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Editors: Michael Cibull, MD, professor emeritus, University of Kentucky College of Medicine, Lexington; Rouzan Karabakhtsian, MD, PhD, associate professor of pathology, Albert Einstein College of Medicine, Montefiore Medical Center, 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.

Fallopian tube involvement in uterine serous carcinomas

The authors investigated the frequency and histopathologic and immunohistochemical characteristics of tubal involvement in uterine serous carcinoma to clarify the relationship between serous tubal intraepithelial carcinoma (STIC) and uterine serous carcinoma. They prospectively collected and reviewed, for the presence of tubal involvement, cases of the latter with complete tubal examination. The authors performed immunohistochemical analysis for p53 and WT1 on the endometrial and tubal tumor in cases with tubal involvement. Of 161 uterine serous carcinoma (USC) cases (pure USC or a component of a mixed carcinoma or a carcinosarcoma), 32 (20 percent) showed tubal involvement (unilateral, n=19; bilateral, n=13). The uterine tumors in cases with tubal involvement showed a trend toward increased likelihood of deep myometrial and lymphovascular invasion compared with those without tubal involvement. The tubal fimbriae were involved in 15 of 32 cases. Tubal involvement was mucosal in 30 of 32 cases, mural in 14 of 32, serosal in five of 32, and invasive in 22 of 32. Lymphovascular invasion was found in the tube in 13 of 32. STIC-like features were seen in 17 of 32 cases (seven as the only pattern of involvement, nine with associated invasive carcinoma, and five with lymphovascular invasion). Immunostaining showed complete concordance of p53 and WT1 between the endometrial and tubal tumors in 26 of 32 cases, the majority being WT1 negative or only focally positive (19 of 26) and all exhibiting mutation-type p53 staining. On the basis of the histologic and immunohistochemical features, the tubal tumor was considered to represent metastatic USC in 26 of 32 cases, most likely metastatic USC in two of 32 cases, an independent tubal primary tumor in three of 32 cases, and uncertain origin in one case. STIC-like lesions were considered to represent metastatic USC in 12 of 17 cases, most likely metastatic USC in two of 17 cases, an independent tubal primary in two of 17 cases, and uncertain origin in one case. Tubal involvement, including STIC-like lesions, is seen in one-fifth of USC when the tubes are examined in their entirety. The tubal involvement is metastatic in the vast majority of cases. In most cases, immunohistochemical studies assist in confirming the metastatic nature of the tubal disease. Consideration should be given to completely examining the fallopian tubes in apparent stage I or II USCs, as this will result in upstaging in a significant minority of cases.

Kommoss F, Faruqi A, Gilks CB, et al. Uterine serous carcinomas frequently metastasize to the fallopian tube and can mimic serous tubal intraepithelial carcinoma. *Am J Surg Pathol.* 2017;41:161–170.

Correspondence: Dr. Friedrich Kommoss at fkommoss@mac.com

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Evaluation of FFPE material for RT-PCR in soft tissue tumor diagnosis

Molecular genetic analysis is a routine ancillary diagnostic modality of the histopathological diagnosis of soft tissue neoplasms, many of which harbor characteristic gene fusions detectable by RT-PCR. Because the final diagnosis often depends on the molecular result, it is important to obtain the optimal yield of patient RNA. The authors assessed the most reliable method of providing formalin-fixed, paraffin-embedded material for optimal RNA yield by comparing three consecutive periods in which different preparations—5 × 10-µm scrolls, 5 × 5-µm sections, and 1 × 10-µm sections—were used for RNA extraction for RT-PCR, with its technical success rate. For 2011, 2012, and 2013, RT-PCR technical failure rates were 13.4, 4.4, and 7.9 percent, respectively. The percentage of failed referral cases was 71.4, 85.7, and 31.3 percent, respectively, and the proportion of core biopsy to excision specimens was 3:15, 2:5, and 13:3, respectively. The authors concluded that the study shows that the effectiveness of RNA extraction and purification depends on specimen type and tissue-sectioning strategy. The failure rate has improved over recent years, particularly for large specimens because large numbers of thick 10-µm scrolls can saturate RNA extraction columns. In contrast, recent technical failures are more frequent in core biopsies, where 1 × 10-µm sections are insufficient for adequate RNA extraction. While previous technical failures occurred primarily in referred cases, this appears to no longer be the case. This is due to improved fixation and processing of specimens in external surgical pathology departments because of widespread recognition of the importance of molecular diagnostics as a vital part of the patient pathway.

Thway K, Wren D, Lee J, et al. Evaluation of the optimal provision of formalin-fixed, paraffin-embedded material for reverse transcription-PCR in soft-tissue tumour diagnosis. *J Clin Pathol.* 2017;70:20–24.

Correspondence: Dr. Khin Thway at khin.thway@rmh.nhs.uk

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Upgrade rates of high-risk breast lesions diagnosed on core needle biopsy

Controversy surrounds the optimal management of high-risk breast lesions detected by mammogram and yielding atypical ductal hyperplasia, flat epithelial atypia, atypical lobular hyperplasia, lobular carcinoma in situ, and radial scar without atypia on core needle biopsy. Therefore, the authors conducted a single-institution retrospective review of 5,750 core needle biopsy cases seen during 14.5 years, including 249 (4.3 percent), 72 (1.3 percent), 50 (0.9 percent), 37 (0.6 percent), and 54 (0.9 percent) cases of atypical ductal hyperplasia, flat epithelial atypia, atypical lobular hyperplasia, lobular carcinoma in situ, and radial scar without atypia, respectively. They recorded patient age, radiologic characteristics, needle gauge, and excision diagnoses. Of 462 high-risk cases analyzed, 333 (72 percent) underwent excision. The upgrade rate to ductal carcinoma in situ, pleomorphic carcinoma in situ, or invasive mammary carcinoma was 18 percent for atypical ductal hyperplasia, 11 percent for flat epithelial atypia, nine percent for atypical lobular hyperplasia, 28 percent for lobular carcinoma in situ, and 16 percent for radial scar. Carcinoma diagnosed on excision was more likely to be in situ than invasive, and if invasive, more likely to be low grade than high grade. Overall, cases that were benign, instead of high risk or carcinoma, on excision were less likely to have residual calcifications after biopsy (17 versus 27 percent; $P = .013$) and more likely to have a smaller mass size (less than 1 cm; 82 versus 50 percent; $P = .001$). On subgroup analysis, atypical ductal hyperplasia cases that were benign, instead of high risk or carcinoma, on excision were more likely to have smaller mass size (less than 1 cm; $P = .025$). Lobular neoplasia diagnosed incidentally on core needle biopsy was less likely to upgrade on excision (5 versus 39 percent; $P = .002$). The authors also performed a comprehensive literature review, identifying 116 studies reporting high-risk lesion upgrade rates. Their upgrade rates were similar to those of more recent larger studies. The authors concluded that careful radiological-pathological correlation is needed to identify high-risk lesion subgroups that may not need excision.

Mooney KL, Bassett LW, Apple SK. Upgrade rates of high-risk breast lesions diagnosed on core needle biopsy: a single-institution experience and literature review. *Mod Pathol.* 2016;29:1471–1484.

Correspondence: Dr. S. K. Apple at sapple@mednet.ucla.edu

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Genetic events that play a role in progression of adenoid cystic carcinoma of the breast

Adenoid cystic carcinoma of the breast is a rare histological type of triple-negative breast cancer with an indolent clinical behavior, often driven by the *MYB-NFIB* fusion gene. The authors conducted a study to define the repertoire of somatic genetic alterations in two adenoid cystic carcinomas associated with high-grade triple-negative breast cancer. The components of each case were subjected to copy number profiling and massively parallel sequencing targeting all exons and selected regulatory and intronic regions of 488 genes. Reverse transcription PCR and FISH were used to investigate the presence of the *MYB-NFIB* translocation. The *MYB-NFIB* fusion gene was detected in adenoid cystic carcinomas and their associated high-grade triple-negative breast cancer components. Although the distinct components of both cases displayed similar patterns of gene copy number alterations, massively parallel sequencing analysis revealed intratumor genetic heterogeneity. In the first case, progression from the trabecular adenoid cystic carcinoma to the high-grade triple-negative breast cancer was found to involve clonal shifts with enrichment of mutations affecting *EP300, NOTCH1, ERBB2,* and *FGFR1* in the high-grade triple-negative breast cancer. In the second case, a clonal *KMT2C* mutation was present in the cribriform adenoid cystic carcinoma, solid adenoid cystic carcinoma, and high-grade triple-negative breast cancer components, whereas a mutation affecting *MYB* was present only in the solid and high-grade triple-negative breast cancer areas, and an additional three mutations targeting *STAG2, KDM6A,* and *CDK12* were restricted to the high-grade triple-negative breast cancer. The authors concluded that adenoid cystic carcinomas of the breast with high-grade transformation are underpinned by the *MYB-NFIB* fusion gene and, similar to other forms of cancer, may be constituted by a mosaic of cancer cell clones at diagnosis. The progression from adenoid cystic carcinoma to high-grade triple-negative breast cancer of no special type may involve the selection of neoplastic clones or the acquisition of additional genetic alterations, or both.

Fusco N, Geyer FC, De Filippo MR, et al. Genetic events in the progression of adenoid cystic carcinoma of the breast to high-grade triple-negative breast cancer. *Mod Pathol.* 2016;29:1292–1305.

Correspondence: Dr. B. Weigelt at weigeltb@mskcc.org

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Harmonized PD-L1 IHC for pulmonary adenocarcinoma and squamous cell carcinoma

Immunohistochemistry of the programmed death-ligand 1 protein may be predictive for anti-programmed death 1 and anti-programmed death-ligand 1 immunotherapy in pulmonary adenocarcinoma and clinically unselected cohorts of non-small cell lung cancer. Several programmed death-ligand 1 (PD-L1) immunohistochemistry assays with custom reagents and scoring criteria were developed in parallel. Biomarker testing and clinical decision-making would profit from harmonized PD-L1 diagnostics, according to the authors. To assess interobserver concordance and PD-L1 immunohistochemistry staining patterns, the authors conducted a study in which 15 pulmonary carcinoma resection specimens (adenocarcinoma, n=11; squamous cell carcinoma, n=4) were centrally stained with the assays 28-8, 22C3, SP142, and SP263 according to clinical trial protocols. Nine pathologists independently evaluated the slides. Proportions of PD-L1–positive carcinoma cells and immune cells were scored according to a six-step system that integrated the criteria employed by the four PD-L1 immunohistochemistry assays. Proportion scoring of PD-L1–positive carcinoma cells showed moderate interobserver concordance coefficients for the six-step scoring system (Light's kappa, 0.47–0.50). The integrated dichotomous proportion cutoffs (≥1, ≥5, ≥10, ≥50 percent) showed good concordance coefficients ($\kappa = 0.6–0.8$). Proportion scoring of PD-L1–positive immune cells yielded low interobserver concordance coefficients for the six-step score ($\kappa < 0.2$) and the

dichotomous cutoffs (κ = 0.12–0.25). The assays 28-8 and 22C3 stained similar proportions of carcinoma cells in 12 of 15 cases. SP142 stained fewer carcinoma cells compared to 28-8, 22C3, and SP263 in four cases, whereas SP263 stained more carcinoma cells in nine cases. SP142 and SP263 stained immune cells more intensely. The data indicate that carcinoma cells can be reproducibly scored in PD-L1 immunohistochemistry for pulmonary adenocarcinoma and squamous cell carcinoma. No differences in interobserver concordance were noticed among the tested assays. The scoring of immune cells yielded low concordance rates and might require specific standardization. The four tested PD-L1 assays did not show comparable staining patterns in all cases. Therefore, studies that correlate staining patterns and response to immunotherapy are required to test the significance of the observed differences.

Scheel AH, Dietel M, Heukamp LC, et al. Harmonized PD-L1 immunohistochemistry for pulmonary squamous-cell and adenocarcinomas. *Mod Pathol.* 2016;29:1165–1172.

Correspondence: Dr. A. H. Scheel at andreas.scheel@uk-koeln.de