. Considered malignant only if capsular and/or vascular invasion is present. [51]
  - o The 2017 WHO classification of thyroid cancers introduced 3 distinct forms with histologic criteria similar to FTC: (i) Minimally invasive oncocytic (Hürthle cell) thyroid carcinoma, (ii) Encapsulated angioinvasive oncocytic (Hürthle cell) thyroid carcinoma, and (iii) Widely invasive oncocytic (Hürthle) cell thyroid carcinoma.
  - o Angioinvasive and widely invasive oncocytic thyroid carcinomas are often aggressive thyroid cancers with high frequency of extrathyroidal extension, locoregional metastasis, and recurrence.
  - o Unlike the majority of DTC, oncocytic (Hürthle cell) thyroid carcinomas rarely concentrate radioactive iodine, therefore complete surgical excision is critical for proper treatment. [51, 52]

5. Management Algorithms

5.1 Surgical Management

- The primary management of DTC remains surgical treatment of the disease. The primary goals of initial therapy are detailed in the ATA guidelines, Section B2, and include: "*improvement in the overall and disease specific survival, reduce the risk of persistent or recurrent disease and its associated morbidity, permit accurate disease staging and risk stratification, and minimizing treatment-related morbidity and unnecessary therapy.*"
- Thyroid cancer should be treated by clinicians who have appropriate training, experience, and continued practice in the management of this potentially complex disease process.
- The relationship between the volume of thyroid surgery by individual surgeons and the outcomes of thyroid surgery has been well-established, demonstrating decreased risk of minor and major complications in higher-volume surgeons. [53]

5.1.1 Pre-op Workup
- Patients should meet with their thyroid surgeon prior to surgery to discuss the risks and benefits of any thyroid surgery.
- All patients should have an up to date diagnostic neck ultrasound to evaluate the thyroid gland and the lateral neck compartments. Suspicious lymphadenopathy that meets criteria should be further evaluated with an USGFNA biopsy. [5, 15, 54]
  - The addition of thyroglobulin levels from the aspirate has been associated with increased rates of diagnosis of metastatic lymph nodes compared to cytopathologic assessment alone. [55-57]
- Patients who present with widely diffuse or bulky lymphadenopathy, or evidence of aerodigestive tract invasion should be further evaluated with CT imaging of the neck and chest with contrast enhancement. [15] (ATA Recommendation 33)
- All patients should have a pre-operative evaluation of their vocal cord mobility, usually with a flexible fiberoptic laryngoscopy, although a mirror exam or ultrasound laryngoscopy may be sufficient in appropriate patients. [54]
  - The surgeon should not rely on symptoms alone, as many patients with a chronic vocal cord paresis may have minimal voice complaints, despite the potential for gross RLN invasion by the tumour.
  - This also gives the surgeon an opportunity to document normal movement of the cords preoperatively.
- Although not mandatory, testing of PTH and calcium preoperatively can be performed to determine if there is any concurrent hyperparathyroidism that may need further work up prior to surgery.
- After discussing all the treatment options with the patient, the surgeon should obtain an informed consent for surgery. Specific complications should be addressed, using surgeon-specific rates of complications, when available. (ATA Recommendation 39)

5.1.2 Surgical Treatment Options
- **Thyroid lobectomy**
  - Synonymous terms: "partial thyroidectomy" "total thyroid lobectomy", "hemithyroidectomy", "thyroid lobectomy, with or without isthmusectomy".
  - Surgery should be limited to the complete removal (or near complete) of one lobe of the thyroid gland, with the pyramidal lobe, with or without the removal of the isthmus.
    - The contralateral gland should be left undissected to prevent scarring or trauma to the RLN and parathyroid glands.
  - A thyroid lobectomy may be considered a diagnostic procedure (and often therapeutic) in cases of indeterminate thyroid nodules.
  - Patients with low-risk DTC (>1cm, <4cm) without evidence of disease in contralateral lobe or metastatic lymphadenopathy should be offered partial thyroidectomy. [58-60] (ATA Recommendation 35)
    - Patients in whom a second anesthetic should be avoided (i.e. advanced age, inability to tolerate multiple operations, etc.) should be considered for total thyroidectomy.
    - Patients with more advanced disease (cancer >4cm, gross extrathyroidal extension, or metastatic disease) may require adjuvant radioactive iodine (RAI) following surgery and should undergo a total thyroidectomy.
  - Limiting the thyroid surgery to one side eliminates the risks of permanent hypoparathyroidism with hypocalcemia as well as bilateral RLN injury.
  - Approximately 20% of patients will require hormone replacement therapy following thyroid lobectomy. [61, 62]

- Patients with Hashimoto's thyroiditis are at higher risk for requiring hormone replacement postoperatively.
- **Total thyroidectomy**
  o A total thyroidectomy is the removal of the entire thyroid gland (both lobes, isthmus, and pyramidal lobe).
  o A total thyroidectomy is indicated for patients with high-risk disease found on pre-operative studies (extrathyroidal extension, nodal metastases, cancer >4cm, bilateral PTC, advanced age), in whom radioactive iodine ablation may be indicated.
  o A total thyroidectomy may be indicated in low-risk patients who may only require a lobectomy but present with coexistent hyperthyroidism.
- **Isthmusectomy**
  o Indicated for select cases of thyroid nodules limited to only the thyroid isthmus.
- **Central neck dissection (CND)**
  o The 2009 ATA consensus statement regarding the terminology of the central neck dissection divides the central neck compartment into four discrete anatomically-based subcompartments based on anatomic location, which can be independently dissected during a central neck dissection for PTC.
    - The central neck compartments are comprised of both Level VI and VII nodal basins, and extend from the trachea to the carotid arteries bilaterally, and the hyoid superiorly to the innominate artery inferiorly. [63, 64]
    - The four discrete nodal subcompartments are: (1) prelaryngeal (Delphian) lymph nodes; (2) pretracheal lymph nodes; (3) right paratracheal lymph nodes; and (4) left paratracheal lymph nodes.
  o An ipsilateral "therapeutic CND" is indicated for patients with clinically involved central neck lymphadenopathy (cN1a). (ATA Recommendation 36)
  o An ipsilateral "prophylactic CND" is indicated for patients undergoing lateral neck dissection for biopsy-proven lateral nodal metastases (pN1b), although a contralateral prophylactic CND may not be indicated. [65, 66] (ATA Recommendation 37)
    - An ipsilateral "prophylactic CND" is not necessary for clinically node-negative PTC (cN0) and most follicular thyroid cancers, but may be indicated in cases of advanced thyroid cancer (T3 or T4) if the results can improve risk stratification. [67]
      - A "prophylactic CND" in patients with clinically negative nodal involvement (cN0 with normal preoperative imaging without intraoperative findings of central lymphadenopathy) is not associated with improvement in long-term patient outcomes and may be associated with higher likelihood of surgical morbidity, including RLN injury and hypoparathyroidism. [68, 69]
      - Additionally, the prophylactic removal of cN0 nodes results in a significant increase in the staging of pN1a disease, often resulting in the recommendation of adding RAI therapy, but with any significant effect on patient outcome.
      - Comprehensive central neck dissection carries increased risk of postoperative hypoparathyroidism.
- **Lateral neck dissection**
  o The lateral neck compartments are divided into different nodal compartments (Levels I-V), which relate to common nodal drainage patterns seen in various disease processes within the head and neck. [70-73]

- Patients with biopsy-proven lateral neck DTC should undergo a therapeutic ipsilateral neck dissection, typically encompassing the levels of disease on imaging and levels at risk. [70] (ATA Recommendation 37)
    - The rates of metastasis to Levels I, IIb, and Va are low and dissection of these nodal compartments is not be necessary in the absence of clinically-evidence disease.
    - At the Princess Margaret Cancer Centre, a formal level Vb neck dissection is performed primarily in the setting of clinically evident level Vb metastases. While a formal level Vb dissection is not performed in patients without clinical evidence of disease in level Vb much of this level can be removed through an anterior approach.
  - The prophylactic dissection of lateral neck nodes in a cN0 patient is not recommended.
  - Risks for lateral neck dissection include bleeding and infection, as well as injury to the great auricular nerve, spinal accessory nerve, cervical plexus, carotid artery, jugular vein, vagus nerve, sympathetic chain, phrenic nerve, and brachial plexus.
    - In high volume surgeons, the risk of minor complications is between 4-7%, and the risk of major complications is around 1%. [72]

5.1.3 Completion thyroidectomy
  - Approximately 10-30% of patients undergoing a thyroid lobectomy for low- to intermediate-risk DTC require the removal of the contralateral thyroid lobe.
  - Completion thyroidectomy is generally performed to facilitate radioactive iodine, thus the indications for completion thyroidectomy should be the same as those for RAI.
  - Indications for completion thyroidectomy include: [74-76] (ATA Recommendation 38)
    - Aggressive features found on final pathology (high-risk subtypes, extensive extrathyroidal extension, size >4cm), which may necessitate RAI ablation.
    - Newly diagnosed lymph node metastatic disease or locally recurrent carcinoma.
    - Patients with a remote history of thyroid lobectomy presenting with new thyroid nodules, where the workup would include thyroid lobectomy for diagnosis or treatment.
    - Staged total thyroidectomy procedures, especially in cases with intraoperative concerns for RLN injury, where a surgeon may want to avoid bilateral RLN injury.
    - In cases of low-risk disease with either micrometastatic central compartment nodes noted incidentally on final pathology, or PTCs > 4cm without adverse features, recommendations for possible completion thyroidectomy with RAI should be discussed with the patient and presented at a multidisciplinary tumour board.
  - Preoperative work up should include a flexible fiberoptic laryngoscopic exam to ensure normal preoperative functioning of the vocal cords.

5.1.4 Revision Thyroidectomy and Central Neck Dissection
- Approximately one-fifth of patients treated for DTC develop recurrent disease, with the majority diagnosed within the first 10 years after surgery. [81-83]
- Although the standard treatment for recurrent thyroid disease remains reoperative thyroid surgery, there are several non-operative options available for select patients, including active surveillance and percutaneous ethanol ablation. [84-89]
  - A study by Tuttle, et al. found that approximately one-third of patients will have small (≤10mm) postoperative thyroid bed nodules after total thyroidectomy. Of these, less than 10% were found to be malignant lymph nodes, and even fewer demonstrated progression over time.
  - A second study demonstrated that lateral neck lymph nodes also have a low potential for disease progression, with only 9% of suspicious lymph nodes increasing in size by 5mm or more during follow up.

- o The thyroglobulin doubling time, as well as tumor growth doubling time are key indicators for determining progression in low-volume disease.
  - Although the majority of patients with small volume disease will remain stable, a thyroglobulin doubling time of less than 1-2 years is a negative prognostic indicator, which should prompt a discussion for intervention.
- Reoperative thyroid surgery is technically challenging because of the anatomic changes that occur. [17, 83, 90, 91]
- Given the technical challenges involved in revision thyroid surgery and the potential non-surgical treatment options, patients should be reviewed in a multi-disciplinary thyroid-specific tumour board.
  - o When surgery is warranted, patients should be treated by high-volume thyroid surgeons with expertise in revision thyroid surgery.
- Patients undergoing reoperative thyroid surgery should have a preoperative assessment of vocal cord function. Intraoperative recurrent laryngeal nerve monitoring should be considered in reoperative thyroid surgery given the variable position of the nerve within scar tissue.

5.1.5 Intraoperative Nerve Monitoring (IONM)
- Intraoperative nerve monitoring involves the use of a nerve-monitoring endotracheal tube (ETT) with electrodes placed at the level of the true vocal cords, which detects stimulation of an intact recurrent laryngeal nerve (RLN). [77, 79, 92]
- The 2015 ATA guidelines give a "weak recommendation, low-quality evidence" for the use of IONM. (ATA Recommendation 42) It states: "Intraoperative neural stimulation (with or without monitoring) may be considered to facilitate nerve identification and confirm neural function."
  - o IONM should not be used to replace routine nerve visualization and preservation.
  - o A recent meta-analysis demonstrated no benefit in the use of nerve monitors in routine thyroid surgery cases.
  - o However, several studies have shown a benefit in certain high-risk surgeries, including revision surgery and locally-advanced thyroid surgery.
- In 2018, the International Neuromonitoring Study Group published guidelines for the optimal use of IONM in thyroid surgery. [77]
  - o Surgeons using IONM should have a thorough understanding of these guidelines as well as the advantages and limitations of nerve monitoring devices.

5.2 Active Surveillance
- Standard treatment for thyroid cancer has traditionally been surgery. With the de-escalation of thyroid cancer treatment, the ATA guidelines mention active surveillance for thyroid cancers with size less than 1cm without high-risk clinical, radiographic, or cytologic features, no evidence of nodal metastases, in whom close observation is feasible. (ATA Recommendation 12).
  - o Patients at high surgical risk from medical co-morbidities, or those with relatively short life expectancy ("watchful waiting") may also be considered for this treatment.
- There have been two prospective trials of active surveillance out of Japan which demonstrate the indolent nature of small thyroid cancers. [31, 32]
  - o The results of these studies show that only a small proportion of patients developed tumour enlargement (>3mm) at 5 and 10 years (5%, 8%, respectively), and only 1.7% and 3.8% of patients developed lymph node metastasis at 5-year and 10-year follow-up.
  - o Further, only one patient (out of 1465) developed disease recurrence after surgical intervention, and there were no cancer deaths and no distant metastases.
- Based on these data, the thyroid oncology group at PMH have developed a multi-institutional, multiphase, prospective, observational clinical trial in which patients with low-risk (size <2cm,

intrathyroidal without extension, not posterior), biopsy-proven PTC are informed about the option of active surveillance on study. The patient is then given the option for surgical intervention or active surveillance. [33, 34] (ClinicalTrials.gov Identifier: NCT03271892)

6. Staging and Risk Stratification

- Following thyroid surgery for thyroid cancer, all patients should be staged according to the AJCC/UICC staging system. (ATA Recommendation 47)
  - The AJCC/UICC Staging System, 8th edition is the most widely used system in North America and was updated in 2018.
  - The AJCC/UICC staging system uses the familiar TNM classification, with staging categories modified for age. (See Table 2)
  - This staging system provides important prognostic information for the risk of *mortality* from thyroid cancer, but does not predict the risk of recurrence in DTC, which is better predicted using the *ATA Initial Risk Stratification for DTC.* [5, 93, 94] (ATA Recommendation 48, See Table 3)

Thyroid Carcinoma (Differentiated)

{Papillary, Follicular, Hurthle; NOT Medullary}

Tx Tumor cannot be assessed
T0 No evidence of primary tumor
T1a Tumor ≤ 1cm, limited to thyroid
T1b Tumor 1-2cm, limited to thyroid
T2 Tumor 2-4cm, limited to thyroid
T3a Tumor >4cm, limited to thyroid
T3b Any size, Grossly invading strap muscles only
T4a Any size, Grossly invading subcutaneous soft tissues, larynx, trachea, esophagus, or RLN
T4b Any size, Grossly invading prevertebral fascia, encasing carotid artery or mediastinal vessels

Nodal Status

Nx Regional nodes not assessed
N0a ≥1 LN confirmed benign (cytology/pathology)
N0b No radiologic/clinical evidence of LAD
N1a Mets (Uni-/Bilateral) to central LN (Level VI/VII)
N1b Mets (Ipsi-/Contra-/Bilateral) to lateral LN (Levels I-V) or retropharyngeal LN

Well-Differentiated Thyroid Cancer				
	T	N	M	Stage
Age <55	Any	Any	0	I
	Any	Any	1	II
Age 55+	1, 2	x/o	0	I
	1, 2	1a/b	0	II
	3	Any		
	4a	Any	0	III
	4b	Any	0	IV-A
	Any	Any	1	IV-B
Anaplastic Thyroid Cancer				
Any Age	1-3a	x/0	0	IV-A
	1-3a	N1	0	IV-B
	3b, 4	Any		
	Any	Any	1	IV-C

Anaplastic Thyroid Carcinoma:
TNM is the same as differentiated thyroid, but the staging is different

Table 2: AJCC/UICC Staging System for Differentiated Thyroid Cancer, 8th ed.

- The **ATA Initial Risk Stratification System** is a three-tiered clinico-pathologic system that predicts the likelihood of disease recurrence in patients *without* structurally identifiable disease after initial definitive treatment (surgery +/- RAI or other adjuvant therapy). (ATA Recommendations 48)
  - It is based on preoperative, intraoperative, and postoperative findings including imaging, serum biomarkers, pathology, and molecular profiling (when available).
  - Patients without structural disease detected after initial therapy are stratified into low, intermediate, and high-risk categories which predict the risk of structural disease recurrence.
- Cancer Care Ontario (CCO) has published the "Differentiated Thyroid Cancer Treatment Pathway Map", which is the provincially-endorsed treatment guidelines for DTC. [10]

- These treatment guidelines are largely based on the 2015 ATA Guidelines, but have modified several key components of the treatment algorithm, including the "Initial Risk Stratification" system. [8, 10]
- The CCO guidelines subdivide the intermediate and high-risk groups into 2 categories each (5 tiers in total).
  - Table 3 outlines the various clinicopathologic features for each of the 5 tiers.
- The CCO guidelines tend to be more prescriptive than the ATA Guidelines and reduces some of the ambiguity in treatment algorithms present in the current ATA Guidelines.
  - See Table 4 for a tabular view of the CCO DTC treatment guidelines.

Low Risk	Low-Intermediate	High-Intermediate	High Risk	Highest Risk
• Minimally invasive FTC • Non-invasive efvPTC or NIFTP • pT1, any age; pT2 <55yo • Microscopic pN1 (<2mm, up to 5 nodes) • No adverse path features*	• ≥55 with tumor 2-4cm, no other RF • pN1a (5 or more), tumor <3cm and <55 yo • Minimal ETE with low/undetectable Tg • pT3, tumor ≥4cm regardless of age	• High Tg post-op • Adverse histopathologic features* • pN1a, tumor ≥3cm • pN1b (lateral neck nodal mets) • pN1a (5 or more) and age ≥55 yo	• Gross ETE but without macroscopic residual disease	• Gross residual disease or distant metastasis
* Adverse histopathologic features: angioinvasion (excluding lymphatic invasion), tall cell (≥30%), hobnail (≥30%), columnar cell change (≥30%), solid growth (≥30%), widely invasive growth, any level of dedifferentiation, and intrathyroidal psammomatous dissemination				

Table 3: CCO Differentiated Thyroid Cancer Treatment Pathway – "Risk Stratification" following surgery, modified from Treatment Pathway Map [10]

7. Radiation Therapy

7.1 Radioactive Iodine-131 (RAI)

- The Cancer Care Ontario (CCO) "Differentiated Thyroid Cancer Treatment Pathway Map" provides a helpful algorithm for the use of RAI after total thyroidectomy, based on their 5-tiered categorization system.
  - Table 4 summarizes these recommendations. [8, 10]
- Depending on the post-surgical risk category of the patient, postoperative radioactive iodine (RAI) treatment may have different goals. (ATA Recommendation 51)
  1. <u>RAI Remnant ablation</u>: recommended for the low-intermediate risk group after total thyroidectomy. Remnant ablative doses allow for the improved detection of recurrent disease through testing of Tg and/or RAI scans. Doses typically do not exceed 30mCi, however it needs to based on the individual patient.
  2. <u>RAI adjuvant therapy</u>: recommended for the high-intermediate risk group. Adjuvant therapy doses are intended to improve disease-free survival by destroying suspected but unproven residual disease. Doses are typically between 70-125mCi, with higher doses administered to patients at higher risk of disease recurrence, lower doses for older patients.
  3. <u>RAI Therapy</u>: recommended for high risk and highest risk groups. Full-dose therapy is intended to improve disease-free survival and disease-specific survival in patients with persistent/residual disease, after attempted re-resection by an appropriately trained surgeon. The doses may be combined with external beam radiotherapy treatment (EBRT) in patients with particularly high-risk disease. Doses may be empirically dosed between 100-200mCi, or dosimetry-guided based on RAI SPECT/CT.

o The low risk category implies a risk of disease recurrence ~3% and studies show that there is no significant impact on survival due to delayed diagnosis and treatment in low-risk patients. Therefore, RAI is generally not recommended in this risk group.

Initial Risk Category	RAI Therapy	Post-Treatment	Initial TSH Goal	6-month Post-Treatment	12-month Post-Treatment	Surveillance
Low Risk, Thyroid lobectomy	No RAI treatment	Routine thyroid labs	0.5-2 (Thyroid hormone replacement, if needed)	- Exam - TSH, Tg level - Neck U/S, if elevated Tg		Surveillance every 1-2 years for 5 years, then discharge to PCP - Exam - TSH, serum Tg - Neck U/S - Some patients (elevated Tg) may require more frequent follow-up (every 6 months)
Low Risk, Total thyroidectomy						
Low-Intermediate Risk, Total thyroidectomy +/- CND	RAI Ablation (30mCi)	- Post-treatment Radioiodine imaging - Post-treatment stimulated Tg	TSH suppression (0.1-0.5 mIU/L)	- Exam - TSH, fT4, Tg level	- Exam - Labs (TSH, fT4, Tg) – High-sensitivity Tg - U/S of neck if post-op Tg is elevated - Diagnostic RAI WBS (following TH withdrawal or rhTSH) → Only for (a) unfavorable histology; (b) older age, ≥55 yo; (c) suppressed Tg >2ng/ml	Surveillance every 1-2 years for 5 years, then discharge to PCP - Exam - TSH, serum Tg - Neck U/S - Some patients (elevated Tg) may require more frequent follow-up (every 6 months)
High-Intermediate Risk, Total thyroidectomy +/- CND	Adjuvant RAI (70-125mCi)	- Post-treatment Radioiodine imaging - Post-treatment stimulated Tg			- Exam - Labs (TSH, fT4, Tg) – High-sensitivity Tg - U/S of neck if post-op Tg is elevated - Diagnostic RAI WBS (following TH withdrawal or rhTSH)	Annual Surveillance for 10 years, then discharge to PCP - Exam - TSH, serum Tg - Neck U/S
High Risk, Total thyroidectomy +/- CND	Reresection, if possible RAI Therapy (100-150mCi) and/or EBRT to neck	- Post-treatment Radioiodine imaging - Post-treatment stimulated Tg	TSH suppression (<0.1 mIU/L)	6 month post-treatment → Then annual surveillance - Exam - TSH, fT4, Tg level - Neck U/S if post-op Tg elevated - Diagnostic whole body RAI scan (following thyroid hormone withdrawal or rhTSH) - PET/CT if Tg >10 ng/mL and negative imaging - CT Neck and thorax if previously positive *If CT remains +, consider further RAI therapy (150-200mCi)	Annual Surveillance for 10 years, then discharge to PCP - Exam - TSH, serum Tg - Neck U/S
Highest Risk, Total thyroidectomy +/- CND	RAI Therapy (200mCi) and/or EBRT to neck If lung or bone mets: RAI Therapy (150-200mCi) and/or EBRT to mets	- Post-treatment Radioiodine imaging - Post-treatment stimulated Tg -Baseline CT neck if not previously done				

Table 4: CCO Differentiated Thyroid Cancer Treatment Pathway – Summary of Treatment Recommendations and Surveillance, modified from Treatment Pathway Map [10]

o Age can play a significant role in the decision to treat with RAI, as well as the dosing of RAI.
- A SEER database review evaluating the utility of RAI in intermediate risk patients (cTxN1 and cT3N0 with size ≥4cm or microETE) demonstrated a 1% absolute risk reduction in patients <45 yo (though OS was 99% with RAI vs 98% without RAI over mean follow-up of 6.8 yrs), while in patients ≥65 yo had a 4% absolute risk reduction with the addition of adjuvant RAI therapy (73% with RAI vs 69% without RAI). [95]
- The maximum tolerable activity (MTA) of ^{131}I is the maximum dose of RAI that can be administered without producing toxic effects in the bone marrow, and is directly related to the retention of ^{131}I in the body. Studies have shown that even when accounting for renal clearance and disease burden, older patients are at risk of receiving RAI at doses higher than the MTA. Older patients (>70 yo) should receive no more than 150 mCi of RAI. [96]
o Aggressive histologies warrant consideration of RAI. Two additional SEER reviews demonstrated that aggressive histologic variants have significantly worse overall survival when RAI is not administered. [48, 49]

- Patients with diffuse sclerosing variant PTC who did not receive RAI were 4.9 times more likely to die from disease compared to those that did receive RAI (p=0.026).
- Patients with tall cell variants who did not receive RAI were 2.1 times more likely to die than those that did receive radiation (p=0.015).
  - o Pulmonary micrometastases should be treated with RAI therapy, which should be repeated as long as disease continues to concentrate RAI and there is evidence of continued clinical improvement.
  - o Patients with *micro*metastatic pulmonary disease (<2mm, possibly detectable on high-resolution CT) classically respond well to repeat RAI doses up to 200mCi. This subgroup has high rates of complete remission with this approach. (ATA Recommendation 77)
    - Patients with *macro*metastatic pulmonary disease (detectable on plain-film chest radiography) may be treated with a similar approach, if there is objective evidence of disease response, but complete remission is uncommon and the survival remains poor for this population. (ATA Recommendation 78)
    - The treatment dose of RAI should be reduced to 150 mCi in patients with widespread pulmonary metastatic disease due to the potential for increased ^{131}I retention with subsequent bone marrow and pulmonary toxicity and older age. [96]
- Thyrotropin-stimulation should be obtained prior to RAI therapy or diagnostic imaging. (ATA Recommendation 53)
  - o Levothyroxine (LT4) should be withdrawn 3-4 weeks prior to treatment with RAI (or RAI-based imaging). Liothyronine (LT3) may be substituted for up to 2 weeks prior to treatment, but should be discontinued at least 2 weeks prior to RAI.
  - o TSH levels should be measured prior to treatment, with a goal of >30 mIU/L.
  - o rhTSH (recombinant human TSH, Thyrogen®) can be used for thyroid hormone (TH) withdrawal with improved quality of life for patients. (ATA Recommendation 54)
    - The CCO working group recommends the use of rhTSH for TSH-stimulation. However, rhTSH is not provincially funded, though it may be available to patients who have additional insurance, are over the age of 65, or if patients pay out of pocket. [8, 10]
  - o rhTSH should be used in patients with significant contraindications for hypothyroidism, including significant medical and psychiatric comorbidities, and patients who are unable to mount a TSH response to thyroid hormone withdrawal. (ATA Recommendation 54D)
  - o A low-iodine diet for 1-2 weeks should be considered for patients undergoing RAI treatment or RAI imaging. (ATA Recommendation 57)
- Following RAI treatment, patients should have a diagnostic whole-body RAI scan. (ATA Recommendation 58)
  - o If possible, this RAI WBS should be performed with SPECT/CT imaging rather than planar imaging. The additional anatomic information helps guide disease staging, risk stratification, and allows for documentation of RAI-avidity of any structural disease. [97, 98]
- Post-treatment thyroglobulin and anti-thyroglobulin antibodies measurements should be performed after RAI to better predict initial response to therapy. (ATA Recommendation 49)

7.2   External Beam Radiotherapy (EBRT)

- EBRT is rarely used in the treatment of DTC, but may be indicated in select patients after peer review. [8, 10, 99, 100]
- EBRT is recommended for patients with gross residual or unresectable locoregional disease (following assessment of resectability by an experienced surgeon).
  - o Younger patients (<55 yo) with limited disease burden and RAI-avid disease should not be treated with EBRT.

- Patients with cT4b (unresectable cancer) and extensive cT4a cancer with poor histologic subtypes that are unlikely to respond to treatment-dose RAI, are good candidates for EBRT, dose 60-70 Gy in conventional fractionation, with IMRT or VMAT
- A standard EBRT regimen used at PMH for resected T4a disease is 66 Gy (in 33 fractions) over 6.5 weeks to the high-risk clinical target volume, taking care to include the areas of extrathyroidal invasion, and a lower dose of 56 Gy (in 33 fractions) to the remainder of the thyroid bed and the adjacent cervical nodal compartments at risk of harboring residual disease.
  - EBRT may be considered in metastatic disease that does not respond to treatment-dosed RAI, if lesions are not surgically resectable.
    - EBRT dose 20-30 Gy in hypofractionated regimens are effective for symptom control.
    - If longer term local control is desirable, higher doses of 30-50 Gy in conventional fractionation will be appropriate, or a SBRT approach for eligible anatomic sites.
    - SBRT may be considered in patients with oligometastatic disease.
    - EBRT may also be considered in patients with oligoprogressive disease to delay the start or the need to change systemic therapy
- The risks of EBRT toxicity must be carefully weighed with any anticipated benefits.
  - Patients receiving EBRT to the neck should be referred to a Registered Dietician and Speech Language Pathologist. [10]

8. Other Therapies

8.1 Systemic Chemotherapy and Targeted Therapies

- Systemic chemotherapy plays a limited role in the treatment of thyroid cancer. [101]
  - Traditional cytotoxic chemotherapy (including docetaxel and cisplatin) may be used in combination with radiation therapy for patients with anaplastic thyroid cancer.
- Advanced thyroid cancer with radioiodine-resistant (RAI-R) metastatic disease has a much more aggressive clinical course than RAI-avid metastatic disease.
  - RAI-refractory disease occurs in ~5% of all patients diagnosed with DTC, and is more common in older patients, patients with larger tumour burdens, and those with more aggressive histologic subtypes. [102, 103]
  - In a study of 444 patients with metastatic DTC treated with ^{131}I, 32% of patients were refractory to ^{131}I treatment, with a 10-year OS of 10% (compared to a 92% 10-year OS in the 68% of patients who responded to RAI therapy). [104]
- Newer systemic "targeted therapies" have recently shown improvements in progression-free survival when used in patients with RAI-R metastatic disease. [102]
  - The main class of these targeted therapies are the multitargeted Tyrosine Kinase Inhibitors (TKI), which inhibit various receptors on DTC.
    - The two most studied targeted therapeutics in DTC are the TKIs lenvatinib and sorafenib, which variably inhibit VEGFR1-3, FGFR1-3, RET, c-KIT, and PDGFR. [105-107]
  - The MEK inhibitor selumetinib works by increasing sodium-iodide symporter expression, thereby increasing ^{131}I uptake in RAI-R cells. This "re-differentiation mechanism" has the potential to revert the RAI-resistant cells back to RAI-avid cells. [102]
  - The BRAF inhibitor dabrafenib has also shown evidence of re-differentiation in patients with BRAF^{V600E} mutations. BRAF^{V600E} is the most common mutation in PTC and is associated with a more aggressive clinical course. In a small Phase II trial, dabrafenib was associated with increased RAI uptake in 60% of patients with BRAF^{V600E} mutations. [102, 108]

- The two currently approved targeted therapies in advanced RAI-refractory DTC are lenvatinib and sorafenib, which provide durable responses with improved survival, but are associated with significant side effects. [105, 106, 109]
    o Based on limited Phase II and III studies, lenvatinib may offer a higher rate of durable response than sorafenib, including all histologic subtypes and metastatic sites, as well as in patients >65 years old.
        - SELECT Trial for lenvatinib vs placebo in patients with RAI-R disease: Median progression-free survival (PFS) was 19.4 months vs 3.7 months in placebo arm, with an estimated 19-month survival advantage. Furthermore, in patients who responded to lenvatinib, the median PFS was 33.1 months. [106, 107]
        - Because of the "dirty" targeting of multiple tyrosine kinases, side effects with lenvatinib can have a major impact on quality of life. Overall, 82% of patients had dose holds, 68% had dose reductions, and 14% had permanent discontinuation due to side effects. [109]

8.2   TSH Suppression:
- DTC expresses the TSH receptor on the cell membrane and responds to TSH stimulation by increasing cellular expression of thyroid proteins and increasing the rate of cell growth[110].
    - Suppression of TSH using supraphysiologic doses of levothyroxine is recommended for intermediate to high risk patients to decrease the risk of recurrence[5, 10]. (ATA Recommendation 59)
        1. Low-risk patients: No TSH suppression necessary. Standard thyroid hormone replacement with a TSH goal of 0.5-2 mIU/L is generally recommended for low-risk patients.
        2. Intermediate-risk patients: TSH suppression therapy with goals of 0.1-0.5 mIU/L are recommended for intermediate risk patients, with a duration of 3-5 years post-treatment. Both the duration and level of suppression should be modified based on patient factors, including comorbid conditions. Patients >70yo should have higher TSH levels to reduce the risks of complications.
        3. High-risk patients: TSH suppression therapy with a goal of <0.1 mIU/L for 3-5 years and may be extended up to 10 years. Duration and level of suppression are dependent on patient factors.
- Risks and complications for TSH suppression include subclinical thyrotoxicosis, angina in patients with ischemic heart disease, increased risk of atrial fibrillation in older adults, and increased risk of osteoporosis in post-menopausal women.
    o Older patients (>70 yo) should have higher TSH levels to reduce the risk of complications. [10]

9.   Surveillance and Follow-up
- Follow-up for thyroid cancer, depending on the type and stage, can be life-long as the disease has a long natural history; late recurrences are uncommon but not unheard of and, in most instances, can be treated successfully.
- The CCO guidelines have developed a surveillance algorithm based on the risk category. (See Table 4)
- Surveillance should include a physical exam, lab work should include TSH and serum Tg (high-sensitivity Tg tests do not require TSH-stimulation) with anti-Tg antibodies (TgAb), and neck ultrasounds.

9.1   Thyroglobulin Measurements
- Thyroglobulin (Tg) is secreted by functioning thyroid epithelial cells, including DTC. Serum measurements of Tg can detect the presence of thyroid cells and is critical in the routine surveillance of DTC. [111-113]

- Rising levels of serum thyroglobulin, especially in patients who had previously had undetectable levels immediately post-treatment, indicates the presence of thyroid cells, and possible disease recurrence.
- Serum thyroglobulin levels should be obtained following surgical treatment (at least one month after surgery) to help with risk stratification. A second post-treatment Tg level should be obtained following definitive treatment with RAI, to identify initial response to treatment. Thyroglobulin and TgAb levels should be obtained during routine annual surveillance. (ATA Recommendation 62)
  - Thyroglobulin doubling time is useful for following the doubling time of a thyroid cancer. Serial measurements in cases of persistent or recurrent disease will help guide appropriate therapy, including active surveillance for slow-growing tumours. [93, 112, 114]
  - Patients who undergo a thyroid lobectomy alone may be followed with periodic measurements of thyroglobulin and thyroglobulin antibodies. A significant increase in Tg/TgAb over time may indicate recurrent or metastatic disease.
- Various thyroglobulin assays are available, but all assays must concurrently report the level of anti-thyroglobulin antibody (TgAb), which will interfere with the detection of thyroglobulin. [115, 116]
  - Although any specific testing platform will have excellent reproducibility, there is considerable inter-test variability because each platform detects a different epitope of Tg.
  - To longitudinally follow a specific patient's Tg and TgAb, testing should ideally be performed at the same lab using the same or comparable assay platform.
- High-sensitivity thyroglobulin assays detect Tg as low as <0.2 ng/mL, generally do not require the use of TSH-stimulation (thyroid hormone withdrawal or rhTSH-stimulation) to detect the presence of low-volume disease. [116]

9.2   Post-Treatment Imaging

- <u>Ultrasound</u>: Recommended at 6 months after definitive treatment, in patients with elevated post-operative Tg levels (Tg >0.2 ng/ml after surgery, but prior to RAI). See CCO guidelines and Table 4.
- <u>Diagnostic whole-body RAI scan (WBS)</u>
  - A post-treatment WBS is recommended after RAI ablation or therapy to inform disease staging and document the RAI avidity of any structural disease. (ATA Recommendation 58).
    - The typical timing for post-treatment WBS is 2-7days after RAI administration.
    - The addition of a SPECT/CT allows for better anatomic detail to determine areas of RAI-avidity, and improves the diagnostic accuracy of WBS. [97, 98]
- <u>Computed Tomography (CT)</u>
  - For patients in the "highest risk" category, a post-treatment baseline CT of the neck and thorax should be obtained if not previously done during the pre-operative workup.
  - The post-treatment CT is performed after the post-treatment RAI WBS, and repeated at 6 months if there are positive findings.
  - If the 6-month post-treatment CT demonstrates persistent micro-metastatic pulmonary disease, the patient should be considered for a second treatment with RAI. (ATA Recommendation 77)
- <u>18-FDG PET/CT</u>
  - Although not routinely used in thyroid cancer, patients with rising thyroglobulin levels (>10 ng/ml) but with negative imaging findings should have further evaluation with PET/CT.
    - As DTC dedifferentiates, cancer cells begin to lose the ability to concentrate RAI.
    - Dedifferentiated DTC is more aggressive with an associated increase in the metabolic activity of these cells.
    - FDG PET/CT may be useful in the initial staging after surgery for poorly differentiated thyroid cancer as well as oncocytic (Hürthle cell) thyroid carcinoma, as these tumours are less likely to be RAI-avid and RAI WBS may miss locoregional and distant metastatic sites. [4, 5, 51, 52]

- o FDG-avidity is a major predictor for RAI-resistance. It is also an independent negative prognostic factor for survival. [5]
- See CCO guidelines and Table 4.

9.3 Dynamic Risk Stratification

- The 2015 ATA guidelines propose the use of a continuous dynamic, real-time model of "risk of recurrence as a continuum", which is designed to provide more individualized recurrence risk estimates based on response to therapy, followed throughout a patient's surveillance.
  - o The dynamic risk stratification looks at evidence of disease recurrence based on imaging and thyroglobulin levels to categorize patients into one of 4 categories, with correlations to the clinical outcomes of patients within each group. [5, 93, 117, 118] (ATA Recommendation 49)
    1. **Excellent response**: Suppressed Tg <0.2ng/ml and negative imaging.
       - 1-4% risk of recurrence
       - <1% disease-specific death
    2. **Biochemical incomplete response:** Abnormal thyroglobulin levels (suppressed Tg >1ng/ml) or rising anti-thyroglobulin levels in the absence of structural disease on ultrasound imaging.
       - 30% spontaneously achieve NED; 20% achieve NED after additional therapy.
       - 20% develop structural disease
       - <1% disease-specific death
    3. **Structural incomplete response**: Persistent or newly identified locoregional disease or distant disease.
       - 50%-85% continue to have persistent disease despite additional therapy
       - Disease-specific death rates as high as 11% with loco-regional metastases and 50% with structural distant disease.
    4. **Indeterminate response:** Non-specific ultrasound findings and/or suppressed Tg detectable but <1ng/ml, stable anti-thyroglobulin levels.
       - 15%-20% will have structural disease identified during follow-up, the remainder will either resolve or remain stable.
       - <1% disease-specific death

9.4 Follow-up

- According to the CCO DTC Treatment Pathway, patients at low and intermediate risk should be followed by their thyroid treatment team with surveillance every 1-2 years for 5 years, while high risk patients should be followed annually for at least 10 years. [10]
  - o After 5 (or 10) years, surveillance can be transitioned to the patient's primary care physician if there is no evidence of disease recurrence.

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