Movat, IgG4 Immunostains Aid in Dx of Autoimmune Pancreatitis

The Role of Movat Pentachrome Stain and Immunoglobulin G4 Immunostaining in the Diagnosis of Autoimmune Pancreatitis.

Chu KE, Papouchado BG, et al:

Mod Pathol; 22 (March): 351-358

IgG4 and Movat immunostains are diagnostically useful for autoimmune pancreatitis, as venulitis and IgG4-positive plasma cells are characteristic features.

Background: Autoimmune pancreatitis (AIP) is a newly characterized lesion in the differential diagnosis of a pancreatic head mass. Given its ability to simulate pancreatic cancer, AIP is a common diagnosis in false-positive Whipple resections presumed to contain a malignancy. Because steroids are highly effective, the preoperative diagnosis of AIP is now critical for avoiding unnecessary surgery and beginning medical therapy. AIP is characterized histologically as having fibrosis with a dense lymphoplasmacytic infiltrate and pancreatic duct damage, but these findings are nonspecific features and can be observed in any chronic pancreatitis. However, plasma cells are characteristically positive for IgG4 immunostain in AIP. In addition, lymphocytic and obliterative phlebitis are frequently observed in AIP but can be easily overlooked without the aid of stain such as Movat.

Objective: To determine whether IgG4 and Movat immunostains are useful in the differential diagnosis of AIP.

Methods: All cases designated chronic pancreatitis of any type were collected and reviewed by at least 3 study pathologists. AIP was diagnosed when there was (1) marked parenchymal fibro-inflammatory destruction, (2) periductal lymphoplasmacytic or histiocytic infiltration, and (3) no other clinical cause of pancreatitis, particularly excluding alcoholism. Whole-tissue staining was performed for Movat and IgG4.

Results: Cases included 15 AIP, 25 usual-type alcoholic or idiopathic pancreatitis, 31 ductal adenocarcinoma-associated pancreatitis, and 20 normal pancreata. AIP patients were 7 women and 8 men with an average age of 56.5 years (range, 24.0 to 78.0 years). Movat staining demonstrated diffuse and marked lymphocytic venulitis in all 15 AIP cases, including those 4 cases that were only needle core biopsies. The venulitis consisted of elastin fiber destruction with incorporation of connective tissue fibers and ground substance into the vein wall. Five of 15 cases also had obliterative venous changes. None of the usual-type pancreatitis and only 1 of 31 ductal adenocarcinoma-associated pancreatitis cases had diffuse venous inflammation. Patchy venous inflammatory changes were seen in 5 of 25 usual-type and 5 of 31 carcinoma-associated cases. Increased IgG4 immunostaining (at least 10 positive plasma cells per x400 field) was seen in 9 of 13 AIP cases but not in any of the control groups.

Conclusions: In evaluating chronic pancreatitis, the combination of Movat stain for highlighting venulitis and IgG4 for highlighting an increase in positive plasma cells may be diagnostically useful for AIP.

Reviewer's Comments: For evaluation of core biopsies, each of these features will have to be interpreted with consideration to sampling problems. The lack of IgG4-positive plasma cells or patchy venulitis on a limited sample would certainly not exclude diagnosis of AIP.

Additional Keywords: Immunostains

print tag: () Refer to original journal article.

When Should Additional Gene Testing for *JAK2* Mutations in MPN Be Performed?

Mutation Profile of JAK2 Transcripts in Patients With Chronic Myeloproliferative Neoplasias.
Ma W, Kantarjian H, et al:
J Mol Diagn; 11 (January): 49-53

Robust reflex testing for *JAK2* gene mutations in myeloproliferative neoplasms might require direct sequencing of the exon 12 through 15 regions, as opposed to limited exon 12 analysis.

Background: Discovery of the *JAK2 V617F* mutation was a major advance in laboratory diagnosis of myeloproliferative neoplasia (MPN). *JAK2 V617F* analysis provides an objective means to confirm BCR/ABL-negative neoplasia in 95% of polycythemia vera and roughly 50% each of essential thrombocythemia and primary myelofibrosis patients. Many laboratories promote their expertise in detecting separate *JAK2* exon 12 mutations and thrombopoietin receptor gene (MPL) mutations as supplementary tests for MPN.

Objective: To characterize the spectrum and distribution of *JAK2* gene mutations by screening RNA from a large number of myeloproliferative neoplasms by a direct sequencing approach.

Methods: Total nucleic acids were extracted from 20,000 blood samples submitted to Quest Diagnostics from suspected MPN patients over a 7-month interval, and RNA was reverse transcribed. cDNA products were amplified at *JAK2* gene exons 12 through 15, and amplicons were direct sequenced.

Results: Among roughly 20,000 candidate MPN samples, 4280 (21.0%) demonstrated *JAK2 V617F* , by far the most common *JAK2* mutation; 23 (0.12%) demonstrated previously described exon 12 mutations. In addition, novel 8 exon 12 mutations, 21 exon 13 mutations, 10 exon 14 mutations, and 2 exon 15 mutations were identified by direct sequencing. Because these novel mutations were absent from numerous remaining samples, they seem unlikely to represent polymorphisms.

Conclusions: Robust reflex testing for *JAK2* gene mutations in myeloproliferative neoplasms might require direct sequencing of the exon 12 through 15 region, as opposed to limited exon 12 analysis.

Reviewer's Comments: Many labs market *JAK2* exon 12 mutational assays. However, *JAK2* exon 12 mutation is useful only in detecting a very small number of polycythemia vera patients, since polycythemia vera is rare at the outset and 95% positive for the *JAK2* (*V617F*) mutation. This study indicates that there are more frequent, uncharacterized *JAK2* mutations than would be detected by current *JAK2* exon 12 assays. Most likely, the best reflex test for MPN patients who are *JAK2* (*V617F*)-negative has yet to be developed, and there may yet be a clinical role for direct sequencing in a small number of MPN patients.

Additional Keywords: *JAK2* Mutation & Direct Sequencing

print tag: () Refer to original journal article.

Which Intraoperative Assessment Is Best for SLNs in Breast Cancer Patients?

A Prospective Study Comparing Touch Imprint Cytology, Frozen Section Analysis, and Rapid Cytokeratin Immunostain for Intraoperative Evaluation of Axillary Sentinel Lymph Nodes in Breast Cancer.

Krishnamurthy S, Meric-Bernstam F, et al:

Cancer; 115 (April 1): 1555-1562

The sensitivity of either frozen section and rapid cytokeratin immunostaining is better than that of touch imprint alone for detection of breast cancer metastasis to axillary sentinel lymph nodes.

Background: Sentinel lymph node (SLN) evaluation is a standard procedure for axillary staging in breast cancer patients. Intraoperative evaluation allows the surgeon to perform a complete axillary dissection at the time of primary surgery if lymph node metastasis is present. Multiple techniques for evaluation are available to the practicing pathologist: touch imprint (TI), frozen section (FS), and, recently, rapid cytokeratin immunostaining (RCI). Each of these has advantages and disadvantages.

Objective: To prospectively evaluate the feasibility and utility of using TI, FS, and RCI in the evaluation of axillary SLNs in breast cancer patients.

Participants/Methods: Patients with a diagnosis of stage I to III breast cancer, node-negative disease prior to surgery, and eligible for SLN mapping were included in the study. SLNs were bisected (when <0.5 cm) or sectioned at 2.0-mm intervals along the short axis. TIs were made of both surfaces, then fixed and stained with H&E. Two FSs were prepared, 1 for H&E staining and 1 for RCI. RCI was performed with a cytokeratin stain and was completed within 25 minutes. Final pathology was considered the gold standard and was assessed by H&E staining and cytokeratin immunostaining.

Results: 100 patients with 297 SLNs were included in the study: 85 had ductal carcinoma, 8 had lobular carcinoma, 5 had mixed features, and 2 had uncommon variant carcinomas. Eighteen patients had a positive SLN by final pathology; an additional 2 patients had micrometastatic carcinoma present during intraoperative evaluation, which was lost on permanent processing. The tumor was macrometastatic in 12 cases and micrometastatic in 8. TI detected 8 (67%) macrometastases and 1 (13%) micrometastasis, FS detected 12 (100%) macrometastases and 3 (37%) micrometastases, and RCI detected 12 (100%) macrometastases and 4 (50%) micrometastases. The sensitivity for detection of lymph node metastasis was 45% for TI, 75% for FS, and 80% for RCI. There was no statistically significant difference between the sensitivity of TI, FS, or RCI.

Conclusions: The sensitivity of FS and RCI was better than that of TI alone for detection of breast cancer metastasis to axillary SLNs. Both FS and RCI identified all macrometastases but failed to detect 50% of micrometastatic foci. RCI can be completed within FS time constrains and may play a role in the intraoperative evaluation of SLNs.

Reviewer's Comments: Requests for intraoperative assessment of SLNs in patients with breast carcinoma varies between institutions and case to case. At our institution, it is requested only when immediate reconstruction is planned, in which case FS is performed. Rapid cytokeratin immunohistochemistry shows only a minimal increase in sensitivity compared to FS, but it may be better at detecting subtle lobular carcinoma or isolated tumor cells.

Additional Keywords: Intraoperative Evaluation

print tag: () Refer to original journal article.

Does Cav-1 Expression Tell Us More Than 1p/19q Status in Oligodendrogliomas?

Caveolin 1 Expression Independently Predicts Shorter Survival in Oligodendrogliomas.

Senetta R, Trevisan E, et al:

J Neuropathol Exp Neurol; 68 (April): 425-431

Caveolin-1 expression independently predicts short survival among patients with gliomas with an oligodendroglial component.

Background: The biologic behavior of tumors with an oligodendroglioma component, such as pure oligodendrogliomas or mixed oligoastrocytomas, has been better characterized since the application of chromosome 1p/19q deletion status. Caveolin-1 (cav-1) is a member of the caveolin family of proteins, which are "flask-shaped" cell membrane domains involved in numerous cell functions. Cav-1 is expressed in glia and in brain tumor cells, where its expression appears to be correlated to tumor grade.

Objective: To describe the expression of cav-1 in oligodendroglial tumors, to determine whether cav-1 expression is correlated with tumor 1p/19q status, and to determine whether cav-1 expression has any prognostic power among these tumors.

Methods: 87 oligodendroglial tumors, diagnosed according to the current WHO classification system, were studied: 33 grade II oligodendrogliomas, 21 grade III oligodendrogliomas, 10 grade II oligoastrocytomas, 16 grade III oligoastrocytomas, and 7 glioblastomas with oligodendroglial components. Pathologic material for each case was independently reviewed by 2 pathologists who were blinded to patient outcome. For each case, cav-1 expression by immunohistochemistry and 1p/19q deletion status by fluorescence in situ hybridization were performed. Clinical and follow-up survival data were available for 63 patients. Statistical analyses were performed.

Results: Cav-1 expression by tumor type was as follows: 9% of grade II oligodendrogliomas, 10% of grade III oligodendrogliomas, 20% of grade II oligoastrocytomas, 44% of grade III oligoastrocytomas, and 71% of glioblastomas with an oligodendroglioma component. Cav-1 expression was significantly associated with tumor grade (P =0.001) and with tumor type (P =0.0001). Co-deletion of chromosomes 1p/19q were identified in 55% of grade II oligodendrogliomas, 62% of grade III oligodendrogliomas, 70% of grade II oligoastrocytomas, 6% of grade III oligoastrocytomas, and 14% of glioblastomas with an oligodendroglial component. Cav-1 was strongly correlated with an absence of a 1p/19q deletion (P =0.0002) and shorter survival. On multivariate analysis, cav-1 expression was the only factor independently predictive of a short survival (P <0.015).

Conclusions: In glial tumors with an oligodendroglioma component, cav-1 expression by immunohistochemistry is an independent predictor of short survival.

Reviewer's Comments: The findings underscore our incomplete, yet growing, understanding of the molecular underpinnings of oligodendroglial tumors. Although the current gold-standard predictor of overall survival and response to treatment is tumor 1p/19q deletion status, the authors present compelling evidence for the practical role of cav-1 expression, as determined by immunohistochemistry.

Additional Keywords: Oligodendroglioma Component

print tag: () Refer to original journal article.

Meningothelial-Like Nodules

Pulmonary Meningothelial-Like Nodules: New Insights Into a Common but Poorly Understood Entity.

Mukhopadhyay S, El-Zammar OA, Katzenstein A-LA:

Am J Surg Pathol; 33 (April): 487-495

Meningothelial-like nodules of the lung are rarely, if ever, found in pediatric specimens.

Background: Minute pulmonary meningothelial-like nodules (PMLNs) have been recognized for nearly 50 years, although they were originally thought to resemble paragangliomas. Use of immunohistochemistry eventually proved the tumors to resemble meningothelium, hence the current nomenclature. Their pathogenesis remains unclear, however.

Objective: To review a large series of lung specimens from patients of different ages with particular attention to presence of PMLNs and their association with other diseases.

Methods: 500 surgical lung biopsies, 25 extensively sampled lobectomies, 20 resections in patients aged <30 years with pneumothoraces, and 92 pediatric autopsies were reviewed for PMLNs. Clinical and histologic findings were noted. Immunohistochemistry was performed with a number of antibodies.

Results: There were 186 PMLNs identified in 81 patients. These were found in 14% of surgical lung biopsies and 48% of extensively sampled lobectomies. None were found in pediatric autopsy cases or resections from patients aged <30 years with pneumothoraces. There was a slight increase in the number of PMLNs found when a greater number of slides were available for any given case. Mean age of patients with PMLNs was 62 years (range, 22 to 84 years). Women were more than twice as likely than men to have lesions. Lesions were most commonly seen with thromboembolic disease and respiratory bronchiolitic-associated interstitial lung disease/desquamative interstitial pneumonia. Most lesions measured between 1 and 2 mm and were identified microscopically. In more than half the cases, only 1 lesion was identified. Only 1 patient appeared to have diffuse pulmonary meningotheliomatosis. Lesions were generally located randomly within the alveolar septa, and entrapped blood vessels were identified in about half the cases. All lesions tested were immunoreactive with antibodies to progesterone receptor (PR), CD56, epithelial membrane antigen (EMA), and vimentin. Other epithelial markers, vascular markers, and muscle markers were negative in all cases tested. Four cases were tested and were not immunoreactive with antibodies to TTF1. Rare PR-positive spindle cells were identified in the interstitium of nearly all cases tested. The cells were non-reactive with antibodies to EMA and CD56.

Conclusions: PMLNs occur in older patients, usually those with concomitant lung disease. Absence of lesions in children suggests they are not congenital.

Reviewer's Comments: This article nicely summarizes the current knowledge about this curious entity. It is interesting that our understanding of these lesions has evolved little since the advent of immunohistochemistry.

Additional Keywords: Immunohistochemistry

print tag: () Refer to original journal article.

Which Paraffin-Based Markers Best Predict *MYC* Gene Status in Aggressive BCLs?

Characteristic Expression Patterns of TCL1, CD38, and CD44 Identify Aggressive Lymphomas Harboring a MYC Translocation.

Rodig SJ, Vergilio J-A, et al:

Am J Surg Pathol; 32 (January): 113-122

Paraffin immunostains for TCL1, CD38, CD44 staining are more sensitive and specific than B-cell lymphoma-2 and CD10 staining for identifying *MYC* + status in aggressive B-cell lymphomas.

Background: Classic Burkitt lymphoma (BL) typically demonstrates reciprocal translocations of *MYC* partnered with Ig genes on chromosomes 14, 2, or 22 in a background of an otherwise simple karyotype. Aggressive diffuse large B-cell lymphomas (BCLs) can also demonstrate *MYC* gene abnormalities but usually in the background of complex chromosomal abnormalities. BL is usually CD10+ and BCL2-with a >95% Ki-67 labeling index, in contrast to diffuse large BCL, which is more often BCL2+ with Ki-67 <95%. Gene expression profiling may define BL more accurately than morphologic, immunophenotypic, and fluorescent in situ hybridization (FISH) methods.

Objective: To identify a panel of paraffin immunohistochemical stains that best predicts presence of *MYC* gene rearrangements in aggressive BCLs.

Methods: Paraffin immunostaining was performed on 67 (61 adult, 6 pediatric) cytogenetically characterized aggressive BCLs identified in the files at Brigham & Women's Hospital or Children's Hospital in Boston. Anti-TCL1 and CD38 (pH 8.0 EDTA) and anti-CD44 (pH 6.0 citrate) staining was performed following heat-induced epitope retrieval and scored positive for >50% tumor cell staining.

Results: 21 cases were positive for *MYC* gene rearrangement in the absence of complex karyotypic abnormality. Among 46 *MYC* -cases, 10 were analyzed by FISH alone. Among 34 with cytogenetics, the majority showed complex karyotypic abnormality including 2 adult cases with *MYC* rearrangement within a complex karyotype. *MYC* + cases were 91% CD10+, 26% BCL2+, 86% TCL1+, 86% CD38+, and 4% CD44+. *MYC* - cases were 55% CD10+, 74% BCL2+, 40% TCL1+, 10% CD38+, and 76% CD44+. Positive staining for CD38 and negative CD44 staining was more specific for *MYC* + status than BCL2 and CD10 staining, and combined TCL1, CD38, CD44 staining was more sensitive.

Conclusions: Paraffin immunostains for TCL1, CD38, CD44 staining are more sensitive and specific than BCL2 and CD10 staining for identifying *MYC* + status in aggressive BCLs.

Reviewer's Comments: This study represents yet another example of paraffin immunohistochemical staining panels that serve as effective surrogate markers for gene expression profiling, in this case for separating simple *MYC* + lymphomas from those that are *MYC* - or *MYC* + with coexisting complex karyotypic abnormality.

Additional Keywords: *MYC*

print tag: () Refer to original journal article.

IGF2BP3+ Ovarian Clear Cell Carcinomas Have Unfavorable Prognosis

IGF2BP3 (IMP3) Expression Is a Marker of Unfavorable Prognosis in Ovarian Carcinoma of Clear Cell Subtype.

Kbel M, Xu H, et al:
Mod Pathol; 22 (March): 469-475

IGF2BP3 is a potential biomarker that is associated with a poor survival rate in low-stage ovarian clear cell carcinomas.

Background: Clear cell carcinoma of the ovary is a rare subtype of carcinoma which frequently presents as low stage. However, while stage is the only validated prognostic marker, the behavior can still be clinically unpredictable. IGF2BP3 (IMP3) is an insulin-like growth factor that has been noted in many malignancies, but it is not present in normal adult tissues. Specifically, expression of IGF2BP3 has been associated with a poor prognosis in clear cell carcinomas of the kidney.

Objective: To characterize IGF2BP3 expression in ovarian carcinoma, and to determine any association with prognosis in clear cell carcinomas of the ovary.

Methods: 475 ovarian carcinomas from a single ovarian cancer registry, plus an additional 150 ovarian clear cell carcinomas were evaluated for IGF2BP3 protein expression by immunohistochemistry (IHC). In addition, 35 ovarian tumors had mRNA expression profiles for correlation.

Results: The protein expression of IGF2BP3 correlated to the mRNA expression in the subset of cases tested (*P* <0.001). Of all tumors in the ovarian cancer registry, 47% were positive for IGF2BP3, but expression differed by subtype. Overall, 86% of mucinous, 52% of clear cell, 50% of serous, and 27% of endometrioid types were positive by IHC. Disease-specific survival was shorter in positive clear cell carcinomas compared to negative clear cell carcinomas (*P* =0.001) but was not significantly different in other subtypes. A risk ratio (RR) of 2.9 (95% CI, 1.4 to 5.8) was calculated independent of stage of disease. For confirmation, an additional 150 ovarian clear cell carcinomas were evaluated with similar results. Combining the series together to evaluate ovarian clear cell carcinomas presenting in stage I or II disease with IGF2BP3 positivity found a RR of 2.8 (95% CI, 1.6 to 5.1) for disease-specific survival. In addition, IGF2BP3- clear cell carcinomas presenting in stage I or II disease have a 5-year disease-specific survival rate of 88% compared to 67% for those with IGF2BP3+ tumors.

Conclusions: Expression of IGF2BP3 in ovarian clear cell carcinomas has prognostic significance as demonstrated by decreased survival in women with stage I or II disease.

Reviewer's Comments: Treatment decisions can be difficult in low-stage, high-grade cancers such as ovarian clear cell carcinoma. Biomarkers like IGF2BP3 may provide additional information in these cases that have been historically unpredictable.

Additional Keywords: Prognostic Markers

print tag: () Refer to original journal article.

Can the New Universal Definition of Acute MI Be Applied in a Standardized Manner?

Impact of Ultrasensitive Cardiac Troponin I Dynamic Changes in the New Universal Definition of Myocardial Infarction.

Casals G, Filella X, et al:

Am J Clin Pathol; 130 (December): 964-968

Ultrasensitive cardiac troponin testing with a 20% threshold for change in serum troponin level detects an increased prevalence of myocardial infarction in emergency department settings.

Background: The recent (2007) universal definition of acute myocardial infarction (MI) requires a demonstrated change (elevation or decrease) in cardiac biomarker level, preferably cTn, one measured level above the 99th percentile of the upper normal reference limit, as well as clinical (ECG) or radiographic evidence for myocardial ischemia. It does not specify a quantified threshold for change. The method of laboratory testing for cTn must demonstrate good precision in the 99th percentile range (CV <10%). However, due to limited test precisions in the 99th percentile range and in order to avoid false-positive cTn results, many clinicians have used clinical decision threshold values higher than the 99th percentile range.

Objective: To assess the universal definition of acute MI using an ultrasensitive troponin method and a quantified 20% threshold for changes in serum troponin level.

Methods: 284 consecutive emergency department admissions with suspected acute coronary syndrome (ACS) and initial cTnI level <0.10 ng/mL (TnI-Ultra assay; ADVIA Centaur CP) were evaluated and given a final clinical diagnosis of MI if there was a >0.1 ng/mL increase in cTnI along with cardiac chest pain or ischemic electrocardiogram changes. Clinical diagnoses were compared with modified universal criteria for MI that included patients with baseline elevations of cTnI >0.04 ng/mL and a 20% increase in cTnI within 24 hours.

Results: Among 284 patients, 37 had final clinical diagnosis of MI along with 33 unstable angina, 8 typical angina, 11 secondary angina, 28 pericarditis, 9 arrhythmia, 90 non-anginal chest pain, 8 respiratory failure, 7 seizure, 10 syncope, 18 atypical angina, and 21 other. When compared with modified universal criteria that include a 20% increase in cTnI, all 37 cases of clinically diagnosed MI ruled in for MI as well, along with an additional 29 cases that included 18 cardiac causes and 11 noncardiac clinical diagnoses. Among 176 patients with cTnI <0.04 ng/mL, 4 (2.3%) were readmitted for angina within 6 months. Among 29 additional patients who ruled in for MI using modified universal criteria, 2 and 1 (10%) were readmitted for MI and unstable angina, respectively.

Conclusions: Ultrasensitive cTnI assays permit strict application of a universal definition of acute MI and appear to detect an increased prevalence of MI in emergency department settings.

Reviewer's Comments: Previous studies show that patients with noncardiac disease often present with mildly elevated troponin levels (<1.0 ng/mL). Thus, a single elevated troponin <1.0 ng/mL does not reliably indicate MI. Instead, it has a positive-predictive value for acute coronary syndrome of only 48% compared to 90% for troponin >1.0 with normal renal function and 27% for troponin 0.1 to 1.0 with renal failure (*Arch Intern Med* 2007;167:276-281).

Additional Keywords: Myocardial Infarction

print tag: () Refer to original journal article.

TT Strong Predictor for Lymph Node Metastasis in OSCC

Predictive Value of Tumor Thickness for Cervical Lymph-Node Involvement in Squamous Cell Carcinoma of the Oral Cavity: A Meta-Analysis of Reported Studies.

Huang SH, Hwang D, et al:

Cancer; 115 (April 1): 1489-1497

Patients with an oral squamous cell carcinoma tumor thickness <4 mm can be spared from subsequent elective neck dissection if clinically indicated.

Background: One of the strongest predictors of survival in patients with oral squamous cell carcinoma (OSCC) is presence of cervical lymph node metastasis. In patients with early stage OSCC, up to 40% will have occult nodal disease. Elective neck dissection is frequently performed in these patients to help determine the need for adjuvant therapy, but this also carries a risk of significant morbidity. The tumor thickness (TT) of OSCCs has previously been associated with increasing risk of lymph node metastasis. However, there is controversy about the optimal cut-off TT for prompting prophylactic neck management.

Objective: To conduct a meta-analysis of previous work examining the optimal cut-off TT.

Methods: An electronic search of the English literature was performed for papers with the following inclusion criteria: OSCC treated with primary surgery, TT measured on the surgical specimen, TT described in relation to the risk of cervical lymph node metastasis, and a minimum of 2 years of follow-up for patients without neck treatment. Studies were excluded if adjuvant chemotherapy or radiation therapy was present. Patients were considered to have a positive lymph node declaration (PLND) if neck dissection pathologically confirmed metastasis, or they developed delayed lymph node metastasis without neck dissection in <2 years from diagnosis. TT cut-off points of 3, 4, 5, and 6 mm were assessed using negative-predictive values (NPVs).

Results: 16 studies met inclusion and exclusion criteria, yielding a total of 1136 patients for meta-analysis. Twelve studies defined TT as "from a theoretical normal mucosal line to the deepest invasion"; 2 studies defined TT as "from the surface excluding keratin, parakeratin, and inflammatory exudates to the deepest invasion"; and 2 studies did not specify the TT definition. The NPV for absence of PLND by tumor thickness was 94.7% at 3 mm, 95.5% at 4 mm, 83.4% at 5 mm, and 87.0% at 6 mm. There was a statistically significant difference in prediction of lymph node metastasis between patients with a TT cut-off of 4 mm and 5 mm; therefore 4 mm was considered the optimal cut-off for management decisions.

Conclusions: Despite the limitations of a retrospective meta-analysis in this study (including vagueness of TT definition), a cut-off of 4 mm TT in OSCC had an NPV of 95%. Accordingly, patients with TT <4 mm can be spared from subsequent elective neck dissection.

Reviewer's Comments: Use of TT determination based on surgical resection specimens allowed more uniformity and accuracy, but it may not be useful for pretreatment evaluation. Additional studies are needed to validate the correlation of TT detection on preoperative ultrasonography or MRI with surgical TT and risk of cervical lymph node metastasis.

Additional Keywords: Cervical Lymph Node Metastasis

print tag: () Refer to original journal article.

New Grading System Introduced for Invasive Lobular Carcinoma

A Newly Proposed Semi-Automated Method of Grading Invasive Lobular Carcinoma: A Unifying Concept and Correlation With Prognostic Markers and Patient Survival.

Stevens E, Kimler BF, et al:

Ann Clin Lab Sci; 39 (Winter): 25-31

While the proposed Nuclear and Proliferation Index system may have some advantages over the well-known Scarff-Bloom-Richardson system, larger studies are needed before this new grading system can be adopted.

Background: Invasive lobular carcinoma (ILC) of the breast comprises about 15% of breast cancers. The modified Scarff-Bloom-Richardson (SBR) system is the most widely used grading system for invasive carcinomas of the breast, although it is much less commonly applied to cases of ILC. Criticisms of the SBR system include its reliance on subjective interpretation of tubule formation, nuclear grade, and mitotic activity, as well as reportedly suboptimal reproducibility. A new grading system using nuclear grade and Ki-67 proliferative activity is proposed.

Objective: To apply the newly proposed Nuclear and Proliferation Index (N+P) system to ILC, to assess whether automated image analysis reduces subjectivity, and to assess whether the N+P system correlates with patient survival and expression of commonly utilized tumor biomarkers.

Methods: 788 primary breast carcinomas were examined, including 650 invasive ductal carcinomas, 58 ILC, 38 mixed ductal and lobular carcinomas, and 42 "other" tumor types, such as colloid, papillary, and metaplastic squamous cell carcinomas. Tumor samples were obtained from core needle biopsy, lumpectomy, and mastectomy specimens. Fifty-eight cases of ILC were evaluated using both the SBR and newly proposed N+P tumor grading systems. Nuclear grade was determined using the following 3-tiered scoring system: score 1 (small regular and uniform nuclei with little variation), score 2 (moderate nuclear variation), and score 3 (marked variation in size and shape of nuclei). Automated Ki-67 proliferation indices were scored based on the following 3 categories: score 1 (9%), score 2 (10% to 25%), and score 3 (>25%). The final N+P grade was determined using the following scheme: grade 1 (tumors with nuclear grade score of 1 or 2 and Ki-67 score of 1 or 2), grade 2 (tumors with a nuclear grade score 3 and Ki-67 score 1 or 2 or a Ki-67 score of 3 and nuclear grade score of 1 or 2), and grade 3 (both nuclear and Ki-67 scores of 3). The results of grading using these 2 methods were then compared in relation to the degree of correlation with the following clinical, pathologic, and immunohistochemical features: overall patient survival, tumor size, tumor grade, angiolymphatic invasion, lymph node status, ploidy status, and Bcl-2, EGFR, p53, Her-2, ER, and PR expression.

Results: In relation to clinical and prognostic parameters, the SBR and N+P grading systems showed overall agreement. Although not statistically significant, the N+P grading system appears to show improved separation between overall survival curves for low-grade (grade I) versus higher-grade (grade II or III) tumors.

Conclusions: The N+P grading system is less subjective than the SBR system, and it may be better at predicting overall patient survival.

Reviewer's Comments: This newly proposed grading system for invasive breast carcinomas, while potentially useful, needs validation with a larger number of cases.

Additional Keywords: Grading Systems

print tag: () Refer to original journal article.

Brenner Tumors, Transitional Cell Carcinomas Follow Different Tumorigenic Pathways

Transitional Cell Tumors of the Ovary: A Comparative Clinicopathologic, Immunohistochemical, and Molecular Genetic Analysis of Brenner Tumors and Transitional Cell Carcinomas.

Cuatrecasas M, Catasus L, et al:

Am J Surg Pathol; 33 (April): 556-567

Brenner tumors and ovarian transitional cell carcinomas are likely not related to one another.

Background: Ovarian transitional cell tumors are uncommon and represent 1% to 2% of ovarian neoplasms. These include both Brenner tumors (which are then further subclassified) and transitional cell carcinomas. Molecular changes seen with these tumors and their relationship with one another have not been investigated in depth.

Objective: To report clinicopathologic, immunohistochemical, and molecular changes seen in a series of Brenner tumors and transitional cell carcinomas.

Methods: 19 transitional cell tumors of the ovary were identified from a single pathologist's consultation files and the files of a single institution. Histology was reviewed and tumors were classified as per WHO. To be diagnosed as a transitional cell carcinoma, the tumor could not be associated with a benign or borderline Brenner tumor and the patient could not have a history of urothelial carcinoma. Tissue microarrays were constructed and immunohistochemistry was performed. Molecular analysis was performed for a number of markers using various methods.

Results: 19 cases were collected that included 13 Brenner tumors (5 benign, 7 borderline, and 1 malignant) and 6 transitional cell carcinomas. Mean age of patients was 58 years, and patients generally presented with a mass or uterine bleeding. The majority of both Brenner tumors and transitional cell carcinomas were unilateral. The transitional cell carcinomas typically presented at higher stage. Benign Brenner tumors were typically solid, although borderline and malignant Brenner tumors were solid and cystic, as were the transitional cell carcinomas. Benign Brenner tumors contained epithelial nests within a fibrous stroma devoid of significant nuclear atypia. Borderline Brenner tumors had confluent nests and papillae of epithelial cells with mild atypia and increased mitotic activity. A mucinous lining of cysts was more conspicuous than that seen with the benign tumors. The malignant Brenner tumor had severe cytologic atypia and signet ring cell change. Vascular invasion was not seen with Brenner tumors. Transitional cell carcinomas were high-grade carcinomas with necrosis and hemorrhage. Brenner tumors showed greater epidermal growth factor receptor (EGFR) immunoreactivity and less p16 and p53 immunoreactivity than transitional cell carcinomas. Increased copy numbers of EGFR were not seen. p53 mutations were identified in transitional cell carcinomas and not in Brenner tumors.

Conclusions: Brenner tumors and transitional cell carcinomas of the ovary are likely not related. The authors state that borderline and malignant Brenner tumors show activation of the P13K/AKT pathway through EGFR, and transitional cell carcinomas typically have p53 mutations.

Reviewer's Comments: A number of ovarian carcinomas show different molecular pathways for development, eg, low- and high-grade serous carcinomas. It is thus not surprising that the same may be true for ovarian transitional cell tumors.

print tag: () Refer to original journal article.

Most PRMTs Behave in Benign Fashion

Primary Retroperitoneal Mucinous Tumors: A Clinicopathologic Study of 18 Cases.

Roma AA, Malpica A:

Am J Surg Pathol; 33 (April): 526-533

Primary retroperitoneal mucinous tumors seem to be nonaggressive neoplasms, except in cases containing anaplastic carcinoma or sarcoma.

Background: Primary retroperitoneal mucinous tumors (PRMT) are uncommon. They occur most often in women over a wide age range, although most cases are seen in women of reproductive age. The tumors, similar to ovarian mucinous tumors, are classified as cystadenomas, borderline tumors, and carcinomas.

Objective: To present clinicopathologic findings of 18 cases of PRMT.

Methods: 18 cases of primary retroperitoneal mucinous tumors were identified from the surgical pathology files of a single institution over 18 years. Tumors with any ovarian involvement were not included. Gross features were retrieved and histologic features were reviewed in all cases. Tumors were classified as cystadenomas, low malignant potential, low malignant potential with intraepithelial carcinoma, microinvasive adenocarcinomas, or frankly invasive carcinomas. Clinical and follow-up information were pursued. Immunohistochemistry was performed with a number of antibodies.

Results: All patients were women aged 20 to 63 years, with a mean age of 39 years. The majority of patients presented with a mass discovered at routine examination or by self-palpation. Two patients presented with pelvic pain. All tumors were unilateral and located exclusively in the retroperitoneum. In nearly half the cases, the ovaries were removed and were histologically normal. Tumors ranged in size from 7 to 26 cm, and the mean size was 13 cm. Six cases were unilocular, 8 were multiloculated, and 4 were solid and cystic. Two cases were classified as cystadenomas, 4 as low malignant potential, 3 as low malignant potential with intraepithelial carcinoma, and 9 as adenocarcinomas, all with an infiltrative pattern of growth. Three adenocarcinomas were anaplastic or sarcomatoid and 1 tumor was associated with a sarcoma. Ovarian stroma and goblet-like cells were seen in about 50% of cases. All cases were CK7 immunoreactive, and two thirds were focally immunoreactive with antibodies to CK20. Forty percent of cases tested were immunoreactive with antibodies to CK17. All patients were treated with resection and 2 received chemotherapy. Follow-up was available for 16 patients, ranging from 1 to 148 months (median, 22 months). Two patients died of disease (1 who had an anaplastic area and 1 who had associated sarcoma). Three other patients had evidence of disease at last follow-up; all had originally had adenocarcinomas. The remaining 10 patients were alive and free of disease.

Conclusions: Most PRMTs are nonaggressive. However, half are associated with adenocarcinoma and these are not infrequently associated with high-grade neoplasia.

Reviewer's Comments: This is the largest series of primary retroperitoneal mucinous tumors reported to date. Some cases associated with anaplastic differentiation or sarcomas do end up leading to the death of patients.

Additional Keywords: Clinical Findings

print tag: () Refer to original journal article.

HPV Rare in SCC of Oral Cavity

Low Prevalence of Human Papillomavirus in Squamous-Cell Carcinoma Limited to Oral Cavity Proper.

Scapoli L, Palmieri A, et al:
Mod Pathol; 22 (March): 366-372

Human papillomavirus is detected by PCR in about 2% of squamous cell carcinomas of the oral cavity (lip, palate, floor of mouth, etc).

Background: Squamous cell carcinomas (SCC) of the head and neck have recently been described as associated with human papillomavirus (HPV). The association may be clinically important, as the HPV-related tumors appear to have a better prognosis than conventional types. The prevalence rates vary considerably in the literature, but have been described as high as 70% in the tonsillar SCC. Within the oral cavity proper, HPV prevalence rates are thought to be much lower, but small study sizes and differences in populations and techniques have led to varying results.

Objective: To evaluate SCC of the oral cavity proper, and to determine the prevalence rate of HPV.

Methods: SCC specimens of the oral cavity proper (including floor of the mouth, cheek, tongue, gingiva, lip, palate, and retromolar area) were collected and evaluated by PCR for HPV 16, -31, -45, and -18, and by in situ hybridization.

Results: The PCR assay detected clinically significant amounts of HPV 16 DNA in 5 oral cavity tumors of the 314 successfully tested. This resulted in a prevalence of 2% (CI, 0.6 to 3). No difference was found in comparison to adjacent normal tissues. In situ hybridization for HPV confirmed only 1 case, which had the highest viral load (>100 viral genomes per cell). The cases with lower viral loads were negative by in situ hybridization. A pair-matched case-control evaluation of 235 SCCs for HPV 16 detected 2 positive cases, demonstrating that HPV did not correlate with SCC (P =0.37). Of unmatched controls, 1 of 79 SCCs and none of 20 controls were positive for HPV (P =0.4). None of the tumors, oral cavity cases, or controls was positive for HPV -31, -5, or -18.

Conclusions: The prevalence of clinically significant amounts of HPV DNA in SCCs of the oral cavity proper is approximately 2%. The similarity found in a matched-pair case-control analysis indicates that HPV is not likely to be an important etiological factor in these tumors.

Reviewer's Comments: HPV-associated lesions of the head and neck appear to be most prevalent in the tonsillar tissues, including the lingual tonsil at the base of the tongue.

Additional Keywords: Human Papillomavirus & Squamous Cell Carcinoma

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Stage, Grade of GISTs Associated With Clinical Behavior

Stage and Histological Grade of Gastrointestinal Stromal Tumors Based on a New Approach Are Strongly Associated With Clinical Behaviors.

Hou Y-Y, Lu S-H, et al:

Mod Pathol; 22 (April): 556-569

Gastrointestinal stromal tumors with gross spread are associated with a poor clinical outcome. In those without gross spread, presence of predictive parameters is associated with a progressively worse outcome.

Background: Given the response of gastrointestinal stromal tumors (GISTs) to imatinib targeted therapy, survival has dramatically increased. However, resistance to therapy can occur, and the selection of patients to receive adjuvant therapy is not clearly defined.

Objective: To characterize the stage and grade of GISTs with correlation to clinical outcome data.

Methods: 613 GISTs were identified from a database of mesenchymal tumors of the gastrointestinal tract, characterized by morphology and KIT-positive immunostain in 95% of cases. Histological features were documented, including predominant cell type, pleomorphism, nuclear atypia, necrosis, perivascular pattern, mitotic count, and invasion. Survival analysis was performed on a subset of 590 patients.

Results: Most GISTs were spindle-cell tumors (82%), with fewer epithelioid (8%) or mixed morphology (10%). They were generally mild to moderately atypical with mild to moderate cellularity, but these features varied at different areas within the tumor. Mitotic rates varied from 0 to >100 per 50 high power field. Ulceration was present in 29%, coagulative necrosis in 25%, muscle infiltration in 32%, perivascular growth pattern in 20%, and mucosal infiltration in 9%. Vascular, nerve, and fat infiltration, as well as lymph node metastases, were rare, while hemorrhage and cystic changes were common. Using 12 predictive parameters of malignancy (liver metastasis; peritoneal dissemination; lymph node metastasis; vascular, fat, nerve, or mucosal infiltration; mitotic count at least 10 per 50 high power field; muscular propria infiltration; coagulative necrosis; perivascular pattern; and severe nuclear atypia), 293 patients had none of these features and had a 5-year disease-free survival (DFS) and overall survival (OS) of 99% and 100%, respectively. A total of 320 patients had between 1 and 6 of these features and had a DFS and OS of 44% and 60%, respectively. The DFS and OS were also significantly different when considering either gross spread or microscopic spread of the disease. For those without gross spread of the disease, the number of predictive parameters of malignancy was associated with a progressive decrease in DFS and OS (P <0.0001).

Conclusions: Using gross spread of disease as a clinical stage for GISTs, grading stage I tumors based on the number of predictive parameters of malignancy appears to have significant correlation to clinical outcome.

Reviewer's Comments: The authors found outcome differences within patients who had gross spread of disease. In the absence of gross spread, the number of positive predictive parameters also correlated with outcome.

Additional Keywords: Clinical Behavior

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Does CLL Arise De Novo or Evolve From Pre-Existing MBL?

B-Cell Clones as Early Markers for Chronic Lymphocytic Leukemia.

Landgren O, Albitar M, et al:

N Engl J Med; 360 (February 12): 659-667

The majority of chronic lymphocytic leukemias evolve from pre-existing monoclonal B-cell populations.

Background: Peripheral blood monoclonal B-cell lymphocytosis (MBL) is phenotypically identical to chronic lymphocytic leukemia (CLL). MBL is found in 3% to 5% of normal asymptomatic adults and progresses to CLL in 5% to 15% of cases.

Objective: To determine whether CLL evolves from a pre-existing MBL or if it arises de novo.

Methods/Participants: 45 consenting patients in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial developed CLL and had sufficient cryopreserved whole blood for analysis of their pre-diagnostic state. Whole blood was thawed and analyzed by 6-color flow cytometry (CD5-FTIC, lambda-PE, CD19-PerCP-Cy5.5, CD10-PE-Cy7, kappa-APC, CD45-APC-H7) on a BD FACSCanto. Immunoglobulin heavy-chain variable (IGHV) gene mutation was measured by RT-PCR and gene sequencing.

Results: 45 patients developed CLL over an average of 3 years after enrollment (range, 3 to 77 months). By flow cytometry, 42 patients (93%) demonstrated MBL in previously obtained cryopreserved whole blood. By RT-PCR, 43 patients (96%) demonstrated clonal IGHV gene rearrangement. By direct sequencing, 27 of 35 patients demonstrated mutated IGHV genes (77%), while 8 (23%) had unmutated genes. Overall, 44 of 45 patients (98%) who developed CLL during enrollment demonstrated a pre-existing monoclonal B-cell population by either flow cytometry or PCR assay. Forty-one patients (91%) were positive by both methods.

Conclusions: The majority of CLL cases evolve from pre-existing monoclonal B-cell populations.

Reviewer's Comments: There were no examples of light chain switching between pre-diagnostic monoclonal B cell populations and subsequent CLL populations, supporting the notion that pre-diagnostic monoclonal B cells represent precursor neoplasia. Regardless of the interval between enrollment and diagnosis, the majority of cases (80%) demonstrated a hypermutated IGHV gene, a favorable prognostic feature in CLL. This represents a relatively higher proportion of hypermutation than reported in a general series of CLL and raises the possibility that some cases of more aggressive (unmutated) CLL may arise de novo.

Additional Keywords: Monoclonal B-Cell Lymphocytosis

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How to Distinguish Primary Pulmonary Adenocarcinoma From Metastatic Breast Carcinoma

Evidence-Based Criteria to Help Distinguish Metastatic Breast Cancer From Primary Lung Adenocarcinoma on Thoracic Frozen Section.

Herbst J, Jenders R, et al:

Am J Clin Pathol; 131 (January): 122-128

In breast cancer patients with lung nodules, frozen section evidence of acini, lepidic growth, nuclear pseudoinclusions, and scar predict a new primary lung tumor.

Background: During intraoperative consultation, pulmonary surgeons may have to decide between wedge/segmental resection for presumed metastatic carcinoma and lobectomy/sleeve resection/pneumonectomy for primary adenocarcinoma. The distinction of primary pulmonary adenocarcinoma from metastatic breast carcinoma is often challenging, especially by frozen section.

Objective: To establish frozen section histological criteria that best distinguish primary pulmonary adenocarcinoma from metastatic breast carcinoma during intraoperative consultation.

Methods: 129 frozen section specimens from 120 women and 1 man with lung nodules and a history of breast cancer were reviewed. Specimens were selected for 20 examples each of primary pulmonary adenocarcinoma or metastatic breast cancer, making up a training and a separate test series comprised of 10 examples each. One dozen histological features were evaluated, 10 at 100x magnification (acini, lepidic growth pattern, scar, subpleural location, lymphovascular invasion, papillary architecture, comedonecrosis, solid nests, and trabecular or cribriform architecture) and 2 at 400x magnification (nuclear pseudoinclusions and macronucleoli).

Results: Among 12 parameters, 8 were significant. Histological evidence for acini, lepidic growth, nuclear pseudoinclusions, and scar were significant predictors of primary pulmonary adenocarcinoma. In contrast, comedonecrosis, solid nests, trabecular architecture, and cribriform architecture were significant predictors of metastatic breast cancer. In patients with multiple pulmonary nodules, a history of breast cancer, and no radiographic evidence of extrapulmonary metastases, the odds ratio of new primary pulmonary carcinoma versus metastatic breast carcinoma was even (1.1), arguing against the notion that such lesions are metastatic until proven otherwise.

Conclusions: In patients with lung nodules and a history of breast cancer, frozen section evidence for acini, lepidic growth, nuclear pseudoinclusions, and scar predict a new primary malignancy, while comedonecrosis, solid nests, trabecular architecture, and cribriform architecture predict metastatic breast cancer.

Reviewer's Comments: The authors suggest that some of their findings are counterintuitive to the preconceived notions of many pathologists. Regardless of whether that is an accurate generalization, these findings should facilitate practical communication of frozen section diagnoses to pulmonary surgeons, who sometimes have nerve-racking decisions to make.

Additional Keywords: Frozen Section

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Does p63 Help Identify Squamous Differentiation in NSCC Cytology Samples?

P63 Differentiates Subtypes of Nonsmall Cell Carcinomas of Lung in Cytologic Samples: Implications in Treatment Selection.

Jorda M, Gomez-Fernandez C, et al:

Cancer Cytopathol; 117 (February 25): 46-50

p63 is a useful marker for detection of squamous differentiation in patients with non-small-cell carcinoma of the lung when used in pulmonary cytology samples.

Background: Lung cancer is the leading cause of cancer-related death in the United States. Of these lung cancers, 85% are non-small-cell carcinoma (NSCC). Bevacizumab, a monoclonal antibody against IgG1, has been shown to prolong overall survival and improve response rates in patients with NSCC. However, patients with tumors showing squamous differentiation are at risk for life-threatening pulmonary hemorrhage. Therefore, it is important in therapeutic decision-making to identify which NSCCs have squamous differentiation (SqD) or non-squamous differentiation (NSqD). p63 is expressed in squamous carcinomas and has been shown to be positive in nearly 100% of cases of NSCC with SqD on formalin-fixed, paraffin-embedded tissue.

Objective: To evaluate use of p63 immunocytochemistry to differentiate between SqD and NSqD in NSCC when cytologic material is the only available diagnostic material.

Participants/Methods: 51 consecutive patients with a cytologic diagnosis of NSCC of the lung and histologic follow-up were included. Cytology samples included fine-needle aspirations, bronchial washings, bronchial brushings, and bronchoalveolar lavages. Alcohol-fixed, Papanicolaou-stained slides were marked with a diamond pen on the backside around malignant cells for localization purposes. These slides were then immunohistochemically stained for p63 without destaining or formalin fixation. Only cells in diamond-marked areas were evaluated, and a strong and well-defined nuclear stain was considered a positive result. Positive benign bronchial reserve epithelium present outside the diamond-marked areas served as a positive internal control.

Results: On histology, 26 NSCCs had SqD. Cytologic examination without immunohistochemistry identified 9 cases with SqD, all of which were SqD NSCC on histologic follow-up. p63 staining on cytologic material was positive in 23 of 26 cases with SqD on follow-up, including the 9 cases identified by cytology alone. An additional 4 cases were also positive for p63 on cytology but did not show SqD on follow-up; however, all 4 of these cases had only core biopsies available for follow-up. The sensitivity of cytology plus p63 staining was 88% for the detection of SqD.

Conclusions: p63 is a useful marker for detection of squamous differentiation in patients with NSCC of the lung when used in pulmonary cytology samples. False-negative cases may be due to sampling error. Caution should be used in selecting areas for interpretation, as normal bronchial reserve epithelial cells will also be positive for p63.

Reviewer's Comments: In an era when more lung tumors are diagnosed by limited sampling techniques (ie, fine-needle aspiration or core needle biopsy), accurate diagnosis is important as many patients will not go on to resection. In addition, neoadjuvant chemotherapy and radiation therapy are commonplace, and patients may be considered for bevacizumab in this setting.

Additional Keywords: p63

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Do Distant LNs Matter in Colorectal Cancer?

Nodal Staging in Colorectal Cancer: Should Distant Lymph Nodes Be Recovered in Surgical Specimens?

Pusztaszeri M, Matter M, et al:
Hum Pathol; 40 (April): 552-557

Accurate lymph node staging can be performed in the pericolonic fat <5 cm from the tumor on both sides in most cases.

Background: The most important factor in predicting survival for patients with colorectal carcinoma is the presence or absence of lymph node (LN) metastasis. The number of LNs required for adequate staging is controversial, with some authors advocating at least 12 LNs.

Objective: To investigate the impact of LN distance from the colorectal carcinoma on acceptable LN sampling and accurate staging.

Participants/Methods: 345 patients with colorectal carcinoma who underwent regional resection were included. The mesocolic fat was divided into 2 sections; fraction A was close to the tumor (<5 cm on either side of the tumor), and fraction B was distant from the tumor (>5 cm from both sides of the tumor). The 2 fractions were separated into different bottles and dissection was performed the next day by participants blinded to the location. A clearing reagent was used to assist with retrieval. LN staging was defined according to the TNM classification: pN0, no involved LNs; pN1, 1 to 3 LNs involved; and pN2, 4 LNs involved.

Results: The overall mean number of sampled LNs was 19 for all resections and specifically 15.4 for rectal specimens. The mean number of LNs present in fraction A was 13.5 for all cases compared to 4.9 in fraction B. Overall, there were 169 pN0 cases, 104 pN1 cases, and 72 pN2 cases. There was no significant difference in total LN mean number between pN categories. When only LNs from fraction A were considered, the pathologic staging was accurate in 97% of colorectal specimens. Ten cases were discrepant; 6 were upstaged from pN0 to pN1 based on fraction B LNs and 4 were upstaged to pN2 from pN1 by fraction B LNs. Of upstaged pN0 cases, 5 were rectal tumors (5.6% of all rectal cases), of which 3 had preoperative radiotherapy. In addition, the median number of LNs sampled in fraction A was below 12 in the 4 cases upstaged to pN2.

Conclusions: In the majority of colonic resections, accurate LN staging can be performed in the pericolonic fat <5 cm from the tumor on both sides. However, in cases with <4 positive LNs and <12 total LNs sampled, additional dissection of the distant fraction should be performed. In addition, sampling of close and distant LNs should be performed in rectal specimens because in rare cases, metastases are detected only in fraction B, particularly in patients who undergo neoadjuvant radiotherapy.

Reviewer's Comments: This well-designed study supports a staged system of LN sampling, with additional dissection performed based on certain criteria. The authors report that in 66% of current study cases, additional dissection would not have been needed according to these criteria.

Additional Keywords: Nodal Staging

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p63 Expression Seen in Various Types of GTD

P63 Expression in Gestational Trophoblastic Disease: Correlation With Proliferation and Apoptotic Dynamics.

Zhang H-J, Xue W-C, et al:

Int J Gynecol Pathol; 28 (January 30): 172-178

p63 expression is associated with cell proliferation in gestational trophoblastic disease, and p63 staining may help distinguish epithelial trophoblastic tumors from placental site trophoblastic tumors.

Background: Gestational trophoblastic disease (GTD) includes complete and partial hydatidiform moles, invasive moles, placenta site trophoblastic tumors, and choriocarcinoma. Besides having different clinical features and biologic behavior, the different forms of GTD are thought to derive from different trophoblastic subpopulations. p63 is a p53-related protein with at least 6 separate isoforms that may be grouped into 2 general isoform types: the proapoptotic/antioncogenic type (TAp63) and the antiapoptotic/pro-oncogenic type (deltaNp63). p63 expression has been described in numerous normal tissues throughout the body, where the general pattern is positivity within basal layers of stratified epithelia. p63 expression has also been described in a large number of solid tumor types.

Objective: To evaluate expression of p63 in normal human placental tissue and various forms of GTD, and to correlate these findings with cell proliferation and apoptosis.

Methods: Formalin-fixed, paraffin-embedded samples of the following tissues were collected: 9 normal first-trimester placentas, 11 normal term placentas, 19 partial moles, 43 complete moles, 9 choriocarcinomas, 5 placenta site trophoblastic tumors, and 2 epithelial trophoblastic tumors. All cases were reviewed for diagnostic consensus, and representative slides from each case, along with positive and negative controls, were stained using mouse monoclonal (clone 4A4) and rabbit polyclonal (clone anti-p40) antibodies against p63. Clone 4A4 recognizes both the TAp63 and deltaNp63 isoforms, while clone anti-p40 only recognizes the deltaNp63 isoform. At least 1000 trophoblastic cells were examined for each case by 3 pathologists, and the percentage of p63 positivity, irrespective of intensity, was recorded. Statistical analysis was then performed.

Results: p63 immunoreactivity was localized to the nucleus of cytotrophoblastic, villous trophoblastic, and chorionic-type intermediate trophoblastic cells. There was a high positive correlation between the staining patterns of the 2 antibodies, although the deltaNp63 isoform appeared to be the predominant isoform observed. Among the different types of GTD, p63 expression was lower in placentas of advanced gestational age, hydatidiform moles showed higher p63 expression than normal placentas, epithelial trophoblastic tumors showed the highest p63 expression, choriocarcinomas showed only focal p63 staining, and placenta site trophoblastic tumors showed no significant p63 staining. There was no significant correlation between p63 expression and the later development of trophoblastic neoplasia in hydatidiform moles; the expression of both antibodies showed significant correlation with the Ki-67 proliferation index.

Conclusions: p63 shows a heterogeneous pattern of expression in various forms of GTD using antibodies against the TAp63 or deltaNp63 isoforms. In most cases of GTD, greater p63 expression is associated with increased proliferation.

Reviewer's Comments: These results suggest that p63 may be most helpful in distinguishing between epithelial trophoblastic tumors and placenta site trophoblastic tumors. However, the number of cases studied was small.

Additional Keywords: p63 Expression

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What Is Glypican-3?

Glypican-3: A Novel Diagnostic Marker for Hepatocellular Carcinoma and More.

Kandil DH, Cooper K, et al:

Adv Anat Pathol; 16 (March): 125-129

Glypican-3 aids in the diagnosis of hepatocellular carcinoma, certain testicular germ cell tumors, and various embryonal tumors.

Background: Glypican-3 (GPC3) is one of many proteins belonging to the family of heparin sulfate proteoglycans. In human tissues, 6 subtypes of glypican proteins have been identified to date (GPC1 to GPC6). These proteins play important roles in cell growth and differentiation through their activity as co-receptors for heparin-binding growth factors. Mice, which lack GPC3, show abnormal cell proliferation. Interestingly, GPC3 is expressed in embryonic liver and placenta, but its expression in corresponding normal adult tissues is silenced. However, expression appears to re-emerge upon malignant transformation of these tissues.

Objective: To review potential applications of GPC3 expression by immunohistochemistry in malignant liver tumors, testicular germ cell tumors, embryonal tumors, and melanoma, among others.

Methods: The authors reviewed the current literature on the application of GPC3 immunostaining in surgical pathology and cytology.

Results: By immunohistochemistry, GPC3 is usually positive in hepatocellular carcinoma (HCC) and negative in normal adjacent liver tissue. It may also prove useful in discriminating HCC from an intrahepatic or extrahepatic cholangiocarcinoma, since GPC3 is down regulated in the latter. One pitfall, however, is that GPC3 may be expressed in active necroinflammatory lesions, such as those seen in severe hepatitis. Among testicular germ cell tumors, GPC3 is strongly positive in most yolk sac tumors and negative in seminoma, intratubular germ cell neoplasia, and benign testicular tissue. Among embryonal tumors, GPC3 is usually positive in Wilms' tumor, hepatoblastoma, and neuroblastoma and negative in medulloblastoma. Among lung cancers, GPC3 is reportedly positive in approximately 25% of cases. Higher expression is usually seen in squamous cell carcinoma compared with adenocarcinoma. In cases of melanoma, conflicting GPC3 expression results have been reported.

Conclusions: GPC3 is a highly sensitive and specific marker for HCC, and it is helpful in the differential diagnosis of HCC and cholangiocarcinoma. GPC3 also has diagnostic utility in differentiating among various testicular germ cell tumors.

Reviewer's Comments: GPC3 immunostaining is probably underutilized in the practice of surgical pathology and cytology. As with any immunohistochemical stain, potential pitfalls should be avoided.

Additional Keywords: Glypican-3 Expression

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Early Onset Colon Cancer Usually High Stage

Clinical, Pathologic, and Molecular Features of Early-Onset Colorectal Carcinoma.

Yantiss RK, Goodarzi M, et al:

Am J Surg Pathol; 33 (April): 572-582

Young patients (ie, aged <40 years) with colon cancer are more likely to have tumors in the rectum.

Background: Colon cancer is the third most common cause of cancer death in patients from the United States. There is evidence that the incidence rate of colon cancer in people aged <40 years has increased, especially the incidence of rectal cancer. Furthermore, some studies have suggested that these tumors behave more aggressively than tumors of older patients.

Objective: To investigate clinicopathologic and molecular features of these tumors.

Methods: The surgical pathology files of 2 institutions were evaluated for cases of colorectal adenocarcinoma occurring in patients aged <40 years. Random control cases of older patients were also gathered. Clinical and follow-up information and histologic materials were reviewed. Immunohistochemistry was performed using numerous antibodies. Microsatellite analysis was performed as well as mutational analysis for a number of genes. Quantitative real-time polymerase chain reaction (PCR) was performed for alpha-methylacyl-CoA racemase (AMACR) and micro-RNAs (miRNAs). Tumors were assessed for human papillomavirus (HPV) using PCR.

Results: 24 cases occurred in patients aged <40 years. The majority presented secondary to symptoms and occurred in the distal colon; >50% occurred in the rectum. Compared to older patients, younger patients had similar sized tumors, although they were much more likely to have tumors in the distal colon and rectum. They were actually less likely to have a family history of colon cancer or cancer in general. The tumors had similar stage and grade when compared to those of older patients. Tumors in younger patients were more likely to have lymphatic and venous invasion and be infiltrating. Tumors did not have significant differences with testing for DNA repair mechanisms, the Wnt signaling pathway, and most tyrosine kinase receptors (although nuclear expression of CXCR was slightly increased in younger patients). The antiapoptotic protein AMACR was somewhat more expressed at the protein level, as were a number of miRNAs that have been shown to be increased in colonic adenocarcinomas. HPV was not identified in any tumors.

Conclusions: Colorectal adenocarcinomas in young patients (aged <40 years) are frequently high stage and show aggressive histologic features. Increased miRNAs may play an important role in the modifications of messenger RNAs in these tumors.

Reviewer's Comments: It is interesting to note that the young patients in this study were unlikely to have family histories of colon cancer. Furthermore, they were no more likely to have defects in DNA repair mechanisms.

Additional Keywords: Features

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Addressing the Controversy of Dx of BE, Requirement for Goblet Cells

Metaplastic Esophageal Columnar Epithelium Without Goblet Cells Shows DNA Content Abnormalities Similar to Goblet Cell-Containing Epithelium.

Liu W, Hahn H, et al:

Am J Gastroenterol; 104 (April): 816-824

DNA content abnormalities are similar in esophageal metaplasia, regardless of presence of goblet cells.

Background: Columnar metaplasia of the esophagus results from gastroesophageal reflux disorder and has been shown to be a precursor lesion for the development of esophageal adenocarcinoma. Currently, the American College of Gastroenterology requires the presence of goblet cells for the diagnosis of Barrett's esophagus (BE), although this criterion remains controversial.

Objective: To review chromosomal abnormalities and aneuploidy seen in a series of specimens from columnar-lined esophaguses that both had and did not have goblet cells.

Methods: Samples from 68 patients with columnar-lined esophaguses sampled in a consistent method were used. Of these, 22 did not have any goblet cells and were noted to have short-segment disease. The patients with goblet cells all had long-segment disease. DNA content abnormalities were compared between patients with and without goblet cells with a series of controls and from different samples with the population of patients noted to have goblet cells. DNA image cytometry was performed.

Results: The DNA and heterozygosity indices were similar for columnar metaplasias with and without goblet cells, and both were significantly higher than the results for the normal controls. Furthermore, the rates of aneuploidy were similar between the 2 groups of columnar metaplasia, both, again, significantly higher than the results seen with control tissues. Results were also similar in samples taken from patients who had portions of columnar cells with goblet cells and portions of columnar cells without goblet cells.

Conclusions: There is no difference in chromosomal abnormalities between columnar metaplasias of the esophagus that either have or do not have goblet cells. The authors speculate that the 2 types of epithelium then may also have the same neoplastic potential.

Reviewer's Comments: This paper again addresses the controversy regarding the diagnosis of BE and the requirement for goblet cells. However, it is unclear whether definitions should be based on ploidy and DNA content findings.

Additional Keywords: Goblet Cells

print tag: () Refer to original journal article.