Anatomic pathology selected abstracts

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Prognostic implications of coexisting precursor lesion types in invasive gallbladder cancer

March 2022—Invasive gallbladder carcinoma is preceded by two main types of precursor lesions—intracholecystic papillary-tubular neoplasms and biliary intraepithelial neoplasias. Invasive gallbladder carcinomas with an intracholecystic papillary-tubular neoplasm (ICPN) component have more favorable prognoses than those without an ICPN component. Some biliary intraepithelial neoplasias show a relatively exophytic papillary pattern but do not meet the ICPN criteria and are called papillary neoplasias by the authors. To clarify the clinical significance of papillary neoplasia, the authors examined 80 invasive gallbladder carcinomas and classified them into three groups based on the type of preinvasive lesions: those with ICPN (ICPN group, n = 35), those with papillary neoplasia (pap-neoplasia group, n = 13), and those without ICPN/papillary neoplasia (group without ICPN/pap-neoplasia, n = 32). They compared the prognostic differences and characterized the tumors in each group by determining the immunohistochemical expressions for various biomarkers. The overall survival periods of the ICPN and papillary neoplasia groups were significantly longer than that of the group without ICPN/pap-neoplasia ($P < 0.0001$ and $P = 0.0036$, respectively). Multivariate analysis revealed that the absence of ICPN/papillary neoplasia was independently associated with poor prognosis ($P = 0.0007$), as were poor differentiation ($P = 0.0395$), presence of preoperative symptoms ($P = 0.0488$), and advanced stage ($P = 0.0234$). Invasive components of the ICPN and papillary neoplasia groups were characterized by higher expressions of p16 and p53 than those of the group without ICPN/pap-neoplasia. Therefore, the prognoses for the invasive gallbladder carcinomas with papillary neoplasia or ICPN were more favorable than those for the invasive gallbladder carcinomas without ICPN/papillary neoplasia. Invasive gallbladder carcinomas with exophytic papillary preinvasive lesions (ICPN and papillary neoplasia) may differ biologically from those without such lesions.

Mochidome N, Koga Y, Ohishi Y, et al. Prognostic implications of the coexisting precursor lesion types in invasive gallbladder cancer. *Hum Pathol*. 2021;114:44–53.

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Evaluating mismatch repair deficiency for solid tumor immunotherapy eligibility

While many landmark solid tumor immunotherapy studies have shown the clinical benefits of immunotherapy for solid tumors with high microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR), the methodologies focus only on confirmatory PCR testing for microsatellite instability status. Because some tumors are only dMMR or MSI-H, clinicians must choose between two testing methods for a broad patient population. The authors investigated the level of correlation between MMR protein IHC and microsatellite PCR testing results in 62 cancer patients. Thirty-five (56.5 percent) of the 62 cases were MSI-H by PCR and 35 (56.5 percent) were dMMR by IHC. Mismatch repair IHC results correlated well with MSI PCR in 32 (91.4 percent) copositive cases and 24 (88.9 percent) conegative cases. Six (9.7 percent) discrepant cases were identified, of which, three were MSI-H and MMR intact and three were dMMR and microsatellite stable. The results of this study highlight the implications of dMMR/MSI testing strategies on precision oncology. The authors concluded that cotesting with MMR IHC and MSI PCR may be an effective screening strategy for evaluating immunotherapy eligibility status for solid tumors.

Saeed OAM, Mann SA, Luchini C, et al. Evaluating mismatch repair deficiency for solid tumor immunotherapy

eligibility: immunohistochemistry versus microsatellite molecular testing. *Hum Pathol*. 2021;115:10–18.

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Impact of specimen type on HER2 status in endometrial serous carcinoma

A recent clinical trial showed prolonged progression-free survival in people with human epidermal growth factor receptor 2 (HER2)-positive advanced stage and recurrent endometrial serous carcinomas when trastuzumab was added to traditional chemotherapy. Approximately one-third of these tumors are HER2 positive and, in recent studies, have been shown to possess unique characteristics of HER2 protein expression and gene amplification, including significant intratumoral heterogeneity. However, there are no standard protocols for selecting an optimal specimen type or algorithm for HER2 testing in endometrial serous carcinoma. The authors evaluated the concordance of HER2 status between endometrial biopsy/curettage and subsequent hysterectomy specimens in endometrial serous carcinoma. Fifty-seven patients with endometrial serous carcinoma with available HER2 status were identified during the study period, 14 (25 percent) of whom were HER2 positive by immunohistochemistry or FISH, or both. The final study cohort of 40 paired endometrial biopsies/curettings and hysterectomies was compiled to include all 14 HER2-positive tumors and 26 select HER2-negative tumors, with the intent of representing an equal distribution of HER2 IHC scores. HER2 FISH was performed on all tumors with an IHC score of 2+. HER2 IHC scores, heterogeneity of HER2 expression, FISH results, and overall HER2 status were compared between the two specimen types. HER2 status was successfully assigned in both specimen types in 37 cases, as three specimens showed inadequate FISH signals. Concordant HER2 status was observed in 84 percent (31 of 37) of cases, with identical HER2 IHC scores in 65 percent (26 of 40) of tumors. Among the six tumors with discordant HER2 status, two were HER2 negative in the biopsy and positive in the hysterectomy, and four were HER2 positive in the biopsy and negative in the hysterectomy. The false-negative HER2 test rate would be 15.4 percent and 26.7 percent if only the biopsy and only the hysterectomy were the basis for the result, respectively. Intratumoral heterogeneity of HER2 protein expression was present in 22 (55 percent) tumors, including all cases with discordant HER2 status. The concordance rate of HER2 status between paired endometrial biopsies/curettings and hysterectomies of endometrial serous carcinoma is lower than the reported rates for breast cancer and comparable to those of gastric carcinomas. Frequent heterogeneity of HER2 protein expression combined with the possibility of a spatially more heterogenous sampling of the endometrial cavity in biopsies and curettings and potential differences in specimen handling and fixation between the two specimen types may explain the authors' findings. HER2 testing of multiple specimens may help identify a greater proportion of patients eligible for targeted trastuzumab therapy and should be taken into account in future efforts to develop an endometrial cancer-specific HER2-testing algorithm.

Rottmann D, Assem H, Matsumoto N, et al. Does specimen type have an impact on HER2 status in endometrial serous carcinoma? Discordant HER2 status of paired endometrial biopsy and hysterectomy specimens in the presence of frequent intratumoral heterogeneity. *Int J Gynecol Pathol*. 2021;40(3):263–271.

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Diagnostic and prognostic impact of cytokeratin 19 expression in tumors

The authors conducted a study to better understand the prevalence and significance of cytokeratin 19 expression in cancer by evaluating cytokeratin 19 (CK19) expression in normal and cancerous tissue. They analyzed 15,977 samples from 122 tumor types and subtypes and 608 samples of 76 normal tissue types using immunohistochemistry. In the normal tissue, CK19 expression occurred in the epithelial cells of most glandular organs, but it was strictly limited to the basal cell layer of nonkeratinizing squamous epithelium and absent in the skin. Thirty-four percent (41 of 122) of the tumor entities showed CK19 expression in more than 90 percent of cases, including adenocarcinomas of the pancreas (99.4 percent), colorectum (99.8 percent), esophagus (98.7 percent), and stomach (97.7 percent). It was also seen in breast cancer (90 to 100 percent), high-grade serous and endometrioid ovarian cancer (99.1 percent and 97.8 percent, respectively), and urothelial carcinoma (92.6 to 100 percent). A low CK19 positivity rate (0.1 to 10 percent) was noted in five of the 122 tumor entities, including

hepatocellular carcinoma and seminoma. A comparison of tumor versus normal tissue findings demonstrated that upregulation and downregulation of CK19 can occur in cancer and that both alterations can be linked to unfavorable phenotypes. CK19 downregulation was linked to high grade ($P = 0.0017$) and loss of estrogen receptor and progesterone receptor expression ($P < 0.0001$ each) in invasive breast carcinoma of no special type. CK19 upregulation was linked to nodal metastases in neuroendocrine tumors and papillary thyroid carcinomas ($P < 0.05$ each) and poor grade in clear cell renal cell carcinoma ($P < 0.05$). CK19 upregulation was particularly common in squamous cell carcinomas. The authors concluded that CK19 IHC might separate primary liver cell carcinoma from liver metastases and seminoma from other testicular tumors and help detect early neoplastic transformation in squamous epithelium.

Menz A, Bauer R, Kluth M, et al. Diagnostic and prognostic impact of cytokeratin 19 expression analysis in human tumors: a tissue microarray study of 13,172 tumors. *Hum Pathol*. 2021;115:19–36.

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An analysis of urinary large-cell neuroendocrine carcinoma

Large-cell neuroendocrine carcinoma of the urinary tract is a rare disease, accounting for less than one percent of all urothelial neoplasms. There is no consensus on standard treatment. The authors described a large cohort of large-cell neuroendocrine carcinoma (LCNEC) and addressed the clinicopathologic and immunohistochemical features of the disease. They searched their institution's database from 2006 to 2020 and found 22 cases of LCNEC of the urinary tract, including 20 from the urinary bladder and two from the ureter. The patients included 16 men and six women who were a median age of 74.5 years. Most LCNEC presented at an advanced stage, with tumors invading the muscularis propria and beyond (21 of 22). Eight cases were pure LCNEC, while 14 were mixed with other histologic types, including conventional urothelial carcinoma (n = 9), carcinoma in situ (n = 7), small cell carcinoma (n = 6), and urothelial carcinoma with glandular features (n = 3). Most LCNEC expressed the neuroendocrine markers synaptophysin (22 of 22), chromogranin (13 of 16), CD56 (seven of seven), TTF1 (eight of eight), and INSM1 (two of three). They were negative for common urothelial markers, including HMWCK (zero of three), p40/p63 (zero of six), and CK20 (zero of 10), and they had variable GATA3 staining (four of eight). Ki-67 stained 25 percent to nearly 100 percent of the tumor cell nuclei in seven cases examined. Patient survival was associated with cancer stage. Pure LCNEC showed worse survival than mixed LCNEC. Compared with small cell carcinoma at similar stages analyzed in a prior study, LCNEC had a worse prognosis only when patients developed metastatic disease. The authors concluded that neoadjuvant chemotherapy followed by radical resection can lead to long-term survival in patients who have organ-confined LCNEC.

Wang G, Yuan R, Zhou C, et al. Urinary large cell neuroendocrine carcinoma: A clinicopathologic analysis of 22 cases. *Am J Surg Pathol*. 2021;45:1399–1408.

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Reappraisal of the relevance of morphologic criteria from the 2019 WHO classification of a CRC cohort

The World Health Organization reclassified colorectal carcinoma subtypes in the 2019 WHO classification of CRC and introduced tumor budding as a second major grading criterion while condensing conventional grading into a two-tiered system. How CRC subtypes, tumor budding, and WHO grade interact with each other and whether they have an independent impact on patient prognosis remains largely unexplored. To address these topics, the authors conducted a retrospective study in which they investigated a large single-center cohort of 1,004 CRC patients. The study reclassified CRCs from two decades based on WHO grade (low versus high), tumor budding (Bd1/Bd2/Bd3), and CRC subtype (adenocarcinoma not otherwise specified, micropapillary, mucinous, serrated, medullary, adenoma like, signet ring cell, mixed adenoneuroendocrine carcinoma/neuroendocrine carcinoma, and undifferentiated) according to the criteria of the 2019 WHO classification. The authors investigated the interaction of these parameters, their connection to stage and microsatellite status, and their significance relative to patient

survival for the various subgroups. Specific subtypes, other than adenocarcinoma not otherwise specified, represented one-third of all CRCs and were unevenly distributed throughout stages and microsatellite subgroups. Subtypes, WHO grade, and tumor budding profoundly impacted all survival parameters ($P < 0.001$ for all analyses), with CRC subtypes and tumor budding—but not WHO grade—being stage-independent prognosticators for all survival comparisons. WHO grade had very limited prognostic value in CRC subtypes, while tumor budding retained its strong prognostic impact in most scenarios. Accurate delineation of CRC subtypes introduced in the 2019 WHO classification provided strong stage-independent prognostic information, supporting the assertion that the subtypes should be considered for inclusion in pathology reports and clinical trials. Within the morphology-based grading schemes included in the 2019 WHO classification, tumor budding outperformed WHO grade.

Jesinghaus M, Schmitt M, Lang C, et al. Morphology matters: a critical reappraisal of the clinical relevance of morphologic criteria from the 2019 WHO classification in a large colorectal cancer cohort comprising 1004 cases. *Am J Surg Pathol*. 2021;45(7):969–997.

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