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Editorial

Advances, Timely Topics, and Updates in Genitourinary Pathology

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This issue of *The Journal of Clinical and Translational Pathology* highlights important advances, timely topics, and updates in the field of genitourinary (GU) pathology. The six articles span the spectrum of GU anatomic sites, including the kidney, urinary system, prostate, and testis. As a common theme, all six papers focus on neoplasms affecting these different sites. This focus is indeed well-timed and valuable, since the 5th edition of the *World Health Organization (WHO) Classification of Tumours: Urinary and Male Genital Tumours* was just recently published in 2022.[1]

The diagnosis of renal neoplasms with oncocytic cytoplasm can be quite challenging, particularly in needle core tissue, and the differential diagnosis includes a number of different entities. In their review, Drs. Hui-Zhi Zhang, Ming Zhao, and Dengfeng Cao provide an update on selected renal cell tumors with oncocytic features.[2] The five renal tumors selected for in-depth analysis and discussion are eosinophilic solid and cystic renal cell carcinoma (RCC), eosinophilic vacuolated tumor, low-grade oncocytic tumor, low-grade fumarate hydratase-deficient RCC, and hybrid oncocytic/chromophobe renal tumor. According to the 2022 WHO classification, eosinophilic solid and cystic RCC and fumarate hydratase-deficient RCC are distinct entities, while eosinophilic vacuolated tumors, low-grade oncocytic tumors, and hybrid oncocytic/chromophobe renal tumors are found in the section describing "Other Oncocytic Tumors of the Kidney,"[3] where eosinophilic vacuolated tumors and low-grade oncocytic tumors are considered to be emerging entities. Dr. Zhang *et al.*[2] present a table that nicely summarizes the critical clinical features, morphology, immunohistochemistry, molecular features, and prognosis of the five tumors. In addition, the figures convey essential diagnostic attributes. While the histomorphological features alone may be diagnostic, the authors emphasize that diagnostic synthesis of histomorphology and immunohistochemistry often is required to arrive at the correct diagnosis. Molecular testing may sometimes be needed.

A major need in clinical medicine is the detection and monitoring of GU neoplasms using novel noninvasive approaches. Drs. Blake Salfer, Feng Li, Yazhen Zhu, Fang-Ming Deng, David T.W. Wong, and Liying Zhang explore the development of urinary biomarkers for bladder, renal, and prostate cancers by reviewing the literature spanning the past five years.[4] Liquid biopsy, as noted by the authors, has mainly utilized plasma; however, urine, including both the sediment and supernatant fractions, should also be considered as a source for biomarker assays. The rationale for the use of urinary biomarkers is well-developed, particularly for bladder cancer, which currently requires invasive cystoscopy for biopsy and regular cystoscopies for follow-up monitoring of many patients with bladder cancer, with the associated patient discomfort and significant cost to health care systems. The authors center their attention on nucleic acids rather than proteins, with sections on circulating tumor DNA/cell-free DNA mutational and fragmentation analyses, DNA methylation, extracellular RNA, and microRNA, especially those associated with exosomes. A variety of analytical techniques have been employed, and these can be seen in their excellent summary table. A number of these assays have shown promising results; nevertheless, as indicated by the authors, the research thus far has generally been preliminary and performed on a small-scale. Validation of these promising approaches is needed, along with testing in powered, randomized, controlled clinical trials. The authors also conclude that a test targeting multiple classes of urinary biomarkers could potentially serve as a multi-GU cancer early-detection urine liquid biopsy test.

The key changes in prostate tumor classification according to the 2022 WHO classification (5th edition) compared to the previous 2016 classification (4th edition) are featured in the article by Drs. Charles C. Guo and Bogdan Czerniak.[5] One terminological shift is that cribriform pattern high-grade prostatic intraepithelial neoplasia (PIN) is no longer recognized. Rather, this *in-situ* neoplastic proliferation is now designated as atypical cribriform proliferation, atypical intraductal proliferation, or atypical intraductal proliferation suspicious for intraductal carcinoma, which occupies an intermediate position between high-grade PIN and intraductal carcinoma. The diagnostic criteria for intraductal carcinoma, as originally proposed by Drs. Guo and Epstein,[6] are largely the same in the 5th edition as compared to the 4th edition. The main difference is that there is no longer a precise size specification for nuclear atypia (that is, nuclear size that is at least six times normal size); instead, a description of enlarged, pleomorphic

Keywords: Pathology; Genitourinary; Prostatic intraepithelial neoplasia; Renal cell carcinoma; Germ cell tumors.

Abbreviations: GCTs, Germ cell tumors; GU, genitourinary; PIN, prostatic intraepithelial neoplasia; RCC, renal cell carcinoma; WHO, World Health Organization.

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nuclei should be used when there is a loose cribriform or micropapillary pattern. A controversy, noted by the authors, pertains to grading intraductal carcinoma when it is detected with invasive adenocarcinoma. The International Society of Urological Pathology recommends incorporating intraductal carcinoma into the Gleason score, while The Genitourinary Pathology Society does not. More definitive evidence is needed to resolve this dispute. In the meantime, pathologists should specify in reports and publications which approach is being followed. A new subtype of prostatic acinar adenocarcinoma is PIN-like adenocarcinoma,[7] which was considered to be a pattern of ductal adenocarcinoma in the 4th edition. PIN-like adenocarcinoma completely lacks basal cells, unlike PIN, and lacks the papillary and cribriform growth of ductal adenocarcinoma. The authors discuss recent advances in the genomic characterization of prostate cancer and underscore the importance of germline and somatic mutations in DNA repair genes, which are enriched in aggressive prostate cancer. The final section addresses neuroendocrine tumors, which are now consolidated into one chapter for all GU tumors, except for treatment-related neuroendocrine prostatic carcinoma, which is included in a separate section called "Glandular Neoplasms of the Prostate." The authors point out that treatment-related prostatic carcinomas, which are thought to arise *via* transdifferentiation and lineage plasticity, behave like small cell neuroendocrine carcinoma but can show a range of histomorphologies from high-grade adenocarcinoma to small cell neuroendocrine carcinoma.

A prognostic factor for cancer is most impactful if it can be measured in a reproducible manner, with standardized methodology of measurement. The percentage of Gleason pattern 4 (GP4%) is a well-established prognostic factor for grade group 2 and 3 adenocarcinomas of the prostate, but limited data exist on the reproducibility of its measurement and the factors that contribute to suboptimal reproducibility. Thus, the data generated by Drs. Jianhong Li, Mark Ettel, Ali Amin, Ritu Bhalla, Kasturi Das, Fang-Ming Deng, Peng Lee, Andres Matoso, Jonathan Melamed, Savvas Mendrinos, Wei Tian, Oksana Yaskiv, Rajal Shah, and Ming Zhou are a welcome contribution to the literature.[8] These investigators found that the reproducibility of quantifying GP4% was only fair amongst 12 pathologists, and the factors that influence reproducibility include the size of the cancer focus, a GP4% of 40–60%, and the presence of a poorly formed gland subpattern. The definition of poorly formed glands has been problematic, and no quantitative measures of the size of the luminal space in a poorly formed gland or the shape/structure of poorly formed glands without luminal spaces are currently used. Artificial intelligence has been used to quantify the amount of prostate cancer in prostate needle core tissue[9] and could potentially be used in the future to quantify GP4%. Three-dimensional analysis of Gleason patterns could also theoretically be useful in the future.[10] For the present time, Li et al. offer practical guidance in reporting of GP4%: Pathologists may consider not providing GP4% for small amounts of grade group 2 prostatic adenocarcinoma, and education of pathologists and urologists related to the limitations of GP4% assessment is needed, along with standardization of methodology.

Standard histopathologic parameters of prognostic importance for prostatic adenocarcinoma in radical prostatectomy cases include pathologic stage, Gleason grade (grade group), and surgical margin status. In addition to a margin-positive vs. a margin-negative status, the Gleason grade at positive margins, the number of positive margins, the tumor length at positive margins, and the positive margin location (apex *vs.* nonapex) are also significant prognostic indicators. However, little is known regarding the effect of positive margin laterality on patient outcomes, particularly in relation to the dominant tumor nodule in the prostate gland. In their article, Drs. Shulin Wu, Sharron X. Lin, Gregory J. Wirth, Alexander O. Subtelny, Min Lu, Jian Lu, Zongwei Wang, Aria F. Olumi, Douglas M. Dahl, Michael L. Blute, and Chin-Lee Wu present data indicating that high-risk patients (with a Gleason score ≥4+3) with a positive surgical margin contralateral to the dominant tumor nodule experienced a significantly higher rate of biochemical recurrence after radical prostatectomy.[11] Their database is excellent, with a large number of patients with positive surgical margins (n = 406) and a lengthy follow-up of 12.6 years (median) after surgery. This observation on margin status in relation to the dominant tumor nodule location is novel and warrants further study so that risk stratification of prostate cancer patients with positive surgical margins can be further refined.

Germ cell tumors (GCTs) of the testis are, in most cases, highly curable cancers. One factor that can lead to a substantially lower cancer-specific survival rate is the presence of a somatic type malignancy in metastatic GCTs. Hence, accurate diagnostic recognition of this entity is crucial. In their comprehensive review article, Drs. Jiaming Fan, Yong Guan, Charles C. Guo, and Gang Wang consider the development of GCTs with somatic malignancy (SM), diagnostic criteria, common histologic subtypes, genetic features, and clinical outcomes.[12] While the testis chapter in the 2022 WHO classification includes somatic malignancies in the category of teratoma with somatic type malignancy, it is of interest that while many patients with a somatic malignancy have teratomatous GCTs, some somatic malignancies can arise from yolk sac tumors. Awareness of the clinical scenario in which GCTs with SM often develop is also important: Fan et al. note the propensity for SM to be resistant to platinum-based chemotherapy, with SM development in late recurrences. The authors present in detail the diverse and different histologic types of SM, including sarcoma, carcinoma, and embryonic-type neuroectodermal tumor (previously known as primitive neuroectodermal tumor), and others such as nephroblastoma (Wilms tumor). The authors stress that the accurate diagnosis of GCTs with SM often requires histology and immunohistochemistry. Another important aspect of the diagnosis they cite is quantitation. That is, SM should be diagnosed when expansile and infiltrative areas of primitive mesenchymal or epithelial cells are larger than 5 mm in diameter. An outstanding section on treatment is provided. The diagnosis of GCT with SM not only provides prognostic information, but it can determine the type of chemotherapy needed based on the type of SM. The authors recommend radical surgical resection of all tumors at any site, when feasible.

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Conflict of interest

Dr. Humphrey has been an editorial board member of *Journal of Clinical and Translational Pathology* since May 2021. The author has no other conflict of interests to declare.

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Dr. Humphrey is the sole author of this editorial.

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