Anatomic Pathology Abstracts, 7/16

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Evaluating perineural invasion as a prognostic factor in colorectal cancer

Perineural invasion is a possible route for metastatic spread in various cancer types, including colorectal cancer. It is linked to poor prognosis, but systematic analyses are lacking. The authors conducted a study in which they systematically reviewed the frequency and impact of perineural invasion in colorectal cancer. They performed a literature search using the PubMed database from inception to Jan. 1, 2014. Data were analyzed using Review Manager 5.3 software. A quality assessment was performed on the basis of modified REMARK (reporting recommendations for tumor marker prognostic studies) criteria. Endpoints were local recurrence, five-year disease-free survival, five-year cancer-specific survival, and five-year overall survival. Meta-analysis was performed in terms of risk ratios and hazard ratios with a 95 percent confidence interval. Fifty-eight articles focusing on 22,900 patients were included in the meta-analysis. Perineural invasion was present in 18.2 percent of tumors. It was correlated with increased local recurrence (risk ratio [RR], 3.22, 95 percent confidence interval [CI], 2.33–4.44) and decreased five-year disease-free survival (RR, 2.35, 95 percent CI, 1.66–3.31), five-year cancer-specific survival (RR, 3.6, 95 percent CI, 2.76–4.72), and five-year overall survival (RR, 2.09, 95 percent CI, 1.68–2.61). In multivariate analysis, perineural invasion remained an independent prognostic factor for five-year disease free, cancer-specific, and overall survival (hazard ratio [HR], 2.35, 95 percent CI, 1.97–3.08; HR, 1.91, 95 percent CI, 1.50–2.42; and HR, 1.85, 95 percent CI, 1.63–2.12, respectively). The authors confirmed that perineural invasion has a strong impact on local recurrence and survival in colorectal cancer. The prognostic value of perineural invasion is similar to that of such well-established prognostic factors as depth of invasion, differentiation grade, lymph node metastases, and lymphatic and extramural vascular invasion. Therefore, perineural invasion should be one of the factors in the standardized reporting of colorectal cancer and might be considered a high-risk feature.

Knijn N, Mogk SC, Teerenstra S, et al. Perineural invasion is a strong prognostic factor in colorectal cancer: a systematic review. *Am J Surg Pathol.* 2016;40:103–112.

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A morphological analysis of unusual features in apoplectic leiomyomas

Leiomyomas with apoplectic change related to progestational effect have not received much attention in the medical literature. In the authors' experience, they frequently cause diagnostic difficulty. The authors reviewed 100 apoplectic leiomyomas to characterize their broad histologic spectrum. The tumors occurred over a wide age range (mean, 41 years), and although two patients were pregnant, in the vast majority, the apoplectic changes were likely due to progestins administered to help control symptoms related to the leiomyomas. The tumors were multiple in 77 percent of patients, averaged 6 cm, and frequently showed gross features of hemorrhage, necrosis, cyst formation, softening, or color that differed from the usual banal leiomyoma. Microscopic examination typically revealed multiple stellate to ovoid zones with a hypercellular periphery and central hemorrhage, necrosis, or hyalinization. The hypercellular areas were often dominated by cells with eosinophilic cytoplasm, pyknotic nuclei, and increased mitoses (up to 14 per 10 high-power fields), but most tumors showed no appreciable cytologic atypia in these regions. Edema was noted in 95 percent; a hyalinized or myxoid matrix, or both, in 92 percent; and cyst formation in 42 percent. Because of these unusual features, difficulty often arose in determining whether the tumors were benign, malignant, or of uncertain malignant potential. Recognition of their wide morphologic spectrum will enable classification of these tumors in the benign category and help prevent undue patient anxiety and potentially unnecessary aggressive management.

Bennett JA, Lamb C, Young RH. Apoplectic leiomyomas: a morphologic analysis of 100 cases highlighting unusual features. *Am J Surg Pathol.* 2016;40:563–568.

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Diagnosis of frozen section to guide resection strategy for lung adenocarcinoma

The authors investigated the accuracy of intraoperative frozen section diagnosis for predicting the final pathology of peripheral small-sized lung adenocarcinoma and evaluated its usefulness in sublobar resection. They reviewed the records of 803 patients with clinical stage one peripheral lung adenocarcinoma who underwent sublobar resection for frozen section diagnosis to guide surgical strategy. The surgical extension was mainly based on frozen section, and the frozen sections were stratified into atypical adenomatous hyperplasia, adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma. The authors evaluated the diagnostic accuracy of frozen section, reasons for the discrepancy between frozen section and final pathology, and clinical influence of the frozen section errors. To assess the survival of patients with different subtypes after surgery, 301 patients were identified for prognosis evaluation. The total concordance rate between frozen section and final pathology was 84.4 percent. When atypical adenomatous hyperplasia, AIS, and MIA were classified together as a low-risk group, the concordance rate was 95.9 percent. Most discrepant cases were the result of underestimation of AIS and MIA. The diagnostic accuracy of frozen section for tumors of 1 cm or less and larger than 1 cm in diameter was 79.6 percent and 90.8 percent, respectively ($P<.01$). The frozen section errors had significant clinical impact on 0.9 percent of the 803 patients due to insufficient resection. The five-year recurrence-free survival rate was significantly better for the patients with AIS/MIA than for patients with invasive adenocarcinoma. The authors concluded that frozen pathology has a high concordance rate with final pathology. Precise diagnosis by intraoperative frozen section is an effective method to guide resection strategy for peripheral small-sized lung adenocarcinoma.

Liu S, Wang R, Zhang Y, et al. Precise diagnosis of intraoperative frozen section is an effective method to guide resection strategy for peripheral small-sized lung adenocarcinoma. *J Clin Oncol.* 2016;34:307–313.

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A finding of ovarian carcinoma histotype based on limited sampling

Growing insights into the biological features and molecular underpinnings of ovarian cancer have prompted a shift toward histotype-specific treatments and clinical trials. As a result, the preoperative diagnosis of ovarian carcinomas based on limited tissue sampling is rapidly gaining importance. However, data in the literature about the accuracy of ovarian carcinoma histotype-specific diagnosis based on small tissue samples remain very limited. The authors described a prospective series of 30 ovarian tumors diagnosed using cytology, frozen section, core needle biopsy, and immunohistochemistry (p53, p16, WT1, HNF-1β, ARID1A, TFF3, vimentin, and PR). The accuracy of histotype diagnosis using each of these modalities was 52 percent, 81 percent, 85 percent, and 84 percent, respectively, using the final pathology report as the reference standard. The accuracy of histotype diagnosis using the calculator for ovarian subtype prediction, which evaluates immunohistochemical stains independent of histopathologic features, was 85 percent. Diagnostic accuracy varied across histotype and was lowest (54 percent) for endometrioid carcinoma across all diagnostic modalities. High-grade serous carcinomas were the most overdiagnosed on core needle biopsy, accounting for 45 percent of misdiagnoses, and clear cell carcinomas were the most overdiagnosed on frozen section, accounting for 36 percent of misdiagnoses. On core needle biopsy, two of 30 (seven percent) cases had a higher grade lesion missed due to sampling limitations. Recognizing the challenges of diagnosing ovarian tumors based on limited tissue sampling can help improve diagnostic accuracy as the medical field moves forward with histotype-specific therapeutic strategies.

Hoang LN, Zachara S, Soma A, et al. Diagnosis of ovarian carcinoma histotype based on limited sampling: a prospective study comparing cytology, frozen section, and core biopsies to full pathologic examination. *Int J Gynecol Pathol.* 2015;34:517–527.

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Lobular carcinoma in situ: clinicopathologic features and breast cancer risk

The increased breast cancer risk conferred by a diagnosis of lobular carcinoma in situ is poorly understood. The authors reviewed their longitudinal experience with lobular carcinoma in situ (LCIS) over 29 years to evaluate factors associated with breast cancer risk. Patients participating in surveillance after an LCIS diagnosis were observed in a prospectively maintained database. Comparisons were made among women choosing surveillance, with or without chemoprevention, and those undergoing bilateral prophylactic mastectomies between 1980 and 2009. The authors identified 1,060 patients with LCIS without concurrent breast cancer. The median age at LCIS diagnosis was 50 years (range, 27–83 years). Fifty-six (five percent) patients underwent bilateral prophylactic mastectomy; 1,004 chose surveillance with (n=173) or without (n=831) chemoprevention. At a median follow-up of 81 months (range, 6–368 months), 150 patients developed 168 breast cancers (63 percent ipsilateral, 25 percent contralateral, 12 percent bilateral), with no dominant histology (ductal carcinoma in situ, 35 percent; infiltrating ductal carcinoma, 29 percent; infiltrating lobular carcinoma, 27 percent; other, nine percent). Breast cancer incidence was significantly reduced in women receiving chemoprevention (10-year cumulative risk: seven percent with chemoprevention and 21 percent with no chemoprevention, P<.001). In multivariate analysis, chemoprevention was the only clinical factor associated with breast cancer risk (hazard ratio, 0.27; 95 percent confidence interval, 0.15–0.50). In a subgroup nested case-control analysis, volume of disease, which was defined as the ratio of slides with LCIS to the total number of slides reviewed, was also associated with breast cancer development (P=.008). The authors observed a two percent annual incidence of breast cancer among women with LCIS. Common clinical factors used for risk prediction, including age and family history, were not associated with breast cancer risk. The lower breast cancer incidence in women opting for chemoprevention highlights the potential for risk reduction in this population.

King TA, Pilewskie M, Muhsen S, et al. Lobular carcinoma in situ: a 29-year longitudinal experience evaluating clinicopathologic features and breast cancer risk. *J Clin Oncol.* 2015;33:3945–3952.

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Prospective validation of a 21-gene expression assay in breast cancer

Prior studies with a prospective-retrospective design including archival tumor samples have shown that gene-expression assays provide clinically useful prognostic information. However, a prospective study in a uniformly treated population provides the highest level of evidence supporting the clinical validity and usefulness of a biomarker. The authors performed a prospective trial involving women with hormone receptor-positive, HER2-negative, axillary node-negative breast cancer with tumors of 1.1 to 5.0 cm in greatest dimension (or 0.6 to 1.0 cm in greatest dimension and intermediate or high tumor grade) who met established guidelines for the consideration of adjuvant chemotherapy on the basis of clinicopathologic features. A reverse transcriptase polymerase chain reaction assay of 21 genes was performed on the paraffin-embedded tumor tissue, and the results were used to calculate the risk of breast cancer recurrence. Patients were assigned to receive endocrine therapy without chemotherapy if they had a recurrence score of zero to 10, indicating a very low risk of recurrence using a scale of zero to 100 (with higher scores indicating a greater risk of recurrence). Of the 10,253 eligible women enrolled, 1,626 (15.9 percent) who had a recurrence score of zero to 10 were assigned to receive endocrine therapy alone without chemotherapy. At five years, the rate of invasive disease-free survival in this patient population was 93.8 percent (95 percent confidence interval [CI], 92.4–94.9), the rate of freedom from recurrence of breast cancer at a distant site was 99.3 percent (95 percent CI, 98.7–99.6), the rate of freedom from recurrence of breast cancer at a distant or local-regional site was 98.7 percent (95 percent CI, 97.9–99.2), and the rate of overall survival was 98 percent (95 percent CI, 97.1–98.6). Among patients with hormone receptor-positive, HER2-negative, axillary node-negative breast cancer who met established guidelines for the recommendation of adjuvant chemotherapy on the basis of clinicopathologic features, those with tumors that had a favorable gene-expression profile had very low rates of recurrence at five years after receiving endocrine therapy alone.

Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med.* 2015;373:2005–2014.

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DICER1 hotspot mutations in ovarian and testicular sex cord-stromal tumors

Sertoli-Leydig cell tumors are characterized by the presence of somatic DICER1 hotspot mutations. The authors conducted a study to define the association between DICER1 hotspot mutations and morphologic subtypes of ovarian Sertoli-Leydig cell tumors. They also aimed to assess whether DICER1 hotspot mutations occur in other ovarian sex cord-stromal tumors, testicular sex cord-stromal tumors, or other female genital tract tumors with rhabdomyosarcomatous differentiation. The authors subjected a series of ovarian Sertoli-Leydig cell tumors (n=32), Sertoli cell tumors (n=5) and gynandroblastomas (n=5), testicular sex cord-stromal tumors (n=15), and a diverse group of female genital tract tumors with rhabdomyosarcomatous morphology (n=10) to DICER1 hotspot mutation analysis using Sanger sequencing. They also tested two gynandroblastomas for the presence of FOXL2 hotspot mutations (p.C134W; c.402C>G). Twenty of 32 (63 percent) Sertoli-Leydig cell tumors harbored a DICER1 hotspot mutation, of which 80 percent had the p.E1705K mutation. No association was found between DICER1 mutation status and heterologous or retiform differentiation in Sertoli-Leydig cell tumors. DICER1 mutations were found at similar frequencies in gynandroblastoma (two of five; 40 percent) and ovarian Sertoli cell tumors (five of eight; 63 percent; P>.1), and all mutated tumors harbored a p.E1705K mutation. DICER1 hotspot mutations were also identified in a single cervical rhabdomyosarcoma and the rhabdomyosarcomatous component of a uterine carcinosarcoma. No DICER1 mutations were detected in testicular sex cord-stromal tumors. Two DICER1 wild-type gynandroblastomas harbored a p.C134W FOXL2 hotspot mutation in both tumor components. The authors

confirmed that DICER1 hotspot mutations occur in more than half of ovarian Sertoli-Leydig cell tumors and are unrelated to tumor differentiation. They also widened the spectrum of ovarian sex cord-stromal tumors with sertoliform differentiation, in which DICER1 mutations are known to occur, to include Sertoli cell tumors and gynandroblastomas. These results suggest that DICER1 mutations may not play a role in testicular sex cord-stromal tumorigenesis.

Conlon N, Schultheis AM, Piscuoglio S, et al. A survey of DICER1 hotspot mutations in ovarian and testicular sex cord-stromal tumors. *Mod Pathol.* 2015;28:1603–1612.

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