Thyroid Cancer

Article *in* International Journal of Otolaryngology and Head & Neck Surgery · January 2019

DOI: 10.4236/ijohns.2019.86024

6 authors, including:

Rodrigo Arrangoiz
Mount Sinai Medical Center
84 PUBLICATIONS **745** CITATIONS
SEE PROFILE

Fernando Cordera
Centro Médico ABC
72 PUBLICATIONS **1,153** CITATIONS
SEE PROFILE

Eduardo Moreno
University of La Serena
74 PUBLICATIONS **975** CITATIONS
SEE PROFILE

Enrique Luque-de-León
Hospital de Especialidades - Centro Médico Nacional Siglo XXI / The American Brit…
113 PUBLICATIONS **2,562** CITATIONS
SEE PROFILE

Scientific Research Publishing

International Journal of Otolaryngology and Head & Neck Surgery, 2019, 8, 217-270
https://www.scirp.org/journal/ijohns
ISSN Online: 2168-5460
ISSN Print: 2168-5452

Thyroid Cancer

Rodrigo Arrangoiz*, Fernando Cordera, David Caba, Eduardo Moreno, Enrique Luque-de-Leon, Manuel Muñoz

Sociedad Quirúrgica S.C., American British Cowdray Medical Center, Mexico City, Mexico
Email: *rodrigo.arrangoiz@gmail.com, fernando.cordera@gmail.com, cabamd@gmail.com, morenomd7@icloud.com, enrique.luque.dl@gmail.com, manuelmunoz1@prodigy.net.mx

How to cite this paper: Arrangoiz, R., Cordera, F., Caba, D., Moreno, E., Luque-de-Leon, E. and Muñoz, M. (2019) Thyroid Cancer. *International Journal of Otolaryngology and Head & Neck Surgery*, **8**, 217-270.
https://doi.org/10.4236/ijohns.2019.86024

Received: October 15, 2019
Accepted: November 11, 2019
Published: November 14, 2019

Abstract

Thyroid tumors include those that originate from follicular cells and those that arise from parafollicular cells (C cells). Differentiated thyroid cancer, which originates from follicular cells, includes papillary carcinoma, follicular carcinoma, oncocytic cell carcinoma (Hürthle), poorly differentiated carcinoma, and anaplastic carcinoma. The incidence of thyroid cancer has been increasing significantly, with an estimated incidence in the United States of America of 53,990 cases by the year 2018. This neoplasm is listed as the most common endocrine tumor and represents approximately 3% of all malignant tumors in humans, with 75% of cases occurring in women, and two-thirds of cases occurring in people under 55 years. The increase in the prevalence/incidence of low-risk thyroid cancer over the last 10 to 20 years has required a re-appraisal of the standard one-size-fits-all approach to differentiated thyroid cancer. This adaptation to a more individualized management of the patient with thyroid cancer has led to a much more risk-adapted approach to the diagnosis, initial therapy, adjuvant therapy, and follow-up of patients with differentiated thyroid cancer. This paper with review the current understanding of the clinical presentation, diagnostic workup, and management of thyroid cancer centered on evidence-based and personalized medicine.

Keywords

Thyroid Nodules, Thyroid Cancer, Thyroid FNA, Thyroid Nodule Workup, Thyroid Cancer Treatment, Molecular Studies for Thyroid Cancer

1. Introduction

Thyroid nodules are a major public health problem. Epidemiological studies have shown that the prevalence of palpable thyroid nodules is approximately 5% in women and 1% in men living in parts of the world with sufficient iodine [1]

[1] [2] [3] [4]. In contrast, high-resolution neck and thyroid ultrasound can detect thyroid nodules in approximately 19% to 68% of randomly selected people, with higher frequencies in women and the elderly [3] [4]. The clinical importance of thyroid nodules lies in the need to exclude thyroid cancer, which occurs between 7% and 15% of cases, depending on age, sex, radiation exposure history, family history, among other factors [5] [6].

Thyroid neoplasms include those that originate from follicular cells and those that arise from parafollicular cells (C cells). Differentiated thyroid cancer, which originates from follicular cells, includes papillary carcinoma, follicular carcinoma, oncocytic cell carcinoma (Hürthle), poorly differentiated carcinoma, and anaplastic carcinoma. These thyroid tumors comprise the vast majority (more than 90% of cases) of all thyroid cancers [7]. Of these subtypes, anaplastic carcinoma is rare and is characterized by its extremely poor prognosis. Similarly, poorly differentiated carcinoma is characterized by its aggressive behavior and its unfavorable prognosis. Between 2010 and 2014, 63,229 patients per year were diagnosed with thyroid carcinoma. Of these 63,229 patients, 89.4% had papillary carcinoma, 4.6% had follicular carcinoma, 2.0% had oncocytic cell carcinoma, 1.7% had medullary carcinoma, and 0.8% had anaplastic carcinoma [8].

The incidence of thyroid cancer has been increasing significantly since the mid-1990s, with an estimated incidence in the United States of America of 53,990 cases by the year 2018 [9]. This cancer is listed as the most common endocrine neoplasm and represents approximately 3% of all malignant tumors in humans, with 75% of cases occurring in women [9] [10], and two-thirds of cases occurring in people under 55 years [9]. Less aggressive forms of these tumors are more common in women and younger people [8]. The thyroid cancer mortality rate has remained stable in women but has increased by approximately 1% per year since 1983 in men and will be responsible for approximately 2060 deaths in 2018 [9]. The relatively low mortality rate compared to the incidence is due, in part, to the indolent nature of the vast majority of thyroid tumors. Patients with differentiated thyroid cancer generally have an excellent long-term prognosis, with five-year survival rates close to 100% for localized disease [8]. Despite the low mortality rates, local recurrence occurs in approximately 20% of patients, and distant metastases occur in about 10% of patients 10 years after diagnosis [11]. Mortality from thyroid cancer has been increasing in the last 18 years [8], which is why progress in the development of new systemic therapies for thyroid cancer refractory to iodine is extremely important. We know that medical development in this field has been delayed compared to the progress observed in the treatment of other solid tumors, however, data from emerging clinical studies suggest that thyroid cancer can be treated with targeted agents, particularly kinase inhibitors, with promising results that overshadow those previously seen with cytotoxic agents [12].

The annual incidence of thyroid cancer has almost tripled from 4.9 cases per 100,000 people in 1975 to 14.3 cases per 100,000 people in 2009 [13]. Almost all of the change has been attributed to an increase in the incidence of papillary

thyroid cancer [8] [9] [13]. 25% of new thyroid tumors diagnosed between 1988 and 1989 were equal to or less than 1 cm in diameter compared to 39% of new thyroid tumors diagnosed between 2008 to 2009 [13]. This may be due to the increasing use of high-resolution neck ultrasound and other diagnostic imaging techniques leading to finding asymptomatic thyroid lesions (incidentalomas), trends that are changing the initial treatment and follow-up of many patients with thyroid cancer [14].

The detection and diagnosis of differentiated thyroid cancer has evolved over the years with increased use of high-resolution neck and thyroid ultrasound, fine needle aspiration biopsy (FNAB), molecular tests, and thyroglobulin as a serum marker. This evolution has led to greater controversy regarding the appropriate medical and surgical management of this cancer. The type of surgical resection (lobectomy vs. total thyroidectomy), the role of lymphadenectomy (central prophylactic vs. therapeutic compartment), and adjuvant medical treatment for differentiated thyroid cancer are currently debated and present unique challenges in the treatment of these patients.

2. Risk Factors

In-depth knowledge of the risk factors that may predispose to developing thyroid cancer is required when a patient is being assessed with complaints related to the thyroid gland such as thyroid nodules, voice changes, or symptoms of dyspnea, dysphagia, or sensation of suffocation These risk factors include a personal or family history of thyroid cancer, certain diseases with a genetic predilection towards the development of thyroid cancer, and previous radiation exposure. Most thyroid cancers are idiopathic. However, the thyroid gland is very sensitive to radiation-induced oncogenesis, and radiation is the main environmental cause of thyroid cancer [15] [16] [17].

Personal history of exposure to ionizing radiation represents approximately 9% of all cases of thyroid cancer, and the risk is inversely related to the age at which the exposure was suffered, but directly related to the radiation dose, increasing linearly to a dose of 20 Gy [16] [18] [19]. Studies evaluating the effects of accident radiation exposure at the Chernobyl nuclear power plant have found a 5 to 6-fold increase in the incidence of thyroid cancer among people who lived in the Chernobyl area and were under 18 years at the time of the accident [10] [16]. When thyroid cancer develops as a result of exposure to ionizing radiation, it is invariably of the papillary type and behaves similarly to sporadic thyroid papillary cancer, although the evidence we have as a result of the Chernobyl nuclear disaster suggests that Radiation dose may be related to the aggressiveness or differentiation of thyroid cancer [16]. Children exposed to the Chernobyl disaster had a higher proportion of thyroid tumors that were less well differentiated and of the papillary subtype of solid variant than patients who had no history of radiation exposure [16]. The type of radiation, along with the radiation dose, has been associated with the aggressiveness of thyroid cancer [18]. Differ-

ent forms of radiation have been linked to different genetic alterations associated with thyroid cancer, resulting in variable aggressiveness. Therefore, radiation exposure plays a critical role in the development of thyroid cancer, especially in patients younger than 15 years, and can play a role in its aggressiveness based on acquired genetic alterations and radiation dose [16] [18] [19] [20].

Having a personal history of thyroid cancer increases the risk of developing subsequent or recurrent thyroid tumors substantially. Most differentiated thyroid cancers are sporadic, and at least 5% of these patients will have family disease [21]. There is evidence of a family predisposition, with several inherited syndromes that demonstrate an increased risk of developing thyroid cancer. The mechanisms underlying these associations are not well known. Certain histological subtypes of thyroid cancer should raise the suspicion of family syndromes that have a genetic predisposition to develop said cancer. As for example, the cribriform-morular variant of papillary thyroid cancer is associated with familial adenomatous polyposis and should raise concerns about a germline mutation of the APC gene and a predisposition to colon and rectum cancer [22]. Familial adenomatous polyposis has been associated with the development of all different subtypes of differentiated thyroid cancer [23] [24]. Families related to familial adenomatous polyposis with cases of thyroid cancer should begin surveillance/screening at age 15, or earlier if family members are affected at younger ages [22] [23] [24] [25].

The Carney complex is a rare genetic condition associated with mutations in the PRKAR1A gene that manifests with skin pigmentation, myxomas, schwannomas and thyroid abnormalities, including differentiated thyroid cancer [26]. Cowden syndrome is caused by a mutation in the PTEN germ line and is associated with the development of benign and malignant breast and thyroid lesions [27]. Peutz-Jeghers syndrome is due to germline defects in STK11 (LKB1) and is associated with gastrointestinal hamartomatous polyps, pigmented mucocutaneous lesions, and differentiated thyroid cancer [28].

During the last decade, significant advances have been made in the identification of genes related to the pathogenesis of thyroid cancer. Studies of the patterns of genetic alterations present in thyroid tumors suggest that there are differences in the pathogenesis of different types of thyroid tumors, which probably explains the variable range of biological behavior observed among thyroid cancers [29] [30] [31]. The initial event in the development of papillary thyroid cancer is usually the result of the accumulation of several mutations [30]. In approximately 50% of cases, a constitutive activation of the BRAF kinase, a member of the Ras/MAPK pathway, is present and is the result of a V600E amino acid substitution [32]. BRAF normally depends on the activation of Ras to propagate the extracellular signal transduction. In certain scenarios, activation of the Ras oncogene (found before BRAF) has also been implicated as an initiating event in papillary thyroid cancer, as well as in follicular thyroid cancer [32]. Somatic mutations have been found in the Ras oncogene in benign and malignant

thyroid tumors, and therefore appear to be an early event in thyroid tumorigenesis [30] [31]. Some studies suggest that Ras mutations are more prevalent in follicular thyroid carcinomas, in the follicular variant of papillary thyroid cancer, and in follicular adenomas [32]. Ras mutations may result in allelic loss or in chromosomal rearrangements that lead to an increase in thyroid follicular cancer formation rates [32]. Chromosomal rearrangements have also been observed in the formation of RET/PTC oncogenes and imply an unfavorable prognosis [33]. There are variable data regarding the usefulness of BRAF, TP53 and TERT mutations tests in risk stratification of patients with thyroid cancer [34] [35]. BRAF V600E mutations have been associated with worse results in papillary thyroid cancer, with higher recurrence and death rates [35].

Thyroid cancers are highly vascularized and elevated levels of vascular endothelial growth factor have been identified in these tumors, suggesting that angiogenic pathways may be a potential target for treatment [29]. In addition, during the past 30 years, thyroid cancers have been shown to be associated with genetic mutations that lead to aberrant intracellular signaling (**Table 1**). Preclinical and clinical data suggest that inhibition of intracellular signaling cascades, including mitogen-activated protein kinase (MAPK) and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathways may be effective in cancer treatment of thyroid [7] [33] [36] [37] [38] [39] [40]. RET kinase activation by a germline mutation is associated with the development of familial medullary thyroid cancer. Similar mutations have been detected in somatic cells that produce greater RAS/RAF activation in approximately 50% of sporadic thyroid medullary cancers [41] [42]. MAPK activation in papillary thyroid cancers can occur through RET/PTC translocations or mutations in RAS or BRAF [32]. The PI3K pathway is also activated by mutations in PAX8/PPARγ in follicular thyroid cancers [43]. This greater understanding of the mutations involved in thyroid tumorigenesis will likely lead to new systemic therapies for the treatment of advanced disease.

Table 1. Prevalence of mutations in different pathological subtypes of thyroid cancer.

Type of Thyroid Cancer	Mutation	Prevalence (%)
Papillary	BRAF V600E	45
	RET/PTC	20
	Copy gain PI3KCA	12
	RAS	10
	PI3KCA	3
	Copy gain BRAF	3
	PTEN	2
Follicular	RAS	45
	PAX8/PPARγ	35
	Copy gain BRAF	35
	Copy gain PI3KCA	12
	PTEN	<10
	PI3KCA	<10
Medullary	RET (hereditary)	>95
	RET (sporadic)	50

The RET proto-oncogene is a tyrosine kinase receptor that is primarily expressed in tumors of neural crest/neuroectoderm origin, which explains the high incidence of these mutations in medullary thyroid carcinomas that originate in para-follicular cells (C cells) [44]. The RET gene is found on chromosome 10 and germline mutations produce activating mutations that change direction that are responsible for 95% of hereditary medullary thyroid carcinomas, including those associated with multiple endocrine neoplasia 2A (Sipple syndrome) and 2B (Wagenmann-Froboese syndrome) and familial medullary thyroid cancer [44] [45]. In 80% of cases of medullary thyroid carcinoma, the disease is sporadic, without an inherited etiology, but a somatic mutation is identified in the RET gene in 40% to 70% of these sporadic cases [41] [42]. In these sporadic cases, mutations are found most frequently in codon 918 that results in the constitutive activation of the RET tyrosine kinase receptor [46]. Almost all patients with multiple endocrine neoplasia 2A or multiple endocrine neoplasia 2B that is transmitted in an autosomal dominant manner will develop medullary thyroid cancer and the detection of germline RET gene mutations has been of great value in the early identification of patients who have a genetic basis for their disease. Even in patients with sporadic medullary thyroid cancer, 6% to 10% of these patients will have a mutation in the RET proto-oncogene germline, which reveals a new family of patients with previously undiagnosed medullary thyroid cancer [41] [42] [45]. The discovery of the RET proto-oncogene has had a significant clinical impact, which affects the scrutiny and prophylactic treatment of patients who are members of the families of patients with multiple endocrine neoplasia or with familial medullary thyroid carcinoma [47].

Anaplastic thyroid carcinoma develops from the dedifferentiation of thyroid tumors, although the specific reason for this transformation has not been well clarified. Mutations in the p53 suppressor gene are frequently found in anaplastic thyroid carcinoma and are absent in well-differentiated thyroid neoplasms [48] [49]. This observation suggests that p53 mutations play a role later in the pathogenesis of the thyroid tumor, specifically, in the transition from dedifferentiation to the anaplastic phenotype. A large number of mutations in other pathways, including the PI3K/Akt and Ras/MAPK pathways have also been implicated in the formation of ATC [48] [49].

3. Pathology

As previously mentioned papillary, follicular, oxytic, medullary, and anaplastic thyroid cancer constitute the vast majority of all thyroid tumors (90%) and the remaining proportion represents lymphoma, squamous cell carcinoma, sarcoma, melanoma or metastatic disease (breast cancer, renal cell cancer, lung cancer, colon/rectal cancer, and gastric carcinomas) [8] [50]. Papillary and follicular thyroid cancer are broadly classified as differentiated thyroid tumors but can be subclassified based on their histological appearance or biological behavior (**Table 2**).

Table 2. Pathological classification of malignant thyroid tumors [8] [50].

Subtype	Histologic Variants	Incidence
Papillary (89.4%)	Conventional/Classic	65% - 85%
	Follicular Variant	15% - 20%
	Tall Cell	5% - 10%
	Solid	1% - 3%
	Diffuse sclerosing	1% - 2%
	Papillary Micro-Carcinoma	
	Oncocytic	
	Columnar Cell	
	Clear Cell	
	Morular Cribriforme	
	Marco-follicular	
	Papillary with HobnailCharateristics	
	Papillarywith stroma similar to fascitis	
	Combined Papillary and Medullary Carcinoma	
	Papillary with dedifferentiation to Anaplastic Carcinoma	
Follicular (4.6%)	Hurthle (2.0%)	
Poorly Differentiated	Insular	
Medullary (1.7%)		
Anaplastic (0.8%)		
Others	Lymphoma	
	Squamous Cell Carcinoma	
	Sarcoma	
	Melanoma	
	Metastatic Tumors	

Papillary thyroid cancer accounts for approximately, based on the most recent statistics, 89.4% of all thyroid malignancies and is the predominant histology observed in patients exposed to radiation [8] [15] [16] [17] [18]. The average age of diagnosis is between 30 and 40 years and women are affected more frequently than men (2:1 ratio) [13] [51] [52]. The macroscopic appearance of papillary thyroid cancer can be very variable. Most tumors tend to be markedly circumscribed, solid, firm, and white in color, but a significant percentage of tumors can be cystic [50]. It is not uncommon to have a solid primary tumor with cystic metastases to a lymph node [50]. Papillary thyroid cancer may have a pattern of infiltrating growth in the thyroid or may show a direct extra extra-thyroid extension to adjacent tissues [51] [52]. Unlike normal thyroid gland or benign thyroid lesions that protrude on sectioning, papillary thyroid cancer remains flat [53]. The diagnosis is made by microscopic evaluation and can be made on the basis of a fine needle biopsy (FNAB) [34] [53].

Conventional papillary thyroid cancer shows a papillary architecture with ramifications [51] [52]. The papillae are covered by cells with eosinophilic cytoplasm and with enlarged nuclei [50] [52]. Cell polarity may be abnormal or completely lost in some tumors [50]. In some cases, squamous metaplasia may be present [50]. Psamoma bodies that are concentric lamellar calcifications composed in part of thyroglobulin are more common in some variants of papillary

thyroid cancer [50] [51] [53]. These psamoma bodies are present in 50% of cases and help ensure the diagnosis of papillary cancer [53]. Some tumors may also contain multinucleated giant cells [50].

The definitive diagnosis is made on the basis of cellular and nuclear characteristics (cytological characteristics) with cells that adopt a cuboidal form with nuclear "grooving" and cytoplasmic inclusions [50] [51] [52] [53]. These characteristic findings are described as the pathognomonic nuclei of "Orphan Annie" [53]. Papillary cancer is characterized by multifocality in 18% to 85% of patients and is associated with an increased risk of lymph node metastasis [53]-[61]. Metastases to cervical lymph nodes are quite common in patients with papillary cancer at the time of diagnosis, with a frequency that varies between 30% to 80% in some series [53] [62] [63] [64]. Despite this high incidence, the 10-year survival rate remains 95% [8].

Follicular cancer represents the second most frequent thyroid cancer, approximately 4.6% of all thyroid cancers [8]. These tumors are most frequently found in geographic areas with iodine deficiency and, like papillary cancer, have a female predominance with a ratio of 3:1 (women/men) [8] [65] [66] [67]. Follicular cancer tends to occur in an older population compared to other differentiated thyroid tumors. Its maximum incidence is between the ages of 40 and 60, compared to the incidence of papillary cancer that reaches an earlier peak (usually 10 years less), between the ages of 30 to 50 years [53] [67]. Follicular cancer is often found in association with benign thyroid disorders, such as endemic goiter, and a relationship between chronic stimulation with thyroid stimulating hormone (TSH) and follicular carcinoma due to the increased incidence of follicular cancer has been suggested in areas with iodine deficiency [65] [66]. Patients generally present with a clinical history of a solitary thyroid nodule, which has often rapidly increased in size [53].

The histopathology of follicular tumors varies from a normal epithelium, well differentiated tumors with a follicular and colloid differentiation (findings associated with a good prognosis) to poorly differentiated tumors with solid growth, absence of follicles, marked nuclear atypia and vascular and/or capsular invasion (characteristics that are associated with a worse prognosis) [68]. Follicular tumors are usually unifocal, well encapsulated, containing highly cellular follicles, and are easily confused with benign follicular adenomas in BAAF [53]. The pathological diagnosis of this malignant neoplasm can only be made by permanent cuts, demonstrating the presence of capsular and/or vascular invasion [53].

In follicular tumors the micro-follicular architecture is uniform with a collection of cuboidal cells that cover the follicles. In addition, features compatible with papillary cancer, such as psamoma bodies and nuclear changes (such as the appearance of frosted glass, longitudinal grooves, nuclear overlap and inclusions), must be absent [50] [52] [69] [70]. Follicular thyroid tumors are classified into one of three groups according to the type and degree of invasion [68] [69] [71]:

- Minimally invasive follicular thyroid cancer, which demonstrates only the invasion of the tumor capsule without vascular invasion (low-risk tumor according to the guidelines of the American Thyroid Association [ATA]) (Table 3);
- Encapsulated angioinvasive follicular thyroid cancer, which demonstrates minor vascular invasion (≤4 foci of angioinvasion within the tumor or tumor capsule) with or without capsular invasion (low-risk ATA tumor) (Table 3);
- Widely invasive follicular thyroid cancer, which is characterized by:
  - Wide invasion of the tumor capsule;
  - A multinodular tumor without a well-defined capsule that invades the normal thyroid surrounding the tumor; and/or
  - Extensive vascular invasion (>4 foci of angioinvasion) (high-risk ATA tumor) (Table 3).

Regional metastasis to cervical lymph nodes is somewhat rare in follicular cancer, being present in 5% to 13% of cases in the initial presentation [53] [72]. Distance dissemination is more common in the initial presentation compared to papillary cancer and is observed in 10% to 33% of patients, most often it presents with hematological dissemination to the lungs or bone (lytic lesions) even in those with small primary tumors, although tumors smaller than 2 cm in size have not been associated with metastatic disease [73]. The 10-year survival rates for follicular thyroid cancer are 70% to 95%, slightly worse than those for papillary cancer, possibly due to late presentation and the presence of distant metastases in the initial diagnosis.

Hürthle cell carcinoma (also known as oncocytes, or Askanasy cells), although

Table 3. ATA risk stratification system to estimate the risk of persistent/recurrent disease.

Low Risk	Intermediate Risk	High Risk
Papillary thyroid cancer with all of the following: • No local or distant metastases • All the macroscopic tumor has been resected (R0) • No invasion of local and regional tissues • The tumor does not have an aggressive histology (aggressive histology's include high-cell, insular tumors, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, Hobnail variant) • Without vascular invasion • There is no uptake of I-131 outside the thyroid bed in the post-treatment examination • Clinical N0 or ≤5 pathological micro-metastases; N1 (<0.2 cm in the largest dimension) • Well-differentiated, encapsulated intra-thyroid follicular cancer • Well-differentiated intra-thyroid follicular thyroid cancer with capsular invasion and zero or minimal vascular invasion (<4 foci) • Intra-thyroid, unifocal or multifocal papillary micro-carcinoma, including mutated BRAF V600E (if known)	**Any of the following present:** • Microscopic invasion of peri-thyroid soft tissues • Cervical ganglionic metastases or avid I-131 metastatic foci in the neck on post-treatment examination after thyroid bed ablation • Tumor with aggressive histology or vascular invasion (aggressive histologies include high cell tumors, columnar, insular cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, Hobnail variant) • Clinical N1 or >5 pathological N1 with all affected lymph nodes < 3 cm in the largest dimension • Multifocal papillary thyroid micro-carcinoma with extra thyroid extension and BRAF V600E mutation (if known)	**Any of the following present:** • Macroscopic tumor invasion • Incomplete tumor resection with macroscopic residual disease • Remote metastasis • Postoperative serum thyroglobulin suggestive of distant metastases • Pathological N1 with any metastatic lymph node ≥ 3 cm in the largest dimension • Follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion)

considered a variant of follicular cancer, deserves a separate discussion since it comprises 2% of all thyroid neoplasms and has a biological behavior and a natural history that distinguishes them from follicular cancer [8] [53] [74]. These tumors are formed by sheets of polygonal and hyperchromatic cells that contain abundant mitochondria [74]. Hürthle tumors are characterized by the presence of a cell population of "oncocytes", mostly eosinophilic oxyphilic cells with abundant cytoplasm, very compact mitochondria and round oval nuclei with prominent nucleoli [74]. Like follicular cancer, Hürthle carcinoma requires a definitive pathological study to identify vascular or capsular invasion [53] [72]. Unlike follicular cancer, Hürthle carcinomas are often multifocal (30%), have regional lymph node metastases (25%), and often fail to concentrate radioactive iodine [53]. In part, due to these factors, patients with Hürthle carcinoma have higher tumor recurrence rates and lower survival rates compared to patients with papillary or follicular carcinomas [53].

Medullary thyroid carcinoma is a neuroendocrine tumor of the parafollicular cells or C cells of the thyroid gland [75]. Approximately 1.7% of thyroid neoplasms are medullary carcinomas [8] [75]. Although most cases are sporadic, 15% to 25% of cases are part of an autosomal dominant hereditary syndrome [75]. Calcitonin production is a characteristic feature of this tumor [53]. C cells originate in the embryonic neural crest; As a result, medullary carcinomas often have the clinical and histological features of other neuroendocrine tumors such as carcinoid tumors and pancreatic islet cell tumors.

The sporadic form of medullary thyroid cancer typically presents as a unilateral solitary nodule (75% to 95% of patients) in the fifth decade of life [76] [77] [78] [79]. Family forms, such as multiple endocrine neoplasia (MEN 2A), multiple endocrine neoplasia (MEN 2B) and familial spinal cancer, occur in the fourth decade and are typically multifocal [76] [77] [78] [79]. Due to the embryological origin of medullary thyroid cancer (C cells), these tumors are located in the upper poles of the thyroid gland where these cells reside [53]. It is believed that the presence of C cell hyperplasia is an omen for the development of hereditary spinal cancer [53] [76] [77] [78] [79]. These tumors are not encapsulated, nor well defined, and consist of a heterogeneous mixture of fusiform or round cells [53] [76] [77] [78] [79]. The cells are separated by fibrous septa and amyloid, the latter of which helps in the diagnosis of spinal cancer by immunohistochemical staining for calcitonin and carcinoembryonic antigen [53]. Although these tumors grow slowly, they have a tendency to metastasize early, usually before the primary tumor has reached 2 cm [53].

Approximately 50% to 70% of patients with medullary thyroid cancer have clinically detectable cervical lymph node involvement at the time of diagnosis [53] [76], about 15% percent have symptoms of compression or invasion of the upper aerodigestive tract, such as dysphagia or hoarseness, and approximately 5% to 10% have distant metastatic disease [75] [80] [81]. The survival of patients with medullary thyroid cancer is between that of differentiated thyroid cancers

and undifferentiated (anaplastic) thyroid cancers. When the disease is limited to the thyroid gland, the 10-year survival rate is 90% compared to patients with distant metastatic disease that has a 10-year survival of only 20% [81].

Anaplastic thyroid tumors are undifferentiated tumors of the thyroid follicular epithelium representing less than 1% of all malignant thyroid tumors [82]. These neoplasms are highly aggressive and are considered one of the most lethal malignancies, with a mortality close to 100% [82] [83]. It is believed that these tumors arise from well differentiated thyroid tumors, but over time they suffer from dedifferentiation [81] [84]. Because activating mutations of the BRAF and RAS genes are observed in both well-differentiated thyroid malignancies and in anaplastic thyroid cancer, it is suspected that these are early events in the pathway of this disease [85]. Late events in disease progression that are most commonly seen in anaplastic cancer compared to well-differentiated tumors include mutations in the p53 tumor suppressor protein [86] [87] [88] [89], 16p [90], catenin (cadherin-associated protein), beta 1, and PIK3CA [91].

The annual incidence of anaplastic cancer is approximately one to two cases per million people and represents between 0.8% and 9.8% of all thyroid cancers worldwide [82] [92] [93] [94] [95]. Patients with anaplastic cancer are generally older at the time of diagnosis than those with differentiated cancer; The average age at diagnosis is 65 years, and less than 10% of patients are under 50 years [96] [97]. The vast majority of patients with anaplastic thyroid cancer (60% to 70%) are women [96] [97]. About 20% of patients with anaplastic thyroid cancer have a history of differentiated thyroid cancer, and 20% to 30% of patients have synchronous differentiated cancer [98] [99] [100] [101] [102]. The vast majority of synchronous thyroid tumors are papillary carcinomasbut coexisting follicular tumors have also been identified. Approximately 10% of patients with Hürthle cell thyroid tumors have foci of anaplastic cancer within Hürthle cell cancer [103].

Patients with anaplastic thyroid carcinoma usually manifest clinically with a rapidly growing tumor and symptoms of dysphagia, dysphonia, or dyspnea secondary to extrinsic compression of the tumor that is often fixed to adjacent structures [53]. However, regional or distant metastases are evident at the time of diagnosis in 90% of cases [101] [103] [104] [105]. Regional extension sites may include peri-thyroid fat and pre-thyroid muscles, lymph nodes, larynx, trachea, esophagus, tonsils, large neck vessels, and the mediastinum [101]. Metastatic disease at diagnosis is found in 15% to 50% of cases [98] [99] [100] [102]. The most common site of distant metastases is the lungs (up to 90% of cases) [99] [100]. These metastases are usually massive intrapulmonary lesions, but there may be pleural involvement. About 5% to 15% of patients have bone metastases [98] [99] [100] [102]. 5% of patients have brain metastases, and some have metastases in the skin, liver, kidneys, pancreas, heart and adrenal glands [99] [100] [101] [106] [107] [108] [109] [110].

The tumor is not encapsulated and often contains areas of necrosis that may result in a non-diagnostic FANB that would lead to an incisional biopsy to en-

sure diagnosis and rule out possible lymphoma [53]. Cells are characteristically large and multinucleated with nuclear polymorphism and high mitotic activity [99]. Surgery rarely has a role in this disease; the most common procedures performed are isthmusectomy or cytoreduction to alleviate tracheal compression [81]. In rare cases that anaplastic carcinoma is diagnosed in the intrathyroid stage, without a coexisting well differentiated thyroid cancer component, thyroid lobectomy with wide margins of adjacent soft tissue on the side of the tumor is an appropriate surgical management [98]. If the anaplastic tumor is very small and completely confined to the thyroid, total thyroidectomy with complete tumor resection does not prolong survival compared to ipsilateral thyroid lobectomy and if it is associated with a higher complication rate [100] [102]. However, some experts prefer total or near total thyroidectomy with dissection of the central and lateral lymph nodes of the neck [111]. The reason for this is that differentiated thyroid cancer and anaplastic thyroid cancer often coexist, and total thyroidectomy offers a greater chance of complete resection [111]. For patients with small intra-thyroid anaplastic tumors associated with a differentiated thyroid cancer, total thyroidectomy is recommended, if complete macroscopic resection and minimal morbidity can be performed, to facilitate subsequent treatment of differentiated cancer [111].

Anaplastic thyroid cancers are extremely aggressive, with a specific mortality close to 100%. The average survival ranges from three to seven months, and the one and five year survival rates, are 20% to 35% percent and 5% to 14%, respectively [101] [102] [105] [112] [113] [114], with 90% of patients dying of the disease within 6 months of diagnosis, usually secondary to local progression [81].

Primary thyroid lymphoma is a rare diagnosis, but it should always be considered in the differential diagnosis of patients with thyroid nodules, goiter, and carcinomas, mainly because their prognosis and treatment differ substantially from other disorders. Lymphomas of the thyroid gland typically manifest in the seventh decade of life (the median and median age is between 65 and 75 years), affect women more commonly than men (with a female 4:1 predominance), and are often associated with a history of Hashimoto's thyroiditis [115]-[120]. They represent less than 2% of all thyroid neoplasms and often present as a rapidly growing tumor with symptoms of dysphagia and dysphonia, possibly confusing the diagnosis with anaplastic thyroid carcinoma [121]. In a Danish epidemiological survey, the annual incidence rate was estimated at 2.1 cases per million people [115]. Pre-existing chronic autoimmune thyroiditis (Hashimoto's disease) is the only known risk factor for primary thyroid lymphoma and is present in approximately half of patients [122]. Among patients with Hashimoto's thyroiditis, the risk of thyroid lymphoma is at least 60 times higher than in patients without thyroiditis [115] [119] [120].

Thyroid lymphoma can be primary or secondary, they are almost always non-Hodgkin (B-cells), since thyroid Hodgkin lymphoma is extremely rare [115] [118] [122]. Only about 2% of extra lymph node lymphomas originate within the thy-

roid gland. Occasional cases of T lymphocyte lymphomas have been described, often in endemic areas for adult T-cell leukemia/lymphoma associated with lymphotropic virus-T (HTLV)-I [123] [124]. Sixty percent to 80% of thyroid lymphomas are diffuse large B-cells of the germinal center type [116] [117] [118] [125] [126]. The second most common subtype (about 30% of cases) is lymphoma of the extra-ganglion marginal marginal zone [32]. Other less common histological subtypes include follicular lymphomas; Small extra lymph node lymphomas have also been described [32]. Extra-lymph node marginal lymphomas of the type of mucous-associated lymphoid tissue (MALT) are generally associated with Hashimoto's thyroiditis [127].

Histologically, the cells are monomorphic and stain positively for lymphocyte markers such as CD20 [81]. Tumors of MALT origin generally have a better prognosis and can often be treated with radiation therapy alone, rather than the multimodal therapy necessary to treat lymphomas other than MALT [81]. Survival rates for lymphoma located in the thyroid gland (stage IE) are generally favorable, with a 5-year survival rate of 75% to 85%. However, patients with diseases on both sides of the diaphragm (stage IIIE) or disseminated disease (stage IV) have a 5-year survival rate of less than 35% [53].

4. Diagnosis

Thyroid cancer is discovered incidentally in the vast majority of cases during imaging studies (computed tomography, positron emission tomography, magnetic resonance imaging or ultrasonography) performed for reasons unrelated to the thyroid. The vast majority of patients with thyroid cancer have no specific symptoms and the results of these incidentalomas will trigger a diagnostic evaluation. When patients present to a doctor with a specific symptom, it is often with the finding of a new tumor/thyroid nodule, an increase in size of a previously detected nodule, pain secondary to a nodule hemorrhage, or a lymph node palpable cervical [53]. Symptoms of dysphagia, dysphonia, or dyspnea often predict a poor prognosis since these symptoms are the result of a local invasion and are usually due to undifferentiated thyroid cancer, since differentiated tumors rarely invade surrounding structures [5].

Performing a medical history and a complete physical exam is the first step in the evaluation of a patient suspected of having thyroid cancer. Special attention should be given to personal history of radiation exposure, family history of thyroid malignancy, or thyroid cancer syndromes (Carney complex, multiple endocrine neoplasia, familial adenomatous polyposis, and Cowden syndrome). Also, ask about the symptoms of dysphagia, dysphonia or dyspnea that an invasive component may suggest. The presence of diarrhea or facial hyperemia in association with nodular thyroid disease should increase suspicion for medullary thyroid carcinoma [79]. The physical examination should focus on findings suggestive of invasion or regional metastases that may include fixation to surrounding structures, presence of tracheal deviation, or vocal cord paralysis [53]. In the ab-

sence of these findings, the presence of slightly grown lymph nodes (1 to 2 cm) together with a thyroid nodule suggests regional metastases [53] [81]. Palpable lymphadenopathy is most frequently identified along the middle and lower portion of the jugular chain. Finally, before any surgical intervention, the extent of the disease in the neck should be evaluated in anticipation of surgical positioning [53].

All patients undergoing thyroid surgery should have a preoperative evaluation of the voice as part of their preoperative physical examination. This should include the description of the patient if he has voice changes, as well as the evaluation of the voice doctor (recommendation # 40 of the American Thyroid Association [ATA]) [34]. The preoperative laryngeal examination should be performed in all patients with voice abnormalities in the preoperative period, a history of cervical or upper thoracic surgery, which puts the recurrent laryngeal or vagus nerve at risk, and in patients with known thyroid cancer with extra posterior thyroid extension or extensive central nodal metastases (ATA recommendation # 41) [34].

The prevalence of palpable thyroid nodules in the general population is approximately 5% to 7% in women and 1% in men living in parts of the world with sufficient iodine [1] [2]. In contrast, high-resolution neck and thyroid ultrasound can detect thyroid nodules in approximately 19% to 68% of randomly selected people, with higher frequencies in women and the elderly [3] [4]. The clinical importance of thyroid nodules lies in the need to rule out thyroid cancer, which occurs between 7% and 15% of cases, varying according to age, sex, radiation exposure history, family history, among other factors [5] [6].

If a thyroid nodule larger than 1 cm in any diameter is identified, a serum level of thyroid stimulating hormone (TSH) should be obtained (recommendation 2 ATA) [34]. If the TSH is low, a thyroid scan should be performed (the only indication today to perform this study) to document if the thyroid nodule is hyperfunctional ("hot", that is, the uptake of the marker is greater than the normal thyroid), isofuncionante ("warm", that is, the uptake of the marker is equal to the surrounding thyroid) or not functioning ("cold", that is, it has a lower uptake than the thyroid tissue) [128]. Because hyperfunctional thyroid nodules rarely contain malignancy, if one that corresponds to the nodule in question is found, a cytological evaluation is not necessary [34]. High serum levels of TSH, even within high ranges of normality, are associated with an increased risk of malignancy in the thyroid nodule, as well as a more advanced stage of thyroid cancer [129].

During the initial assessment of thyroid nodules, it is not recommended to routinely obtain serum thyroglobulin (Tg) (ATA recommendation 3) [34]. Serum levels of Tg may be elevated in the vast majority of thyroid diseases (benign and malignant) and is an insensitive and nonspecific test for thyroid cancer [130] [131]. The utility of serum calcitonin in the initial assessment of thyroid nodules has been evaluated in prospective non-randomized studies [132] [133]

[134] [135], with mixed results, therefore, the ATA cannot recommend either for or against the measurement Routine serum calcitonin in patients with thyroid nodules (ATA recommendation 4) [34].

High-resolution neck and thyroid ultrasound should be performed in all patients suspected of having thyroid nodules, nodular goiter, or any radiographic abnormality that suggests a thyroid nodule detected incidentally in another imaging study (computed tomography or magnetic resonance imaging), or 18FDG-PET) (ATA recommendation 6) [34]. Ultrasound of the neck and thyroid should evaluate the following characteristics [34]: the thyroid parenchyma (if homogeneous or heterogeneous), the size of the thyroid gland, the size, location, and ultrasonographic characteristics of any nodule, and finally the presence or absence of suspicious cervical lymph nodes in the central or lateral compartments [34] [53]. **Table 4** shows the characteristics that should be assessed in the high-resolution neck and thyroid ultrasound.

The ultrasonographic pattern associated with a thyroid nodule confers a risk of malignancy, and combined with the size of the nodule, guides decision making (**Table 5**). The ultrasound pattern of high suspicion of malignancy includes solid, hypoechoic nodules, or nodules with mixed components (solid hypoechoic and partially cystic nodule) with one or more of the following characteristics: irregular margins (infiltrative, micro-lobulated), microcalcifications, higher form than wide, calcifications at the edge of the cyst, evidence of extra thyroid extension [136] [137] [138].

The most accurate and cost-effective method for evaluating thyroid nodules is fine needle aspiration biopsy (FNAB) (ATA recommendation 7) [34]. Thyroid nodules with a higher probability of obtaining a non-diagnostic cytology (cystic component greater than 25% to 50%) or a sampling error (nodules difficult to palpate or located in the posterior portion of the thyroid lobe), it is preferred to perform a FNAB guided by ultrasound [139] [140]. **Figure 1** and **Figure 2** provide

Table 4. The characteristics that should be assessed in the ultrasound [233] [234].

- Node size (in three dimensions)
- The location (example—right upper lobe/if anterior or posterior)
- Description of the ultrasonographic characteristics of the thyroid nodule:
  - Composition of the nodule:
    - Solid, cystic or spongiform
  - Ecogenicity:
    - Isoechoic, hyperechoic, hypoechoic
  - Margins:
    - Regular
    - Irregular:
    - Defined as infiltrative, microlobed or spiculated
  - Presence and type of calcifications:
    - Marcocalcifications or microcalcifications
  - Shape:
    - If the nodule is taller than wide
  - Vascularity:
    - Central or peripheral

Table 5. Ultrasonographic patterns of thyroid nodules, estimated risk of malignancy, and management guide for thyroid nodules with FNAB [34] [143].

Ultrasonographic Pattern	Ultrasonographic Characteristics	Estimated Risk of Malignancy	Size to perform FNAB
High Risk	Hypoechoic, solid nodules, or nodules with mixed components (solid and partially cystic hypoechoic nodule) with one or more of the following characteristics: irregular margins (infiltrative, microlobed), microcalcifications, taller than wide, calcifications on the edge of the cyst, evidence of extra thyroid extension	Greater than 70% - 90%	FNAB is recommended if its dimensions are equal to or greater than 1.0 cm
Intermediate Risk	Hypoechoic solid nodule with smooth (regular) margins without microcalcifications, no evidence of extra thyroid extension, and the shape is not taller than wide	10% al 20%	FNAB is recommended if its dimensions are equal to or greater than 1.0 cm
Low Risk	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, no microcalcification, no irregular margin, no evidence of extra thyroid extension, no taller than wide	5% al 10%	FNAB is recommended if its dimensions are equal to or greater than 1.5 cm
Very Low Risk	Spongiform or partially cystic nodules without any of the ultrasonographic features described in low, intermediate, or high suspicion patterns	Less than 3%	FNAB can be considered if its dimensions are equal to or greater than 2.0 cm Observation without BAAF is also reasonable
Benign	Purely cystic nodules (without solid component)	Less than 1%	Do not perform FNAB

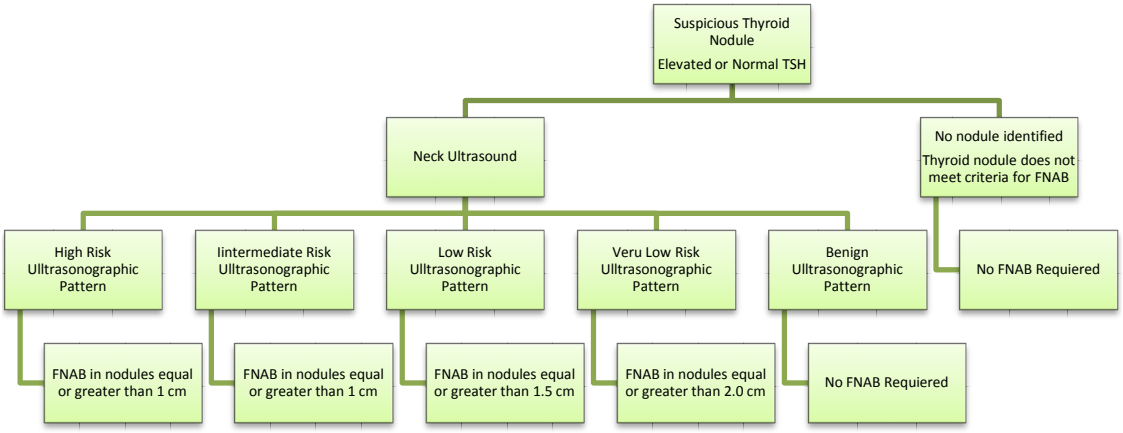

Figure 1. Algorithm for the initial evaluation and treatment of patients with thyroid nodules according to the ultrasonographic pattern.

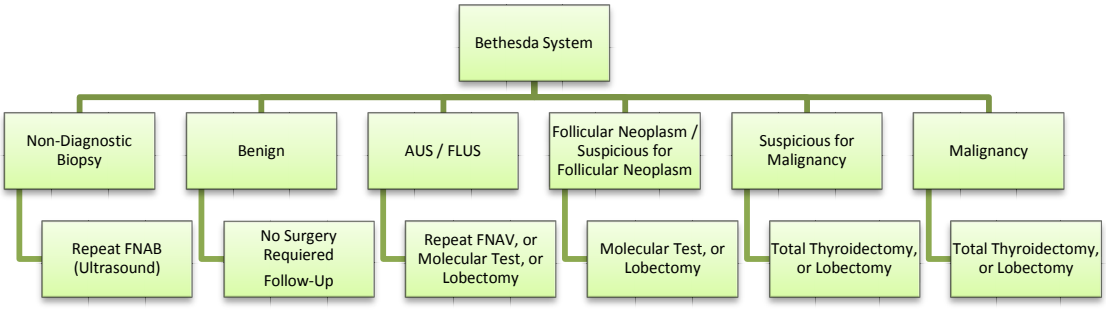

Figure 2. Algorithm for the treatment of patients with thyroid nodules according to the pattern the result of the FNAB [143].

an algorithm for the initial evaluation and management of patients with thyroid nodules based on their ultrasonographic pattern and the results of the FNAB [34].

Non-diagnostic or unsatisfactory FNABs (Bethesda 1) are those that do not meet the quantitative or qualitative requirements established to say that the cytological assessment is adequate (*i.e.*, the presence of at least six groups of well-visualized follicular cells, each group containing at least 10 well-preserved epithelial cells, preferably in a single lamella) [141] [142] [143]. When a BAAF is performed in a thyroid nodule and the initial cytology result is non-diagnostic, the BAAF should be repeated with the support of ultrasound; and if available, the cytological evaluation should be performed at the time of the FNAB (recommendation 10 of the ATA) [34] [144] [145] [146]. It has been suggested that FNAB should be repeated no earlier than three months after the initial FNAB to avoid a falsely positive interpretation due to biopsy-induced reactive changes [147]. Two recent studies have questioned the need for a waiting period of three months after the first FNAB because they found no correlation between the diagnostic performance and accuracy of the second FNAB and the waiting time between procedures [148] [149]. The ATA tells us that a waiting period of three months after a non-diagnostic biopsy is likely not necessary [34]. Thyroid nodules that have had multiple FNABs that turned out to be non-diagnostic without having a highly suspected ultrasonographic pattern may be recommended observation vs. surgical excision to have a definitive histopathological diagnosis (ATA recommendation 10) [34].

In published series of patients classified according to the Bethesda system, non-diagnostic samples constituted 2% to 16% of all FNAB samples, of which 7% to 26% were resected [150] [151] [152]. The frequency of malignancy among all FNABs initially rated as non-diagnostic was 2% to 4% and among the non-diagnostic samples that were finally resected the frequency of malignancy 9% to 32% [150] [151] [152].

If the thyroid nodule turns out to be benign in cytology after a FNAB (Bethesda 2), no additional diagnostic studies or immediate treatment are required (ATA recommendation 11) [34]. Although prospective studies are lacking, the rates of malignancy in the retrospective series range from 1% to 2% [143] [153] [154] [155].

FNAB classified as atypia of undetermined significance or follicular lesion of undetermined significance (Bethesda 3), is characterized by having specimens containing cells with architectural and/or nuclear atypia that are more prominent than expected for benign changes, but not sufficient for be located in one of the highest risk diagnostic categories [141] [143] [156]. In the studies that used the criteria established by the Bethesda System, the risk of cancer for patients with atypical nodules of undetermined significance or follicular lesion of undetermined significance who underwent surgery was 6% to 18% if NIFT (follicular thyroid neoplasia. Non-invasive with papillary nuclear characteristics) is not

considered as cancer, and 10% to 30% if NIFT is considered as a cancer [143].

For thyroid nodules with atypical cytology of undetermined significance or follicular lesion of undetermined significance after a FNAB, with worrying clinical and ultrasonographic characteristics, the assessment can be continued by repeating the BAAF or if you have the technology you can use molecular tests to complement the risk assessment of malignancy instead of proceeding directly with either a surveillance strategy or diagnostic surgery (lobectomy) [143]. Patient preference should be considered in decision making (recommendation 15 of the ATA) [34]. If the FNAB is not repeated, and molecular tests are not performed, or both studies proved inconclusive, a diagnostic surgical excision can be performed for thyroid nodules with Bethesda 3 classification, according to clinical risk factors, ultrasound pattern and patient preference (ATA recommendation 15) [34].

The diagnostic category of the Bethesda IV, follicular neoplasm/suspected cytology of follicular neoplasm is used for cellular aspirates:

- Composed of follicular cells arranged in an altered architectural pattern characterized by cell crowding and/or microfilm formation, lacking nuclear characteristics of papillary carcinoma; or
- Compounds almost exclusively of oncocytic cells (Hurthle) [141] [143] [157] [158].

This is an intermediate risk category of malignancy in the Bethesda system, with an estimated risk of malignancy between 10% to 40% if NIFT is not considered as cancer, and between 25% to 40% if NIFT is considered as cancer [143]. This category represents 1% to 25% (average, 10%) of all FNAB samples [34].

Diagnostic surgical excision (lobectomy) is the long-established standard for the treatment of thyroid nodules with Bethesda IV cytology. However, today if the technology is taken into account, after taking into account the clinical assessment and ultrasonographic characteristics, molecular tests can be used to complement the assessment of the risk of malignancy rather than proceed directly with surgery (recommendation 16 of the ATA) [34]. Patient preference should be considered in clinical decision making. If molecular tests cannot be performed or are undetermined, surgical removal can be considered for the definitive diagnosis of thyroid nodules classified as Bethesda IV (ATA recommendation 16) [34].

The diagnostic category of the Bethesda V system, suspected cytology for malignancy represents 1% to 6% of all FNABs, and is reserved for aspirates with cytological characteristics that generate a high suspicion of malignancy (mainly for papillary thyroid carcinoma) but that they are not sufficient for a conclusive diagnosis [141] [143] [159]. This is the category with the highest risk of undetermined cytology in the Bethesda System, with an estimated cancer risk of 45% to 60% if NIFT is not considered as cancer and 50% to 75% if NIFT is considered as cancer [143]. Due to the high risk of cancer, the diagnosis of suspicious papillary carcinoma is an indication for surgery [34].

If the FNAB results in a suspicious cytology for papillary thyroid carcinoma, surgical treatment should be very similar to the management of a frankly reported FNAB. Factors that we must take into account in offering the definitive treatment with a suspicious cytology for papillary thyroid carcinoma, are the clinical risk factors, the ultrasonographic characteristics, the patient's preference and possibly the results of the molecular tests (BRAF, RAS, RET/PTC, PAX8/PPAR) (ATA recommendation 17) [34].

If the cytological result is a diagnosis of primary thyroid malignancy, Bethesda VI, surgery is generally recommended (ATA recommendation 12) [34]. A diagnostic cytology of primary thyroid malignancy will almost always lead to thyroid surgery. However, in some parts of the world under active research protocol active surveillance can be offered as an alternative to immediate surgery in certain patients who meet some very specific criteria [160] [161]:

- Patients with very low risk tumors (for example, papillary microcarcinomas without clinically evident metastases or local invasion, and without convincing cytological evidence of aggressive disease);
- Patients with high surgical risk due to multiple comorbidities;
- Patients with a relatively short lifespan (for example, severe cardiopulmonary disease, other malignant diseases, very old age);
- Patients with concurrent medical or surgical problems that must be addressed before thyroid surgery.

5. Molecular Studies in the Valuation of Thyroid Nodes

In recent years, advances have been made in the identification of genes related to the origin of thyroid cancer (see **Table 1**). Studies of the patterns of genetic alterations found in thyroid tumors suggest that there are differences in the pathogenesis of different types of thyroid tumors, which probably explains the range of biological behavior observed between different types of thyroid neoplasms [81]. The genomic panorama of papillary thyroid cancer was recently described as part of The Cancer Genome Atlas (TCGA) project in which a low frequency of somatic mutations was found compared to other carcinomas and there was a dominant role and mutual exclusivity of generating genetic mutations, somatic in the MAPK and PI3K pathways [162]. In approximately 50% to 60% of cases, a constitutive activation of the BRAF kinase, a member of the Ras/MAPK pathway, is present and generally results from a substitution of amino acids V600E [32] [162]. BRAF normally depends on the activation of Ras to propagate extracellular signal transduction [30].

The TCGA work indicated that papillary thyroid tumors that have the BRAF V600E mutation represent a diverse group of tumors and should not be considered a homogeneous group; and I conclude that more studies are needed to capture their genetic diversity [162]. On certain occasions, activation of the Ras oncogene, located before BRAF, has also been implicated as an initiating event of papillary thyroid carcinoma, as well as in follicular thyroid tumors [30] [162].

Somatic mutations have been identified in the Ras oncogene (H-, K-, N-Ras) in benign and malignant thyroid tumors (in 12% of papillary thyroid carcinomas in TCGA), and therefore appear to be an early event in thyroid tumorigenesis [162]. Some studies suggest that Ras mutations are more prevalent in follicular thyroid cancers, the follicular variant of papillary thyroid cancer, and in follicular adenomas [163]. Ras mutations can result in allelic loss or in chromosomal rearrangements that lead to increased rates of thyroid follicular cancer formation [163]. There are differences in signaling in papillary thyroid tumors driven by Ras and BRAF V600E; Papillary tumors with BRAF mutations signal primarily through MAPK while papillary tumors with Ras mutations signal through MAPK and PI3K; This may have broad implications for targeted therapies [30] [163].

Chromosomal rearrangements have been observed in the formation of RET/PTC fusion oncogenes; radiation-induced papillary tumors harbor this alteration [164]. There are other relatively rare oncogenic fusions described in papillary thyroid tumors such as BRAF, PAX8/PPARG, ETV6/NTRK3 and RBPMS/NTRK3 [165].

The RET proto-oncogene is a tyrosine kinase receptor that is expressed primarily in tumors of neural crest origin, which explains the high incidence of mutations in medullary thyroid cancers that originate in parafollicular cells (C cells) [166]. The RET gene is found on chromosome 10 and germline mutations result in missense activating mutations that are responsible for 95% of hereditary medullary thyroid carcinomas, including those associated with multiple endocrine neoplasia 2A and 2B [166] [167]. In 80% of cases of medullary thyroid cancer, the disease is sporadic, without a hereditary etiology, but a somatic mutation is identified in the RET gene in 40% of these sporadic cases [79] [81] [167]. In sporadic cases, mutations are found most often in codon 918 that results in the constitutive activation of the RET tyrosine kinase receptor [75]. Almost all patients with multiple endocrine neoplasia 2A and 2B that are transmitted in an autosomal dominant manner will develop medullary thyroid cancer and the detection of germline mutations in the RET gene has been of great value in the early identification of patients who have a genetic basis for your disease [75]. Even in patients with sporadic medullary thyroid carcinoma, 6% to 10% of these patients will have a mutation in the RET proto-oncogene germ line, which reveals a new family of patients with previously undiagnosed medullary thyroid carcinoma [81]. The discovery of the RET proto-oncogene has had a very important clinical impact, which affects screening and prophylactic treatment of patients who are members of families with multiple endocrine neoplasia and relatives of medullary thyroid cancer [81]. The somatic mutation in the Ras gene is observed in approximately 15% of patients with sporadic medullary thyroid carcinoma [167].

Larger studies on the use of molecular tests in patients with undetermined BAAF respectively evaluated a panel of seven genes of genetic mutations and chromosomal reconstructions (BRAF, RAS, RET/PTC, PAX8/PPAR) [168], an expres-

sion classifier gene (GEC 167; expression of messenger RNA of 167 genes) [169], and the immunohistochemistry of galectin-3 (in cell blocks) [170]. There is currently no single optimal molecular test that can definitively confirm or rule out a malignant neoplasm in all cases of undetermined cytology, and more studies are needed long-term results that demonstrate clinical utility before the standard becomes, but the future of the evaluation of thyroid nodules and management is going in this direction.

6. Treatment of Thyroid Cancer

The treatment of thyroid tumors, and in some cases, when more tissue is needed to properly diagnose a thyroid nodule, is surgical resection. The goal of thyroid cancer management remains the complete elimination of the disease with minimal morbidity [81]. Adequate surgical treatment will allow careful postoperative follow-up, adjuvant therapies if necessary, and minimizes the possibility of disease recurrence.

Surgery for thyroid cancer is a vital element of a multifaceted treatment approach. The recommended operation must be compatible with the general management strategy and the monitoring plan recommended by the multidisciplinary team. Experienced surgeons should be referred to patients with high-risk characteristics (clinical disease N1, concern for invasion of the recurrent laryngeal nerve, or extremely invasive disease), since both the quality of the surgery and the experience of the surgeon may have a significant impact on clinical outcomes and complication rates [171] [172] [173] [174].

Because papillary thyroid cancer has an extremely low mortality rate, recurrence of the disease has become the main objective of interest when deciding on optimal surgical management for most patients [81]. For patients with papillary thyroid cancer measuring more than 1 cm, the surgery that has historically been recommended is a total thyroidectomy that certainly remains the appropriate operation for well-differentiated high-risk thyroid cancers [34]. The reasons used to consider performing a total thyroidectomy in low-risk thyroid carcinoma include lesions identified within the contralateral thyroid lobe because papillary thyroid cancer foci are found bilaterally in up to 85% of cases and in 5% to 10% of cases of recurrence the focus of recurrence is in the contralateral lobe when a thyroid lobectomy is performed [81]. From the postoperative point of view, the remaining thyroid tissue, if a more conservative resection is performed, makes radioactive iodine ablation of the remaining gland prohibitive. In addition, the measurement of serum thyroglobulin as a marker of persistent or recurrent disease after thyroid lobectomy is more difficult to interpret given the remaining thyroid tissue [81]. A total thyroidectomy avoids these difficulties and minimizes re-operative surgery that is associated with an increase in complication rates.

If surgical treatment is chosen for patients with thyroid cancer less than 1 cm without extra thyroid extension and without clinical evidence of nodal metastas-

es (cN0), the initial surgical procedure should be a thyroid lobectomy unless there are clear indications to remove the contralateral lobe (ATA recommendation 35) [34]. Thyroid lobectomy is a suitable treatment for small, unifocal intra-thyroid carcinomas, in the absence of previous radiation to the head and neck, familial thyroid carcinomas, or clinically detectable cervical lymph node metastases (ATA recommendation 35) [34]. The patient's preference should always be taken into account during the treatment discussion.

For patients with thyroid cancer greater than 1 cm and less than 4 cm without extra thyroid extension, and without clinical evidence of nodal metastases (cN0), the initial surgical procedure may be a bilateral procedure (almost total or total thyroidectomy) or a unilateral procedure (lobectomy) (ATA recommendation 35) [34]. Thyroid lobectomy may be the initial treatment for low-risk papillary and follicular carcinomas; however, the team managing the patient can choose total thyroidectomy to allow treatment with radioactive iodine or to facilitate the follow-up of these patients (ATA recommendation 35) [34]. The patient's preference should always be taken into account during the treatment discussion.

There is controversy over whether it should be performed and the extent of prophylactic dissection of the lymph nodes in order to prevent local recurrence, provide more accurate staging, and increase survival. The distinction between a dissection of the therapeutic versus prophylactic (or elective) central compartment is that a therapeutic dissection implies that nodal disease has already occurred and has been detected clinically or by preoperative imaging (cN1 disease) [53] [81]. A dissection of the elective or prophylactic central compartment implies that there is no clinical or radiographic evidence of nodal metastases [53] [81]. This difference is important because the impact of having clinically detectable lymph nodes on survival and local recurrence may differ compared to microscopically detected disease. Similarly, a dissection of the central compartment can be ipsilateral (the same side as the dominant tumor) or bilateral (ipsilateral and contralateral) and it is important to document this distinction in the surgical note.

The central compartment (level VI) is limited superiorly by the hyoid bone, inferiorly by the innominate artery, and laterally by the carotid arteries [34]. Therapeutic dissection of the central compartment (level VI of the neck) for patients with clinically involved central nodes should accompany total thyroidectomy to provide complete resection of the disease (ATA recommendation 36) [34]. Preventive/prophylactic dissection of the central compartment (ipsilateral or bilateral) in patients with papillary thyroid carcinoma with clinically non-involved lymph nodes (cN0) in patients with advanced primary tumors (T3 or T4), or clinically compromised lymph nodes in the lateral compartment of the neck (cN1b), or if the information will be used to plan additional steps in therapy (ATA recommendation 36) [34]. Thyroidectomy without prophylactic dissection of the central compartment is appropriate for small papillary tumors (T1 or T2), non-invasive, with clinically negative lymph nodes (cN0) and for most follicular cancers (ATA recommendation 36) [34]. Therapeutic dissection of the lymph nodes

in the lateral compartment should be performed in patients with metastatic lateral cervical lymphadenopathy proven by biopsy (ATA recommendation 37) [34]. The isolated removal of the affected lymph nodes, known as "berry picking," violates the central compartment without adequately addressing the full extent of the disease and may be associated with higher rates of recurrence and morbidity in revision surgery [81].

Usually, the diagnosis of a follicular cell carcinoma or Hürthle is made after the surgical procedure, which is usually a thyroid lobectomy. In these circumstances, a total thyroidectomy is often performed in high-risk patients when it is anticipated that the patient will require adjuvant treatment with radioactive iodine, since all thyroid tissue must be removed for radioactive iodine to be effective [53] [81]. Patients who underwent a thyroid lobectomy should be offered to complete the total thyroidectomy to patients who would have recommended a bilateral thyroidectomy if the diagnosis had been available before the initial surgery (ATA recommendation 38) [34]. Therapeutic dissection of the lymph nodes in the central compartment should be included if the lymph nodes are clinically involved (ATA recommendation 38) [34]. Thyroid lobectomy alone can be considered as a sufficient management for low-risk papillary and follicular carcinomas (ATA recommendation 38) [34]. Ablation with radioactive iodine instead of completing thyroidectomy is not routinely recommended; however, it can be used to burn the remaining lobe in selected cases (ATA recommendation 38) [35].

Anaplastic carcinoma represents a unique challenge because it is rarely diagnosed in a timely manner, so surgical management is usually only offered as a palliative option [53] [81] [95]. In the rare case in which anaplastic carcinoma has been diagnosed incidentally or at the beginning of its evolution, total thyroidectomy with central compartment lymphadenectomy and ipsilateral modified radical lymphadenectomy offers the best chance of survival in the exceptional case that the tumor is intra-thyroid [91] [95] [101]. Given the aggressive nature and limited survival for patients with anaplastic carcinoma, aggressive surgical intervention involving resection of adjacent structures, such as the larynx, pharynx or esophagus, is often avoided due to the associated excessive morbidity [101]. Resection of disease that extends beyond the thyroid gland may be appropriate in highly selected individuals as part of a multimodal treatment regimen along with radiation, chemotherapy, and immunotherapy [99].

7. Staging of Thyroid Cancer

Staging of thyroid carcinoma is performed more frequently using the American Joint Committee on Cancer (AJCC) system [175]. Other staging systems validated by multiple studies have been used to predict the specific survival of thyroid cancer, including AGES (age, grade, extent, size), AMES (age, metastasis, extension, size), MACIS (metastasis, age, resection, invasion and size integrity) and EORTC (European Organization for Research and Treatment of Cancer). In

the medical literature between 1960 and 1970 several articles were published confirming that the cell of origin of thyroid cancer was crucial to discuss the prognosis of these tumors [176] [177]. The Mayo Clinic group reported its results from a population of 859 patients with papillary thyroid cancer treated at their institution between 1940 and 1970. Their results suggested that an advanced age at diagnosis, extra thyroid extension, and metastasis at a distance they were strong predictors of death. These results were replicated by several groups including that of Mazzaferri who reported similar results to those of the Mayo Clinic in a population of 576 patients with papillary thyroid cancer [178] [179].

The Mayo Clinic combined the risk factors of age, histological grade of the tumor, extent of the disease, and the size of the lesion in the AGES system to predict the risk of mortality (low risk or high risk). Subsequently, this system was improved to include resection quality by reporting the system as MACIS [180]. Cady *et al.* they reviewed the Lahey clinic database that included more than 800 patients treated over a period of four decades reporting very similar results introducing the AMES system that included age, distant metastasis, extra thyroid extension, and the size of the lesion by classifying patients in high risk or low risk groups for mortality [181]. A similar group of risk factors was reported by the Memorial Sloan Kettering Cancer Center group that resulted in the GAMES system (which included the histological grade) [182]. They separated patients and tumors into two groups, one high risk and the other low risk for mortality [182]. They also introduced an intermediate group for young patients with tumor risk factors of poor prognosis, or for elderly patients without tumor risk factors for poor prognosis [183]. The impact of lymph node metastases on thyroid cancer mortality is very limited, which is why it has not been included as a risk factor in most predictive mortality systems. The first works of Cady *et al.* they suggested that lymph node metastases had a protective effect [184], a finding that can be explained because their cohort consisted of young patients, and the association of young age with excellent survival and a higher incidence of lymph node metastases. Subsequently Hughes *et al.* showed that in patients younger than 45 years regional metastases were not associated with a higher mortality. However, in older patients, lymph node metastases had a significant impact on mortality [185]. From the last edition of the AJCC, nodal metastases (N) were included as part of staging in patients older than 45 years [186].

Many similar risk prediction tools have been published focusing on the risk of death from well-differentiated thyroid cancer [187]. Unfortunately, none of the staging systems, including the AJCC system, have been shown to be superior [175]. The ATA in 2009 and with its recent modifications in 2015 published guidelines for staging patients based on their risk of recurrence [34]. Again, predictive risk factors for recurrence include the quality of surgical resection, the presence of distant metastases, the presence of extra thyroid extension, and high-risk histopathological factors. None of the staging systems have a better predictive value than the other in the prediction of recurrent disease, especially

in individuals who develop thyroid cancer at an early age [175]. Unlike the previously cited staging systems that calculate the risk of death, nodal metastases do have an intermediate risk of recurrence. As almost no well-differentiated thyroid cancer patient is going to die of their disease, a staging system designed to predict the risk of recurrence rather than mortality can prove to be of greater clinical utility for modern physicians.

Staging using the AJCC system is recommended for all patients with differentiated thyroid cancer, depending on its usefulness in predicting disease mortality and its requirement for cancer registries (ATA recommendation 478) [175]. The 8th edition of the AJCC staging system modified the definitions of the primary tumor and nodal metastases (**Tables 6-8**) [175]. Age at the time of diagnosis is

Table 6. AJCC staging system for papillary, follicular, poorly differentiated, Hürthle cell, and anaplastic thyroid cancer [175].

Definition of the Primary Tumor (T)
TX—Primary tumor cannot be evaluated
T0—No evidence of primary tumor
T1—Tumor ≥ 2 cm in the largest dimension limited to the thyroid: T1a—Tumor ≤ 1 cm in the largest dimension limited to the thyroid T1b—Tumor > 1 cm, but ≤ 2 cm in the largest dimension limited to the thyroid
T2—Tumor > 2 cm, but ≤ 4 cm in the largest dimension limited to the thyroid
T3—Tumor > 4 cm limited to the thyroid or extra gross thyroid extension that invades only the pre-thyroid muscles: T3a—Tumor > 4 cm limited to the thyroid T3b—Extra macroscopic thyroid extension that invades only pre-thyroid muscles (sternohyoid, sternothyroid, thyroid or omohyoid muscles) of a tumor of any size
T4—Includes extra gross thyroid extension: T4a—Extra macroscopic thyroid extension that invades subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve of a tumor of any size T4b—Extra macroscopic thyroid extension that invades the prevertebral fascia, or covers the carotid artery, or mediastinal vessels, of a tumor of any size
Definition of regional lymph nodes (N)
NX—Regional lymph nodes cannot be evaluated
N0—There is no evidence of loco-regional lymph node metastasis: N0a—One or more benign lymph nodes cytologically or histologically confirmed N0b—There is no radiological or clinical evidence of regional crazy lymph node metastases
N1—Metastasis to regional nodes: N1a—Metastasis to lymph nodes of level VI or VII (pretracheal, paratracheal or prelaringeal/Delphiano or upper mediastinal). This may be a unilateral or bilateral disease. N1b—Metastasis in the lateral, lateral bilateral lymph nodes, or contralateral (level I, II, III, IV or V), or retropharyngeal lymph nodes
Definition of distant metastasis (M)
M0—No distant metastasis M1—Remote metastasis

Table 7. Prognostic groups based on AJCC staging in well differentiated thyroid cancer [175].

Age at diagnosis	T	N	M	Stage
<55 years	Any T	Any N	M0	I
<55 years	Any T	Any N	M1	II
≥55 years	T1	N0/NX	M0	I
≥55 years	T1	N1	M0	II
≥55 years	T2	N0/NX	M0	I
≥55 years	T2	N1	M0	II
≥55 years	T3a/T3b	Any N	M0	II
≥55 years	T4a	Any N	M0	III
≥55 years	T4b	Any N	M0	IVA
≥55 years	Any T	Any N	M1	IVB

Table 8. Prognostic groups based on AJCC staging in anaplastic thyroid cancer [175].

T	N	M	Stage
T1-T3a	N0/NX	M0	IVA
T1-T3a	N1	MO	IVB
T3b	Any N	M0	IVB
T4	Any N	M0	IVB
Any T	Any N	M1	IVC

perhaps one of the most important predictive factors for patients with well-differentiated thyroid cancer, as evidenced by their inclusion in the AJCC manual, as well as in each of the other staging systems mentioned previously [175] [178]-[183]. It has also been shown in some studies that the male gender is an independent predictor of survival, since in these studies thyroid cancer is more aggressive in men [188] [189] [190], although this variable is not specifically included in any system of staging because. In general, the prognosis of patients with well-differentiated thyroid carcinoma is based on their age, sex, extent of disease and the size of their primary tumor. The issue of lymph node metastases and prognosis is still debated as previously mentioned in the text, since lymph node involvement predicts local recurrence but does not contribute significantly to patient survival [175]. Involvement of lymph nodes affects the classification of AJCC staging only in patients older than 55 years [175].

The AJCC staging for thyroid cancer stratifies patients in four stages according to the TNM classification, with the exception of anaplastic tumors, which are always considered stage IV [175]. Staging is based on the histology of the primary tumor and the patient's age (for differentiated cancer), which demonstrates the importance of these parameters in survival and prognosis. The eighth edition of the AJCC staging system for differentiated thyroid cancer has been updated

compared to previous editions as the age of diagnosis increased from 45 years to 55 years [175]. The limited extra thyroid extension was eliminated from the definition of T3 disease [175]. T3a is now a new category and refers to tumors larger than 4 cm in the largest dimension, but still limited to the thyroid gland [175]. T3b is also a new category defined as a tumor of any size with extra gross thyroid extension that invades only the pre-thyroid muscles [175]. Importantly, the definition of the central compartment was expanded to include both level VI and level VII lymph nodes [175].

Survival rates for various thyroid cancers are presented in **Table 9**. Although similar for stage I disease, survival for follicular thyroid cancer is slightly worse than for papillary cancer and this is probably due to the trend of hematogenous dissemination, age and the most advanced stage at the time of diagnosis [81]. Anaplastic thyroid cancer has one of the worst survival rates of all malignant neoplasms with a 1-year survival of 17% and a 5-year survival of approximately 6%, which demonstrates the aggressiveness of this disease [175]. In general, the prognosis for patients diagnosed with thyroid cancer is good with survival rates greater than 85% to 90% for most stages, probably as a result of the indolent nature of the disease.

8. Adjuvant Treatment

The objectives of adjuvant treatment include prolonging survival and reducing future recurrence of thyroid cancer. Retrospective cohort studies of patients followed postoperatively for several decades suggest that multimodal adjuvant therapy may decrease local recurrence and may improve survival [53] [81] [191] [192] [193] [194] [195]. The ATA recently created and updated the initial risk stratification system (**Table 10**), recommending its use for patients with differentiated thyroid cancer treated with thyroidectomy, based on its usefulness in predicting the risk of recurrence and/or persistence of disease [175]. This initial risk stratification system for well-differentiated thyroid cancer utilizes the histology,

Table 9. Relative stage-specific survival for thyroid cancer [175].

	Stage I	Stage II	Stage III	Stage IV
Papillary Cancer				
1 year	99.9%	100%	97.7%	77.6%
5 years	99.8%	100%	93.3%	50.7%
Follicular Cancer				
1 year	99.7%	99.6%	91.1%	78.5%
5 years	99%	99.7%	71.1%	50.4%
Medullary Cancer				
1 year	100%	100%	96%	64.3%
5 years	100%	97.9%	81%	27.7%
Anaplastic Cancer				
1 year	N/A	N/A	N/A	18%
5 years	N/A	N/A	N/A	6.9%

Table 10. ATA modified initial risk stratification system [34].

ATA Low Risk	Papillary thyroid cancer (with all of the following): • Does not have local or distant metastases • The entire macroscopic tumor has been resected • It has no tumor invasion of loco-regional structures or tissues • The tumor has no aggressive histology (high cell carcinoma, Hobnail variant, and columnar cell carcinoma) • If I131 is administered, avid metastatic foci outside the thyroid bed should not be identified in the first post-treatment full-body thyroid scan • Without vascular invasion • cN0 or ≤5 pN1 micro-metastases (<0.2 cm in the largest dimension) Papillary thyroid cancer of intra-thyroid follicular variant, encapsulated Intra-thyroid well differentiated follicular thyroid cancer with capsular invasion and no or minimal vascular invasion (<4 foci) Intra-thyroid, unifocal or multifocal papillary microcarcinoma, including mutated BRAF V600E (if known)
ATA Intermediate Risk	Microscopic invasion of the tumor to the peri-thyroid soft tissues Avid metastatic foci of radioactive iodine in the neck at the first full-body scan post-treatment Aggressive histology (high cell carcinoma, Hobnail variant, and columnar cell carcinoma) Papillary thyroid cancer with vascular invasion cN1 or >5 pN1 with all lymph nodes affected <3 cm in greatest dimension Multifocal papillary microcarcinoma with extra thyroid extension and mutated BRAF V600E (if known)
ATA High Risk	Macroscopic invasion of peri-thyroid soft tissue tumor Incomplete tumor resection Distant metastasis Postoperative serum thyroglobulin suggestive of distant metastases pN1 with any metastatic lymph node ≥ 3 cm in greatest dimension Follicular thyroid cancer with extensive vascular invasion (>4 foci of vascular invasion)

characteristics of the pathology, and the mutational state of the cancer (**Table 10**) to aid in decision-making for the start of adjuvant therapy [175]. The initial ATA risk stratification system recommends using it for patients with differentiated thyroid cancer treated with thyroidectomy, based on its usefulness in predicting the risk of recurrence and/or persistence of the disease (ATA recommendation 48) [175]. Additional prognostic variables (such as the degree of lymph node involvement, mutational status and/or the degree of vascular invasion in thyroid follicular cancer) not included in the 2009 ATA initial risk stratification system can be used to further refine plus risk stratification for differentiated thyroid cancer (**Table 10**) in the modified initial risk stratification system (ATA recommendation 48) [175]. However, the incremental benefit of adding these specific prognostic variables to the 2009 internal risk stratification system has not been established.

The basis of adjuvant treatment for well-differentiated thyroid carcinoma is treatment with radioactive iodine (I131) and suppression of TSH [34]. The use of radioactive therapeutic ablation of the remaining thyroid tissue after thyroidectomy is well established, but the criteria for the use of this treatment vary

between institutions. The majority (≥75%) of follicular cell thyroid carcinomas retain the ability of normal thyroid follicular cells to absorb and concentrate iodine [196]. This iodine concentration capacity is less efficient than that observed in normal thyroid glands, due to the abnormal architecture of follicular structures within cancer, it makes it difficult to organize and retain the isotope, which explains why cancers typically look as "cold" nodules in isotopic images on thyroid scintigraphy [196] [197]. However, this conserved differentiated function allows radioactive isotopes of iodine to be used both for localization and for the treatment of residual thyroid carcinoma [198] [199].

When administered orally, all iodine isotopes are rapidly and very efficiently absorbed from the proximal gastrointestinal tract, circulate transiently in the bloodstream, and are concentrated in tissues that express a functional sodium iodide transporter (NIS) [200]. The remaining isotope is filtered and excreted through the kidneys, with radiation exposure to the entire urinary tract. Tissues that actively concentrate iodine include normal and cancerous thyroid tissue, salivary gland, breast (particularly during breastfeeding), stomach, kidney, and colon [200] [201]. The absorption of iodine in normal and malignant thyroid tissue, although not in most other tissues, depends on the activity of the TSH receptor, which regulates expression and increases the activation of NIS in thyroid tissue [202]. Similarly, thyroid tissue is capable of organizing iodine to thyroglobulin, a reaction that requires at least one partially intact follicular structure [203]. Such organization increases the biological half-life of iodine, increasing the exposure of thyroid tissue to irradiation and improving cell injury and cell death induced by radiation [203].

Radioactive isotopes of iodine in clinical use (I131, I123) emit γ rays, which can be detected using an appropriate detection device (a gamma camera), allowing imaging of tissues that concentrate iodine and therefore the detection and localization of thyroid cancer metastasis or residues, after stimulation with TSH [204]. This full-body scanning technique became the pillar of postoperative surveillance of thyroid cancer in North America in the 80s and 90s, although it has been used less frequently in recent years, due to improved technology. of ultrasound, cross-sectional images, and measurements of thyroglobulin that proved to be more sensitive and more specific [205]. However, the introduction of single photon emission tomography (SPECT), in particular, to more accurately locate areas of iodine concentration ensures that isotope images continue to play a useful role in the evaluation of patients with cancer of residual thyroid [206].

Although γ rays are high energy, their absorption in the tissue is low and most of these particles do not interact with the cell in which the iodine is concentrated, or with the surrounding tissue [207] [208]. Although this is optimal for imaging, because it provides good image resolution, γ rays are not particularly effective in the treatment of residual thyroid carcinoma, which instead depends on the emission of beta particles, the main particle emitted by the decomposition of the I131 but not of I123 [208]. Moderately high energy beta particles emitted by I131 have a medium length and a short path in human tissues, traveling, on

average, only 0.5 cm before interacting with the surrounding tissue [209]. The resulting ionization causes DNA damage, including single and double stranded DNA breaks [210]. This DNA lesion is detected by the cell, activating the p53 pathway, which is commonly intact in differentiated thyroid carcinoma cells [210]. Faced with minor damage to the DNA, cell repair mechanisms are activated, and usually restore the cell to its normal state, although with the potential for induction of additional mutations or chromosomal rearrangements. However, with more extensive DNA damage, activation of p53 triggers apoptosis (programmed cell death) of the affected cell [211] [212]. Because cancer cells, including in thyroid cancer, often lack efficient mechanisms to repair double-stranded DNA ruptures, there is reason to believe that residual thyroid cancer is susceptible to the effects of beta irradiation, more than the surrounding normal tissue, although there are still no in vitro or clinical data to support this hypothesis [213].

The disease status in the postoperative period (*i.e.* the presence or absence of persistent disease) should be considered when deciding whether additional treatment (for example, radioactive iodine, surgery or other treatment) may be needed (ATA recommendation 50) [34]. Postoperative serum thyroglobulin (during treatment with thyroid hormone or after TSH stimulation) can help assess the persistence of residual disease or thyroid and predict the possible recurrence of the disease in the future (ATA recommendation 50) [34]. Thyroglobulin should reach its nadir in 3 to 4 weeks after the operation in most patients. The optimal cut-off value of postoperative serum thyroglobulin or the state in which it should be measured (under treatment with thyroid hormones or after TSH stimulation) to guide decision-making regarding iodine administration is unknown radioactive.

Scanning of the entire body diagnosis with postoperative radioactive iodine may be useful when the extent of thyroid remnant or residual disease cannot be determined accurately from the surgical report or neck ultrasound, and when the results may alter the decision to treat with radioactive iodine or the activity of the radioactive iodine to be administered (ATA recommendation 50) [34]. The identification and location of the foci of uptake can be improved by computed tomography by concomitant single photon emission (SPECT/CT). When these studies are carried out in a diagnostic manner before starting the definitive treatment, I123 (1.5 to 3 mCi) or a low activity of I131 (1 to 3 mCi) must be performed, with the therapeutic activity optimally administered within 72 hours of the activity for diagnosis (ATA recommendation 50) [34].

Ablation of the possible thyroid remnant with radioactive iodine is not routinely recommended after thyroidectomy for patients with differentiated thyroid cancer at low risk of recurrence based on the ATA classification (ATA recommendation 51) [34]. Ablation of the possible thyroid remnant with radioactive iodine is not routinely recommended after lobectomy or total thyroidectomy in patients with unifocal papillary microcarcinoma, in the absence of other adverse features (ATA recommendation 51) [34]. Ablation of the possible thyroid rem-

nant with radioactive iodine is not routinely recommended after thyroidectomy in patients with multifocal papillary microcarcinoma in the absence of other adverse features (ATA recommendation 51) [34]. The consideration of the specific characteristics of the individual patient that could modulate the risk of recurrence, the implications of the disease follow-up and the preferences of the patient are relevant for the decision making of the RAI. Adjuvant therapy with radioactive iodine should be considered after total thyroidectomy in patients with differentiated thyroid cancer with a risk of intermediate recurrence based on the ATA classification (ATA recommendation 51) [34]. Adjuvant radioactive iodine therapy is routinely recommended after total thyroidectomy for patients with differentiated thyroid cancer with a high risk of recurrence based on the ATA classification (ATA recommendation 51) [34].

The role of molecular tests to guide the postoperative use of radioactive iodine has not yet been established; therefore, the ATA guidelines (ATA recommendation 52) [34] and the NCCN cannot recommend the use of molecular tests to guide the postoperative use of radioactive iodine at this time [34] [80].

If abstention from thyroid hormone intake (levothyroxine/T4) is planned before radioactive iodine therapy or diagnostic tests, levothyroxine should be suspended for 3 to 4 weeks. Liothyronine (T3) can be substituted for levothyroxine in the initial weeks, if it is planned to withdraw levothyroxine for 4 or more weeks, and in such circumstances, liothyronine should be withdrawn for at least 2 weeks. Serum TSH should be measured before administration of the radioisotope to assess the degree of elevation of TSH (ATA recommendation 53) [34]. In general, a TSH goal of greater than 30 mIU/L is recommended in preparation for treatment with radioactive iodine or before performing diagnostic tests, but there is uncertainty regarding the optimal level of TSH associated with the improvement in long-term results [214] [215].

In patients categorized by the classification of the ATA with low risk and intermediate risk ATA of recurrence without extensive lymph node involvement (T1-T3, N0/NX/N1a, M0), in whom the ablation of the remnant with radioactive iodine is planned or adjuvant therapy, preparation with recombinant human TSH hormone stimulation (rhTSH) is an acceptable alternative to thyroid hormone withdrawal to achieve thyroid remnant ablation, based on clinical evidence of superior short-term quality of life, the non-inferiority of the efficacy of ablation to the remnant, and multiple observational studies that suggest a non-significant difference in long-term outcomes (ATA recommendation 54) [34] [216] [217] [219]. In patients with intermediate-risk thyroid cancer based on the classification of ATA who have extensive lymph node disease (multiple clinically involved nodes) in the absence of distant metastases, preparation with rhTSH stimulation can be considered as an alternative to abstinence from Thyroid hormone before adjuvant treatment with RAI (ATA recommendation 54) [34]. In patients with high-risk thyroid cancer based on the classification of ATA with higher associated risks of disease-related mortality and morbidity, more data from controlled studies with long-term outcomes are needed before recom-

mending the preparation of rhTSH for adjuvant treatment with radioactive iodine (ATA recommendation 54) [34]. In patients with thyroid cancer at any level of risk with significant comorbidity that may prevent thyroid hormone withdrawal before radioactive iodine administration, the preparation of rhTSH should be considered. Significant comorbidity may include: 1) a significant medical or psychiatric illness that could be exacerbated acutely with hypothyroidism, which could lead to a serious adverse event; or 2) inability to establish an adequate endogenous TSH response with withdrawal from thyroid hormone (ATA recommendation 54) [34].

If the ablation of the remnant with radioactive iodine is performed after total thyroidectomy for low-risk thyroid cancer according to the classification of ATA or intermediate risk disease with lower risk characteristics (*i.e.* low volume central lymph node metastases without other disease known macroscopic residual or any other adverse characteristics), the administered activity of approximately 30 mCi is generally favored by the higher administered activities (ATA recommendation 55) [34]. Higher administered activities may have to be considered for patients receiving less than a total or near-total thyroidectomy in which a larger remnant is suspected or in which adjuvant therapy is desired (ATA recommendation 55) [34]. When radioactive iodine is intended as an initial adjuvant therapy to treat residual microscopic disease, activities administered above those used for ablation of the remnant of up to 150 mCi (in the absence of known distant metastases) are generally recommended. It is not clear whether the systematic use of higher administered activities (>150 mCi) in this context will reduce the recurrence of structural disease for T3 and N1 disease (ATA recommendation 56) [34].

A low iodine diet should be considered for approximately 1 to 2 weeks before the administration of radioactive iodine for patients who undergo ablation or treatment of the remnant (ATA recommendation 57) [34] [219] [220] [221]. A full-body scan (with or without SPECT/CT) is recommended after ablation or treatment of the remnant with radioactive iodine, to report disease staging and document the avidity of radioactive iodine to any structural disease (ATA recommendation 58) [34].

Patients receiving hormone replacement treatment as part of the adjuvant management of thyroid cancer are started with sodium levothyroxine at a dose between 1.8 to 2.1 μg/kg/day [222] [223]. The dose may vary between patients and is adjusted to achieve an adequate level of TSH suppression, as determined based on the risk status of the individual patient. Patients with high-risk thyroid cancer, the appropriate degree of initial TSH suppression is recommended below 0.1 mU/L (ATA recommendation 59) [34]. For patients with intermediate-risk thyroid cancer, the initial suppression of TSH is recommended around 0.1 to 0.5 mU/L (ATA recommendation 59) [34]. Low-risk patients according to the ATA classification that have had a remnant ablation and have undetectable thyroglobulin levels, TSH can be maintained at the lower end of the reference range (0.5 to 2 mU/L) while continuing with surveillance for recurrence (recommendation

59 of the ATA) [34]. This recommendation is valid for low-risk patients who have not undergone ablation of the remnant and have undetectable levels of thyroglobulin. Low-risk patients who have undergone ablation of the remnant and have detectable but low levels of thyroglobulin, TSH can be maintained at a slightly lower level than normal (0.1 to 0.5 mU/L) while continuing surveillance for recurrence (recommendation 59 of the ATA) [34]. This recommendation is valid for low-risk patients who have not undergone ablation of the remnant, even if the levels of thyroglobulin are high and monitoring for recurrence is continued (ATA recommendation 59) [34]. For low-risk patients who have undergone a hemithyroidectomy (lobectomy), TSH can be maintained in the mid-to-lower reference range (0.5 to 2 mU/L) while continuing surveillance for recurrence (recommendation 59 of the ATA) [34]. Thyroid hormone therapy may not be necessary if patients can maintain their TSH in this target range.

The role of radiotherapy as part of the initial adjuvant treatment regimen for differentiated thyroid cancer is controversial. Several retrospective series have reported that local control can be improved with external radiotherapy, specifically in patients with macroscopic residual disease after surgical resection or in patients considered to have a high risk of relapse; however, possible side effects should be considered [224] [225]. Currently, radiotherapy is most commonly used to alleviate metastatic or locally advanced disease, such as bone metastases or recurrences in the thyroid bed not suitable for additional surgical resection, or in an attempt to avoid more extensive surgery such as laryngectomy [34] [53] [81]. The ATA does not recommend routine adjuvant external radiation therapy for the neck in patients with differentiated thyroid cancer after complete surgical excision (ATA recommendation 60) [34].

In general, traditional chemotherapy has not been very effective in the treatment of thyroid carcinomas. Chemotherapy has a very limited use in the treatment of differentiated thyroid cancer and ATA does not recommend routine systemic adjuvant therapy in patients with differentiated thyroid cancer (beyond radioactive iodine therapy and TSH suppressive therapy) (ATA recommendation 61) [34]. However, chemotherapy, in combination with radiotherapy and surgery, is used more frequently to treat anaplastic cancer, for which there is a lack of effective therapies [111] [113] [226]. Intravenous bisphosphonates can be administered in patients with bone metastases [226].

In general, differentiated thyroid cancer is considered advanced (possibly requiring additional therapy) when recurrent or metastatic lesions no longer absorb radioactive iodine, or have increased in size as part of a recent treatment with radioactive iodine (refractory to radioactive iodine), or if the recommended lifetime dose of radioactive iodine (600 mCi) has been exceeded. Exceeding a lifetime dose of 600 to 1000 mCi increases the risk of pulmonary and spinal toxicity. Loss of radioactive iodine absorption is often associated with increased fluorodeoxyglucose uptake (FDG) in positron emission tomography (PET); therefore, additional sites of the disease are often detected with this imaging modality. Once the carcinoma no longer responds to treatment with radioactive iodine and is

PET positive, survival drops (2.5 to 3.5 years) [227]. There is an exception, those that have only one metabolically active focus (positive PET) that is suitable for resection or other modalities of local ablation [227] [228].

Considerable progress has been made in the management of patients with locally advanced and metastatic thyroid cancer. Several tyrosine kinase inhibitors have shown activity in this context, exploiting the vascular nature of these tumors and/or the strong association with genetic mutations that lead to aberrant intracellular signaling (**Table 11**). The majority (motesanib, sunitinib, sorafenib and pazopanib) target mitogen-activated protein kinase (MAPK) and antiangiogenic pathways [33] [36] [38] [39]. In a phase I study with 17 patients, sorafenib produced a partial response in 30% of patients, and stable disease in 41% of patients with differentiated thyroid cancer refractory to radioactive iodine [229]. In a phase III study of 417 patients (DECISION), the efficacy and safety of sorafenib against placebo were investigated in patients with progressive differentiated thyroid cancer and refractory to radioactive iodine [230]. Patients treated with sorafenib experienced significantly longer mean survival compared to the 10.8 month placebo group against 5.8 months (HR: 0.58, 95% CI 0.45 - 0.75; $p < 0.0001$), had a better response rate (12.2% against 0.5%; $p < 0.0001$), and stable disease ≥ 6 months (42% vs. 33%). Most of the adverse events related to this treatment were manageable (grade 1 or 2) and tended to occur at the beginning of treatment [231].

Based on these results, the US Food and Drug Administration (FDA) approved sorafenib for the treatment of well-differentiated locally advanced or metastatic, progressive thyroid cancer, refractory to radioactive iodine treatment. The recommended dose of sorafenib is 400 mg (two 200 mg tablets) twice daily without food (at least 1 hour before or 2 hours after a meal).

Lenvatinib is an oral tyrosine kinase inhibitor that targets VEGFR, fibroblast growth factor receptor, RET, KIT, and platelet-derived growth factor receptor

Table 11. Results of clinical studies of agents targeted for differentiated thyroid cancer.

Intervention	Baseline characteristics (%)	N	Free survival without progression (median/months)	Partial response (%)	Stable disease (%)
Axitinib [235]	Papillary (50), medullary (18), follicular/Hurthle (25/18), anaplastic (3)	60	18.1	30	48
Axitinib [236]	Well differentiated thyroid cancer (71), medullary (29)	41		34	25
Motesanib [237]	Papillary (61), follicular/Hurthle (34)	93	10	14	67
Pazopanib [238]	Differentiated thyroid cancer (progression in <6 months)	37	12	49	
Selumetinib [239]	Papilla with or without follicular elements (100)	39	8	3	54
Sorafenib/temsirolimus [240]	Papillary (62), follicular/Hurthle (14), poorly differentiated (16), anaplastic (3)	37		22	57
Sunitinib [241]	Differential thyroid cancer (74%), medullary (26)	51		17	74
Vandetanib [242]	Papillary (40), follicular (13), poorly differentiated (47)	72	11.1	1	56

(PDGFR) approved for the treatment of patients with differentiated thyroid cancer, locally advanced or metastatic, progressive, and refractory to radioactive iodine. In the phase III study called SELECT, Schlumberger *et al.*, investigated the efficacy and safety of Lenvatinib versus placebo in patients (N = 392) with well-differentiated progressive thyroid cancer and refractory to radioactive iodine [231]. Patients treated with Lenvatinib experienced a significantly longer median free survival versus placebo 18.3 months versus 3.6 months (HR: 0.21, 99% CI: 0.14 - 0.31, $p < 0.0001$), as well as a significantly higher response rate (64.8% vs. 1.5; $p < 0.0001$). Adverse effects related to Lenvatinib of special interest with grade ≥ 3 include hypertension (42.9%), proteinuria (10%), arterial thromboembolic effects (2.7%) and venous thromboembolic effects (3.8%) [231].

Additional studies are underway to evaluate more agents targeting other pathways known to be altered in thyroid tumors, including the endothelial growth factor receptor and the AKT/phosphatidylinositol-4,5-bisphosphate 3-kinase pathways (**Table 11**). Some of the tyrosine kinase inhibitors are approved for use in the management of other tumors, and patients who do not have the ability to participate in a clinical study are sometimes treated with these agents outside the protocol [232].

9. Follow-Up of Patients with Thyroid Cancer

Most recurrences in patients with differentiated thyroid cancer occur within the first five years after initial treatment, but recurrences may also occur several decades later [34] [53] [81]. Patients with papillary cancer usually recur locally and regionally in the neck, while patients with follicular cancer recur more frequently in distant sites [34] [53] [81]. Spinal cancer can recur locally and regionally in the neck or at distant sites [75] [53] [81]. The most common site of distant metastases for thyroid tumors are the lungs, bones, soft tissues, brain, liver, and adrenal glands [34] [53] [81]. Pulmonary metastases are more common in young patients, while bone metastases occur more often in older patients [81].

Follow-up consultations for patients with differentiated thyroid carcinoma generally include a complete medical history, physical examination, blood tests that include thyroglobulin, TSH, and a high resolution medial and lateral neck ultrasound [81]. The complete physical examination and ultrasound of the medial and lateral neck serve to detect local recurrences in the surgical bed or regional lymph nodes in the neck [81]. Thyroglobulin values usually fall after thyroidectomy and ablation and serve as a sensitive indicator of recurrent or persistent disease. However, it is important to keep in mind that the production of thyroglobulin depends on TSH; therefore, TSH levels may affect the sensitivity of thyroglobulin measurements in the detection of recurrent disease [34] [53] [81]. It is important to remember that 25% of patients with differentiated thyroid cancer have anti-thyroglobulin antibodies, which falsely reduce serum thyroglobulin levels [81]. Thyroglobulin levels should always be interpreted in the context of the status of anti-thyroglobulin antibodies [34].

The NCCN and ATA guidelines recommend that during the initial follow-up, measure serum thyroglobulin (with the patient taking levothyroxine) six to 12 months (ATA recommendation # 62) [34] [80]. Checking thyroglobulin levels more frequently may be appropriate for patients at high risk of recurrence based on the ATA classification [34]. Patients with a low to intermediate risk ATA classification that achieve an excellent response to therapy, there is no evidence on the usefulness of continuing with subsequent thyroglobulin intakes (ATA recommendation # 62) [34]. The time interval between thyroglobulin measurements can be extended to at least every 12 to 24 months (ATA recommendation # 62) [34]. Serum TSH levels should be measured at least every 12 months in all patients receiving thyroid hormone therapy (ATA recommendation # 62) [34]. For patients with a high-risk ATA classification (regardless of treatment response) and all patients with incomplete biochemical response, an incomplete structural response, or an undetermined response should continue to measure thyroglobulin at least every 6 to 12 months for several years (ATA recommendation # 62) [34].

Patients with low to intermediate risk based on the classification of ATA who have had remnant ablation or adjuvant therapy, and a negative neck ultrasound, thyroglobulin should be measured at 6 to 18 months (with the patient taking levothyroxine) with one trial of sensitive thyroglobulin (<0.2 ng/ml) or after stimulation with TSH to verify the absence of disease (ATA recommendation # 63) [34]. It is not recommended to repeat the TSH stimulated thyroglobulin test for low to intermediate risk patients with excellent treatment response [34]. It may be considered to obtain stimulated levels of thyroglobulin in patients with an undetermined response, an incomplete biochemical response, or an incomplete structural response after additional treatments have been performed or when a spontaneous decrease in thyroglobulin levels is observed (with the patient being treated with levothyroxine) over time to reassess the response to treatment (ATA recommendation # 63) [34].

In patients who have undergone a thyroidectomy lower than the total (lobectomy) and in patients who have undergone total thyroidectomy but not ablation of the remnant with radioactive iodine it is recommended to obtain periodic levels of thyroglobulin (with the patient being treated with levothyroxine) during follow-up (ATA recommendation # 64) [34]. Although specific levels of thyroglobulin that optimally distinguish normal residual thyroid tissue from persistent thyroid cancer are unknown, increasing levels of thyroglobulin over time are suspected of a recurrence of the disease [34].

The NCCN and ATA guidelines recommend that during the initial follow-up, high resolution medial and lateral neck ultrasound is used to evaluate the surgical bed and the central and lateral cervical ganglion compartments at 6 to 12 months after surgery, and then periodically, depending on the patient's risk for recurrent disease and the levels of thyroglobulin (ATA recommendation # 65) [34] [80]. If a positive result would change the management of patients, suspicious ultrasound lymph nodes measuring ≥8 to 10 mm in the smallest diameter

should have a BAAF to send cytology with a thyroglobulin measurement in the lavage fluid of the needle [34]. Low-risk patients who have had remnant ablation, a negative neck ultrasound, and a low thyroglobulin (with the patient being treated with levothyroxine) that was obtained from a sensitive trial (<0.2 ng/mL) or after stimulation with TSH (thyroglobulin < 1 ng/mL) can be followed up mainly with clinical examination and non-stimulated thyroglobulin levels (ATA recommendation # 65) [34].

After the first full-body scan with post-treatment radioactive iodine (performed after remnant ablation or adjuvant therapy), low-to-intermediate risk patients with undetectable thyroglobulin (with the patient being treated with levothyroxine) without anti-antibody Thyroglobulin, and a negative neck ultrasound (excellent response to treatment) do not require full-body scans with routine radioactive iodine during follow-up (ATA recommendation # 66) [34]. Full-body scanning with radioactive iodine, after suspension of thyroid hormone or with recombinant human TSH, 6 to 12 months after adjuvant therapy with radioactive iodine may be useful in monitoring patients with high or intermediate risk of persistent or recurrent disease and should be performed with I123 or I131 of low activity (ATA recommendation # 67) [34].

The use of 18FDG-PET should be considered in patients with high-risk thyroid cancer with elevated serum thyroglobulin levels (generally > 10 ng/ml) with negative radioactive iodine studies (ATA recommendation # 68) [34].

The follow-up for patients with medullary thyroid cancer differs from that of tumors of origin of the follicular epithelium (papillary and follicular cancer). Therefore, the measurement of thyroglobulin has no role in the detection of recurrent disease in patients with spinal cancer. Instead, monitoring should consist of measuring serum levels of calcitonin and carcinoembryonic antigen in addition to routine neck ultrasound. Serum levels of calcitonin and carcinoembryonic antigen should be measured three months after surgery, and if they are not detected or are within the normal range, they should be measured every six months for a year and then every year thereafter (recommendation # 46 of the ATA) [75]. Patients with high levels of calcitonin in the postoperative period, but less than 150 pg/ml should undergo a complete physical examination and have a high resolution medial and lateral neck ultrasound (ATA recommendation # 47) [75]. If studies are negative, patients should be followed up with a medical history and physical examination, measurement of serum levels of calcitonin and carcinoembryonic antigen, and neck ultrasound every six months (ATA recommendation # 47) [75]. If serum levels of postoperative calcitonin exceed 150 pg/ml, an evaluation should be performed with imaging studies, including an ultrasound of the neck, computed tomography of the chest, magnetic resonance with contrast or computed tomography of the liver with three contrast phases, and bone scintigraphy and magnetic resonance imaging of the pelvis and axial skeleton (ATA recommendation # 48) [75]. In patients with serum levels of calcitonin and carcinoembryonic antigen detectable after a thyroidect-

omy, these markers should be measured at least every six months to determine their doubling times (ATA recommendation # 49) [75].

For patients diagnosed with MEN 2A or 2B, annual examinations should be performed to rule out the diagnosis of a pheochromocytoma (MEN 2A and MEN 2B) and hyperparathyroidism (MEN2A) [75]. Anaplastic carcinoma and lymphoma cannot be followed in the same way as patients with differentiated thyroid cancer. Normally the protocol includes a medical history, physical examination, neck ultrasound, computed tomography or additional MRI, and measurement of the carcinoembryonic antigen and LDH [81].

10. Conclusion

The striking increase in the prevalence/incidence of low-risk thyroid cancer over the last 10 to 20 years has required a re-assessment of the conventional one-size-fits-all approach to differentiated thyroid cancer. This conversion to a more individualized management of the patient with thyroid cancer has led to a much more risk-adapted approach to the diagnosis, initial therapy, adjuvant therapy, and follow-up of patients with differentiated thyroid cancer. This has necessitated a complete re-appraisal of our management approach to the likelihood of disease-specific mortality and the risk of structural/biochemical disease recurrence. During the last 10 years, there has seen significant adjustments to the AJCC/TNM staging system, the elaboration and validation of the ATA risk stratification system for prognostication of disease recurrence, and the identification and implementation of dynamic risk stratification to allow real-time, ongoing re-evaluation of risk from initial detection to final follow-up. Contemporary treatment of patients with thyroid malignancy requires a multidisciplinary approach involving an endocrinologist, a thyroid surgeon, a radiologist, and, on occasion, medical and radiation oncologists. In selected patient's radioactive iodine therapy are usually effective for most patients with differentiated thyroid cancer resulting in excellent long-term outcomes in most cases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Vander, J.B., Gaston, E.A. and Dawber, T.R. (1968) The Significance of Nontoxic Thyroid Nodules. Final Report of a 15-Year Study of the Incidence of Thyroid Malignancy. *Annals of Internal Medicine*, **69**, 537-540. https://doi.org/10.7326/0003-4819-69-3-537

[2] Tunbridge, W.M., *et al.* (1977) The Spectrum of Thyroid Disease in a Community: The Whickham Survey. *Clinical Endocrinology*, **7**, 481-493. https://doi.org/10.1111/j.1365-2265.1977.tb01340.x

[3] Tan, G.H. and Gharib, H. (1997) Thyroid Incidentalomas: Management Approaches to Nonpalpable Nodules Discovered Incidentally on Thyroid Imaging. *Annals of Internal Medicine*, **126**, 226-231.

https://doi.org/10.7326/0003-4819-126-3-199702010-00009

[4] Guth, S., *et al.* (2009) Very High Prevalence of Thyroid Nodules Detected by High Frequency (13 MHz) Ultrasound Examination. *European Journal of Clinical Investigation*, **39**, 699-706. https://doi.org/10.1111/j.1365-2362.2009.02162.x

[5] Hegedus, L. (2004) Clinical Practice. The Thyroid Nodule. *The New England Journal of Medicine*, **351**, 1764-1771. https://doi.org/10.1056/NEJMcp031436

[6] Mandel, S.J. (2004) A 64-Year-Old Woman with a Thyroid Nodule. *JAMA*, **292**, 2632-2642. https://doi.org/10.1001/jama.292.21.2632

[7] Sherman, S.I. (2003) Thyroid Carcinoma. *The Lancet*, **361**, 501-511. https://doi.org/10.1016/S0140-6736(03)12488-9

[8] Howlader, N., Krapcho, M., *et al.* (2017) SEER Cancer Statistics Review, 1975-2014, Based on November 2016 SEER Data Submission. National Cancer Institute, Bethesda.

[9] Society, A.C. (2018) American Cancer Society: Cancer Facts and Figures 2018. American Cancer Society, Atlanta.

[10] Chen, A.Y., Jemal, A. and Ward, E.M. (2009) Increasing Incidence of Differentiated Thyroid Cancer in the United States, 1988-2005. *Cancer*, **115**, 3801-3807. https://doi.org/10.1002/cncr.24416

[11] Eustatia-Rutten, C.F., *et al.* (2006) Survival and Death Causes in Differentiated Thyroid Carcinoma. *The Journal of Clinical Endocrinology & Metabolism*, **91**, 313-319. https://doi.org/10.1210/jc.2005-1322

[12] Gild, M.L., *et al.* (2011) Multikinase Inhibitors: A New Option for the Treatment of Thyroid Cancer. *Nature Reviews Endocrinology*, **7**, 617-624. https://doi.org/10.1038/nrendo.2011.141

[13] Davies, L. and Welch, H.G. (2014) Current Thyroid Cancer Trends in the United States. *JAMA Otolaryngology—Head & Neck Surgery*, **140**, 317-322. https://doi.org/10.1001/jamaoto.2014.1

[14] Leenhardt, L., *et al.* (2004) Advances in Diagnostic Practices Affect Thyroid Cancer Incidence in France. *European Journal of Endocrinology*, **150**, 133-139. https://doi.org/10.1530/eje.0.1500133

[15] Nagataki, S. and Nystrom, E. (2002) Epidemiology and Primary Prevention of Thyroid Cancer. *Thyroid*, **12**, 889-896. https://doi.org/10.1089/105072502761016511

[16] Cardis, E., *et al.* (2006) Cancer Consequences of the Chernobyl Accident: 20 Years on. *Journal of Radiological Protection*, **26**, 127-140. https://doi.org/10.1088/0952-4746/26/2/001

[17] Network, N.C.C. (2017) Clinical Practice Guidelines in Oncology: Thyroid Carcinoma. Vol. 2.

[18] Furukawa, K., *et al.* (2013) Long-Term Trend of Thyroid Cancer Risk among Japanese Atomic-Bomb Survivors: 60 Years after Exposure. *International Journal of Cancer*, **132**, 1222-1226. https://doi.org/10.1002/ijc.27749

[19] Kleinerman, R.A. (2006) Cancer Risks Following Diagnostic and Therapeutic Radiation Exposure in Children. *Pediatric Radiology*, **36**, 121-125. https://doi.org/10.1007/s00247-006-0191-5

[20] Brenner, A.V., *et al.* (2011) I-131 Dose Response for Incident Thyroid Cancers in Ukraine Related to the Chornobyl Accident. *Environmental Health Perspectives*, **119**, 933-939. https://doi.org/10.1289/ehp.1002674

[21] Richards, M.L. (2010) Familial Syndromes Associated with Thyroid Cancer in the

Era of Personalized Medicine. *Thyroid*, **20**, 707-713.
https://doi.org/10.1089/thy.2010.1641

[22] Tomoda, C., *et al.* (2004) Cribriform-Morular Variant of Papillary Thyroid Carcinoma: Clue to Early Detection of Familial Adenomatous Polyposis-Associated Colon Cancer. *World Journal of Surgery*, **28**, 886-889.
https://doi.org/10.1007/s00268-004-7475-4

[23] Soravia, C., *et al.* (1999) Familial Adenomatous Polyposis-Associated Thyroid Cancer: A Clinical, Pathological, and Molecular Genetics Study. *The American Journal of Pathology*, **154**, 127-135. https://doi.org/10.1016/S0002-9440(10)65259-5

[24] Cetta, F., *et al.* (2000) Germline Mutations of the APC Gene in Patients with Familial Adenomatous Polyposis-Associated Thyroid Carcinoma: Results from a European Cooperative Study. *The Journal of Clinical Endocrinology & Metabolism*, **85**, 286-292. https://doi.org/10.1210/jc.85.1.286

[25] Choi, W.J. and Kim, J. (2014) Dietary Factors and the Risk of Thyroid Cancer: A Review. *Clinical Nutrition Research*, **3**, 75-88.
https://doi.org/10.7762/cnr.2014.3.2.75

[26] Stratakis, C.A., *et al.* (1997) Thyroid Gland Abnormalities in Patients with the Syndrome of Spotty Skin Pigmentation, Myxomas, Endocrine Overactivity, and Schwannomas (Carney Complex). *The Journal of Clinical Endocrinology & Metabolism*, **82**, 2037-2043. https://doi.org/10.1210/jcem.82.7.4079

[27] Ngeow, J., *et al.* (2011) Incidence and Clinical Characteristics of Thyroid Cancer in Prospective Series of Individuals with Cowden and Cowden-Like Syndrome Characterized by Germline PTEN, SDH, or KLLN Alterations. *The Journal of Clinical Endocrinology & Metabolism*, **96**, E2063-E2071.
https://doi.org/10.1210/jc.2011-1616

[28] Giardiello, F.M., *et al.* (1987) Increased Risk of Cancer in the Peutz-Jeghers Syndrome. *The New England Journal of Medicine*, **316**, 1511-1514.
https://doi.org/10.1056/NEJM198706113162404

[29] Klein, M., *et al.* (1999) Vascular Endothelial Growth Factor Gene and Protein: Strong Expression in Thyroiditis and Thyroid Carcinoma. *Journal of Endocrinology*, **161**, 41-49. https://doi.org/10.1677/joe.0.1610041

[30] Higgins, M.J., Forastiere, A. and Marur, S. (2009) New Directions in the Systemic Treatment of Metastatic Thyroid Cancer. *Oncology* (*Williston Park*), **23**, 768-775.

[31] Schlumberger, M.J., *et al.* (2009) Phase II Study of Safety and Efficacy of Motesanib in Patients with Progressive or Symptomatic, Advanced or Metastatic Medullary Thyroid Cancer. *Journal of Clinical Oncology*, **27**, 3794-3801.
https://doi.org/10.1200/JCO.2008.18.7815

[32] Kondo, T., Ezzat, S. and Asa, S.L. (2006) Pathogenetic Mechanisms in Thyroid Follicular-Cell Neoplasia. *Nature Reviews Cancer*, **6**, 292-306.
https://doi.org/10.1038/nrc1836

[33] Hong, D.S., *et al.* (2011) Inhibition of the Ras/Raf/MEK/ERK and RET Kinase Pathways with the Combination of the Multikinase Inhibitor Sorafenib and the Farnesyltransferase Inhibitor Tipifarnib in Medullary and Differentiated Thyroid Malignancies. *The Journal of Clinical Endocrinology & Metabolism*, **96**, 997-1005.
https://doi.org/10.1210/jc.2010-1899

[34] Haugen, B.R., *et al.* (2016) 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules

and Differentiated Thyroid Cancer. *Thyroid*, **26**, 1-133. https://doi.org/10.1089/thy.2015.0020

[35] Pak, K., *et al.* (2015) Prognostic Value of Genetic Mutations in Thyroid Cancer: A Meta-Analysis. *Thyroid*, **25**, 63-70. https://doi.org/10.1089/thy.2014.0241

[36] Ahmed, M., *et al.* (2011) Analysis of the Efficacy and Toxicity of Sorafenib in Thyroid Cancer: A Phase II Study in a UK Based Population. *European Journal of Endocrinology*, **165**, 315-322. https://doi.org/10.1530/EJE-11-0129

[37] Carr, L.L., *et al.* (2010) Phase II Study of Daily Sunitinib in FDG-PET-Positive, Iodine-Refractory Differentiated Thyroid Cancer and Metastatic Medullary Carcinoma of the Thyroid with Functional Imaging Correlation. *Clinical Cancer Research*, **16**, 5260-5268. https://doi.org/10.1158/1078-0432.CCR-10-0994

[38] Robinson, B.G., *et al.* (2010) Vandetanib (100 mg) in Patients with Locally Advanced or Metastatic Hereditary Medullary Thyroid Cancer. *The Journal of Clinical Endocrinology & Metabolism*, **95**, 2664-2671. https://doi.org/10.1210/jc.2009-2461

[39] Lam, E.T., *et al.* (2010) Phase II Clinical Trial of Sorafenib in Metastatic Medullary Thyroid Cancer. *Journal of Clinical Oncology*, **28**, 2323-2330. https://doi.org/10.1200/JCO.2009.25.0068

[40] Gupta-Abramson, V., *et al.* (2008) Phase II Trial of Sorafenib in Advanced Thyroid Cancer. *Journal of Clinical Oncology*, **26**, 4714-4719. https://doi.org/10.1200/JCO.2008.16.3279

[41] Learoyd, D.L. and Robinson, B.G. (2009) Routine Screening for Germline RET Mutations Is Recommended for All Patients with Medullary Thyroid Cancer. *Nature Clinical Practice Endocrinology & Metabolism*, **5**, 6-7. https://doi.org/10.1038/ncpendmet1020

[42] Learoyd, D.L., *et al.* (2000) Molecular Genetics of Thyroid Tumors and Surgical Decision-Making. *World Journal of Surgery*, **24**, 923-933. https://doi.org/10.1007/s002680010164

[43] Diallo-Krou, E., *et al.* (2009) Paired Box Gene 8-Peroxisome Proliferator-Activated Receptor-Gamma Fusion Protein and Loss of Phosphatase and Tensin Homolog Synergistically Cause Thyroid Hyperplasia in Transgenic Mice. *Endocrinology*, **150**, 5181-5190. https://doi.org/10.1210/en.2009-0701

[44] Wells, S.A. and Santoro, M. (2009) Targeting the RET Pathway in Thyroid Cancer. *Clinical Cancer Research*, **15**, 7119-7123. https://doi.org/10.1158/1078-0432.CCR-08-2742

[45] Eng, C. (1996) Seminars in Medicine of the Beth Israel Hospital, Boston. The RET Proto-Oncogene in Multiple Endocrine Neoplasia Type 2 and Hirschsprung's Disease. *The New England Journal of Medicine*, **335**, 943-951. https://doi.org/10.1056/NEJM199609263351307

[46] Elisei, R., *et al.* (2008) Prognostic Significance of Somatic RET Oncogene Mutations in Sporadic Medullary Thyroid Cancer: A 10-Year Follow-Up Study. *The Journal of Clinical Endocrinology & Metabolism*, **93**, 682-687. https://doi.org/10.1210/jc.2007-1714

[47] Moo-Young, T.A., Traugott, A.L. and Moley, J.F. (2009) Sporadic and Familial Medullary Thyroid Carcinoma: State of the Art. *Surgical Clinics of North America*, **89**, 1193-204. https://doi.org/10.1016/j.suc.2009.06.021

[48] Guerra, A., *et al.* (2013) Genetic Mutations in the Treatment of Anaplastic Thyroid Cancer: A Systematic Review. *BMC Surgery*, **13**, S44. https://doi.org/10.1186/1471-2482-13-S2-S44

[49] McFadden, D.G., *et al.* (2014) p53 Constrains Progression to Anaplastic Thyroid Carcinoma in a Braf-Mutant Mouse Model of Papillary Thyroid Cancer. *Proceedings of the National Academy of Sciences of the United States of America*, **111**, E1600-E1609. https://doi.org/10.1073/pnas.1404357111

[50] Lloyd, R.V., Buehler, D. and Khanafshar, E. (2011) Papillary Thyroid Carcinoma Variants. *Head and Neck Pathology*, **5**, 51-56. https://doi.org/10.1007/s12105-010-0236-9

[51] Lloyd, R.V. (2010) Endocrine Pathology: Differential Diagnosis and Molecular Advances. 2nd Edition, Springer, New York.

[52] DeLellis, R.A., Heitz, P.U., Eng, C., *et al.* (2004) Pathology and Genetics of Tumours of Endocrine Organs. World Health Organization Classification of Tumours, IARC Press, Lyon.

[53] Thomas, R.M., Perrier, N.D., Grubbs, E.G., *et al.* (2012) Well Differentiated Carcinoma of the Thyroid and Neoplasms of the Parathyroid Glands. Fourth Edition. In: Ching, B.W.F.C.D., Ed., *The M.D. Anderson Surgical Oncology Handbook*, Fifth Edition, Vol. 1, Lippincott Williams and Wilkins, Philadelphia, 900.

[54] Pacini, F., *et al.* (2001) Contralateral Papillary Thyroid Cancer Is Frequent at Completion Thyroidectomy with No Difference in Low- and High-Risk Patients. *Thyroid*, **11**, 877-881. https://doi.org/10.1089/105072501316973145

[55] Kim, H.J., *et al.* (2013) Multifocality, But Not Bilaterality, Is a Predictor of Disease Recurrence/Persistence of Papillary Thyroid Carcinoma. *World Journal of Surgery*, **37**, 376-384. https://doi.org/10.1007/s00268-012-1835-2

[56] Carcangiu, M.L., *et al.* (1985) Papillary Carcinoma of the Thyroid. A Clinicopathologic Study of 241 Cases Treated at the University of Florence, Italy. *Cancer*, **55**, 805-828. https://doi.org/10.1002/1097-0142(19850215)55:4<805::AID-CNCR2820550419>3.0.CO;2-Z

[57] Schindler, A.M., *et al.* (1991) Prognostic Factors in Papillary Carcinoma of the Thyroid. *Cancer*, **68**, 324-330. https://doi.org/10.1002/1097-0142(19910715)68:2<324::AID-CNCR2820680220>3.0.CO;2-S

[58] Mazzaferri, E.L. and Jhiang, S.M. (1994) Long-Term Impact of Initial Surgical and Medical Therapy on Papillary and Follicular Thyroid Cancer. *The American Journal of Medicine*, **97**, 418-428. https://doi.org/10.1016/0002-9343(94)90321-2

[59] Chow, S.M., *et al.* (2003) Papillary Microcarcinoma of the Thyroid-Prognostic Significance of Lymph Node Metastasis and Multifocality. *Cancer*, **98**, 31-40. https://doi.org/10.1002/cncr.11442

[60] Sciuto, R., *et al.* (2009) Natural History and Clinical Outcome of Differentiated Thyroid Carcinoma: A Retrospective Analysis of 1503 Patients Treated at a Single Institution. *Annals of Oncology*, **20**, 1728-1735. https://doi.org/10.1093/annonc/mdp050

[61] Lin, J.D., *et al.* (2009) High Recurrent Rate of Multicentric Papillary Thyroid Carcinoma. *Annals of Surgical Oncology*, **16**, 2609-2616. https://doi.org/10.1245/s10434-009-0565-7

[62] Wang, T.S., *et al.* (2004) Incidence of Metastatic Well-Differentiated Thyroid Cancer in Cervical Lymph Nodes. *Archives of Otolaryngology—Head and Neck Surgery*, **130**, 110-113. https://doi.org/10.1001/archotol.130.1.110

[63] Wang, L.Y. and Ganly, I. (2016) Nodal Metastases in Thyroid Cancer: Prognostic Implications and Management. *Future Oncology*, **12**, 981-994.

https://doi.org/10.2217/fon.16.10

[64] Wada, N., *et al.* (2003) Lymph Node Metastasis from 259 Papillary Thyroid Microcarcinomas: Frequency, Pattern of Occurrence and Recurrence, and Optimal Strategy for Neck Dissection. *Annals of Surgery*, **237**, 399-407. https://doi.org/10.1097/01.SLA.0000055273.58908.19

[65] Pettersson, B., *et al.* (1991) Trends in Thyroid Cancer Incidence in Sweden, 1958-1981, by Histopathologic Type. *International Journal of Cancer*, **48**, 28-33. https://doi.org/10.1002/ijc.2910480106

[66] Harach, H.R., *et al.* (1985) Thyroid Carcinoma and Thyroiditis in an Endemic Goitre Region before and after Iodine Prophylaxis. *Acta Endocrinologica*, **108**, 55-60. https://doi.org/10.1530/acta.0.1080055

[67] Aschebrook-Kilfoy, B., *et al.* (2013) Follicular Thyroid Cancer Incidence Patterns in the United States, 1980-2009. *Thyroid*, **23**, 1015-1021. https://doi.org/10.1089/thy.2012.0356

[68] Collini, P., *et al.* (2003) Minimally Invasive (Encapsulated) Follicular Carcinoma of the Thyroid Gland Is the Low-Risk Counterpart of Widely Invasive Follicular Carcinoma But Not of Insular Carcinoma. *Virchows Archiv*, **442**, 71-76.

[69] D'Avanzo, A., *et al.* (2004) Follicular Thyroid Carcinoma: Histology and Prognosis. *Cancer*, **100**, 1123-1129. https://doi.org/10.1002/cncr.20081

[70] Baloch, Z.W. and LiVolsi, V.A. (2001) Prognostic Factors in Well-Differentiated Follicular-Derived Carcinoma and Medullary Thyroid Carcinoma. *Thyroid*, **11**, 637-645. https://doi.org/10.1089/105072501750362709

[71] Baloch, Z.W. and LiVolsi, V.A. (2014) Follicular-Patterned Afflictions of the Thyroid Gland: Reappraisal of the Most Discussed Entity in Endocrine Pathology. *Endocrine Pathology*, **25**, 12-20. https://doi.org/10.1007/s12022-013-9293-4

[72] Rosai, J., De Lellis, R.A., *et al.* (1992) Tumors of the Thyroid Gland. Atlas of Tumor Pathology. Armed Forces Institute of Pathology, Fascicle 5, Washington DC.

[73] Machens, A., Holzhausen, H.J. and Dralle, H. (2005) The Prognostic Value of Primary Tumor Size in Papillary and Follicular Thyroid Carcinoma. *Cancer*, **103**, 2269-2273. https://doi.org/10.1002/cncr.21055

[74] Cibas, E.S. and Ali, S.Z. (2009) The Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*, **19**, 1159-1165. https://doi.org/10.1089/thy.2009.0274

[75] Wells, S.A., *et al.* (2015) Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma. *Thyroid*, **25**, 567-610. https://doi.org/10.1089/thy.2014.0335

[76] Saad, M.F., *et al.* (1984) Medullary Carcinoma of the Thyroid. A Study of the Clinical Features and Prognostic Factors in 161 Patients. *Medicine* (*Baltimore*), **63**, 319-342. https://doi.org/10.1097/00005792-198411000-00001

[77] Dottorini, M.E., *et al.* (1996) Multivariate Analysis of Patients with Medullary Thyroid Carcinoma. Prognostic Significance and Impact on Treatment of Clinical and Pathologic Variables. *Cancer*, **77**, 1556-1565. https://doi.org/10.1002/(SICI)1097-0142(19960415)77:8<1556::AID-CNCR20>3.0.CO;2-Y

[78] Gagel, R.F., Cote, G.J., *et al.* (2005) Medullary Thyroid Carcinoma. In: *The Thyroid*, Lippincott Williams & Wilkins, Philadelphia, 9th Edition, 967.

[79] Kebebew, E., *et al.* (2000) Medullary Thyroid Carcinoma: Clinical Characteristics, Treatment, Prognostic Factors, and a Comparison of Staging Systems. *Cancer*, **88**, 1139-1148. https://doi.org/10.1002/(SICI)1097-0142(20000301)88:5<1139::AID-CNCR26>3.0.CO;2-Z

[80] NCCN (2017) NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma. Vol. 2.

[81] Grubbs, K.L. (2019) Carcinoma of the Thyroid Gland and Neoplasms of the Parathyroid Glands. In: Barry, M. and Feig, W., Eds., *The MD Anderson Surgical Oncology Handbook*, Wolters Kluwer, Philadelphia, Sixth Edition, 463-491.

[82] Howlader, N., Krapcho, M., *et al.* (2017) SEER Cancer Statistics Review, 1975-2014, Based on November 2016 SEER Data Submission. N.C. Institute, Bethesda.

[83] Neff, R.L., *et al.* (2008) Anaplastic Thyroid Cancer. *Endocrinology & Metabolism Clinics of North America*, **37**, 525-538. https://doi.org/10.1016/j.ecl.2008.02.003

[84] Ricarte-Filho, J.C., *et al.* (2009) Mutational Profile of Advanced Primary and Metastatic Radioactive Iodine-Refractory Thyroid Cancers Reveals Distinct Pathogenetic Roles for BRAF, PIK3CA, and AKT1. *Cancer Research*, **69**, 4885-4893. https://doi.org/10.1158/0008-5472.CAN-09-0727

[85] Quiros, R.M., *et al.* (2005) Evidence That One Subset of Anaplastic Thyroid Carcinomas Are Derived from Papillary Carcinomas Due to BRAF and p53 Mutations. *Cancer*, **103**, 2261-2268. https://doi.org/10.1002/cncr.21073

[86] Nakamura, T., *et al.* (1992) p53 Gene Mutations Associated with Anaplastic Transformation of Human Thyroid Carcinomas. *Japanese Journal of Cancer Research*, **83**, 1293-1298. https://doi.org/10.1111/j.1349-7006.1992.tb02761.x

[87] Ito, T., *et al.* (1992) Unique Association of p53 Mutations with Undifferentiated But Not with Differentiated Carcinomas of the Thyroid Gland. *Cancer Research*, **52**, 1369-1371.

[88] Ito, T., *et al.* (1993) Genetic Alterations in Thyroid Tumor Progression: Association with p53 Gene Mutations. *Japanese Journal of Cancer Research*, **84**, 526-531. https://doi.org/10.1111/j.1349-7006.1993.tb00171.x

[89] Moretti, F., *et al.* (1997) p53 Re-Expression Inhibits Proliferation and Restores Differentiation of Human Thyroid Anaplastic Carcinoma Cells. *Oncogene*, **14**, 729-740. https://doi.org/10.1038/sj.onc.1200887

[90] Komoike, Y., *et al.* (1999) Comparative Genomic Hybridization Defines Frequent Loss on 16p in Human Anaplastic Thyroid Carcinoma. *International Journal of Oncology*, **14**, 1157-1162. https://doi.org/10.3892/ijo.14.6.1157

[91] Smallridge, R.C., Marlow, L.A. and Copland, J.A. (2009) Anaplastic Thyroid Cancer: Molecular Pathogenesis and Emerging Therapies. *Endocrine-Related Cancer*, **16**, 17-44. https://doi.org/10.1677/ERC-08-0154

[92] Akslen, L.A., *et al.* (1990) Incidence of Thyroid Cancer in Norway 1970-1985. Population Review on Time Trend, Sex, Age, Histological Type and Tumour Stage in 2625 Cases. *APMIS*, **98**, 549-558. https://doi.org/10.1111/j.1699-0463.1990.tb01070.x

[93] Burke, J.P., *et al.* (2005) Long-Term Trends in Thyroid Carcinoma: A Population-Based Study in Olmsted County, Minnesota, 1935-1999. *Mayo Clinic Proceedings*, **80**, 753-758. https://doi.org/10.1016/S0025-6196(11)61529-2

[94] Davies, L. and Welch, H.G. (2006) Increasing Incidence of Thyroid Cancer in the United States, 1973-2002. *JAMA*, **295**, 2164-2167. https://doi.org/10.1001/jama.295.18.2164

[95] Smallridge, R.C. and Copland, J.A. (2010) Anaplastic Thyroid Carcinoma: Pathogenesis and Emerging Therapies. *Clinical Oncology*, **22**, 486-497. https://doi.org/10.1016/j.clon.2010.03.013

[96] Kebebew, E., *et al.* (2005) Anaplastic Thyroid Carcinoma. Treatment Outcome and

Prognostic Factors. *Cancer*, **103**, 1330-1335. https://doi.org/10.1002/cncr.20936

[97] Nagaiah, G., *et al.* (2011) Anaplastic Thyroid Cancer: A Review of Epidemiology, Pathogenesis, and Treatment. *Journal of Oncology*, **2011**, Article ID: 542358. https://doi.org/10.1155/2011/542358

[98] Nel, C.J., *et al.* (1985) Anaplastic Carcinoma of the Thyroid: A Clinicopathologic Study of 82 Cases. *Mayo Clinic Proceedings*, **60**, 51-58. https://doi.org/10.1016/S0025-6196(12)65285-9

[99] Carcangiu, M.L., *et al.* (1985) Anaplastic Thyroid Carcinoma. A Study of 70 Cases. *American Journal of Clinical Pathology*, **83**, 135-158. https://doi.org/10.1093/ajcp/83.2.135

[100] Venkatesh, Y.S., *et al.* (1990) Anaplastic Carcinoma of the Thyroid. A Clinicopathologic Study of 121 Cases. *Cancer*, **66**, 321-330. https://doi.org/10.1002/1097-0142(19900715)66:2<321::AID-CNCR2820660221>3.0.CO;2-A

[101] Tan, R.K., *et al.* (1995) Anaplastic Carcinoma of the Thyroid: A 24-Year Experience. *Head Neck*, **17**, 41-47. https://doi.org/10.1002/hed.2880170109

[102] McIver, B., *et al.* (2001) Anaplastic Thyroid Carcinoma: A 50-Year Experience at a Single Institution. *Surgery*, **130**, 1028-1034. https://doi.org/10.1067/msy.2001.118266

[103] Chiu, A., Oliveira, A.A., Schultz, P.N., Ordonez, N.G. and Sherman, S.I. (1996) Prognostic Clinicopathologic Features in Hürthle Cell Neoplasia. *Thyroid*, **6**, S29.

[104] Aldinger, K.A., *et al.* (1978) Anaplastic Carcinoma of the Thyroid: A Review of 84 Cases of Spindle and Giant Cell Carcinoma of the Thyroid. *Cancer*, **41**, 2267-2275. https://doi.org/10.1002/1097-0142(197806)41:6<2267::AID-CNCR2820410627>3.0.CO;2-7

[105] Tennvall, J., *et al.* (2002) Anaplastic Thyroid Carcinoma: Three Protocols Combining Doxorubicin, Hyperfractionated Radiotherapy and Surgery. *British Journal of Cancer*, **86**, 1848-1853. https://doi.org/10.1038/sj.bjc.6600361

[106] Nishiyama, R.H., Dunn, E.L. and Thompson, N.W. (1972) Anaplastic Spindle-Cell and Giant-Cell Tumors of the Thyroid Gland. *Cancer*, **30**, 113-127. https://doi.org/10.1002/1097-0142(197207)30:1<113::AID-CNCR2820300118>3.0.CO;2-E

[107] Hadar, T., *et al.* (1987) Anaplastic Thyroid Carcinoma Metastatic to the Tonsil. *The Journal of Laryngology & Otology*, **101**, 953-956. https://doi.org/10.1017/S0022215100103044

[108] Phillips, D.L., *et al.* (1987) Isolated Metastasis to Small Bowel from Anaplastic Thyroid Carcinoma. With a Review of Extra-Abdominal Malignancies That Spread to the Bowel. *Journal of Clinical Gastroenterology*, **9**, 563-567. https://doi.org/10.1097/00004836-198710000-00017

[109] Murabe, H., *et al.* (1992) Anaplastic Thyroid Carcinoma with Prominent Cardiac Metastasis, Accompanied by a Marked Leukocytosis with a Neutrophilia and High GM-CSF Level in Serum. *Internal Medicine*, **31**, 1107-1111. https://doi.org/10.2169/internalmedicine.31.1107

[110] Hadar, T., *et al.* (1993) Anaplastic Carcinoma of the Thyroid. *European Journal of Surgical Oncology*, **19**, 511-516.

[111] Smallridge, R.C., *et al.* (2012) American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer. *Thyroid*, **22**, 1104-1139. https://doi.org/10.1089/thy.2012.0302

[112] Haigh, P.I., *et al.* (2001) Completely Resected Anaplastic Thyroid Carcinoma Combined with Adjuvant Chemotherapy and Irradiation Is Associated with Prolonged Survival. *Cancer*, **91**, 2335-2342. https://doi.org/10.1002/1097-0142(20010615)91:12<2335::AID-CNCR1266>3.0.CO;2-1

[113] Pierie, J.P., *et al.* (2002) The Effect of Surgery and Radiotherapy on Outcome of Anaplastic Thyroid Carcinoma. *Annals of Surgical Oncology*, **9**, 57-64. https://doi.org/10.1245/aso.2002.9.1.57

[114] Spires, J.R., Schwartz, M.R. and Miller, R.H. (1988) Anaplastic Thyroid Carcinoma. Association with Differentiated Thyroid Cancer. *Archives of Otolaryngology—Head and Neck Surgery*, **114**, 40-44. https://doi.org/10.1001/archotol.1988.01860130044012

[115] Pedersen, R.K. and Pedersen, N.T. (1996) Primary Non-Hodgkin's Lymphoma of the Thyroid Gland: A Population Based Study. *Histopathology*, **28**, 25-32. https://doi.org/10.1046/j.1365-2559.1996.268311.x

[116] Skarsgard, E.D., Connors, J.M. and Robins, R.E. (1991) A Current Analysis of Primary Lymphoma of the Thyroid. *Archives of Surgery*, **126**, 1199-1203. https://doi.org/10.1001/archsurg.1991.01410340037006

[117] Junor, E.J., Paul, J. and Reed, N.S. (1992) Primary Non-Hodgkin's Lymphoma of the Thyroid. *European Journal of Surgical Oncology*, **18**, 313-321.

[118] Logue, J.P., *et al.* (1992) Primary Malignant Lymphoma of the Thyroid: A Clinicopathological Analysis. *International Journal of Radiation Oncology Biology Physics*, **22**, 929-933. https://doi.org/10.1016/0360-3016(92)90790-O

[119] Holm, L.E., Blomgren, H. and Lowhagen, T. (1985) Cancer Risks in Patients with Chronic Lymphocytic Thyroiditis. *The New England Journal of Medicine*, **312**, 601-604. https://doi.org/10.1056/NEJM198503073121001

[120] Hyjek, E. and Isaacson, P.G. (1988) Primary β Cell Lymphoma of the Thyroid and Its Relationship to Hashimoto's Thyroiditis. *Human Pathology*, **19**, 1315-1326. https://doi.org/10.1016/S0046-8177(88)80287-9

[121] Freeman, C., Berg, J.W. and Cutler, S.J. (1972) Occurrence and Prognosis of Extranodal Lymphomas. *Cancer*, **29**, 252-260. https://doi.org/10.1002/1097-0142(197201)29:1<252::AID-CNCR2820290138>3.0.CO;2-#

[122] Wang, S.A., *et al.* (2005) Hodgkin's Lymphoma of the Thyroid: A Clinicopathologic Study of Five Cases and Review of the Literature. *Modern Pathology*, **18**, 1577-1584. https://doi.org/10.1038/modpathol.3800501

[123] Mizukami, Y., *et al.* (1990) Primary Lymphoma of the Thyroid: A Clinical, Histological and Immunohistochemical Study of 20 Cases. *Histopathology*, **17**, 201-209. https://doi.org/10.1111/j.1365-2559.1990.tb00708.x

[124] Ohsawa, M., Noguchi, S. and Aozasa, K. (1995) Immunologic Type of Thyroid Lymphoma in an Adult T-Cell Leukemia Endemic Area in Japan. *Leukemia & Lymphoma*, **17**, 341-344. https://doi.org/10.3109/10428199509056842

[125] Tsang, R.W., *et al.* (1993) Non-Hodgkin's Lymphoma of the Thyroid Gland: Prognostic Factors and Treatment Outcome. The Princess Margaret Hospital Lymphoma Group. *International Journal of Radiation Oncology Biology Physics*, **27**, 599-604. https://doi.org/10.1016/0360-3016(93)90385-9

[126] DiBiase, S.J., *et al.* (2004) Outcome Analysis for Stage IE and IIE Thyroid Lymphoma. *American Journal of Clinical Oncology*, **27**, 178-184.

https://doi.org/10.1097/01.coc.0000054891.30422.B5

[127] Burke, J.S. (1999) Are There Site-Specific Differences among the MALT Lymphomas—Morphologic, Clinical? *American Journal of Clinical Pathology*, **111**, S133-S143.

[128] Gharib, H. and Papini, E. (2007) Thyroid Nodules: Clinical Importance, Assessment, and Treatment. *Endocrinology & Metabolism Clinics of North America*, **36**, 707-735. https://doi.org/10.1016/j.ecl.2007.04.009

[129] Haymart, M.R., *et al.* (2008) Higher Serum Thyroid Stimulating Hormone Level in Thyroid Nodule Patients Is Associated with Greater Risks of Differentiated Thyroid Cancer and Advanced Tumor Stage. *The Journal of Clinical Endocrinology & Metabolism*, **93**, 809-814. https://doi.org/10.1210/jc.2007-2215

[130] Suh, I., *et al.* (2010) Serum Thyroglobulin Is a Poor Diagnostic Biomarker of Malignancy in Follicular and Hurthle-Cell Neoplasms of the Thyroid. *The American Journal of Surgery*, **200**, 41-46. https://doi.org/10.1016/j.amjsurg.2009.08.030

[131] Lee, E.K., *et al.* (2012) Preoperative Serum Thyroglobulin as a Useful Predictive Marker to Differentiate Follicular Thyroid Cancer from Benign Nodules in Indeterminate Nodules. *Journal of Korean Medical Science*, **27**, 1014-1018. https://doi.org/10.3346/jkms.2012.27.9.1014

[132] Elisei, R., *et al.* (2004) Impact of Routine Measurement of Serum Calcitonin on the Diagnosis and Outcome of Medullary Thyroid Cancer: Experience in 10,864 Patients with Nodular Thyroid Disorders. *The Journal of Clinical Endocrinology & Metabolism*, **89**, 163-168. https://doi.org/10.1210/jc.2003-030550

[133] Hahm, J.R., *et al.* (2001) Routine Measurement of Serum Calcitonin Is Useful for Early Detection of Medullary Thyroid Carcinoma in Patients with Nodular Thyroid Diseases. *Thyroid*, **11**, 73-80. https://doi.org/10.1089/10507250150500694

[134] Niccoli, P., *et al.* (1997) Interest of Routine Measurement of Serum Calcitonin: Study in a Large Series of Thyroidectomized Patients. The French Medullary Study Group. *The Journal of Clinical Endocrinology & Metabolism*, **82**, 338-341. https://doi.org/10.1210/jcem.82.2.3737

[135] Costante, G., *et al.* (2007) Predictive Value of Serum Calcitonin Levels for Preoperative Diagnosis of Medullary Thyroid Carcinoma in a Cohort of 5817 Consecutive Patients with Thyroid Nodules. *The Journal of Clinical Endocrinology & Metabolism*, **92**, 450-455. https://doi.org/10.1210/jc.2006-1590

[136] Horvath, E., *et al.* (2009) An Ultrasonogram Reporting System for Thyroid Nodules Stratifying Cancer Risk for Clinical Management. *The Journal of Clinical Endocrinology & Metabolism*, **94**, 1748-1751. https://doi.org/10.1210/jc.2008-1724

[137] Tae, H.J., *et al.* (2007) Diagnostic Value of Ultrasonography to Distinguish between Benign and Malignant Lesions in the Management of Thyroid Nodules. *Thyroid*, **17**, 461-466. https://doi.org/10.1089/thy.2006.0337

[138] Ito, Y., *et al.* (2007) Ultrasonographic Evaluation of Thyroid Nodules in 900 Patients: Comparison among Ultrasonographic, Cytological, and Histological Findings. *Thyroid*, **17**, 1269-1276. https://doi.org/10.1089/thy.2007.0014

[139] Alexander, E.K., *et al.* (2002) Assessment of Nondiagnostic Ultrasound-Guided Fine Needle Aspirations of Thyroid Nodules. *The Journal of Clinical Endocrinology & Metabolism*, **87**, 4924-4927. https://doi.org/10.1210/jc.2002-020865

[140] Danese, D., *et al.* (1998) Diagnostic Accuracy of Conventional versus Sonography-Guided Fine-Needle Aspiration Biopsy of Thyroid Nodules. *Thyroid*, **8**, 15-21. https://doi.org/10.1089/thy.1998.8.15

[141] Baloch, Z.W., *et al.* (2008) Diagnostic Terminology and Morphologic Criteria for

Cytologic Diagnosis of Thyroid Lesions: A Synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. *Diagnostic Cytopathology*, **36**, 425-437. https://doi.org/10.1002/dc.20830

[142] Crothers, B.A. and Firat, P. (2010) Nondiagnostic/Unsatisfactory. In: Cibas, E.S. and Ali, S.Z., Eds., *The Bethesda System for Reporting Thyroid Cytopathology*, Springer, Berlin, 5-14. https://doi.org/10.1007/978-0-387-87666-5_2

[143] Cibas, E.S. and Ali, S.Z. (2017) The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid*, **27**, 1341-1346. https://doi.org/10.1089/thy.2017.0500

[144] Baloch, Z.W., *et al.* (2000) Ultrasound-Guided Fine-Needle Aspiration Biopsy of the Thyroid: Role of On-Site Assessment and Multiple Cytologic Preparations. *Diagnostic Cytopathology*, **23**, 425-429. https://doi.org/10.1002/1097-0339(200012)23:6<425::AID-DC14>3.0.CO;2-3

[145] Braga, M., *et al.* (2001) Efficacy of Ultrasound-Guided Fine-Needle Aspiration Biopsy in the Diagnosis of Complex Thyroid Nodules. *The Journal of Clinical Endocrinology & Metabolism*, **86**, 4089-4091. https://doi.org/10.1210/jcem.86.9.7824

[146] Wu, H.H., Rose, C. and Elsheikh, T.M. (2012) The Bethesda System for Reporting Thyroid Cytopathology: An Experience of 1,382 Cases in a Community Practice setting with the Implication for Risk of Neoplasm and Risk of Malignancy. *Diagnostic Cytopathology*, **40**, 399-403. https://doi.org/10.1002/dc.21754

[147] Layfield, L.J., *et al.* (2008) Post-Thyroid FNA Testing and Treatment Options: A Synopsis of the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. *Diagnostic Cytopathology*, **36**, 442-448. https://doi.org/10.1002/dc.20832

[148] Singh, R.S. and Wang, H.H. (2011) Timing of Repeat Thyroid Fine-Needle Aspiration in the Management of Thyroid Nodules. *Acta Cytologica*, **55**, 544-548. https://doi.org/10.1159/000334214

[149] Lubitz, C.C., *et al.* (2012) Diagnostic Yield of Nondiagnostic Thyroid Nodules Is Not Altered by Timing of Repeat Biopsy. *Thyroid*, **22**, 590-594. https://doi.org/10.1089/thy.2011.0442

[150] Theoharis, C.G., *et al.* (2009) The Bethesda Thyroid Fine-Needle Aspiration Classification System: Year 1 at an Academic Institution. *Thyroid*, **19**, 1215-1223. https://doi.org/10.1089/thy.2009.0155

[151] Luu, M.H., *et al.* (2011) Improved Preoperative Definitive Diagnosis of Papillary Thyroid Carcinoma in FNAs Prepared with Both ThinPrep and Conventional Smears Compared with FNAs Prepared with ThinPrep Alone. *Cancer Cytopathology*, **119**, 68-73. https://doi.org/10.1002/cncy.20124

[152] Bongiovanni, M., *et al.* (2012) The Bethesda System for Reporting Thyroid Cytopathology: A Meta-Analysis. *Acta Cytologica*, **56**, 333-339. https://doi.org/10.1159/000339959

[153] Orlandi, A., *et al.* (2005) Repeated Fine-Needle Aspiration of the Thyroid in Benign Nodular Thyroid Disease: Critical Evaluation of Long-Term Follow-Up. *Thyroid*, **15**, 274-278. https://doi.org/10.1089/thy.2005.15.274

[154] Chehade, J.M., *et al.* (2001) Role of Repeated Fine-Needle Aspiration of Thyroid Nodules with Benign Cytologic Features. *Endocrine Practice*, **7**, 237-243. https://doi.org/10.4158/EP.7.4.237

[155] Oertel, Y.C., *et al.* (2007) Value of Repeated Fine Needle Aspirations of the Thyroid: An Analysis of over Ten Thousand FNAs. *Thyroid*, **17**, 1061-1066. https://doi.org/10.1089/thy.2007.0159

[156] Krane, J.F., Renshaw, A.A., *et al.* (2010) Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance. In: Ali, S.Z. and Cibas, E.S., Eds., *The Bethesda System for Reporting Thyroid Cytopathology*, Springer, Berlin, 37-49. https://doi.org/10.1007/978-0-387-87666-5_4

[157] Henry, M.R., Berezowski, K., *et al.* (2010) Follicular Neoplasm/Suspicious for a Follicular Neoplasm. In: Ali, S.Z. and Cibas, E.S., Eds., *The Bethesda System for Reporting Thyroid Cytopathology*, Springer, Berlin, 51-58. https://doi.org/10.1007/978-0-387-87666-5_5

[158] Faquin, W.C., Renshaw, A.A., *et al.* (2010) Follicular Neoplasm, Hurthle Cell Type/Suspicious for a Follicular Neoplasm, Hurthle Cell Type. In: Ali, S.Z. and Cibas, E.S., Eds., *The Bethesda System for Reporting Thyroid Cytopathology*, Springer, Berlin, 59-73. https://doi.org/10.1007/978-0-387-87666-5_6

[159] Wang, H.H., Clark, D.P., *et al.* (2010) Suspicious for Malignancy. In: Ali, S.Z. and Cibas, E.S., Eds., *The Bethesda System for Reporting Thyroid Cytopathology*, Springer, Berlin, 75-89. https://doi.org/10.1007/978-0-387-87666-5_7

[160] Ito, Y., *et al.* (2014) Patient Age Is Significantly Related to the Progression of Papillary Microcarcinoma of the Thyroid under Observation. *Thyroid*, **24**, 27-34. https://doi.org/10.1089/thy.2013.0367

[161] Sugitani, I., *et al.* (2010) Three Distinctly Different Kinds of Papillary Thyroid Microcarcinoma Should Be Recognized: Our Treatment Strategies and Outcomes. *World Journal of Surgery*, **34**, 1222-1231. https://doi.org/10.1007/s00268-009-0359-x

[162] Killock, D. (2014) Genetics: The Cancer Genome Atlas Maps Papillary Thyroid Cancer. *Nature Reviews Clinical Oncology*, **11**, 681. https://doi.org/10.1038/nrclinonc.2014.193

[163] Howell, G.M., Hodak, S.P. and Yip, L. (2013) RAS Mutations in Thyroid Cancer. *Oncologist*, **18**, 926-932. https://doi.org/10.1634/theoncologist.2013-0072

[164] Hamatani, K., *et al.* (2008) RET/PTC Rearrangements Preferentially Occurred in Papillary Thyroid Cancer among Atomic Bomb Survivors Exposed to High Radiation Dose. *Cancer Research*, **68**, 7176-7182. https://doi.org/10.1158/0008-5472.CAN-08-0293

[165] Stransky, N., *et al.* (2014) The Landscape of Kinase Fusions in Cancer. *Nature Communications*, **5**, 4846. https://doi.org/10.1038/ncomms5846

[166] Figlioli, G., *et al.* (2013) Medullary Thyroid Carcinoma (MTC) and RET Proto-Oncogene: Mutation Spectrum in the Familial Cases and a Meta-Analysis of Studies on the Sporadic Form. *Mutation Research*, **752**, 36-44. https://doi.org/10.1016/j.mrrev.2012.09.002

[167] Gagel, R.F., Cote, G.J., *et al.* (2005) Medullary Thyroid Carcinoma. In: *The Thyroid*, Lippincott Williams & Wilkins, Philadelphia, 9th Edition, 167-178. https://doi.org/10.1007/978-0-387-24472-3_12

[168] Nikiforov, Y.E., *et al.* (2011) Impact of Mutational Testing on the Diagnosis and Management of Patients with Cytologically Indeterminate Thyroid Nodules: A Prospective Analysis of 1056 FNA Samples. *The Journal of Clinical Endocrinology & Metabolism*, **96**, 3390-3397. https://doi.org/10.1210/jc.2011-1469

[169] Alexander, E.K., *et al.* (2012) Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology. *The New England Journal of Medicine*, **367**, 705-715. https://doi.org/10.1056/NEJMoa1203208

[170] Bartolazzi, A., *et al.* (2008) Galectin-3-Expression Analysis in the Surgical Selection of Follicular Thyroid Nodules with Indeterminate Fine-Needle Aspiration Cytology:

A Prospective Multicentre Study. *The Lancet Oncology*, **9**, 543-549. https://doi.org/10.1016/S1470-2045(08)70132-3

[171] Sosa, J.A., *et al.* (1998) The Importance of Surgeon Experience for Clinical and Economic Outcomes from Thyroidectomy. *Annals of Surgery*, **228**, 320-330. https://doi.org/10.1097/00000658-199809000-00005

[172] Loyo, M., Tufano, R.P. and Gourin, C.G. (2013) National Trends in Thyroid Surgery and the Effect of Volume on Short-Term Outcomes. *Laryngoscope*, **123**, 2056-2063. https://doi.org/10.1002/lary.23923

[173] Gourin, C.G., *et al.* (2010) Volume-Based Trends in Thyroid Surgery. *Archives of Otolaryngology*: *Head and Neck Surgery*, **136**, 1191-1198. https://doi.org/10.1001/archoto.2010.212

[174] Stavrakis, A.I., *et al.* (2007) Surgeon Volume as a Predictor of Outcomes in Inpatient and Outpatient Endocrine Surgery. *Surgery*, **142**, 887-899. https://doi.org/10.1016/j.surg.2007.09.003

[175] Tuttle, R.M., *et al.* (2018) Thyroid—Differentiated and Anaplastic Carcinoma. In: *AJCC Cancer Staging Manuel*, Vol. 1, Springer International Publishing, Berlin, Eight Edition, Pages.

[176] Woolner, L.B., *et al.* (1961) Classification and Prognosis of Thyroid Carcinoma. A Study of 885 Cases Observed in a Thirty Year Period. *The American Journal of Surgery*, **102**, 354-387. https://doi.org/10.1016/0002-9610(61)90527-X

[177] Byar, D.P., *et al.* (1979) A Prognostic Index for Thyroid Carcinoma. A Study of the E.O.R.T.C. Thyroid Cancer Cooperative Group. *European Journal of Cancer*, **15**, 1033-1041. https://doi.org/10.1016/0014-2964(79)90291-3

[178] Mazzaferri, E.L., *et al.* (1977) Papillary Thyroid Carcinoma: The Impact of Therapy in 576 Patients. *Medicine* (*Baltimore*), **56**, 171-196. https://doi.org/10.1097/00005792-197705000-00001

[179] Mazzaferri, E.L. and Young, R.L. (1981) Papillary Thyroid Carcinoma: A 10 Year Follow-Up Report of the Impact of Therapy in 576 Patients. *The American Journal of Medicine*, **70**, 511-518. https://doi.org/10.1016/0002-9343(81)90573-8

[180] Hay, I.D., *et al.* (1993) Predicting Outcome in Papillary Thyroid Carcinoma: Development of a Reliable Prognostic Scoring System in a Cohort of 1779 Patients Surgically Treated at One Institution during 1940 through 1989. *Surgery*, **114**, 1050-1057.

[181] Cady, B. and Rossi, R. (1988) An Expanded View of Risk-Group Definition in Differentiated Thyroid Carcinoma. *Surgery*, **104**, 947-953. https://doi.org/10.1016/S0039-6060(98)70034-0

[182] Shah, J.P., *et al.* (1992) Prognostic Factors in Differentiated Carcinoma of the Thyroid Gland. *The American Journal of Surgery*, **164**, 658-661. https://doi.org/10.1016/S0002-9610(05)80729-9

[183] Shaha, A.R., Shah, J.P. and Loree, T.R. (1996) Risk Group Stratification and Prognostic Factors in Papillary Carcinoma of Thyroid. *Annals of Surgical Oncology*, **3**, 534-538. https://doi.org/10.1007/BF02306085

[184] Cady, B., *et al.* (1976) Changing Clinical, Pathologic, Therapeutic, and Survival Patterns in Differentiated Thyroid Carcinoma. *Annals of Surgery*, **184**, 541-553. https://doi.org/10.1097/00000658-197611000-00003

[185] Hughes, C.J., *et al.* (1996) Impact of Lymph Node Metastasis in Differentiated Carcinoma of the Thyroid: A Matched-Pair Analysis. *Head Neck*, **18**, 127-132. https://doi.org/10.1002/(SICI)1097-0347(199603/04)18:2<127::AID-HED3>3.0.CO;2-3

[186] Edge, S.B. (2010) Thyroid—Differentiated and Anaplastic Carcinoma. In: *American*

Joint Committee on Cancer, *AJCC Cancer Staging Manual*, Vol. 1, Springer, New York, 7th Edition, 873-890.

[187] Sherman, S.I., *et al.* (1998) Prospective Multicenter Study of Thyroiscarcinoma Treatment: Initial Analysis of Staging and Outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. *Cancer*, **83**, 1012-1021. https://doi.org/10.1002/(SICI)1097-0142(19980901)83:5<1012::AID-CNCR28>3.0.CO;2-9

[188] Frazell, E.L., Schottenfeld, D. and Hutter, R.V. (1970) The Prognosis and Insurability of Thyroid Cancer Patients. *CA*: *A Cancer Journal for Clinicians*, **20**, 270-275. https://doi.org/10.3322/canjclin.20.5.270

[189] Mitchell, I., *et al.* (2007) Trends in Thyroid Cancer Demographics and Surgical Therapy in the United States. *Surgery*, **142**, 823-828. https://doi.org/10.1016/j.surg.2007.09.011

[190] Machens, A., Hauptmann, S. and Dralle, H. (2006) Disparities between Male and Female Patients with Thyroid Cancers: Sex Difference or Gender Divide? *Clinical Endocrinology*, **65**, 500-505. https://doi.org/10.1111/j.1365-2265.2006.02623.x

[191] Jonklaas, J., *et al.* (2006) Outcomes of Patients with Differentiated Thyroid Carcinoma Following Initial Therapy. *Thyroid*, **16**, 1229-1242. https://doi.org/10.1089/thy.2006.16.1229

[192] Jonklaas, J., *et al.* (2010) Radioiodine Therapy in Patients with Stage I Differentiated Thyroid Cancer. *Thyroid*, **20**, 1423-1424. https://doi.org/10.1089/thy.2010.0308

[193] Sacks, W., *et al.* (2010) The Effectiveness of Radioactive Iodine for Treatment of Low-Risk Thyroid Cancer: A Systematic Analysis of the Peer-Reviewed Literature from 1966 to April 2008. *Thyroid*, **20**, 1235-1245. https://doi.org/10.1089/thy.2009.0455

[194] Sawka, A.M., *et al.* (2008) An Updated Systematic Review and Commentary Examining the Effectiveness of Radioactive Iodine Remnant Ablation in Well-Differentiated Thyroid Cancer. *Endocrinology & Metabolism Clinics of North America*, **37**, 457-480. https://doi.org/10.1016/j.ecl.2008.02.007

[195] Creach, K.M., *et al.* (2012) Radioactive Iodine Therapy Decreases Recurrence in Thyroid Papillary Microcarcinoma. *ISRN Endocrinology*, **2012**, Article ID: 816386. https://doi.org/10.5402/2012/816386

[196] Grebe, S.K. and Hay, I.D. (1997) Follicular Cell-Derived Thyroid Carcinomas. *Cancer Treatment and Research*, **89**, 91-140. https://doi.org/10.1007/978-1-4615-6355-6_6

[197] Als, C., *et al.* (1997) Scintigraphic Method in the Quantification of Morphological and Functional Changes of Thyroid Autonomy before and after Iodine Radiotherapy. *Schweizerische Medizinische Wochenschrift*, **127**, 102-106.

[198] Beierwaltes, W.H. (1978) The Treatment of Thyroid Carcinoma with Radioactive Iodine. *Seminars in Nuclear Medicine*, **8**, 79-94. https://doi.org/10.1016/S0001-2998(78)80009-9

[199] Wartofsky, L., *et al.* (1998) The Use of Radioactive Iodine in Patients with Papillary and Follicular Thyroid Cancer. *The Journal of Clinical Endocrinology & Metabolism*, **83**, 4195-4203. https://doi.org/10.1210/jcem.83.12.5293-1

[200] Ajjan, R.A., *et al.* (1998) Regulation and Tissue Distribution of the Human Sodium Iodide Symporter Gene. *Clinical Endocrinology*, **49**, 517-523. https://doi.org/10.1046/j.1365-2265.1998.00570.x

[201] Spitzweg, C., *et al.* (1998) Analysis of Human Sodium Iodide Symporter Gene Ex-

pression in Extrathyroidal Tissues and Cloning of Its Complementary Deoxyribonucleic Acids from Salivary Gland, Mammary Gland, and Gastric Mucosa. *The Journal of Clinical Endocrinology & Metabolism*, **83**, 1746-1751. https://doi.org/10.1210/jcem.83.5.4839

[202] Filetti, S., *et al.* (1999) Sodium/Iodide Symporter: A Key Transport System in Thyroid Cancer Cell Metabolism. *European Journal of Endocrinology*, **141**, 443-457. https://doi.org/10.1530/eje.0.1410443

[203] Schlumberger, M., *et al.* (2007) Defects in Iodide Metabolism in Thyroid Cancer and Implications for the Follow-Up and Treatment of Patients. *Nature Clinical Practice Endocrinology & Metabolism*, **3**, 260-269. https://doi.org/10.1038/ncpendmet0449

[204] Griggs, W.S. and Divgi, C. (2008) Radioiodine Imaging and Treatment in Thyroid Disorders. *Neuroimaging Clinics of North America*, **18**, 505-515. https://doi.org/10.1016/j.nic.2008.03.008

[205] Mazzaferri, E.L. (1999) An Overview of the Management of Papillary and Follicular Thyroid Carcinoma. *Thyroid*, **9**, 421-427. https://doi.org/10.1089/thy.1999.9.421

[206] Blum, M., *et al.* (2011) I-131 SPECT/CT Elucidates Cryptic Findings on Planar Whole-Body Scans and Can Reduce Needless Therapy with I-131 in Post-Thyroidectomy Thyroid Cancer Patients. *Thyroid*, **21**, 1235-1247. https://doi.org/10.1089/thy.2011.0010

[207] Chen, C.Z. and Watt, D.E. (1986) Biophysical Mechanism of Radiation Damage to Mammalian Cells by X- and Gamma-Rays. *International Journal of Radiation Biology and Related Studies in Physics, Chemistry, and Medicine*, **49**, 131-142. https://doi.org/10.1080/09553008514552301

[208] Feinendegen, L.E. (1993) Contributions of Nuclear Medicine to the Therapy of Malignant Tumors. *Journal of Cancer Research and Clinical Oncology*, **119**, 320-322. https://doi.org/10.1007/BF01208838

[209] Wheldon, T.E., *et al.* (1991) The Curability of Tumours of Differing Size by Targeted Radiotherapy Using 131I or 90Y. *Radiotherapy and Oncology*, **21**, 91-99. https://doi.org/10.1016/0167-8140(91)90080-Z

[210] Rydberg, B. (1996) Clusters of DNA Damage Induced by Ionizing Radiation: Formation of Short DNA Fragments. II. Experimental Detection. *Radiation Research*, **145**, 200-209. https://doi.org/10.2307/3579175

[211] Radford, I.R. and Aldridge, D.R. (1999) Importance of DNA Damage in the Induction of Apoptosis by Ionizing Radiation: Effect of the Scid Mutation and DNA Ploidy on the Radiosensitivity of Murine Lymphoid Cell Lines. *International Journal of Radiation Biology*, **75**, 143-153. https://doi.org/10.1080/095530099140591

[212] Mallya, S.M. and Sikpi, M.O. (1999) Requirement for p53 in Ionizing-Radiation-Inhibition of Double-Strand-Break Rejoining by Human Lymphoblasts. *Mutation Research*, **434**, 119-132. https://doi.org/10.1016/S0921-8777(99)00020-8

[213] Dobosz, T., *et al.* (2000) Microsatellite Instability in Thyroid Papillary Carcinoma and Multinodular Hyperplasia. *Oncology*, **58**, 305-310. https://doi.org/10.1159/000012117

[214] Leboeuf, R., *et al.* (2007) L-T3 Preparation for Whole-Body Scintigraphy: A Randomized-Controlled Trial. *Clinical Endocrinology*, **67**, 839-844. https://doi.org/10.1111/j.1365-2265.2007.02972.x

[215] Lee, J., *et al.* (2010) Quality of Life and Effectiveness Comparisons of Thyroxine Withdrawal, Triiodothyronine Withdrawal, and Recombinant Thyroid-Stimulating

Hormone Administration for Low-Dose Radioiodine Remnant Ablation of Differentiated Thyroid Carcinoma. *Thyroid*, **20**, 173-179. https://doi.org/10.1089/thy.2009.0187

[216] Robbins, R.J., *et al.* (2006) Recombinant Human Thyrotropin-Assisted Radioiodine Therapy for Patients with Metastatic Thyroid Cancer Who Could Not Elevate Endogenous Thyrotropin or Be Withdrawn from Thyroxine. *Thyroid*, **16**, 1121-1130. https://doi.org/10.1089/thy.2006.16.1121

[217] Chianelli, M., *et al.* (2009) Low-Activity (2.0 GBq; 54 mCi) Radioiodine Post-Surgical Remnant Ablation in Thyroid Cancer: Comparison between Hormone Withdrawal and Use of rhTSH in Low-Risk Patients. *European Journal of Endocrinology*, **160**, 431-436. https://doi.org/10.1530/EJE-08-0669

[218] Mallick, U., *et al.* (2012) Ablation with Low-Dose Radioiodine and Thyrotropin Alfa in Thyroid Cancer. *The New England Journal of Medicine*, **366**, 1674-1685. https://doi.org/10.1056/NEJMoa1109589

[219] Sawka, A.M., *et al.* (2010) Dietary Iodine Restriction in Preparation for Radioactive Iodine Treatment or Scanning in Well-Differentiated Thyroid Cancer: A Systematic Review. *Thyroid*, **20**, 1129-1138. https://doi.org/10.1089/thy.2010.0055

[220] Pluijmen, M.J., *et al.* (2003) Effects of Low-Iodide Diet on Postsurgical Radioiodide Ablation Therapy in Patients with Differentiated Thyroid Carcinoma. *Clinical Endocrinology*, **58**, 428-435. https://doi.org/10.1046/j.1365-2265.2003.01735.x

[221] Morris, L.F., *et al.* (2001) Reevaluation of the Impact of a Stringent Low-Iodine Diet on Ablation Rates in Radioiodine Treatment of Thyroid Carcinoma. *Thyroid*, **11**, 749-755. https://doi.org/10.1089/10507250152484583

[222] Baehr, K.M., *et al.* (2012) Levothyroxine Dose Following Thyroidectomy Is Affected by More than Just Body Weight. *Laryngoscope*, **122**, 834-838. https://doi.org/10.1002/lary.23186

[223] Jin, J., Allemang, M.T. and McHenry, C.R. (2013) Levothyroxine Replacement Dosage Determination after Thyroidectomy. *The American Journal of Surgery*, **205**, 360-363. https://doi.org/10.1016/j.amjsurg.2012.10.015

[224] Ford, D., *et al.* (2003) External Beam Radiotherapy in the Management of Differentiated Thyroid Cancer. *Clinical Oncology*, **15**, 337-341. https://doi.org/10.1016/S0936-6555(03)00162-6

[225] Terezakis, S.A., *et al.* (2009) Role of External Beam Radiotherapy in Patients with Advanced or Recurrent Nonanaplastic Thyroid Cancer: Memorial Sloan-kettering Cancer Center Experience. *International Journal of Radiation Oncology Biology Physics*, **73**, 795-801. https://doi.org/10.1016/j.ijrobp.2008.05.012

[226] Orita, Y., *et al.* (2011) Zoledronic Acid in the Treatment of Bone Metastases from Differentiated Thyroid Carcinoma. *Thyroid*, **21**, 31-35. https://doi.org/10.1089/thy.2010.0169

[227] Robbins, R.J., *et al.* (2006) Real-Time Prognosis for Metastatic Thyroid Carcinoma Based on 2-[18F]fluoro-2-deoxy-D-glucose-positron Emission Tomography Scanning. *The Journal of Clinical Endocrinology & Metabolism*, **91**, 498-505. https://doi.org/10.1210/jc.2005-1534

[228] Schluter, B., *et al.* (2001) Impact of FDG PET on Patients with Differentiated Thyroid Cancer Who Present with Elevated Thyroglobulin and Negative *131I Scan. Journal of Nuclear Medicine*, **42**, 71-76.

[229] Marotta, V., *et al.* (2013) Sorafenib in Advanced Iodine-Refractory Differentiated Thyroid Cancer: Efficacy, Safety and Exploratory Analysis of Role of Serum Thyroglobulin and FDG-PET. *Clinical Endocrinology*, **78**, 760-767.

https://doi.org/10.1111/cen.12057

[230] Brose, M.S., *et al.* (2014) Sorafenib in Radioactive Iodine-Refractory, Locally Advanced or Metastatic Differentiated Thyroid Cancer: A Randomised, Double-Blind, Phase 3 Trial. *The Lancet*, **384**, 319-328. https://doi.org/10.1016/S0140-6736(14)60421-9

[231] Schlumberger, M., *et al.* (2015) Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer. *The New England Journal of Medicine*, **372**, 621-630. https://doi.org/10.1056/NEJMoa1406470

[232] Cabanillas, M.E., *et al.* (2010) Treatment with Tyrosine Kinase Inhibitors for Patients with Differentiated Thyroid Cancer: The M. D. Anderson Experience. *The Journal of Clinical Endocrinology & Metabolism*, **95**, 2588-2595. https://doi.org/10.1210/jc.2009-1923

[233] Smith-Bindman, R., *et al.* (2013) Risk of Thyroid Cancer Based on Thyroid Ultrasound Imaging Characteristics: Results of a Population-Based Study. *JAMA Internal Medicine*, **173**, 1788-1796. https://doi.org/10.1001/jamainternmed.2013.9245

[234] Brito, J.P., *et al.* (2014) The Accuracy of Thyroid Nodule Ultrasound to Predict Thyroid Cancer: Systematic Review and Meta-Analysis. *The Journal of Clinical Endocrinology & Metabolism*, **99**, 1253-1263. https://doi.org/10.1210/jc.2013-2928

[235] Cohen, E.E., *et al.* (2008) Axitinib Is an Active Treatment for All Histologic Subtypes of Advanced Thyroid Cancer: Results from a Phase II Study. *Journal of Clinical Oncology*, **26**, 4708-4713. https://doi.org/10.1200/JCO.2007.15.9566

[236] Capdevila, J., *et al.* (2017) Axitinib Treatment in Advanced RAI-Resistant Differentiated Thyroid Cancer (DTC) and Refractory Medullary Thyroid Cancer (MTC). *European Journal of Endocrinology*, **177**, 309-317. https://doi.org/10.1530/EJE-17-0243

[237] Sherman, S.I., *et al.* (2008) Motesanib Diphosphate in Progressive Differentiated Thyroid Cancer. *The New England Journal of Medicine*, **359**, 31-42. https://doi.org/10.1056/NEJMoa075853

[238] Bible, K.C., *et al.* (2010) Efficacy of Pazopanib in Progressive, Radioiodine-Refractory, Metastatic Differentiated Thyroid Cancers: Results of a Phase 2 Consortium Study. *The Lancet Oncology*, **11**, 962-972. https://doi.org/10.1016/S1470-2045(10)70203-5

[239] Hayes, D.N., *et al.* (2012) Phase II Efficacy and Pharmacogenomic Study of Selumetinib (AZD6244; ARRY-142886) in Iodine-131 Refractory Papillary Thyroid Carcinoma with or without Follicular Elements. *Clinical Cancer Research*, **18**, 2056-2065. https://doi.org/10.1158/1078-0432.CCR-11-0563

[240] Sherman, E.J., *et al.* (2017) Phase 2 Study Evaluating the Combination of Sorafenib and Temsirolimus in the Treatment of Radioactive IODINE-Refractory Thyroid Cancer. *Cancer*, **123**, 4114-4121. https://doi.org/10.1002/cncr.30861

[241] Cohen, E.E., Cullen, K.J., *et al.* (2008) Phase 2 Study of Sunitinib in Refractory Thyroid Cancer *Journal of Clinical Oncology*, **26**, 6025. https://doi.org/10.1200/jco.2008.26.15_suppl.6025

[242] Leboulleux, S., *et al.* (2012) Vandetanib in Locally Advanced or Metastatic Differentiated Thyroid Cancer: A Randomised, Double-Blind, Phase 2 Trial. *The Lancet Oncology*, **13**, 897-905. https://doi.org/10.1016/S1470-2045(12)70335-2