Anatomic Pathology Selected Abstracts, 11/14

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Final trial report of sentinel-node biopsy versus nodal observation in melanoma

Sentinel-node biopsy, a minimally invasive procedure for regional melanoma staging, was evaluated in a phase three trial. The authors evaluated outcomes in 2,001 patients with primary cutaneous melanomas who were randomly assigned to undergo wide excision and nodal observation, with lymphadenectomy for nodal relapse (observational group), or wide excision and sentinel-node biopsy, with immediate lymphadenectomy for nodal metastases detected on biopsy (biopsy group). They found no significant treatment-related difference in the 10-year melanoma-specific survival rate in the overall study population (20.8 percent with nodal metastases and 79.2 percent without such metastases). Mean 10-year disease-free survival rates were significantly improved in the biopsy group compared with the observation group among patients with intermediate-thickness melanomas, defined as 1.2 to 3.5 mm (71.3±1.8 percent versus 64.7±2.3 percent; hazard ratio for recurrence or metastasis, 0.76; P=0.01), and those with thick melanomas, defined as greater than 3.5 mm (50.7±4.0 percent versus 40.5±4.7 percent; hazard ratio, 0.70; P=0.03). Among patients with intermediate-thickness melanomas, the 10-year melanoma-specific survival rate was 62.1±4.8 percent among those with metastasis versus 85.1±1.5 percent for those without metastasis (hazard ratio for death from melanoma, 3.09; P<0.001). Among patients with thick melanomas, the respective rates were 48.0±7.0 percent and 64.6±4.9 percent (hazard ratio, 1.75; P=0.03). Biopsy-based management improved the 10-year rate of distant disease-free survival (hazard ratio for distant metastasis, 0.62; P=0.02) and the 10-year rate of melanoma-specific survival (hazard ratio for death from melanoma, 0.56; P=0.006) for patients with intermediate-thickness melanomas and nodal metastases. Accelerated-failure-time latent-subgroup analysis was performed to account for the fact that nodal status was initially known only in the biopsy group, and a significant treatment benefit persisted. The authors concluded that biopsy-based staging of intermediate-thickness or thick primary melanomas provides important prognostic information and identifies patients with nodal metastases who may benefit from immediate complete lymphadenectomy. Biopsy-based management prolongs disease-free survival for all patients and prolongs distant disease-free survival and melanoma-specific survival for patients with nodal metastases from intermediate-thickness melanomas.

Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370:599–609.

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Surgical pathology report defects: a CAP Q-Probes study of 73 institutions

The rate of surgical pathology report defects is an indicator of quality and affects clinician satisfaction. The College of American Pathologists conducted a study to establish benchmarks for defect rates and defect fractions through a large, multi-institutional prospective application of standard taxonomy. Participants in this 2011 CAP Q-Probes study prospectively reviewed all surgical pathology reports that underwent changes to correct defects and reported details regarding the defects. The 73 institutions that submitted data for the study reported 1,688 report defects discovered in 360,218 accessioned cases, for an aggregate defect rate of 4.7 per 1,000 cases. The median institutional defect rate was 5.7 per 1,000 (10th to 90th percentile range, 13.5–0.9). Defect rates were higher in

institutions with a pathology training program (8.5 versus 5.0 per 1,000; P=0.01) and when a set percentage of cases were reviewed after sign-out (median, 6.7 versus 3.8 per 1,000; P=0.10). Of the defects, 14.6 percent were misinterpretations, 13.3 percent misidentifications, 13.7 percent specimen defects, and 58.4 percent other report defects. Overall, defects were most often detected by pathologists (47.4 percent), followed by clinicians (22 percent). Misinterpretations and specimen defects were most often detected by pathologists (73.5 percent and 82.7 percent, respectively; P<0.001), while misidentifications were most often discovered by clinicians (44.6 percent; P<0.001). Misidentification rates were lower when all malignancies were reviewed by a second pathologist before sign-out (zero versus 0.6 per 1,000; P<0.001), and specimen defect rates were lower when intradepartmental review of difficult cases was conducted after sign-out (zero versus 0.4 per 1,000; P=0.02). The authors concluded that this study provides benchmarking data on report defects and defect fractions using standardized taxonomy.

Volmar KE, Idowu MO, Hunt JL, et al. Surgical pathology report defects: a College of American Pathologists Q-Probes study of 73 institutions. *Arch Pathol Lab Med.* 2014;138(5):602–612.

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Thyroid transcription factor-1 immunoreactivity relative to endometrioid adenocarcinoma of the uterine corpus

Thyroid transcription factor-1 is expressed in a small percentage of primary gynecological adenocarcinomas. Following the finding of TTF-1 positivity in a number of endometrioid adenocarcinomas of the uterine corpus that behaved aggressively, the authors performed immunohistochemical staining of a large series of endometrial adenocarcinomas of various types to investigate whether its expression is of prognostic significance. TTF-1 was performed on tissue microarrays containing 102 low-grade (grade one or two) endometrioid adenocarcinomas, 101 grade three endometrioid adenocarcinomas, 89 serous adenocarcinomas, and 29 clear cell carcinomas. All categories of endometrial adenocarcinoma exhibited TTF-1 staining in a small subset of cases (two percent low-grade endometrioid, 11 percent grade three endometrioid, nine percent serous, and seven percent clear cell). TTF-1 was less frequently expressed in low-grade endometrioid adenocarcinomas compared with other subtypes. Endometrioid adenocarcinomas that expressed TTF-1 had a statistically significantly worse prognosis with poorer disease-specific survival, and this was also statistically significant in the group of low-grade endometrioid adenocarcinomas. The authors concluded that TTF-1 is expressed in a small but not insignificant proportion of endometrial adenocarcinomas. TTF-1 positivity in low-grade endometrioid adenocarcinomas is an indicator of poorer prognosis.

Ervine A, Leung S, Gilks CB, et al. Thyroid transcription factor-1 (TTF-1) immunoreactivity is an adverse prognostic factor in endometrioid adenocarcinoma of the uterine corpus. *Histopathol.* 2014;64(6):840–846.

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Frequent expression of KIT in endometrial stromal sarcoma with YWHAE genetic rearrangement

Endometrial stromal sarcomas with the YWHAE-NUTM2A/B genetic fusion characteristically contain high-grade round to epithelioid cell component that is strongly and diffusely cyclin D1-positive and may show an associated low-grade fibroblastic/myxoid cell component. The sarcomas are clinically more aggressive than endometrial stromal sarcomas with the JAZF1-SUZ12 genetic fusion and frequently demonstrate extrauterine extension at initial clinical presentation. In this setting, the tumor may be misdiagnosed as gastrointestinal stromal tumor. The authors conducted a study in which they examined the expression of KIT and ANO1 in 14 YWHAE-NUTM2A/B tumors by immunohistochemistry. Staining localization was determined to be membranous or cytoplasmic, or both, and staining intensity was assessed as negative, weak, moderate, or strong. Of the 14 tumors, six contained only a high-grade round cell component, two only a low-grade fibroblastic component, and six both components in the

slides evaluated. The high-grade round cell component displayed moderate to strong membranous/cytoplasmic KIT staining in all tumors. The low-grade fibroblastic cell component showed only weak cytoplasmic KIT staining in three of eight tumors. In contrast, ANO1 was negative in all 14 neoplasms, irrespective of the component evaluated. Sanger sequencing analysis (exons 9, 11, 13, and 17) and Ampliseq Cancer Panel mutation screen (Ion Torrent) demonstrated no KIT mutations in three KIT-positive YWHAE-NUTM2A/B tumors. The study shows that the high-grade round cell component of YWHAE-NUTM2A/B endometrial stromal sarcoma consistently expresses KIT but lacks KIT hotspot mutations. KIT expression may represent a potential diagnostic pitfall in the evaluation of YWHAE-NUTM2A/B endometrial stromal sarcoma presenting with pelvic/abdominal mass, particularly in situations where its uterine origin is not definitive. Therefore, a panel of antibodies that includes ANO1 and cyclin D1 is necessary.

Lee CH, Hoang LN, Yip S, et al. Frequent expression of KIT in endometrial stromal sarcoma with YWHAE genetic rearrangement. *Mod Pathol.* 2014;27:751–757.

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Testicular embryonal carcinoma: a study highlighting unusual and unemphasized aspects

A total of 180 consecutive testicular cancers containing a component of embryonal carcinoma were reviewed to assess the morphologic features of the component. Embryonal carcinoma (EC) predominantly (84 percent) occurred as a component of a mixed germ cell tumor, but 16 percent were pure. Solid (55 percent), glandular (17 percent), and papillary (11 percent) were the most common primary patterns (predominant architectural pattern occupying at least 50 percent), whereas other less common primary patterns included nested (three percent), micropapillary (two percent), anastomosing glandular (one percent), sieve-like glandular (less than one percent), pseudopapillary (less than one percent), and blastocyst like (less than one percent). Occasionally, EC developed predominantly in the context of polyembryoma-like (six percent) and diffuse embryoma-like ("necklace" pattern; three percent) proliferations. In all, 69 percent had secondary architectural patterns, the most frequent being glandular (31 percent), papillary (14 percent), and solid (12 percent). An appliqué appearance, in which smudged and degenerate-appearing EC cells appear to be applied to the tumor periphery, was common (67 percent). EC cells with clear cytoplasm and distant cell membranes (seminoma like) were present in 11 percent, and dense lymphocytic infiltration and granulomatous inflammation were seen in seven percent and three percent, respectively. Features simulating yolk sac tumor and teratoma—pseudoendodermal sinuses (34 percent), columnar cells (20 percent), and secretory-type subnuclear cytoplasmic vacuoles (six percent)—were also seen. Syncytiotrophoblast cells were frequent (46 percent). Intratubular EC, typically partly necrotic and calcified, occurred in 24 percent. The associated stroma was more often non-neoplastic (53 percent) than neoplastic (29 percent). The rarity of some poorly characterized patterns of EC (micropapillary, blastocyst like, anastomosing glandular, and sieve-like glandular) and some that overlap with those of other germ cell tumors, as well as some uncommon cytologic features, may result in misinterpretation, potentially impacting management. The association of EC with other more common patterns and typical cytologic features, together with awareness of these variant morphologies, is helpful in establishing a diagnosis of EC.

Kao CS, Ulbright TM, Young RH, et al. Testicular embryonal carcinoma: a morphologic study of 180 cases highlighting unusual and unemphasized aspects. *Am J Surg Pathol.* 2014;38(5):689–697.

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Link between ARID1A loss and mismatch repair deficiency and intact p53 expression in high-grade endometrial carcinomas

BAF250a (ARID1A) loss is a frequent event in high-grade endometrial cancers. It has been proposed that ARID1A is a driver gene, with ARID1A mutations occurring secondary to deregulated mismatch repair mechanism in gastric

cancers, representing an alternative oncogenic pathway to p53 alteration. The prognostic significance of ARID1A loss is controversial. The authors conducted a study in which they investigated the frequency of BAF250a immunohistochemical loss in a cohort of high-grade endometrial cancers (n=190) and correlated it with mismatch repair (hMLH1, hMSH2, hMSH6, and hPMS2) and p53 protein expression. The 190 cases consisted of 82 high-grade endometrioid, 88 serous, 10 clear cell, and 10 mixed (carcinosarcomas and mixed histology). BAF250a loss was noted in 55 of 190 (29 percent) cancers, most commonly in high-grade endometrioid carcinomas (46 versus nine percent in serous carcinomas; P<0.0001). Loss of any mismatch repair proteins was observed in 63 of 190 (33 percent) cancers, most commonly in high-grade endometrioid carcinomas (57 versus 10 percent in serous carcinomas; P<0.0001). Aberrant p53 expression was found in 86 of 190 (45 percent) cancers, more commonly in serous carcinomas (77 versus 18 percent in high-grade endometrioid carcinomas; P<0.0001). BAF250a loss was associated with mismatch repair loss (P<0.0001) and normal p53 expression (P<0.0001). These associations were maintained in the subset analysis within the high-grade endometrioid (P=0.026 and P=0.0083, respectively) and serous carcinoma (P=0.0031 and P<0.0001, respectively) cases. Survival analysis revealed a superior progression-free survival rate (P=0.017) for patients with BAF250a loss within the entire cohort but not within the high-grade endometrioid and serous subtypes. Data from The Cancer Genome Atlas were extracted to correlate mutations in ARID1A, TP53, and MMR genes. The authors found that ARID1A mutations were negatively associated with TP53 mutations but were unrelated to mismatch repair gene mutations. They concluded that BAF250a loss is more common in high-grade endometrioid carcinomas than in other high-grade endometrial cancers and is associated with mismatch repair deficiency and normal p53 expression.

Allo G, Bernardini MQ, Wu RC, et al. ARID1A loss correlates with mismatch repair deficiency and intact p53 expression in high-grade endometrial carcinomas. *Mod Pathol.* 2014;27:255–261.

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Frequent phosphatidylinositol-3-kinase mutations in proliferative breast lesions

The phosphatidylinositol-3-kinase pathway is one of the most commonly altered molecular pathways in invasive breast carcinoma, with phosphatidylinositol-3-kinase catalytic subunit (PIK3CA) mutations in 25 percent of invasive carcinomas. Ductal carcinoma in situ (DCIS), benign papillomas, and small numbers of columnar cell lesions harbor an analogous spectrum of PIK3CA and AKT1 mutations, yet there are little data on usual ductal hyperplasia and atypical ductal and lobular neoplasias. The authors conducted a study in which they screened 192 formalin-fixed, paraffin-embedded breast lesions from 75 patients for point mutations using a multiplexed panel encompassing 643 point mutations across 53 genes, including 58 PIK3CA substitutions. PIK3CA point mutations were identified in 31 of 62 (50 percent) proliferative lesions (usual ductal hyperplasia and columnar cell change), 10 of 14 (71 percent) atypical hyperplasias (atypical hyperplasia and flat epithelial atypia), seven of 16 (44 percent) lobular neoplasias (atypical lobular hyperplasia and lobular carcinoma in situ), 10 of 21 (48 percent) DCIS, and 13 of 37 (35 percent) invasive carcinomas. In genotyping multiple lesions of different stage from the same patient or specimen, the authors found considerable heterogeneity; most notably, in 12 specimens the proliferative lesion was PIK3CA mutant but the concurrent carcinoma was wild type. In 11 additional specimens, proliferative epithelium and cancer contained different point mutations. The authors concluded that the frequently discordant genotypes of usual ductal hyperplasia/columnar cell change and concurrent carcinoma support a role for PIK3CA-activating point mutations in breast epithelial proliferation, perhaps more so than transformation. These data also suggest that proliferative breast lesions are heterogeneous and may represent nonobligate precursors of invasive carcinoma.

Ang DC, Warrick AL, Shilling A, et al. Frequent phosphatidylinositol-3-kinase mutations in proliferative breast lesions. *Mod Pathol.* 2014;27:740–750.

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An interobserver variability study of lymph nodes and pericolonic tumor deposits in colonic adenocarcinoma

The American Joint Committee on Cancer's Cancer Staging Manual, seventh edition, defines pericolonic tumor deposits as discrete tumor foci in pericolic fat showing no evidence of residual lymph node. This definition relies on subjective features rather than size (fifth edition) or shape (sixth edition) and introduced the category N1c. Although typically straightforward, metastases are encountered for which the distinction between lymph nodes and tumor deposits is unclear. For data to be meaningful, agreement on distinguishing features between positive lymph nodes and tumor deposits is needed. The authors conducted a study to assess agreement among gastrointestinal pathologists evaluating difficult metastases and to report the distinguishing features they found helpful. Twenty-five tumor metastases from right-sided colonic adenocarcinomas in which the distinction between positive lymph nodes and tumor deposits was challenging were selected. Virtual slides were reviewed by seven gastrointestinal pathologists. A list of features potentially helpful in differentiating positive lymph nodes and tumor deposits was ranked for usefulness by each pathologist. Each metastasis was diagnosed as a positive lymph node or tumor deposit. For each case diagnosed as a positive lymph node, reviewers were asked to list every feature used in diagnosis. Complete agreement was found for 11 of 25 metastases—five positive lymph nodes and six tumor deposits (κ statistic, 0.48; 95 percent confidence interval, 0.28–0.67). Top-ranked features included round shape, peripheral lymphocyte rim, peripheral lymphoid follicles, possible subcapsular sinus, residual lymph node in surrounding fibroadipose tissue, and thick capsule. The top used features were similar among reviewers. The authors concluded that significant agreement on positive lymph nodes and tumor deposits in difficult colonic adenocarcinoma metastases was found among evaluators but inconsistency remains. Round shape, peripheral lymphocyte rim, peripheral lymphoid follicles, possible subcapsular sinus, residual lymph node in surrounding fibroadipose tissue, and thick capsule were most often used to aid in diagnosis.

Rock JB, Washington MK, Adsay NV, et al. Debating deposits: an interobserver variability study of lymph nodes and pericolonic tumor deposits in colonic adenocarcinoma. *Arch Pathol Lab Med.* 2014;138(5):636–642.

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