Anatomic Pathology Abstracts, 3/18

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Magee equation 3 for predicting response to chemotherapy in some breast tumors

Magee equations were derived as an inexpensive, rapid alternative to the Oncotype DX commercial assay. Magee equation 3 uses immunohistochemical and FISH data for estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 for its calculation: 24.30812+ERIHC×(–.02177)+PRIHC×(−0.02884)+(0 for HER2 negative, 1.46495 for equivocal, 12.75525 for HER2 positive)+Ki-67×0.18649. The authors hypothesized that Magee equation 3 scores from pretherapy core biopsy can predict response to neoadjuvant systemic chemotherapy. They reviewed, retrospectively, a prospectively maintained database of patients who received neoadjuvant systemic therapy at a single institution from 2010 to 2014. Pathologic complete response was defined as absence of invasive tumor in the breast and regional lymph nodes. Excluded from the 614 cases were tumors that were missing immunohistochemical results and those that were ER negative or HER2 positive. This left 237 ER-positive, HER2-negative/equivocal tumors for the study. The Magee equation 3 scores were divided into categories similar to Oncotype DX—that is, low (less than 18), intermediate (18 to 30), and high (more than 30). The pathologic complete response rate for low, intermediate, and high Magee equation 3 scores was zero, four percent, and 36 percent, respectively. Patients with high Magee equation 3 scores were 13 times more likely to achieve pathologic complete response than those with Magee equation 3 scores of less than 31 (95 percent confidence interval, 5.09–32.87; $P<.0001$). For patients who did not achieve pathologic complete response, high Magee equation 3 correlated with higher recurrence rate, with the majority occurring in patients with positive lymph nodes in the resection specimen. A Magee equation 3 score of 31 or higher predicts pathologic complete response in the neoadjuvant setting and for tumor recurrence when pathologic complete response is not achieved. These results show the utility of Magee equation 3 for predicting which patients will benefit from chemotherapy, but they warrant prospective multi-institutional validation.

Farrugia DJ, Landmann A, Zhu L, et al. Magee Equation 3 predicts pathologic response to neoadjuvant systemic chemotherapy in estrogen receptor positive, HER2 negative/equivocal breast tumors. *Mod Pathol.* 2017;30:1078–1085.

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BCOR as an immunohistochemical marker of high-grade endometrial stromal sarcoma

Recognition of high-grade endometrial stromal sarcoma is important because of its aggressive clinical behavior. The morphologic features of *YWHAE-NUTM2* high-grade endometrial stromal sarcoma may overlap those of other uterine sarcoma types. The authors studied BCOR immunoexpression in these tumors and their morphologic mimics to assess its diagnostic utility. They performed BCOR immunohistochemical staining on archival tissue from 28 high-grade endometrial stromal sarcomas with classic morphology (20 *YWHAE-NUTM2*, five *ZC3H7B-BCOR*, and three *BCOR-ZC3H7B*), three high-grade endometrial stromal sarcomas with unusual morphology and unknown gene rearrangement status, 66 low-grade endometrial stromal sarcomas, 21 endometrial stromal nodules, 38 uterine leiomyosarcomas, and 19 uterine leiomyomas. The authors recorded the intensity of nuclear staining and percentage of positive tumor cells. They noted strong diffuse nuclear BCOR staining (defined as more than 95 percent of tumor cells) in the round cell component of all 20 classic *YWHAE-NUTM2* high-grade endometrial stromal sarcomas and the three unusual high-grade endometrial stromal sarcomas, which prompted FISH studies to confirm *YWHAE* rearrangement in two of the latter tumors. Genomic polymerase chain reaction confirmed BCOR exon 16 internal tandem duplication in the third case. Diffuse BCOR staining was strong in three and weak in one BCOR-rearranged high-grade endometrial stromal sarcoma and absent in the remaining four BCOR-rearranged tumors. BCOR staining was weakly positive in fewer than five percent of tumor cells in four of the 66 (six percent) low-grade endometrial stromal sarcomas and one of 18 (six percent) endometrial stromal nodules and weakly to moderately positive in fewer than five percent to 40 percent of tumor cells in six of 31 (19 percent) leiomyosarcomas. No BCOR staining was seen in the remaining low-grade endometrial stromal sarcomas, endometrial stromal nodules, or leiomyosarcomas, or any of the leiomyomas. BCOR immunohistochemical staining is a highly sensitive marker for *YWHAE-NUTM*2 high-grade endometrial stromal sarcoma with classic and unusual morphology and identifies a subset of high-grade endometrial stromal sarcoma with BCOR alterations, including BCOR rearrangement and internal tandem duplication.

Chiang S, Lee CH, Stewart CJR, et al. BCOR is a robust diagnostic immunohistochemical marker of genetically diverse high-grade endometrial stromal sarcoma, including tumors exhibiting variant morphology. *Mod Pathol.* 2017;30:1251–1261.

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Breast implant capsule–associated squamous cell carcinoma

The use of prosthetic implants does not increase the risk of conventional mammary carcinoma, and the implants are rarely associated with anaplastic large cell lymphoma. The authors reported on two cases of breast implant capsule-associated squamous cell carcinoma with poor clinical outcomes. Both patients—a 56-year-old woman and an 81-year-old woman—had long-standing implants (greater than 25 years) and presented with acute unilateral breast enlargement. In both cases, squamous cell carcinoma arose in (focally dysplastic) squamous epithelium-lined breast implant capsules and widely invaded the surrounding breast parenchyma or the chest wall. Neither patient had evidence of a primary mammary carcinoma or squamous cell carcinoma at any other anatomic site. Within one year, one patient developed extensive, treatment-refractory, locoregional soft tissue metastasis and the other developed hepatic and soft tissue metastases and died of disease. Two prior cases of implant-associated squamous cell carcinoma appear in the plastic surgery literature; no pathologic staging or outcome information was provided for one, and the other was a capsule-confined squamous cell carcinoma. The four cases share notable commonalities: The patients had long-standing breast implants and presented with acute unilateral breast pain and enlargement secondary to tumors arising on the posterior aspect of squamous epithelialized implant

capsules. The authors concluded that because of its rarity and unusual clinical presentation, implant capsule-associated squamous cell carcinoma may be underrecognized. The aggressive behavior of the tumors in this series underscores the importance of excluding malignancy in patients with long-standing breast implants who present with acute unilateral breast pain and enlargement.

Olsen DL, Keeney GL, Chen B, et al. Breast implant capsule-associated squamous cell carcinoma: a report of 2 cases. *Hum Pathol.* 2017;67:94–100.

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Solitary fibrous tumors of the head and neck: a clinicopathologic study

Solitary fibrous tumors of the head and neck are uncommon. Lesions previously diagnosed in the head and neck as hemangiopericytomas (HPCs), giant cell angiofibromas (GCAs), and orbital fibrous histiocytomas (OFHs) are now recognized as within the expanded spectrum of solitary fibrous tumors (SFTs). To better understand the clinicopathologic profile of head and neck SFTs, the authors performed a multi-institutional study of 88 examples. There was no sex predilection (female:male ratio, 1.2), and the median patient age was 52 years (range, 15 to older than 89 years). The sinonasal tract and orbit were the most common sites involved at 30 percent and 25 percent, respectively, followed by the oral cavity and salivary glands at 15 percent and 14 percent, respectively. Original diagnoses included HPC (25 percent), SFT (67 percent), and OFH (six percent), with one SFT and one OFH noted as showing GCA-like morphology. On review, the predominant histologic pattern was classic SFT-like in 53 percent and cellular (former HPC-like) in 47 percent. Lipomatous differentiation (eight percent) and GCA-like pattern (seven percent) were less prevalent. Subsets demonstrated nuclear atypia (23 percent), epithelioid morphology (15 percent), or coagulative necrosis (six percent). Infiltrative growth (49 percent) and osseous invasion (82 percent) were prevalent among evaluable cases. Of the 48 SFTs with follow-up (median, 43 months), 19 showed recurrence (40 percent). Of those, four patients were alive with disease and four dead of disease. Size and mitotic rate were negative prognosticators using a joint prognostic proportional hazards regression model. Three patients experienced metastasis—to lungs, parotid, bone, and skull base—including one case showing overtly sarcomatous “dedifferentiation.” As a group, SFTs present in a wide anatomic and morphologic spectrum in the head and neck. Only rare examples metastasize or cause death from disease. However, the fairly high local recurrence rate underscores the aggressive potential of SFTs and highlights the importance of prospective recognition.

Smith SC, Gooding WE, Elkins M, et al. Solitary fibrous tumors of the head and neck: a multi-institutional clinicopathologic study. *Am J Surg Pathol.* 2017;41(12):1642–1656.

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Reliability of TIL and tertiary lymphoid structure assessment in breast cancer

Tumor-infiltrating lymphocytes, reflecting host immune activity, are frequently correlated with better clinical outcomes, particularly in HER2-positive and triple-negative breast cancer. Recent findings suggest that organization of immune infiltrates in tertiary lymphoid structures also has a beneficial effect on survival. The authors investigated inter- and intra-observer variation in tumor-infiltrating lymphocyte (TIL) assessment using conventional H&E versus immunohistochemical staining to identify immune cells. Global, intratumoral, and stromal TIL, as well as tertiary lymphoid structures, were scored independently by experienced pathologists on full-face tumor sections (n=124). The study also assessed the fidelity of scoring infiltrates in core biopsies compared with surgical specimens, and pathological assessment compared with quantitative digital analysis. The inter-observer

concordance correlation coefficient was 0.80 for global, 0.72 for intratumoral, and 0.71 for stromal TIL, while the intra-observer concordance correlation coefficient was 0.90 for global, 0.77 for intratumoral, and 0.89 for stromal TIL using immunohistochemical stains. Correlations were lower with H&E stains, particularly for intratumoral TIL, while global scores had the highest concordance correlation coefficients. The study concluded that tertiary lymphoid structures are accurately and consistently scored using immunohistochemical but not H&E stains. A strong association was observed between TIL in core biopsies and surgical samples ($R^2 = 0.74$), but this did not extend to tertiary lymphoid structures ($R^2 = 0.26$). TILs scored by pathologists and digital analysis were correlated, but the study revealed a constant bias between the methods. These data challenge the criteria for TIL and tertiary lymphoid structure assessment in breast cancer and support re-examining how pathologists evaluate immune infiltrates.

Buisseret L, Desmedt C, Garaud S, et al. Reliability of tumor-infiltrating lymphocyte and tertiary lymphoid structure assessment in human breast cancer. *Mod Pathol.* 2017;30:1204–1212.

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Expression of LEF1 in tubal-peritoneal junctions

It has been reported that serous tubal intraepithelial carcinoma, the likely precursor of ovarian/extra-uterine high-grade serous carcinoma, is frequently located in the vicinity of tubal-peritoneal junctions, consistent with the cancer-prone features of many epithelial transitional regions. To test if p53 signatures and secretory cell outgrowths (SCOUTs) also localize to tubal-peritoneal junctions, the authors examined these lesions in the fallopian tubes of patients undergoing salpingo-oophorectomy for sporadic high-grade serous carcinomas or as a prophylactic procedure for carriers of familial BRCA1 or BRCA2 mutations. Serous tubal intraepithelial carcinomas (STICs) were located closest to the tubal-peritoneal junctions, with an average distance of 1.31 mm, while SCOUTs were not detected in the fimbriated end of the fallopian tube. Because many epithelial transitional regions contain stem cells, the authors also determined the expression of stem cell markers in the normal fallopian tube, tubal intraepithelial lesions, and high-grade serous carcinomas. Of those, LEF1 was consistently expressed in the tubal-peritoneal junctions and all lesions, independent of p53 status. All SCOUTs demonstrated strong nuclear expression of β-catenin consistent with LEF1 participation in the canonical Wnt pathway. However, β-catenin was preferentially located in the cytoplasm of cells comprising STICs and p53 signatures, suggesting a Wnt-independent function of LEF1 in those lesions. Both frequency of LEF1 expression and β-catenin nuclear expression correlated with the worst five-year patient survival rates, supporting the important role of both proteins in high-grade serous carcinoma. Taken together, these findings suggest the existence of a stem cell niche within the tubal-peritoneal junctions. Furthermore, they support the notion that the pathogenesis of SCOUTs is distinct from that of STICs and p53 signatures. The location and discrete patterns of LEF1 and β-catenin expression may serve as highly sensitive and reliable ancillary markers for the detection and differential diagnosis of tubal intraepithelial lesions.

Schmoeckel E, Odai-Afotey AA, Schleißheimer M, et al. LEF1 is preferentially expressed in the tubal-peritoneal junctions and is a reliable marker of tubal intraepithelial lesions. Mod Pathol. 2017;30:1241–1250.

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Clinical indices of disease severity in children with ulcerative colitis

The authors conducted a study to characterize rectal histology in an inception cohort of children newly diagnosed with ulcerative colitis and to explore its relationship with clinical indices of disease severity. The PROTECT (Predicting Response to Standardized Pediatric Colitis Therapy) study enrolled children 17 years of age and

younger who were newly diagnosed with ulcerative colitis. It evaluated baseline rectal biopsies for acute and chronic inflammation, eosinophilic inflammation (peak eosinophil count greater than 32 eosinophils/high-powered field, eosinophilic cryptitis or abscesses), and architectural/nonarchitectural chronic changes. Correlation with clinical indices, including Mayo endoscopy subscore and Pediatric Ulcerative Colitis Activity Index, was performed. The authors reviewed rectal biopsies from 369 patients (mean age, 12.9±3.1 years; 50 percent female). Cryptitis was found in 89 percent of biopsies, crypt abscesses in 25 percent, and eosinophilic inflammation in 58 percent. Crypt distortion/atrophy was present in 98 percent of specimens. Higher grades of acute and chronic inflammation were associated with the presence of basal plasmacytosis ($P<.0001$), basal lymphoid aggregates ($P<.0001$), and surface villiform changes ($P<.0001$). A severe Mayo endoscopy subscore was most common among those with severe acute and chronic inflammation, although this relationship was not linear. Severe Pediatric Ulcerative Colitis Activity Index scores were associated with the absence of eosinophilic inflammation or only mild eosinophilic inflammation (fewer than 32 eosinophils/high-powered field; $P<.03$) and the presence of surface villiform changes ($P<.005$). Acute and chronic inflammation, eosinophilic inflammation, and chronic changes are common in children newly diagnosed with ulcerative colitis. The clinical and biological implication of low to absent eosinophilic inflammation and the presence of surface villiform changes require further study.

Boyle B, Collins MH, Wang Z, et al., on behalf of the PROTECT Study Group. Histologic correlates of clinical and endoscopic severity in children newly diagnosed with ulcerative colitis. *Am J Surg Pathol.* 2017;41:1491–1498.

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P53 alteration in morphologically normal/benign breast luminal cells in BRCA carriers

Germline mutations in BRCA genes have been shown to predispose patients to breast cancer. Studies have suggested that p53 alteration is a necessary step in tumorigenesis in BRCA carriers. The authors' previous study showed p53 alteration in morphologically normal/benign breast luminal cells, the so-called breast p53 signature, in sporadic breast cancer patients. In this study, the authors analyzed p53 status in the breasts of 66 BRCA1/2 carriers: 29 patients with breast carcinoma (two with bilateral breast carcinomas) and 37 without. Seven of the 12 (58 percent) triple-negative breast carcinomas in BRCA carriers were positive for p53 alteration (immunohistochemical stain or sequencing, or both), the same frequency as in sporadic triple-negative breast carcinomas. Focal p53 positivity in adjacent normal/benign luminal cells was identified in four of the seven (57 percent) cases with p53-positive carcinomas but not in breasts with p53-negative carcinomas, indicating that p53 positivity in normal/benign breast luminal cells is not a random event. Furthermore, in BRCA carriers' prophylactic mastectomies, 12 of the 94 (12.77 percent) breasts had focal p53 positivity in normal/benign luminal cells, with two cases in bilateral breasts, compared with none in previously studied mammoplasty specimens. The authors concluded that their study suggests that germline BRCA gene mutations could result in genomic instability and an elevated gene mutation rate in breast luminal cells, predisposing BRCA carriers to develop p53-positive/triple-negative breast carcinomas.

Wang X, El-Halaby AA, Zhang H, et al. P53 alteration in morphologically normal/benign breast luminal cells in BRCA carriers with or without history of breast cancer. *Hum Pathol.* 2017;68:22–25.

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