Anatomic pathology selected abstracts

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Applying deep convolutional neural networks to diagnostic breast biopsies

December 2018—The breast stromal microenvironment is a pivotal factor in breast cancer development, growth, and metastases. Although pathologists often detect morphologic changes in stroma by light microscopy, visual classification of such changes is subjective and nonquantitative, limiting its diagnostic utility. To gain insight into stromal changes associated with breast cancer, the authors applied automated machine-learning techniques to the digital images of 2,387 hematoxylin-and-eosin–stained tissue sections of benign and malignant image-guided breast biopsies. The biopsies were performed to investigate mammographic abnormalities in 882 patients, ages 40 to 65 years, who were enrolled in the Breast Radiology Evaluation and Study of Tissues (BREAST) Stamp Project. Using deep convolutional neural networks, the authors trained an algorithm to discriminate between stroma surrounding invasive cancer and stroma from benign biopsies. In test sets (928 whole-slide images from 330 patients), this algorithm could distinguish biopsies diagnosed as invasive cancer from benign biopsies based solely on stromal characteristics (area under the receiver operating characteristic curve, 0.962). Furthermore, without being trained specifically using ductal carcinoma in situ as an outcome, the algorithm detected tumor-associated stroma in greater amounts and at larger distances from grade 3 versus grade 1 ductal carcinoma in situ. Collectively, these results suggest that algorithms based on deep convolutional neural networks that evaluate only stroma may be useful in classifying breast biopsies and aid in understanding and evaluating the biology of breast lesions.

Bejnordi BE, Mullooly M, Pfeiffer RM, et al. Using deep convolutional neural networks to identify and classify tumor-associated stroma in diagnostic breast biopsies. *Mod Pathol.* 2018. doi:10.1038/s41379-018-0073-z.

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Association between comedonecrosis and intraductal carcinoma of prostate

Since the advent of the Gleason grading system for prostate cancer, cancer displaying intraluminal necrotic cells or karyorrhexis, or both, within cribriform/solid architecture—a phenomenon termed comedonecrosis—has been assigned pattern 5. Intraductal carcinoma of the prostate (IDC-P) shows morphologic overlap with high-grade cribriform/solid adenocarcinoma architecturally and cytologically and may also show central necrosis. However, due to the presence of basal cells at the duct periphery, it is not assigned a grade in clinical practice. On the basis of observations from routine clinical cases, the authors hypothesized that comedonecrosis was more significantly associated with IDC-P than invasive disease. From a large series of mapped radical prostatectomy specimens (n=933), they identified 125 high-grade (Gleason score of 4+3=7 or greater), high-volume tumors with available slides for review. All slides were examined for unequivocal comedonecrosis. Standard immunohistochemistry (IHC) for basal cell markers was performed to detect basal cell labeling in these foci. Nineteen of 125 (15 percent) cases showed some ducts with comedonecrosis—nine cases with one focus and 10 cases with two or more foci. Seventy-three foci of true comedonecrosis were evaluated. IHC stains revealed labeling for basal cell markers in a basal cell distribution for at least some comedonecrosis foci in 18 of 19 (95 percent) cases—12 with IDC-P exclusively and six with a mix of IDC-P and invasive carcinoma comedonecrosis foci. These results suggest that comedonecrosis is strongly associated with IDC-P. Therefore, the routine assignment of pattern 5 to carcinoma exhibiting comedonecrosis should be reconsidered.

Fine SW, Al-Ahmadie HA, Chen YB, et al. Comedonecrosis revisited: Strong association with intraductal carcinoma of the prostate. *Am J Surg Pathol.* 2018;42(8):1036–1041.

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Use of genome profiling to avoid STUMP classification of uterine smooth muscle lesions

The diagnosis of a uterine smooth muscle lesion is, in the majority of cases, straightforward. However, in a small number of cases, the morphological criteria for such lesions cannot differentiate with certainty a benign from a malignant lesion. Therefore, a diagnosis of smooth muscle tumor with uncertain malignant potential (STUMP) is made. Uterine leiomyosarcomas are often easy to diagnose, but it is difficult or even impossible to identify a prognostic factor at the moment of diagnosis, with the exception of stage. The authors hypothesized, for uterine smooth muscle lesions, that there is a gradient of genomic complexity that correlates with outcome. They tested this hypothesis on STUMP lesions in a previous study and demonstrated that this gray category could be split into two groups according to genomic index: a benign group, with a low to moderate alteration rate without recurrence, and a malignant group, with a highly rearranged profile similar to uterine leiomyosarcomas. In this study, the authors analyzed 77 uterine smooth muscle lesions from 76 patients that were morphologically classified as leiomyomas (19), STUMP (14), and leiomyosarcomas (44). They confirmed that a genomic index with a cutoff of 10 is a predictor of recurrence ($P<.0001$) and with a cutoff of 35 is a marker for poor overall survival ($P=.035$). For the tumors confined to the uterus, stage as a prognostic factor was not useful for predicting survival. At stage I, among the tumors reclassified as molecular leiomyosarcomas (that is, a genomic index of 10 or more), the poor prognostic markers were 5p gain (overall survival, $P=.0008$), genomic index at a cutoff of 35 (overall survival, $P=.0193$), 13p loss including *RB1* (overall survival, $P=.0096$), and 17p gain including *MYOCD* gain (overall survival, $P=.0425$). Based on these findings and the feasibility of genomic profiling by array-comparative genomic hybridization, the genomic index and 5p and 17p gains are prognostic factors that could be evaluated in future prospective chemotherapy trials.

Croce S, Ducoulombier A, Ribeiro A, et al. Genome profiling is an efficient tool to avoid the STUMP classification of uterine smooth muscle lesions: A comprehensive array-genomic hybridization analysis of 77 tumors. *Mod Pathol.* 2018;31:816–828.

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Gastrointestinal tract vasculopathy: description of a potential new entity with protean features

Noninfectious gastrointestinal vasculopathic disorders are rare and, therefore, are often overlooked in histopathologic examination or when forming differential diagnoses. However, involvement of the GI tract may lead to serious complications, including ischemia and perforation. Because awareness of the types of vasculopathies that may involve the GI tract is central to arriving at a correct diagnosis, the authors reviewed their institutional experience with GI tract vasculopathy. They reported the clinical and histologic features of 16 cases (excluding 16 cases of immunoglobulin A vasculitis) diagnosed during a 20-year period. Of the 16 patients, 14 presented with symptoms related to GI vasculopathy, including two presenting with a mass on endoscopic examination. The remaining two patients presented with incarcerated hernia and invasive adenocarcinoma. The vasculopathy was not associated with systemic disease and appeared limited to the GI tract in eight patients. Eight had associated systemic disease, but only six had a prior diagnosis. The underlying diagnoses in these six patients included systemic lupus erythematosus (one), dermatomyositis (two), rheumatoid arthritis (one), eosinophilic granulomatosis with polyangiitis (one), and Crohn's disease (one). One patient with granulomatous polyangiitis and one with systemic lupus erythematosus initially presented with GI symptoms. The eight cases of isolated GI tract vasculopathy consisted of enterocolic lymphocytic phlebitis (four), idiopathic myointimal hyperplasia of the sigmoid colon (one), idiopathic myointimal hyperplasia of the ileum (one), granulomatous vasculitis (one), and polyarteritis nodosa-like arteritis (one). The authors concluded that isolated GI tract vasculopathy is rare but appears to be

almost as common as that associated with systemic disease. The chief primary vasculopathies are enterocolic lymphocytic colitis and idiopathic myointimal hyperplasia. Although the latter occurs predominantly in the left colon, rare examples occur in the small bowel and likely represent a complex, more protean disorder.

Louie CY, DiMaio MA, Charville GW, et al. Gastrointestinal tract vasculopathy: clinicopathology and description of a possible “new entity” with protean features. *Am J Surg Pathol.* 2018;42(7):866–876.

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Banff survey of antibody-mediated rejection clinical practices in kidney transplantation

The authors conducted a study to determine how the Banff antibody-mediated rejection classification for kidney transplantation is interpreted in practice and impacts therapy. The Banff Antibody-Mediated Injury Workgroup electronically surveyed clinicians and pathologists worldwide regarding diagnosis and treatment for six case-based scenarios. The diagnoses assigned to the participants (95 clinicians and 72 renal pathologists) were compared with the Banff intended diagnoses, which were used as a reference standard. The assigned diagnoses and reference standard differed by 26.1 percent (standard deviation [SD], 28.1 percent) for pathologists and 34.5 percent (SD, 23.3 percent) for clinicians. The greatest discordance between the reference standard and clinicians’ diagnoses was when histologic features of antibody-mediated rejection (ABMR) were present but donor-specific antibody was undetected (49.4 percent [43 of 87]). For pathologists, the greatest discordance was in the case of acute/active ABMR C4d staining negative in a positive crossmatch transplant recipient (33.8 percent [23 of 68]). Treatment approaches were heterogeneous but linked to the assigned diagnosis. When acute/active ABMR was diagnosed by the clinician, treatment was recommended 95.3 percent (SD, 18.4 percent) of the time versus only 77.7 percent (SD, 39.2 percent) of the time when chronic active ABMR was diagnosed ($P < .0001$). The authors concluded that the Banff ABMR classification is vulnerable to misinterpretation, which potentially has patient-management implications. Continued efforts are needed to improve understanding and standardized application of ABMR classification in the transplant community.

Schinstock CA, Sapir-Pichhadze R, Naesens M, et al. Banff survey on antibody-mediated rejection clinical practices in kidney transplantation: Diagnostic misinterpretation has potential therapeutic implications [published online ahead of print June 23, 2018]. *Am J Transplant.* doi:10.1111/ajt.14979.

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Data set for reporting of carcinomas of the cervix: ICCR recommendations

A comprehensive pathologic report is essential for optimal patient management, cancer staging, and prognostication. In many countries, proforma reports are used, but their content is variable. The International Collaboration on Cancer Reporting is an alliance formed by the Royal College of Pathologists (United Kingdom), Royal College of Pathologists of Australasia, College of American Pathologists, Canadian Partnership Against Cancer, and European Society of Pathology to develop standardized, evidence-based reporting data sets for each cancer site. This will reduce the burden of cancer data set development and reduplication of effort by the international institutions that commission, publish, and maintain standardized cancer-reporting data sets. The resultant standardization of cancer reporting benefits not only those countries directly involved in the collaboration but also others not in a position to develop their own data sets. The authors described the development of an evidence-based cancer data set by the International Collaboration on Cancer Reporting expert panel for the reporting of primary cervical carcinomas and presented the required and recommended elements for a pathology report as well as an explanatory commentary. The data set encompasses the International Federation of Obstetricians and Gynaecologists and Union for International Cancer Control staging systems for cervical neoplasms and the updated World Health Organization classification of gynecologic tumors. The data set also addresses controversial issues such as tumor grading and measurement, including measurement of multifocal carcinomas. The widespread implementation of this data set will facilitate consistent and accurate data collection,

comparison of epidemiological and pathologic parameters between populations, and research, and it may improve patient management.

McCluggage WG, Judge MJ, Alvarado-Cabrero I, et al. Data set for the reporting of carcinomas of the cervix: Recommendations from the International Collaboration on Cancer Reporting (ICCR). *Int J Gynecol Pathol.* 2018;37(3):205–228.

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