Anatomic pathology selected abstracts

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HER2: a pan-cancer event highly enriched in AR-driven breast tumors

November 2018—Approximately one in five breast cancers is driven by amplification and overexpression of the HER2 receptor kinase, and HER2 enriched is one of four major transcriptional subtypes of breast cancer. The authors conducted a study to understand the genomics of *HER2* amplification independent of subtype, as well as the underlying drivers and biology of HER2-enriched (HER2E) tumors. They investigated published genomic data from 3,155 breast tumors and 5,391 nonbreast tumors. The authors found that *HER2* amplification is a distinct driver event seen in all breast cancer subtypes, rather than a subtype marker, with major characteristics restricted to amplification and overexpression of *HER2* and neighboring genes. The HER2E subtype has a distinctive transcriptional landscape independent of HER2A that reflects androgen-receptor signaling as a replacement for estrogen receptor-driven tumorigenesis. *HER2* amplification is also an event in 1.8 percent of nonbreast tumors. The authors concluded that their findings reveal therapeutic opportunities for combining anti-HER2 therapy with anti-androgen agents in breast cancer and highlight the potential for broader therapeutic use of HER2 inhibitors.

Daemen A, Manning G. HER2 is not a cancer subtype but rather a pan-cancer event and is highly enriched in AR-driven breast tumors. *Breast Cancer Res.* 2018;20:8. doi:10.1186/s13058-018-0933-y.

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Invasive mucinous carcinoma of the breast and response patterns after neoadjuvant chemotherapy

Neoadjuvant chemotherapy is often used to treat localized invasive breast cancer. Invasive mucinous carcinoma (IMC) is considered an indolent form of invasive breast cancer and is rarely treated with this form of chemotherapy. The authors assessed seven patients who had IMC treated with neoadjuvant chemotherapy and reported a characteristic, but not well recognized, pattern of pathological response. Three patients presented with locally advanced disease; three patients had tumors that were HER2/*neu* positive; and four patients had tumors with admixed mucinous and micropapillary features. Clinical and imaging assessment of response showed persistent and, in some cases, progressive disease, despite evidence of significant pathological response in these cases. Pathological assessment after neoadjuvant chemotherapy demonstrated marked reduction in tumor cellularity but persistent space-occupying mucin pools, showing acellular mucin in one case, less than one percent tumor cellularity in three cases, and five to 10 percent cellularity in three cases in both the treated breast and axillary lymph nodes. The authors concluded that persistent mass-forming low-cellular or acellular mucin pools can result in discordant clinical, imaging, and pathological findings in IMC treated with neoadjuvant chemotherapy.

Didonato R, Shapiro N, Koenigsberg T, et al. Invasive mucinous carcinoma of the breast and response patterns after neoadjuvant chemotherapy (NAC). *Histopathol.* 2018;72(6):965–973.

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Correlation of Oncotype DX DCIS results with histopathologic findings and clinical management decisions

Given the increased detection rates for ductal carcinoma in situ and the limited overall survival benefit from

adjuvant breast irradiation after breast-conserving surgery, there is interest in identifying subsets of patients who have low rates of ipsilateral breast tumor recurrence such that they might safely forgo radiation. The Oncotype DCIS score is a reverse transcription-PCR (RT-PCR)-based assay that was validated to predict which ductal carcinoma in situ (DCIS) cases are most likely to recur. The results may be used to help identify DCIS patients who might safely forgo radiation therapy after breast-conserving surgery. However, little information is available regarding how this test is being used in practice. The authors conducted a study to examine traditional histopathologic features used in predicting DCIS risk with Oncotype DCIS results and how these results affected clinical decision-making at the authors' academic institution. Histopathologic features and management decisions for 37 cases with Oncotype DCIS results over the past four years were collected. Necrosis, high nuclear grade, biopsy site change, estrogen receptor and progesterone receptor positivity of less than 90 percent on immunohistochemistry, and a Van Nuys prognostic index score of eight or greater were significant predictors of an intermediate–high recurrence score on multivariate regression analysis ($P < .02$). Low Oncotype DCIS scores and low nuclear grade were associated with lower rates of radiation therapy ($P < .008$). The authors considered seven (19 percent) cases with Oncotype DCIS results to be unexpected in relation to the histopathologic findings—that is, high nuclear grade with comedonecrosis and a low Oncotype score, or hormone receptor discrepancies. Overall, pathologic features correlate with Oncotype DCIS scores but unexpected results do occur, making individual recommendations challenging in some cases.

Lin CY, Mooney K, Choy W, et al. Will Oncotype DX DCIS testing guide therapy? A single-institution correlation of Oncotype DX DCIS results with histopathologic findings and clinical management decisions. *Mod Pathol.* 2018;31:562–568.

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Poorly differentiated clusters predict colon cancer recurrence: analysis of invasive-front prognostic markers

The authors conducted a study to compare common histologic markers at the invasive front of colon adenocarcinoma in terms of prognostic accuracy and interobserver agreement. They identified consecutive patients who underwent curative resection for stages I to III colon adenocarcinoma at a single institution from 2007 to 2014. They then analyzed poorly differentiated clusters (PDCs), tumor budding, perineural invasion, desmoplastic reaction, and Crohn-like lymphoid reaction at the invasive front, as well as the World Health Organization (WHO) grade of the entire tumor. The authors compared prognostic accuracies for recurrence-free survival and assessed interobserver agreement among three pathologists. The study cohort consisted of 851 patients. All of the histologic markers, except WHO grade, were significantly associated with recurrence-free survival (PDCs, tumor budding, perineural invasion, and desmoplastic reaction: $P < .001$; Crohn-like lymphoid reaction: $P = .021$). But PDCs (grade 1 [G1], n=581; G2, n=145; G3, n=125) showed the largest separation of three-year recurrence-free survival in the full cohort (G1, 94.1 percent; G3, 63.7 percent; hazard ratio [HR], 6.39; 95 percent confidence interval [CI], 4.11–9.95; $P < .001$) and in stage II patients (G1, 94 percent; G3, 67.3 percent; HR, 4.15; 95 percent CI, 1.96–8.82; $P < .001$) and stage III patients (G1, 89 percent; G3, 59.4 percent; HR, 4.50; 95 percent CI, 2.41–8.41; $P < .001$). PDCs had the highest prognostic accuracy for recurrence-free survival, with a concordance probability estimate of 0.642, and WHO grade had the lowest. Interobserver agreement was the highest for PDCs, with a weighted kappa of 0.824. The risk of recurrence over time peaked earlier for worse PDCs grade. The authors concluded that PDCs are the best invasive-front histologic marker in terms of prognostic accuracy and interobserver agreement. They may replace WHO grade as a prognostic indicator.

Konishi T, Shimada Y, Lee LH, et al. Poorly differentiated clusters predict colon cancer recurrence: an in-depth comparative analysis of invasive-front prognostic markers. *Am J Surg Pathol.* 2018;42(6):705–714.

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Distinguishing appendiceal goblet cell carcinoids and adenocarcinomas ex-goblet cell carcinoid from colorectal-type adenocarcinomas of appendix

The appendix gives rise to goblet cell carcinoids, which represent special carcinomas with distinct biological and histological features. Their genetic background and molecular relationship to colorectal adenocarcinoma is largely unknown. Therefore, the authors performed a next-generation sequencing analysis of 25 appendiceal carcinomas, including 11 goblet cell carcinoids, seven adenocarcinomas ex-goblet cell carcinoid, and seven primary colorectal-type adenocarcinomas, using a modified colorectal cancer-specific panel comprising 32 genes linked to colorectal and neuroendocrine tumorigenesis. The mutational profiles of these neoplasms were compared with those of conventional adenocarcinomas, mixed adenoneuroendocrine carcinomas, and neuroendocrine carcinomas of the colorectum. In addition, a large-scale pan-cancer sequencing panel covering 409 genes was applied to selected cases of goblet cell carcinoid/adenocarcinoma ex-goblet cell carcinoid (n=2, respectively). Mutations in colorectal cancer-related genes, such as *TP53, KRAS,* and *APC*, were rare to absent in goblet cell carcinoids and adenocarcinomas ex-goblet cell carcinoid but frequent in primary colorectal-type adenocarcinomas of the appendix. Additional large-scale sequencing of selected goblet cell carcinoids and adenocarcinomas ex-goblet cell carcinoid revealed mutations in Wnt-signaling–associated genes—*USP9X, NOTCH1, CTNNA1, CTNNB1,* and *TRRAP*. These data suggest that appendiceal goblet cell carcinoids and adenocarcinomas ex-goblet cell carcinoid constitute a morphomolecular entity that is histologically and genetically distinct from appendiceal colorectal-type adenocarcinomas and its colorectal counterparts. Altered Wnt-signaling–associated genes, apart from *APC*, may act as potential drivers of these neoplasms. The absence of *KRAS/NRAS* mutations might render some of these tumors eligible for anti-EGFR–directed therapy regimens.

Jesinghaus M, Konukiewitz B, Foersch S, et al. Appendiceal goblet cell carcinoids and adenocarcinomas ex-goblet cell carcinoid are genetically distinct from primary colorectal-type adenocarcinoma of the appendix. *Mod Pathol.* 2018;31:829–839.

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Differences between hereditary and sporadic diffuse gastric carcinoma

The authors conducted a study to identify histopathologic features unique to hereditary diffuse gastric cancer, or HDGC, by comparing it with its sporadic counterpart, SDGC. The specimens of 11 patients with confirmed *CDH1* mutation who were found to have HDGC in a prophylactic total gastrectomy were collected. The HDGC patients were a median age of 39 years (range, 24–57 years). All HDGC cases had intramucosal signet ring cell carcinoma. Twenty-three invasive tumor foci from seven patients with HDGC were available for ancillary studies, and the authors evaluated each focus separately. Twenty of 23 showed two distinct tumor cell populations, namely large signet ring cells and small signet ring cells. The large cells were located just beneath the surface epithelium and were positive for mucicarmine and pCEA, while the small cells were found in the deeper lamina propria and were mostly negative for mucicarmine and pCEA. A subset of small cells (six foci from two resected stomachs) showed poorly differentiated morphology with p16 positivity. All other tumor cells with well-differentiated signet ring cell morphology were negative for p16. In contrast, 18 of 20 SDGCs were positive for p16. In addition, all HDGCs were negative for CDX2, while 19 of 20 SDGCs were positive. The authors propose that there are three distinct tumor cell populations in HDGC: well-differentiated large cells, well-differentiated small cells, and poorly differentiated small cells, and that the latter group with aberrant p16 expression may represent a more aggressive phenotype. The absence of CDX2 in HDGC suggests that HDGC may develop along a carcinogenetic pathway different from that of SDGC.

Lee HE, Smyrk TC, Zhang L. Histologic and immunohistochemical differences between hereditary and sporadic diffuse gastric carcinoma. *Hum Pathol.* 2018;74:64–72.

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T1a and T1b carcinoma arising in mucinous cystic neoplasm of pancreas

Mucinous cystic neoplasm of the pancreas is a precursor lesion of pancreatic ductal adenocarcinoma. The five-year disease-specific survival rate for noninvasive mucinous cystic neoplasms (MCNs) was 100 percent, and it was 20 to 60 percent for those with pancreatic ductal adenocarcinoma arising in an MCN. However, the significance of T1a (0.5 cm or less) and T1b (0.5–1.0 cm) carcinoma arising in MCN, as defined by the eighth American Joint Committee on Cancer staging system for pancreatic cancer, is unclear. The authors conducted a study in which they examined three cases of MCN with T1a or T1b carcinoma and compared their clinicopathologic characteristics and survival to 46 cases of MCN with low-grade dysplasia (MCN-LGD), seven cases of MCN with high-grade dysplasia (MCN-HGD), and seven cases of MCN with advanced invasive carcinoma (T2 or higher T stage). The tumors from all three cases were submitted in their entirety in 123, 296, and 200 blocks, respectively. All three patients were alive with no recurrence during the follow-up periods of 20, 113.8, and 137.2 months, respectively. Similarly, none of the patients who had MCN with low-grade or high-grade dysplasia had recurrence or died of disease. In contrast, five of seven patients who had MCN with advanced invasive carcinoma had recurrence and later died of disease, with a median survival rate of 22.9 months ($P<.001$). The study showed that MCN with T1a and T1b carcinoma had an excellent prognosis that was similar to MCNs with low-grade or high-grade dysplasia after complete tumor sampling for histologic examination. The results, along with previous studies, suggest that close follow-up, rather than aggressive systemic therapy, may be a better approach for these patients.

Hui L, Rashid A, Foo WC, et al. Significance of T1a and T1b carcinoma arising in mucinous cystic neoplasm of pancreas. *Am J Surg Pathol.* 2018;42(5):578–586.

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Genomic profiling of metaplastic breast carcinomas

Metaplastic breast carcinomas comprise a histologically heterogenous group of tumors. Although most are triple (estrogen/progesterone receptor, HER2) negative, these rare tumors are clinicopathologically distinct from other triple-negative carcinomas and may be aggressive, with worse chemotherapy responses. On the other hand, metaplastic carcinomas are histologically diverse, which is reflected in gene-expression differences among subtypes. Whether metaplastic carcinomas are genetically distinct from other triple-negative cancers and whether genetic differences underlie histologic subtypes remains poorly understood. The authors conducted a study in which they sequenced 408 cancer-related genes in 28 metaplastic carcinomas, including chondroid matrix-producing carcinomas (n = 10), spindle cell carcinomas (n = 5), and carcinomas with squamous (n = 5), mixed spindle/squamous (n = 5), and mixed metaplastic (n = 3) differentiation. Metaplastic carcinomas were highly enriched for *PIK3CA/PIK3R1* (61 percent) and Ras-MAP kinase (25 percent) pathway aberrations compared with other triple-negative carcinomas (The Cancer Genome Atlas [TCGA] dataset, 14 percent, $P<.001$, and seven percent, $P = .005$, respectively) and harbored a high frequency of *TP53* (64 percent) and *TERT* promoter (25 percent) mutations, but this varied among subtypes. Chondroid-matrix–producing carcinomas lacked PI 3-kinase and Ras-MAP kinase aberrations and *TERT* promoter mutations, compared to 100 percent, 39 percent, and 39 percent of non-matrix–producing tumors, respectively. *TERT* promoter mutations were enriched (47 percent) in spindle cell carcinomas and tumors with squamous or spindle/squamous differentiation. Spindle cell carcinomas lacked *TP53* mutations, in contrast to other subtypes (78 percent, $P = .003$). Separate analysis of paired ductal carcinoma in situ and metaplastic carcinoma revealed shared clonality in all cases (n = 8). Activating PI 3-kinase and Ras pathway mutations were early events. Inactivating mutations in tumor suppressors, including *RB1, CDKN2A*, and *TP53*, were associated with invasion in individual cases. Metaplastic components of two tumors showed genetic progression from separately sequenced paired invasive ductal carcinoma. The findings suggest that metaplastic carcinomas are genetically distinct from other triple-negative breast cancers and highlight genetic heterogeneity that broadly correlates with histologic subtype. Heterologous elements progress from associated ductal carcinoma.

Krings G, Chen YY. Genomic profiling of metaplastic breast carcinomas reveals genetic heterogeneity and relationship to ductal carcinoma [published online ahead of print June 26, 2018]. *Mod Pathol.*

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