Anatomic Pathology Abstracts, 2/17

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Findings in hysterectomy specimens of women with Lynch syndrome

Women with Lynch syndrome have a high risk of developing endometrial carcinoma and, less frequently, ovarian carcinoma. Because it is not uncommon for endometrial cancer to be the first malignancy, prophylactic hysterectomy has been increasingly implemented. The authors conducted a study of the relationship between Lynch syndrome and carcinoma in which they reported the clinicopathologic features of a series of 70 Lynch syndrome patients who underwent either prophylactic hysterectomy (n = 39) or nonprophylactic hysterectomy (n = 31) at three tertiary referral centers. Among the 39 patients who underwent prophylactic hysterectomy, two had endometrial tumors seen grossly and 37 showed no macroscopic lesions. Total inclusion of the endometrium was performed in 24 of 39 (61.5 percent). Abnormal histologic findings were identified in nine of 39 (23.1 percent) prophylactic hysterectomies: three endometrial endometrioid carcinomas (EECs), including the two macroscopic and one microscopic (0.6 cm), and four atypical and six nonatypical hyperplasias. Nonprophylactic hysterectomy included those performed for endometrial and ovarian cancer treatment. Tumor sampling followed standard protocols. Endometrial carcinomas comprised 26 EECs and one clear cell carcinoma, with a median size of 3.7 cm. Hyperplasia was observed in 10 (33.3 percent) as background in endometrial carcinoma, in four showing atypia. Eight (29.6 percent) tumors, all of which were EECs, were centered in the lower uterine segment. EECs were predominantly well differentiated (53.8 percent) and FIGO stage I (77.8 percent). A papillary architecture was common (51.9 percent) and associated with microcystic elongated and fragmented foci in four. Mucinous differentiation was observed in 25.9 percent of endometrial tumors, typically representing less than 10 percent. Most (81.5 percent) endometrial tumors showed tumor-infiltrating lymphocyte counts of at least 42/10 high-power fields. Four tumors showed extensive necrosis. Eight patients had ovarian tumors (four synchronous), including two endometrioid carcinomas, two clear cell carcinomas, one borderline clear cell adenofibroma, one Müllerian carcinoma of mixed cell types, one primitive neuroectodermal tumor, and one metastatic melanoma. The authors concluded that total inclusion of the endometrium should be performed in all Lynch syndrome patients' surgical specimens without macroscopic lesions because some of these patients harbor preneoplastic or neoplastic conditions that can be treated at an early stage. The phenotype of Lynch syndrome-associated endometrial and ovarian tumors is variable and frequently includes features not commonly observed in sporadic cancers. However, in the authors' experience, carcinomas were generally low grade and low stage.

Bartosch C, Pires-Luís AS, Meireles C, et al. Pathologic findings in prophylactic and nonprophylactic hysterectomy specimens of patients with Lynch syndrome. *Am J Surg Pathol.* 2016;40:1177–1191.

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Percentages and architectural types of Gleason pattern 4 cancer in radical prostatectomy

The 2014 consensus meeting of the International Society of Urological Pathology (ISUP) recommended a novel grade grouping for prostate cancer that included dividing Gleason score 7 into grade groups 2 (Gleason score 3+4) and 3 (Gleason score 4+3). This division of Gleason score 7, essentially determined by the percentage of Gleason pattern 4 (more or less than 50 percent), raises the question of whether a more exact quantification of the percentage of Gleason pattern 4 within Gleason score 7 will yield additional prognostic information. ISUP also made modifications to the definition of Gleason pattern 4 by including four main architectural types: cribriform, glomeruloid, poorly formed, and fused glands. The authors conducted a study to analyze the prognostic significance of the percentage of Gleason pattern 4 and main architectural types of Gleason pattern 4 according to the 2014 ISUP grading criteria in radical prostatectomies. The study cohort included 585 radical prostatectomy cases of Gleason score 6 (40.2 percent), 3+4 (49 percent), and 4+3 (10.8 percent) prostate cancers. Five-year biochemical recurrence-free survival rates that varied significantly were observed among Gleason score 6 (99 percent; 95 percent confidence interval [CI], 97–100 percent), 3+4 (81 percent; 95 percent CI, 76–86 percent), and 4+3 (60 percent; 95 percent CI, 45–71 percent) cancers (P<.01). Dividing the Gleason pattern 4 percentage into quartiles showed a five-year biochemical recurrence-free survival rate of 84 percent (95 percent CI, 78–89 percent) for one percent to 20 percent of cases, 74 percent (95 percent CI, 62–83 percent) for 21 percent to 50 percent of cases, 66 percent (95 percent CI, 50–78 percent) for 51 percent to 70 percent of cases, and 32 percent (95 percent CI, nine–59 percent) for more than 70 percent of cases (P<.001). Among the Gleason pattern 4 architectures, cribriform was the most prevalent (43.7 percent), and a combination of architectures with cribriform present was more frequently observed in Gleason score 4+3 (60.3 percent). Glomeruloid was mostly (67.1 percent) seen combined with other Gleason pattern 4 architectures. Unlike the other Gleason pattern 4 architectures, glomeruloid as the sole Gleason pattern 4 was observed only as a secondary pattern—that is, 3+4. Among patients with Gleason score 7 cancer, the presence of cribriform architecture was associated with decreased five-year biochemical recurrence-free survival when compared with Gleason score 7 cancers without this architecture (68 versus 85 percent; P<.01), whereas the presence of glomeruloid architecture was associated with improved five-year biochemical recurrence-free survival when compared with Gleason score 7 cancers without this architecture (87 versus 75 percent; P=.01). However, Gleason score 7 disease having only the glomeruloid architecture had significantly lower five-year biochemical recurrence-free survival than Gleason score 6 cancers (86 versus 99 percent; P<.01). A multivariable Cox proportional hazards regression model for factors associated with biochemical recurrence among Gleason score 7 cancers identified age (hazard ratio [HR], 0.95; P<.01), preoperative prostate-specific antigen (HR, 1.07; P<.01), positive surgical margin (HR, 2.70; P<.01), percentage of Gleason pattern 4 (21–50 percent [HR, 2.21]; 51–70 percent [HR, 2.59]; greater than 70 percent [HR, 6.57]; all P<.01), presence of cribriform glands (HR, 1.78; P=.02), and presence of glomeruloid glands (HR, 0.43; P=.03) as independent predictors. The authors concluded that their study shows that increments in percentage of Gleason pattern 4 correlate with increased risk for biochemical recurrence supporting the ISUP recommendation of recording the percentage of Gleason pattern 4 in Gleason score 7 prostate cancers at radical prostatectomy. However, additional larger studies are needed to establish the optimal interval for reporting percentage Gleason pattern 4 in Gleason score 7 cancers. Among the Gleason pattern 4 architectures, cribriform independently predicts biochemical recurrence, whereas glomeruloid reduces the risk of such recurrence. Distinction should be made between cribriform and glomeruloid architectures, despite glomeruloid being considered an early stage of cribriform, as cribriform confers a higher risk for poorer outcome.

Choy B, Pearce SM, Anderson BB, et al. Prognostic significance of percentage and architectural types of

contemporary Gleason pattern 4 prostate cancer in radical prostatectomy. *Am J Surg Pathol.* 2016;40:1400–1406.

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PTEN loss and chromosome 8 alterations in Gleason grade 3 prostate cancer cores

Men who enter active surveillance because their biopsy exhibits only Gleason grade 3 (G3) frequently have higher grade tumor missed by biopsy. Therefore, biomarkers that, when measured on G3 tissue, can predict the presence of higher grade tumor in the whole prostate are needed. The authors evaluated whether *PTEN* loss, chromosome 8q gain (*MYC*), or 8p loss *(LPL*) measured only on G3 cores is associated with unsampled G4 tumor. A tissue microarray of prostatectomy tissue from patients whose prostates exhibited only Gleason score 3+3, only 3+4, or only 4+3 tumor (n=50 per group) was constructed. Cores sampled only from areas of G3 were evaluated for *PTEN* loss by immunohistochemistry, and *PTEN* deletion, *LPL*/8p loss, and *MYC*/8q gain by FISH. Conditional logistic regression was used to compare biomarker results between Gleason score 6 versus score 7 tumors. *PTEN* protein loss (odds ratio, 4.99; P=.033), *MYC*/8q gain (odds ratio, 5.36; P=.010), and *LPL*/8p loss (odds ratio, 3.96; P=.003) were significantly more common in G3 cores derived from Gleason 7 versus Gleason 6 tumors. *PTEN* gene deletion was not statistically significant. Associations were stronger comparing Gleason 4+3 versus 6 than for Gleason 3+4 versus 6. *MYC*/8q gain, *LPL*/8p loss, and *PTEN* protein loss measured in G3 tissue microarray cores strongly differentiate whether the core comes from a Gleason 6 or Gleason 7 tumor. The authors concluded that if validated to predict upgrading from G3 biopsy to prostatectomy, these biomarkers could reduce the likelihood of enrolling high-risk men and facilitate safe patient selection for active surveillance.

Trock BJ, Fedor H, Gurel B, et al. *PTEN* loss and chromosome 8 alterations in Gleason grade 3 prostate cancer cores predicts the presence of an un-sampled grade 4 tumor: implications for active surveillance. *Mod Pathol.* 2016;29:764–771.

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Conflicting interpretation of genetic variants and cancer risk by commercial laboratories

Massively parallel sequencing allows simultaneous testing of multiple genes associated with cancer susceptibility. Guidelines are available for variant classification; however, interpretation of these guidelines by laboratories and providers may differ and lead to conflicting reporting and, potentially, inappropriate medical management. The authors described conflicting variant interpretations between CLIA-approved commercial clinical laboratories, as reported to the Prospective Registry of Multiplex Testing (PROMPT) online genetic registry. Clinical data and genetic testing results were gathered from 1,191 people tested for inherited cancer susceptibility and self-enrolled in PROMPT between September 2014 and October 2015. Overall, 518 participants (603 genetic variants) had a result interpreted by more than one laboratory, including at least one submitted to the ClinVar public archive. These were used as the final cohort for the authors' analysis. Of the 603 variants, 221 (37 percent) were classified as a variant of uncertain significance, 191 (32 percent) as pathogenic, and 34 (six percent) as benign. The interpretation differed among reporting laboratories for 155 (26 percent) variants. Conflicting interpretations were most frequently reported for *CHEK2* and *ATM*, followed by *RAD51C, PALB2, BARD1, NBN*, and *BRIP1*. Among the 518 participants, 56 (11 percent) had a variant with conflicting interpretations ranging from pathogenic/likely pathogenic to variant of uncertain significance, a discrepancy that may alter medical management. The authors concluded that conflicting interpretations of genetic findings from multiplex panel testing used in clinical practice are frequent and may have implications for medical-management decisions.

Balmaña J, Digiovanni L, Gaddam P, et al. Conflicting interpretation of genetic variants and cancer risk by commercial laboratories as assessed by the Prospective Registry of Multiplex Testing. *J Clin Oncol.* 2016;34:4071–4078.

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Lymph node count from neck dissection predicts mortality in head and neck cancer

Multiple smaller studies have demonstrated an association between overall survival and lymph node count from neck dissection in patients with head and neck cancer. The authors conducted a large cohort study to examine these associations using the National Cancer Database to identify patients who underwent upfront nodal dissection for mucosal head and neck squamous cell carcinoma between 2004 and 2013. Patients were stratified into those with fewer than 18 lymph nodes and those with 18 or more lymph nodes on the basis of prior work. A multivariable Cox proportional hazards regression model was constructed to predict hazard of mortality. Stratified models predicted hazard of mortality for patients who were both node negative and node positive. The authors examined 45,113 patients with 18 or more lymph nodes and 18,865 patients with fewer than 18 lymph nodes. The group with fewer lymph nodes had more favorable tumor characteristics than the group with more lymph nodes, as well as a lower proportion of T3 and T4 lesions (27.9 versus 39.8 percent), fewer patients with positive nodes (46.6 versus 60.5 percent), and lower rates of extracapsular extension (9.3 versus 15.1 percent). Risk-adjusted Cox models predicting hazard of mortality by lymph node count showed an 18 percent increased hazard of death for patients with fewer than 18 nodes examined (hazard ratio [HR], 1.18; 95 percent confidence interval [CI], 1.13–1.22). When stratified by clinical nodal stage, an increased hazard of death was noted in both groups (node negative: HR, 1.24; 95 percent CI, 1.17–1.32; node positive: HR, 1.12; 95 percent CI, 1.05–1.19). The authors concluded that their study demonstrates a significant overall survival advantage in both patients who are clinically node negative and node positive when 18 or more lymph nodes are examined after neck dissection, which suggests that lymph node count is a potential quality metric for neck dissection.

Divi V, Chen MM, Nussenbaum B, et al. Lymph node count from neck dissection predicts mortality in head and neck cancer. *J Clin Oncol.* 2016;34:3892–3897.

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Assessing the adequacy of lymph node yield for papillary thyroid cancer

Patients who undergo surgery for papillary thyroid cancer with limited lymph node examination are thought to be at risk for harboring occult disease. This risk should be quantified objectively as it may have implications for subsequent management and surveillance. Data from the National Cancer Database, from 1998 to 2012, were used to characterize the distribution of nodal positivity of adult patients diagnosed with localized (1 cm or more) papillary thyroid cancer who underwent thyroidectomy with examination of one or more lymph nodes. A β-binomial distribution was used to estimate the probability of occult nodal disease as a function of total number of lymph nodes examined and pathologic tumor stage. A total of 78,724 patients met the study criteria, and 38,653 of those patients had node-positive disease. The probability of falsely identifying a patient as node negative was estimated to be 53 percent for patients who had a single node examined and decreased to less than 10 percent for patients who had more than six lymph nodes examined. To rule out occult nodal disease with 90 percent confidence, six, nine, and 18 nodes would need to be examined for patients with T1b, T2, and T3 disease, respectively. Sensitivity analyses limited to patients likely undergoing prophylactic central neck dissection resulted in three, four, and eight nodes needed to provide comparable adequacy of lymph node evaluation. The authors concluded that their study provides empirically based estimates of occult nodal disease risk in patients after surgery for papillary thyroid

cancer as a function of primary tumor stage and number of lymph nodes examined. Their estimates provide an objective guideline for evaluating the adequacy of lymph node yield for surgeons and pathologists in the treatment of papillary thyroid cancer, especially intermediate-risk disease, for which use of adjuvant radioactive iodine and surveillance intensity are not standardized.

Robinson TJ, Thomas S, Dinan MA, et al. How many lymph nodes are enough? Assessing the adequacy of lymph node yield for papillary thyroid cancer. *J Clin Oncol.* 2016;34(28):3434–3439.

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Addressing perceived versus actual agreement in breast pathology interpretation

The authors examined the manner in which pathologists process their perceptions of how their interpretations of breast pathology diagnoses agree with a reference standard. To accomplish this, they created an individualized, self-directed continuing medical education program that shows pathologists who interpret breast specimens how their interpretations on a test set compare with a reference diagnosis developed by a consensus panel of experienced breast pathologists. After interpreting a test set of 60 cases, 92 participating pathologists were asked to estimate how their interpretations compared with the standard for benign without atypia, atypia, ductal carcinoma in situ, and invasive cancer. The authors then asked pathologists their thoughts about assessing differences in their perceptions compared with actual agreement. They found that, overall, participants tended to overestimate their agreement with the reference standard, with a mean difference of 5.5 percent (75.9 percent actual agreement; 81.4 percent estimated agreement), especially for atypia. They were least likely to overestimate agreement for invasive breast cancer. Nonacademic-affiliated pathologists were more likely to more closely estimate their performance compared to academic-affiliated pathologists (77.6 versus 48 percent, respectively; P=.001), whereas participants affiliated with an academic medical center were more likely to underestimate agreement with their diagnoses compared with nonacademic-affiliated pathologists (40 versus six percent, respectively). Prior to the continuing medical education program, 54.9 percent of participants could not estimate whether they would overinterpret the cases or underinterpret them relative to the reference diagnosis. Furthermore, 79.8 percent of participants reported learning new information from the individualized Web-based continuing medical education program, and 23.9 percent of pathologists identified strategies for which they would change their practice to improve. The authors concluded that when evaluating breast pathology specimens, pathologists do a good job of estimating their diagnostic agreement with a reference standard. However, they tend to overestimate diagnostic agreement for atypia cases. Many participants were able to identify ways to improve.

Carney PA, Allison KH, Oster NV, et al. Identifying and processing the gap between perceived and actual agreement in breast pathology interpretation. *Mod Pathol.* 2016;29:717–726.

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Cost-effectiveness of Oncotype DX DCIS score for guiding treatment of DCIS

The Oncotype DX DCIS Score short form, or DCIS score, estimates the risk of an ipsilateral breast event in patients with ductal carcinoma in situ (DCIS) treated with breast-conserving surgery without adjuvant radiation therapy. The authors determined the cost-effectiveness of strategies using this test. They developed a Markov model simulating 10-year outcomes for 60-year-old women eligible for the Eastern Cooperative Oncology Group E5194 study (cohort one: low/intermediate-grade DCIS, ≤ 2.5 cm; cohort two: high-grade DCIS, ≤ 1 cm) using five strategies: no testing and no radiation therapy; no testing, with radiation therapy only for cohort two; no radiation therapy for low-grade

DCIS and test for intermediate- and high-grade DCIS, with radiation therapy for intermediate- or high-risk scores; test all, with radiation therapy for intermediate- or high-risk scores; and no testing, with radiation therapy for all. The authors used utilities and costs extracted from the literature and Medicare claims to determine incremental cost-effectiveness ratios and examined the number of women needed to irradiate per ipsilateral breast event prevented. No strategy using the DCIS score was cost-effective. The most cost-effective strategy—radiation therapy for none or for all—was sensitive to small differences between the utilities of receiving or not receiving radiation therapy and remaining without recurrence. The numbers needed to irradiate per ipsilateral breast event prevented were 10.5, 9.1, 7.5, and 13.1 for strategies two to five, respectively, relative to strategy one. The authors concluded that strategies using the DCIS score lowered the proportion of women undergoing radiation therapy per ipsilateral breast event prevented. However, no strategy incorporating the DCIS score was cost-effective. The cost-effectiveness of radiation therapy was utility sensitive, highlighting the importance of obtaining patient preferences in this decision. Physicians should discuss with each patient the trade-offs associated with omitting or adding adjuvant radiation therapy to maximize quality-of-life outcomes.

Raldow AC, Sher D, Chen AB, et al. Cost effectiveness of the Oncotype DX DCIS score for guiding treatment of patients with ductal carcinoma in situ. *J Clin Oncol.* 2016;34:3963–3968.

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