Anatomic Pathology Abstracts

Neuroendocrine differentiation in breast carcinoma

Primary neuroendocrine breast carcinoma has a wide range of prevalence and poorly defined clinical behavior. The authors evaluated the prevalence, clinicopathological features, and clinical outcome of the disease. Immunohistochemical staining for synaptophysin and chromogranin A was performed on whole sections from 1,232 consecutive cases of invasive breast carcinoma. The authors divided primary neuroendocrine breast carcinoma (NEBC) into focal (10 to 49 percent positive cells) and diffuse (50 percent or more positive cells) and compared the outcome of patients with NEBC with strictly matched non-NEBC patients. A total of 128 breast carcinomas showed neuroendocrine differentiation (10.4 percent): 84 diffuse (6.8 percent) and 44 focal (3.6 percent). Neuroendocrine differentiation showed a significant association with T4 stage (P=.001), solid papillary and mucinous histotype (P<.0001), G2 grading (P=.002), and positive estrogen receptor (P=.003) and progesterone receptor (P=.002). Almost 90 percent of NEBCs were ER+/HER2– and more than half ER+/HER2–/Ki67≥14 percent. Kaplan-Meier analysis revealed that patients with NEBC had worse disease-free survival (DFS) rates (P=.04) than matched non-NEBC patients. The authors did not find significant differences regarding clinicopathological features, DFS rates, and cancer-specific survival rates between diffuse and focal neuroendocrine breast carcinoma. They concluded that their study demonstrates that NEBC represents seven to 10 percent of invasive breast carcinomas and that neuroendocrine differentiation does not affect the prognosis of breast carcinoma in terms of cancer-specific survival.

Bogina G, Munari E, Brunelli M, et al. Neuroendocrine differentiation in breast carcinoma: clinicopathological features and outcomes. *Histopathol.* 2016;68:422–432

Correspondence: Giuseppe Bogina at giuseppe.bogina@sacrocuore.it

[hr]

Comparison of bilateral versus unilateral multifocal papillary thyroid cancer

Bilaterality is common in papillary cancer, but its clinical and prognostic implications remain controversial, and it is still unclear if its behavior is more aggressive than multifocal. The authors reviewed the clinicopathologic features

of 2,211 consecutive patients with papillary thyroid cancer (PTC) who underwent surgical treatment at their institute between 1997 and 2011. Among these surgical patients, 425 had bilateral PTCs and 1,786 had unilateral PTCs. The patients who had unilateral PTCs were subdivided into a group with unilateral-multifocal PTCs (210 patients) and a group with solitary PTCs (1,576 patients). The 10-year disease-free survival (DFS) rates were calculated to compare the prognosis between groups. B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutation status was examined by direct DNA sequencing. Patients who had bilateral PTCs were likely to have larger tumors, higher rates of extrathyroid extension and lymph node metastasis, and more advanced tumor stage than those who had unilateral-multifocal PTCs. Multivariate analysis identified only lymph node metastasis as an independent risk factor for PTC recurrence ($P<.001$). The 10-year DFS rate for patients with bilateral PTCs was much lower than that for those with unilateral-multifocal and solitary PTCs (78.8 versus 85.7 percent and 89.3 percent, respectively; $P=.005$). It is noteworthy that patients who had bilateral PTCs with lymph node metastasis had the worst prognosis in terms of DFS. Incidence of the BRAF V600E mutation (valine to glutamic acid mutation at position 600) was higher in the bilateral PTC group than in the unilateral and unilateral-multifocal PTC groups. The authors concluded that these results provide initial evidence that bilateral PTCs are more aggressive than unilateral-multifocal PTCs, and patients who have bilateral disease have more advanced stage and shorter DFS rates. The poorer outcome of patients with bilateral PTCs may be caused, in part, by these patients' high incidence of lymph node metastasis.

Wang W, Su X, He K, et al. Comparison of the clinicopathologic features and prognosis of bilateral versus unilateral multifocal papillary thyroid cancer: An updated study with more than 2000 consecutive patients. *Cancer.* 2016;122:198–206.

Correspondence: Dr. Lisong Teng at lsteng@zju.edu.cn and Dr. Xiaodong Teng at teng1723@163.com

[hr]

Use of immunohistochemical and cytogenetic analyses to diagnose metanephric adenoma

Metanephric adenoma is a benign renal neoplasm for which the morphology overlaps that of the solid variant of papillary renal cell carcinoma and epithelial-predominant nephroblastoma. To aid in resolving this differential diagnosis, the authors investigated the utility of immunohistochemical and molecular analyses in distinguishing between these entities. They analyzed 37 tumors originally diagnosed as metanephric adenomas (two of which were reclassified as papillary renal cell carcinomas), 13 solid variant papillary renal cell carcinomas, and 20 epithelial-predominant nephroblastomas using a combination of immunohistochemistry and FISH to assess for trisomy of chromosomes 7 and 17 and loss of Y. Immunohistochemical staining was performed for CK7, AMACR, WT1, and CD57. The combination of CK7–, AMACR–, WT1+, and CD57+ was considered characteristic of metanephric adenoma. Approximately 84 percent (31 of 37) of the tumors originally diagnosed as metanephric adenomas showed the expected staining pattern of metanephric adenoma (CK7–, AMACR–, WT1+, and CD57+). Of the six tumors with discordant immunophenotype, two tumors were reclassified as papillary renal cell carcinoma after cytogenetic workup. It is recommended that all adult cases histologically resembling metanephric adenoma undergo immunohistochemical staining for WT1, CD57, CK7, and AMACR. If the staining pattern is characteristic for metanephric adenoma (CK7–, AMACR–, WT1+, and CD57+, including membranous staining), no other diagnostic tests are necessary. However, when there is a different immunostaining pattern, the authors recommend FISH analysis.

Kinney SN, Eble JN, Hes O, et al. Metanephric adenoma: the utility of immunohistochemical and cytogenetic analyses in differential diagnosis, including solid variant papillary renal cell carcinoma and epithelial-predominant nephroblastoma. *Mod Pathol.* 2015;28:1236–1248.

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

[hr]

Genomic instability of PTEN in clinically insignificant and significant prostate cancer

Patients with clinically insignificant prostate cancer remain a majorly overtreated population. *PTEN* loss is one of the most recurrent alterations in prostate cancer associated with an aggressive phenotype. However, *PTEN* loss in insignificant prostate cancer has not been reported, and its role in separating insignificant from significant prostate cancer is unclear. An integrated analysis of *PTEN* loss was, therefore, performed for structural variations, point mutations, and protein expression in clinically insignificant (48 cases) and significant (76 cases) prostate cancers treated by radical prostatectomy. Whole-genome mate pair sequencing was performed on tumor cells isolated by laser-capture micro-dissection to characterize *PTEN* structural alterations. FISH probes were constructed from the sequencing data to detect the spectrum of these *PTEN* alterations. *PTEN* loss by mate pair sequencing and FISH occurred in two percent of insignificant, 13 percent of large volume Gleason score 6, and 46 percent of Gleason score 7 and higher cancers. In Gleason score 7 cancers with *PTEN* loss, *PTEN* alterations were detected in Gleason pattern 3 and 4 in 57 percent of cases by mate pair sequencing, 75 percent by in situ hybridization, and 86 percent by immunohistochemistry. *PTEN* loss by sequencing was strongly associated with *TMPRSS2-ERG* fusion, biochemical recurrence, *PTEN* loss by in situ hybridization, and protein loss by immunohistochemistry. The complex nature of *PTEN* rearrangements was unveiled by sequencing, detailing the heterogeneous events leading to homozygous loss of *PTEN*. *PTEN* point mutations were present in five percent of clinically significant tumors and no insignificant cancers or high-grade prostatic intraepithelial neoplasias. *PTEN* loss is infrequent in clinically insignificant prostate cancer and is associated with higher grade tumors. Detection of *PTEN* loss in Gleason score 6 cancer in a needle biopsy specimen indicates a higher likelihood of clinically significant prostate cancer.

Murphy SJ, Karnes RJ, Kosari F, et al. Integrated analysis of the genomic instability of *PTEN* in clinically insignificant and significant prostate cancer. *Mod Pathol.* 2016;29:143–156.

Correspondence: Dr. G. Vasmatzis at vasmatzis.george@mayo.edu or Dr. J. C. Cheville at cheville.john@mayo.edu

[hr]

Targeted genomic profiling in mesonephric carcinomas of the female genital tract

Mesonephric carcinoma is a rare form of gynecologic cancer derived from mesonephric remnants usually located in the lateral wall of the uterine cervix. An analogous tumor occurs in the adnexa, female adnexal tumor of probable Wolffian origin. The pathogenesis and molecular events in mesonephric carcinoma are not known. The authors conducted a study to examine the molecular alterations in mesonephric carcinoma to identify driver mutations and mutations that could be targeted therapeutically. The study consisted of 19 tumors from 17 patients: 18 mesonephric carcinomas (15 primary tumors and three metastatic tumors) and one female adnexal tumor of probable Wolffian origin. In two patients, both primary and metastatic tumors were available. Genomic DNA was isolated, and targeted next-generation sequencing was performed to detect mutations, copy number variations, and structural variants by surveying full exonic regions of 300 cancer genes and 113 selected intronic regions across 35 genes. FISH for 1p and 1q was performed in two cases. Eighty-one percent (13 of 16) of mesonephric carcinomas had either a *KRAS* (n=12) or *NRAS* (n=1) mutation. Mutations in chromatin remodeling genes—*ARID1A, ARID1B,* or *SMARCA4*—were present in 62 percent of mesonephric carcinomas. All mesonephric carcinomas lacked mutations in *PIK3CA* and *PTEN*. The most common copy number alteration was 1q gain, found in 12 (75 percent) mesonephric carcinomas; this was confirmed by FISH in two cases. Mesonephric carcinoma is characterized by molecular alterations that differ from those of more common variants of cervical and endometrial adenocarcinoma, which harbor *KRAS/NRAS* mutations in seven percent and 25 percent of cases, respectively. *KRAS/NRAS* mutations are common in mesonephric carcinoma and are often accompanied by gain of 1q and mutations in chromatin remodeling genes. Targeting inhibitors of the RAS/MAPK pathway may be useful in treating mesonephric carcinoma.

Mirkovic J, Sholl LM, Garcia E, et al. Targeted genomic profiling reveals recurrent *KRAS* mutations and gain of chromosome 1q in mesonephric carcinomas of the female genital tract. *Mod Pathol.* 2015;28:1504–1514.

Correspondence: Dr. B. E. Howitt at bhowitt@partners.org

[hr]

Assessing tumor-infiltrating lymphocytes in sentinel lymph node melanoma metastases

Melanoma patients with sentinel lymph node metastases have variable five-year survival rates of 39 to 70 percent. The prognostic significance of tumor-infiltrating lymphocytes in sentinel lymph node metastases from such patients is unknown. Anti-PD-1/PD-L1 inhibitors have significantly improved clinical outcome in unresectable American Joint Committee on Cancer stage IIIC/IV metastatic melanoma patients and are being trialled in the adjuvant setting in advanced stage disease. However, their role in early stage (sentinel lymph node-positive) metastatic disease remains unclear. The authors conducted a study to characterize, in sentinel lymph nodes, the subpopulations of lymphocytes that interact with metastatic melanoma cells and analyze their associations with outcome. They also sought to determine tumor PD-L1 expression, as this may provide a rational scientific basis for the administration of adjuvant anti-PD-1/PD-L1 inhibitors in sentinel lymph node-positive metastatic melanoma patients. Sentinel lymph nodes containing metastatic melanoma from 60 treatment-naive patients were analyzed for CD3, CD4, CD8, FOXP3, PD-1, and PD-L1 using immunohistochemistry on serial sections. The results were correlated with clinicopathologic features and outcome. The authors observed positive correlations between recurrence-free/overall survival with the number of CD3+ tumor-infiltrating lymphocytes (hazard ratio, 0.36 [0.17–0.76], P=.005; hazard ratio, 0.29 [0.14–0.61], P=.0005, respectively), the number of CD4+ tumor-infiltrating lymphocytes (hazard ratio, 0.34 [0.15–0.77], *P*=.007; hazard ratio, 0.32 [0.14–0.74], *P*=.005, respectively), and the number of CD8+ tumor-infiltrating lymphocytes (hazard ratio, 0.42 [0.21–0.85], *P*=0.13; hazard ratio, 0.32 [0.19–0.78], *P*=.006, respectively). They also observed negative correlation with the number of peritumoral PD-1+ lymphocytes (hazard ratio, 2.67 [1.17–6.13], *P*=.016; hazard ratio, 2.74 [1.14–6.76], *P*=.019, respectively). Tumoral PD-L1 expression was present in 26 (43 percent) cases but did not correlate with outcome. The findings suggest that T-cell subsets in sentinel lymph node metastases can predict melanoma patient outcomes. Furthermore, the relatively high number of PD-L1–positive sentinel lymph node melanoma metastases provides a rationale for anti-PD-1 therapy trials in sentinel lymph node-positive melanoma patients, particularly those with peritumoral PD-1+ lymphocytes.

Kakavand H, Vilain RE, Wilmott JS, et al. Tumor PD-L1 expression, immune cell correlates and PD-1+ lymphocytes in sentinel lymph node melanoma metastases. *Mod Pathol.* 2015;28:1535–1544.

Correspondence: H. Kakavand at hojabr.kakavand@melanoma.org.au