Anatomic pathology selected abstracts

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Clinical validation of AI-augmented pathology diagnosis in prostate cancer

February 2024—The gold standard for prostate cancer diagnosis is the pathological examination of prostate biopsy tissue by light microscopy. The application of artificial intelligence (AI) to digitized whole slide images (WSIs) can aid pathologists in cancer diagnosis, but robust, diverse evidence in a simulated clinical setting is lacking. The authors conducted a study to compare the diagnostic accuracy of pathologists who read WSIs of prostatic biopsy specimens with and without AI assistance. Eighteen pathologists, two of whom were genitourinary subspecialists, evaluated 610 prostate needle core biopsy WSIs prepared at 218 institutions, with the option for deferral. Two evaluations were performed sequentially for each WSI: the first without assistance and the second, conducted immediately thereafter, aided by Paige Prostate (Paige, New York City). The latter is a deep learning-based system that provides a WSI-level binary classification of suspicious for cancer or benign and that pinpoints the location that has the greatest probability of harboring cancer on suspicious WSIs. Pathologists' changes in sensitivity and specificity between the assisted and unassisted modalities were assessed, along with the impact of Paige Prostate output on the assisted reads. The study revealed that pathologists improved their sensitivity and specificity across all histologic grades and tumor sizes using Paige Prostate. Accuracy gains on both benign and cancerous WSIs could be attributed to Paige Prostate, which correctly classified 100 percent of the WSIs showing corrected diagnoses in the Paige Prostate-assisted phase. The authors concluded that this study demonstrates the effectiveness and safety of an AI tool for pathologists in simulated diagnostic practice, bridging the gap between computational pathology research and its clinical application, and resulted in the first Food and Drug Administration marketing authorization of an AI system in pathology.

Raciti P, Sue J, Retamero JA, et al. Clinical validation of artificial intelligence-augmented pathology diagnosis demonstrates significant gains in diagnostic accuracy in prostate cancer detection. *Arch Pathol Lab Med*. 2023;147(10):1178–1185.

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Prognostic factors affecting colonic adenocarcinomas invading the muscularis propria

Depth of invasion through the intestinal wall, categorized as primary tumor stage, is an important prognostic factor in colorectal cancer. However, additional variables that may affect clinical behavior among tumors involving the muscularis propria (pT2) have not been examined at length. The authors evaluated 109 patients with pT2 colonic adenocarcinomas (median age, 71 years; interquartile range, 59–79 years) using various clinicopathologic parameters, including invasion depth, regional lymph node involvement, and disease progression after resection. In multivariate analysis, tumors extending to the outer muscularis propria (pT2b) were associated with older patient age ($P = .04$), larger tumor size ($P < .001$), higher likelihood of lymphovascular invasion (LVI; $P = .03$), and higher lymph node stage (pN; $P = .04$) compared with tumors limited to the inner muscle layer (pT2a). LVI was the most important variable predicting regional lymph node metastasis at resection in these tumors ($P = .001$). Kaplan-Meier analysis during a median clinical follow-up of 59.7 months (interquartile range, 31.5–91.2) revealed that disease progression was more likely in pT2 tumors that exhibited, at the time of staging, size greater than 2.5 cm ($P = .039$), perineural invasion (PNI; $P = .047$), high-grade tumor budding ($P = .036$), higher pN stage ($P = .002$), and distant metastasis ($P < .001$). Cox proportional hazards regression identified high-grade tumor budding ($P = .02$) as

an independent predictor of shorter progression-free survival in pT2 tumors. Among cases that would not ordinarily be candidates for adjuvant treatment—that is, pT2N0M0—high-grade tumor budding was significantly associated with disease progression ($P = .04$). These data suggest that during the diagnosis of pT2 tumors, pathologists may want to pay particular attention and ensure adequate reporting of such variables as tumor size, depth of invasion within the muscularis propria (that is, pT2a versus pT2b), LVI, PNI, and, especially, tumor budding, as these may affect clinical treatment decisions and patient prognostication.

Paulsen JD, Polydorides AD. Prognostic factors among colonic adenocarcinomas invading into the muscularis propria. *Am J Surg Pathol*. 2023;47(8):859–868.

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Expression of trichorhinophalangeal syndrome type 1 in male breast carcinoma

There is a paucity of highly specific and sensitive markers to identify breast carcinoma in males. IHC stains commonly used for unmasking primary breast carcinomas include estrogen receptor and GATA3. However, these markers are commonly expressed in carcinomas originating from other organ systems and can be reduced in breast carcinomas with higher histologic grades. Androgen receptor may be used to highlight primary male breast cancer, but this marker can also be expressed in other carcinomas. The authors conducted a study in which they evaluated TRPS1, a highly sensitive and specific marker for female breast carcinoma, in cases of male breast carcinoma. Through an institutional database search, they identified 72 cases of primary invasive breast carcinoma in male patients. Ninety-seven percent of estrogen receptor/progesterone receptor-positive cancers showed intermediate or high positivity for TRPS1 and GATA3. Among HER2-positive cancers, 100 percent showed intermediate or high positivity for TRPS1 and GATA3. One case of triple-negative breast cancer was collected, and it showed high positivity for TRPS1 and negativity for GATA3. Androgen receptor staining was nonspecific and heterogeneous: 76 percent of cases showed high positivity and 24 percent showed low or intermediate positivity. Among 29 cases of metastatic carcinoma of male breast tissue, 93 percent were negative for TRPS1 and seven percent, which were carcinomas from salivary gland primary tumors, were intermediate positive. The authors concluded that TRPS1 is a sensitive and specific marker for unmasking male primary invasive breast carcinoma across different subtypes. Furthermore, TRPS1 is not expressed in metastatic carcinomas of multiple primaries, with the exception of salivary gland primaries.

Law T, Piotrowski MJ, Ning J, et al. Trichorhinophalangeal syndrome type 1 (TRPS1) expression in male breast carcinoma. *Hum Pathol*. 2023;138:62–67.

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Diagnostic challenge of urine cytology findings in pseudocarcinomatous urothelial hyperplasia of bladder

Pseudocarcinomatous urothelial hyperplasia mimics cancer architecturally and cytologically. Its urine cytology features have not been described previously. Therefore, the authors conducted a study to describe pseudocarcinomatous urothelial hyperplasia (PCUH) features in urine cytology. They reviewed urine cytology cases with concurrent PCUH tissue specimens from five academic institutions and classified them using Paris System criteria. The review included 39 patients (31 men and eight women) who were a mean age of 67 years (range, 39–87 years). All patients had prior pelvic irradiation and most presented with hematuria (n = 27). The specimens included voided urine (n=16); bladder washing (n=11); and urine, not otherwise specified (n=12). Specimen preparation included the use of cytospin (n = 29) and Hologic ThinPrep (n = 10). Original interpretations were negative for high-grade urothelial carcinoma (n = 28), atypical urothelial cells (n = 10), and high-grade urothelial carcinoma (HGUC; n = 1). Twenty-five (64 percent) urine specimens had findings of PCUH. These specimens were moderately cellular and comprised of sheets, cohesive groups, or isolated urothelial cells. Nucleoli were present in

23 cases. The nuclear membrane was smooth to irregular (n = 9), smooth (n = 8), or irregular (n = 8). The chromatin was glassy (n = 8), vesicular (n = 7), hyperchromatic (n = 7), or vesicular to finely granular (n = 3). The cytoplasm varied from dense squamoid, to finely vacuolated, to vacuolated. Nucleomegaly was observed in all 25 specimens, and nucleo-cytoplasmic ratio greater than 0.5 was seen in 11 of 25 (44 percent) cases. The background contained acute inflammation (n = 14), was clean (n = 9), or contained red blood cells (n = 2). All cases originally interpreted as atypical urothelial cells and HGUC had features of PCUH. PCUH urine features can overlap those of atypical urothelial cells, HGUC, and nonurothelial malignancies. In the study cohort, 44 percent (11 of 25) of urine specimens with PCUH changes were initially misclassified. The authors concluded that it is important to recognize cytologic features of PCUH to avoid overcalling reactive changes.

Velez Torres JM, Gonzalez ML, Duarte EM, et al. Urine cytology findings in cases of pseudocarcinomatous urothelial hyperplasia of the bladder often represent a diagnostic challenge. *Arch Pathol Lab Med*. 2023;147:716–721.

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Encapsulated papillary carcinoma of breast: Does it have a native basement membrane?

Encapsulated papillary carcinoma is surrounded by a thick fibrous capsule-like structure, which is considered a thickened basement membrane. The authors conducted a study to describe the geometric characteristics of the encapsulated papillary carcinoma (EPC) capsule and determine whether it is an expansion of the basement membrane or a stromal reactive process. For the study, 100 cases of normal and neoplastic breast tissue were divided into four groups of 25 each. The groups included EPC, as well as ductal carcinoma in situ (DCIS), normal breast tissue, and invasive carcinoma as control groups. Representative slides from each case were stained with picrosirius red and examined using polarized microscopy. Images were analyzed using the ImageJ, CT-FIRE, and Curve Align image-analysis programs. Compared with the normal and DCIS basement membrane, the EPC capsule showed a significant increase in collagen fiber width, straightness, and density, and a decrease in fiber length. The fibers in the EPC capsule were less aligned and had a more perpendicular arrangement. Furthermore, the EPC capsule was enriched with disorganized collagen type one (stromal collagen) fibers. Compared with the other groups, the EPC capsule showed significant variation in the thickness, evenness, and distribution of collagen fibers, as well as significant intracapsular heterogeneity. Compared with the basement membrane-like material in the invasive group, the EPC capsule had a higher density of collagen fiber with longer, straighter, and more aligned fibers but no difference in the distribution of collagen types one and three. No differences were found between EPC and encapsulated papillary thyroid carcinoma (EPTC) capsules, except that the fibers in the EPC capsule were straighter. Although differences in collagen fiber density, straightness, orientation, and alignment were detected between normal ducts and lobules and DCIS basement membrane, both were significantly different from the EPC capsule. This study provided evidence that the EPC capsule is a reactive process rather than a thickened native basement membrane characteristic of normal and in situ lesions. It provides further evidence that EPC is an indolent invasive carcinoma based on capsule characteristics.

Ghannam SF, Rutland CS, Allegrucci C, et al. Encapsulated papillary carcinoma of the breast: does it have a native basement membrane? *Histopathology*. 2023;83(3):376–393.

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