Anatomic Pathology Selected Abstracts, 2/14

Anatomic pathology abstracts editors: Michael Cibull, MD, professor of pathology, University of Kentucky, Lexington; Rouzan Karabakhtsian, MD, attending pathologist, Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, 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.

Early stage triple-negative breast cancer treated with mastectomy without adjuvant radiotherapy

The authors conducted a study to evaluate and identify patterns of failure and prognostic factors for locoregional recurrence that could justify postmastectomy radiotherapy after modified radical mastectomy in patients with early stage triple-negative breast cancer. Between January 2000 and July 2007, the authors retrospectively analyzed 390 patients who had triple-negative breast cancer with T1/T2 tumors and from zero to three positive lymph nodes (pathologic T1-T2N0-N1) and who underwent modified radical mastectomy without postmastectomy radiotherapy at the authors' institution. The five-year cumulative incidence for events was calculated using Kaplan-Meier analysis, and subgroups were compared using the log-rank test. Multivariate analysis was performed using a Cox proportional hazards model. Overall, 86.4 percent of patients received chemotherapy. At a median followup of 60.5 months, the five-year cumulative rates of local recurrence, regional recurrence, locoregional recurrence, and distant metastasis were 5.4 percent, 4.7 percent, eight percent, and 13.4 percent, respectively. On multivariate analysis, age younger than 50 years, presence of lymphovascular invasion, grade 3 tumor, and three involved lymph nodes were significantly associated with an increased risk of locoregional recurrence. The five-year locoregional recurrence rate for patients who had zero or one risk factor, two risk factors, and three or four risk factors was 4.2 percent, 25.2 percent, and 81 percent ($P<0.0001$), respectively. The presence of lymphovascular invasion and having three involved lymph nodes were statistically significant predictors of regional recurrence, and the patients who had regional recurrence had a significantly greater risk of distant metastases compared with patients who had local recurrence (59.1 percent versus 20.9 percent; $P<0.0001$). The authors concluded that several risk factors were identified in this study that correlated independently with a greater incidence of locoregional recurrence in patients who had early stage triple-negative breast cancer. The results indicated that postmastectomy radiotherapy should be considered for those patients who have two or more of these factors.

Chen X, Yu X, Chen J, et al. Analysis in early stage triple-negative breast cancer treated with mastectomy without adjuvant radiotherapy: Patterns of failure and prognostic factors. *Cancer.* 2013;119(13):2366–2374.

Correspondence: Dr. Xiaomao Guo at guoxiaomao188@gmail.com

Predicting recurrence after limited resection versus lobectomy for small lung adenocarcinoma

The authors analyzed the prognostic significance of the new International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) lung adenocarcinoma classification for patients undergoing resection for small (2 cm or less) lung adenocarcinoma and to investigate whether histologic subtyping can predict recurrence after limited resection (LR) versus lobectomy (LO). Comprehensive histologic subtyping was performed according to the IASLC/ATS/ERS classification on all consecutive patients who underwent limited resection or lobectomy for small lung adenocarcinoma between 1995 and 2009 at Memorial Sloan-Kettering Cancer Center. Clinical characteristics and pathologic data were retrospectively evaluated for 734 consecutive patients (LR, 258; LO, 476). Cumulative incidence of recurrence (CIR) was calculated using competing risks analysis and compared across groups using Grey's test. All statistical tests were two-sided. Application of IASLC/ATS/ERS lung adenocarcinoma histologic subtyping to predict recurrence demonstrates that, in the limited resection group but not the lobectomy group, a micropapillary component of five

percent or greater was associated with an increased risk of recurrence, compared with a micropapillary component of less than five percent (LR: five-year CIR, 34.2 percent; 95 percent confidence interval [CI], 23.5–49.7 percent versus five-year CIR, 12.4 percent; 95 percent CI, 6.9–22.1 percent; P<0.001/LO: five-year CIR, 19.1 percent; 95 percent CI, 12–30.5 percent versus 15-year CIR, 12.9 percent; 95 percent CI, 7.6–21.9 percent; P=0.13). In the limited resection group, among patients with tumors with a micropapillary component of five percent or greater, most recurrences (63.4 percent) were locoregional. A micropapillary component of five percent or greater was statistically significantly associated with increased risk of local recurrence when the surgical margin was less than 1 cm (five-year CIR, 32 percent; 95 percent CI, 18.6–46 percent for micropapillary of five percent or greater versus five-year CIR, 7.6 percent; 95 percent CI, 2.3–15.6 percent for micropapillary of less than five percent; P=0.007) but not when the surgical margin was 1 cm or greater (five-year CIR, 13 percent; 95 percent CI, 4.1–22.1 percent for micropapillary of five percent or greater versus five-year CIR, 3.4 percent; 95 percent CI, zero–7.7 percent for micropapillary of less than five percent; P=0.10). The authors concluded that application of the IASLC/ATS/ERS classification identifies a micropapillary component of five percent or greater as independently associated with risk of recurrence in patients treated with limited resection.

Nitadori J, Bograd AJ, Kadota K, et al. Impact of micropapillary histologic subtype in selecting limited resection vs lobectomy for lung adenocarcinoma of 2 cm or smaller. *J Natl Cancer Inst.* 2013;105(16):1212–1220.

Correspondence: Dr. Prasad S. Adusumilli at adusumip@mskcc.org

HER2 amplification in gastric cancer: a rare event restricted to intestinal phenotype

The authors conducted a study to identify HER2 prevalence in gastric cancer and correlate it with location, phenotype, and followup. Immunohistochemistry (IHC) with the Hercep Test was performed for consecutive gastric cancer patients who provided tissue blocks, gross data, and followup data. Chromogenic and fluorescence in situ hybridization were performed on IHC-positive tumors from 269 patients (median age, 61 years). In 172 gastrectomized patients, histotypes were diffuse (72; 41.8 percent), intestinal (63; 36.6 percent), and mixed (37; 21.5 percent). HER2 IHC expression was zero in 167, 2+ in two, and 3+ in three tumors. Only endoscopic biopsies were available in 97 patients, and HER2 IHC expression was zero in 88, 1+ in three, 2+ in four, and 3+ in two patients. Ten of the 269 tumors (3.7 percent) had HER2 amplification. Amplified tumors were intestinal adenocarcinomas located throughout the various regions of the stomach. Heterogeneity was documented in four widely sampled tumors. HER2 amplification was restricted to the intestinal phenotype. It is a rare event, and its screening should be driven by gastric cancer histotype.

Cruz-Reyes C, Gamboa-Dominguez A. HER2 amplification in gastric cancer is a rare event restricted to the intestinal phenotype. *Int J Surg Pathol.* 2013;21(3):240–246.

Correspondence: Dr. Armando Gamboa-Dominguez at agamboad@gmail.com

Gleason score undergrading on biopsy sample of prostate cancer

The authors conducted a population-based study to investigate the degree of concordance between Gleason scores obtained from prostate biopsies and those obtained from prostatectomy specimens, as well as the determinants of biopsy understaging. The study included all 371 prostate cancer patients recorded at the Geneva Cancer Registry, diagnosed from 2004 to 2006, who underwent a radical prostatectomy. Kappa statistics were used to evaluate the Gleason score concordance from biopsy and prostatectomy specimens. Logistic regression was used to determine the parameters that predict undergrading of Gleason score in prostate biopsies. The kappa statistic between biopsy and prostatectomy Gleason score was 0.42 (P<0.0001), with 67 percent of patients matched exactly and 26 percent (n=95) of patients with Gleason score underestimated by biopsy. In a multi-adjusted model, biopsy undergrading was independently associated with increasing age, advanced clinical stage, having fewer than 10 biopsy cores, and longer delay between the two procedures. In particular, the proportion of exact matches increased to 72 percent when the patients had 10 or more needle biopsy cores. The main limitation

of the study was that biopsy and prostatectomy specimens were examined by different laboratories. The authors concluded that the data show that concordance between biopsy and prostatectomy Gleason scores lies within the classic clinical standards in this population-based study. The number of biopsy cores appears to strongly impact concordance between biopsy and radical prostatectomy Gleason score.

Rapiti E, Schaffar R, Iselin C, et al. Importance and determinants of Gleason score undergrading on biopsy sample of prostate cancer in a population-based study. *BMC Urol.* 2013;13:19 or www.biomedcentral.com/1471-2490/13/19

Correspondence: Elisabetta Rapiti at elisabetta.rapiti@unige.ch

Fallopian tube intraluminal tumor spread from noninvasive precursor lesions

Pelvic serous carcinoma is usually advanced stage at diagnosis, indicating that abdominal spread occurs early in carcinogenesis. Recent discovery of a precursor sequence in the fallopian tube, culminating in serous tubal intraepithelial carcinoma (STIC), provides an opportunity to study early disease events. The authors conducted a study to explore novel metastatic routes in STICs. A BRCA1 mutation carrier (patient A) who presented with a STIC and tubal intraluminal shedding of tumor cells on prophylactic bilateral salpingo-oophorectomy (PBSO) instigated scrutiny of an additional 23 women who underwent PBSO and 40 patients with pelvic serous carcinoma involving the fallopian tubes. Complete serial sectioning of the tubes and ovaries of patient A did not reveal invasive carcinoma, but subsequent staging surgery showed disseminated abdominal disease. STIC, intraluminal tumor cells, and abdominal metastases displayed an identical immunohistochemical profile (p53/WT1/PAX8/PAX2) and TP53 mutation. In 16 serous carcinoma patients (40 percent), tubal intraluminal tumor cells were found, while none were found in the PBSO group. This is the first description of an STIC that plausibly metastasized without invasion, through intraluminal shedding of malignant surface epithelial cells in the fallopian tube, and subsequently spread throughout the peritoneal cavity. These findings warrant reconsidering the malignant potential of STICs and indicate that intraluminal shedding could be a risk factor for early intraperitoneal metastasis. Although rare in the absence of invasive cancer, the authors showed that intraluminal shedding of tumor cells in the fallopian tubes of women with serous carcinoma is common and a likely route of abdominal spread.

Bijron JG, Seldenrijk CA, Zweemer RP, et al. Fallopian tube intraluminal tumor spread from noninvasive precursor lesions: a novel metastatic route in early pelvic carcinogenesis. *Am J Surg Pathol.* 2013;37(8):1123–1130.

Correspondence: Dr. Paul J. van Diest at p.j.vandiest@umcutrecht.nl

Factors that influence histopathological diagnosis of differentiated vulvar intraepithelial neoplasia

No published data concerning intraobserver and interobserver variability in the histopathological diagnosis of differentiated vulvar intraepithelial neoplasia (DVIN) are available, although the histopathological diagnosis is widely accepted to be subtle and difficult. The authors evaluated the reproducibility of the histopathological diagnosis of DVIN in a study. They also investigated the possible improvement in reproducibility after providing guidelines with histological characteristics, and they tried to identify the histological characteristics that are most important for recognizing DVIN. A total of 34 hematoxylin-and-eosin–stained slides were included in this study. They were analyzed by six pathologists, each with a different level of education. The pathologists reviewed the slides before and after studying a guideline with histological characteristics of DVIN. Kappa statistics were used to compare interobserver variability. Pathologists who had substantial agreement were asked to rank items by their usefulness for identifying DVIN. The interobserver agreement during the first session varied between 0.08 and 0.54. It increased slightly during the second session to between -0.01 and 0.75. Pathologists who specialized in gynecopathology reached substantial agreement (kappa, 0.75). The top five criteria identified as the most useful for diagnosing DVIN included atypical mitosis in the basal layer, basal cellular atypia, dyskeratosis, prominent

nucleoli and elongation, and anastomosis of rete ridges. The authors concluded that the histopathological diagnosis of DVIN is difficult, as expressed by low interobserver agreement. Only with experienced pathologists who were trained in gynecopathology, and after strict guidelines were provided, did kappa values reach substantial agreement. Therefore, it is recommended that specimens with an unclear diagnosis or clinical suspicion for DVIN, or both, be assessed by a pathologist who specializes in gynecopathology. <p class=”>Van den Einden LC, de Hullu JA, Massuger LF, et al. Interobserver variability and effect of education in the histopathological diagnosis of differentiated vulvar intraepithelial neoplasia. *Mod Pathol.* 2013;26:874–880.

Correspondence: Dr. L. C. van den Einden at l.vandeneinden@obgyn.umcn.nl

Impact of molecular analysis on final sarcoma diagnosis

Sarcomas are rare, heterogenous, and, often, difficult to classify. A large proportion of sarcomas are associated with specific molecular genetic lesions, such as translocations, mutations, and amplifications, which are helpful for diagnosing individual cases. However, the exact impact of molecular genetics on the final diagnosis of sarcomas is unknown. The authors conducted a study in which all soft tissue and visceral sarcomas in patients living in three European regions in two countries (representing 13 million inhabitants) were collected and reviewed during two consecutive years. A molecular analysis was performed for suspicion of sarcomas with specific genetic lesions—mutations of KIT/PDGFRA in gastrointestinal stromal tumors (GISTs), reciprocal translocation, or amplification of MDM2 in atypical lipomatous tumors/well-differentiated liposarcoma-dedifferentiated liposarcoma (ALT/WDLPS-DDLPS). To evaluate the impact of molecular tests, a premolecular analysis diagnosis with three categories of certainty—certain, probable, or possible—was proposed. A molecular analysis was performed for 763 of 1,484 tumors corresponding to 295 cases in which GIST was suspected, 248 sarcomas with a suspicion of translocation, and 220 cases in which ALT/WDLPS-DDLPS was suspected. Molecular analysis was found to be useful, confirming a probable diagnosis, in 11 GISTs (four percent), 62 suspicions of translocation (26 percent), and 66 suspicions of ALT/WDLPS-DDLPS (31 percent). It was found to be necessary, allowing a possible diagnosis, in two GISTs (fewer than one percent), 31 suspicions of translocation (12 percent), and 19 suspicions of ALT/WDLPS-DDLPS (nine percent). The authors concluded that this study, performed in an epidemiological setting, demonstrates the significant impact of molecular analysis on the final sarcoma diagnosis and favors such an analysis on any tumor with a suspicion of a specific genomic abnormality and for which the diagnosis is uncertain.

Neuville A, Ranchère-Vince D, Dei Tos AP, et al. Impact of molecular analysis on the final sarcoma diagnosis: a study on 763 cases collected during a European epidemiological study. *Am J Surg Pathol.* 2013;37(8): 1259–1268.

Correspondence e-mail not provided.

Distinguishing primary bladder adenocarcinoma from secondary involvement by colorectal adenocarcinoma

Glandular neoplasms involving the urinary bladder carry a challenging differential diagnosis including primary and secondary processes. The authors investigated the potential diagnostic utility of cadherin-17 and GATA3 in 25 primary adenocarcinomas of the urinary bladder, as compared with other commonly used markers, including β-catenin and p63. Urothelial carcinoma with glandular differentiation (11), colorectal adenocarcinoma secondarily involving the bladder (25), and primary colorectal adenocarcinoma (22) were also analyzed and the results compared using a Fisher exact test. Cadherin-17 was expressed in 23 of 25 primary bladder adenocarcinomas (92 percent), 23 of 25 colorectal adenocarcinomas involving the bladder (92 percent), and 21 of 22 primary colorectal adenocarcinomas (95 percent) and was entirely negative (zero of 11) in both components of urothelial carcinoma with glandular differentiation ($P<0.001$). In urothelial carcinoma with glandular differentiation, positive nuclear staining for GATA3 was evident in the urothelial component for 18 percent (two of 11) and the glandular component for nine percent (one of 11), with additional tumors showing only cytoplasmic staining. Nuclear reactivity for GATA3 was not present in primary bladder adenocarcinoma and primary/secondary colorectal adenocarcinoma ($P<0.05$). Positive nuclear and cytoplasmic immunostaining for β-catenin was evident in 21 of 22

primary colorectal adenocarcinomas (95 percent) and 23 of 25 cases of secondary involvement by colorectal adenocarcinoma (92 percent). In contrast, positive membranous and cytoplasmic staining for β-catenin was observed in 23 of 25 primary bladder adenocarcinomas (92 percent) and 11 of 11 urothelial carcinomas with glandular differentiation (100 percent; P<0.001). P63 was expressed only in the urothelial component of urothelial carcinoma with glandular differentiation and not in the glandular component (P<0.001). The authors concluded that cadherin-17 is a relatively specific and sensitive marker for primary adenocarcinoma of the urinary bladder, distinguishing if from urothelial carcinoma with glandular differentiation. However, it does not distinguish primary bladder adenocarcinoma from secondary involvement by colorectal adenocarcinoma. The pattern of reactivity for β-catenin remains the most useful marker for distinguishing these two tumors.

Rao Q, Williamson SR, Lopez-Beltran A, et al. Distinguishing primary adenocarcinoma of the urinary bladder from secondary involvement by colorectal adenocarcinoma: extended immunohistochemical profiles emphasizing novel markers. *Mod Pathol.* 2013;26:725–732.

Correspondence: Dr. L. Cheng at liang_cheng@yahoo.com

Determining if close margins warrant postoperative adjuvant radiotherapy in oral squamous cell carcinoma

Institutions vary widely with regard to recommending postoperative adjuvant therapy for adverse features in patients with oral squamous cell carcinoma (SCC). The authors' practice has been to not recommend adjuvant therapy on the basis of close margins (less than 5 mm but uninvolved) unless there are additional adverse features. The authors conducted a study to assess whether the local control achieved in this patient cohort was acceptable. In a single-institution, retrospective analysis, local control was the primary endpoint, and disease-specific survival was the secondary endpoint. Differences in survival were determined using the log-rank test, and survival curves were generated using the Kaplan-Meier method. One hundred forty-four patients (79 men and 65 women; median age, 64.1 years; mean followup, 3.3 years) underwent surgery alone for oral squamous cell carcinoma with curative intent and were recorded as having close tumor margins on histology. The local control rate for all patients who underwent surgery alone was 91 percent (95 percent confidence interval, 81.9–95.2 percent), and the disease-specific survival rate at five years was 84 percent (95 percent confidence interval, 74–89.9 percent). There was no pattern of worse local control or disease-specific survival rates with the ordered stratification of close margins. The five-year local control rates for having zero, one, two, and three additional adverse features were 100 percent, 96 percent, 83 percent, and 71 percent, respectively (P=0.004; trend test). The authors concluded that surgery alone without postoperative adjuvant therapy offered acceptable local control in patients who had close margin status as their only adverse feature and may be reasonable in the presence of one other adverse clinicopathologic feature.

Ch'ng S, Corbett-Burns S, Stanton N, et al. Close margin alone does not warrant postoperative adjuvant radiotherapy in oral squamous cell carcinoma. *Cancer.* 2013;119(13):2427–2437.

Correspondence: Dr. Sydney Ch'ng at snchng@xtra.co.nz

Three methodological approaches for defining basal-like lesions in triple-negative breast carcinoma

Basal-like invasive breast cancer is an important clinical group because of its association with a triple-negative phenotype defined by the lack of expression of estrogen, progesterone, and human epidermal growth factor receptor 2; relative lack of therapeutic options; and poor prognosis. However, depending on the method used to define these lesions—morphological assessment, immunohistochemical markers, or gene expression—a different set of tumors is captured. The authors conducted a study to investigate the consequences of using different methodological approaches to define basal-like lesions among triple-negative breast carcinomas with regard to their clinicopathological features and patient outcomes. The cohort consisted of 142 invasive breast cancers with

triple-negative receptor status. Each was reviewed histologically, and those with morphological basal-like features were characterized as “path-basal.” Then the “core basal” immunohistochemical lesions, defined as cytokeratin 5/6 or epidermal growth factor receptor 1-positive, or both, within the triple-negative breast cancers, were identified, and their classification based on gene-expression profiling was retrieved. Those in the molecular “PAM50 basal-like” subtype were recorded. The study identified 116 basal-like breast cancers among the 142 triple-negative breast cancers by at least one of the three classifications (80 percent), but only 13 samples were defined as basal-like with all three methods. None of these 13 tumors were associated with lymphovascular invasion. The 34 morphological path-basal lesions were significantly associated with a lack of nodal metastases. Comparing the estimates of death in the three classifications, the highest risk of death was seen for the core basal group. The authors concluded that the definition of basal-like breast cancer based on different methodologies varies significantly and does not identify the same lesions. This incomplete overlap of cases emphasizes the need for consistent or new approaches to improve identification.

Gazinska P, Grigoriadis A, Brown JP, et al. Comparison of basal-like triple-negative breast cancer defined by morphology, immunohistochemistry and transcriptional profiles. *Mod Pathol.* 2013;26:955–966.

Correspondence: S. E. Pinder at sarah.pinder@kcl.ac.uk