

Contents

Preface: Endocrine Pathology: Practical Suggestions, Emerging Diagnostics, and New Frontiers	xiii
Nicole A. Cipriani	
A Triumvirate: Correlating Thyroid Cytopathology, Molecular Testing, and Histopathology	1
Jaylou M. Velez Torres, Youley Tjendra, and Darcy A. Kerr	
<p>Risk stratification is essential in the preoperative evaluation and management of thyroid nodules, most of which are benign. Advances in DNA and RNA sequencing have shed light on the molecular drivers of thyroid cancer. Molecular testing of cytologically indeterminate nodules has helped refine risk stratification, triage patients for surgery, and determine the extent of surgery. Molecular platforms with high negative predictive values can help identify nodules that may be spared surgery and can be managed conservatively. Here we discuss the importance of integrating cytomorphologic, molecular, and histologic features to help avoid errors and improve patient management.</p>	
To Freeze or Not to Freeze? Recommendations for Intraoperative Examination and Gross Prosection of Thyroid Glands	15
Fouad R. Zakka and Nicole A. Cipriani	
<p>The use of intraoperative consultation for indeterminate thyroid lesions is not advocated but is still requested by some surgeons. Obscured cytomorphology and nonrepresentative sampling limit the specificity of intraoperative assessment. Formalin fixation of thyroid glands before sectioning also minimizes artifacts introduced by fresh sectioning. Inking of thyroid may vary based on institutional preferences and information desired by clinical teams. Sectioning may occur in the conventional transverse method or the modified transverse vertical method to more thoroughly evaluate the lesion's periphery. Gross examination of thyroid lesions should always consider possible high-grade features, such as necrosis or extrathyroidal extension.</p>	
Challenges in Encapsulated Follicular-Patterned Tumors: How Much Is Enough? Evaluation of Nuclear Atypia, Architecture, and Invasion	27
Kristine S. Wong and Justine A. Barletta	
<p>Thyroid pathology is notoriously fraught with high interobserver variability, and follicular-patterned tumors are among some of the most challenging to assess accurately and reproducibly. Given that encapsulated or well-circumscribed follicular-patterned tumors often have similar molecular profiles, that is, frequent RAS or RAS-like alterations, the diagnosis usually relies on histopathologic examination alone. Unfortunately, many of the features that are used for diagnosis and prognosis of these tumors have long been controversial and frequently debated topics, both due to their subjectivity and their evolving (or not yet resolved) definitions. In more recent years, the introduction of noninvasive follicular thyroid neoplasm with papillary-like nuclear features has added further complexity to this discussion. In particular, the criteria and significance of nuclear features of papillary thyroid carcinoma, architectural patterns, and invasive growth still pose significant diagnostic challenges and confusion. This review explores some of the challenges in evaluating encapsulated follicular-patterned tumors, focusing on those histologic elements.</p>	

No Longer Well-Differentiated: Diagnostic Criteria and Clinical Importance of Poorly Differentiated/High-Grade Thyroid Carcinoma 45

Vincent Cracolici

Poorly differentiated thyroid carcinoma (PDTC) and differentiated high-grade thyroid carcinoma (DHGTC) are uncommon thyroid malignancies, recently (re)codified into distinct entities with overlapping clinical significance. Recognizing them may be challenging for the general practitioner and subspecialty pathologist alike. This article will describe the required features to diagnose PDTC and DHGTC, differential diagnostic considerations, molecular findings, and clinical implications. It is intended to be a general synopsis of the most critical elements of PDTC and DHGTC as well as a summary of points in approaching these challenging cases.

This is Your Thyroid on Drugs: Targetable Mutations and Fusions in Thyroid Carcinoma 57

Ying-Hsia Chu

This review aims to provide an overview of the molecular pathogenesis thyroid carcinomas, emphasizing genetic alterations that are therapeutically actionable. The main pathways in thyroid carcinogenesis are the MAPK and PI3K pathways. Point mutations and gene rearrangements affecting the pathway effectors and receptor tyrosine kinases are well-known drivers of thyroid cancer. Research over the past few decades has successfully introduced highly effective treatments for unresectable thyroid cancer, evolving from multi-kinase inhibitors to structurally selective agents, with constantly improving toxicity profiles and coverage of resistance mechanisms. The pros and cons of major laboratory techniques for therapeutic target identification are discussed.

It Does Exist! Diagnosis and Management of Thyroid Carcinomas Originating in Struma Ovarii 75

Lynelle P. Smith, Lindsay W. Brubaker, and Rebecca J. Wolsky

Thyroid carcinoma originating in struma ovarii comprises a small minority of all cases of struma ovarii. Given the rarity of this diagnosis, literature to guide evaluation and management is limited. The most common carcinoma originating from struma ovarii is papillary thyroid carcinoma. Treatment includes surgery, including a fertility sparing approach if disease is confined to the ovary, with consideration of total thyroidectomy and radioactive iodine ablation for high-risk pathologic features or disease spread beyond the ovary. This review discusses the histopathologic findings, molecular pathology, clinical implications and management, and prognosis of thyroid carcinomas originating in struma ovarii.

Preoperative, Intraoperative, and Postoperative Parathyroid Pathology: Clinical Pathologic Collaboration for Optimal Patient Management 87

Hailey L. Gosnell and Peter M. Sadow

Parathyroid disease typically presents with parathyroid hyperfunction as result of neoplasia or a consequence of non-neoplastic systemic disease. Given the parathyroid gland is a hormonally active organ with broad physiologic implications and serologically accessible markers for monitoring, the diagnosis of parathyroid disease is predominantly a clinical pathologic correlation. We provide the current pathological correlates of parathyroid disease and discuss preoperative, intraoperative, and postoperative pathology consultative practice for optimal patient care.

Para This, Fibromin That: The Role of CDC73 in Parathyroid Tumors and Familial Tumor Syndromes

97

Emad Ababneh and Vania Nosé

CDC73 alterations are associated with three main parathyroid lesions according to the World Health Organization (WHO) classification of tumors of the endocrine system. These include hyperparathyroidism-jaw tumor (HPT-JT) syndrome-associated adenomas, atypical parathyroid tumors (APTs), and parathyroid carcinomas (PCs). The loss of nuclear parafibromin expression, which serves as a surrogate marker for the underlying CDC73 alteration, encompasses these tumors under the term parafibromin-deficient parathyroid tumors. They have distinct morphologic features of more abundant eosinophilic cytoplasm with perinuclear clearing surrounding a large nucleus as well as prominent dilated branching “hemangiopericytoma-like” vasculature and a thick capsule as well as variably sized cystic spaces. These tumors include cases that show unequivocal histologic features fulfilling the criteria for PCs with growing data indicating a higher rate of recurrence or metastasis compared with parafibromin intact PCs. More importantly, the loss of parafibromin expression can be used in clinical practice to recognize APTs that fall short of a conclusive diagnosis of PCs, but clinically behave akin to them. Moreover, recognizing these tumors can lead to an underlying germline mutation and a diagnosis of HPT-JT, which impacts long-term treatment and surveillance for patients and close family.

On the Chopping Block: Overview of DICER1 Mutations in Endocrine and Neuroendocrine Neoplasms

107

Carl Christofer Juhlin

Mutational inactivation of the *DICER1* gene causes aberrant micro-RNA maturation, which in turn may have consequences for the posttranscriptional regulation of gene expression, thereby contributing to tumor formation in various organs. Germline *DICER1* mutations cause *DICER1* syndrome, a pleiotropic condition with an increased risk of various neoplastic conditions in the pleura, ovaries, thyroid, pituitary, pineal gland, and mesenchymal tissues. Somatic *DICER1* mutations are also frequently observed in a wide variety of solid tumors, thereby highlighting the importance of this gene in tumor development. In this review, the importance of *DICER1* inactivation in endocrine tumors is discussed.

Back to Biochemistry: Evaluation for and Prognostic Significance of SDH Mutations in Paragangliomas and Pheochromocytomas

119

Sounak Gupta and Lori A. Erickson

There is increasing recognition of the high prevalence of hereditary predisposition syndromes in patients diagnosed with paraganglioma/pheochromocytoma. It is widely acknowledged that germline pathogenic alterations of the succinate dehydrogenase complex genes (SDHA, SDHB, SDHC, SDHD, SDHAF2) contribute to the pathogenesis of most of these tumors. Herein, we have provided an update on the biology and diagnosis of succinate dehydrogenase-deficient paraganglioma/pheochromocytoma, including the molecular biology of the succinate dehydrogenase complex, mechanisms and consequences of inactivation of this complex, the prevalence of pathogenic alterations, and patterns of inheritance.

All Together Now: Standardization of Nomenclature for Neuroendocrine Neoplasms across Multiple Organs

131

Pari Jafari, Aliya N. Husain, and Namrata Setia

Neuroendocrine neoplasms (NENs) span virtually all organ systems and exhibit a broad spectrum of behavior, from indolent to highly aggressive. Historically,

nomenclature and grading practices have varied widely across, and even within, organ systems. However, certain core features are recapitulated across anatomic sites, including characteristic morphology and the crucial role of proliferative activity in prognostication. A recent emphasis on unifying themes has driven an increasingly standardized approach to NEN classification, as delineated in the World Health Organization's Classification of Tumours series. Here, we review recent developments in NEN classification, with a focus on NENs of the pancreas and lungs.

Light It Up! The Use of DOTATATE in Diagnosis and Treatment of Neuroendocrine Neoplasms

151

Jason L. Schwarz, Jelani K. Williams, Xavier M. Keutgen, and Chih-Yi Liao

Radiolabeled somatostatin analogs are increasingly used in the diagnosis and treatment of neuroendocrine tumors. Diagnostic imaging with ⁶⁸Ga-DOTATATE PET/CT has demonstrated the improved sensitivity in detecting primary and metastatic neuroendocrine lesions compared with conventional imaging and prior generation somatostatin receptor imaging. Peptide receptor radionuclide therapy with ¹⁷⁷Lu-DOTATATE is now frequently included in the management of neuroendocrine neoplasms, with prospective randomized control studies demonstrating its beneficial impact on survival and quality of life. Nonetheless, peptide receptor radionuclide therapy is still considered palliative rather than curative and may be accompanied by adverse effects.

Scarless Surgery: Clinical Indications for Transoral Endocrine Surgery and Implications for Pathologists

163

Jordan M. Broekhuis, Benjamin C. James, and Raymon H. Grogan

Transoral endocrine surgery (TES) is a scarless approach to thyroidectomy and parathyroidectomy for well-selected patients. Criteria for the TES approach to thyroidectomy include thyroid diameter less than or equal to 10 cm, benign nodule less than or equal to 6 cm, or confirmed or suspected malignant nodule less than or equal to 2 cm. Although fragmentation of surgical specimens has been reported in TES, additional studies are needed to evaluate the implications of TES on pathologic examination.

Applications of Deep Learning in Endocrine Neoplasms

167

Siddhi Ramesh, James M. Dolezal, and Alexander T. Pearson

Machine learning methods have been growing in prominence across all areas of medicine. In pathology, recent advances in deep learning (DL) have enabled computational analysis of histological samples, aiding in diagnosis and characterization in multiple disease areas. In cancer, and particularly endocrine cancer, DL approaches have been shown to be useful in tasks ranging from tumor grading to gene expression prediction. This review summarizes the current state of DL research in endocrine cancer histopathology with an emphasis on experimental design, significant findings, and key limitations.