Anatomic Pathology Abstracts, 3/17

Editors: Michael Cibull, MD, professor emeritus, University of Kentucky College of Medicine, Lexington; Rouzan Karabakhtsian, MD, attending pathologist, Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; Thomas Cibull, MD, dermatopathologist, Evanston Hospital, NorthShore University HealthSystem, Evanston, Ill.; and Rachel Stewart, DO, resident physician, Department of Pathology and Laboratory Medicine, University of Kentucky.

An immunohistochemical algorithm for ovarian carcinoma typing

Five major histotypes of ovarian carcinoma exist. Diagnostic typing criteria have evolved over time, and past cohorts may be misclassified by current standards. The authors undertook an endeavor to reclassify the recently assembled Canadian Ovarian Experimental Unified Resource and Alberta Ovarian Tumor Type cohorts using immunohistochemical (IHC) biomarkers and to develop an IHC algorithm for ovarian carcinoma histotyping. They focused on reclassifying 1,626 ovarian carcinoma samples from the Canadian Ovarian Experimental Unified Resource and the Alberta Ovarian Tumor Type by comparing the original with the predicted histotype. Histotype prediction was derived from nominal logistic regression modeling using a previously reclassified cohort (n=784) with the binary input of eight IHC markers. Cases with discordant original or predicted histotypes were subjected to arbitration. After reclassification, 1,762 cases from all cohorts were subjected to prediction models ($\chi 2$ automatic interaction detection, recursive partitioning, and nominal logistic regression) with variable IHC marker input. The histologic type was confirmed in 1,521 of 1,626 (93.5 percent) cases of the Canadian Ovarian Experimental Unified Resource and the Alberta Ovarian Tumor Type cohorts. The highest misclassification occurred in the endometrioid type, where most of the changes involved reclassification from endometrioid to high-grade serous carcinoma, which was supported by mutational data and outcome. Using the reclassified histotype as the endpoint, a four-marker prediction model correctly classified 88 percent of the 1,762 cases, while a six-marker classified 91 percent and an eight-marker classified 93 percent. The authors concluded that this study provides statistically validated, inexpensive IHC algorithms that have versatile applications in research, clinical practice, and clinical trials.

Koebel M, Rahimi K, Rambau PF, et al. An immunohistochemical algorithm for ovarian carcinoma typing. *Int J Gyn Pathol.* 2016;35:430–441.

Correspondence: Dr. Martin Koebel at martin.koebel@cls.ab.ca

[hr]

Analysis of interobserver agreement in usual interstitial pneumonia diagnosis

This histopathologic criteria for idiopathic pulmonary fibrosis were revised in the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines in 2011. However, the evidence supporting diagnosis based on the guidelines needs further investigation. The

authors conducted a study to examine whether the revised histopathologic criteria for idiopathic pulmonary fibrosis improved interobserver agreement among pathologists and the predicted prognosis in patients with interstitial pneumonia. Twenty consecutive surgical lung biopsy specimens from cases of interstitial pneumonia were examined for histologic patterns by 11 pathologists without knowledge of clinical and radiologic data. Diagnosis was based on the American Thoracic Society/European Respiratory Society guidelines of 2002 and 2011. Pathologists were grouped by cluster analysis, and interobserver agreement and association with patient prognosis were compared with the diagnoses for each cluster. The generalized kappa coefficient of diagnosis for all pathologists was 0.23. If the diagnoses were divided into usual interstitial pneumonia/probable UIP (the UIP group) and possible/not UIP (the non-UIP group), according to the 2011 guidelines, the kappa coefficient of diagnosis improved to 0.37. The pathologists were subdivided into two clusters, one of which showed an association between UIP group diagnosis and patient prognosis ($P<.05$). The authors concluded that agreement about the pathologic diagnosis of interstitial pneumonia is low. However, results after division into UIP and non-UIP groups provided favorable agreement. The cluster analysis revealed that one of the two clusters provided strong interobserver agreement and prediction of patient prognosis.

Hashisako M, Tanaka T, Terasaki Y, et al. Interobserver agreement of usual interstitial pneumonia diagnosis correlated with patient outcome. *Arch Pathol Lab Med.* 2016;140:1375–1382.

Correspondence: Dr. Junya Fukuoka at fukuokaj@nagasaki-u.ac.jp

[hr]

Region of interest identification and diagnostic agreement in breast pathology

While a pathologist's accurate interpretation relies on identifying relevant histopathological features, little is known about the relationship between feature identification and diagnostic decision-making. The authors hypothesized that greater overlap between a pathologist's selected diagnostic region of interest (ROI) and a consensus-derived ROI is associated with higher diagnostic accuracy. To test their hypothesis, they developed breast biopsy test cases that included atypical ductal hyperplasia (n=80), ductal carcinoma in situ (n=78), and invasive breast cancer (n=22). They excluded benign cases due to the absence of specific abnormalities. Three experienced breast pathologists conducted an independent review of the 180 digital whole slide images, established a reference consensus diagnosis, and marked one or more diagnostic ROIs for each case. Forty-four pathologists independently diagnosed and marked ROIs on the images. Participant diagnoses and ROI were compared with consensus reference diagnoses and ROI. Regression models tested whether percentage overlap between participant ROI and consensus reference ROI predicted diagnostic accuracy. Each of the 44 participants interpreted 39 to 50 cases for a total of 1,972 individual diagnoses. Percentage ROI overlap with the expert reference ROI was higher among pathologists who self-reported academic affiliation (69 versus 65 percent; $P=.002$). Percentage overlap between participants' ROI and consensus reference ROI was then classified into ordinal categories: zero, one to 33 percent, 34 to 65 percent, 66 to 99 percent, and 100 percent overlap. For each incremental change in the ordinal percentage ROI overlap, diagnostic agreement increased by 60 percent (odds ratio, 1.6; 95 percent confidence interval, 1.5–1.7; $P<.001$) and the association remained significant even after adjusting other covariates. The magnitude of the association between ROI overlap and diagnostic agreement rose with increasing diagnostic severity. The results indicate that pathologist findings are more likely to converge with an expert reference diagnosis when they identify an overlapping diagnostic image region, suggesting that future computer-aided detection systems that highlight potential diagnostic regions could improve accuracy and education.

Nagarkar DB, Mercan E, Weaver DL, et al. Region of interest identification and diagnostic agreement in breast pathology. *Mod Pathol.* 2016;29:1004–1011.

Correspondence: Dr. J. G. Elmore at jelmore@uw.edu

[hr]

Feasibility of standardized evaluation of TIL in breast cancer

Multiple independent studies have shown that tumor-infiltrating lymphocytes are prognostic in breast cancer with potential relevance for response to immune-checkpoint inhibitor therapy. Although many groups are evaluating tumor-infiltrating lymphocytes (TIL), no standardized system exists for diagnostic applications. The authors conducted a study in which they reported the results of two ring studies investigating TIL that were conducted by the International Immuno-Oncology Biomarker Working Group. The intent of the study was to determine the intraclass correlation coefficient (ICC) for evaluation of TIL by different pathologists. A total of 120 slides were evaluated by a large group of pathologists with a Web-based system in ring study one and a more advanced software system that included an integrated feedback with standardized reference images in ring study two. The predefined aim for success in ring studies one and two was an ICC above 0.7 (lower limit of 95 percent confidence interval [CI]). In ring study one, the prespecified endpoint was not reached (ICC, 0.70; 95 percent CI, 0.62–0.78). On the basis of an analysis of sources of variation, a more advanced digital image evaluation system was developed for ring study two, which raised the ICC to 0.89 (95 percent CI, 0.85–0.92). Fleiss' kappa value for less than 60 percent versus 60 percent or greater TIL improved from 0.45 in ring study one to 0.63 in ring study two, and the mean concordance improved from 88 percent to 92 percent. The authors concluded that this large international standardization project shows that reproducible evaluation of TIL is feasible in breast cancer. This opens the way for standardized reporting of tumor immunological parameters in clinical studies and diagnostic practice. The software-guided, image-evaluation approach used in ring study two may be of value as a tool for evaluating TIL in clinical trials and diagnostic practice. Furthermore, the experience gained from this approach might help standardize other diagnostic parameters in histopathology.

Denkert C, Wienert S, Poterie A, et al. Standardized evaluation of tumor-infiltrating lymphocytes in breast cancer: results of the ring studies of the international immuno-oncology biomarker working group. *Mod Pathol.* 2016;29:1155–1164.

Correspondence: Dr. C. Denkert at carsten.denkert@charite.de

[hr]

CCNE1 and centrosome amplification in serous tubal intraepithelial carcinoma

Aberration in chromosomal structure characterizes almost all cancers and has profound biological significance in tumor development. It can be facilitated by various mechanisms, including overexpression of cyclin E1 and centrosome amplification. Because ovarian high-grade serous carcinoma has pronounced chromosomal instability, the authors sought to determine whether increased copy number of CCNE1, which encodes cyclin E1, and centrosome amplification (more than two copies) occur in its putative precursor, serous tubal intraepithelial carcinoma. They found CCNE1 copy number gain/amplification in eight of 37 (22 percent) serous tubal intraepithelial carcinomas and 12 of 43 (28 percent) high-grade serous carcinomas. A correlation in CCNE1 copy number was found between serous tubal intraepithelial carcinoma and high-grade serous carcinoma in the same patients ($P<.001$). There was no significant difference in the percentage of CCNE1 gain/amplification between serous tubal intraepithelial carcinoma and high-grade serous carcinoma ($P=.61$). Centrosome amplification was recorded in only five of 37 (14 percent) serous tubal intraepithelial carcinomas and 10 of 25 (40 percent) high-grade serous carcinomas. The percentage of cells with centrosome amplification was higher in high-grade serous carcinoma than in serous tubal intraepithelial carcinoma ($P<.001$). Induced expression of cyclin E1 increased the percentage of fallopian tube epithelial cells showing centrosome amplification. These findings suggest that gain/amplification of CCNE1 copy number occurs early in tumor progression and precedes centrosome amplification. The more prevalent centrosome amplification in high-grade serous carcinoma than in serous tubal intraepithelial carcinoma supports the view that serous tubal intraepithelial carcinoma precedes the development of many high-grade serous carcinomas.

Kuhn E, Wang TL, Doberstein K, et al. CCNE1 amplification and centrosome number abnormality in serous tubal

intraepithelial carcinoma: further evidence supporting its role as a precursor of ovarian high-grade serous carcinoma. *Mod Pathol.* 2016;29:1254–1261.

Correspondence: Dr. E. Kuhn at elisabettakuhn@hotmail.it or Dr. I. M. Shih at ishih@jhmi.edu