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Anaplastic Thyroid Cancer

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Continuing Education Activity

Anaplastic **thyroid** carcinoma is a rare, highly aggressive, undifferentiated **thyroid** tumor, accounting for 2% to 3% of all **thyroid** cancers. This malignancy is known for rapid local invasion and early distant metastasis, making anaplastic **thyroid** carcinoma one of the most fatal malignancies. Anaplastic **thyroid** carcinoma often presents as a rapidly enlarging neck mass with compressive symptoms, such as dysphagia and dyspnea. The diagnosis of this malignancy typically involves fine-needle aspiration or core needle biopsy. The management approach of anaplastic **thyroid** carcinomas, which are all classified as stage IV, includes surgery, radiation, chemotherapy, and targeted therapies—though most cases are unresectable at diagnosis. Recent advances in molecular testing offer potential for future targeted treatments.

This course provides participants with the tools to promptly recognize and diagnose anaplastic **thyroid** carcinoma, focusing on early identification and advanced diagnostic techniques, such as molecular testing. The course also explores current and emerging treatment strategies, including using targeted therapies to improve patient outcomes. By fostering collaboration among an interprofessional team—including endocrinologists, oncologists, pathologists, and surgeons—this approach ensures comprehensive care for patients. Coordinated team efforts enhance timely diagnosis and optimize treatment planning for this aggressive cancer.

Objectives:

- Identify the clinical signs and symptoms of anaplastic **thyroid** carcinoma, including rapidly enlarging neck masses and compressive symptoms.
- Assess patients with anaplastic **thyroid** cancer with recommended diagnostic studies.
- Create individualized management plans for anaplastic **thyroid** cancer based on patient-specific factors and tumor characteristics.
- Apply interprofessional team strategies to improve care coordination and outcomes for patients with anaplastic **thyroid** cancer.

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Introduction

Anaplastic **thyroid** carcinoma is a rare, aggressive malignant tumor accounting for 2% to 3% of all **thyroid gland** neoplasms. In contrast to differentiated **thyroid** malignancies such as papillary and follicular **thyroid** cancers, anaplastic **thyroid** cancer is undifferentiated. Furthermore, anaplastic **thyroid** cancer is highly locally invasive, with a propensity for early lymph node positivity and distant metastatic disease.

Anaplastic **thyroid** cancer typically presents as a rapidly growing anterior neck mass and may have compressive symptoms early in the disease. The diagnosis is typically made by fine needle aspiration cytology, although a core needle biopsy is more sensitive and specific. All patients with anaplastic **thyroid** cancer should be assessed for

systemic disease. While patients with locoregional disease can occasionally be cured, the disease is uniformly fatal with distant spread.[1][2] Treatment can include surgery, radiation, chemotherapy, and, more recently, targeted therapy. Recent advances in molecular diagnostics have identified several mutations that could be targeted in the future.[3]

Etiology

The etiology of anaplastic **thyroid** cancer is unknown. Apart from its association with differentiated **thyroid** cancers in about 20% of cases, anaplastic **thyroid** cancer has no clear causative factors. Evidence supports the theory that some anaplastic cancers may arise from preexisting differentiated **thyroid** cancers by dedifferentiation.[4][5]

Epidemiology

Anaplastic **thyroid** cancer is a rare form of **thyroid** cancer, accounting for between 1% and 10% of all **thyroid** cancers globally and 1.7% of cases in the United States.[6] Given the rarity and high mortality rate of this cancer, the precise incidence remains uncertain. Despite its infrequency, anaplastic **thyroid** cancer is responsible for up to 50% of all deaths related to **thyroid** cancers. Anaplastic **thyroid** cancer typically occurs in older individuals with a mean age of 65 and, like other **thyroid** cancers, is more prevalent in women than in men.[6][7]

Pathophysiology

Anaplastic **thyroid** cancer is associated with differentiated **thyroid** cancers, with roughly 20% of patients having a history of differentiated **thyroid** cancer.[8] In addition, up to a third of patients have coexisting differentiated **thyroid** cancer, usually papillary **thyroid** cancer, when they are diagnosed. The molecular pathogenesis is similar to well-differentiated **thyroid** cancers, and our understanding of these molecular drivers continues to improve with ongoing research.

Mutations in the *TERT* promoter region and *TP53* are common, with *TERT* promoter mutations associated with *RAS* and *BRAF* mutations. Other targetable mutations may be seen, including *NTRK* and *ALK* rearrangements.[9] **Thyroid**-specific rearrangements *RET/PTC* and *PAX8/PPARγ* are rarely found in poorly differentiated or undifferentiated **thyroid** cancer, suggesting that these genetic alterations do not predispose cells to dedifferentiation.[10]

Histopathology

Macroscopic Histology Examination

Histopathologic findings associated with anaplastic **thyroid** cancer lesions include:

- Bulky mass (mean: 6 cm)
- Homogeneous and variegated appearance
- Light tan and fleshy with zones of necrosis and hemorrhage on cut sections
- Infiltrating, often into adjacent soft tissues and organs [11]

Microscopic Histology Examination

The highly variable microscopic appearances of anaplastic **thyroid** cancer are broadly categorized into the following 3 patterns (see **Image**. Anaplastic **Thyroid** Cancer), which can occur alone or in any combination:

- **Sarcomatoid**: The sarcomatoid form is malignant spindle cells with features commonly seen in high-grade pleomorphic sarcoma.
- **Giant cell**: The giant cell comprises highly pleomorphic malignant cells, some containing multiple nuclei.
- **Epithelial**: The epithelial form manifests squamoid or squamous cohesive tumor nests with abundant eosinophilic cytoplasm; occasional keratinization can be present.

Necrosis, an elevated mitotic rate, and an infiltrative growth pattern are common in all 3 forms. Vascular invasion is also often present.

Immunohistochemistry

Immunohistochemistry helps to distinguish anaplastic carcinoma from other undifferentiated malignancies using a cluster of differentiation 45 and other lymphoid markers along with melanocytic markers to exclude lymphoma and melanoma, respectively. Common **thyroid**-lineage markers (eg, **thyroid** transcription factor-1 and thyroglobulin) are usually absent, whereas the paired box gene, also a **thyroid**-lineage marker, is retained in approximately half of all cases. Positive cytokeratin expression supports the epithelial nature of anaplastic **thyroid** cancer, but negative immunostaining for cytokeratin does not exclude the diagnosis.[12]

History and Physical

Anaplastic **thyroid** cancer almost invariably presents with a rapidly growing anterior neck mass, which may be causing compressive or invasive symptoms. The trachea, esophagus, and vocal cords may be involved, resulting in dysphagia, dyspnea, hoarseness, and recurrent aspiration. Additionally, 20% of patients have a history of differentiated **thyroid** cancer or chronic multinodular goiter.

A physical examination typically identifies a firm mass fixed to the trachea. Unlike other less invasive **thyroid** cancers, anaplastic **thyroid** cancer often invades surrounding structures, resulting in an immobile mass with swallowing on examination. While the mass is typically solid, larger lesions may have regions of fluctuance due to tumor necrosis or hemorrhage. Cervical lymph nodes should be examined as these nodes are involved in up to 40% of anaplastic **thyroid** cancer cases. A laryngoscopy is also important to identify and document recurrent laryngeal nerve injury.[13][14][15]

Evaluation

Diagnostic Imaging Studies

Anaplastic **thyroid** cancer evaluation should begin with a neck ultrasound. Findings associated with malignancy include solid masses, marked hypodensity, irregular margins, internal calcifications, wider-than-tall nodules, and cervical lymph node involvement. These features are scored using the **thyroid** imaging reporting and data system, predicting the probability of a malignant **thyroid** lesion. However, no specific findings on sonography have been established that can reliably differentiate anaplastic **thyroid** cancer from other **thyroid** malignancies.[16]

Since all anaplastic **thyroid** cancers are considered stage IV tumors and up to 50% will have metastatic disease at the time of presentation, all patients should be staged with a fluorodeoxyglucose F18 positron emission tomography (PET) scan or computed tomography (CT) scan of the brain, neck, chest, abdomen, and pelvis. See **Image.** Hypermetabolic **Thyroid** Mass, Positron Emission Tomography-Computed Tomography Scan (PET-CT). The lungs are the most common site of metastasis, followed by the intrathoracic and cervical lymph nodes.[17] Local invasion and the tumor's relationship to surrounding structures may be better defined with magnetic resonance imaging (MRI).[18][19][20]

Biopsy Confirmation

To histologically identify a **thyroid** lesion, fine-needle aspiration or core needle **thyroid** biopsies should be performed without delay. Findings suggestive of anaplastic **thyroid** cancer include increased cellularity with cells and clusters with epithelioid to spindle cells, severe pleomorphism with very aberrant nuclei, high mitotic rate, and significant necrosis. Lymphocytic infiltration and acute inflammation may also be seen. In addition, perineural and vascular invasion, as well as extrathyroidal extension, frequently occur. Given the degree of abnormality, distinguishing anaplastic **thyroid** cancer from other high-grade tumors, including lymphomas and melanoma, may be difficult.[21]

Diagnostic Molecular Testing

BRAF status, microsatellite instability, *NTRK, RET, ALK* mutations, and tumor mutational burden should be assessed. In particular, *BRAF* mutations should be evaluated, as these mutations can change the determined treatment approaches.[22]

Laryngoscopy and Bronchoscopy

Laryngoscopy with an evaluation of the vocal cords should be performed in all patients, as recurrent laryngeal nerve invasion is prevalent at presentation. If a high suspicion of airway involvement exists, a bronchoscopy should be performed. Patients with airway involvement often require a tracheostomy for airway protection.[23]

Treatment / Management

Surgical resection is the treatment of choice for localized anaplastic **thyroid** cancer. Chemotherapy and radiation are used as adjuncts or as definitive therapy in patients with metastatic disease.[3] Most cases of anaplastic **thyroid** cancer are unresectable at presentation.

Differential Diagnosis

The differential diagnosis for anaplastic **thyroid** cancer includes:

- Metastatic disease to the **thyroid**, including metastatic clear-cell renal carcinoma
- Primary **thyroid** lymphoma
- Primary **thyroid** sarcoma
- Poorly differentiated **thyroid** carcinoma
- Squamous cell **thyroid** carcinoma
- Medullary carcinoma [24]

Surgical Oncology

When anaplastic **thyroid** cancer is localized to the **thyroid gland**, without invasion of critical structures (eg, the trachea), complete surgical resection offers the best chance of cure. A total thyroidectomy with a therapeutic lymph node dissection is currently recommended. Adjacent structures may need to be resected en bloc if they are involved and can be sacrificed, as the ultimate goal is to obtain a negative margin. *BRAF/V600E* mutant anaplastic **thyroid** cancer can be treated with neoadjuvant dabrafenib/trametenib, especially if the tumor is borderline resectable.[11] [25] Routine tracheostomy should be avoided and performed only in cases of true airway compromise.[23]

Radiation Oncology

Radiation therapy can be used in adjuvant settings and in patients with nonresectable or metastatic diseases. External beam radiation therapy (EBRT) is recommended after resection and, when combined with concurrent chemotherapy, improves overall survival. As anaplastic **thyroid** cancer is so aggressive and is seldom resected with negative margins, radiation with concurrent EBRT should be started as soon as possible. Using newer techniques, eg, intensity-modulated radiation therapy, improves targeting.[23] In patients with locally advanced disease, higher doses of EBRT can delay local spread and some of its devastating consequences, including airway compromise.

Medical Oncology

Cytotoxic chemotherapy alone is of limited benefit. Taxanes, doxorubicin, and cisplatin have been used with variable success. Paclitaxel, doxorubicin, and carboplatin are often used as radiosensitizing agents in administering concurrent chemoradiation. Identifying molecular targets has heralded a new therapy era, with treatments targeting specific mutations.[23] These include the following molecular targets and the respective agents:

- ***BRAF/V600E* mutations**: Dabrafenib/trametenib
- ***NTRK* gene fusions**: Larotrectinib, entrectinib, repotrectinib
- ***RET* gene fusions**: Pralsetinib, selpercatinib

Anaplastic **thyroid** cancer with high tumor mutational burden may respond to programmed cell death protein 1/programmed cell death ligand 1 inhibitors, including pembrolizumab and nivolumab. Neoadjuvant

dabrafenib/trametinib is now a category 2B National Comprehensive Cancer Network recommendation for patients with resectable and borderline resectable tumors.[26]

Staging

Thyroid carcinoma staging is according to the 8th edition of the American Joint Committee on Cancer (AJCC) classification. According to the International Union Against Cancer—TNM staging (primary tumor, regional lymph node involvement, and distant metastases) and AJCC system, all anaplastic **thyroid** cancers are considered stage IV.[3] Stage IVA and IVB patients have intrathyroidal tumors (stage IVA) and extrathyroidal tumors (stage IVB) and no distant metastatic disease, whereas stage IVC patients have distant metastasis.[23]

Prognosis

Anaplastic **thyroid** cancer is lethal. Historic survival estimates from Surveillance, Epidemiology, and End Results database studies report that 35% of patients have a median overall survival between 4 and 6 months.[2] More recent data incorporating patients who have received multimodality therapy, including targeted therapy, is more promising, with a median overall survival of 9.5 months. However, patients with *BRAF* mutant disease who received targeted therapy had a 94% survival rate at 1 year.[2] These data suggest that refinements in targeted therapy will continue to prolong survival.

Prognostic Factors

The favorable prognostic indicators of anaplastic **thyroid** cancer include:

- Younger age (aged 60 or younger)
- An absence of cervical or distant metastases
- Small tumors (≤5 to 7 cm)
- Unilateral tumors
- An absence of local invasion of the surrounding tissue or nodal involvement
- An incidental finding of anaplastic **thyroid** cancer within a thyroidectomy specimen [27][28][29][30]

Complications

Local invasion occurs in almost 70% of patients, including the muscles (65%), trachea (46%), esophagus (44%), laryngeal nerves (27%), and larynx (13%). Additionally, lymph node metastases are a feature in almost 40% of patients.[31] The progression of anaplastic **thyroid** cancer is rapid, and most patients die from local airway obstruction or complications of pulmonary metastases within 1 year.[11] Metastases occur in up to 75% of patients. They most frequently involve the lungs (80%), the brain (5% to13%), and bones (6% to 15%).

Deterrence and Patient Education

Anaplastic **thyroid** cancer is an aggressive and rapidly progressive type of **thyroid gland** cancer. Patients should be aware of warning signs, eg, rapid growth of a mass in the front of the neck, hoarseness, or neck pain. If these symptoms occur, immediate medical evaluation is necessary. Individuals with long-standing goiters or a history of other types of **thyroid** cancer should be especially vigilant for these symptoms. Surgery is the only curative treatment once diagnosed. Unfortunately, most patients have locally advanced or distant metastatic disease at the time of diagnosis, which cannot be cured.

Enhancing Healthcare Team Outcomes

Collaboration among healthcare professionals is essential to improve patient-centered care, safety, and outcomes in managing anaplastic **thyroid** cancer. Advanced clinicians bring clinical expertise to diagnose and formulate personalized treatment plans, while nurses provide direct patient care and emotional support and ensure adherence to therapies. Pharmacists play a key role in medication management, while other specialists contribute to a comprehensive approach involving surgery, radiation, and palliative care.

Effective interprofessional communication fosters teamwork, informing all clinicians of patient progress and treatment updates, which helps prevent delays. Given the disease's aggressive nature, care coordination is crucial, and ethical considerations, such as end-of-life care, ensure that treatment respects patient values. The healthcare team enhances patient safety, outcomes, and overall performance through shared decision-making and responsibility.

Review Questions

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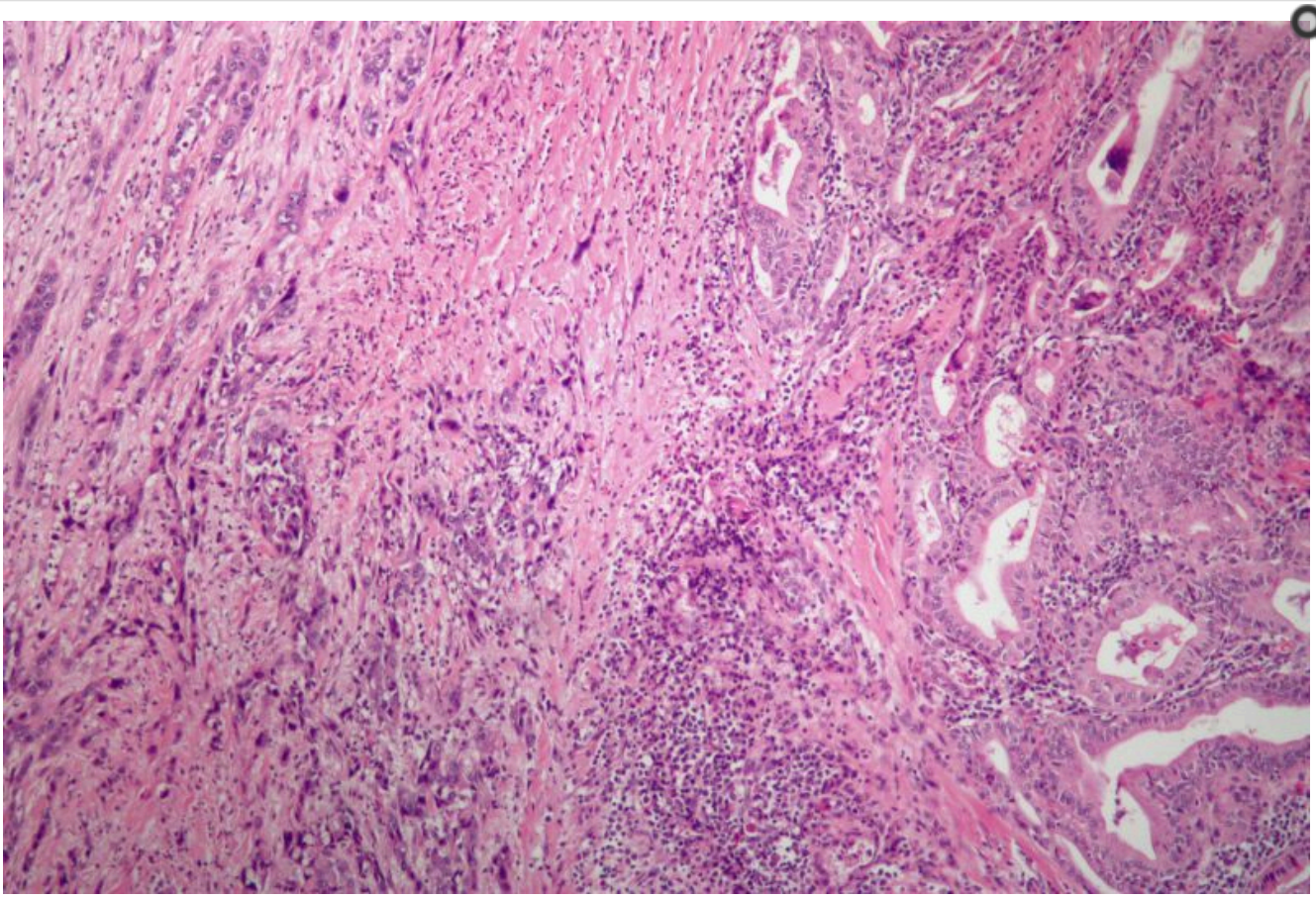
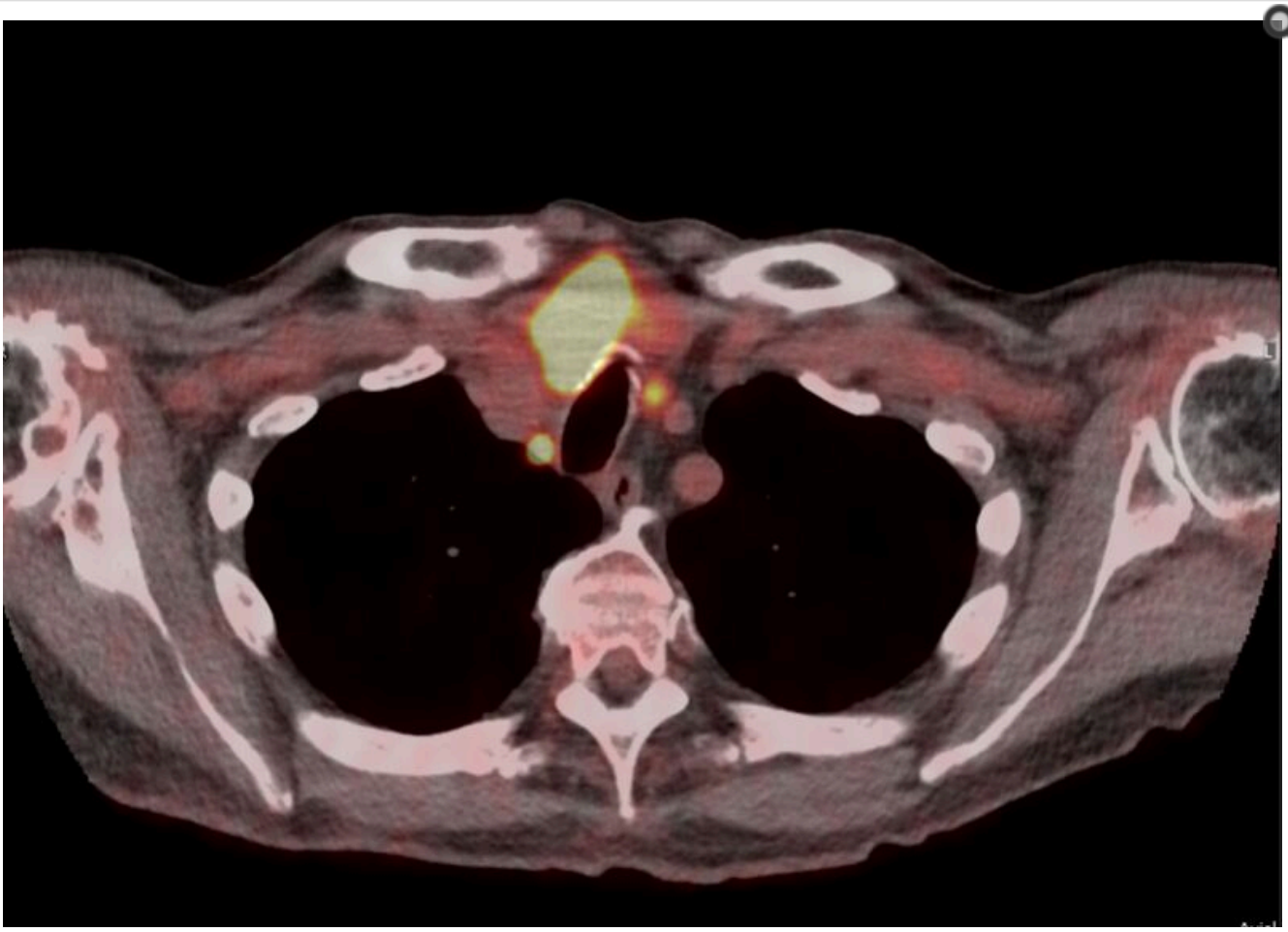
Figures



Anaplastic **Thyroid** Cancer. Low-power magnification microscopic examination of anaplastic **thyroid** cancer. Nephron, Public Domain, via Wikimedia Commons



Hypermetabolic **Thyroid** Mass, Positron Emission Tomography-Computed Tomography Scan (PET-CT). This image shows a hypermetabolic **thyroid** mass with tracheal deviation and multiple fludeoxyglucose avid lymph nodes on PET-CT scan. Contributed by G Menon, MD

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