

Anatomic Pathology Selected Abstracts, 11/13

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Diagnostic and prognostic morphometric features in WHO 2003 invasive endometrial stromal tumors

The authors conducted a study to determine the value of morphometric features in distinguishing between mild and moderate atypia and predicting the recurrence of World Health Organization 2003-defined endometrial stromal sarcoma and highly malignant undifferentiated endometrial sarcoma. For the study, nuclear and cytological size, shape, and arrangement were morphometrically evaluated in 41 cases with a consensus of no/mild atypia (n=38) or moderate atypia (n=3). None of the cases showed necrosis. The authors also assessed the prognostic value of these features in predicting recurrence. Seven features differed. The mean and standard deviation of the nuclear volume and distance between nuclei were the best discriminators between no/mild atypia and moderate atypia, with the maximum of the nuclear volume being a practical and rapidly evaluable alternative. With the use of these features, all mild and moderate atypias were classified correctly. Seven cases recurred. The distance between the nuclei and the percentage of nuclei with one neighbor (assessed with morphometric minimum spanning tree analysis) predicted recurrence. The authors concluded that in invasive endometrial stromal tumors, morphometric features are useful diagnostic support tools for distinguishing mild from moderate atypia and predicting recurrence.

Feng W, Malpica A, Yinhua Y, et al. Diagnostic and prognostic morphometric features in WHO2003 invasive endometrial stromal tumours. *Histopathology*. 2013;62:688-694.

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Association of tumor staging with adverse clinical outcome in neuroendocrine tumors of appendix

Appendiceal neuroendocrine neoplasms are rare and are usually discovered incidentally. While most cases are clinically indolent, the rare aggressive ones are difficult to predict. The authors conducted a study to test the applicability and prognostic significance of the new World Health Organization classification and the several pathologic features and tumor-node-metastasis staging systems (American Joint Committee on Cancer and European Neuroendocrine Tumor Society) in these tumors. A multi-institutional retrospective series of 138 appendiceal neuroendocrine neoplasms (NENs) was selected on the basis of the availability of pathologic material and clinical information, including followup data. All cases were reviewed to record pathologic features and to apply year 2000 and 2010 WHO classifications, as well as European Neuroendocrine Tumor Society and American Joint Committee on Cancer TNM stages. Clinical and pathologic characteristics were compared with disease outcome by contingency, univariate, and multivariate survival analyses. Although up to one-third of cases presented several malignancy-associated pathologic features, only four patients died of the disease. Adverse outcome was significantly associated with extramural extension, including mesoappendix, well-differentiated carcinoma diagnosis (2000 WHO classification), pT3-4 stage, older age, and presence of positive resection margins, but not with tumor size, mitotic or proliferative indices, and, consequently, 2010 WHO grading. The authors concluded that in the appendix, at variance with midgut/hindgut NENs, the 2000 WHO classification performs better than the grading-based 2010 WHO scheme and, with tumor stage, is the most relevant parameter associated with clinical aggressiveness.

Volante M, Daniele L, Asioli S, et al. Tumor staging but not grading is associated with adverse clinical outcome in

neuroendocrine tumors of the appendix: a retrospective clinical pathologic analysis of 138 cases. *Am J Surg Pathol*. 2013;37(4): 606-612.

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Detection of HPV capsid proteins L1 and L2 in squamous intraepithelial lesions

While cervical cancer screening relies on cervical cytology and high-risk human papillomavirus detection, histologic diagnosis, and specifically lesion grade, is the main parameter that drives clinical management of screen-positive women. Morphologically diagnosed squamous intraepithelial lesions (SIL/CIN) regress spontaneously in more than half of cases, but identifying those likely to persist and progress is not possible based on morphology. Lack of major capsid protein L1 expression has been suggested as a feature in progressive lesions, whereas expression of the minor capsid protein L2 has not been evaluated extensively. The authors conducted a study to evaluate the immunohistochemical expression of L1 and L2 in correlation with lesion grade in SILs. A total of 150 cervical specimens with SILs were selected based on HPV 16 or HPV 18 detection by quantitative polymerase chain reaction. These included 89 low-grade SILs (LSIL/CIN 1) and 123 high-grade SILs (75 HSIL/CIN 2 and 48 HSIL/CIN 3). More than one lesion/grade was identified in 53 specimens. The presence and grade of SIL were determined by a panel of pathologists. Capsid protein expression was assessed by immunohistochemistry using MAB 837 for L1 and RG-1 for L2. Lesions of different grades in the same specimen were scored separately. Expression of capsid proteins was detected in 34 of 89 (40 percent) LSIL/CIN 1, five of 75 (six percent) HSIL/CIN 2, and none of 48 HSIL/CIN 3. L1 and L2 were co-expressed in the same area of the lesion in 22 cases. In addition, L1 alone was expressed in six lesions and L2 alone in 11 lesions. Among the cases with multiple lesion grades in the same specimen, none with HSIL/CIN 3 expressed capsid proteins in any portion/grade of the lesion. The authors concluded that HPV capsid proteins are expressed almost exclusively in LSIL/CIN 1 and rarely in HSIL/CIN 2. Additional studies are warranted to examine lack of L1 and L2 expression in LSIL/CIN 1 as a predictor of persistence or progression to HSIL/CIN 3, the precursor of cervical cancer.

Yemelyanova A, Gravitt PE, Ronnett BM, et al. Immunohistochemical detection of human papillomavirus capsid proteins L1 and L2 in squamous intraepithelial lesions: potential utility in diagnosis and management. *Mod Pathol*. 2013;26:268-274.

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Feasibility and safety of sequential research-related tumor core biopsies in clinical trials

Interest in serial research biopsies in studies of targeted therapies is increasing. A definition of patient characteristics and optimal target tissue for safe research tumor biopsy in the era of antiangiogenic and targeted agents is needed. The authors conducted an institutional review board-approved, retrospective study that included chart and interventional radiology case review from six phase I/II studies at the National Cancer Institute. One hundred forty-two of 150 protocol patients who were approached for the study gave consent for research biopsies. Patients were a median age of 56 years (range, 27-78 years) and had a median body mass index of 25.8 kg/m² (range, 14.4-46.2 kg/m²). They also had an Eastern Cooperative Oncology Group performance status of zero or one and normal end-organ function. Baseline biopsies were collected from 138 of 142 patients (97 percent), and paired specimens were collected from 96 (70 percent). Most patients had metastatic gynecologic cancers (85 percent), and 78 percent had target disease below the diaphragm with a median size of 2.7 cm (range, 1-14.5 cm). Protocol therapies included kinase inhibitors (35 percent), angiogenesis inhibitors (54 percent), and olaparib/carboplatin (11 percent). Therapy was not interrupted for biopsies. All adverse events were uncomplicated and observed in four patients (liver subcapsular hematoma in one patient, vasovagal syncope in two patients, and pneumothorax in one patient). The complication rate in obese patients was similar to that in nonobese patients (three of 108 patients versus one of 34 patients, respectively). Sixty-seven patients (48 percent) were receiving

bevacizumab at the time of subsequent biopsies. The complication rate was not different between patients who were and were not receiving bevacizumab (three of 67 patients versus one of 71 patients, respectively). Ninety-five percent of biopsies yielded useable material. The authors concluded that serial percutaneous core-needle biopsies can be obtained safely and yield material applicable for multiple translational applications. Obesity or concomitant antiangiogenic therapy, or both, and depth of disease did not increase the risk of complications or preclude the acquisition of useful tissue.

Lee JM, Hays JL, Noonan AM, et al. Feasibility and safety of sequential research-related tumor core biopsies in clinical trials. *Cancer*. 2013;119:1357-1364.

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Evaluation of breast amyloidosis finds AL type most prevalent

Amyloidosis is a disorder characterized by extracellular deposition of proteins in an abnormal fibrillar configuration. Amyloidosis can be localized or systemic and may affect any organ. Breast involvement by amyloidosis has rarely been reported. The authors conducted a study in which they described the characteristics of 40 cases of breast amyloidosis that were reviewed in the division of anatomic pathology at the Mayo Clinic from 1995 to 2011. The cohort included 39 women and one man who were a mean age of 60 years. The type of amyloidosis, determined by immunohistochemistry or mass spectrometry-based proteomics in 26 patients, was immunoglobulin-associated in all cases (AL-kappa type in 15 [58 percent], AL-lambda in 10 [38 percent], and mixed heavy and light chains in one [four percent]). Mass spectrometry-based proteomics was able to determine the type of amyloidosis in 95 percent of cases tested compared with 69 percent of cases by immunohistochemistry. In addition to amyloidosis, the breast biopsy showed a hematologic disorder in 55 percent of cases, most commonly mucosa-associated lymphoid tissue (MALT) lymphoma. One patient had concurrent intraductal carcinoma, but none had invasive carcinoma. Of the 15 patients seen at this institution, 53 percent had localized amyloidosis and 47 percent had extramammary amyloid involvement, which was diagnosed before breast amyloidosis in most patients. M-spike was detected in the blood in 62 percent. After a median followup of 33.5 months in 12 patients, five died, mostly from complications of lymphoma or leukemia. The authors concluded that these findings indicate that breast amyloidosis is of the AL type in the vast majority of patients and is usually kappa. It is associated with systemic amyloidosis in close to half of patients and with hematologic malignancy in the breast in more than half of patients. Therefore, further work-up to rule out hematologic malignancy or systemic amyloidosis, or both, is recommended. Mass spectrometry-based proteomics is superior to immunohistochemistry for the typing of breast amyloidosis.

Said SM, Reynolds C, Jimenez RE, et al. Amyloidosis of the breast: predominantly AL type and over half have concurrent breast hematologic disorders. *Mod Pathol*. 2013;26:232-238.

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Outside case review of surgical pathology for referred patients: impact on patient care

Pathologists at the Mayo Clinic review externally acquired surgical pathology materials from a referred patient prior to that patient's clinical evaluation and treatment. The authors conducted a study to identify the rate of major disagreements between Mayo's findings and those of other institutions and to characterize the nature and impact of discordant diagnoses on patient care. The authors identified and reviewed all surgical pathology cases, except for medical liver, medical renal, and cardiac pathology cases, from Jan. 1, 2005 to Dec. 31, 2010 to determine the overall frequency of major disagreements, defined as any change in diagnosis having a substantial impact on patient management. The authors' review of 71,811 cases identified 457 (0.6 percent) major disagreements. The most frequent areas of disagreement were gastrointestinal (80 cases; 17.5 percent), lymph node (73; 16 percent), bone/soft tissue (47; 10.3 percent), and genitourinary (43; 9.4 percent). For a subset of 166 cases reviewed between July 1, 2009 and Dec. 31, 2010, followup data were available for 140 (84.3 percent). Treatment was

affected by a changed diagnosis in 126 cases (90 percent), and prognosis was affected in 129 cases (92.1 percent). For 86 (51.8 percent) of the 166 cases, additional tissue was obtained. Revised diagnoses concurred with followup tissue diagnosis in 84.9 percent (73 cases) and differed from followup tissue diagnosis in 15.1 percent (13 cases). The authors concluded that outside case review of pathology materials for referred patients is valuable, and they suggest that it decreases the likelihood of diagnostic errors and provides better protection for patients.

Swapp RE, Aubry MC, Salomao DR, et al. Outside case review of surgical pathology for referred patients: the impact on patient care. *Arch Pathol Lab Med*. 2013;137:233-240.

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Reporting trends for right-sided hyperplastic and sessile serrated polyps

An audit of serrated polyps diagnosed over the four-year period of 2009 to 2012 was undertaken to ascertain the reporting trends for such polyps. All right-sided hyperplastic polyps proximal to the splenic flexure and all polyps designated as sessile serrated polyps (SSPs) were retrieved for the study period. Three pathologists blinded to the original diagnosis re-examined the slides. Recent American College of Gastroenterology guidelines for diagnosing SSP were used. No cases of SSP were diagnosed in 2009. In 2010, 32 right-sided cases were diagnosed, while 83 were confirmed in 2011 and 134 in 2012. The vast majority of these were right-sided. Twenty of 66 right-sided hyperplastic polyps were reclassified as SSP in 2009 (30 percent), 58 of 91 in 2010 (64 percent), 42 of 106 (40 percent) in 2011, and 69 of 206 in 2012 (33 percent). The authors concluded that an almost exponential increase in the diagnosis of SSP occurred over a four-year period. Reclassification of 30 percent to 64 percent of right-sided hyperplastic polyps as SSP over the four-year period suggests that greater awareness of the diagnostic criteria for SSP is required. Sessile serrated polyps are an important precursor lesion in the serrated pathway of colorectal cancer. Recognizing them is important for purposes of surveillance and determining therapeutic strategies.

Gill P, Wang LM, Bailey A, et al. Reporting trends of right-sided hyperplastic and sessile serrated polyps in a large teaching hospital over a 4-year period (2009-2012). *J Clin Pathol*. 2013; 66(8):655-658.

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Atypical leiomyomas of the uterus: a clinicopathologic study of 51 cases

Atypical leiomyoma is a well-described smooth muscle neoplasm of the uterus. Only one study has addressed long-term clinical followup in a large series, and little is known about the adequacy of treatment by myomectomy. For this study, the surgical pathology archives were searched for consecutive cases of uterine atypical leiomyoma from 1992 to 2003. Glass slides were reviewed to confirm diagnoses, and patient age, treatment modality, and clinical followup data were recorded. Fifty-one atypical leiomyomas with available glass slides and clinical followup data were identified. Thirty tumors exhibited diffuse, moderately to severely atypical cells; 21 showed atypical cells in a more focal or patchy distribution. Twelve had ischemic-type necrosis. By the highest count method, 37 cases were found to have no more than one mitotic figure per 10 high-power fields; 13 showed one to three mitotic figures per 10 high-power fields; and one was nearly entirely necrotic, precluding mitotic assessment. Among the 46 cases in which adjacent non-neoplastic tissue was well visualized, all were found to have pushing margins. The average tumor size was 6.8 cm (median, 6.5 cm; range, 0.7-14 cm). The average patient age was 42.5 years (median, 42 years; range, 21-72 years). In all cases, the initial diagnostic procedure was hysterectomy (34) or myomectomy (17). Average followup was 42 months (range, 0.3-121.8 months). Of those treated with hysterectomy, one had recurrent atypical leiomyoma in the retroperitoneum at 87.5 months, one died of other causes, and the remaining 32 (94 percent) were free of disease. Of the myomectomy group, 82 percent had no evidence of recurrent disease on followup; two had residual atypical leiomyoma in the subsequent hysterectomy specimen; and one underwent second myomectomy for atypical leiomyoma with two subsequent successful pregnancies. The authors concluded that atypical leiomyoma has a low rate of extrauterine, intra-abdominal recurrence (less than two percent), with a negligible risk for distant metastasis. Patients may be treated by myomectomy alone with successful pregnancy but should be monitored for local intrauterine residual/recurrent disease.

Ly A, Mills AM, McKenney JK, et al. Atypical leiomyomas of the uterus: a clinicopathologic study of 51 cases. *Am J Surg Pathol*. 2013;37(5):643-649.

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Pathological diagnostic criterion of blood and lymphatic vessel invasion in colorectal cancer

The authors conducted a study with the intent of creating an objective pathological diagnostic system for blood and lymphatic vessel invasion. They reviewed 1,450 surgically resected colorectal cancer specimens from eight hospitals. The first phase of the study involved comparing the current practice of pathology assessment among eight hospitals. Then eight pathologists from these hospitals assessed hematoxylin-and-eosin-stained slides with or without histochemical/immunohistochemical staining, and concordance of blood and lymphatic vessel invasion (BLI) diagnosis was checked. Histological findings associated with BLI having good concordance were also reviewed. Based on these results, a framework for developing a diagnostic criterion was developed using the Delphi method. The new criterion was evaluated using 40 colorectal cancer specimens. The frequency of BLI diagnoses and the number of blocks obtained and stained to assess BLI varied among the eight hospitals. Concordance was low for BLI diagnosis and did not improve when histochemical/immunohistochemical staining was provided. All histological findings associated with BLI from hematoxylin-and-eosin staining had poor agreement. However, observation of elastica-stained internal elastic membrane covering more than half the circumference of the tumor cluster as well as the presence of D2-40-stained endothelial cells covering more than half the circumference of the tumor cluster showed high concordance. Based on this observation, the authors developed a framework for a pathological diagnostic criterion using the Delphi method. This criterion was found to be useful in improving concordance of BLI diagnoses. It may serve as the basis for creating a standardized procedure for pathological diagnosis.

Kojima M, Shimazaki H, Iwaya K, et al. Pathological diagnostic criterion of blood and lymphatic vessel invasion in colorectal cancer: a framework for developing an objective pathological diagnostic system using the Delphi method, from the Pathology Working Group of the Japanese Society for Cancer of the Colon and Rectum. *J Clin Pathol*. 2013;66(7):551-558.

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