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Thyroid Follicular Epithelial Cell-Derived Cancer: New Approaches and Treatment Strategies

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Brief Title: Thyroid Follicular Epithelial Cell-Derived Cancer

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Abstract:

Thyroid follicular epithelial cell-derived cancer includes papillary carcinoma, follicular carcinoma, Hurthle cell carcinoma, poorly differentiated thyroid cancer, and anaplastic thyroid carcinoma. Although thyroid cancer incidence has increased over the past thirty years, there has not been a significant increase in patient mortality. Utilization of increasingly sensitive detection methods such as high resolution imaging have enabled earlier detection and better characterization of the thyroid malignancies. In the past several years, researchers have evaluated genetic mutations promoting thyroid carcinogenesis and oncogenesis. The identification of genetic mutations is not only important in understanding tumor initiation and progression but also serve as potential diagnostic or prognostic indicators and therapeutic molecular targets.

Key Words: ATC- anaplastic thyroid carcinoma, FTC- follicular thyroid carcinoma, PTC- papillary thyroid carcinoma, MAPK- mitogen activated protein kinase

Definitions:

Differentiation- The process by which a cell becomes specialized in order to perform a specific function.

Dedifferentiation- The process by which cells regress from a specialized function to a simpler state within the same lineage.

De novo- From the beginning. In terms of cancer, it describes the first occurrence of cancer in the body.

Driver mutation- Provides a selective growth advantage by disrupting signaling, regulatory or metabolic pathways that promote carcinogenesis

Microcarcinoma- Tumors with less than 1 cm diameter.

Mitotic rate- The number of cells in mitosis in each microscopic high-power field per tissue sections.

Nuclear pleomorphism- Variability in the size, shape and staining of cells and/or their nuclei.

Oncogene- Genes that have the potential to cause cancer.

Proto-oncogenes- Genes that normally participate in cell growth, however when mutated become oncogenes.

Receptor tyrosine kinase- A type of cell-surface receptor that mediates cell to cell communication.

Thyroid cancer is the 12th most common type of cancer in the United States. According to the National Cancer Institute, over 850,000 people were living with thyroid cancer in the United States in 2017, and it is estimated that there will be 52,890 new cases of thyroid cancer in 2020 (*1*). Women are disproportionately affected across all age groups, with thyroid cancer incidence being three times more common in women than men. Thyroid cancer is more common in adults over 30 years, with peak incidence for women in their 40s-50s and men in their 60s-70s (*2*). Thyroid cancer rarely affects children and adolescents; however it accounts for 1.4% of pediatric malignancies (*3*). The incidence of thyroid cancer has also increased worldwide, but may be variable due to healthcare access, use of population-level screening, ethnic/racial differences, exposure to ionizing radiation, and iodine intake excess or deficiency (*4*, *5*). The rise in thyroid carcinoma incidence, particularly small papillary carcinomas, is largely due to the utilization of increasingly sensitive detection methods such as high resolution imaging and ultrasensitive thyroglobulin assays which allow for the detection of previously undetectable thyroid cancers (*6*, 7, *8*). Improved technology has not only allowed for an earlier detection of small carcinomas, but also a better characterization of the lesions prompting revisions in clinical management.

The Basics

Thyroid cancer includes six main types: papillary, follicular, Hurthle cell, medullary, poorly differentiated, and anaplastic. Clinicians often categorize the six main types of thyroid cancer based on the origination cell type (follicular epithelial cell vs. parafollicular C cell) and preservation of cell type (differentiated, poorly differentiated, undifferentiated) as these characteristics relate to diagnosis, prognosis, and treatment (*8*). Follicular cells, also called

thyroid epithelial cells or thyrocytes, line the colloid follicles and concentrate iodine for thyroid hormone synthesis. These cells give rise to papillary, follicular, Hurthle cell, poorly differentiated, and anaplastic thyroid cancers (*9*). The parafollicular or C cells are neuroendocrine cells that are scattered throughout the thyroid follicles and are responsible for the synthesis, storage, and secretion of calcitonin. Parafollicular cells give rise to medullary thyroid cancer (*9*). This continuing education article will only focus on follicular epithelial cell-derived thyroid cancers which include papillary, follicular, Hurthle cell, poorly differentiated, and anaplastic carcinomas.

Preservation of Cell Type

Differentiated thyroid cancer represents the majority (90-95%) of all types of thyroid cancers and includes papillary, follicular, and Hurthle cell carcinomas (*6*). Cellular differentiation is a central aspect in the histopathological classification for thyroid follicular epithelial cell-derived cancers and refers to the process by which a cell becomes specialized in order to perform a specific function. Differentiated thyroid cancers maintain the characteristics and behavior of normal follicular epithelial cells in thyroid tissue. These cells retain many of the physiological functions of thyroid cells, including thyroid stimulating hormone (TSH, also called thyrotropin) stimulation of growth, iodine uptake (expression of sodium iodine symporter), and thyroid hormone production (*9*). Differentiated thyroid cancers maintain radioiodine avidity which permits the utilization of radioiodine scintigraphy and treatment as part of the disease management strategy. As a general rule, differentiated cancers tend to be less aggressive than undifferentiated cancers (*9*).

Poorly differentiated thyroid cancer (PDTC) was at one time considered a variant of differentiated thyroid cancer, however the World Health Organization began recognizing it as a distinct pathologic entity in 2004 because the clinical and histological features occupy an intermediate position between differentiated thyroid cancer and undifferentiated thyroid cancer (*10*, *11*, *12*, *13*). PDTC occurs de novo; however, there is also a theory that PDTC may also transform from differentiated thyroid cancers through the accumulation of genetic abnormalities (*11*, *14*). This theory is supported by the frequent co-occurrence of PDTC and differentiated thyroid cancer in the same tumor specimen and the overlap of genetic mutations (*11*). When PDTC and well differentiated thyroid cancer are present in the same tissue sample, it is important to note the presence of PDTC as prognosis and treatment strategies may be guided by the PDTC component (*10*). Given that poorly differentiated thyroid cancers are often resistant to radioiodine therapy, these cancers present a therapeutic challenge (*11*, *12*). Outcome statistics for poorly differentiated thyroid cancers are worse than differentiated thyroid cancers. In poorly differentiated thyroid cancers, approximately 50% of patients survive after ten years, whereas with differentiated thyroid cancers, particularly papillary thyroid carcinoma (PTC), 95% of patients survive after ten years (*13*).

Undifferentiated thyroid cancer includes anaplastic thyroid carcinoma (ATC), a very rare form of thyroid carcinoma accounting for <1% of all thyroid carcinomas (*15*). Undifferentiated thyroid cancer may occur de novo or may transform from a previously differentiated thyroid cancer (more commonly papillary thyroid carcinoma, but also follicular thyroid carcinoma and poorly differentiated thyroid cancer) (*12*, *14*). A signature attribute of many advanced tumors is cellular dedifferentiation, whereby cancerous cells maintain little to no resemblance to the

normal cells from which the cancer originated. In the context of thyroid cancer, loss of radioiodine avidity most commonly develops from cellular dedifferentiation resulting in the impairment of the sodium iodine symporter function (*14*, *15*). Loss of iodine avidity excludes the use of radioiodine (RAI) scintigraphy and treatment. It is important to note that as thyroid cancer cells dedifferentiate, their glucose metabolism increases, allowing for evaluation with 18F-FDG PET/CT (*16*). Overall outcomes and survival statistics are poor for undifferentiated thyroid cancer, with a mean survival of 0.5 years after diagnosis (*15*).

Figure 1: Cellular differentiation and diagnostic/prognostic implications

This figure illustrates the cellular differentiation stage for follicular epithelial derived thyroid carcinomas and how it relates to radioiodine scintigraphy/treatment and overall prognosis.

Overview of Follicular Epithelial Cell-Derived Thyroid Cancers

Papillary thyroid carcinoma (PTC) overview

Papillary thyroid carcinoma (PTC) is the most commonly occurring form of differentiated thyroid cancer and accounts for 80-85% of all thyroid cancer (*17*). Patients are often asymptomatic, but may have cervical lymphadenopathy, hoarseness, and dysphagia. Risk factors for PTC include radiation exposure, particularly during childhood, family history of thyroid malignancy, and inherited conditions such as familial adenomatous polyposis or Cowden's syndrome (*18*). PTC most often affects middle-aged females. Thyroid carcinoma accounts for 1.4% of pediatric malignancies, with PTC being the most common thyroid carcinoma affecting children (*3*).

In 2017, the World Health Organization recognized 15 histological subtypes of papillary thyroid carcinoma: conventional/classic; papillary microcarcinoma (<1 cm in diameter); encapsulated; follicular; diffuse sclerosing; tall cell; columnar cell; cribriform-morular; hobnail; papillary thyroid carcinoma with fibromatosis/fascitiis-like stroma; oncocytic; solid/trabecular; spindle cell; clear cell; and warthin like variant (*12*, *13*). Conventional/classic, papillary microcarcinoma, encapsulated, follicular, diffuse sclerosing, and tall cell are the most common and well documented histological subtypes (*12*, *13*). As histological subtypes relate to biological aggressiveness and prognosis, these distinctions are valuable in terms of disease management strategies and recommendations. The papillary microcarcinoma and encapsulated variants are considered the least biologically aggressive. The tall cell and hobnail variants have the potential to be more aggressive than the conventional/classic variant and as a result, patients with these tumors may require a more aggressive disease management strategy than are those with conventional/classic papillary cancer of the same stage (*12*).

In addition to the histological subtype, PTC tumors range in size and extent of the primary lesion (*17*). While there may be microcarcinomas (< 1cm diameter) and intrathyroidal lesions (>1.5 cm diameter) that are confined to the thyroid capsule, it is not uncommon for patients to have multifocal disease, extrathyroidal extension, and cervical lymph node metastasis (*17*). Up to 27% of patients have cervical lymph metastasis at initial presentation (*17*). Children more commonly present with lymph node involvement or metastasis to distant sites such as the lungs when compared to the adult population (*3*). Overall, patients with PTC typically have a good prognosis. Increased risk for recurrence or poor prognosis is often related

to age (persons >55 years of age at diagnosis), increased vascular invasion, invasion into the adjacent neck structures, and distant metastasis (*17*).

Follicular thyroid carcinoma (FTC) overview

Follicular thyroid carcinoma (FTC) is the second most common type of thyroid cancer after PTC and accounts for 10% of differentiated thyroid cancers (*19*). Unlike PTC, FTC is rarely associated with previous radiation exposure, but may be associated with iodine deficiency. FTC typically occurs in a slightly older age group than PTC (40-60 years) and is also less common in pediatrics (*20*). Minimally invasive FTC is limited to microscopic capsular and/or vascular invasion, whereas widely invasive tumors may have multiple foci and extensive, widespread invasion (*21*). Given that vascular invasion is commonly found with FTC, metastatic disease may be noted even when the primary thyroid lesion is small. Distant metastatic spread to the lungs or bones is more commonly found with FTC than PTC (*19*, *20*, *21*). Poor prognosis is often related to tumor size, degree of vascular and capsular invasion, and age (*20*).

Hurthle cell carcinoma (HCC) overview

Hurthle cell carcinoma (HCC) accounts for 3% of all thyroid cancers. Previously, Hurthle cell carcinoma was classified as an oxyphilic variant of follicular thyroid carcinoma (FTC); however, data from genetic and molecular analysis suggest that HCC is a distinct entity (*22*, *23*). Just as with FTC, HCC occurs in a slightly older age group than PTC. Unlike FTC, HCC has more of a propensity to spread to cervical lymph nodes and has a higher risk distant metastatic disease, particularly skeletal and pulmonary metastasis (*24*). Another important distinction relevant for

patient management is that while metastatic lesions in follicular thyroid carcinoma often concentrate radioactive iodine, HCC metastatic foci are often radioactive iodine refractory (*23*, *25*).

Poorly differentiated thyroid cancer (PDTC) overview

Poorly differentiated thyroid cancer has not been studied as commonly as other follicular epithelial-derived thyroid cancers partly due to its overall rarity, but also because it was not classified as an independent thyroid cancer histotype until 2004 (*11*). Determination for PDTC by the Turin proposal includes carcinoma of follicular cell derivation, architectural patterns (solid/trabecular/insular architecture), as well as high-grade features such as nuclear pleomorphism, tumor necrosis, and/or high mitotic rate (*11*, *12*, *13, 14*). PDTC more commonly occurs in females 60-70 years of age and is associated with aggressive characteristics such as extrathyroidal extension, regional lymph node metastasis, and distant metastasis. Just as with other forms of follicular epithelial cell-derived thyroid cancers, the most common sites of distant metastasis include the lungs and bones; however, less common metastatic sites also include the liver, skin, ovaries, and retroperitoneal space (*11*). Despite the fact that poorly differentiated thyroid cancer accounts for only 4-7% of all thyroid cancers, it represents the main cause of death from non-anaplastic follicular cell-derived thyroid cancer (*11*).

Anaplastic thyroid carcinoma (ATC) overview

Anaplastic thyroid carcinoma (ATC) is the most aggressive and rarest thyroid cancer. Despite that ATC only accounts for 1-2% of all thyroid cancer incidences, it is responsible for

14%-39% of deaths related to thyroid malignancy (*26*). ATC occurs primarily in the geriatric population and is more common in persons 60-70 years of age. Patients with ATC often have a large, palpable thyroid mass associated with hoarseness, dyspnea, dysphagia, and vocal cord paralysis (*26*). The extent of disease may be restricted to the neck region or include distant metastasis to the lungs, bone, or brain. Although ATC may develop as a singular entity, it may also evolve from or coexist with differentiated thyroid cancer (*12*, *13*, *26*). Given that ATC is a type of undifferentiated thyroid cancer, these cells will not maintain the characteristics and behavior of normal follicular epithelial cells and thus will not concentrate radioiodine.

Genetic Changes Involved in Thyroid Carcinogenesis

TABLE 1: Genetic abbreviations

This table will define abbreviations that will be used in the genetics of thyroid carcinogenesis discussion.

Mitogen Activated Protein Kinase (MAPK) Pathway

In recent years, there have been multiple studies evaluating the genetic alterations and molecular mechanisms underlying thyroid carcinogenesis and their prevalence in follicular epithelial cell-derived thyroid carcinomas. An understanding of these mutations may explain the diverse clinical characteristics of thyroid follicular epithelial-derived carcinomas and provide diagnostic information relative to treatment. Mutations in both oncogenes and tumor suppressor genes acquired along the path of tumor progression allow cancerous cells to evade the normal control of cell cycle and apoptotic processes and promote the transition from localized to metastatic disease. Oncogenic activation of the mitogen activated protein kinase

(MAPK) is considered the most common molecular alterations in thyroid cancer and is believed to initiate carcinogenesis (*6*). The MAPK pathway is a key molecular signaling pathway responsible for the regulation of several diverse cellular functions including cellular growth, proliferation, and angiogenesis. In the normal functioning cell, the MAPK pathway is triggered by the binding and activation of receptor tyrosine kinases (RTKs) which transmit growth signals from the plasma membrane to the nucleus (*6*). Oncogenic alterations in the MAPK pathway influence processes that are crutial for cancer development and progression. In oncogenic cells, the MAPK pathway is driven by mutations including *RET*/*PTC*, *RAS*, and *BRAF* (*6*). These "driver mutations" are initiating mutations and occur early in thyroid carcinogenesis (*14*).

RET/PTC rearrangements

RET proto-oncogene rearrangements are most commonly found in papillary thyroid carcinoma (termed *RET/PTC* rearrangements) and leads to the constitutive activation of the RET tyrosine kinase domain and subsequent activation of the MAPK signaling pathway (*27*). *RET*/*PTC* rearrangements are found in 20 to 70% of PTCs and more commonly associated with pediatric thyroid cancers (*27*). Although 13 *RET*/*PTC* rearrangements have been found, *RET/PTC1* and *RET/PTC3* are most common. *RET/PTC1* is more prevalent in sporadic PTC and *RET/PTC3* is highly prevalent in radiation induced PTC. *RET*/*PTC* rearrangements are also found in the follicular variant of PTC (PTC-FV) and in FTC (*15*). The prognostic significance of *RET*/*PTC* rearrangements is not fully established. *RET*/*PTC1* does not correlate with clinical pathological features of PTC; however *RET*/*PTC3* is associated with aggressive characteristics and poor

prognostic factors including greater primary tumor size, cellular variations, and a more advanced stage at diagnosis (*15*, *27*).

***RAS* mutations**

The *RAS* oncogene mutations play an important role in thyroid oncogenesis through the regulation of two important signaling pathways; the MAPK cascade, which is responsible for cellular proliferation; and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway, which is important for cell survival (see figure 2) (*6*, *15*). Oncogene activation in the three *RAS* proto-oncogenes (*HRAS*, *KRAS*, and *NRAS*) is found in most human cancers, including thyroid cancer. *RAS* mutations occur in almost every type of thyroid cancer and in benign follicular adenomas: 20-25% of benign follicular adenomas, 10-20% of papillary thyroid carcinoma (PTC), 30–45 % follicular variant papillary thyroid cancer (PTC-FV), 30-35% of follicular thyroid carcinoma (FTC), 20-40% of poorly differentiated thyroid cancers, 10–20 % anaplastic thyroid cancer (ATC) (*9*, *28*). *RAS* mutation alone is most likely associated with limited aggressiveness of thyroid cancer; however, *RAS* may coexist with other mutations such as telomerase reverse transcriptase (*TERT*) promoter or phosphatase and tensin homolog (*PTEN*), both of which have been implicated in aggressive clinicopathological behavior (*28*, *29*).

***BRAF* mutations**

While greater than forty point mutations have been documented in *BRAF*, the most frequent mutation is *T1799A BRAF* resulting in V600E protein kinase (*6*). *BRAF* V600E is exclusive to PTC, PTC derived poorly differentiated thyroid cancer, and anaplastic thyroid carcinoma. The *BRAF* V600E mutation occurs in about 40-45% of all PTC and in about 60% of

BRAF- associated PTCs (*30*). *BRAF* V600E mutations are noted in the potentially more aggressive PTC variants including multinodular/diffuse forms of PTC-FV (*15*). *BRAF* V600E mutation causes constitutive activation of the BRAF kinase and MAPK signaling pathway and has been associated with aggressive clinicopathological features including extrathyroidal invasion, lymph node metastasis, vascular invasion, and advanced tumor stage in the primary tumor (*15*). In *BRAF*-associated PTC, both vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) are upregulated (*31*, *32*). Vascular endothelial growth factor and platelet derived growth factor are potent stimulators of angiogenesis, a process that is vital to carcinogenesis. *BRAF* mutations have also been implicated in the loss of cellular differentiation resulting in decreased expression of sodium iodide symporter, TSH receptor, and thyroglobulin, thereby creating a situation for iodine refractory disease (*6*, *9*, *14*). Although *BRAF* mutations have been implicated in aggressive behavior, there is no clear consensus. Frequently, classic PTC and papillary microcarcinomas (mPTC) have associated *BRAF* mutations. Despite these mutations, classic PTC and papillary microcarcinomas maintain an excellent prognosis. Isolated *BRAF* mutations may not substantially contribute to risk stratification and increased specific disease mortality. Cancer evolution is triggered by the sequential accumulation of mutations that bestow metastatic potential. *BRAF* mutations are frequently associated with *TERT* promoter mutations. Thyroid cancers displaying both *BRAF* V600E and *TERT* promoter mutations exhibit more aggressive clinicopathologic behavior than in thyroid cancers displaying only *BRAF* mutations (*29*).

Non-MAPK Genetic Mutations

TERT promoter mutations

A genetic alteration in the human telomerase reverse transcriptase promoter (hTERTp, encoded by *TERT*), has been associated with increased aggressiveness and poor patient prognosis. Telomerase is the enzyme involved in telomere elongation, whose main function is preservation of chromosome integrity and genomic stability. Telomeres are repetitive DNA sequences at the ends of chromosomes acting as protective caps. Telomeres are continually shortened with each successive generation. When telomeres reach a critically short length, the chromosomes participate in "breakage-fusion-breakage" cycles resulting in cell crisis and apoptosis (*29*). Therefore, telomeres only allow a cell to replicate a certain number of times. Since cancer cells seek to grow at an unconstrained rate, the shortened telomeres and subsequently restricted replication present a significant problem. In cancer cells, telomere length is maintained by telomerase, which functions to elongate telomeric DNA by utilizing its two components; an RNA template and a reverse transcriptase (*29*). Mutations in *TERT* are sufficient to restore the activity of the telomerase complex (*15*). Most adult, differentiated cells do not express or have very low expression of telomerase; however telomerase is significantly expressed in 90% of human cancers including differentiated, poorly differentiated, and undifferentiated thyroid cancers (*29*). By expressing higher levels of reverse transcriptase, and therefore allowing for increased telomerase activity, carcinoma cells prevent critically short telomeres and apoptosis, meaning the oncogenic changes bestow an extended life or immortality.

Independent of its function in telomere length maintenance*, TERT* mutations have also been associated with metastatic capability and cellular dedifferentiation (*15*, *29*). Studies have indicated that *TERT* may encourage metastasis through the activation of the epithelial-mesenchymal transition. The epithelial mesenchymal transition is a process where epithelial cells lose their normal characteristics such as intercellular adhesion and lack of motility and acquire mesenchymal cell properties such as reduced intercellular adhesion, increased motility, invasiveness, and apoptosis resistance (*29*). Activation of the epithelial-mesenchymal transition process is triggered by various stimuli resulting in the silencing of intracellular adhesion molecules such as epithelial cadherin and the upregulation genes promoting the mesenchymal shift (*29*). The epithelial-mesenchymal transition is also suggested to promote the dedifferentiation process resulting in poorly differentiated or undifferentiated cancers (*29*).

***Tp53* mutation**

Alterations in several tumor suppressor genes have been associated with thyroid oncogenesis, but the most widely studied is the tumor protein (*Tp53)* gene. P53 is key tumor suppressor protein known as the "guardian of the genome" because of its functions in maintaining genomic integrity through control of cell division, apoptosis, DNA repair, and angiogenesis (*15*). Cancer cells with a *Tp53* mutation have evolved the ability to bypass the cell cycle checkpoints, favor anti-apoptotic pathways, and proliferate uncontrollably. The amount of p53 in normal cells is maintained at a very low level; however *Tp53* mutations and p53 over-expression are frequent in several human cancers and occur in well differentiated thyroid cancers (40% of PTCs and in 22% of oncocytic FTCs) as well as in a high proportion of poorly differentiated thyroid cancers and ATCs (particularly those originating from PTC), which

indicates that *Tp53* mutations promote the transition from differentiated to undifferentiated thyroid cancer (*15*). *Tp53* mutations are most noted in the later stages of oncogenesis and occur simultaneously with a substantial increase in cellular proliferation (*15*). *Tp53* mutations have been noted in cancers with *BRAF* mutations and *RET*/PTC rearrangements and are believed to promote extrathyroidal extension and distant metastasis (*15*).

Figure 2: Thyroid cancer pathways

"This image was originally published in The Lancet. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet. 2016;388:2783-95 © by Elsevier https://www-sciencedirect-com.ezlib.gatewaycc.edu/science/article/pii/S0140673616301726?via%3Dihub."

This figure illustrates key molecular signaling pathways involved in thyroid cancer initiation and progression. The left box shows the mitogen activated protein kinase (MAPK) pathway which is activated by mutations in *RET*, *RAS*, and *BRAF*. The box on the right shows the pathways involved in tumor progression, including PI3K/AKT, p53 tumor suppressor, and *TERT*. The blue boxes represent molecular targets for therapies approved by the US Food and Drug Administration.

AKT= Protein kinase B

ERK = extracellular-signal-regulated kinase

MEK= mitogen/extracellular signal-regulated kinase

mTOR = mammalian target of rapamycin

PI3K = phosphatidylinositol-3-kinase

p53= TP53 or tumor protein

RAF= rapidly accelerated fibrosarcoma

RAS= rat sarcoma point mutations

RET= rearrangement during transfection

TERT= Telomerase reverse transcriptase

TABLE 2: Summary of genetic mutations and associated prognostic significance

This table will review genetic mutations associated with thyroid carcinogenesis.

Assessment and Treatment

Thyroid cancers of follicular epithelial cell origin exhibit highly variable clinical manifestation including microcarcinomas with very low tumor-specific morbidity or mortality to very aggressive thyroid carcinomas such as anaplastic carcinoma. Diagnostic workup and standard treatments such as the use of surgery, radioactive iodine (RAI) therapy, and thyrotropin suppression therapy are individualized to the patient and the clinical objectives. Despite the increased incidence of thyroid carcinoma in the past 30 years, there has not been a substantial increase in mortality (*6*, *7*, *33*). This has sparked a discussion in the medical community about the potential for "over diagnosis and treatment". In 2015, American Thyroid Association (ATA) guidelines for medical management of adult patients with thyroid nodules and differentiated thyroid cancer emphasized a distinction between low risk and high risk patient groups where physicians identify patients requiring more aggressive treatment while sparing patients with low risk from unnecessary diagnostic procedures and treatments (*33*). It is important to note that the 2015 ATA guidelines are not inclusive of all proper approaches or methods and were met with controversy in the medical community. In 2018, the Martinique Working Group (MWG) composed of representatives from the ATA, the European Association of Nuclear Medicine (EANM), the European Thyroid Association (ETA), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) published an authoritative report called "The Martinique Principles" which highlighted controversies in the medical management of

thyroid cancer (*34*). Although this essay will not highlight the spectrum of expert opinions presented by members of the Martinique Working Group, it should be stated that there is still debate within the medical community regarding disease management strategies.

Treatment decisions for patients with differentiated thyroid cancer are based on strategies for risk assessment that consider symptom manifestation, histology, tumor size, tumor invasiveness, lymph node involvement, distant metastasis, and diagnostic imaging. Cervical lymph node sonography, which provides information on the size, number, and location of thyroid lesions, vascularity, lymph node involvement, and adjacent tissue invasion is widely used as the primary imaging tool when determining surgery and treatment options (*6*). The 2015 ATA guidelines recommend preoperative sonography for patients undergoing surgery for confirmed or suspected thyroid malignancy (*33*). Preoperative cervical lymph node sonography identifies 20-30% of suspicious lymph nodes which may change the surgical plan and allow for a more complete initial surgical dissection (*6*, *33*). For patients with papillary microcarcinomas 1 cm or smaller and with no evidence of lymph node metastasis, non-surgical management may be possible (*6*, *7*, *33*). If surgery is indicated, a hemithyroidectomy is potentially an option for unifocal tumors <4cm and with no evidence of lymph node metastasis or invasion into adjacent neck structures; however, a total thyroidectomy may be indicated if the disease management team believes RAI therapy will be utilized and when structural changes dictate surgical preferences (*6*, *7*, *33*).

In addition to sonography, 2015 ATA guidelines advocate for the pre-surgical use of cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) when there is sonographic evidence for extrathyroidal extension, significant cervical

lymphadenopathy, tumor adherence to neck structures, or patient symptoms such as hoarseness and dysphagia, as these situations are potentially "high risk" (*33*). Use of iodinated contrast in these patients may delay radioactive iodine (RAI) imaging and therapy for several months; however, the complete surgical excision of all thyroid tissue and locoregional metastasis is a critical element in patient management (*33*). Rarely, additional preoperative imaging is required for differentiated thyroid cancer, unless there is suspicion for widespread or distant metastasis. 18F-FDG PET/CT may be indicated for initial staging in these cases, but is more commonly utilized for postsurgical evaluation in RAI refractory disease (*5*).

After surgery the disease management team will determine the need for radioiodine ablation or thyrotropin suppression therapy, or both. The 2015 ATA guidelines identify high, intermediate, and low risk for thyroid cancer recurrence and include clinical symptoms, post-surgical thyroglobulin levels, and pathological features in the determination of risk of recurrence (*6*). The extent of surgery will influence the acceptable ranges for thyroglobulin as patients who had a hemithyroidectomy will have a higher thyroglobulin level because of the remaining thyroid tissue, which is likely benign (*7*).

Thyroid hormone suppression therapy, also known as thyrotropin suppression therapy (TST)

In patients who have had a partial or total thyroidectomy, thyroid hormone replacement may be utilized not only to replace endogenous thyroid hormone, but also to inhibit tumor progression or recurrence because TSH (also called thyrotropin) encourages cellular proliferation in differentiated thyroid cancer cells. Thyrotropin suppression therapy significantly reduces recurrence and thyroid cancer related mortality (*6*, *35*). The goal of

thyrotropin suppression therapy is to reduce TSH to below the normal range (normal= 0.4-4.5 mIU/L). The appropriate TSH concentration as determined by the disease management team may be variable between patients given the extent of surgery and distinction between low risk and high risk status. Reducing TSH concentrations to 0.1 mIU/L can improve outcomes for high risk patients; however, this requires doses of thyroid hormone replacement that may induce subclinical hyperthyroidism (*6*). Potential adverse effects include osteoporosis in postmenopausal women, angina, and atrial fibrillation (*6*). In patients with low risk thyroid cancer, a more conservative approach with the goal of thyroid hormone replacement therapy to maintain TSH at or slightly below the lower limit of normal (0.1-0.5 mIU/L) may be appropriate (*35*). Patients who undergo a lobectomy instead of total thyroidectomy may not require thyrotropin suppression therapy if their TSH serum levels are maintained at the lower limit of normal (0.5–2.0 mIU/L) (*35*).

Figure 3: Thyroid hormone synthesis negative feedback loop

TRH- Thyrotropin releasing hormone

TSH- Thyroid stimulating hormone (Thyrotropin)

T4- Tetraiodothyronine (Thyroxine)

T3- Triiodothyronine

Blue arrow with blue plus sign indicates stimulation

Orange arrow with negative sign indicates inhibition

This figure illustrates the negative feedback loop for thyroid hormone synthesis. The hypothalamic-pituitary axis regulates TSH release through a negative feedback loop. TRH stimulates anterior pituitary thyrotrophs to secrete thyroid stimulating hormone (TSH). When TSH binds to the TSH receptor on thyroid follicular cells, it stimulates iodine uptake, thyroid hormone (T3, T4) secretion, and thyroid gland

growth and differentiation. Of the thyroid hormones released, approximately 80% is in the form of T4 and 20% in the form of T3 (*36*). T3 has a short half-life but is most active on the nuclear receptor, whereas T4 has a long half-life but is less active in binding to the nuclear receptor. Because T4 becomes de-iodinated and converted into T3 by most tissues (especially the liver and kidneys), T4 acts as a reservoir for T3 (*36*). Serum levels of thyroid hormone exert negative feedback control on TRH and TSH. High thyroid hormone levels decrease TSH secretion whereas low thyroid hormone levels stimulate TSH synthesis and secretion. As this relates to thyroid cancer, patients who have had a total thyroidectomy require thyrotropin suppression therapy (TST) for two reasons: 1) replace endogenous thyroid hormone and 2) suppress TSH. TSH suppression is an important aspect of treatment because TSH may stimulate cellular proliferation in differentiated thyroid cancer cells.

Radioactive iodine (RAI) therapy

In previous years, many clinicians routinely recommended RAI therapy for all patients with differentiated thyroid cancer, except in patients with papillary microcarcinoma. However, the 2015 ATA guidelines propose a more conservative approach based on specific histopathological features that could modulate risk of recurrence or disease-specific mortality, disease follow-up implications, potential adverse effects, and physician and patient preferences (*6*, *7*, *33*). The goals of RAI therapy are remnant ablation, adjuvant therapy, and treatment of known residual or recurrent disease.

Remnant ablation eliminates residual clusters of presumably normal or benign thyroid tissue, which incorporates iodine and produces thyroglobulin, thereby complicating efforts to use thyroglobulin serum assays and RAI scintigraphy to identify persistent disease or recurrence (*6*). Potential benefits to remnant ablation include improved initial staging and the clinical utilization of RAI whole body scintigraphy and thyroglobulin serum assays as a follow-up for cancer recurrence. However, use of RAI whole body scintigraphy is not utilized as commonly as

it once was because of the increased sensitivity of cervical lymph node sonography (*6*). Cervical lymph node sonography is cheaper by comparison, more widely available, has no associated radiation exposure, no potential side effects, and does not require discontinuation of thyroid hormone replacement therapy or use of thyrotropin alpha injections (*6*). Cervical lymph node sonography combined with post-operative serum thyroglobulin (either with the patient taking thyroid hormone replacement or after TSH stimulation) are very sensitive methods for detecting persistent disease or thyroid remnant, predicting potential for disease recurrence, and tailoring future diagnostic and therapeutic approaches (*6*, *33*). Post-operative whole body RAI scintigraphy may still be indicated when the extent of thyroid remnant or residual disease cannot be accurately determined from cervical lymph node sonography and surgical reports or when the results of the whole body RAI scintigraphy may alter treatment decisions. If remnant ablation is deemed appropriate for low-intermediate risk patients, lower dose ranges for I-131 NaI (1110 MBq or 30 mCi) may be preferred over high doses depending on the size of the remnant (*7*, *33*).

Use of RAI for initial adjuvant therapy destroys microscopic foci that may or may not be present in the thyroid remnant or elsewhere in the body following surgical resection. The goals of adjuvant therapy are to reduce the risk disease recurrence and improve long-term outcomes. Given that patients are selected for adjuvant therapy in regards to risk of recurrence instead of known disease, some patients who receive adjuvant therapy may have been adequately treated by their primary surgery (*34*). For patient selection and RAI dose determination, clinicians evaluate several factors such as the likelihood of improved clinical outcomes, potential side effects, results of post-surgical follow up RAI scintigraphy, thyroglobulin assays, the extent of

thyroid surgery, and the preferences of the patient and disease management team (*34*). If RAI is indicated as adjuvant therapy for patients without known distant metastasis, a dose range of up to 5,550 MBq (150 mCi) is generally recommended, but should be tailored to the specific patient based on individual risk, the lowest activity needed for effective treatment, and specific recommendations from the disease management team (*33*).

The third use for RAI therapy is for patients with known iodine avid metastatic disease and/or for recurrence. Typical doses are 3,700-7,400 MBq (100-200 mCi) and may be determined based on observations and experiences of the disease management team or estimated by dosimetry with the goal of limiting excess radiation exposure to the bone marrow and avoiding hematopoietic toxicities (*7*, *33*). Just as with adjuvant RAI therapy, there may be multiple factors which account for the determined dose. Dose related impairment of testicular function and transient ovarian failure have been observed following RAI therapy. General recommendations include avoidance of pregnancy for at least 6 months post treatment or for longer if additional RAI therapy may be indicated. For men who may receive multiple RAI treatments, consideration for sperm banking may be necessary if there is an anticipated cumulative I-131 sodium iodide dose greater than 14 GBq (378 mCi) (*37*).

For patients with iodine refractory disease, RAI therapy is less likely to provide benefit. For the determination of iodine refractory disease, the Martinique Working Group described five common clinical scenarios that may indicate an iodine refractory state: no RAI uptake on a diagnostic whole body scan; no RAI uptake on the post-therapy scan performed several days after RAI therapy administration; lack of RAI uptake in all tumor foci; progression of differentiated thyroid cancer metastasis despite RAI uptake; progression of differentiated

thyroid cancer metastasis despite cumulative doses of >22.2 GBq I-131 NaI (600 mCi) (*34*). Potential treatments for iodine refractory disease include external radiation therapy, chemotherapy, and targeted molecular therapy (to be discussed below).

Molecular targeted therapy for advanced differentiated thyroid cancer

TABLE 3: Targets in molecular therapy

This table will define abbreviations used in the molecular targeted therapy for advanced differentiated thyroid cancer discussion.

Both papillary and follicular carcinomas are well differentiated thyroid cancers and are considered highly treatable by conventional treatments, which include surgery, RAI ablation, and TSTs suppression as previously discussed. Although Hurthle cell carcinoma is also considered differentiated and may also be treated with conventional treatments, it may prove more radioiodine-resistant than PTC and FTC. A small percentage of patients with differentiated thyroid cancer develop iodine refractive metastatic disease thereby limiting treatment options (*38*). While conventional treatments may also be used in PDTC, many cases are radioiodine resistant (*14*). Thyroid cancers that are no longer responsive to RAI therapy are still candidates for other forms of treatment including standard chemotherapy and targeted therapy. Targeted therapy and chemotherapy differ in their mechanism of cancer treatment. Targeted drug therapy specifically prohibits the action of key proteins involved in cancer-specific activities, whereas traditional chemotherapy affects all rapidly proliferating cells, including normal cells. Targeted drug therapy is an active area of cancer research and currently there are two approved drugs that target the MAPK cascade. The US Food and Drug Administration (FDA) approved two multikinase inhibitors for the treatment of advanced

differentiated thyroid cancer refractory to RAI treatment: sorafenib (approved 2013) and lenvatinib (approved 2015). Multikinase inhibitors block the effect of tyrosine kinases that are overactive in the MAPK pathways. Sorafenib is a kinase inhibitor which inhibits multiple intracellular and cell surface kinases (KIT, FLT- 3, RET, RET/PTC, VEGFR-1, VEGFR- 2, VEGFR- 3, and PDGFR-ß) (*39*) that are implicated in tumor cell signaling, angiogenesis and apoptosis. Lenvatinib is also a kinase inhibitor that inhibits the vascular endothelial growth factor receptors as well as other kinases (FGF receptors, PDGFα, KIT, and RET) associated with pathogenic angiogenesis, tumor growth, and cancer progression (*38*, *40*). In addition to the multikinase inhibitors, selective kinase inhibitors are also therapeutic options for advanced differentiated thyroid carcinoma. In May 2020, the FDA approved a highly selective kinase inhibitor, selpercatinib, for the treatment of iodine refractive *RET*-positive advanced thyroid cancer (*38*, *41*).

A promising utilization of kinase inhibitors in iodine refractory differentiated thyroid cancer is the re-sensitization to radioiodine. *BRAF V600E* mutations coincide with reduced sodium iodine symporter expression, thereby inhibiting RAI uptake (*38*). In a study conducted by Rothenberg et al, ten patients with iodine refractory thyroid cancer received a *BRAF* inhibitor for twenty-five days. Six of the ten patients demonstrated a positive uptake of RAI and could be re-treated with RAI (*38*). Radioiodine re-sensitization has also been documented in a phase II trial with MEK inhibitor, selumetinib, in patients expressing *BRAF* or *RAS* mutation (*38*). Figure two illustrates the key molecular signaling pathways involved in thyroid cancer initiation and progression. MEK is a downstream protein in the RAS/RAF/MEK MAPK signaling cascade. Selumentinib inhibits the overstimulation of this pathway. Of the twenty patients in

the trial (nine with *BRAF* mutation and five with *NRAS* mutation), twelve patients demonstrated positive RAI uptake in response to selumentinib use. Eight of the twelve patients could be treated with radioiodine. Of the eight patients who received another RAI treatment, five had *NRAS* mutations and one had a *BRAF* mutation (*38*).

Treatment for undifferentiated thyroid carcinoma

Anaplastic thyroid cancer is a diagnostic and therapeutic challenge because it is very rare, advances quickly, and non-iodine avid which prevents the use of RAI for evaluation and treatment. In these cases, 18F-FDG PET is useful for evaluation and follow-up to treatments. Initial treatment includes surgical resection and airway management (often a tracheostomy) followed by external beam radiation therapy (EBRT) with or without use of doxorubicin and/or taxanes or cisplatin (*6*, *38*, *42*). Patients who have unresectable cancer but without distant metastasis are generally treated with palliative chemoradiation (*6*). Genetic marker analysis has led to the development of therapeutic agents that target specific molecular pathways associated with ATC. For example, clinical trials with *BRAF* inhibitors (ex. Dabrafenib), MEK inhibitors (ex. Trametinib and Lenavatinib), mTOR inhibitors, or PPARγ inhibitors may be appropriate treatments for patients with anaplastic thyroid carcinoma (*38*, *42*). MEK is a key protein in the MAPK signaling cascade, whereas mTOR is a key protein in the PI3K-AKT pathway. PPARγ acts as a tumor suppressor gene, upregulating important enzymes that control the cell cycle (*6*, *42*).

Conclusion:

Thorough evaluation of decades worth of data on thyroid carcinoma incidence, treatment, and outcomes have called into question the most appropriate management of patients with follicular epithelial-derived thyroid carcinoma. The 2015 ATA guidelines called for a more conservative approach for low risk malignancies but take into account the physician and patient preferences. However, given the lack of consensus regarding the recommendations for a reduction in the extent of surgery and radioiodine therapy, disease management team preferences may vary among institutions. The controversy regarding the 2015 ATA guidelines for diagnostic and therapeutic use of radioiodine prompted a collegial discussion among members of the greater nuclear medicine community and resulted in an authoritative paper termed "the Martinque Principles". The Martinique Principles helped to define common terminology for the goals of RAI therapy (ablation, adjuvant treatment, or treatment of known residual or recurrent disease), reiterated the importance of evaluating multiple factors when determining the appropriateness of RAI therapy, and acknowledged the limitations of current scientific literature. Most importantly, the Martinique Working Group established a platform for the evaluation of current practices, exchange of ideas, and critique of literature which will help guide future research and optimize thyroid cancer diagnosis and management.

Genetic and molecular evaluation of thyroid carcinoma have identified two key signaling pathways primarily involved in carcinogenesis and oncogenesis. The MAPK pathway is implicated in loss of differentiation, cell growth and proliferation, and angiogenesis, while the PI3K-AKT pathway promotes tumor progression. Many genetic alterations coexist and as these mutations accumulate the MAPK and PI3K-AKT pathways are activated. The use of molecular

analysis to classify malignancies and predict tumor progression will evolve as more molecular markers are developed. This will likely lead to new prognostic tools and potential therapeutic agents for improved patient management and treatment strategies.

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Figure Legend

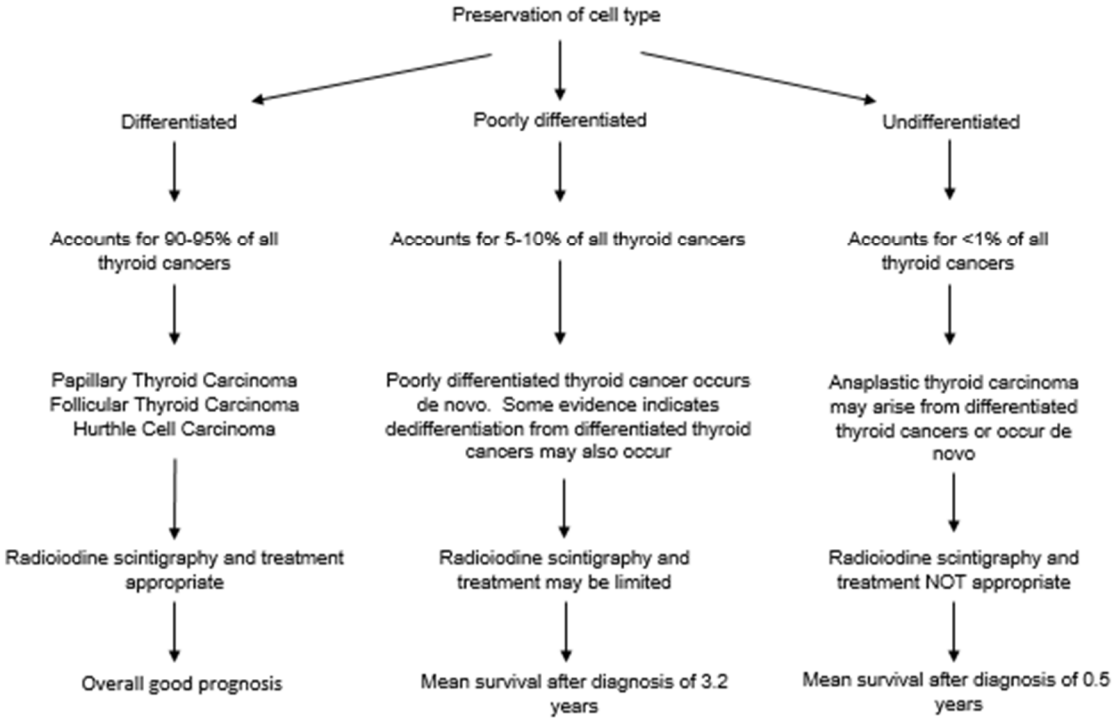
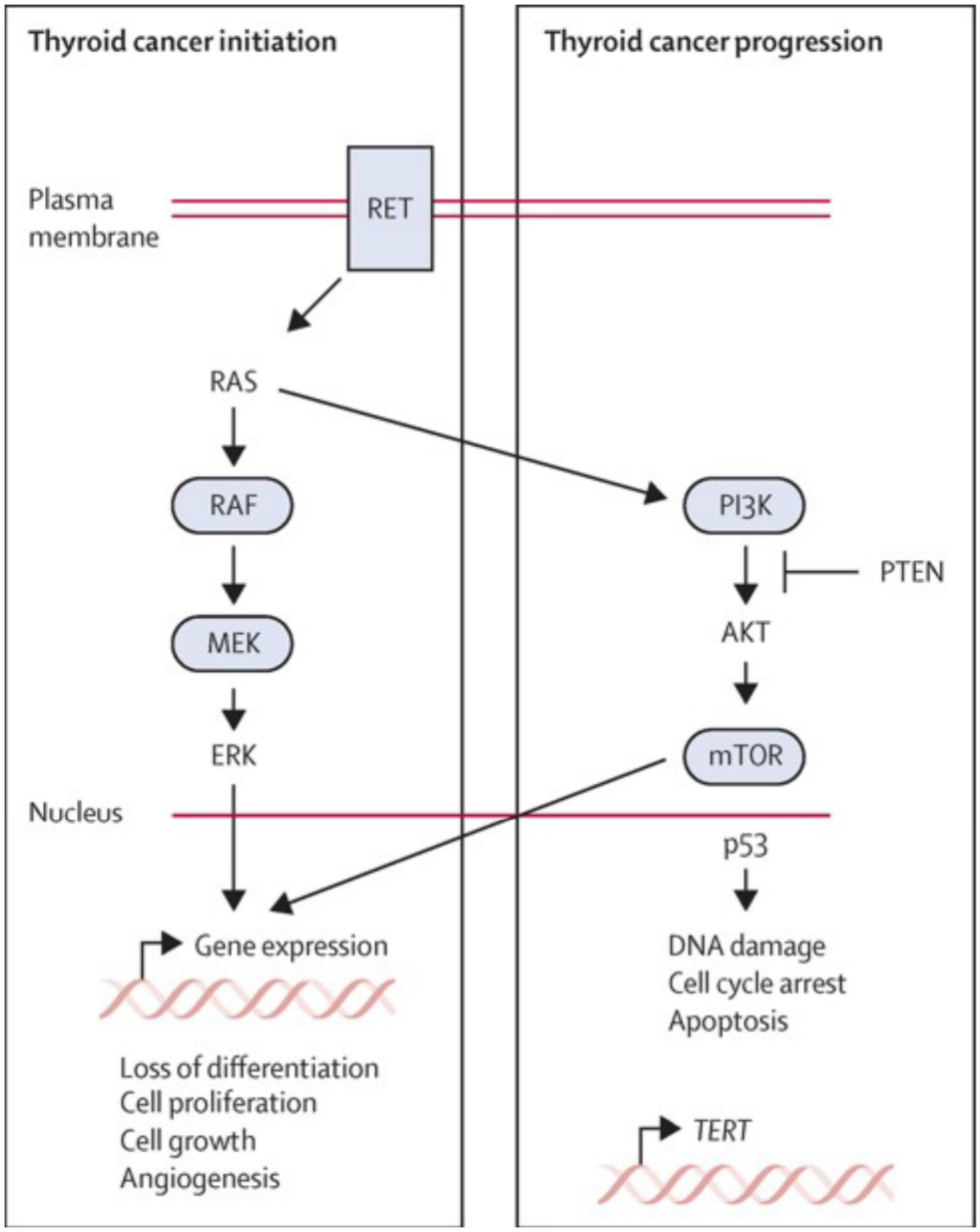


Figure 1: Cellular differentiation and diagnostic/prognostic implications

This figure illustrates the cellular differentiation stage for follicular epithelial derived thyroid carcinomas and how it relates to radioiodine scintigraphy/treatment and overall prognosis.



“This image was originally published in The Lancet. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet. 2016;388:2783-95 © by Elsevier https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30172-6/fulltext.”

Figure 2: Thyroid cancer pathways

This figure illustrates key molecular signaling pathways involved in thyroid cancer initiation and progression. The left box shows the mitogen activated protein kinase (MAPK) pathway which is activated

by mutations in *RET*, *RAS*, and *BRAF*. The box on the right shows the pathways involved in tumor progression, including PI3K/AKT, p53 tumor suppressor, and *TERT*. The blue boxes represent molecular targets for therapies approved by the US Food and Drug Administration.

AKT= Protein kinase B

ERK = extracellular-signal-regulated kinase

MEK= mitogen/extracellular signal-regulated kinase

mTOR = mammalian target of rapamycin

PI3K = phosphatidylinositol-3-kinase

p53= TP53 or tumor protein

RAF= rapidly accelerated fibrosarcoma

RAS= rat sarcoma point mutations

RET= rearrangement during transfection

TERT= Telomerase reverse transcriptase

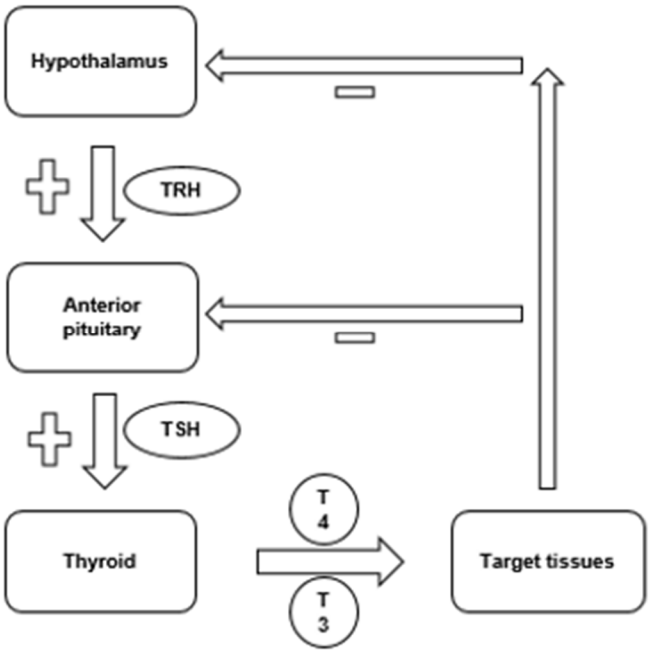


Figure 3: Thyroid hormone synthesis negative feedback loop

TRH- Thyrotropin releasing hormone

TSH- Thyroid stimulating hormone (Thyrotropin)

T4- Tetraiodothyronine (Thyroxine)

T3- Triiodothyronine

Left side arrow with blue plus sign indicates stimulation

Right side arrow with negative sign indicates inhibition

This figure illustrates the negative feedback loop for thyroid hormone synthesis. The hypothalamic-pituitary axis regulates TSH release through a negative feedback loop. TRH stimulates anterior pituitary thyrotrophs to secrete thyroid stimulating hormone (TSH). When TSH binds to the TSH receptor on thyroid follicular cells, it stimulates iodine uptake, thyroid hormone (T3, T4) secretion, and thyroid gland growth and differentiation. Of the thyroid hormones released, approximately 80% is in the form of T4 and 20% in the form of T3 (*36*). T3 has a short half-life but is most active on the nuclear receptor, whereas T4 has a long half-life but is less active in binding to the nuclear receptor. Because T4 becomes de-

iodinated and converted into T3 by most tissues (especially the liver and kidneys), T4 acts as a reservoir for T3 (*36*). Serum levels of thyroid hormone exert negative feedback control on TRH and TSH. High thyroid hormone levels decrease TSH secretion whereas low thyroid hormone levels stimulate TSH synthesis and secretion. As this relates to thyroid cancer, patients who have had a total thyroidectomy require thyrotropin suppression therapy (TST) for two reasons: 1) replace endogenous thyroid hormone and 2) suppress TSH. TSH suppression is an important aspect of treatment because TSH may stimulate cellular proliferation in differentiated thyroid cancer cells.

Table 1: Genetic abbreviations

Name	Abbreviation
Mitogen activated protein kinase	MAPK
Rearrangement during transfection/papillary thyroid cancer mutations	*RET*/*PTC*
Rat sarcoma point mutations	*RAS*
V-raf murine sarcoma viral oncogene homolog B1 mutations	*BRAF*
Telomerase reverse transcriptase	*TERT*
Tumor protein	*Tp53*
Phosphatase and tensin homolog deleted from chromosome 10	*PTEN*

Table 2: Summary of genetic mutations and associated prognostic significance

Genetic mutation	Cancers displaying genetic mutation	Prognostic significance
BRAF	PTC (*BRAF* V660E) PDTC ATC	No clear consensus on prognostic significance Linked to extrathyroidal invasion, lymph node metastasis, vascular invasion, advanced tumor stage in the primary tumor, and multifocality Linked to cellular de-differentiation Linked to loss of iodine avidity Upregulates platelet derived growth factor Upregulates vascular endothelial growth factor
PTEN	Differentiated thyroid cancers PDTC	Uncontrolled cell growth and proliferation
RAS	PTC PTC-FV FTC PDTC ATC	*RAS* mutations alone likely associated with limited aggressiveness
RET/PTC rearrangements	PTC (adult and pediatric) PTC-FV FTC	Not fully established *RET/PTC1* does not correlate with clinical pathological features *RET*/*PTC3* is associated greater primary tumor size, cellular variations, and a more advanced stage at diagnosis
TERT	90% of human cancers Differentiated thyroid cancers PDTC ATC	Restores telomerase complex activity (prevents apoptosis) Promotes epithelial mesenchymal transition which promotes metastasis and cellular dedifferentiation
Tp53	PTC FTC PDTC ATC	Extrathyroidal extension Distant metastasis Potentially promotes cellular dedifferentiation

BRAF- v-raf murine sarcoma viral oncogene homolog B1 mutation

PTC- papillary thyroid carcinoma

PDTC- poorly differentiated thyroid cancer

ATC- anaplastic thyroid carcinoma

PTEN- phosphatase and tensin homolog mutation

RAS- rat sarcoma point mutation

PTC-FV- follicular variant of papillary thyroid cancer

FTC- follicular thyroid carcinoma

RET/PTC- rearrangement during transfection/papillary thyroid cancer (*RET*/*PTC*) mutation

TERT- telomerase reverse transcriptase mutation

Tp53- tumor protein mutation

Table 3: Targets in molecular therapy

Abbreviation	Definition
FGF	Fibroblast growth factor
FLT- 3	FMS-like receptor tyrosine kinase-3
KIT	Type of receptor tyrosine kinase and a type of tumor marker
MEK	Mitogen/extracellular signal-regulated kinase
mTOR	Mammalian target of rapamycin
PDGFα	Platelet derived growth factor alpha
PDGFR-ß	Platelet derived growth factor receptor beta
PPARγ	Peroxisome proliferator-activated receptor gamma
RET	Rearrangement during transfection
RET/PTC	Rearrangement during transfection/papillary thyroid cancer
VEGFR	Vascular endothelial growth factor receptor