Anatomic Pathology Selected Abstracts, 3/13

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Immunohistochemical assay versus Oncotype DX qRT-PCR assay for estrogen and progesterone receptors

Estrogen receptor status is a strong predictor of response to hormonal therapy in breast cancer patients. Its presence and level of expression have been shown to correlate with time to recurrence in patients undergoing therapy with tamoxifen or aromatase inhibitors. Risk reduction is known to occur in estrogen receptor-negative, progesterone receptor-positive patients treated with hormonal therapy. Since the 1990s, immunohistochemistry has been the primary method for assessing hormone receptor status. As a component of its Oncotype DX assay, Genomic Health recently began reporting quantitative estrogen and progesterone receptor results determined by quantitative reverse transcription polymerase chain reaction (qRT-PCR). As part of an ongoing quality assurance program at Magee-Womens Hospital in Pittsburgh, the authors reviewed 464 breast cancer cases evaluated for estrogen and progesterone receptor by both immunohistochemistry and the Oncotype DX assay. They found good correlation for estrogen receptor status between both assays (98.9 percent concordance), with immunohistochemistry being slightly more sensitive. Concordance for progesterone receptor was 94.2 percent between immunohistochemistry and qRT-PCR, with immunohistochemistry again more sensitive. The results also showed linear correlation between immunohistochemistry H-scores and qRT-PCR expression values for estrogen receptor (correlation coefficient, 0.579) and progesterone receptor (correlation coefficient, 0.685). Due to hormone receptor immunohistochemistry having higher sensitivity and additional advantages—that is, preservation of morphology, less expensive, faster, and more convenient—the authors concluded that immunohistochemistry is preferable to qRT-PCR for determining estrogen and progesterone receptor expression.

Kraus JA, Dabbs DJ, Beriwal S, et al. Semi-quantitative immunohistochemical assay versus Oncotype DX qRT-PCR assay for estrogen and progesterone receptors: an independent quality assurance study. *Mod Pathol*. 2012;25:869–876.

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Accuracy and precision of endometrial intraepithelial neoplasia diagnosis

Endometrial intraepithelial neoplasia applies specific diagnostic criteria to designate a monoclonal endometrial preinvasive glandular proliferation known from previous studies to confer a 45-fold increased risk for endometrial cancer. The authors conducted an international study in which they estimated the accuracy and precision of endometrial intraepithelial neoplasia (EIN) diagnosis among 20 reviewing pathologists who were in different practice environments and had differing levels of experience and training. Sixty-two endometrial biopsies diagnosed as benign, EIN, or adenocarcinoma by consensus of two expert subspecialty pathologists were used as a reference comparison to assess the diagnostic accuracy of the 20 reviewing pathologists. Interobserver reproducibility among the 20 reviewers provided a measure of diagnostic precision. Before evaluating cases, observers were self-trained by reviewing published textbook or online EIN diagnostic guidelines, or both. The demographics of the reviewing pathologists and their impressions regarding implementation of EIN terminology were recorded. Seventy-nine percent of the 20 reviewing pathologists' diagnoses were exactly concordant with the expert consensus. The interobserver weighted kappa values of three-class EIN scheme (benign, EIN, carcinoma) diagnoses between expert consensus and each of the reviewing pathologists averaged 0.72. The reviewing pathologists demonstrated one of three diagnostic styles, which varied in the repertoire of diagnoses commonly

used, in their nonrandom response to potentially confounding diagnostic features, such as endometrial polyp, altered differentiation, background hormonal effects, and technically poor preparation. The authors concluded that EIN diagnostic strategies can be learned and implemented from standard teaching materials with a high degree of reproducibility, but they are influenced by the personal diagnostic style of each pathologist in responding to potential diagnostic confounders.

Usubutun A, Mutter GL, Saglam A, et al. Reproducibility of endometrial intraepithelial neoplasia diagnosis is good, but influenced by the diagnostic style of pathologists. *Mod Pathol.* 2012;25:877–884.

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Histologic patterns and molecular characteristics of lung adenocarcinoma

Lung adenocarcinoma is histologically heterogeneous and has five distinct histologic growth patterns: lepidic, acinar, papillary, micropapillary, and solid. No consensus exists regarding the clinical utility of these patterns. The authors performed a detailed semiquantitative assessment of histologic patterns of 240 lung adenocarcinomas and determined the association with patients' clinicopathologic features, including recurrence-free survival and overall survival rates. In a subset of tumors, expression levels of two prognostic molecular markers were evaluated: thyroid transcription factor-1 (TTF-1; n=218) and a panel of five proteins (referred to as the FILM signature index; n=185). Four mutually exclusive tumor histology pattern groups were identified: any solid (38 percent), any papillary but no solid (14 percent), lepidic and acinar but no solid or papillary (30 percent), and acinar only (18 percent). Patients in group three had a higher recurrence-free survival rate than patients in group one (hazard ratio [HR], 0.4510; *P*=.0165) and group two (HR, 0.4253; *P*=.0425). Solid pattern tumors (group one) were associated with a lower overall survival rate than nonsolid pattern tumors (all stages: HR, 1.665; *P*=.0144; stages I and II: HR, 2.157; *P*=.008). In the patients who had tumors with a nonsolid pattern, high TTF-1 expression was associated significantly with a higher recurrence-free survival rate (HR, 0.994; *P*=.0017) and overall survival rate (HR, 0.996; *P*=.0276) in all stages. A high FILM signature index score was associated with lower recurrence-free and overall survival rates in all stages (recurrence-free survival: HR, 1.343; *P*=.0192; overall survival: HR, 1.371; *P*=.0156) and in stages I and II (recurrence-free survival: HR, 1.419; *P*=.0095; overall survival: HR, 1.315; *P*=.0422). The authors concluded that the presence of a solid histologic pattern was identified as a marker of unfavorable prognosis in patients with primary lung adenocarcinoma. High TTF-1 expression and low FILM signature index scores were associated with better prognosis for patients who had tumors with a nonsolid pattern.

Solis LM, Behrens C, Raso MG, et al. Histologic patterns and molecular characteristics of lung adenocarcinoma associated with clinical outcome. *Cancer*. 2012;118:2889–2899.

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MicroRNA expression profiling as a diagnostic tool for thyroid cancer

Approximately 30 percent of fine-needle aspiration biopsies of thyroid nodules are indeterminate or nondiagnostic. Recent studies suggest microRNA (miRNA, miR) is differentially expressed in malignant tumors and may play a role in carcinogenesis, including thyroid cancer. Therefore, the authors tested the hypothesis that miRNA expression analysis would identify putative markers that could distinguish benign from malignant thyroid neoplasms that are often indeterminate on fine-needle aspiration (FNA) biopsy. They used an miRNA array to identify differentially expressed genes (five-fold higher or lower) in pooled normal, malignant, and benign thyroid tissue samples. Real-time quantitative polymerase chain reaction was used to confirm miRNA array expression data in 104 tissue samples and 125 indeterminate clinical FNA samples. The 104 tissue samples were seven normal thyroid, 14 hyperplastic nodule, 12 follicular variant of papillary thyroid cancer, eight papillary thyroid cancer, 15 follicular adenoma, 12 follicular carcinoma, 12 Hurthle cell adenoma, 20 Hurthle cell carcinoma, and four anaplastic carcinoma cases. The diagnostic accuracy of differentially expressed genes was determined by analyzing receiver

operating characteristics. The authors found that 10 miRNAs showed greater than five-fold expression difference between benign and malignant thyroid neoplasms on miRNA array analysis. Four of the 10 miRNAs were validated to be significantly differentially expressed between benign and malignant thyroid neoplasms by quantitative polymerase chain reaction ($P<.002$): MiR-100, miR-125b, miR-138, and miR-768-3p were overexpressed in malignant samples of follicular origin ($P<.001$) and in Hurthle cell carcinoma samples alone ($P<.01$). Only miR-125b was significantly overexpressed in follicular carcinoma samples ($P<.05$). The accuracy for distinguishing benign from malignant thyroid neoplasms was 79 percent overall and was 98 percent for Hurthle cell neoplasms and 71 percent for follicular neoplasms. MiR-138 was overexpressed in the FNA samples ($P=.04$) that were malignant on final pathology with an accuracy rate of 75 percent. The authors concluded that microRNA expression differs for normal, benign, and malignant thyroid tissue. Expression analysis of differentially expressed miRNA could help distinguish benign from malignant thyroid neoplasms that are indeterminate on thyroid FNA biopsy.

Vriens MR, Weng J, Suh I, et al. MicroRNA expression profiling is a potential diagnostic tool for thyroid cancer. *Cancer.* 2012;118(13):3426–3432.

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Inflammation and preneoplastic lesions in benign prostate as risk factors for prostate cancer

Benign changes ranging from atrophy and inflammation to high-grade prostatic intraepithelial neoplasia are common findings on prostate core needle biopsies. Although atrophy and inflammation may be precursors of prostate cancer, only high-grade prostatic intraepithelial neoplasia (HGPIN) is recommended for inclusion in surgical pathology reports. To determine whether these benign findings increase prostate cancer risk, the authors conducted a case-control study nested within a historical cohort of 6,692 men who had a benign prostate specimen collected between 1990 and 2002. The analytic sample included 574 case-control pairs comprised of cases diagnosed with prostate cancer a minimum of one year after cohort entry and controls matched to cases on date and age at cohort entry, race, and type of specimen. The initial benign specimen was reviewed for the presence of HGPIN, atrophy (simple, lobular, and partial), and inflammation (glandular or stromal, or both). HGPIN significantly increased the risk for prostate cancer (odds ratio [OR], 2.00; 95 percent confidence interval [CI], 1.25–3.20). Inflammation within the stromal compartment was associated with decreased risk (OR, 0.66; CI, 0.52–0.84), and diffuse stromal inflammation of severe grade had the strongest inverse association with risk (OR, 0.21; CI, 0.07–0.62). In a model adjusted for prostate-specific antigen level at cohort entry and inflammation, simple atrophy was associated with a 33 percent increased prostate cancer risk that was marginally significant ($P=.03$). The authors concluded that clinicians should consider patterns and extent of inflammation when managing high-risk patients with negative biopsy results. Identifying benign inflammatory processes that underlie high prostate-specific antigen levels would help reduce the number of unnecessary repeat prostate biopsies.

Kryvenko ON, Jankowski M, Chitale DA, et al. Inflammation and preneoplastic lesions in benign prostate as risk factors for prostate cancer. *Mod Pathol*. 2012;25:1023–1032.

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Reclassification of serous ovarian carcinoma using a two-tier system

A Gynecologic Oncology Group study was undertaken to use a two-tier system to reclassify the grade of serous ovarian tumors previously classified using the International Federation of Gynecology and Obstetrics (FIGO) three-tier system. The study also sought to determine the progression-free and overall survival rates of patients treated via Gynecologic Oncology Group (GOG) Protocol 158. The authors retrospectively reviewed the demographic, pathologic, and survival data for 290 patients with stage III serous ovarian carcinoma treated with surgery and chemotherapy via GOG Protocol 158, a cooperative multicenter group trial. A panel of six gynecologic pathologists performed a blinded pathology review to verify histology and regrade tumors using the two-tier system. The

association of tumor grade with progression-free and overall survival was assessed. The authors found that for 241 cases, both systems demonstrated substantial agreement when combining FIGO grades two and three (overall agreement, 95 percent; kappa statistic, 0.68). By using the two-tier system, patients with low-grade versus high-grade tumors had significantly longer progression-free survival rates (45 versus 19.8 months, respectively; *P*=.01). Using FIGO criteria, the median progression-free survival for patients with grades one, two, and three tumors was 37.5, 19.8, and 20.1 months, respectively (*P*=.07). In multivariate analysis, there was no difference in clinical outcome for patients with grade two or three tumors. Women with high-grade versus low-grade tumors demonstrated significantly higher risk of death (hazard ratio, 2.43; 95 percent confidence interval, 1.17–5.04; *P*=.02). The authors concluded that women with high-grade versus low-grade serous carcinoma of the ovary represent two distinct patient populations. Adopting the two-tier grading system provides a simple yet precise framework for predicting clinical outcomes.

Bodurka DC, Deavers MT, Tian C, et al. Reclassification of serous ovarian carcinoma by a 2-tier system: A Gynecologic Oncology Group study. *Cancer*. 2012;118(12):3087–3094.

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