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Prostate Cancer: Update on Grading and Reporting **579**

Ezra Baraban and Jonathan Epstein

The Gleason scoring system and Grade Group systems facilitate accurate grading and reporting of prostate cancer, which are essential tasks for surgical pathologists. Gleason Pattern 4 is critical to recognize because it signifies a risk for more aggressive behavior than Gleason Pattern 3 carcinoma. Prostatic adenocarcinoma with radiation or androgen therapy effect, with aberrant P63 expression, or with Paneth cell-like differentiation represent pitfalls in prostate cancer grading because although they display architecture associated with aggressive behavior in usual prostatic adenocarcinoma, they do not behave aggressively and using conventional Gleason scoring in these tumors would significantly overstate their biologic potential.

Cribriform Lesions of the Prostate Gland **591**

Qi Cai and Rajal B. Shah

Cribriform lesions of the prostate represent an important and often diagnostically challenging spectrum of prostate pathology. These lesions range from normal anatomical variation, benign proliferative lesions, premalignant, suspicious to frankly malignant and biologically aggressive entities. The concept of cribriform prostate adenocarcinoma (CrP4) and intraductal carcinoma of the prostate (IDC-P), in particular, has evolved significantly in recent years with a growing body of evidence suggesting that the presence of these morphologies is important for clinical decision-making in prostate cancer management. Therefore, accurate recognition and reporting of CrP4 and IDC-P architecture are especially important. This review discusses a contemporary diagnostic approach to cribriform lesions of the prostate with a focus on their key morphologic features, differential diagnosis, underlying molecular alterations, clinical significance, and reporting recommendations.

Diagnosis and Pathologic Reporting of Prostate Cancer in the Era of MRI-Targeted Prostate Biopsy **609**

Benjamin L. Coiner, Soroush Rais-Bahrami, and Jennifer B. Gordetsky

Historically, the detection of prostate cancer relied upon a systematic yet random sampling of the prostate by transrectal ultrasound guided biopsy. This approach was a nontargeted technique that led to the under detection of cancers at biopsy and the upgrading of cancers at radical prostatectomy. Multiparametric MRI-targeted prostate biopsy allows for an image-directed approach to the identification of prostate cancer. MRI-targeted biopsy of the prostate is superior for the detection of clinically significant prostate cancer. As this technique has become more

prevalent among urologists, pathologists need to recognize how this development impacts cancer diagnosis and reporting.

Molecular Genetics of Prostate Cancer and Role of Genomic Testing

617

Dilara Akhoundova, Felix Y. Feng, Colin C. Pritchard, and Mark A. Rubin

Prostate cancer (PCa) is characterized by profound genomic heterogeneity. Recent advances in personalized treatment entail an increasing need of genomic profiling. For localized PCa, gene expression assays can support clinical decisions regarding active surveillance and adjuvant treatment. In metastatic PCa, homologous recombination deficiency, microsatellite instability-high (MSI-H), and CDK12 deficiency constitute main actionable alterations. Alterations in DNA repair genes confer variable sensitivities to poly(ADP-ribose)polymerase inhibitors, and the use of genomic instability assays as predictive biomarker is still incipient. To date there is a lack of consensus as to testing standards.

Update on Flat and Papillary Urothelial Lesions: Genitourinary Pathology Society Consensus Recommendations

629

Eva Comp erat, Andr e Oszwald, Gabriel Wasinger, Shahrokh Shariat, and Mahul Amin

The reporting recommendations on “flat and papillary urothelial neoplasia,” published in 2 position articles by the Genitourinary Pathology Society in July 2021, was a collective contribution of 38 multidisciplinary experts aiming to clarify nomenclature, classification of flat and papillary urothelial neoplasia and controversial issues. In this review, we discuss some of these recommendations including nomenclature, practical approaches, and their importance for clinical practice.

Urothelial Carcinoma: Divergent Differentiation and Morphologic Subtypes

641

Jatin S. Gandhi, Jie-Fu Chen, and Hikmat Al-Ahmadie

Urothelial carcinoma (UC) is known to encompass a wide spectrum of morphologic features and molecular alterations. Approximately 15% to 25% of invasive UC exhibits histomorphologic features in the form of “divergent differentiation” along other epithelial lineages, or different “subtypes” of urothelial or sarcomatoid differentiation. It is recommended that the percentage of divergent differentiation and or subtype(s) be reported whenever possible. Recent advances in molecular biology have led to a better understanding of the molecular underpinning of these morphologic variations. In this review, we highlight histologic characteristics of the divergent differentiation and subtypes recognized by the latest version of WHO classification, with updates on their molecular and clinical features.

Urothelial Carcinoma: Update on Staging and Reporting, and Pathologic Changes Following Neoadjuvant Chemotherapies

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Manju Aron and Ming Zhou

Staging and reporting of cancers of the urinary tract have undergone major changes in the past decade to meet the needs for improved patient management. Substantial progress has been made. There, however, remain issues that require further clarity, including the substaging of pT1 tumors, grading and reporting of tumors with grade heterogeneity, and following NAC. Multi-institutional collaborative studies with prospective data will further inform the accurate diagnosis, staging, and reporting of

these tumors, and in conjunction with genomic data will ultimately contribute to precision and personalized patient management.

Molecular Taxonomy and Immune Checkpoint Therapy in Bladder Cancer 681

Charles C. Guo and Bogdan Czerniak

Bladder cancer is a heterogeneous disease, which exhibits a wide spectrum of clinical and pathologic features. Recent genomic studies have revealed that distinct molecular alterations may underlie the diverse clinical behaviors of bladder cancer, leading to a novel molecular classification. The intrinsic molecular subtypes exhibit distinct gene expression signatures and different clinicopathologic features. Genomic alterations also underlie the development of bladder cancer histologic subtypes. Genomic characterization provides new insights to understanding the biology of bladder cancer and improves the diagnosis and treatment of this complex disease. Biomarkers can aid the selection of patients for immune checkpoint therapy.

How New Developments Impact Diagnosis in Existing Renal Neoplasms 695

Mahmut Akgul and Sean R. Williamson

In recent years, several emerging diagnostic entities have been described in renal cell carcinoma (RCC). However, our understanding of well-known and established entities has also grown. Clear cell papillary RCC is now relabeled as a tumor rather than carcinoma in view of its nonaggressive behavior. Renal tumors with a predominantly infiltrative pattern are very important for recognition, as most of these have aggressive behavior, including fumarate hydratase-deficient RCC, SMARCB1-deficient medullary carcinoma, collecting duct carcinoma, urothelial carcinoma, and metastases from other cancers.

Kidney Tumors: New and Emerging Kidney Tumor Entities 713

Farshid Siadat, Mehdi Mansoor, Ondrej Hes, and Kiril Trpkov

This review summarizes current knowledge on several novel and emerging renal entities, including eosinophilic solid and cystic renal cell carcinoma (RCC), RCC with fibromyomatous stroma, anaplastic lymphoma kinase-rearranged RCC, low-grade oncocytic renal tumor, eosinophilic vacuolated tumor, thyroidlike follicular RCC, and biphasic hyalinizing psammomatous RCC. Their clinical features, gross and microscopic morphology, immunohistochemistry, and molecular and genetic features are described. The diagnosis of most of them rests on recognizing their morphologic features using immunohistochemistry. Accurate diagnosis of these entities will further reduce the category of “unclassifiable renal carcinomas/tumors” and will lead to better clinical management and improved patient prognostication.

Testicular Tumors: New Developments in Germ Cell and Sex Cord Stromal Tumors 729

Abhishek Dashora, Thomas Wagner, and Daniel M. Berney

This article reviews the recent advances and potential future changes in the classification of testicular germ cell and sex cord stromal tumors, highlighting changes in the classification system and terminology with description on newer entities. A discussion on approaching difficult areas and diagnostic pitfalls is also included along with the utility of ancillary investigations. Areas with limited knowledge are highlighted to providing direction for future studies and a bulleted summary in the form of critical care points is provided.

Testicular Cancer: Contemporary Updates in Staging

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Khaleel I. Al-Obaidy, Martin J. Magers, and Muhammad T. Idrees

Testicular tumors are the most common solid tumors in young men, the vast majority of which are of germ cell origin. The staging of human cancers is paramount to correct patient management. Staging systems have passed through several developments leading to the release of the most recent 8th edition of the American Joint Committee for Cancer (AJCC) staging manual, which is based on the current understanding of tumor behavior and spread. In this review, the authors summarize the current AJCC staging of the germ cell tumors, highlight essential concepts, and provide insight into the most important parameters of testicular tumors.

Applications of Digital and Computational Pathology and Artificial Intelligence in Genitourinary Pathology Diagnostics

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Ankush Uresh Patel, Sambit K. Mohanty, and Anil V. Parwani

As machine learning (ML) solutions for genitourinary pathology image analysis are fostered by a progressively digitized laboratory landscape, these integrable modalities usher in a revolution in histopathological diagnosis. As technology advances, limitations stymying clinical artificial intelligence (AI) will not be extinguished without thorough validation and interrogation of ML tools by pathologists and regulatory bodies alike. ML solutions deployed in clinical settings for applications in prostate pathology yield promising results. Recent breakthroughs in clinical artificial intelligence for genitourinary pathology demonstrate unprecedented generalizability, heralding prospects for a future in which AI-driven assistive solutions may be seen as laboratory faculty, rather than novelty.