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Review Article

Advances in Diagnosis and Treatment of Thyroid Cancer

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ABSTRACT

Thyroid cancer is the most common type of endocrine malignancy and affects millions of people worldwide [1]. It is estimated that in the United States alone, over 52,890 adults will be diagnosed with thyroid cancer this year [2]. With recent advances in medicine over the last couple of years, access to more efficient imaging and diagnostic technology has led to a staggering increase in the number of people being diagnosed with thyroid cancer. In this paper, we will review the recent advances in thyroid cancer diagnosis and treatment through the use of novel diagnostic approaches and explore recently approved clinical drugs and trials for treatment.

1. Introduction

Located in the neck overlying and on both sides of the trachea, the thyroid is an important endocrine gland that takes up iodine and secretes thyroid hormone. Thyroid hormone is crucial to metabolism and among other things, influences heart rate, blood pressure, and body temperature, as well as aiding in muscle control, brain development, and digestion [3]. While the specific cause of thyroid cancer remains unknown, there are many risk factors associated with the development of thyroid cancer. Risk factors, such as a family history of goiter, genetic predisposition, exposure to ionizing radiation from medical intervention or the environment, have all been linked to increased risk of thyroid cancer, according to the American Thyroid Association [4, 5].

Recently, researchers have begun elucidating specific genetic markers that are believed to have a role in increasing the risk of thyroid tumors [6-9]. The different contributors to the genesis of thyroid cancer notwithstanding, the presentation of the disease is similar for most patients. A thyroid nodule is usually the first tell-tale sign of thyroid neoplasia. In the clinical setting, thyroid nodules are being detected with a higher frequency than in previous years due, in large part, to the growing use of diagnostic imaging [2, 5, 7, 10]. While some patients have non-palpable or palpable lesions that are malignant, over 90% of thyroid nodules are small, benign lesions that will not develop into a clinically significant tumor [11].

2. Signs and Symptoms

Even though the majority of thyroid nodules are benign, the majority of cancers in this gland present with a nodule or lump that is often discovered on palpation of the thyroid. The incidence of thyroid nodules has steadily increased over the last couple of years as imaging and diagnostic technology such as ultrasound, PET scans, and others have become more accessible [2]. After risk factors and pertinent criteria have been assessed, a clinician can determine the likelihood that this newly found nodule is malignant (Table 1). In addition to a palpable nodule in the thyroid, some patients with thyroid cancer can present with swelling of the central neck, have trouble breathing and/or swallowing, or develop changes in their voice (MedlinePlus, Link 1). The thyroid gland is comprised of two main types of epithelial cells: follicular cells, and parafollicular or C-cells. Most thyroid cancers are of follicular origin, which includes papillary thyroid cancers (PTC), the most common thyroid malignancy representing about 8 out of 10 thyroid cancer cases, follicular thyroid cancers (FTC) (1 out of 10), and anaplastic thyroid cancers (ATC) (~2% of all thyroid cases), whereas, the medullary

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thyroid cancers (MTC) derive from the C-cells (~4% of all thyroid cases) (NIH, Link 2).

The remaining cases (~4%) consist mainly of thyroid sarcomas, lymphomas, or other rare tumors not classified below. Due to the type of differentiation and torpid tumor growth, PTC and FTC are considered to be differentiated thyroid cancers (DTC) [7]. Being in the well-differentiated category, papillary thyroid cancers tend to grow and metastasize slowly (NIH, Link 2). Follicular thyroid carcinoma, the other type of DTC, tends to be more aggressive than PTC, and can be associated with an iodine deficiency [12]. Anaplastic thyroid cancers are the most dangerous. They metastasize early on and quickly to surrounding lymph nodes and other sites and have the highest mortality among all thyroid malignancies. Anaplastic and medullary thyroid cancers are considered poorly differentiated cancers [3]. Lastly, medullary thyroid cancer, originating in the C-cells of the thyroid gland, are associated with excess calcitonin production and can be associated with other familial endocrine disorders [12] (NIH, Link 2).

TABLE 1: American Cancer Society information & statistics on thyroid cancer.

Type of Thyroid Cancer	Signs & Symptoms	Description	Occurrence
Papillary (PTC)	Slow growing, can spread to LN. (DTC)	Most common, considered differentiated	8 out of 10 of all thyroid cancers
Follicular (FTC)	Rarely spread to LN but do spread to other body parts. (DTC)	Second most common. More common in countries with iodine deficiency	1 out of 10 of all thyroid cancers
Medullary (MTC)	Can spread to LN, lungs, or liver. Alters blood-calcium levels	Develop in the C cells of thyroid gland. Can be familial. Linked to increased risk of having other tumors.	4% of all thyroid cancer cases
Anaplastic (ATC)	Cancer cells do not resemble normal thyroid cells (UTC)	Most rare, very aggressive and difficult to treat, can metastasize quickly to other parts of the body.	2% of all thyroid cancers
Less Common Thyroid Cancers	Vary.	These include rare tumors, sarcomas, and lymphomas.	4% of thyroid cancer cases.

Source: American Cancer Society: What is Thyroid Cancer? (Link)

3. Diagnostic Check-Up

Upon discovery of a thyroid nodule, a diagnostic work up is performed to determine if it is malignant or benign. Initially, a clinician will begin by obtaining a history, including relevant risk factors and family history and then conduct a physical examination. A blood test is then performed to determine the levels of thyroid-stimulating hormone (TSH), which evaluates thyroid function and helps to differentiate between functioning and non-functioning nodules [12]. Nodules are then evaluated with ultrasound imaging to assess the size and characteristics of the nodule and suspicious nodules can then be sampled with a needle that removes cells (fine needle aspiration or FNA) for evaluation by a cytopathologist. The FNA biopsy is usually done in an office setting by an endocrinologist, radiologist, or a surgeon, and slides are prepared for microscopic evaluation by a pathologist. Other imaging modalities that can assess thyroid nodules are computerized tomography (CT) scans, magnetic resonance imaging (MRI) scans, or thyroid nuclear medicine scans. However, ultrasound has the advantage of not using radiation and being inexpensive and portable. Recently, the use of artificial intelligence (AI) has aided in reducing subjectivity in the medical interpretation of thyroid nodules [13-15]. Through the use of AI, clinicians are able to detect malignancy with improved accuracy relative to the traditional diagnostic techniques previously mentioned, thereby avoiding more invasive testing such as FNA [13]. Performance of AI is tested against experienced radiologists; the AI system provided sufficient assistance in differentiating between benign and malignant thyroid nodules with comparable sensitivity and accuracy [14, 16].

4. Thyroid Cancer and Staging

Upon confirmation of a thyroid cancer diagnosis, the clinician will discuss with the patient the type and stage of the tumor, and what the treatment options are (Table 2).

5. Treatment Options

Treatment options for thyroid cancer vary depending on the type of cancer (histology), disease stage and patient characteristics, as seen in (Table 2). At present, traditional therapies include the use of surgery (thyroidectomy), radioactive iodine, targeted therapies such as tyrosine kinase inhibitors or chemotherapeutic drugs, and external beam radiation. Recent surgical advances include the use of robotic and endoscopic approaches for thyroid removal [16, 17]. These approaches may be an option for selected patients interested in avoiding a neck incision. However, this approach is much more costly, time-consuming, and has only been studied in papillary thyroid carcinomas with minimally invasive surgery needed [16]. RAI is typically used after thyroid gland removal in order to ablate any remaining thyroid tissue in the neck or elsewhere. However, this no longer becomes an option for patients whose tumors become radioiodine refractory because if the tumor cells no longer take up iodine, they cannot be killed with RAI.

These patients have an increased risk of cancer recurrence and are more likely to die of their disease. For patients with recurrent or persistent thyroid cancer (e.g., PTC or FTC), the options are usually surgical resection and/or RAI ablation. When that is not possible of feasible, then EBRT can be considered [15]. As stated previously, surgery and radioactive iodine therapy are the primary treatment option for patients with metastatic thyroid cancer [3]. When this is not an option, other treatment methods are needed. Although EBRT can be used for some of these patients, this can be associated with debilitating side-effects and also the risk of developing other radiation-induced cancers in the future.

TABLE 2: NCI treatment recommendations for thyroid cancer.

Type of Thyroid Cancer	Disease Status	Treatment Options
Papillary & Follicular	Localized/regional	Surgery (total thyroidectomy or lobectomy) or active surveillance
Papillary and follicular	Metastatic	**Surgery** followed by**:** **Iodine-Sensitive:** RAI or Thyroid-suppression therapy **Iodine-resistant:** Thyroid-suppression, targeted therapy **EBRT**
Recurrent papillary and follicular	-	Surgery (with or without Post-Op RAI), targeted therapy, EBRT, or Chemotherapy
Medullary	Localized disease	Total thyroidectomy +/- lymphadenectomy, EBRT
Medullary	Metastatic	Targeted therapy, Palliative Chemotherapy
Anaplastic	-	Surgery, EBRT, Systemic Therapy

Source: National Cancer Institute. Thyroid cancer treatment (PDQ) (Link).

In the progression of thyroid cancer, many genetic modifications can be observed, especially those involving tyrosine kinase signalling pathways. Genes like RAF/BRAF, RET, or RAS activate the tyrosine kinase domain and are interconnected with vascular endothelial growth factor (VEGF) and its receptor [6-8]. Gain-of-function mutations can occur and lead to increased expression of growth factors like VEGF, which makes this a great target to control disease progression [8, 18, 19], (Target Oncology, Link 3). However, much more research is needed to elucidate down-stream effects of these targeted molecular therapies.

TABLE 3: FDA-approved drugs for treatment of thyroid cancer.

Drug Name	Pertains to	Function
Sorafenib (Nexavar)	PTC, FTC	Blocks angiogenesis.
Lenvatinib (Lenvima)	PTC, FTC	Blocks angiogenesis.
Vandetanib (Caprelsa)	MTC	Blocks angiogenesis.
Cabozantinib (Cometriq)	MTC	Inhibits c-Met, VEGFR2, AXL, and RET
Dabrafenib (Tafinlar)	ATC	BRAF inhibitor
Trametinib (Mekinist)	ATC	Inhibits MEK1 and MEK2
Larotrectinib (Vitrakvi)	Advanced Thyroid Cancers	Target NTRK gene

TABLE 4: Recent clinical trials for treatment of thyroid cancer.

Name of Clinical Trial	Phase	Institute	Drug Name	Goal
Iodine I-131 with or without Selumetinib in Treating Patients with Recurrent or Metastatic Thyroid Cancer	Randomized, phase II	Academic and Community Cancer Research United	Selumetinib	Assess if Selumetinib helps make radioactive iodine therapy more effective.
A Phase I/II Trial of Crolibulin (EPC2407) Plus Cisplatin in Adults With Solid Tumors With a Focus on Anaplastic Thyroid Cancer (ATC)	Phase I/II	National Institutes of Health Clinical Center (CC)	Crolibulin (EPC2407)	Assess safety and tolerability of combination therapy of Crolibulin with cisplatin on treatment of anaplastic thyroid cancer.
Pembrolizumab, Chemotherapy, and Radiation Therapy With or Without Surgery in Treating Patients With Anaplastic Thyroid Cancer	Phase II	Mayo Clinic	Pembrolizumab	To test if combination of monoclonal antibody with radiation and surgery aids in treatment of ATC.
Sunitinib Malate in Treating Patients With Thyroid Cancer That Did Not Respond to Iodine I 131 and Cannot Be Removed by Surgery	Phase II	National Cancer Institute (NCI)	Sunitinib malate	Assess effectiveness of Sunitinib malate on the treatment of thyroid cancers resistant to RAI and not removable by surgery.
Inolitazone Dihydrochloride and Paclitaxel in Treating Patients With Advanced Anaplastic Thyroid Cancer	Phase II	Alliance for Clinical Trials in Oncology	dihydrochloride (efatutazone dihydrochloride) and paclitaxel	To test success of this drug combination in treating metastatic ATC.

We also know that BRAF mutations occur in 45-70% of papillary thyroid carcinomas, and in 2018, the FDA approved a new combination therapy with BRAF inhibitors (Target Oncology, Link 4). These drugs are dabrafenib (Tafinlar) and the MEK inhibitor trametinib (Mekinist) for patients with papillary or anaplastic thyroid cancers with mutations in the BRAF gene. Table 3 lists recently released drugs used to treat thyroid cancer [19] (Target Oncology, Link 3; Target Oncology, Link 4; American Cancer Society, Link 5). Even with these new targeted therapies, more research is needed to test novel agents for the treatment of more aggressive thyroid cancers. Table 4 lists clinical trials aimed at patients with advanced-staged cancer.

6. Conclusion

The incidence of thyroid cancer is on the rise with over fifty-two thousand new cancer diagnoses in the US each year [7]. The treatment of thyroid cancer depends on the histology (the type of cancer) and disease stage. Technological advances such as the use of artificial intelligence now have the possibility to aid clinicians in diagnosing malignancy and whether surgery needs to be considered. Surgery and radioactive iodine therapy remain the staple in treating thyroid cancer and have increased survival while decreasing recurrence in patients. For patients with refractory thyroid cancers, research shows great promise in alternative therapies and in therapies that target the uptake of iodine into the thyroid gland. Targeted therapies, like tyrosine kinase inhibitors, and other chemotherapeutic agents, have been approved and are in the process of being approved for treating patients with advanced thyroid cancers. Although much is still unknown regarding the exact cause of thyroid cancer, researchers hope to find better treatments for patients battling thyroid cancers and in particular, the very aggressive anaplastic thyroid cancers. Finally, understanding the biology of thyroid cancer cells has helped to keep mortality rates for these cancers relatively low.

Data Availability

Online information for (Table 3) can be found via the following links:
Target Oncology Advancing the Treatment of Thyroid Cancer With Targeted Therapies 2019: Link 3; Target Oncology Expert Explores Advancements in Aggressive Thyroid Cancers 2019: Link 4; American Cancer Society Targeted Therapy for Thyroid Cancer 2019: Link 5.

Information for (Table 4) regarding current drugs undergoing clinical trials can be found via the following NIH links:
NIH, National Cancer Institute, Iodine I-131 with or without Selumetinib in Treating Patients with Recurrent or Metastatic Thyroid Cancer: Link 6; NIH, U.S. National Library of Medicine Clinical Trials, A Phase I/II Trial of Crolibulin (EPC2407) Plus Cisplatin in Adults With Solid Tumors With a Focus on Anaplastic Thyroid Cancer (ATC): Link 7; NIH, U.S. National Library of Medicine Clinical Trials, Pembrolizumab, Chemotherapy, and Radiation Therapy With or Without Surgery in Treating Patients With Anaplastic Thyroid Cancer: Link 8; NIH, U.S. National Library of Medicine Clinical Trials, Sunitinib Malate in Treating Patients With Thyroid Cancer That Did Not Respond to Iodine I 131 and Cannot Be Removed by Surgery: Link 9; NIH, U.S. National Library of Medicine Clinical Trials, Inolitazone Dihydrochloride and Paclitaxel in Treating Patients With Advanced Anaplastic Thyroid Cancer: Link 10.

Conflicts of Interest

None.

Abbreviations

AI: Artificial Intelligence
ATC: Anaplastic Thyroid Cancer
DTC: Differentiated Thyroid Cancer
EBRT: External Beam Radiation Therapy
FNA: Fine-Need Aspiration (Biopsy)
FTC: Follicular Thyroid Cancer
LN: Lymph Node
MTC: Medullary Thyroid Cancer
PTC: Papillary Thyroid Cancer
RAI: Radioactive Iodine, ^{131}I
TKI: Tyrosine Kinase Inhibitor
TSH: Thyroid-Stimulating Hormone
UTC: Undifferentiated Thyroid Cancer
VEGF: Vascular Endothelial Growth Factor

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