For both prostate biopsies and prostatectomy specimens, there may be a trend toward higher Gleason grade assignment by pathologists since publication of the 2005 ISUP consensus guidelines.

**Background:** Donald F. Gleason's system for grading prostate cancer remains in use decades after its initial proposal in the 1960s. The system has evolved since then, mainly in response to the advent of the needle core biopsy technique. However, differences in the interpretation and application of this grading system exist -- issues that stem primarily from the dependence of the system on subjective interpretation. Problematic issues have included the following: knowing the extent of size and shape variations allowable for Gleason pattern (GP) 3; determining what represents the scope of gland fusion patterns for GP4; how to grade ill-defined glands without well-formed lumina; grading and reporting of tertiary patterns; and defining the morphological spectrum of cribriform glands. In 2005, the International Society of Urological Pathology (ISUP) convened for a consensus conference to clarify and resolve some of these issues related to the application of Gleason grading in prostate cancer.

**Objective:** To determine whether and how the 2005 ISUP consensus recommendations regarding modifications of the Gleason grading system have influenced pathology practice in the interpretation and grading of prostate cancer in biopsy and prostatectomy specimens.

**Methods:** Gleason scores were compared in 2 consecutive patient cohorts at a single institution with matched prostate needle core biopsies and prostatectomies. The first cohort included 908 patients whose specimens were collected and examined before the 2005 ISUP conference (July 2000-June 2004). The second cohort included 423 patients whose specimens were reviewed after the conference (October 2005-June 2007). Preoperative patient characteristics, prostatectomy characteristics, and Gleason scores for the biopsy and prostatectomy samples were collected.

**Results:** After the ISUP consensus, there was a significantly higher percentage of biopsies showing GS ≥7 (32% pre-ISUP vs 43% post-ISUP) as well as a higher percentage of prostatectomies showing similar findings (53% pre-ISUP vs 68% post-ISUP). The results were statistically significant ($P<0.001$).

**Conclusions:** Based on this single institution’s experience, there was a trend toward assigning both biopsies and prostatectomy specimens a higher Gleason score after the ISUP results were published. In addition, there was better complete agreement in the assignment of higher grades to both specimen types after the consensus.

**Reviewer’s Comments:** Accurately determining the impact of consensus practice guidelines on practice patterns is not an easy task, but the authors’ ideas and study design based on the Gleason grading issue appear sound. It is not known whether the diagnosis of higher Gleason scores, as reported here, is a general phenomenon, but the implications of such a trend are likely to have significant clinical impact. (Reviewer-T. David Bourne, MD).

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Keywords: Cancer, Gleason Grading

Print Tag: Refer to original journal article
Brain IPTs May Be Part of IgG4-Related Disease Spectrum

Inflammatory Pseudotumors of the Central Nervous System.
Lui PC, Fan YS, et al:
Hum Pathol 2009; 40 (November): 1611-1617

Many inflammatory pseudotumors of the central nervous system show a significant number of IgG4-positive plasma cells. Therefore, these lesions may be part of the spectrum of IgG4-related diseases.

Background: Inflammatory pseudotumor (IPT) is a heterogenous group of diseases characterized by variable numbers of spindle cells admixed with a lymphoplasmacytic infiltrate. In a subset of IPTs considered neoplastic, chromosomal rearrangements involving the anaplastic lymphoma kinase (ALK) gene have been described. Recently another subset of IPTs has been shown to have increased numbers of IgG4+ plasma cells. Central nervous system (CNS) involvement by IPT is rare.

Objective: To report 4 cases of intracranial IPTs, with emphasis on ALK protein expression and evaluation for IgG4+ plasma cells.

Methods: Four cases diagnosed as CNS IPT were included. Each case was evaluated by H&E and was immunohistochemically (IHC) stained with antibodies for IgG4, S-100, ALK-1, desmin, smooth muscle actin, lambda light chain, kappa light chain, EMA, and CD34. In situ hybridization for Epstein-Barr virus (EBV) was performed in each case. The assessment of IgG4+ plasma cell density was performed in 3 high-power fields (HPFs). The IgG4+ plasma cell density was considered marked when >30/HPF, moderate when 11 to 30/HPF, weak with 5 to 10/HPF, and none when <5/HPF. Serum IgG4 levels were not tested preoperatively in any case.

Results: None of the patients had systemic symptoms or a coexisting diagnosis of IPT in a different location. All lesions were dural based or inside the ventricle. Three patients underwent gross total resection, and case 4 was treated with high-dose dexamethasone and thalidomide after an open-biopsy diagnosis of IPT. All 4 cases showed similar morphologic findings: rare bland spindle cells were present in an abundant inflammatory background composed of lymphocytes and plasma cells. IHC demonstrated polyclonal plasma cells in all cases. Spindle cells were positive for smooth muscle actin and were negative for all other markers, including ALK-1. EBV was negative in all cases. Three cases showed a marked density of IgG4+ plasma cells, but the additional case had no significant IgG4+ plasma cells. Case 4 had a marked IgG4+ plasma cell density, and after treatment, had significant resolution of clinical symptoms and MRI-documented reduction in lesion size.

Conclusions: Most intracranial ALK-negative IPTs have increased IgG4+ plasma cells, suggesting these lesions may be part of the spectrum of IgG4-related diseases. A trial of corticosteroid therapy may be valid after histologic confirmation of a diagnosis of IPT.

Reviewer's Comments: The spectrum of IgG4-related disease continues to expand and has been shown to involve almost all body sites. It is important to be aware of this diagnosis because unnecessary surgical procedures can often be prevented through appropriate use of serum IgG4 levels and high-dose steroid therapy. (Reviewer-Deborah J. Chute, MD).

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Keywords: CNS Inflammatory Pseudotumors

Print Tag: Refer to original journal article
Avoid Misdiagnosing Spark's Nevi as Malignant Melanoma


Ko CJ, McNiff JM, Glusac EJ:

J Cutan Pathol 2009; 36 (October): 1063-1068

Spark's nevi have architectural features of Clark/dysplastic nevus and cytologic features of Spitz nevus. Spark's nevi should not be confused with malignant melanoma.

Background: Clark (dysplastic) nevi and Spitz nevi are 2 distinct melanocytic lesions. Dysplastic nevi are associated with an increased risk of melanoma. Histopathologic criteria include variable cytologic atypia of junctional melanocytes, a lentiginous growth pattern, bridging of nests, and lamellar and concentric fibrosis. Spitz nevi demonstrate epithelioid and spindled melanocytes, which are monomorphous “atypical.” These melanocytes have large, uniform nuclei with prominent nucleoli. Nests of spindled cells (classically not pigmented) are frequently found perpendicular to the epidermis. “Spark's” nevi are melanocytic lesions with features of both Clark/dysplastic and Spitz nevi.

Objective: To review the clinicopathologic characteristics and differential diagnosis of Spark's nevi.

Methods: 27 nevi with characteristics of both Clark/dysplastic and Spitz nevi were identified retrospectively, and the clinicopathologic features were studied.

Results: The mean age at presentation was 33 years (range, 6-64 years) with a female predominance (17 of 27 cases). The trunk and lower extremities were the most common sites (n=20). No patient had a personal history of melanoma. Clinically, the lesions were atypical in shape and color, and they varied in size from 3 mm to 1 cm. No history of recent change was noted. In 12 cases, mean follow-up was 10 years, and there were no documented recurrences. Microscopically, the lesions appeared horizontally oriented and symmetric with sharp circumscription. The melanocytes formed nests of similar size and shape, however with extensive bridging across the rete, more irregular nests were present. Kamino bodies were present in 23 cases. A uniform Spitzoid cytology was noted, with large, generally monomorphic melanocytes found predominantly at the tips of rete ridges. Melanocytes were predominantly confined to the epidermis and/or papillary dermis. Focal pagetoid scatter of melanocytes was noted, and occasional junctional mitoses could be found.

Conclusions: Although uncommon, Spark's nevi are not rare. The differential diagnosis includes small diameter melanoma (<6 mm), which are often recent lesions with a history of change and patients tend to have a positive history of clinically atypical nevi. Single atypical melanocytes can be appreciated at all levels of the epidermis with lack of dermal maturation. Small melanomas may be well-circumscribed but usually have a depth of >0.70 mm. Further differential diagnoses include Clark/dysplastic nevi and Spitz nevi. Although the authors admit that the classification is inherently arbitrary, importance is placed on not diagnosing Spark's nevi as aggressively behaving melanocytic processes.

Reviewer's Comments: Melanocytic lesions are common and challenging cases. This study addresses the clinicopathologic features of Spark's nevi. These lesions are uncommon but not rare and should not be considered as aggressive melanocytic lesions, such as small melanomas. (Reviewer-William A. Kanner, MD).

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Keywords: Melanocytic Nevi, Spark's Nevi

Print Tag: Refer to original journal article
Phyllodes Tumor of Breast More Likely to Recur if High Grade

Karim RZ, Gerega SK, et al:

Breast 2009; 18 (June): 165-170

High-grade phyllodes tumors of the breast are more likely to occur in older women and be of greater size. These high-grade tumors tend to recur more commonly, but not at a statistically significant rate.

**Background:** Phyllodes tumors (PT) of the breast are fibroepithelial neoplasms closely related to the more common fibroadenoma. Differentiation between the 2 lesions can be difficult because they remain on a spectrum of disease. However, phyllodes tumors are managed differently due to the potential for recurrence and even metastases. At the other end of the spectrum, high-grade PT may be mistaken for a sarcoma if the epithelial component is not sampled or is overlooked. Multiple grading systems are utilized to characterize the malignant potential of PT, including 2- and 3-tiered systems. Management consists primarily of surgery, with most suggesting a 1-cm margin of clearance that, in some cases, may have cosmetic implications.

**Objective:** To collect the clinicopathologic data from a large cohort of PTs from a single institution with uniform approach to evaluate multiple grading systems for biologic relevance.

**Methods:** Archived files representing 16 years of cases were searched to collect PTs. Original slides were reviewed for confirmation and to document histologic characteristics. In brief, PT tumors were benign if low cellularity, no stromal overgrowth, mild stromal atypia, pushing margins, and mitotic counts ≤2/10 HPFs. Malignant PT had stromal overgrowth, infiltrative margins, and mitotic counts of ≥5/10 HPFs. Those in between were considered borderline (BL). For the 2-tiered system, benign PTs were considered low-grade (LG), while BL and malignant PTs were considered high-grade (HG).

**Results:** Classification revealed 34 benign, 23 BL, and 8 malignant PTs, or 34 LG and 31 HG PTs. Nine of the 65 tumors were recurrences, including 4 LG/benign and 3 BL plus 2 malignant (5 HG), lacking statistical significance. Patients of Asian descent (n=19) represented 67% of the recurrences but were 31% of the overall study population. No metastases or deaths were observed. The mean age is 43 years overall, but there is a significant correlation between tumor grade and age. A significant correlation is also observed between tumor grade and tumor volume/maximum dimension.

**Conclusions:** Of a series of 65 PTs, age, tumor volume, and maximum dimension of tumor directly correlated with grade, but neither a 2- or 3-tiered grading system was predictive of recurrence. Women of Asian descent may be at higher risk for local recurrences.

**Reviewer's Comments:** Cellularity and stromal nuclear atypia were not included as features of a high-grade tumor. However, it was noted that all malignant PTs did have moderate to high cellularity and moderate to severe cytologic atypia. (Reviewer-Mary T. Galgano, MD).

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Keywords: Phyllodes Tumors

Print Tag: Refer to original journal article
PSA testing has resulted in a great number of clinically negligible prostate cancers. For men aged <50 years, the incidence is now 7 times greater than before the advent of PSA screening in 1986.

**Background:** Screening tests are notorious for leading to the overdiagnosis of cancers. In these scenarios, cancers are diagnosed that would not have been diagnosed if one waited to present with them clinically. Thus, more patients are diagnosed with malignancies that would not actually influence their overall survival, regardless of treatment. Examples of such tumors include thyroid, breast, and prostate carcinomas. It is now recommended that men aged >75 years not be screened with a prostate-specific antigen (PSA) test.

**Objective:** To investigate the impact of PSA screening on the diagnosis of prostate cancer during the past 20 years.

**Methods:** The incidence of prostate cancer prior to screening (1986) was compared to the incidence of prostate cancer through 2006. Specific age incidences were recorded and used to calculate population trends. Data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results program were also used to determine initial treatments received by these patients. Mortality rates of prostate cancer were also recorded, and all decreases in mortality were considered secondary to screening. Mortality and incidence changes were compared.

**Results:** The incidence of prostate cancer increased rapidly after the advent of PSA screening until 1992 and then decreased until 1995. It has since stabilized at an incidence about 26% higher than it was in 1986. The incidence has shown the greatest increase for younger patients. For example, for those aged <50 years, the incidence is now 7 times greater than in 1986. The incidence has actually fallen somewhat for older patients because of earlier diagnosis. An estimated 1.3 million additional cases of prostate cancer were diagnosed secondary to PSA screening. Given little change in treatment trends throughout the years, it was estimated that approximately 1 million additional men have undergone prostatectomy secondary to PSA screening. Given the slight improvement in mortality trends for prostate cancer, it was estimated that 56,000 deaths have been avoided since 1986 compared to what would have been expected had mortality rates remained as they were. Therefore, an estimated 23 additional men had to be diagnosed with prostate cancer (18 of these had to be treated with surgery) for each life saved due to PSA testing.

**Conclusions:** Even using the assumption that the entire decline in mortality seen with prostate cancer is secondary to PSA screening, the overall benefits compared to risk seem limited at best. The authors state that men undergoing PSA testing should have the risks and benefits of the screening adequately explained to them.

**Reviewer’s Comments:** The dilemma remains for younger men – should they undergo PSA screening or not? Something must be done to identify the 1 in 20 prostate cancers that actually need to be resected and to distinguish it from those that do not. (Reviewer-Edward B. Stelow, MD).
Background: Reviewing "outside" pathology slides from patients who are seen in consultation for treatment or second opinion is an important part of pathology practice at many institutions.

Objectives: To determine whether sending entire sets of slides from a given case, rather than sending selected slides, results in a change in the frequency of diagnostic disagreement between the original pathologist and the second reviewer.

Methods: The authors reviewed all cases of patient and clinician-requested interdepartmental consultations during a 5-year period. During the first 4 years, only selected slides were routinely sent for review. During the fifth year, all routine slides were sent. Original material rather than recut slides were sent during all 5 years. The original and consultation reports were reviewed, and in cases of diagnostic disagreement, all original pathology slides were reviewed. Those cases for which the number of slides sent for review contributed to the diagnostic disagreement were identified.

Results: Of 596 cases, 81 (13.6%) had a disagreement between the original pathologist and the second reviewer. The disagreement rate was lower when only selected slides were sent. Only 5 cases seemed “slide-related.” In 1 case, the diagnostic slide was inadvertently not included with the slides sent for review. In 2 cases, the reviewing laboratory disagreed with the interpretation of the number of positive lymph nodes (all slides sent). In a fourth case, the reviewing lab missed a focus of microinvasive carcinoma, which was present on only 1 of 10 slides (all slides sent). In the fifth case, the reviewing lab missed ductal carcinoma in situ adjacent to an invasive ductal carcinoma, which was present on only 1 of 5 slides (all slides sent). In none of these cases did the reviewing pathologist contact the original lab to discuss the discrepancy. When the reviewing pathologist missed a diagnostic finding when all slides had been sent, no effort was documented to show that an attempt was made to resolve the discrepancy. In cases where only selected slides were sent, no screening errors were identified.

Conclusions: Sending all slides when cases are requested for outside review is associated with higher discrepancy rates. However, the disagreement comes from both the introduction and the correcting of errors.

Reviewer’s Comments: Fortunately, the error rate from such slide-related factors is small. This article certainly reinforces the need for the primary and referral pathologists to be thoughtful when sending out and reviewing such cases. We believe that any meaningful discrepancies should always be discussed before the second report is finalized. (Reviewer-Stacey E. Mills, MD).

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Keywords: Slide Consultation Review

Print Tag: Refer to original journal article
Kidney Transplant -- Cell-Free Plasma DNA Detects AR

Cell-Free DNA as a Noninvasive Acute Rejection Marker in Renal Transplantation.

García Moreira V, Prieto García B, et al:


Cell-free plasma DNA, if used in conjunction with plasma procalcitonin, may be a useful biomarker to help diagnose kidney allograft rejection when renal biopsy is contraindicated.

Background: In renal transplant patients, the initial 3-month period after transplantation is a crucial time to detect complications and diseases associated with transplantation, including acute rejection (AR), acute tubular necrosis (ATN), and infection. Making a rapid, accurate diagnosis of AR is especially important in terms of immediate therapy and long-term prognosis. To date, no reliable biomarkers of AR have been discovered.

Objectives: To determine whether cell-free DNA (CF-DNA), as measured in the circulation and/or urine, might be useful as a biomarker of AR in the setting of renal transplantation.

Methods: During the first 3 months after transplantation, plasma was collected from 100 patients. Total CF-DNA (tCF-DNA) was assessed by amplification of the hemoglobin beta gene (HBB) by quantitative PCR. Donor-derived CF-DNA (ddCF-DNA) was assessed by amplification of the testis specific protein, Y-linked 1 (TSPY1). This latter test was only performed in women who had received kidney allografts from male donors. Plasma procalcitonin (PCT) was also measured as a marker of sepsis on the day of diagnosis in any patient who developed infection or clinical AR. Cell-free urine DNA (Tr-DNA) was measured in 30 of the 100 patients. Medical records were retrospectively reviewed, showing 19 episodes of AR, 13 of which were confirmed with biopsy. Other complications, such as infection or ATN, were also recorded. Plasma and urine from 125 healthy donors were used as negative controls.

Results: The concentration of tCF-DNA increased substantially during episodes of AR and decreased after treatment for rejection was initiated. Using a cutoff value of 12,000 genome equivalents/mL of tCF-DNA carried diagnostic sensitivity and specificity values of 89% and 85%, respectively. Combining the tCF-DNA values and the PCT results significantly increased the diagnostic specificity to 98%. Assessment of ddCF-DNA and Tr-DNA showed no added value.

Conclusions: Measuring plasma tCF-DNA in combination with the sepsis marker PCT provides a noninvasive means of detecting acute cellular rejection in patients after kidney transplant. While such testing cannot replace the gold standard of kidney biopsy, it may provide helpful diagnostic information in patients who have a contraindication for renal biopsy.

Reviewer’s Comments: This paper represents yet another important application of plasma CF-DNA measurement. The authors seem to have provided a solution to the relative nonspecificity of increases in CF-DNA by adding PCT measurements. Performing the study using a significantly larger patient sample and defining the relationship between tCF-DNA levels and markers of antibody-mediated rejection would be important and interesting next steps. (Reviewer-T. David Bourne, MD).

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Keywords: Transplantation, Rejection, Plasma DNA Testing

Print Tag: Refer to original journal article
The sensitivity of routine Pap test screening improved significantly after implementation of rapid prescreening as a quality control measure. Cytotechnologists may find RPS to be a motivating avenue to improvement.

**Background:** All cytopathology laboratories utilize quality control (QC) methods to improve the sensitivity of Pap test screening. Most labs perform full rescreening of randomly selected negative Pap tests, but this has been criticized as being inefficient and insensitive. A recently proposed alternative is rapid prescreening (RPS), which shows comparable gains in sensitivity to rapid rescreening.

**Objective:** To analyze the effect of RPS on the performance of routine screening (RS) by the overall laboratory and individual cytotechnologists (CTs).

**Methods:** For 16 consecutive months, RPS was performed on all conventional Pap smears. Eleven CTs rapidly prescreened 1 set of approximately 20 slides per day in 15 to 30 minutes without marking the slides or paperwork. RPS interpretations were recorded as abnormal (R) if equivalent to atypical squamous cells of undetermined significance or worse, or negative (N) on a standardized worksheet. The cases were then fully screened by a different CT without knowledge of the RPS result. The final and RPS diagnoses were compared. When both interpretations were N, the case was finalized by the CT. When one or both interpretations were R, the case was referred to the cytopathologist for final evaluation, which was considered the gold standard. The sensitivity of RPS and RS was calculated over the initial 8 months and the second 8 months for both the overall laboratory and individual CTs.

**Results:** Approximately 50,000 Pap tests underwent RPS and RS. The sensitivity of RPS during the entire study was 44% for any abnormality and 72% for high-grade squamous intraepithelial lesion. The RPS performance of CTs in the first and second study periods showed equal fluctuations in both directions. The overall sensitivity of RS for the first 8 months was 85% for any abnormality, which increased to 91% during the second 8 months. Most CTs demonstrated a better RS performance in the second study period. Most CTs with an RS sensitivity of <95% showed significant improvement from the first period to the second period. In contrast, none of the CTs with a sensitivity ≥95% showed significant improvement.

**Conclusions:** In addition to the general improvement of Pap test screening that QC measures affect, rapid prescreening use over time may play a role in improving cytotechnologist performance on routine screening. This effect is particularly seen in cytotechnologists with an overall lower sensitivity.

**Reviewer’s Comments:** Rapid prescreening is a promising alternative to random rescreening. In our experience, cytotechnologists are frequently resistant to change. However, if sufficiently engaged, they may find that RPS can be a motivating avenue to improvement. (Reviewer-Deborah J. Chute, MD).

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Keywords: Pap Test Screening, Lab Quality Control

Print Tag: Refer to original journal article
The diagnosis and treatment of hip and knee prosthetic joint infection critically depends on various areas of medicine, of which pathology plays a central role.

**Background:** The number of primary total hip and knee arthroplasties has significantly increased during the last decade. However, prosthetic joints may fail and need revising secondary to aseptic loosening, infection, dislocation, and fracture of the prosthesis or bone. Infection occurs in 0.8% to 1.9% of knee and 0.3% to 1.7% of hip arthroplasties. *Staphylococcus aureus* and coagulase-negative *Staphylococcus species* are implicated in >50% of cases, however other bacteria and fungi have been speciated. Acute infections often manifest within 3 months, while chronic infections may not present until many months or years later. **Diagnosis:** To determine if a failed joint is infected, the most important laboratory test, in the absence of underlying inflammatory disease, is C-reactive protein. Currently, imaging studies are hampered by low sensitivities, low specificities, and the artifact produced by the prosthesis. The most useful preoperative test is aspiration of joint synovial fluid for a differential count and culture. If these tests are not definitive, intraoperative frozen section examination can be performed. The criteria for diagnosing infection include the presence of 5 polymorphonuclear cells in a high-power field in 5 separate fields, excluding fibrin and surface exudate. Also, intraoperative microbiologic testing can and should be performed in such cases. Maximal detection is achieved when 5 to 6 specimens are sent and 2 to 3 are speciated. Intraoperative Gram stain and swab cultures are not recommended due to poor sensitivity. The implant can be sonicated to remove microorganisms that have potentially formed a biofilm. **Treatment:** Management of these cases is complex. Antimicrobial therapy alone often fails. In patients who have an acute infection and meet criteria, debridement with retention of the prosthesis and antimicrobial therapy may be attempted. In chronic infection, resection arthroplasty as a one- or two-stage exchange with antimicrobial therapy is offered. Additional management considerations are needed for patients who have failed multiple treatments or will have poor joint function. Antimicrobial therapy for patients undergoing debridement may last for 3 to 6 months for hip and knee prostheses, respectively. For patients undergoing a 2-stage revision, 4 to 6 weeks of systemic antimicrobial therapy is needed. In many cases, prophylactic antimicrobial therapy is administered immediately before surgery. **Conclusions:** Infection associated with prosthetic joints is an increasing and important area in medicine. Diagnosis and treatment of infection critically depends on various areas of medicine and the laboratory. **Reviewer's Comments:** This broad overview addresses the important problem of diagnosing and managing infection associated with prosthetic joints. Both anatomic and clinical pathology are significantly involved in these cases. (Reviewer-William A. Kanner, MD).
Although the prognosis is good, long-term follow-up is necessary for malignant struma ovarii. Even benign and adenomatous-appearing follicular lesions can be clinically aggressive.

**Background:** Given the rarity of malignant struma ovarii, little is known about their biologic potential. The criteria for diagnosis of malignancy and the subsequent prognosis of women with struma ovarii are not well explored.

**Objective:** To study the long-term outcome of a large series of struma ovarii with histologic features or biologic evidence of malignancy.

**Methods:** Data were collected from previously published cases made available for review (n=19), consultation material (n=64), and primary diagnoses at the authors’ institutions (n=5). Cases were excluded if the malignant focus was minor in association with a struma carcinoid or in the presence of a second malignancy. Biologic malignancy was defined as extraovarian disease, ovarian surface involvement, or recurrence.

**Results:** 88 cases were collected with either biological or histological features of malignancy. Of the histologically malignant cases, 4 were follicular carcinomas, as determined by multifocal intravascular tumor growth (n=2) or ovarian capsular penetration with growth along the serosa (n=2). Nine cases had equivocal intravascular tumor, and some of these had tumor on a surface fibrous “pseudocapsule,” but criteria were purposefully stringent. Twenty cases were papillary carcinoma using traditional nuclear features and the presence of papillary architecture. Four cases were the follicular variant of papillary carcinoma, diagnosed by diffuse nuclear features of papillary carcinoma (focal changes not sufficient). Of the 27 tumors with biologic malignancy, 12 were histologically malignant, while 13 appeared as “adenomas” and 2 appeared as benign thyroid tissue. Peritoneal implants also appeared as benign thyroid tissue in biologically malignant tumors, including 1 patient who died of widespread disease. No histologic feature was predictive of the biologic potential, but generally, the diameter of the struma correlated with clinical behavior, and the smallest tumor to recur was 4 cm. Dense and numerous adhesions and large-volume bloody ascites were more common in clinically malignant tumors. The survival rate overall was 89% at 10 years and 84% at 25 years, but for those with histological malignancy, it was 81% at 10 years and 60% at 25 years.

**Conclusions:** Regarding the malignant potential of a struma ovarii, important factors to consider are size, the presence of adhesions and ascites, and thorough assessment of the tumor and the ovarian serosa. Even benign and adenomatous-appearing (“proliferative”) follicular lesions can be clinically aggressive.

**Reviewer’s Comments:** Granulosa cell tumors were the most common misdiagnoses in the consultation material. The diagnosis may not be immediately obvious, especially in one of the proliferative lesions.

(Reviewer-Mary T. Galgano, MD).

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**Keywords:** Struma Ovarii

**Print Tag:** Refer to original journal article
A new reporting scheme has been described for thyroid fine-needle aspiration specimens. The “atypia of undetermined significance” category will be new to many pathologists.

**Background:** Fine-needle aspiration (FNA) of the thyroid is an effective tool for guiding the management of patients with thyroid nodules. Importantly, it allows some patients to avoid resection. Since its routine use, the percentage of thyroid resections with malignancies has increased from 15% to >50%. Throughout the years, thyroid FNA results are reported differently from institution to institution, creating confusion among clinicians regarding diagnoses and hindering our overall ability to assess the test’s function.

**Objective:** This review summarized the Bethesda System for the reporting of thyroid FNA specimens.

**Results/Conclusions:** During the past few years, a conference hosted by the National Cancer Institute was held in Bethesda, Maryland. Physicians from around the country, especially pathologists, discussed the current state and reviewed our understanding of thyroid FNA. Most discussion focused on terminology for reporting thyroid FNA specimens. After publication of summary articles, it was decided that an atlas would be published to recapitulate the most widely used diagnostic frameworks. This atlas is soon to be published. The system recommends that each thyroid FNA specimen first be classified within 1 of 6 diagnostic categories, including (1) nondiagnostic or unsatisfactory; (2) benign; (3) atypia of undetermined significance or follicular lesion of undetermined significance; (4) follicular neoplasm or suspicious for follicular neoplasm; (5) suspicious for malignancy; or (6) malignant. Nondiagnostic specimens are those considered inadequate for interpretation, including bloody smears without follicular cells, poorly prepared or obscured specimens, and specimens that show only cyst changes. Patients with this diagnosis will undergo re-aspiration. Benign specimens include hyperplastic lesions as well as inflammatory conditions. These lesions can be followed up clinically and are usually associated with about a 1% risk for malignancy. The “atypia of undetermined significance” category will be new to many. In general, this will include samples considered adequate but without sufficient features to be interpreted as benign or potentially neoplastic. For example, this diagnosis may be used with sparsely cellular aspirates that show little or no colloid. Patients with this diagnosis will usually be treated with re-aspiration. The categories “follicular neoplasm,” “suspicous for malignancy” and “malignant” are already used by most pathologists and are associated with about a 25%, 65%, and 98% risk for malignancy, respectively. Patients with these diagnoses will generally proceed to resection.

**Reviewer’s Comments:** This article is extremely important, and all pathologists who sign out cytopathology specimens should read it. Uniform reporting of thyroid FNA specimens will be of great assistance to clinicians who manage these patients. (Reviewer-Edward B. Stelow, MD).

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Keywords: Nodules, Fine-Needle Aspiration, Reporting

Print Tag: Refer to original journal article
**Skyrocketing Costs Make Screening Cost-Effective**

*Effect of Rising Chemotherapy Costs on the Cost Savings of Colorectal Cancer Screening.*

Lansdorp-Vogelaar I, van Ballegooijen M, et al:


With colorectal adenocarcinomas, most screening methods will soon be found to decrease the overall cost of the disease without resulting in an over-diagnosis of disease.

**Background:** Nearly 150,000 cases of colorectal cancer are diagnosed each year in the United States, and about a third of these patients will die from the disease. Chemotherapy has continued to offer significant increases in overall survival times. However, this has come at a cost. An estimated 10 billion dollars are spent annually on the management of patients with colorectal cancer. Antivascular endothelial growth factor antibodies have increased the cost of drugs for treatment by nearly 350 times. Screening using fecal occult blood testing (FOBT) and endoscopy improve mortality and incidence rates of colorectal adenocarcinomas because colon cancers typically have a long preclinical phase and significantly better prognosis when found at an earlier stage.

**Objective:** To determine if the increased cost of chemotherapy for advanced disease has made screening for colorectal carcinoma a cost-saving measure.

**Methods:** A complex and previously validated colorectal cancer model system was used that is based on (1) the adenoma-carcinoma progression theory for colorectal adenocarcinomas and (2) the interruption of detected disease by various screening methodologies. Various treatment costs and screening strategies were assessed. The functions and survival benefits of various screening tests were estimated using previously reviewed data.

**Results:** It was estimated that 66 of 1000 individuals aged >50 years would be diagnosed with colorectal carcinoma per year. Without screening, 50% of these tumors would be high stage. Annual FOBT decreased the number of cancers diagnosed per year by 37%, and colonoscopy every 10 years decreased the number of cancers by 56%. With screening, tumors also presented at earlier stage. Higher-stage tumors were estimated to have higher treatment costs, especially using the most advanced treatments available. Given the increase in costs for the treatment of high-stage colorectal adenocarcinomas in the future, most screening methods were actually found to decrease the total net costs of colorectal cancer treatment. Complete colonoscopy remains the only screening strategy that increases total net cost.

**Conclusions:** Screening is generally desired because it decreases the overall incidence and mortality of the screened cancer. With colorectal adenocarcinomas, most screening methods will soon be found to decrease the overall cost of the disease.

**Reviewer's Comments:** Unlike some other screening tests, screening for colon cancer does not lead to over-diagnosis of disease. Skyrocketing costs of chemotherapy are yet one more reason to detect colon cancer early and to prevent it. (Reviewer-Edward B. Stelow, MD).

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Keywords: Adenocarcinoma, Screening, Costs

Print Tag: Refer to original journal article
Good Specimen Labeling Prevents ABO Mistransfusions

Strict Adherence to a Blood Bank Specimen Labeling Policy by All Clinical Laboratories Significantly Reduces the Incidence of “Wrong Blood in Tube”.

O’Neill E, Richardson-Weber L, et al:


In one institution’s blood bank, an educational initiative and adherence to a strict specimen labeling policy reduced mislabeled and “wrong blood in tube” specimens, thus reducing the risk of ABO mistransfusions.

Background: One of every 19,000 units of blood is mistransfused with ABO-incompatible red blood cells. Death occurs at a rate of 1 in 600,000 transfusions, which is higher than the risk of contracting HIV. Vital to the prevention of ABO mistransfusions is the specimen collection process, especially proper specimen labeling. Mislabeled specimens increases 40-fold the risk of having a specimen with the wrong patient's blood.

Objective: To review the effect of laboratory wide enforcement of a strict specimen labeling policy and a low-cost educational program on the incidence of mislabeled and wrong blood in tube (WBIT) specimens detected by one institution's blood bank.

Methods: The existing specimen labeling policy required the collection date, 2 unique patient identifiers, and the phlebotomist’s identifying information. Blood bank incident reports from 2001 through 2007 were examined for the mislabeled specimens, WBIT specimens, and ABO/Rh typings recorded each year. In 2004, strict adherence to the specimen labeling policy was enforced, and this was accompanied by an educational campaign. Phlebotomists were targeted because they collected 64% of all blood samples at this hospital. The program (cost: $4139) included a 1-hour classroom session, 30 minutes of direct observation (managers posed as patients until time of venipuncture), and an additional observation with 4 patients. An informational meeting was held with the nursing managers, and all hospital staff members were notified by e-mail with a 3-month grace period before inadequate specimens would no longer be accepted.

Results: From 2001 to 2004, 36 WBIT and 28 mislabeled specimens were detected with 106,174 ABO/Rh typings. From 2005 to 2007, 9 WBIT and 4 mislabeled specimens were detected with 104,860 ABO/Rh typings. This resulted in a 73.5% decrease in WBIT and an 84.6% decrease in mislabeled specimens (both statistically significant). An extinction effect was noted as the incidence of WBIT and mislabeled specimens had increased over time (especially in 2007), although no incident could be attributed to the phlebotomists.

Conclusions: A statistically significant decrease in the number of WBIT and mislabeled specimens was achieved after instituting a policy of strict adherence to a specimen labeling requirement and a low-cost, relatively short educational program. Additional audiences to be targeted by such a program include the nursing staff.

Reviewer’s Comments: This practical article from the field of transfusion medicine serves as a model to decrease the incidence of mislabeled and “wrong blood in tube” specimens. (Reviewer-William A. Kanner, MD).

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Keywords: Specimen Labeling, ABO Mistransfusions

Print Tag: Refer to original journal article
Clear Cell RCC May Predict Worse Outcomes

Prognostic Impact of Histological Subtype on Surgically Treated Localized Renal Cell Carcinoma.

Teloken PE, Thompson RH, et al:
J Urol 2009; 182 (November): 2132-2136

In patients with localized renal cell carcinoma, clear cell histology may be associated with worse outcomes when compared to chromophobe and papillary histology.

**Background:** Renal cell carcinoma (RCC) is subclassified into 5 distinct malignant histologic subtypes: conventional clear cell; papillary; chromophobe; collecting duct; and unclassified RCC. Prognosis depends on TNM stage, Fuhrman grade, tumor size, and patient performance status.

**Objective:** To investigate if RCC histology independently impacts prognosis in patients undergoing surgery for localized RCC.

**Methods:** Between 1989 and 2006, 1863 patients were identified retrospectively who were managed with either partial or complete nephrectomy for localized RCC. Collecting duct and unclassified types were excluded due to the small number of cases, as were cases with multiple tumors since these patients might be syndromic. Clinical follow-up data were reviewed. Age, gender, operation type, ASA score, TNM stage, and tumor size were all adjusted for in this study. Fuhrman grading was not incorporated into the multivariate analysis.

**Results:** 1333 tumors (72%) had clear cell histology, 310 (17%) had papillary histology, and 220 (12%) had chromophobe histology. The patients had a mean follow-up of 3.4 years, and 187 events (first occurrence of metastasis or disease-specific death) were reported. Of these events, 161 were associated with clear cell histology, 17 with papillary histology, and 9 with chromophobe histology. On univariate analysis, patients with clear cell histology had a 5-year event-free survival probability of 86% (95% CI 84, 88), while patients with papillary and chromophobe histologies had a 5-year event-free survival probability of 95% (95% CI 91, 97) and 92% (95% CI 85, 96), respectively. No statistical significance was associated with patient survivals between papillary and chromophobe tumors. On multivariate analysis, there was a significant association between tumor histology and an event ($P=0.014$). Chromophobe tumors (HR 0.40; 95% CI 0.20, 0.80; $P=0.010$) were associated with a better outcome than were clear cell tumors. Statistical significance was not achieved between clear cell and papillary tumors, however the data indicated that patients with clear cell histology fared worse. Although Fuhrman grading was not incorporated into this study, sensitivity analysis as the covariate was performed and the data (which was not shown in the paper) supported the findings.

**Conclusions:** In this study, the data suggest that localized tumors with clear cell histology independently portend a worse prognosis compared with papillary and chromophobe subtypes.

**Reviewer's Comments:** This study was a collaborative effort between urologists and pathologists. Accounting for many variables, the authors found an independent association with clear cell histology and worse outcome in patients compared to tumors with chromophobe and papillary histologies. (Reviewer-William A. Kanner, MD).

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Keywords: Renal Cell Carcinoma, Histology, Prognosis

Print Tag: Refer to original journal article
Obtain Superior Quality Smears With FNCC


Sajeev S, Siddaraju N:

Diagn Cytopathol 2009; 37 (November): 787-791

Compared with fine-needle aspiration cytology, fine-needle capillary cytology is equally efficacious in the diagnosis of lymph node lesions and may show an improvement in technical quality of the prepared material.

**Background:** Fine-needle aspiration cytology (FNAC) is a widely used, simple, rapid, and safe technique for the diagnosis of superficial lesions. Fine-needle capillary cytology (FNCC) is similar to FNAC, except the use of suction pressure is avoided and material is obtained by the capillary action of the needle.

**Objective:** To evaluate the efficacy of FNCC in the diagnosis of superficial lymph node lesions as compared to FNAC.

**Methods:** Patients were collected prospectively and included adult patients with superficial lymph node enlargement amenable to FNAC. At each site, both FNAC and FNCC were performed by a single cytopathologist using a 23-gauge needle. No specific order of the procedures was followed except in cases of suspected cystic lesions, when FNAC was performed first. Smears from both techniques were examined and scored by 2 observers. Five objective criteria were assessed: amount of background blood, amount of cellular degeneration, degree of cellular degeneration, degree of cellular trauma, and retention of appropriate cellular architecture. Each criterion was scored from 0 to 2, for a total score of 0 to 10, where 10 represented the highest quality specimen possible.

**Results:** 30 lymph node sites from 26 patients had both FNAC and FNCC performed. The cytologic diagnoses included metastatic squamous cell carcinoma (n=12), metastatic adenocarcinoma (n=3), non-Hodgkin lymphoma (n=4), granulomatous inflammation (n=5), and reactive hyperplasia (n=6). In all cases, adequate material for diagnosis was present on both biopsy preparations. There was a trend for less blood on FNCC when compared to FNAC. The average total scores for FNAC and FNCC were 7.70 and 8.70, respectively, and this difference was statistically significant (P<0.04). In addition, the cytopathologist noted that FNCC allowed a better grip/easier manipulation of the lesion and minimized patient apprehension of the procedure. FNCC was less useful in cystic lesions because fluid could not be removed for centrifugation preparations.

**Conclusions:** The efficacy of FNCC was identical to that of FNAC in the diagnosis of superficial lymph node lesions. FNCC showed an improvement in technical quality of cytologic smears when compared to FNAC, although FNCC was less useful in the evaluation of cystic lesions.

**Reviewer's Comments:** At our institution, FNCC is an integral part of our approach to cytopathologist-performed superficial fine-needle aspiration biopsies. Anecdotally, we have also observed improved control and targeting in the biopsy of superficial lesions with FNCC, particularly those which are mobile or <1 cm in size. (Reviewer-Deborah J. Chute, MD).

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Keywords: Fine-Needle Capillary Cytology vs Aspiration Cytology

Print Tag: Refer to original journal article
Grade 1 cervical intraepithelial neoplasia with marked atypia does not show a significantly increased risk of high-grade squamous intraepithelial lesions on short-term follow-up.

**Background:** Approximately 1 million women are diagnosed with grade 1 cervical intraepithelial neoplasia (CIN 1) each year. Between 11% and 21% of these lesions will progress to a high-grade squamous intraepithelial lesion (HSIL) or invasive cancer. However, there are no morphologic or immunohistochemical features that distinguish which CIN 1 lesions will progress. A recent small study by Park and colleagues suggested that cervical biopsies with CIN 1 and marked nuclear atypia have a significantly higher rate of HSIL on short-term follow-up than does conventional CIN 1 without nuclear atypia.

**Objective:** To evaluate the significance of marked cytologic atypia in CIN 1 in a larger cohort of patients at a different institution.

**Methods:** All cervical biopsies with a diagnosis of CIN 1 during a 3-month period were reviewed. Cases were divided into 2 groups: cases with marked cytologic atypia (group 1), and conventional CIN 1 (group 2). All follow-up Pap tests and cervical biopsies performed up to 24 months after the index biopsy were recorded. Pap tests with an interpretation of atypical squamous cells of uncertain significance (ASC-US), which were also HPV-positive, were included in the LSIL category for comparative purposes. When >1 sample was available during follow-up, the most severe interpretation was used.

**Results:** 352 cervical biopsies met the study criteria. Thirty-one (8.8%) had marked cytologic atypia (group 1). Follow-up samples were available in 91% of cases. Only Pap tests were available for follow-up in group 1, while Pap tests and cervical biopsies were available for group 2. On follow-up, group 1 patient samples were interpreted as LSIL in 65% of patients and as HSIL in 10% of patients. Group 2 patient samples were interpreted as LSIL in 62% of patients and as HSIL in 12% of patients ($P=0.1$).

**Conclusions:** Grade 1 CIN with marked cytologic atypia does not have a higher follow-up HSIL rate than does conventional CIN 1 in this population. Further studies are required to address whether these patients should be managed differently.

**Reviewer's Comments:** The paper published by Park and colleagues suggested that patients with CIN 1 with marked cytologic atypia should be considered for excisional cone biopsy because of the higher rate of HSIL or worse. In the current much larger study, that conclusion does not appear to be warranted, although the follow-up of group 1 patients did not include biopsy confirmation. (Reviewer-Deborah J. Chute, MD).

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Keywords: Cervical Intraepithelial Neoplasia, Nuclear Atypia

Print Tag: Refer to original journal article
**Mucinous, NE Carcinomas of Breast Are Similar**

*Mucinous and Neuroendocrine Breast Carcinomas Are Transcriptionally Distinct From Invasive Ductal Carcinomas of No Special Type.*

Weigelt B, Geyer FC, et al:

Mod Pathol 2009; 22 (November): 1401-1414

The gene expression profiles of cellular mucinous (type B) and neuroendocrine carcinomas of the breast are more like each other than either is like a conventional ductal carcinoma.

**Background:** Mucinous carcinoma of the breast is a rare subtype consisting of large volumes of extracellular mucin. Some have reported a distinction between paucicellular lesions (mucinous A) and hypercellular lesions (mucinous B), the latter of which are noted to have neuroendocrine features. Neuroendocrine (NE) carcinoma of the breast is another rare subtype characterized by features comparable to NE tumors of other organs, but a mucinous variant is also described. Expression profiling of breast cancer variants has categorized both the mucinous and NE carcinomas as the luminal molecular subtype, but direct comparison of the 2 variants has not been performed.

**Objective:** To compare the molecular characteristics of mucinous and NE carcinomas of the breast with conventional ductal carcinoma.

**Methods:** Pure mucinous, NE, and conventional ductal carcinomas of the breast were collected from a frozen tissue bank and subjected to a gene expression array for matched comparison.

**Results:** All mucinous A (n=10), all mucinous B (n=8), and 5 of 6 NE carcinomas were of luminal A phenotype. The sixth NE carcinoma was of luminal B phenotype. Hierarchical clustering analysis showed the mucinous and NE carcinomas clustered together but were separate from the conventional ductal carcinomas matched by grade and molecular subtype (n=91). When the subtypes were analyzed separately, the mucinous A formed a discrete cluster, while mucinous B and NE carcinomas were not distinguished from each other, and no transcriptional differences were found between the latter 2 groups.

**Conclusions:** At the transcriptional level, mucinous B carcinomas of the breast are strikingly similar to NE carcinomas of the breast, both of which are distinctly different from conventional ductal carcinomas matched for grade and molecular subtype.

**Reviewer's Comments:** The authors cite work from Capella and colleagues for the classification of mucinous carcinomas. Type A tumors are defined as the “classic” mucinous lesions composed of 60% to 90% mucin within which the cellular component is scattered. Type B tumors are 30% to 75% mucin with densely packed cellular areas, and many cells have intracellular mucin. (Reviewer-Mary T. Galgano, MD).

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Keywords: Carcinoma Subtypes, Mucinous vs Neuroendocrine

Print Tag: Refer to original journal article
Background: Blood culture incubators loaded only during specific laboratory hours may delay growth of causative agents while patients remain on empirical antibiotic therapy. Switching to more specific and appropriate antibiotics can have implications for patient morbidity and mortality and can decrease costs.

Objective: To decrease the turnaround time for blood culture results by implementing an immediate incubator that is continuously monitored, even outside routine hours of laboratory operation.

Methods: The laboratory in a tertiary care center with an active infectious disease consultation service implemented a continuously monitoring blood culture incubator that was placed outside the laboratory facility to be loaded outside the normal hours of operation with closed Vacutainer™ needle system culture bottles collected at the bedside. The incubator was scheduled for a random and blinded on/off routine, and while off, it served as an ambient storage cabinet for the culture bottles to be transferred to the routine incubator in the morning. Only new bacteremias aged >18 years who were being treated in the hospital or emergency room with cultures brought to the laboratory outside the hours of operation were included. Outcome measure was the time of specimen collection to the first change in the antibiotic regimen after detection of bacterial colony growth. Secondary outcomes included turnaround times, duration of hospital stay, and hospital mortality.

Results: The Bactec™ incubator was on for 104 days of the intervention period and off for 107 days of the control period, during which 70 and 85 patients were identified, respectively. The time from specimen collection to detection of growth decreased 10.1 hours for patients in the intervention arm. The time to first change in antibiotic regimen was 42.8 hours in the intervention arm and was 64.0 hours in the control arm. The two groups did not differ in the number of patients whose antibiotics were changed, length of stay, or hospital mortality.

Conclusions: Immediate incubation of blood cultures decreases the amount of time until growth and decreases the amount of time until specific antibiotic therapy can replace empirical therapy, but it does not appear to decrease morbidity or mortality.

Reviewer's Comments: Switching to specific therapy may have greater implications by decreasing the use of broad spectrum empirical therapy that fosters emerging resistance. (Reviewer-Mary T. Galgano, MD).

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Keywords: Automated Incubation of Blood Cultures

Print Tag: Refer to original journal article
High-Risk HPV Lacking in Esophageal Basaloid SCC


Basaloid squamous cell carcinomas of the esophagus are not related to human papillomavirus infection. In this study, patients with these tumors had a significant smoking history.

**Background:** Human papillomavirus (HPV) is the etiologic agent of a number of human malignancies, including squamous cell carcinoma (SCC) of the cervix, anus, and head and neck. Its relationship to SCC of the esophagus is controversial. Studies of HPV prevalence with these tumors have shown widely disparate results ranging from 0% to 70%. Basaloid SCCs are variants of SCCs that lack keratinization, are high-grade, and are composed of predominately basaloid-type cells with little cytoplasm. These tumors have been noted in the head and neck and within the anus to be associated with HPV infection. They also have been reported in the esophagus where they are rare.

**Objective:** To investigate the prevalence of HPV in basaloid esophageal SCCs.

**Methods:** Nine cases of esophageal basaloid SCC seen at 1 institution were reviewed. These cases conformed to previous definitions of the histology. Twenty-two control nonbasaloid SCCs were also retrieved. In situ hybridization (ISH) was performed for HPV. Immunohistochemistry was performed with antibodies to p16, cyclin D1, and p53. Staining was scored semiquantitatively.

**Results:** The 9 basaloid SCCs were from 3 women and 6 men with a mean age of 63 years. All patients had a significant smoking history, and one-third had significant drinking histories. No significant differences were present when compared to the control group. All tumors were uniformly negative for HPV by ISH. No tumors showed strong diffuse immunoreactivity with antibodies to p16 as is typically seen with HPV-related tumors. Indeed, basaloid SCCs were more likely than keratinizing tumors to show a complete absence of p16 immunoreactivity. Cyclin D1 staining was similar for both groups and was weak. Interestingly, p53 immunoreactivity was seen in both tumors but tended to be stronger and diffuse in keratinizing tumors.

**Conclusions:** Unlike basaloid SCCs of the head and neck, those of the esophagus are not related to HPV infection. Indeed, HPV infection with esophageal SCC appears to be very uncommon. There may be some molecular differences between the tumors, however, as esophageal basaloid SCCs appear to be more likely to have lost p16 expression, whereas keratinizing SCCs are more likely to overexpress p53 protein.

**Reviewer's Comments:** Although the literature varies, HPV infection appears not to be related to most esophageal SCCs, just as is the case with SCCs of the lungs. Non-HPV-related basaloid SCCs are typically bad actors wherever they occur. (Reviewer—Edward B. Stelow, MD).

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Keywords: Squamous Cell Carcinoma, Human Papillomavirus

Print Tag: Refer to original journal article
There may be a slight increased risk for prostate cancer developing in men who are infected with *Trichomonas vaginalis*.

**Background:** Chronic inflammatory conditions are frequently associated with the development of malignancies. Examples include (1) chronic inflammatory bowel disease and the development of colorectal adenocarcinomas and (2) *Helicobacter pylori*-induced gastritis and the development of gastric cancer. Some have even suggested that chronic inflammatory conditions may be related to the development of prostate cancer in men, and others have shown the presence of serum antibodies to *Trichomonas vaginalis* (TV) is associated with the subsequent development of prostatic adenocarcinomas. This infection in men is relatively uncommon, but it is an occasional cause of nongonococcal urethritis. Often, infection may even be asymptomatic. While the acute infection may involve the urethra, occasional chronic infections have been noted with the organisms as well as inflammatory changes within the prostate.

**Objective:** To further investigate the relationship between TV serostatus and prostate cancer incidence.

**Methods:** Men who had given blood samples from the Physicians’ Health Study were evaluated. The study included 673 patients who developed prostate cancer and 673 control patients who did not. Plasma was tested for IgG antibodies to TV. Case and control results were compared.

**Results:** The average patient age was 69 years. Of case patients, 25% had IgG antibodies to TV, whereas 21% of controls were seropositive for antibodies to TV. Although the odds ratio for the development of prostate cancer was greater for seropositive individuals at 1.23, these results were not statistically significant. However, the odds ratio for the development of high-stage disease was 2.17, and the odds ratio for death or metastatic disease was 2.69; both of these ratios were found to be statistically significant.

**Conclusions:** This large case-control study provides further evidence that TV infection may be related to the development of prostate cancer. Of interest, the relationship seems greatest for clinically significant prostate cancer, that is, prostate cancer with extraprostatic spread, metastasis, and lethal disease.

**Reviewer’s Comments:** It seems unlikely to this reviewer that TV infection is truly related to prostate cancer, especially given the prevalence of prostate cancer. Perhaps the obstructive symptoms caused by cancer or hyperplasia make the individual more likely to develop TV infection. (Reviewer-Edward B. Stelow, MD).

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Keywords: Cancer, *Trichomonas vaginalis*, Inflammation

Print Tag: Refer to original journal article
For patients with RET proto-oncogene mutations and no clinical signs or symptoms of medullary thyroid carcinoma, total thyroidectomy with cervicocentral lymphadenectomy is sufficient prophylactic treatment.

**Background:** Medullary thyroid carcinoma (MTC) comprises approximately 5% of thyroid malignancies. Most cases are sporadic, while approximately 25% are due to RET proto-oncogene mutations (codon 634 most common site of mutation). Of these familial cases with RET proto-oncogene mutations, most are associated with the multiple endocrine neoplasia (MEN) syndrome, type 2A. Since the initiation of screening programs for individuals at-risk for developing MTC based on family history, the issue of determining the best therapy for such individuals arises. The main surgical treatment considerations to date include total thyroidectomy or total thyroidectomy plus neck dissection (lymphadenectomy).

**Objectives:** To determine whether so-called “prophylactic” total thyroidectomy plus bilateral cervicocentral lymphadenectomy is an adequate treatment for patients who have laboratory proven RET proto-oncogene mutations involving codon 634. **Methods:** The authors studied 17 patients (median age, 13 years) who underwent total thyroidectomy with bilateral cervicocentral lymphadenectomy procedures for known RET proto-oncogene mutations involving codon 634. “Cervicocentral” lymphadenectomy involved methodical dissection of all lymphoid tissue within the cervicocentral compartment, which extends from the hyoid bone to the sternum. No patient had any signs or symptoms of thyroid tumor at the time of surgery. For follow-up, patients and their general practitioners were contacted for telephone interviews. Among the data collected and analyzed were baseline and current calcitonin levels, overall survival, and disease-free survival.

**Results:** Classification of pathologic findings in the thyroidectomy specimens included C-cell hyperplasia (n=3 or 18%); MTC, size T1 neoplasms <1 cm (n=12 or 71%); and MTC, size T1 neoplasms >1 cm (n=2 or 12%). Two patients had evidence of lymph node metastases (12%), and recurrent disease developed. Two patients had elevated postoperative calcitonin levels. One patient’s calcitonin did not fall to baseline levels after initial surgery and required an additional procedure. The second patient continues to have elevated serum calcitonin levels even after multiple operations for MTC.

**Conclusions:** Total thyroidectomy with bilateral cervicocentral lymphadenectomy serves the purpose of “prophylactic” treatment for patients with RET proto-oncogene mutations. If serum calcitonin levels fail to normalize or increase after initial surgery, cervicolateral lymphadenectomy is then indicated.

**Reviewer’s Comments:** For the pathologist, this article reinforces the fact that curative treatment for MTC is still surgical. It seems, however, that the indication for lymphadenectomy in such cases is less clear. As with other specimens encountered under the heading of “prophylactic surgical pathology,” such as bilateral salpingo-oophorectomy specimens from BRCA mutation carriers, pathologists must take great care in the gross examination and microscopic sampling of such thyroidectomy cases. (Reviewer-T. David Bourne, MD).

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Keywords: Medullary Thyroid Carcinoma, Prophylactic Thyroidectomy

Print Tag: Refer to original journal article
Take 6 Biopsies When Suspect Tumor at Colonoscopy

What Is the Optimal Number of Biopsies to Diagnose a Tumor Found During Colonoscopy?

Colleypriest BJ, Marden PF, Linehan JD:

J Clin Gastroenterol 2009; 43 (10): 1012-1013

Six may represent the optimal number of biopsies to take during colonoscopy for a diagnosis of colon cancer. Six or more biopsies collected during the index colonoscopy have a sensitivity of 98%.

Background: Gastroenterologists sometimes face the dilemma of not knowing how many biopsies to take of a lesion encountered during colonoscopy to maximize the chances of providing diagnostic material to the pathologist. To minimize the need for repeat colonoscopy to obtain additional tissue samples, a decision which carries inherent risks and patient inconvenience, determining the optimal number of biopsies to initially collect is a key decision. There are reportedly no current guidelines that recommend such an optimal biopsy number.

Objectives: To determine the optimal number of biopsies to collect during colonoscopy when a suspected tumor is encountered.

Methods: The authors retrospectively reviewed all endoscopy (colonoscopy) reports during a 26-month period and identified cases of suspected cancer. For these cases, the authors collected the colonoscopy reports, the pathologic findings from biopsy, and the pathologic findings from subsequent surgical resection specimens. The patients were then classified into 1 of 2 groups: patients with suspected carcinoma for whom a diagnosis of colon cancer was rendered from the initial set of biopsies, and patients with suspected carcinoma for whom a definitive diagnosis of cancer was only possible after biopsies from a repeat colonoscopy or surgical resection specimen. For each group, the number of biopsies taken during each colonoscopy was analyzed using a Mann-Whitney test. Sensitivities for correctly diagnosing colon cancer were then calculated for each individual number of biopsies.

Results: Of 217 patients, 198 had a histologic diagnosis of colon cancer. Of these, 182 were correctly diagnosed with colon cancer based on the initial index biopsies. The remaining 16 patients required either repeat colonoscopy with biopsy or surgical resection for a definitive diagnosis. For these 16 cases, the mean number of biopsies taken (4.25; 95% CI 3.39-5.10) was significantly lower than the mean number of biopsies taken from patients for whom the diagnosis was correctly made after the initial biopsies (5.72; 95% CI 5.45-6.00; \(P=0.0020\)). Taking at least 6 biopsies during the index colonoscopy had a sensitivity of 98% for a diagnosis of colon cancer.

Conclusions: Six biopsies represent the minimum number of biopsies recommended for a diagnosis of colon cancer when a suspected tumor is found during colonoscopy.

Reviewer’s Comments: Given the widespread use of colonoscopy and biopsy, it is surprising that there appears to be a paucity of data to support guidelines for gastroenterologists regarding the optimal number of colon biopsies to take at the time of index colonoscopy. This topic may be an interesting one to discuss with your gastroenterology colleagues. (Reviewer-T. David Bourne, MD).

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Keywords: Colon Cancer, Diagnosis, Biopsies

Print Tag: Refer to original journal article