Anatomic pathology selected abstracts

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Evaluation of gastroesophageal glomus tumors for features that may predict malignancy

May 2023—Although criteria for malignancy have been established for glomus tumors of soft tissue, no accepted criteria exist for gastroesophageal glomus tumors, which are considered to behave unpredictably. Benign and aggressive gastroesophageal glomus tumors have been shown to harbor *CARMN::NOTCH2* fusions, but genetic features that predict clinical behavior have not been identified. The authors conducted a study in which they evaluated 26 gastroesophageal glomus tumors to investigate histologic and genetic features that may predict malignancy. Seventeen of the 26 (65 percent) patients were male. The median age at presentation was 54.5 years (range, 16–81 years). Primary sites were stomach (25 tumors) and distal esophagus (one). The median tumor size was 4.05 cm (range, 0.8–19.5 cm). Tumors were composed of lobules of rounded cells with sharp borders, palely eosinophilic to clear cytoplasm, and round nuclei. All tumors involved the muscularis propria, and 12 also involved the serosal surface. Mitoses ranged from less than one to 53 per 10 high-power fields (HPF) (median, five per 10 HPF). Sixteen tumors, including all 15 with mitoses of two or more per 10 HPF, showed atypia (three mild, 10 moderate, three severe), defined as spindle cell morphology, nuclear irregularity, nuclear size variability, enlarged nuclei, or coarse chromatin. Considering these histologic features and clinical behavior, tumors were classified as malignant (15 tumors) if they measured 5 cm or more or showed both atypia and mitoses of two or more per 10 HPF, and benign (11 tumors) if these criteria were not met. Follow-up was available for 19 patients (73 percent; range, 1–15 years; median, 5.8 years), including seven who had benign tumors and 12 who had malignant tumors. Two patients who had malignant tumors had metastases at presentation and seven subsequently developed metastases. Follow-up was available for eight of nine patients who had metastatic disease. Two were alive with disease at their most recent follow-up. One underwent resection of a liver metastasis with no subsequent metastases in three years of follow-up. Five patients died of metastatic disease. By immunohistochemistry, smooth muscle actin was diffusely positive in all tumors, and caldesmon and synaptophysin were positive in 94 percent and 73 percent, respectively. Sequencing identified *NOTCH2* alterations in four (80 percent) benign tumors and eight (80 percent) malignant tumors, including *CARMN::NOTCH2* fusions in two benign and five malignant tumors. All five sequenced benign tumors lacked complex copy number alterations, whereas all 10 sequenced malignant tumors showed complex copy number alterations, including recurrent loss of 9p21.3 (four of 10, variably including *CDKN2A/B* and *MTAP*) and *ATRX* inactivation (four of 10). Complex copy number alterations were identified in all sequenced tumors that were 5 cm or more, exhibited both cytologic atypia and two or more mitoses per 10 HPF, and involved the serosa or metastasized. The authors propose that gastroesophageal glomus tumors of 5 cm or more or that have atypia and mitoses of two or more per 10 HPF should be considered malignant. Copy number analysis may be helpful in borderline cases.

Papke DJ Jr, Sholl LM, Doyle LA, et al. Gastroesophageal glomus tumors: clinicopathologic and molecular genetic analysis of 26 cases with a proposal for malignancy criteria. *Am J Surg Pathol.* 2022;46(10):1436–1446.

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Clinicopathologic parameters and outcomes of mucinous neoplasms confined to the appendix

Appendiceal mucinous neoplasms, which are characterized by expansile or "pushing" growth of neoplastic epithelium through the appendix wall, are sometimes accompanied by peritoneal involvement, the extent and grade of which largely determine clinical presentation and long-term outcome. However, the prognosis for patients with tumors confined to the appendix is still being debated. Furthermore, confusion remains regarding the biologic behavior of such tumors and, consequently, their clinical management and diagnostic nomenclature. The authors evaluated appendiceal mucinous neoplasms (AMNs) limited to the appendix for 337 patients (median age, 58 years; interquartile range, 47–67), 194 (57.6 percent) of whom were women and 143 (42.4 percent) of whom were men. The most common clinical indication for surgery was mass or mucocele, which was found in 163 (48.4 percent) patients. Most (n=322; 95.5 percent) cases were classified as low grade, but 15 (4.5 percent) were classified as high-grade dysplasia. Lymph nodes were harvested in 102 (30.3 percent) cases, with a median of 6.5 lymph nodes (interquartile range, 2–14) obtained per specimen for a total of 910 lymph nodes. All of the lymph nodes were negative for metastatic disease. Histologic slide review for 279 cases revealed that 77 (27.6 percent) tumors extended to the mucosa, 101 (36.2 percent) to the submucosa, 33 (11.8 percent) to the muscularis propria, and 68 (24.4 percent) to subserosal tissue. In multivariate analysis, deeper tumor extension was associated with older age (P=.032; odds ratio [OR], 1.02; 95 percent confidence interval [CI], 1.00–1.03), indication of mass or mucocele (P<.001; OR, 2.09; CI, 1.41–3.11), and wider gross appendiceal diameter (P<.001; OR, 1.61; CI, 1.28–2.02). Importantly, among 194 cases with at least six months of follow-up (median, 56.1 months; interquartile range, 24.4–98.5), including nine that were high grade, there was no disease recurrence or progression, peritoneal involvement (pseudomyxoma peritonei), or disease-specific mortality. These data reinforce the conclusion that AMNs confined to the appendix are characterized by benign biologic behavior and excellent clinical prognosis and, accordingly, suggest that revisions to their nomenclature and staging would be appropriate. This includes reverting to the diagnostic term mucinous adenoma to describe a subset of AMNs.

Polydorides AD, Wen X. Clinicopathologic parameters and outcomes of mucinous neoplasms confined to the appendix: a benign entity with excellent prognosis. *Mod Pathol.* 2022;35(11):1732–1739.

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Measuring depth of invasion in endoscopic mucosal resections for Barrett-associated adenocarcinoma

Endoscopic mucosal resection has made it possible for Barrett esophagus patients who have superficial cancers to be treated without undergoing esophagectomy. Recent guidelines recommend measuring depth of invasion (DOI) in submucosal cancers based on reports that in low-risk cancers, submucosal invasion of 500 µm or less is associated with low nodal metastasis rates. However, reproducibly measuring DOI presents challenges to pathologists. The authors conducted a study to determine how often DOI measurements could impact treatment and to evaluate reproducibility in measuring submucosal DOI in endoscopic mucosal resection specimens. Consecutive endoscopic mucosal resection

cases of adenocarcinoma were identified, including cases of low histologic-risk submucosal cancer, defined as those with negative deep margins and without high-grade histology (G3) and lymphovascular invasion. Seven pathologists measured submucosal DOI according to guidelines of the Rodger C. Haggitt Gastrointestinal Pathology Society and European Society for Gastrointestinal Endoscopy. Of 213 endoscopic mucosal resection cases displaying invasive adenocarcinoma, 46 were submucosa invasive and six were low histologic-risk submucosal cancers for which measurement could impact decision-making. Of the low histologic-risk cases, three were categorized as superficial, indicating that measurement would be a clinically actionable decision point in only 1.4 percent of adenocarcinoma endoscopic mucosal resections. Interobserver agreement for categorization of depth between the seven pathologists was moderate ($\kappa = 0.42$). Despite this, the range of measurements spanned the clinically relevant threshold of depth (500 µm) in 40 of 55 (72.7 percent) measured samples. While therapeutic decisions for patients in this cohort would rarely have depended on DOI measurements alone, interobserver variability raises concerns about using DOI measurements as a sole factor for offering patients conservative therapy. Responsibly reporting submucosal DOI measurements and using them clinically will require practical experience troubleshooting common histologic artifacts and multidisciplinary awareness of the impact of variable specimen-handling practices.

Taylor AS, Setia N, Alpert L, et al. Measuring the submucosal depth of invasion in endoscopic mucosal resections for Barrett-associated adenocarcinoma: Practical issues and relevance for the decision for esophagectomy. *Arch Pathol Lab Med.* 2022;146:1338–1344.

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Value of a proposed grading system for predicting prognosis and mediastinal nodal metastasis in lung adenocarcinoma

The International Association for the Study of Lung Cancer recently proposed a grading system for lung adenocarcinoma. The authors conducted a study to validate the prognostic performance of the IASLC grading system and explore its role in guiding the strategy for lymph node dissection. They retrospectively assessed 1,029 patients with clinical stage I lung adenocarcinoma who underwent surgery between 2011 and 2013. The authors evaluated the association between mediastinal nodal metastasis and the grading system. Three pathologists evaluated the feasibility of identifying the grading system using frozen section diagnosis. The differences in prognosis between all neighboring grades were highly significant based on the grading system ($P<.001$). Notably, pN2 disease was found in only 1.4 percent of grade 1 lung adenocarcinoma patients, whereas higher rates were found in those with grade 2 lung adenocarcinoma (9.6 percent) and grade 3 lung adenocarcinoma (18.3 percent) ($P<.001$). Multivariate logistic regression analysis revealed that higher tumor grade was an independent predictor of mediastinal nodal metastasis ($P=.002$). Moreover, limited mediastinal lymph node dissection had an equivalent prognosis in grade 1 lung adenocarcinoma but a significantly worse prognosis in grade 2 and grade 3 lung adenocarcinoma than systematic mediastinal lymph node dissection. The overall accuracy of using intraoperative frozen section diagnosis to identify the IASLC grading system was 85.4 percent ($\kappa=0.765$), and substantial agreement was observed. The authors concluded that the IASLC grading system could accurately stratify prognosis and predict mediastinal nodal metastasis in patients with clinical stage I lung adenocarcinoma. Frozen section diagnosis was feasible for identifying the grading system.

Xu L, Su H, Hou L, et al. The IASLC proposed grading system accurately predicts prognosis and mediastinal nodal metastasis in patients with clinical stage I lung adenocarcinoma. *Am J Surg Pathol.*

2022;46(12):1633-1641.

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