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Overview

Rare Thyroid Malignancies: an Overview for the Oncologist

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Abstract

Anaplastic thyroid cancer, medullary thyroid cancer, primary thyroid lymphoma and primary thyroid sarcoma are rare thyroid cancers that comprise 5–10% of all thyroid malignancies. Unlike well-differentiated thyroid cancers, these malignancies have few treatment options and carry a worse prognosis. The literature surrounding these pathologies is limited, but remains an area of active research. Despite the rarity of these conditions, they remain an important part of the differential diagnosis for any thyroid nodule. Awareness of their presentation, work-up and management is critical for oncologists and head and neck surgeons. The purpose of this article is to provide a broad overview of these malignancies with an emphasis on emerging clinical research and therapies.

Key words: Anaplastic thyroid carcinoma; medullary thyroid cancer; primary thyroid lymphoma; primary thyroid sarcoma; thyroid cancer

Statement of Search Strategies Used and Sources of Information

PubMed, Cochrane Library and ClinicalTrials.gov were queried for 'anaplastic thyroid cancer', 'medullary thyroid cancer', 'thyroid lymphoma', 'thyroid sarcoma', 'undifferentiated thyroid cancer', 'poorly differentiated thyroid cancer' and 'head and neck sarcoma'. All relevant articles were reviewed and incorporated as appropriate.

Introduction

The National Cancer Institute estimates that about 64 300 new thyroid cancer diagnoses were made in 2016 in the USA. Most patients with thyroid malignancies have well-differentiated lesions [1–3]. These malignancies have been extensively studied and have consensus guidelines for diagnosis and management. The minority of patients outside of this category, comprising about 5–10% of all patients with thyroid cancer [4], carry a diagnosis of a rare thyroid cancer with an uncommon aetiopathogenesis. As a result of the low incidence of these malignancies, there is a paucity of literature and often a lack of evidence-based physician congruency regarding management. This review coalesces the literature to provide interdisciplinary teams with an overview of these pathologies. We highlight the newest evidence regarding disease presentation and management for the following four malignancies: anaplastic thyroid cancer (ATC), medullary thyroid cancer (MTC), primary thyroid lymphoma (PTL) and primary thyroid sarcoma (PTS).

Anaplastic Thyroid Cancer

ATC has an annual incidence of one to two cases per million people [5] and comprises 0.9% of all thyroid cancers [3]. Although this only amounts to what the National Cancer Institute estimates to be 600 new cases in 2016, it is among the most aggressive malignancies, contributing to 14–50% of intra-yearly thyroid deaths [3,5]. ATC can arise *de novo* or from a well-differentiated cancer, which is estimated to co-exist in half of patients with this malignancy [6,7]. The

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average age at diagnosis is 71 years [8], with a 3:2 female:male ratio [9]. Patients with ATC most commonly present with an enlarging neck mass and associated pain, dysphonia or dyspnoea that is progressive in nature [1].

Pure ATC carries an incredibly poor prognosis, with a median survival time of 6 months [10]. Patients with small foci of ATC within a larger well-differentiated tumour carry substantially higher 5 year survival rates, reported as high as 81% versus 14% for those with pure ATC [11,12]. Half of patients with ATC have distant metastases at presentation and less than 10% present solely with intrathyroidal disease [8,9,13]. The natural history of ATC often results in death secondary to asphyxiation or vessel compression [1]. With airway management via tracheostomy, death more commonly results from respiratory insufficiency caused by pulmonary metastases[14].

When evaluating any type of enlarging neck mass, airway stability is critical and should be determined before any further work-up. Computed tomography and rarely magnetic resonance imaging (MRI) are indicated to characterise the mass. Fine-needle aspiration (FNA) is carried out in attempt to ascertain a tissue diagnosis. In our combined experience, larger samples from core or surgical biopsy are often needed to rule out lymphoma [1]. Nevertheless, FNA can be sufficient for diagnosis with the help of an expert cytopathologist and should always be attempted before proceeding to more invasive measures. Patients must be monitored after biopsy due to the risk of tumour bleeding that may cause mass expansion and exacerbate airway compression.

Microscopic tissue examination shows undifferentiated spindle, giant or squamoid cells with areas of necrosis [10]. After diagnosis, staging is determined by measuring tumour burden with 18F-FDG positron emission tomography/computed tomography (PET/CT) scan before a treatment plan may be devised [15]. Lesions confined to the thyroid gland are classified as stage IVA. Stage IVB characterises lesions that have grown outside of the thyroid capsule without distal spread; stage IVC is reserved for any lesion with associated distant metastases [16].

The American Thyroid Association (ATA) guidelines on the management of ATC serve as a thorough resource for clinicians [17]. This review provides an overview of those principles and discusses recent publications and advances in disease management. Before any treatment decisions are made, a fundamental understanding of the patient's goals of care must be obtained. Patients should be encouraged to draft advance directives with their families early in the disease process.

Treatment options include a combination of radiation, surgery or chemotherapy. The hallmark of treatment for stage IVa and resectable cases of stage IVb disease is surgical excision of gross disease and lymph node dissection with subsequent intensity-modulated radiation therapy. Adjuvant systemic chemotherapy should be considered on a case-by-case basis. However, no consensus exists on its use for locoregional disease [17]. For patients with unresectable local disease, radiation with or without systemic chemotherapy is recommended and surgery should only be considered if the lesion later becomes resectable.

Metastatic disease is treated with combination chemoradiation therapy. In accordance with the ATA guidelines, any patient with a poor performance status or unresectable disease should be offered the option of supportive palliative care in lieu of aggressive treatment. Patients with higher stage disease commonly require tracheostomy and nutritional support with a gastrostomy tube [1,6]. However, routine tracheostomy is not advocated without a frank discussion regarding changes to quality of life [8,18]. No standard chemotherapeutic regimen exists, although the ATA recommends several combinations of paclitaxel, docetaxel, carboplatin and doxorubicin [17]. In recent studies, there have been more promising results with new drug modalities. The combination of carfilzomab, a proteasome inhibitor, and CUDC-101, a histone deacetylase, has been shown to induce apoptosis in ATC cells [19]. Another recent study has shown positive results through the use of doxorubicin nanospheres combined with extracorporeal shock wave therapy [20].

Although the ATA guidelines advise against tumour debulking for unresectable disease, the role of surgery in patients with tumour extension beyond the thyroid gland has become controversial [15]. Disease extending significantly beyond the thyroid gland has typically represented unresectable malignancy, but the determinants of this classification are not entirely clear [21–26]. The positive predictive value and accuracy for computed tomography scans correctly staging disease when compared with post-surgical pathology reports has not been thoroughly studied and requires an experienced surgeon to decipher tumour scans and their operative correlates [27–29]. A recent study by Brown and Ducic [30] seemingly supports this notion, showing longer-term survival in a cohort of select patients with stage IVB disease after undergoing variable resections involving the larynx, trachea and oesophagus, as dictated by the extent of disease. In these patients, without disease extension beyond the carotid arteries, who underwent surgery and adjuvant radiation, 50% had long-term disease-free survival ranging from 9 months to 8 years [30]. Other recent studies support the use of aggressive multimodality treatment including surgery and curative radiation therapy [31,32]. On multivariate analysis of factors predictive of survival, Mohebati *et al.* [32] showed hazard ratios less than 0.5 for patients receiving multimodality treatment with surgery and those whose surgery resulted in complete or near complete resection with only residual microscopic disease.

Ongoing research attempts to further characterise the mutations that enable the development of ATC, including the importance of: TP53 (50–80%), CTNNB1 (5–60%) and AKT1 (5–10%), which are unique to ATC [33,34]. The lack of effectiveness of current chemotherapeutic regimens is driving the search for more targeted therapies. Within the past 5 years, multiple trials have tested the efficacy of newly developed drugs, which are summarised in Table 1. Despite minimal improvements in outcomes, none has proved to be a breakthrough treatment. The most recent of these newly tested medications, fosbretabulin, was studied in the 2014 FACT Trial (Fosbretabulin in Anaplastic Cancer of the

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