Follicular Lesion of Undetermined Significance in Thyroid FNA--How Is It Used?

Implications of the Proposed Thyroid Fine-Needle Aspiration Category of "Follicular Lesion of Undetermined Significance": A Five-Year Multi-Institutional Analysis.

Layfield LJ, Morton MJ, et al:

Diagn Cytopathol 2009; 37 (October): 710-714

The diagnostic category of "follicular lesion of undetermined significance" in thyroid FNA demonstrates malignancy on follow-up in 5% to 10% of patients, similar to the NCI recommendations.

Background: Fine-needle aspiration (FNA) is the current standard for triaging patients with thyroid nodules into operative and nonoperative therapy. In 2007, the National Cancer Institute (NCI) held a Thyroid FNA State of the Science Conference, where a 6-tiered classification system was proposed to standardize reporting of thyroid FNA results. One category, designated "follicular lesion of undetermined significance" (FLUS), was proposed to incorporate cases with insufficient benign or atypical material for a definitive diagnosis of "benign" or "follicular neoplasm." This category was stated to have a 5% to 10% risk of malignancy, to represent no more than 7% of all thyroid FNA diagnoses, and be followed by repeat FNA in 3 to 6 months. Precise cytomorphologic criteria for this diagnosis were not defined.
Objective: To investigate how frequently the term FLUS is used and to evaluate the histopathologic follow-up, when available.
Methods: All thyroid FNAs from 3 institutions over 5 years were reviewed for a previous diagnosis of FLUS or older equivalent diagnostic terms, which included "atypia of undetermined significance," "atypical cells cannot exclude neoplasm," "atypical cells cannot exclude follicular neoplasm," or "follicular proliferation, follicular neoplasm cannot be excluded." The frequency of use for the term FLUS or its equivalents was calculated, and correlating surgical pathology reports were obtained when available.
Results: Of 6872 thyroid FNAs, 664 cases (12%) were diagnosed as FLUS or its equivalent. The percentage of cases diagnosed as FLUS varied by pathologist, ranging from 2.5% to 28.6%. Correlating surgical pathology reports were available for 127 cases (19%), of which 36 cases (28%) demonstrated malignancy. The overall rate of malignancy for FLUS cases was 5% (assuming appropriate clinical follow-up and repeat FNA). The malignant histopathologic diagnoses included 8 papillary carcinomas, 17 follicular variant of papillary carcinomas, 7 follicular carcinomas, and 1 lymphoma. Of all papillary carcinomas, 12 (48%) were incidental findings, unrelated to the index nodule.
Conclusions: The diagnostic category of FLUS for thyroid FNA substantially varies among pathologists, and more rigorously defined morphologic criteria are needed. Currently, it appears to be used more often than the NCI's recommendations. The risk of malignancy in this study is in concordance with the stated frequency of malignancy at 5% to 10%, which suggests that the follow-up recommendation for re-aspiration of these nodules is appropriate.
Reviewer's Comments: Similar to how the category of "atypical cells of undetermined significance" in cervical cytology has undergone significant changes over the last 10 years, it is likely that the category of FLUS in thyroid FNA will undergo similar revisions. As with any change in practice, adequate education of surgeons and endocrinologists regarding the predicted risk and appropriate follow-up of patients with a diagnosis of FLUS is important for patient care. (Reviewer-Deborah J. Chute, MD).

Keywords: FNA, Thyroid, Follicular Proliferation, Undetermined Significance

Print Tag: Refer to original journal article

Stratifying Appendiceal Mucinous Neoplasms

Appendiceal Mucinous Neoplasms: Clinicopathologic Study of 116 Cases With Analysis of Factors Predicting Recurrence.

Pai RK, Beck AH, et al:

Am J Surg Pathol 2009; 33 (October): 1425-1439

The behavior of appendiceal mucinous neoplasms can be predicted histologically.

Background: The classification of appendiceal mucinous neoplasms remains controversial and confusing. Although we know that most cases of pseudomyxoma peritonei develop from appendiceal mucinous neoplasms, it remains difficult to predict which appendiceal tumors are going to behave poorly. The prognosis of limited peritoneal involvement by tumor, especially when such involvement consists only of acellular mucus, remains unclear.
Objective: To review a large series of appendiceal mucinous neoplasms and focus on cases that pose diagnostic difficulties. The authors also propose a classification system for mucinous appendiceal neoplasms.
Methods: A single institution's pathology database was searched for all cases of appendiceal mucinous neoplasms seen over a 30-year period. The type of surgery and subsequent therapy were recorded. All slides from original or subsequent surgeries were reviewed. The degree of cytologic atypia, architectural complexity, presence or absence of extra-appendiceal mucus, extent of neoplastic epithelium, and appendiceal margin status were recorded, as were follow-up results.
Results: Most patients were women, and their mean age was 54 years. Twenty-seven cases were labeled as group 1 with low-grade mucinous neoplasms limited to the appendix. Thirty-two cases were considered group 2 with low-grade neoplasms that had extra-appendiceal mucus but not extra-appendiceal epithelial cells. There were 42 cases with low-grade neoplasms that had extra-appendiceal neoplastic epithelium and 15 cases with infiltrating adenocarcinomas. Appendicitis was the most common presentation for group 1 and 2 tumors, whereas group 3 and 4 tumors most often presented as masses. Rupture of the appendix was not seen with group 1 tumors. There were no deaths or recurrences for patients with group 1 tumors. One of 14 patients with group 2 tumors developed recurrent disease, and no patients died. Thirteen of 27 cases of group 3 tumors were associated with persistent disease, and 54% of patients were dead of disease at 10 years. Of group 4 tumors, 7 of 9 patients had persistent disease, and 6 patients died of disease. Factors associated with decreased survival included extra-appendiceal mucinous epithelium, high-grade cytology, complex architecture, and invasive growth. The authors suggest that group 1 tumors be designated as mucinous adenomas, group 2 tumors as low-grade mucinous neoplasms with low risk of recurrence, group 3 tumors as low-grade mucinous neoplasms with high risk of recurrence, and group 4 tumors as mucinous adenocarcinomas.
Conclusions: One can stratify appendiceal mucinous neoplasms into 4 distinctive groups based on histology, with different rates of recurrence and mortality.
Reviewer's Comments: This study confirms some older trials regarding appendiceal mucinous neoplasms. The presence of extra-appendiceal neoplastic epithelium and its grade and invasive properties are the most important risk factors for recurrent disease. (Reviewer-Edward B. Stelow, MD).

Keywords: Mucinous Neoplasia, Cystadenoma, Pseudomyxoma, Adenocarcinoma

Print Tag: Refer to original journal article

Specificity of TLE1 for Synovial Sarcoma

TLE1 Expression Is Not Specific for Synovial Sarcoma: A Whole Section Study of 163 Soft Tissue and Bone Neoplasms.

Kosemehmetoglu K, Vrana JA, Folpe AL:

Mod Pathol 2009; 22 (July): 872-878

TLE1 is not entirely specific for synovial sarcoma and should be used only in the context of a panel of antibodies and with consideration of other diagnostic features.

Background: Well-differentiated synovial sarcomas can be easily recognized, especially when there is a prominent biphasic pattern. However, limited samples and less obvious examples can require additional studies for confirmation. The immunohistochemical stains currently employed for diagnosis lack specificity and overlap with other soft-tissue and bone lesions. Molecular diagnostic methods improve specificity by detecting the characteristic t(X;18)(*SS*18-*SSX*1-2), but this usually requires submission to a referral center where preserved genetic material may not even be extracted from processed tissue. TLE1, a transcriptional repressor involved in the Wnt/β-catenin signaling pathway, was identified from a DNA tissue microarray study to be expressed consistently in synovial sarcomas, but not commonly in other soft-tissue lesions. Immunohistochemical studies confirmed protein overexpression, but this was also performed on tissue microarrays.
Objective: To confirm the test characteristics of TLE1 immunohistochemistry on full-tissue sections of synovial sarcoma and other mesenchymal neoplasms.
Methods: 163 whole tissue sections of bone and soft-tissue tumors were submitted for TLE1 staining (sc-9121, 1:100; Santa Cruz Biochemicals). Each case was reviewed by 2 authors for confirmation of the clinical diagnosis. Only nuclear staining was scored as negative (<5%), 1+ (5% to 25%), 2+ (25% to 50%) and 3+ (>50% of cells positive).
Results: TLE1 was positive in 18 of 20 synovial sarcomas (90%), with 16 of these showing 2-3+ staining. Of all nonsynovial sarcomas, TLE1 was observed in 53 of 143 tumors (37%), but only 36 were 2-3+. These included many peripheral nerve sheath tumors (100% of schwannomas, 30% of malignant peripheral nerve sheath tumors, and 33% of neurofibromas), and scattered other tumors, such as rhabdomyosarcomas and liposarcomas, among others.
Conclusions: TLE1 expression in full-tissue sections of various mesenchymal tumors demonstrates good sensitivity for synovial sarcoma, while lacking ideal specificity, particularly in differentiating peripheral nerve sheath tumors.
Reviewer's Comments: Interpreting immunohistochemistry on a small-tissue biopsy includes accounting for sampling effects. Studies evaluating new antibodies should also be confirmed on full-tissue sections to document variable staining patterns. TLE1 was presented as a specific marker for synovial sarcoma, but this manuscript demonstrates overlapping expression, particularly in peripheral nerve sheath tumors. (Reviewer-Mary T. Galgano, MD).

Keywords: Neoplasms, TLE1 Immunohistochemistry

Print Tag: Refer to original journal article

LDH Isoenzyme Subtyping in CSF May Distinguish Bacterial From Aseptic Meningitis

Cerebrospinal Fluid Lactate Dehydrogenase Isoenzymes in Children With Bacterial and Aseptic Meningitis.

Nussinovitch M, Finkelstein Y, et al:

Transl Res 2009; 154 (October): 214-218

Different patterns of LDH isoenzyme expression in the CSF are associated with bacterial versus aseptic meningitis.

Background: Measurements of opening pressure during lumbar puncture, white blood cell (WBC) counts in the cerebrospinal fluid (CSF), CSF protein and glucose levels, and Gram staining have variable sensitivity for the diagnosis of meningitis. Lactate dehydrogenase is a fermentative enzyme found in various body tissues, including CSF. There are 5 lactate dehydrogenase (LDH) isoenzymes, some of which have been associated with either bacterial or aseptic meningitis. However, a comprehensive quantitative analysis of the isoenzyme patterns in bacterial versus aseptic meningitis has not yet been undertaken.
Objective: To determine the isoenzyme pattern of LDH in the CSF of patients with bacterial and aseptic meningitis.
Participants/Methods: Subjects consisted of 157 previously healthy pediatric patients (age range, 1 day to 18 years) treated for suspected meningitis during an 8-year period at a tertiary care medical center. The first CSF sample was collected on the day of admission and submitted for white blood cell (WBC) counts (total and differential), protein and glucose determination, and viral and bacterial cultures. All specimens were collected before initiation of empiric antibiotic therapy. The diagnosis of bacterial meningitis was made based on isolation of specific bacteria from culture or from positive bacterial antigen assays to various tested bacteria. For aseptic meningitis, the diagnosis was made using accepted diagnostic criteria (reported elsewhere), a negative Gram stain, and a negative bacterial culture result. The reference group consisted of patients for whom CSF studies showed no WBC abnormalities and negative CSF culture results. Total CSF LDH was measured, and then LDH isoenzyme analysis was performed by a blinded investigator.
Results: 31 subjects (19.7%) had bacterial meningitis, 65 (41.4%) subjects had aseptic meningitis, and 61 (38.9%) had no laboratory evidence of meningitis. *Neisseria meningitidis* was the most common isolate (n=12), followed by various other bacteria. Enteroviruses caused aseptic meningitis in 24 patients. None of the subjects died during hospitalization or during a 2-month follow-up. Subjects with bacterial meningitis had significantly higher CSF protein and WBC counts and significantly lower CSF glucose levels. Total LDH activity in the CSF was highest in the bacterial meningitis group. Bacterial meningitis showed a unique pattern of consistently low LDH-2 levels, while aseptic meningitis was most often associated with high LDH-3 levels.
Conclusions: Patterns of CSF LDH isoenzyme levels in the CSF may assist in the diagnosis of meningitis, including helping to differentiate bacterial from aseptic cases. These results may guide empiric therapy while culture results are still pending.
Reviewer's Comments: The authors present evidence for the use of LDH isoenzyme testing in cases of suspected meningitis. The testing could be implemented in most laboratories with relative ease and at low relative cost. (Reviewer-T. David Bourne, MD).

Keywords: LDH Isoenzyme Testing, CSF

Print Tag: Refer to original journal article

Is IMP3 a Potential Marker for Bile Duct Dysplasia and Carcinoma?

IMP3 Expression in Lesions of the Biliary Tract: A Marker for High-Grade Dysplasia and an Independent Prognostic Factor in Bile Duct Carcinomas.

Riener M-O, Fritzsche FR, et al:

Hum Pathol 2009; 40 (October): 1377-1383

IMP3 expression is overexpressed in high-grade dysplasia but not reactive bile duct epithelium or low-grade dysplasia.

Background: Bile duct carcinomas (BDCs) are often detected at a late stage and have a poor prognosis. Correct diagnosis is complicated by inflammatory and reactive changes in the bile duct epithelium, as many of these patients have had stents placed previously. The oncofetal protein IMP3 has recently been shown to be overexpressed in several malignancies, including stomach, colon, lung, kidney, and liver cancers. In particular, IMP3 has been reported to have a high sensitivity and specificity for the diagnosis of pancreaticobiliary adenocarcinoma.
Objective: To examine the utility of IMP-3 immunohistochemical staining in normal, reactive, and neoplastic biliary epithelium.
Methods: Tissue sections from patients with resection specimens of the extrahepatic biliary tract were selected. These included 36 normal bile ducts, 26 reactive bile ducts, 9 ducts with low-grade dysplasia, and 11 ducts with high-grade dysplasia, according to the World Health Organization criteria. A tissue microarray was constructed with tumor tissue from an additional 115 patients with BDC (19 intrahepatic cholangiocarcinomas, 58 extrahepatic cholangiocarcinomas, and 38 gallbladder carcinomas). Each sample was immunohistochemically stained with an antibody against IMP3. IMP3 was considered positive when at least 10% of cells showed cytoplasmic staining; these were grouped into weak (0-1+) or strong (2-3+) staining. Survival data for patients with BDC were obtained from patient records.
Results: All normal bile ducts, reactive bile ducts, and low-grade dysplasia showed negative or weak staining for IMP3. One hundred percent of ducts with high-grade dysplasia showed strong staining for IMP3. IMP3 was differentially expressed in the various types of BDC; 37% of intrahepatic cholangiocarcinomas, 50% of extrahepatic cholangiocarcinomas, and 82% of gallbladder carcinomas showed strong positivity for IMP3. Strong IMP3 expression in BDC was significantly associated with reduced overall survival on both univariate and multivariate analysis.
Conclusions: IMP3 expression is frequently expressed in BDC and is an independent prognostic marker of survival. In addition, IMP3 may be useful as a diagnostic aid in distinguishing reactive from dysplastic bile duct epithelium.
Reviewer's Comments: It is important to note that normal and reactive biliary epithelium showed weak staining (1+); therefore, IMP3 staining should be interpreted with caution. Studies by different authors on IMP3 immunohistochemistry have set different criteria for positivity, which affects cross-study comparison. Additional trials are needed to confirm these findings in a larger patient cohort. (Reviewer-Stacey E. Mills, MD).

Keywords: IMP3, KOC, Immunohistochemistry, Bile Duct Carcinoma, Dysplasia

Print Tag: Refer to original journal article

Is YAP a New Prognostic Marker for Hepatocellular Carcinoma?

Yes-Associated Protein Is an Independent Prognostic Marker in Hepatocellular Carcinoma.

Xu MZ, Yao T-J, et al:

Cancer 2009; 115 (October 1): 4576-4585

YAP is an independent predictor of overall survival and disease-free survival in patients with HCC.

Background: Hepatocellular carcinoma (HCC) has a poor prognosis, with a 5-year survival rate of <10%. Investigations in a mouse model of liver cancer identified a novel candidate oncogene, Yes-associated protein (YAP). YAP functions as a transcriptional mediator involved in cell growth, proliferation, and apoptosis.
Objective: To investigate the expression of YAP in human HCC and its clinical significance.
Participants/Methods: 177 patients with HCC who underwent hepatectomy were included in the study. A portion of tumor and adjacent normal tissue from each case was procured at the time of surgery and snap-frozen, along with conventionally submitted formalin-fixed tissue for histology. Each tissue sample was immunohistochemically stained with an antibody against human YAP, with the percentage of positive cells graded as 0 (<10%), 1 (10% to 30%), 2 (30% to 50%), or 3 (>50%). Total RNA and protein lysates were extracted from frozen tissue. TaqMan real-time PCR was used to quantitatively evaluate human YAP mRNA levels, normalized to the internal 18S rRNA control. Western blot analysis was performed on the protein lysates to quantitate YAP protein expression, normalized relative to the internal beta-catenin protein control.
Results: YAP was positive by immunohistochemistry in 62% of HCCs, whereas only 9% of nontumor specimens showed any positivity. YAP was predominantly present in the nuclei of tumor cells but was only weakly present in the cytoplasm of nontumor samples. YAP protein and mRNA levels were approximately 2 to 4 times higher in tumors than in matched nontumor tissue. YAP overexpression was significantly associated with worse overall 5-year survival (58% in YAP-negative tumors vs 36% in YAP-positive tumors) and disease-free survival (median, 27 months in YAP-negative tumors vs 14 months in YAP-positive tumors). In the subset of patients with HCC without evidence of tumor vascular invasion, YAP remained an independent predictor of decreased disease-free survival (49 months in the YAP-negative tumors vs 18 months in the YAP-positive tumors).
Conclusions: YAP is an independent predictor of overall survival and disease-free survival in patients with HCC.
Reviewer's Comments: This well-designed study demonstrates a novel protein associated with significantly worse survival in patients with HCC. This study was based on an Asian cohort associated with very high rates of HBV infection; further trials are needed to validate YAP in other patient populations. (Reviewer-Deborah J. Chute, MD).

Keywords: Hepatocellular Carcinoma, Hippo Signaling, Prognostic Marker, Tumor Recurrence, Yes-Associated Protein

Print Tag: Refer to original journal article

Thyroid FNA With Atypia of Undetermined Significance--Necessary or Optional Category?

Thyroid Fine-Needle Aspiration With Atypia of Undetermined Significance: A Necessary or Optional Category?

Shi Y, Ding X, et al:

Cancer Cytopathol 2009; (August 26): epub ahead of print

The category "atypia of undetermined significance" is helpful with thyroid FNAs.

Background: The usefulness of the diagnosis "atypia of undetermined significance" remains unclear with respect to thyroid fine-needle aspiration (FNA). According to the National Cancer Institute's statement regarding the reporting of thyroid FNA, this diagnosis is to be used with thyroid FNA showing findings that cannot be designated as benign yet lack the features to be considered either suspicious for follicular neoplasm or suspicious for malignancy. The validity of this category has been challenged by some, not in the least because of the lack of well-defined diagnostic criteria and potential lack of diagnostic reproducibility. Nonetheless, a number of authors have shown the category to have a follow-up rate of malignancy between 5% and 10%.
Objective: To investigate the possible impact of eliminating the category at an institution that has used it with thyroid FNA for >10 years.
Methods: Results of all thyroid FNAs at a single institution diagnosed as "atypia of undetermined significance" over 5 years were collected. These represented 2.1% of all thyroid FNAs. Forty cases were available that had histologic follow-up and slides that could be reviewed. Two reviewers reclassified these specimens without using the atypical category. New diagnoses were compared to histologic follow-up.
Results: Of the 40 cases, the majority were from women, and the mean patient age was 50 years. On follow-up, 17 cases were nonneoplastic, 12 were follicular neoplasms (of which 3 were carcinomas), and 11 were papillary thyroid carcinomas. When the category of atypia was removed, both reviewers misclassified 7 cases as benign that, on follow-up, were papillary carcinomas and 3 that were follicular neoplasms. Of the 25 cases that the reviewers agreed with one another regarding the new diagnoses, 5 papillary thyroid carcinomas and 2 follicular neoplasms were incorrectly classified as nonneoplastic. Interobserver and intraobserver agreement were poor.
Conclusions: If one eliminates an atypical category with thyroid FNA interpretation, one decreases the sensitivity of the test. The authors suggest keeping the category and limiting its use.
Reviewer's Comments: The "atypia of undetermined significance" category with thyroid FNA is important as it allows for some adequate thyroid FNAs to be treated differently than those diagnosed as benign or possibly malignant. It would have been interesting if the authors had discussed whether patients had been re-aspirated and diagnosed differently prior to resection. (Reviewer-Edward B. Stelow, MD).

Keywords: FNA, Atypia, National Cancer Institute Guidelines

Print Tag: Refer to original journal article

Penile Verrucous Carcinoma Unlike Usual Penile Squamous Carcinoma

HPV Infection and Immunochemical Detection of Cell-Cycle Markers in Verrucous Carcinoma of the Penis.

Stankiewicz E, Kudahetti SC, et al:

Mod Pathol 2009; 22 (September): 1160-1168

Penile verrucous carcinoma has a weaker association with HPV and the proteins commonly associated with HPV-related disease than typical squamous cell carcinoma of the penis.

Background: Verrucous carcinoma is a rare variant of squamous cell carcinoma (SCC) that is locally aggressive by invading with blunted and bulbous projections composed of well-differentiated squamous cells. In the penis, diagnostic variability of this unusual and rare lesion has complicated studies in the literature. Penile SCC of all types appears to be related to chronic inflammation, phimosis, and poor hygiene, but the role of human papillomavirus (HPV) in the subtype of verrucous carcinoma is not clear. Cell-cycle proteins, some of which are surrogate markers for HPV-related disease, have not been assessed in a series of verrucous carcinomas.
Objective: To evaluate the expression of p53, p21, RB, p16, and Ki67 in a series of penile verrucous carcinomas to assess the relationship to HPV.
Methods: 148 SCCs of the penis were retrospectively reviewed to identify 15 verrucous carcinomas, 14 verruciform carcinomas with mixed histology, 17 basaloid, 5 warty, and 97 usual-type SCC. Only the pure verrucous carcinomas were studied, using the usual-type SCC as a control. Immunohistochemistry was performed for p53, p21, RB, p16, and Ki67 and then scored in a semiquantitative manner accounting for nuclear staining, except p16, which was nuclear plus cytoplasmic. PCR for HPV was performed from archived wax blocks when possible.
Results: p53 was positive in 13 of 15 verrucous carcinomas (87%) but was confined to the basal and parabasal cells. In the usual-type SCC, p53 was more diffuse; however, no statistical difference was noted. p21 was positive in 10 of 13 verrucous carcinomas with focal and weak intensity, but this was not statistically different from the usual-type SCC. RB was strongly positive in 13 of 15 verrucous carcinomas (87%), a trend higher than that seen in usual-type SCC (P =0.441). p16 was noted only in 1 of 15 verrucous carcinomas, and this was significantly different than the usual-type SCC (P =0.0019). Ki67 was positive in 10 of 15 verrucous carcinomas (67%), mostly in a basal pattern. This expression was significantly lower than that of the usual-type SCC. HPV DNA was identified in 3 of 13 penile verrucous carcinomas (23%) as a low-risk (HPV 11), a high-risk (HPV 51, 52), and a mixed infection (31, 33, 44, 45).
Conclusions: Rare verrucous carcinomas of the penis have lower levels of p16 and Ki67 expression and HPV DNA detection than usual-type SCC, suggesting a weaker association with HPV.
Reviewer's Comments: When narrowly defined to include well-differentiated tumors with almost no cytologic atypia but a broad bulbous invasive front, verrucous carcinomas are rare lesions. In this study, there was only a weak association with HPV. (Reviewer-Mary T. Galgano, MD).

Keywords: Squamous Carcinoma, Verrucous Type

Print Tag: Refer to original journal article

Multinucleated Giant Cells in Neurofibroma--Markers for NF1?

Multinucleate Giant Cells in Neurofibromas: A Clue to the Diagnosis of Neurofibromatosis.

Taungjaruwinai WM, Goldberg LJ:

J Cutan Pathol 2009; 36 (November): 1164-1167

While not specific for NF1, finding easily identifiable multinucleated giant cells in a neurofibroma might increase your index of suspicion for the presence of NF1.

Background: Neurofibromas (NFs) are relatively common skin tumors encountered with significant frequency in a busy dermatopathology or surgical pathology practice. Although a majority of NFs are sporadic, some are associated with neurofibromatosis type 1 (NF1). NF1 is associated with café-au-lait macules, iris hamartomas (Lisch nodules), axillary freckling, optic gliomas, and distinctive osseous lesions. The NF variant known as the plexiform neurofibroma is thought to be specific for NF1. The plexiform NF is seen in approximately 30% of patients with NF1, and it is associated with an increased risk of developing malignant peripheral nerve sheath tumors. Typical NFs are spindle cell tumors with haphazardly arranged, wavy spindle cells set in a loose stroma. While multinucleated giant cells have been previously reported in NF, the possibility of their association with NF1 has not been investigated.
Objective: (1) To report a case of an individual with NF1 whose many NFs contained multinucleated giant cells, and (2) to determine, through a large case series, the frequency of finding multinucleated giant cells in sporadic NFs.
Methods: The findings from an index case of a 54-year-old man with NF1 are reported, followed by a retrospective review of all cases of NF diagnosed at Boston University during a 2-year period. These cases consisted of routinely processed, paraffin-embedded specimens stained with hematoxylin and eosin. All sections were evaluated for the presence of multinucleated giant cells. These histologic findings were recorded, along with patient age, sex, lesion location, and lesion size.
Results: 53 NFs from 51 patients were evaluated as part of the retrospective review. No patient was reported to have NF1. The average patient age was 60 years, and the lesions were located on the back, head and neck, chest, extremities, and abdomen. Of 53 cases, 3 NFs from 3 separate patients were found to have multinucleated giant cells. These giant cells were not well developed, and it took careful scrutiny to find them. In contrast, the giant cells were easily identified in the index patient with NF1. They were arranged in a linear or wreath-like pattern.
Conclusions: Multinucleated giant cells were identified in all 20 NFs removed from a patient known to have NF1. In contrast, multinucleated giant cells were found in only 3 of 53 sporadic NFs, where they were difficult to find and poorly formed. Thus, the finding of easily identifiable multinucleated giant cells with linear or wreath-like configurations in an otherwise typical NF should alert one to the possibility of the NF1 syndrome.
Reviewer's Comments: Based on the authors' observations, it certainly does not appear that giant cells alone possess the specificity that the plexiform variant of NF has for the NF1 syndrome. (Reviewer-T. David Bourne, MD).

Keywords: Neurofibroma, Giant Cells

Print Tag: Refer to original journal article

Elevated Serum PSA and Negative Biopsies--What Happens Next?

Extensive Biopsies and Transurethral Prostate Resection in Men With Previous Negative Biopsies and High or Increasing Prostate Specific Antigen.

Ploussard G, Dubosq F, et al:

J Urol 2009; 182 (October): 1342-1349

Among men with elevated serum PSA and at least 2 previous negative biopsy procedures, combined transrectal and transurethral biopsies under general anesthesia detect cancer in one-fourth of patients.

Objective: To evaluate the utility of transurethral prostate resection as a diagnostic method for the treatment of men with elevated serum PSA who have undergone 2 previous negative biopsy procedures.
Background: Most prostate cancers arise in the peripheral zone, which is why <2% of transitional zone biopsies contain cancer. Therefore, in men with elevated serum PSA, transrectal prostate biopsies are the logical first choice of prostate biopsy. If initial biopsies are negative, repeat extensive transrectal biopsies are performed. However, what should the third approach be if repeat biopsies are negative? Is transurethral resection of the prostate (TURP) indicated when 2 sets of transrectal biopsies are negative?
Participants/Methods: 113 consecutive patients with increased serum PSA and 2 negative 21-core biopsy procedures underwent an additional transrectal 21-core biopsy protocol under general anesthesia coincident with TURP.
Results: Among 113 men with elevated serum PSA and at least 2 previous negative biopsy procedures, 27 (24%) demonstrated histologic evidence for carcinoma by this procedure. Extended transrectal biopsy detected cancer in 18.6% of cases, but the detection rate was increased to 23.9% by TURP; 17 cases (63%) were positive for cancer by biopsy alone, 4 (14.8%) were positive for cancer by both biopsy and TURP, and 6 (22.2%) were positive for cancer by TURP alone. Neither age, free-to-total PSA ratio, prostate volume, nor high PSA density predicted TURP-only cancer detection.
Conclusions: Among men with elevated serum PSA and at least 2 previous negative biopsy procedures, combined transrectal and transurethral biopsies under general anesthesia detect cancer in approximately one-fourth of patients.
Reviewer's Comments: Unexplained elevations in serum PSA are troubling for patients and urologists since some of these patients harbor clinically significant disease. This study indicates that an additional transrectal 21-core biopsy protocol under general anesthesia detects cancer in roughly one-fifth of such patients. However, transitional zone cancers tend to be lower volume and curable. Therefore, the survival impact of performing diagnostic TURP under general anesthesia in men with increased serum PSA and 2 negative extensive biopsy procedures remains uncertain. (Reviewer-Guy E. Nichols, MD, PhD).

Keywords: Prostate, Prostatic Neoplasms, Biopsy, PSA, TURP

Print Tag: Refer to original journal article

Categorizing Thyroid Cyst FNAs

Predictors of Malignancy in Thyroid Fine-Needle Aspirates "Cyst Fluid Only" Cases: Can Potential Clues of Malignancy Be Identified?

Jaragh M, Carydis VB, et al:

Cancer Cytopathol 2009; 117 (August 26): 305-310

Fine-needle aspiration of thyroid glands that shows cyst change are more likely to be associated with malignant follow-up if epithelial atypia is present.

Background: Although cystic degeneration is most often seen with benign thyroid disease, it can also be seen with malignancy, especially papillary carcinoma. It is known that, in general, fine-needle aspiration (FNA) specimens that show only cystic change (that is, macrophages, especially hemosiderin-laden macrophages, scant colloid, and rare, benign follicular cells) are associated with a <5% rate of follow-up malignancy. Nonetheless, a recent National Cancer Institute consensus conference stated that such specimens should be considered "nondiagnostic" and interpreted as "cyst fluid only."
Objective: To review a large series of cytologic specimens showing cyst fluid only that had follow-up to potentially discover any factors that may be useful for predicting malignancy.
Methods: A single institution's files were reviewed for all thyroid FNAs interpreted as cyst fluid only that had follow-up surgical pathology (resection) over a 3-year period. Patient demographics, follow-up diagnoses, and types of preparation were recorded. All FNA slides were reviewed for the presence and number of follicular cells, foamy macrophages, pigment-laden macrophages, colloid, blood, and neutrophils. Follicular cell atypia, including the presence of syncytial groups, nuclear crowding and overlapping, powdery chromatin, micronucleoli, nuclear grooves and pseudoinclusions, was noted.
Results: 76 cases were identified that had been cytologically interpreted as cyst fluid only and had surgical follow-up; these cases represented <10% of all cases interpreted as cyst fluid only. The majority of the cases were from women, with a mean age of 50 years. In 10 cases, an ipsilateral papillary carcinoma that measured ≥1 cm in greatest dimension was diagnosed at surgical pathology. There was no association with the presence and amount of macrophages, hemosiderin-laden macrophages, colloid, and blood with malignant outcome. Malignancies were more likely to be associated with adequate numbers of follicular cells and were more likely to be associated with follicular cells showing some degree of cytologic atypia.
Conclusions: The authors suggest that FNA specimens showing predominately cyst changes with any cytologic atypia should be categorized as atypical rather than as nondiagnostic, cyst fluid only.
Reviewer's Comments: This paper presents an intermediate-sized series of thyroid FNAs showing cyst fluid only that had follow-up. Cytopathologists should carefully search for epithelial atypia with these cases. (Reviewer-Edward B. Stelow, MD).

Keywords: Thyroid, Cyst, FNA, Atypia, Malignancy

Print Tag: Refer to original journal article

Identifying Prognostic Factors in Melanoma

Clinical Considerations on Sentinel Node Biopsy in Melanoma From an Italian Multicentric Study on 1,313 Patients (SOLISM-IMI).

Testori A, De Salvo GL, et al:

Ann Surg Oncol 2009; 16 (July): 2018-2027

The status of the sentinel lymph node (SLN) is an important prognostic factor for melanoma patients; however, the accuracy of SLN biopsy for melanoma is not optimal.

Objective: To determine outcomes after sentinel lymph node (SLN) biopsy for melanoma.
Design: Observational, multicenter prospective study.
Participants/Methods: The Italian Melanoma Intergroup study included consecutive patients with melanomas >1 mm or ≤1 mm with at least 1 of the following features: regression, ulceration, and/or Clark level IV or V. Patients with clinical lymphadenopathy were excluded. Twenty-three centers participated in the study, and 1313 patients were enrolled. SLN biopsy was performed using radioactive tracer and blue dye; lymphoscintigraphy was also performed. False-negative cases were defined as patients who had a negative SLN biopsy but developed lymph node metastasis as a first site of recurrence.
Results: The overall SLN identification rate was 99.3%; only 1 lymphatic basin was identified in 86% of patients. The mean number of excised SLNs was 2 per patient. On univariate analysis, male gender, increased tumor thickness, higher Clark level, ulceration, and absence of tumor regression were associated with SLN metastases. Median follow-up was 4.5 years. Among patients with a negative SLN biopsy, there were 36 patients who developed lymph node metastases (false-negative rate, 14%). On multivariate analysis, SLN status, male gender, age, increased tumor thickness, and Clark level were predictors of overall survival. The 5-year overall survival rate for patients with positive SLNs and positive non-SLNs was 50%; the 5-year survival rate for patients with positive SLNs and negative non-SLNs was 71%.
Conclusions: The status of the SLN is an important prognostic factor for melanoma patients. However, the accuracy of SLN biopsy for melanoma is not optimal.
Reviewer's Comments: This study identified several factors associated with SLN metastases. Recent reports have identified the presence of mitotic figures as a significant predictor of SLN metastases. Additional research is needed to identify factors associated with false-negative cases. (Reviewer-Todd M. Tuttle, MD).

Keywords: Melanoma, Sentinel Node Biopsy

Print Tag: Refer to original journal article

Clinical vs Pathologic Stage of Bladder Cancer

Residual Pathological Stage at Radical Cystectomy Significantly Impacts Outcomes for Initial T2N0 Bladder Cancer.

Isbarn H, Karakiewicz PI, et al:

J Urol 2009; 182 (August): 459-465

Down-staging from muscle-invasive cancer at transurethral resection of a bladder tumor to nonmuscle-invasive tumor found in the pathology specimen at radical cystectomy improves cancer-specific mortality.

Objective: To determine whether patients who have muscle-invasive disease found at transurethral resection of a bladder tumor and who have a lower pathologic stage found at radical cystectomy have improved outcomes compared to patients with residual muscle-invasive disease found at radical cystectomy.
Design/Methods: The records of 208 patients with T2N0 stage disease found at transurethral bladder tumor resection whose tumors were organ confined at radical cystectomy were retrospectively reviewed. None of these patients had received chemotherapy. The effect of residual muscle-invasive disease found at radical cystectomy on cancer-specific mortality rates was analyzed.
Results: In these patients with T2N0 (muscle-invasive disease) seen at transurethral bladder resection, residual pathologic stage at radical cystectomy was P0 in 12% of patients, Pa in 4% of patients, PCIS in 11% of patients, P1 in 17% of patients, and P2 in 57% of patients. Mean follow-up was approximately 5 years. The 5-year recurrence-free survival rate in patients with superficial disease including carcinoma in situ was 100%. In those who had invasion of the lamina propria seen only on the radical cystectomy specimen, the 5-year recurrence-free survival rate was 85%. In patients who had residual muscle-invasive disease found on pathology following radical cystectomy, the 5-year recurrence-free survival rate was 75%. Those who did not have muscle-invasive disease found on the pathology specimen at the time of radical cystectomy had a statistically significant improvement in both recurrence and cancer-specific mortality.
Conclusions: The authors believe that down-staging from muscle-invasive cancer at transurethral resection of a bladder tumor to nonmuscle-invasive tumor found in the pathology specimen at radical cystectomy improves cancer-specific mortality.
Reviewer's Comments: This is a worthwhile paper. The authors have shown that residual disease of P1 or lower found in the radical cystectomy specimen independently predicts decreased recurrence and cancer-specific mortality. The results of this paper have implications for the use of neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer found at transurethral resection of a bladder tumor. Many patients who receive chemotherapy may receive chemotherapy unnecessarily. In addition, these results appear to help guide the selective use of adjuvant chemotherapy following radical cystectomy for those at high risk for recurrence based on surgical pathology. This is a good paper that describes the fate of patients whose bladder tumor is pathologically down-staged from the time of transurethral bladder resection to the surgical pathology specimen following radical cystectomy. (Reviewer-George S. Benson, MD).

Keywords: Bladder Cancer, Radical Cystectomy, Pathologic Stage

Print Tag: Refer to original journal article

Survival Improved With Adjuvant XRT for Prostate Cancer

Adjuvant Radiotherapy for Pathological T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-Term FollowUp of a Randomized Clinical Trial.

Thompson IM, Tangen CM, et al:

J Urol 2009; 181 (March): 956-962

Adjuvant external radiation for pathologically staged T3N0 prostate cancer significantly improves survival in patients.

Background: Radical prostatectomy will be used on about one third of American men diagnosed with prostate cancer. About one third of those undergoing prostatectomy will have positive margins, with another 9% having seminal vesicle invasion, both of which are associated with increased risk of biochemical failure. T3 disease (AJCC 6th edition) is extracapsular extension (T3a), with invasion of the seminal vesicles being T3b.
Objective: To determine if adjuvant radiation therapy is necessary for patients with high-risk prostate cancer.
Design: Prospective, randomized trial conducted by the Southwest Oncology Group (study 8794).
Participants: Patients with clinical stage T1-2 prostate cancer who underwent radical prostatectomy and were found to have extracapsular extension, positive margins, or seminal vesicle invasion were evaluated. Initially, the patients were required to have a negative lymphadenectomy, but standards were relaxed to not require lymphadenectomy in low-risk patients.
Methods: Patients were randomized to observation or 60 to 64 Gy of periprostatic XRT. The primary end point was metastasis-free survival.
Results: From 1988 until 1997, 425 men were enrolled and eligible for this trial. Median follow-up was 12.5 to 12.7 years; 54% of observed men versus 43% of those receiving adjuvant XRT have died or had metastatic disease (P =0.016; HR, 0.71 with adjuvant XRT). Looking at overall 10-year survival, 52% of observed men have died versus 41% of treated men (P =0.023; HR of death with adjuvant XRT, 0.72). The median survival improved from 13.3 to 15.2 years. The 10-year survival rates were 74% versus 66%, and the difference in the curves appears to be widening.
Conclusions: Even with the relatively modest doses of XRT used 20 years ago, and despite the effects of salvage XRT, adjuvant XRT improved survival. This was in spite of the fact that the observed group had almost double the rate of hormone use. A quality of life (QOL) analysis found that, at 6 weeks, 47% of the treated group had tenderness or urgency of bowel movements. However, by 2 years, there was little difference between the treated and observed patients. There was no difference in erectile dysfunction between groups. Global assessment of the QOL, while initially worse in the XRT patients, became concordant at 2 years and favored the XRT patients in the succeeding 3 years.
Reviewer's Comments: Interestingly, even the observed patients who had salvage XRT had a higher rate of distant metastases than patients who had immediate XRT. I love that this trial demonstrated a survival benefit rather than just a biochemical control end point. With the advent of better technology, we believe higher doses can be achieved with even fewer side effects, and this should be the standard of care. The other take-home point is that the best therapy probably matters most to those men destined to survive >10 years. (Reviewer-Jonathan J. Beitler, MD, MBA).

Keywords: Adjuvant Radiation, Prostatectomy T3

Print Tag: Refer to original journal article

FISH for Alveolar Rhabdomyosarcoma Works on Formalin-Fixed Tissue

The Utility of FOXO1 Fluorescence In Situ Hybridization (FISH) in Formalin-Fixed Paraffin-Embedded Specimens in the Diagnosis of Alveolar Rhabdomyosarcoma.

Downs-Kelly E, Shehata BM, et al:

Diagn Mol Pathol 2009; 18 (September): 138-143

FISH on formalin-fixed paraffin-embedded tissue for *FOXO1* rearrangement shows high sensitivity and specificity in the detection of alveolar rhabdomyosarcoma.

Background: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of children and adolescents and is divided into 2 subtypes: alveolar rhabdomyosarcoma (ARMS) and embryonal rhabdomyosarcoma (ERMS). A distinction between these subtypes, as well as from other small round blue cell tumors, is important due to significant differences in treatment and survival. However, morphologic differentiation can be difficult, especially in small biopsy specimens. Nearly all ARMS have nonrandom chromosomal translocations at *t*(2;13) or *t*(1;13), which result in *PAX3/FOXO1* and *PAX7/FOXO1* gene fusions, respectively. These translocations are specific to ARMS, and are not seen in ERMS and other sarcomas.
Objective: To evaluate the utility of fluorescence in situ hybridization (FISH) for *FOXO1* translocation in a series of small round blue cell neoplasms.
Methods: 52 cases of neoplasms, for which a diagnosis of ARMS was in the differential diagnosis and sufficient formalin-fixed paraffin-embedded tissue was available were studied (25 ARMS, 8 ERMS, 15 Ewing's sarcoma/primitive neuroectodermal tumor, 2 desmoplastic round cell tumors, 1 round cell liposarcoma and 1 neuroblastoma). Tumors were classified by final histologic features supported by immunohistochemistry and/or reverse transcription polymerase chain reaction (RT-PCR) and cytogenetics. A dual-color, break-apart probe spanning the genomic breakpoints of the *FOXO1* (13q14) gene was used for FISH analysis on each case. A positive result for FISH was reported when >10% of tumor nuclei (of 100 counted) demonstrated a split signal.
Results: FISH analysis was positive for *FOXO1* rearrangement in 88% (22/25) of ARMS cases, with a mean of 91% of tumor cells positive. Eleven cases of ARMS had correlative RT-PCR and/or cytogenetics demonstrating *t*(2;13) or *t*(1;13); of these cases, 100% were positive for *FOXO1* rearrangement by FISH. All non-ARMS cases were negative for FISH rearrangement, with a mean of 1.4% of tumor cells positive.
Conclusions: FISH on formalin-fixed paraffin embedded tissue for *FOXO1* (13q14) rearrangement shows high sensitivity (88%) and specificity (100%) in the detection of alveolar rhabdomyosarcoma. This may have particular utility in small biopsy specimens where insufficient material for cytogenetics is available.
Reviewer's Comments: Detection of *FOXO1* rearrangements will likely identify most ARMS translocations. However, there is a significantly worse prognosis for patients with *PAX3*/*FOXO1* fusion transcripts compared to patients with *PAX7/FOXO1* fusion transcripts. Additional commercial development of FISH probes for the partner genes is needed to supply clinicians with both diagnostic and prognostic information. (Reviewer-Deborah J. Chute, MD).

Keywords: FISH, Alveolar Rhabdomyosarcoma,*FOXO1*,*FKHR*, Ewing Sarcoma/Primitive Neuroectodermal Tumors

Print Tag: Refer to original journal article

Can ISH Distinguish Between *Actinomyces* and *Nocardia*?

In Situ Hybridization for the Differentiation of Actinomyces and Nocardia in Tissue Sections.

Isotalo PA, Qian X, et al:

Diagn Mol Pathol 2009; 18 (September): 183-188

In situ hybridization is highly specific for distinguishing between *Actinomyces* and *Nocardia* spp. in tissue sections.

Background: Culture is considered the gold standard for identification of infectious organisms. However, cultures are not rapid tests and can be limited by fastidious organisms and prior antimicrobial therapy. In some patients, cultures may not be initially obtained, and subsequent histopathologic evaluation may demonstrate an infectious process. While special histochemical stains (Grocott methenamine silver [GMS] and Gram stains) are useful to highlight organisms, in many cases, the infectious organism cannot be distinguished by morphology alone. This is true of the filamentous bacteria, *Actinomyces* and *Nocardia*.
Objective: To evaluate the utility of in situ hybridization (ISH) for the differentiation of filamentous bacteria in tissue sections.
Materials/Methods: 26 formalin-fixed, paraffin-embedded tissue sections containing filamentous bacteria were studied. Tissue sites included the lungs, bone/soft tissue, and brain tissue. Each case was histochemically stained with GMS, Gram stain, and Fite stain. On the basis of morphology, clinical features and culture results, cases were classified as *Actinomyces*-related (n=13) or *Nocardia* related (n=13). Six cases of *Actinomyces* and 11 cases of *Nocardia* were culture proven. ISH was performed using DNA probes designed to detect the 16S rRNA sequences of *Actinomyces* and *Nocardia* spp. most commonly isolated from human specimens.
Results: All cases of *Actinomyces* and *Nocardia* spp. were positive for GMS and Gram stain, which demonstrated filamentous bacteria. All cases were negative for Fite stain, and insufficient material was present to perform additional acid-fast stains. ISH in positive cases demonstrated blue filamentous organisms in a pink background. The *Actinomyces* probe cocktail was positive in 10 of 13 *Actinomyces*-related cases, and negative in all *Nocardia*-related cases. The *Nocardia* probe cocktail was positive in 10 of 13 *Nocardia*-related cases, and negative in all *Actinomyces*-related cases. The sensitivity and specificity of ISH for correct organism identification was 77% and 100%, respectively.
Conclusions: ISH is highly specific for distinguishing between *Actinomyces* and *Nocardia* spp. in tissue sections. Although histochemical stains are more sensitive, ISH is a promising supplementary stain for the identification of filamentous bacterial infections.
Reviewer's Comments: *Nocardia* spp are generally considered partially acid-fast organisms, which in many cases will distinguish them from the acid-fast negative *Actinomyces*. However, in our experience, the acid-fast staining can be difficult to interpret; indeed in this series all cases were negative for Fite staining. ISH for filamentous bacteria is a promising alternative, particularly in cases without material for culture. (Reviewer-Deborah J. Chute, MD).

Keywords: In Situ Hybridization,*Actinomyces*,*Nocardia*, Histopathology, Ribosomal RNA

Print Tag: Refer to original journal article

Some Lipomatous Tumors of Retroperitoneum May Be Lipomas

Retroperitoneal Lipomatous Tumors Without Cytologic Atypia: Are They Lipomas? A Clinicopathologic and Molecular Study of 19 Cases.

Macarenco RS, Erickson-Johnson M, et al:

Am J Surg Pathol 2009; 33 (August 3): 1470-1476

Some differentiated lipomatous tumors of the retroperitoneum appear to be lipomas.

Background: It is almost considered dogma that all differentiated retroperitoneal lipomatous tumors are well-differentiated liposarcomas. At other sites, the distinction between lipomas and well-differentiated liposarcomas is usually easy and is made using histologic features, such as the presence or absence of lipoblasts or fibrous septa with enlarged, hyperchromatic cells. The diagnostic difficulty with retroperitoneal tumors has to do with the fact that benign lipomas are so uncommon at this location. The tumors are cytogenetically different; Lipomas typically have rearrangement of chromosome 12q15, while liposarcomas typically show amplification of this and surrounding areas, often with giant ring or marker chromosomes. Amplified genes include *MDM2*, *CPM*, *SAS*, *CDK4*, *DDIT3*, and *HMGA4*.
Objective: To report on the clinicopathologic features of a relatively large series of retroperitoneal lipomatous tumors devoid of features of liposarcoma.
Methods: 19 cases of retroperitoneal lipomatous tumors, devoid of cytologic atypia, seen at a single institution and by consultation pathologists were reviewed. Clinical information was retrieved. Twenty matched retroperitoneal well-differentiated liposarcomas were also studied. Cytogenetic results were gathered. Fluorescence in situ hybridization (FISH) was performed with formalin-fixed, paraffin-embedded tissue for *MDM4*, *CPM*, *SAS*, *CDK4*, *DDIT3*, and *HMGA2*. Reverse transcription-polymerase chain reaction was performed for *HMGA2-LPP*.
Results: Of the 19 lipomatous tumors devoid of atypia, 10 were from men and 9 were from women; the median age of the patients was 56 years. Tumors ranged in size from 8 to 46 cm. At a median of 6 months, no tumors with follow-up recurred. Four of the 20 well-differentiated liposarcomas recurred, each at >12 months follow-up. No tumor devoid of atypia had ring or giant chromosomes, and 4 of 7 that were karyotyped had rearrangements at 12q15. By FISH, 8 of 19 had rearrangements. *MDM2*, *CPM*, *SAS*, *CDK4*, *DDIT3*, and *HMGA2* were not amplified.
Conclusions: Some lipomatous tumors of the retroperitoneum may indeed be lipomas. Not only do they fail to show any cytologic atypia, but they also show cytogenetic and molecular findings most consistent with lipomas.
Reviewer's Comments: The dogma that all lipomatous tumors of the retoperitoneum are liposarcomas is apparently not true. However, more follow-up will be needed to determine the behavior of these rare tumors. (Reviewer-Edward B. Stelow, MD).

Keywords: Lipoma, Retroperitoneum, Molecular, Cytogenetics

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Synovial Sarcomas of Head Have Predilection for Parotid, Temporal Areas

Synovial Sarcoma Involving the Head: Analysis of 36 Cases With Predilection to the Parotid and Temporal Regions.

Al-Daraji W, Lasota J, et al:

Am J Surg Pathol 2009; 33 (October): 1494-1503

Synovial sarcomas of the head frequently involve the parotid area.

Background: Synovial sarcomas usually occur within the extremities and are relatively uncommon in the head and neck. Indeed, head and neck synovial sarcomas represent <5% of all synovial sarcomas in most series. Most occur in the hypopharyngeal or parapharyngeal region. True involvement of the head is very uncommon.
Objective: To review the clinicopathologic features of a large series of synovial sarcomas specifically involving the head and seen at a single institution.
Methods: All synovial sarcomas involving the head and seen at a single institution over a 30-year period were retrieved. Tumors involving the upper aerodigestive tract and brain were excluded. Slides were reviewed for the subtype of synovial sarcoma, tissues involved, status of the margins, mitotic rate, calcification, and tumor necrosis. Follow-up information was pursued. Immunohistochemistry was performed with numerous antibodies. Fluorescence in situ hybridization (FISH) was performed with a break-apart probe to the *SYT* gene.
Results: There were 36 tumors from 19 men and 17 women, and the median age of the participants was 35 years. Fourteen tumors were located in the parotid region, 9 in the temporal region, 4 in the cheek, 2 in the infratemporal fossa, and 2 in the mastoid area. Tumors ranged in size from 0.6 cm to 7.0 cm. Most were firm, with a solid off-white to hemorrhagic cut surface and had solid circumscribed, lobulated, or nodular appearances. Excisions typically had involved margins, although many wider excisions were performed. No lymph node metastases were identified when lymph node excisions were performed. Many cases involved skeletal muscle, and only 4 were histologically found to involve the parotid. Ten tumors were biphasic, and 2 of these tumors had poorly differentiated areas with abundant mitotic activity. Twenty-five cases were monophasic, and 4 of these contained poorly differentiated areas; 1 tumor was entirely poorly differentiated. Tumor necrosis was seen in 7 cases, and calcifications were present in 7 cases. All cases studied showed at least focal immunoreactivity with antibodies to cytokeratin cocktail, and all but 1 showed immunoreactivity with antibodies to epithelial membrane antigen. S100 protein immunoreactivity was seen in 8 of 18 case studied. No cases were immunoreactive with antibodies to *CD34*, *SMA*, and desmin. All cases with evaluable signal showed *SYT* gene rearrangements. Ten of the 29 patients with follow-up died of disease, with a median survival of 27 months.
Conclusions: The authors note that synovial sarcomas of the head have a striking predilection for the parotid and temporal area. Many patients survive for prolonged periods of time.
Reviewer's Comments: It is unclear why it is interesting that once the aerodigestive tract is excluded, most synovial sarcomas of the head occur where the greatest amount of soft tissue is. This paper would have been more interesting had the authors included all head and neck synovial sarcomas seen at their institution. (Reviewer-Edward B. Stelow, MD).

Keywords: Synovial Sarcoma, Head, Parotid, Immunohistochemistry

Print Tag: Refer to original journal article

Be Careful...CDX2 Also Stains Yolk Sac Components of Testicular GCTs

CDX2 Expression in Yolk Sac Component of Testicular Germ Cell Tumors.

Bing Z, Pasha T, et al:

Int J Surg Pathol 2009; 17 (October): 373-377

Yolk sac components of testicular germ cell tumors may show CDX2 positivity, so include this possibility in your differential diagnosis of a CDX2-positive tumor with glandular differentiation.

Background: Among primary testicular and metastatic germ cell tumors (GCTs), yolk sac tumor (YST) is associated with the most histologic diversity. In metastatic tumors in particular, the glandular formations seen in some YST components may resemble those seen in adenocarcinomas from other metastatic sites. CDX2, which is expressed during the normal development of the alimentary tract, is expressed in a high percentage of gastrointestinal-tract adenocarcinomas. The expression of CDX2 in GCTs has not been systematically examined.
Objectives: To examine the expression of CDX2 in GCTs, with an emphasis on YSTs.
Materials/Methods: 40 primary testicular GCTs and 8 metastatic GCTs were retrieved. Thirteen of these cases were described as "classic" seminomas, while the remaining 27 cases consisted of mixed GCTs with varying components of YST, embryonal carcinoma, seminoma, mature teratoma, immature teratoma, and intratubular germ cell neoplasia. Six of the metastatic mixed GCTs had a YST component. Tissue sections were stained using a mouse monoclonal antibody against CDX2. Sections were also stained with antibodies against glypican 3 (GPC3), a recently described YST marker. CDX2 was semiquantitatively scored based on the extent of nuclear staining: negative (<1% of cell staining); focally positive (1% to 25%), and diffusely positive (>25% positive). GPC3 was scored based on the sum of staining intensity (0, negative; 1, weak; 2, moderate; 3, strong) and the extent of immunoreactivity (0, negative; 1, <30%; 2, 30% to 70%; 3, >70%) divided by 2.
Results: YST was identified morphologically and by immunohistochemistry using GPC3 in 20 primary testicular mixed GCTs. All cases with YST components were detected with GPC3. Eight of these 20 cases showed focal CDX2 positivity within the YST component, while other primitive GCT components were CDX2 negative. Of the metastatic tumors with a YST component, 4 cases were CDX2 positive (2 cases with focal staining and 2 cases with diffuse staining).
Conclusions: CDX2 expression is seen in up to 40% of YSTs, either as a component of a primary testicular mixed GCT or as a component of metastatic GCT. Thus, the possibility of YST should be considered in the differential diagnosis of gland-forming tumors exhibiting CDX2 expression.
Reviewer's Comments: The authors correctly emphasize that CDX2 expression within a tumor showing glandular differentiation should not necessarily imply a gastrointestinal tract origin. In CDX2-positive cases, using GPC3 may help differentiate YST (ie, GCT) from a gastrointestinal adenocarcinoma. (Reviewer-T. David Bourne, MD).

Keywords: CDX2 expression/yolk sac tumor

Print Tag: Refer to original journal article

Looking at the Cancer Stem-Cell Marker CD133 in Rectal Cancer

Cancer Stem Cell Marker CD133+ Tumour Cells and Clinical Outcome in Rectal Cancer.

Wang Q, Chen Z-G, et al:

Histopathology 2009; 55 (September): 284-293

The stem cell marker CD133 is expressed in rectal cancer cells, and its expression is increased in patients with less favorable disease-free and overall survival.

Background: CD133 is a recognized stem cell marker for both normal cells and cancer cells. Its precise function is unknown. In cancers of the breast and brain, it has been shown that CD133+ cells are often more resistant to chemotherapy and radiation compared to CD133- cells. It has been postulated that recurrent tumors, such as recurrent rectal carcinoma, have increased the numbers of these stem cells.
Objectives: To study the expression of the cancer stem-cell marker CD133 by immunohistochemistry in rectal cancer, and to correlate this expression with pathological response to both preoperative radiation therapy and survival data.
Methods: Tissue samples consisted of formalin-fixed, paraffin-embedded sections of tumor from each of 73 patients who underwent excision for rectal cancer. All patients were treated with preoperative radiation, and all patients were followed clinically for at least 3 years or until time of death. All patients received external beam radiation treatments to the pelvis based on the MRI or endoscopic ultrasound finding of T3-4 and/or N1 disease. Patients underwent surgery 2 to 4 weeks after radiation treatment. Tumors were graded according to the current World Health Organization (WHO) classification system, and tumors were staged using 2002 American Joint Committee on Cancer (AJCC) staging guidelines. Tumor regression was graded semiquantitatively using a 5-point scale: 0, no regression; 1, minor regression; 2, moderate regression; 3, good regression; and 4, total regression. Normal rectal tissue, peritumoral tissue, and tumor tissue were stained using CD133 (rabbit polyclonal), and the degree of staining was classified as negative, ≤10%, 11% to 50%, and >50%. The association between both disease-free survival and overall survival and CD133 expression was determined, and multivariate analysis was performed to determine the prognostic effect of CD133 expression with various clinical variables (age, sex, WHO grade, TNM stage, lymphatic invasion, and tumor regression).
Results: In normal and peritumoral tissue, CD133 was seen within the apical portions of cells located in the crypt base. In tumor tissue, CD133 was mainly seen in the luminal portions of tumor cells. There was an inverse relationship between CD133 expression and tumor cell differentiation. Based on multivariate analysis, the proportion of CD133-positive cells was a significant prognostic factor for both overall survival and adverse disease-free survival. This was independent of tumor stage, grade, or presence of lymphatic invasion.
Conclusions: Increased expression of the stem antigen CD133 in samples of rectal cancer from patients who received preoperative radiation therapy correlates with decreased disease-free and overall survival.
Reviewer's Comments: Looking at CD133 expression in biopsy samples taken before radiation therapy might be an interesting next step. As the authors indicate, this antigen may represent a possible target for neoadjuvant chemotherapy. (Reviewer-T. David Bourne, MD).

Keywords: CD133 Expression, Rectal Carcinoma, Prognosis

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11% of Endometrial Adenocarcinomas Will Have Positive Peritoneal Washings

Prognostic Significance and Treatment Implications of Positive Peritoneal Cytology In Endometrial Adenocarcinoma: Unraveling a Mystery.

Wethington SL, Barrena Medel NI, et al:

Gynecol Oncol 2009; 115 (October): 18-25

Endometrial adenocarcinoma with positive peritoneal washings has an association with extrauterine disease, but its independent prognostic value is uncertain.

Background: Peritoneal washings are routinely performed in gynecological oncology surgery. Positive cytology is generally considered evidence of peritoneal disease, and can upstage an adenocarcinoma without tissue confirmation of extra-ovarian or uterine disease. This has prognostic value for recurrent potential, and may shape treatment decisions that range from observation to aggressive chemoradiation protocols. However, the scenario of low-grade and low primary tumor stage endometrial endometrioid adenocarcinomas (EEA) that are upstaged by cytology has been questioned. For example, some have speculated that low-grade carcinomas can transiently cause peritoneal fluid colonization resulting from hysteroscopy or bimanual examinations. Regardless, stage III disease represents a variable disease distribution, and further elucidation of positive washing should be reviewed.
Objective: To perform a literature review of the significance of positive peritoneal washing in EEA.
Methods: Multiple literature databases were reviewed to identify relevant articles with prognostic information regarding positive peritoneal cytology in EEA. Cases are considered "low-risk" if stage I EEA, FIGO 1 or 2, <50% invasion of the myometrium, no lymph vascular space invasion (LVSI), and no cervical involvement. Stage IIIA1 includes patients who meet the criteria for stage IIIA only by positive cytology. Stage IIIA2 includes patients who have histologically confirmed serosal or adnexal disease. The studies were adapted to these subsets and analyzed.
Results: Positive peritoneal washings are found in 11% of endometrial adenocarcinoma patients. In otherwise low-risk stage IIIA1 EEA, 4.1% of completely staged women have a recurrence. However, high-risk stage IIIA1 EEA has a recurrence rate of 32%, despite higher use of adjuvant therapy. Some studies show that positive cytology is associated with extrauterine disease, and speculate that full staging may be required if not performed initially. In contrast, there does not appear to be an association with positive cytology and high-risk features of the primary tumor. But there still is no clear answer to whether positive cytology alone is an adverse factor in otherwise low-risk disease.
Conclusions: 11% of endometrial adenocarcinomas will have positive peritoneal washings, which are associated with extrauterine disease, but not necessarily associated with high-risk features of the primary tumor. Given this, complete surgical staging should be performed if not done initially. There is still no clear consensus on the prognostic significance of positive washings in the absence of other extrauterine disease.
Reviewer's Comments: This is a complicated problem of determining the prognostic significance of stage IIIA disease based on positive cytology alone. But in the absence of other high-risk features, only 4.1% will recur. (Reviewer-Mary T. Galgano, MD).

Keywords: Endometrial Adenocarcinoma, Positive Peritoneal Cytology, Prognosis, Treatment

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COLD-PCR Methodology Has Improved Sensitivity vs Conventional PCR

Application of COLD-PCR for Improved Detection of KRAS Mutations in Clinical Samples.

Zuo Z, Chen SS, et al:

Mod Pathol 2009; 22 (August): 1023-1031

Using co-amplification-at-lower denaturation-temperature PCR for detection of *KRAS* mutation in clinical samples improves the sensitivity over conventional PCR in a variety of tumors.

Background: Activating mutations of the *KRAS* gene can result in constitutive activation. This has been detected in up to 30% of all human tumors, especially those of the lung, colon, pancreas, and hematopoietic system. The clinical application of finding *KRAS* mutations is broad and includes tumor surveillance in lymphomas and poor prognostic significance in lung cancer. Perhaps most importantly, detection of a *KRAS* mutation predicts a lack of response to anti-epidermal growth factor receptor (EGFR) antibody therapy, such as cetuximab and panitumumab in colorectal, lung, and head and neck cancers. Thus, the demand for mutational analysis on clinical samples is dramatically increasing. Most protocols utilize conventional polymerase chain reaction (PCR) amplification and sequencing, which has a sensitivity of 10% to 20%. This process is limited in the ability to detect low levels of mutation-bearing tumor cells.
Objective: To determine whether a recently described process of using co-amplification-at-lower denaturation-temperature PCR (COLD-PCR) improves the sensitivity in clinical samples.
Methods: 50 clinical samples, including 20 fresh bone-marrow aspirates. and 30 archived blocks of solid tumors were subjected to conventional PCR and COLD-PCR for comparison.
Results: Dilutional studies demonstrated indistinguishable mutation peaks at 1:8 with conventional PCR, while the peaks were still present at 1:32 with COLD-PCR. This heterozygous sample translates to a 6% detection sensitivity for conventional PCR, and a 1.5% sensitivity for COLD-PCR. Of the 50 samples, 35 had a *KRAS* mutation at codon 12, 2 at codon 13, and 13 were negative for a *KRAS* mutation. COLD-PCR detected all samples positive by conventional PCR with an improved mutant-to-wild-type ratio (>4.74-fold).
Conclusions: COLD-PCR methodology has improved sensitivity over conventional PCR for the detection of *KRAS* mutations in fresh and formalin-fixed paraffin-embedded clinical samples.
Reviewer's Comments: In the context of tumor surveillance and low tumor cell volume where small amounts of mutant sequences can be missed by conventional PCR, COLD-PCR provides increased sensitivity for detection that may alter therapeutic decisions. (Reviewer-Mary T. Galgano, MD).

Keywords:*KRAS*Mutation, Detection, COLD-PCR

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Are CGH Oligonucleotide Arrays Ready for Clinical Application?

Validation of the Agilent 244K Oligonucleotide Array-Based Comparative Genomic Hybridization Platform for Clinical Cytogenetic Diagnosis.

Yu S, Bittel DC, et al:

Am J Clin Pathol 2009; 132 (September): 349-360

Comparative genomic hybridization using a whole genome-spanning oligonucleotide microarray (Agilent 244K) is a clinically valid diagnostic tool for demonstration of chromosomal imbalances.

Background: Comparative genomic hybridization (CGH) involves co-hybridization of patient and reference DNAs, which have been labeled with different fluorochromes, to whole genome-spanning oligonucleotide microarrays. Copy-number variations due to genetic deletions and duplications are detected as altered fluorescent ratios. The high resolution of array-CGH suggests high clinical sensitivity in detecting clinically significant copy-number variations.

Objective: To apply American College of Medical Genetics guidelines to clinical validation of a commercial, array-based (CGH) platform.

Methods: DNA isolated from 45 specimens, including blood, fixed cytogenetic preparations (cell pellets), bone marrow, and cultured cells, was digested and labeled with cyanine (Cy)3-deoxyuridine triphosphate (dUTP) and then co-hybridized with normal reference DNA labeled with Cy5-dUTP using the Agilent Human Genome Microarray Kit 244K, which consists of 236,381 60-mer oligonucleotide probes, with 6.4 Kb average probe spacing. In order to score a positive copy-number variation, the authors required a minimum of 3 consecutive probes showing identical divergence of fluorescent ratio.

Results: All 45 hybridizations were successful, regardless of whether test specimens were blood, fixed cell pellets, or marrow, requiring down to 0.8 µg genomic DNA. Among 43 specimens with previously characterized genetic abnormalies, the Agilent 244K microarray correctly detected all 43. Nonblinded comparison of 32 specimens with abnormalities previously defined by G-banding, fluorescence in situ hybridization, or array-CGH was totally concordant with results using the Agilent 244K microarray. Blinded comparison of 13 specimens confirmed identical results for 2 normal and 10 abnormal specimens. In 1 other case, the Agilent 244K microarray detected a duplication 1p32.3p31.11 as opposed to a previously reported duplication 1q42.3q32.3. In this discordant case, outside laboratory review confirmed the Agilent 244K result.

Conclusions: CGH using a whole genome-spanning oligonucleotide microarray (Agilent 244K) is a clinically valid diagnostic tool for demonstration of chromosomal imbalances.

Reviewer's Comments: Clinical materials used in this validation originated from patients with constitutional disorders leading to mental retardation or developmental delay. Identical methodology can be applied to investigation of chromosomal imbalances associated with neoplasia and malignancy. In the future, array-based CGH might supplement or replace traditional karyotyping analysis for clinical characterization of leukemias, myelodysplastic syndromes, and other malignancies. However, it is important to note that CGH cannot detect balanced translocations and therefore must be supplemented by techniques that can. (Reviewer-Guy E. Nichols, MD, PhD).

Keywords: Array-Based Comparative Genomic Hybridization, Oligonucleotide, Chromosome Abnormality, Copy Number Variant, Validation

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What Is the Most Accurate Method for Colorectal Cancer Screening?

Screening for Colorectal Cancer.

Lieberman DA:

N Engl J Med 2009; 361 (September 17): 1179-1187

Screening reduces the risk of death from colorectal cancer, but different methods have different benefits and risks. Colonoscopy is the preferred screening method recommended by the American College of Gastroenterology.

Objective: To review formal guidelines and make clinical recommendations on screening for colorectal cancer.
Results: Screening significantly reduces the risk of death from colorectal cancer. A number of screening methods and strategies are available. Fecal occult blood guaiac tests are low-cost, noninvasive tests that can be performed at home. When performed in triplicate, they have a sensitivity of 50% to 75% for detecting cancer. Fecal immunochemical tests employ antibody reagents and may be more sensitive, but have reported variable performances. Patient compliance with testing, compliance with follow-up colonoscopy, and costs of follow-up colonoscopy make the cost of screening by fecal occult blood testing similar to colonoscopy screening. Stool DNA tests that employ polymerase chain reaction (PCR) amplification for colorectal cancer-associated mutations are improving toward more sensitive, second-generation assays that remain unproven with respect to sensitivity, cost, screening interval, and management recommendations. This may be a promising future method for colorectal cancer screening and is recommended by the American Cancer Society, but is not recommended by the U.S. Preventive Services Task Force. CT colonography is 90% sensitive for detecting polyps ≥10 mm with a false-positive rate of 14%, but is less accurate for polyps <6 mm and has unproven predictive value in routine practice. It is recommended by the American Cancer Society, but not by the U.S. Preventive Services Task Force. Colonoscopy outcomes have not been effectively compared to other screening methods. In the U.S., sigmoidoscopy (distal only) is limited by its inaccessibility to proximal lesions and by patient discomfort. Colonoscopy is the preferred screening method recommended by the American College of Gastroenterology, but has room for improvement, especially in its false-negative detection of flat adenomas. Significant bleeding or perforation is uncommon, occurring in 0.3% to 0.5% of colonoscopies.
Conclusions: Screening reduces the risk of death from colorectal cancer, but different methods have different benefits and risks. Colonoscopy is the preferred screening method recommended by the American College of Gastroenterology.
Reviewer's Comments: Screening recommendations for different populations may vary. For example, blacks may benefit from screening at age 45 years as opposed to age 50. Colonoscopy is not generally recommended after the age of 75 years, but may be indicated in persons with no previous screening. (Reviewer-Guy E. Nichols, MD, PhD).

Keywords: Colorectal Cancer, Colonoscopy, Fecal Testing

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What Molecular Tests Predict Colorectal Cancer Resistance to Monoclonal Antibody-EGFR Inhibitor Therapy?

Biomarkers Predicting Clinical Outcome of Epidermal Growth Factor Receptor-Targeted Therapy in Metastatic Colorectal Cancer.

Siena S, Sartore-Bianchi A, et al:

J Natl Cancer Inst 2009; 101 (October 7): 1308-1324

In addition to *KRAS* mutations, which are established predictors of resistance to monoclonal antibody-EGFR inhibitor therapy in colorectal cancer, *BRAF* and *PIK3CA* mutations may have similar predictive value.

Objective: To review molecular tests with potential for predicting colorectal cancer response or resistance to epidermal growth factor receptor (EGFR) targeted monoclonal antibody therapies.
Results: The monoclonal antibody-EGFR inhibitors cetuximab and panitumumab are effective in the treatment of colorectal cancer. In contrast, small molecule EGFR inhibitors work against lung cancer, but not colorectal cancer. Investigators are evaluating molecular features that will identify colorectal cancer patients who respond to cetuximab and panitumumab. Together, *KRAS, BRAF, or PIK3CA* mutations occur in >50% of colorectal cancers with approximate incidences of 40%, 15%, and 20%, respectively. Mutations in *KRAS* and *BRAF* rarely coexist. *KRAS, BRAF,* and *PIK3CA* mutations appear to activate carcinogenic pathways downstream and independent of EGFR activation, and *KRAS* mutations are established predictors of resistance to cetuximab and panitumumab therapy in colorectal cancer. In other words, colorectal cancers that are *KRAS*+ do not respond to cetuximab or panitumumab. Similar to *KRAS*, colorectal cancer *BRAF* mutations also predict resistance to cetuximab and panitumumab. In contrast to wild-type *BRAF* colorectal cancers, which have a median progression-free interval of 10.4 months following first-line cetuximab/capecitabine/oxaliplatin bevacizumab, mutant *BRAF* tumors have a progression-free interval of 6.6 months (CAIRO-2 study). There may be additional molecular predictors of colorectal cancer response to monoclonal antibody-inhibitors. *PIK3CA* mutations may predict resistance to cetuximab. Immunohistochemically determined EGFR phosphorylation status, EGFR gene mutations, or gene copy-number may predict drug response as well.
Conclusions: In addition to *KRAS* mutations, which are established predictors of resistance to monoclonal antibody-EGFR inhibitor therapy in colorectal cancer, *BRAF* and *PIK3CA* mutations may have similar predictive value.
Reviewer's Comments: By analogy, with lung cancer, for which acquired resistance to small molecule EGFR inhibitors arises from secondary EGFR gene mutation, we can expect acquired colorectal cancer resistance to monoclonal antibody inhibitors. It seems likely that molecular testing will play a role in the management of colorectal cancer patients who develop resistance to cetuximab and panitumumab. (Reviewer-Guy E. Nichols, MD, PhD).

Keywords: Cetuximab, Panitumumab,*KRAS, BRAF , PIK3CA*

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