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Comparison of methods for analyzing gene amplification in gastric cancers

The prognosis for patients with gastric carcinoma at an advanced stage remains dismal, necessitating novel therapeutic modalities. Because of the successful targeting of amplified *ERBB2* with a humanized monoclonal antibody, the amplified genes of other receptor tyrosine kinases, such as *EGFR, FGFR2,* and *MET*, as well as those of other cell regulator genes, are being considered as candidate targets of molecular therapy. The authors conducted a study to determine the amplification status of 26 genes, which are frequently amplified in solid cancers, in advanced gastric carcinomas. They examined 93 formalin-fixed and paraffin-embedded advanced gastric cancer tissues by multiple ligation-dependent probe amplification. Thirty-two cases with “gain” or “amplified” status of 16 genes were further examined for the respective gene amplification by FISH and for the respective protein overexpression by immunohistochemistry. The frequencies of gene amplifications in advanced gastric cancers were: *ERBB2,* 13 cases, 14 percent; *FGFR2*, seven cases, eight percent; *MYC*, seven cases, eight percent; *TOP2A*, seven cases, eight percent; *MET*, four cases, four percent; *MDM2*, four cases, four percent; *CCND1*, three cases, three percent; *FGF10*, two cases, three percent; and *EGFR*, one case, one percent. Amplification of the receptor tyrosine kinases genes occurred in a mutually exclusive manner, except for one tumor in which ERBB2 and FGFR2 were amplified but in different cancer cells. Co-amplification of *ERBB2* and *MYC*, and *EGFR* and *CCND1*, in a single nuclei but on different amplicons was confirmed in one case each. Attempts at correlating the FISH status with the immunohistochemical staining pattern showed variable results ranging from complete concordance to no correlation. The authors concluded that combining multiple ligation-dependent probe amplification and FISH analysis is a feasible approach for obtaining the semi-comprehensive genetic information necessary for personalized molecular targeted therapy.

Ooi A, Oyama T, Nakamura R, et al. Semi-comprehensive analysis of gene amplification in gastric cancers using multiplex ligation-dependent probe amplification and fluorescence in situ hybridization. *Mod Pathol.* 2015;28:861–871.

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Uterine smooth muscle tumor analysis by comparative genomic hybridization

The diagnosis and management of uterine smooth muscle tumors of uncertain malignant potential are often challenging, and genomic data on these lesions and on uterine smooth muscle lesions are limited. The authors tested the hypothesis that genomic profile determination by array comparative genomic hybridization (array-CGH) could split smooth muscle tumors of uncertain malignant potential (STUMP) into a benign group with scarce chromosomal alterations akin to leiomyoma and a malignant group with high chromosomal instability akin to leiomyosarcoma. Array-CGH genomic profile analysis was conducted for a series of 29 cases of uterine STUMP. A group of 10 uterine leiomyomas and 10 uterine leiomyosarcomas served as controls. The mean age of the participants was 50 years (range, 24–85 years) and follow-up ranged from 12 to 156 months (average, 70 months). Since STUMP is a heterogenous group of tumors with genomic profiles that can harbor few to many chromosomal alterations, the authors compared genomic indices in leiomyomas and leiomyosarcomas and set a genomic index=10 threshold. Tumors with a genomic index of less than 10 were classified as nonrecurring STUMPs, and those with a genomic index greater than 10 represented STUMPs with recurrences and unfavorable outcomes. Therefore, the genomic index threshold split the STUMP category into two groups of tumors with different outcomes: a group comparable to leiomyomas and another similar to leiomyosarcomas but more indolent. In these STUMP series, genomic analysis by array-CGH is an innovative diagnostic tool for problematic smooth muscle uterine lesions complementary to the morphological evaluation approach. The authors concluded that they provided an improved classification method for distinguishing truly malignant tumors from benign lesions within the category of STUMP.

Croce S, Ribeiro A, Brulard C, et al. Uterine smooth muscle tumor analysis by comparative genomic hybridization: a useful diagnostic tool in challenging lesions. *Mod Pathol.* 2015;28:1001–1010.

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Role of TAZ in aggressive types of endometrial cancer

TAZ, the final effector of the Hippo pathway that modulates epithelial to mesenchymal transition and stemness, has been implicated in the development of various types of cancer, but its role in endometrial cancer has not been studied. Therefore, the authors evaluated the expression of TAZ in different types of endometrial cancer by immunohistochemistry. TAZ expression was detected in 76 percent of undifferentiated endometrial carcinomas, 54 percent of endometrial carcinosarcomas, 46 percent of endometrial serous carcinomas, 36 percent of grade 3 endometrioid carcinomas, and 18 percent of grade 1–2 endometrioid carcinomas, with statistically significant differences. The authors analyzed the WWTR1 gene that encodes TAZ by FISH and MassArray mass spectrometry, ruling out gene amplification and differential promoter methylation as the main mechanisms that modulate TAZ expression in endometrial tumors. However, the authors detected a significant association between Scribble hypoexpression and delocalization with TAZ expression. Moreover, they demonstrated that TAZ promoted invasiveness, and it favored cell motility and tumor growth in endometrial cancer cell lines. In addition, TAZ expression was associated with the transition from an epithelial to mesenchymal phenotype, both in vitro and in human tumors. These data reveal a previously unknown role for TAZ and the Hippo pathway in the progression of aggressive subtypes of endometrial cancer.

Romero-Pérez L, Garcia-Sanz P, Mota A, et al. A role for the transducer of the Hippo pathway, TAZ, in the development of aggressive types of endometrial cancer. *Mod Pathol.* 2015;28:1492–1503.

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Reclassification of resected lung carcinomas diagnosed as squamous cell carcinoma

Non-small cell lung carcinomas are primarily classified using light microscopy. However, recent studies have shown that poorly differentiated tumors are more accurately classified using immunohistochemistry. The authors conducted a study in which they investigated the use of immunohistochemical analysis in reclassifying lung carcinomas that were originally diagnosed as squamous cell carcinoma. Tumor slides and blocks were available for histologic evaluation, and tissue microarrays were constructed from 480 patients with resected lung carcinomas originally diagnosed as squamous cell carcinoma between 1999 and 2009. Immunohistochemical analyses were performed for p40, p63, thyroid transcription factor-1 (TTF-1; clones SPT24 and 8G7G3/1), napsin A, chromogranin A, synaptophysin, and CD56. Staining intensity (weak, moderate, or strong) and distribution (focal or diffuse) were also recorded. A total of 449 (93.5 percent) patients were confirmed as having squamous cell carcinoma; the cases were mostly diffusely positive for p40 and negative for TTF-1 (8G7G3/1). Twenty (4.2 percent) cases were reclassified as adenocarcinoma because they were positive for TTF-1 (8G7G3/1 or SPT24) with either no p40 expression or focal p40 expression, and all of them were poorly differentiated with squamoid morphology. One case was reclassified as adenosquamous carcinoma, four cases as large cell carcinoma, four cases as large cell neuroendocrine carcinoma, and two cases as small cell carcinoma. In poorly differentiated non-small cell lung carcinomas, an accurate distinction between squamous cell carcinoma and adenocarcinoma cannot be reliably determined by morphology alone and requires immunohistochemical analysis, even in resected specimens. The authors determined that their findings suggest that TTF-1 8G7G3/1 may be better suited as the primary antibody in differentiating adenocarcinoma from squamous cell carcinoma.

Kadota K, Nitadori J, Rekhtman N, et al. Reevaluation and reclassification of resected lung carcinomas originally diagnosed as squamous cell carcinoma using immunohistochemical analysis. *Am J Surg Pathol.* 2015;39:1170–1180.

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Sequencing of cancer genes in ampullary carcinoma shows trends in histologic subtypes

The biological relevance of histological subtyping of ampullary carcinoma into intestinal versus pancreaticobiliary types remains to be determined. In an effort to create a molecular profile of these subtypes of ampullary carcinomas, the authors conducted a two-phase study. In the discovery phase, they identified 18 pancreatobiliary-type ampullary carcinomas and 14 intestinal-type ampullary carcinomas using stringent pathologic criteria. They then performed next-generation sequencing on those tumors, targeting 279 cancer-associated genes. Although the results showed overlapping genomic alterations between the two subtypes, the authors observed trends, including more frequent KRAS alterations in pancreatobiliary-type ampullary carcinoma (61 percent versus 29 percent) and more frequent mutations in APC in intestinal-type ampullary carcinoma (43 percent versus 17 percent). In the cohort of 32 tumors, the most frequently mutated gene was TP53 (n=17); the most frequently amplified gene was ERBB2 (n=5); and the most frequently deleted gene was CDKN2A (n=6). In the second phase of the study, the authors sought to validate their observation on ERBB2. They assessed ERBB2 amplification and protein overexpression in a series of 100 ampullary carcinomas. The authors found that gene amplification and immunohistochemical overexpression of ERBB2 occurred in 13 percent of all ampullary carcinomas, providing a potential target for anti-HER2 therapy in these tumors. They also found that amplification and immunohistochemical expression correlated in all cases, indicating that immunohistochemistry could be used to screen tumors. Furthermore, none of the 14 ERBB2-amplified tumors harbored any downstream driver mutations in KRAS/NRAS, whereas 56 percent of the cases negative for ERBB2 amplification did. This observation was clinically pertinent because downstream mutations may cause primary resistance to inhibition of EGFR family members.

Hechtman JF, Liu W, Sadowska J, et al. Sequencing of 279 cancer genes in ampullary carcinoma reveals trends relating to histologic subtypes and frequent amplification and overexpression of ERBB2 (HER2). *Mod Pathol.* 2015;28(8):1123–1129.

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Prognostic significance of the 2014 ISUP grading system for prostate cancer

The 2005 International Society of Urological Pathology modified Gleason grading system was further amended in 2014 with the establishment of grade groupings (ISUP grading). The authors examined the predictive value of ISUP grading, comparing results with recognized prognostic parameters. Of 3,700 men undergoing radical prostatectomy, reported at Aquesta Pathology, Queensland, Australia, between 2008 and 2013, 2,079 had a positive needle biopsy available for review. The authors examined the association between needle biopsy 2014 ISUP grade and 2005 modified Gleason score, tumor volume, pathological stage of the subsequent radical prostatectomy tumor, as well as biochemical recurrence-free survival (BRFS). The median age of the study participants was 62 years (range, 32–79 years). The median serum PSA was 5.9 (range, 0.4–69 ng/mL). For needle biopsies, 280 (13.5 percent), 1,031 (49.6 percent), 366 (17.6 percent), 77 (3.7 percent), and 325 (15.6 percent) were 2014 ISUP grades 1–5, respectively. Needle biopsy 2014 ISUP grade showed a significant association with radical prostatectomy tumor volume (P<.001), TNM pT and N stage (P<.001), and BRFS (P<.001). Multivariate analysis using the Cox proportional hazards regression model showed serum PSA at the time of diagnosis and ISUP grade greater than two to be significantly associated with BRFS. The authors concluded that this study provides evidence of the prognostic significance of ISUP grading for thin core needle biopsy of the prostate.

Samaratunga H, Delahunt B, Gianduzzo T, et al. The prognostic significance of the 2014 International Society of Urological Pathology (ISUP) grading system for prostate cancer. *Pathology.* 2015;47:515–519.

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