Atypical bare nuclei on ThinPrep Pap tests are associated with high-grade lesions (HSIL or worse).

**Background:** Naked nuclei in cervical Pap tests are a well-recognized finding. They are usually bland-looking and associated with atrophy, stripped endocervical cells, or cytolysis. However, atypical bare nuclei are rarely seen, and the clinical significance of this finding is uncertain.

**Objective:** To review cases of ThinPrep® Pap tests with atypical bare nuclei to determine if they are associated with clinically significant lesions.

**Methods:** 4736 ThinPrep Pap tests over 1 year were reviewed for the presence of bare nuclei. Bare nuclei were considered atypical if they had completely lost their cytoplasm and had any of the following criteria: hyperchromasia, irregular nuclear contours, coarse and irregular chromatin, or variation in nuclear size and shape. Bare nuclei associated with cytolysis or atrophy were excluded. The Pap tests with atypical bare nuclei were reviewed for bare nuclei features and any other squamous or glandular abnormalities. Tissue biopsies, when available, were reviewed.

**Results:** 10 cases (0.2%) demonstrated atypical bare nuclei in the absence of cytolysis or atrophy. The Pap test interpretation was high-grade squamous intraepithelial lesion (HSIL) in 9 cases and was endometrial adenocarcinoma in 1 case. No cases were associated with low-grade intraepithelial lesion (LSIL). Eight cases had histologic follow-up confirming a diagnosis of cervical intraepithelial neoplasia grade 3 in 7 cases, 5 of which had endocervical glandular involvement. Endometrial biopsy demonstrated uterine papillary serous carcinoma in the last case. All cases showed single atypical bare nuclei, and 2 also had clustered nuclei. The nuclei were round to oval in all cases and were predominantly small (same size as intermediate cell nucleus) to intermediate in size (size >2 times that of an intermediate cell nucleus). Prominent nucleoli were not present in any case.

**Conclusions:** The presence of atypical bare nuclei on a ThinPrep Pap test is associated with HSIL or worse, but not with LSIL. This finding may also suggest the possibility of endocervical gland involvement by HSIL.

**Reviewer's Comments:** The most difficult and unanswered question by this study is what to do when atypical bare nuclei are present on a Pap test with otherwise unremarkable findings. This is particularly important as these results suggest that this finding is associated with a high-grade lesion. In our laboratory, if bare nuclei are seen in the absence of atrophy, cytolysis, or other diagnostic findings, many of our cytopathologists will report a diagnosis of atypical squamous cell of uncertain significance to ensure close follow-up and HPV testing. (Reviewer-Deborah J. Chute, MD).

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Keywords: Neoplasms, ThinPrep Pap Tests, Atypical Bare Nuclei

Print Tag: Refer to original journal article
MF and SS Treatment Depends on Stage of Disease

How I Treat Mycosis Fungoides and Sézary Syndrome.

Prince HM, Whittaker S, Hoppe RT:

Blood 2009; 114 (November 12): 4337-4353

To correctly manage mycosis fungoides and Sézary syndrome first requires an accurate diagnosis. Treatment requires an individualized approach that depends, in part, on the stage of disease.

**Background:** The most common forms of cutaneous T-cell lymphoma (CTCL) include mycosis fungoides (MF) and its leukemic variant Sézary syndrome (SS). Management relies on a stage-based approach. Stage I is defined as skin patches and plaques (body surface area involved: IA <10%; IB ≥10%). Clinically evident lymphadenopathy without pathologic nodal infiltration defines stage IIA, cutaneous tumors define stage IIB, generalized erythroderma defines stage III, pathologically positive nodes define stage IVA, and visceral disease represents stage IVB. In the clinically based system, limited-stage disease encompasses stages IA, IB, and IIA, while advanced-stage disease incorporates everything else. While considered incurable, MF/SS usually behaves in an indolent manner, and most MF patients present with stage IA/B disease. **Early-Stage MF:** A nonaggressive approach is aimed at improving symptoms and cosmesis while limiting toxicity. Initial treatment consists of skin directed therapy (SDT), including topical or intralesional corticosteroids, psoralen plus ultraviolet A radiation (PUVA), or ultraviolet B (UVB). Topical steroids often control the disease for many years. Although CTCLs are highly radiosensitive, eradication of disease is not possible. However, radiation provides excellent palliation of symptoms. **Advanced-Stage Disease:** Treatment of this condition is more problematic. SDT or biologic response modifying agents should be used before systemic chemotherapy. The authors of this study design separate treatments for patients with stage IIB, III/SS, IV and transformed disease. Second-line agents include interferon-α, bexarotene, vorinostat, and denileukin diftitox. Systemic agents include alkylating agents, anthracyclines, purine analogs, and etoposide. Chemotherapy produces high response rates, but the responses are not durable. Stem cell transplantation may induce complete and durable responses, but infection rates are high. **Transformed Disease:** Transformed disease can be due to either increasing depth of the small atypical lymphocytes or as a result of large-cell transformation. Biopsy is critical in these cases. For younger patients, systemic chemotherapy is instituted early with consideration of transplantation. In the elderly or in frail patients with unifocal disease, local radiation therapy is used. **Sézary Syndrome:** These patients are either stage III or IV. Management is hampered secondary to severe pruritus, high risk of infection, and frequent relapses. Treatment is similar to advanced-stage MF. However, extracorporeal photophoresis (ECP) is more effective in SS than other stages of MF. Patients with SS and circulating lymphocytes should have an initial trial with ECP. Second-line therapies and clinical trials are also under investigation.

**Reviewer's Comments:** These diagnoses require clinicopathologic correlation. It is important for us as pathologists to understand the treatment implications of these diseases. (Reviewer-William A. Kanner, MD).

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Keywords: Mycosis Fungoides, Sézary Syndrome

Print Tag: Refer to original journal article
CD10 Confirms VD Tissue in Vasectomy Specimens

Use of Immunohistochemical Markers to Confirm the Presence of Vas Deferens in Vasectomy Specimens.

Sasaki K, Bastacky SI, et al:


CD10, as well as pankeratin, may be helpful in confirming the presence of vas deferens tissue in suboptimal vasectomy specimens.

Background: Some urologists routinely send vasectomy specimens for pathologic evaluation and confirmation that a complete transverse section of the vas deferens (VD) was removed. Because of suboptimal orientation during embedding, epithelial denudation, or other factors, confirmation of VD tissue is sometimes challenging. It has been previously reported that CD10 is relatively sensitive (although not specific) for wolffian-derived tissues, including epithelia of the prostate, seminal vesicles, vas deferens, and epididymis.

Objective: To determine whether CD10 is useful in confirming the presence of VD tissue in vasectomy specimens.

Methods: 103 consecutive vasectomy specimens were collected from the University of Pittsburgh Department of Pathology archives. All tissue samples were submitted to the histology laboratory unsectioned and fixed in 10% formalin. Individual specimens were each sectioned at the time of initial embedding. H&E staining was performed, and all cases were then reviewed by 3 pathologists. Tissues from radical prostatectomy and orchiectomy specimens were also examined (VD, seminal vesicle, ejaculatory duct, prostate, and spermatic cord). Immunohistochemical (IHC) staining using antibodies against CD10, pankeratin, and CD31 was performed on all samples. The percent of cells staining positive was scored semiquantitatively as follows: score of 0, <5% of cells staining; score of 1+, 5%–10% of cells staining; score of 2+, 11%–50% of cells staining; and score of 3+, >50% of cells staining.

Results: 92 of the 103 vasectomy cases (89.3%) had identifiable surface columnar epithelial and basal cells for IHC analysis. CD10 showed strong apical and membranous staining of surface epithelial cells in all cases (score of 3+, 99%) and cytoplasmic staining in basal epithelial cells in most cases (score of 3+, 95%). Pankeratin showed strong membranous and cytoplasmic staining in apical (3+, 92%) and basal layers (3+, 96%). CD31 did not show any epithelial cell staining. Of the 103 cases, 11 (10.7%) were difficult to recognize as VD tissue on H&E-stained sections. CD10 and pankeratin highlighted the thinned or distorted epithelium in all of these cases. All separate wolffian duct tissues were CD10-positive.

Conclusions: CD10 and pankeratin can be used to confirm the presence of VD in vasectomy specimens with thinned or distorted epithelium.

Reviewer's Comments: While immunostains cannot solve true embedding problems, the results of this practical study support the utility of CD10 and pankeratin in confirming the presence of VD epithelium in difficult cases. In case of a medicolegal complaint, histologic examination can certainly help confirm that the surgeon initially performed a complete transection. (Reviewer-T. David Bourne, MD).

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Keywords: Vasectomy, Vas Deferens in Specimens, Identifying

Print Tag: Refer to original journal article
**Background:** Morphologic overlap between breast and ovarian carcinomas can occasionally provide a difficult diagnostic dilemma. A panel of immunohistochemical (IHC) stains may be employed, but results are frequently not conclusive. Given the novel use of PAX 2 as a marker for ovarian serous carcinomas (OSC) and other müllerian lesions, its profile in breast cancers is of great interest, especially the micropapillary subtype.

**Objective:** To characterize the expression of PAX 2 in primary breast carcinomas with a comparison to various müllerian lesions.

**Methods:** Tissue microarrays of conventional breast carcinoma as well as those designated micropapillary, mixed micropapillary, or “with notable retraction artifact” were used for PAX 2 IHC staining. In addition, a variety of müllerian tissues were stained for comparison, including 5 breast metastases of OSC (confirmed with nuclear WT-1 staining).

**Results:** All 89 breast carcinomas were negative for PAX 2, and all 5 OSC metastatic to the breast were positive for moderate to strong nuclear staining. OSC, ovarian clear cell, and uterine papillary serous carcinomas (UPSC) were frequently positive for PAX 2, but some cases were weak and/or focal. Only a few endometrioid adenocarcinomas of the endometrium were positive. Endocervical adenocarcinomas, ovarian Brenner tumors, and pleural mesotheliomas were generally negative. Normal and benign epithelia of ovary, fallopian tube, and endometrium were also positive.

**Conclusions:** PAX 2 staining may prove to be a valuable marker of müllerian carcinomas and lends support for a diagnosis of ovarian carcinoma rather than breast carcinoma. While not entirely sensitive, PAX 2 stained many OSC, ovarian clear cell carcinomas (although weak), and UPSC, but none of the breast carcinomas.

**Reviewer’s Comments:** PAX 2 seems to have better specificity than sensitivity since not all cases of OSC (or clear cell carcinoma) were positive and some were focal or weakly positive. Not surprisingly, uterine serous carcinomas had a staining profile similar to OSC. One might assume that primary fallopian tube and peritoneal serous carcinomas would also be positive, but these were not evaluated. (Reviewer-Mary T. Galgano, MD).

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Keywords: Metastasis vs Primary Cancer

Print Tag: Refer to original journal article
Primary screening for cervical intraepithelial lesions using DNA testing and follow-up triaging is at least as specific as primary cytology screening.

**Background:** Cervical intraepithelial neoplasia (CIN) and cancer of the cervix develop secondary to infection by oncogenic human papillomavirus (HPV). DNA testing for these viruses is currently used most often for triaging patients with atypical Pap tests. It has also been suggested that DNA testing be used as a primary screening method. Furthermore, due to the high sensitivity of DNA testing and its high negative predictive value, it has been suggested that the test could be used to extend screening intervals.

**Objective:** To investigate the age-specific performance of primary HPV screening versus cytology.

**Methods:** This study was conducted in Finland where women are invited to be screened for cervical neoplasia every 5 years. For 3 years, women were invited to be screened either by HPV DNA testing followed with cytology triage or by conventional cytology testing. Women in the conventional screening program had conventional Pap smears. Women assigned to the HPV DNA primary screening arm underwent testing by Hybrid Capture 2 (HC2). This was done with material collected by the HC2 brush after a routine smear was made. These smears were only evaluated for women with positive HPV tests. Based on standard guidelines and the doctors’ discretion, follow-up was performed with colposcopy and loop electrosurgical excision.

**Results:** >35,000 women were included in both arms of the study. In the HPV screening arm, 7% had abnormal HPV tests. Of these, >20% had abnormal cytology. Approximately, 7% of those undergoing conventional screening had abnormal Pap smears. However, the number of women referred to colposcopy in both arms was slightly >400. About 40% more cases of CIN II or worse were found in the HPV primary screening group. Thus, HPV screening alone had a lower specificity than conventional Pap smear screening. However, HPV screening with cytology triaging had a similar overall specificity with greater specificity in older age groups. HPV screening with cytology triage had a higher positive predictive value than cytology screening in all age groups.

**Conclusions:** Not only is primary HPV screening more sensitive than conventional Pap smear screening, it also has a similar specificity when it is coupled with cytology triaging.

**Reviewer’s Comments:** A number of studies are now being reported that suggest HPV testing as the primary screening test for cervical neoplasia. Unfortunately, these studies use inconsistent smear technologies (this study uses conventional smears) and do not have definitive triage policies for women with abnormalities. (Reviewer-Edward B. Stelow, MD).

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Keywords: Cervical Carcinoma, HPV, Pap Test, DNA

Print Tag: Refer to original journal article
The Gleason grading system has been revised and refined as the use of PSA screening has become widespread and as our understanding of the morphologic spectrum and outcomes of prostate cancer has improved.

**Background:** There has been a shift in disease staging toward low-volume, low-stage prostate cancer. This has resulted in important changes and practices in the Gleason grading of prostate cancer. **Objective:** To summarize current perspectives on the Gleason grading of prostate cancer. **Discussion:** First, a diagnosis of Gleason grade 1 or 2 should rarely, if ever, be made on a prostate biopsy. In practice, prostatectomy specimens almost always demonstrate higher grade tumor. From a practical standpoint, Gleason grading starts with pattern 3, that of variably sized individual glands infiltrating between benign glands. Second, most cribriform carcinomas are Gleason pattern 4. This histologic pattern includes large cribriform glands and cribriform glands with irregular borders or with ductal differentiation. It is associated with an aggressive course, and if comedonecrosis is present, a pattern of 5 should be considered. A pattern of 3 is reserved only for well-rounded, circumscribed cribriform glands that are the same size as normal glands. A Gleason grade of 4 should also be diagnosed for a large cluster of poorly formed glands without obvious lumina, that which is outside the spectrum of tangential sectioning. The reporting of Gleason grading, depending on how the cores are received, has also been reviewed. If the cores are received separately, it is fitting to assign a total Gleason score for each core. There are no guidelines addressing overall grading if the cores are combined for each side of the prostate. At our institution, we give a diagnosis that represents the “global” Gleason score for each side, representing the highest patterns seen among all cores. For management issues, it is important to report the highest pattern, even if it does not represent the primary or secondary pattern. Likewise, it is important to quantify the amount of the highest pattern. Intraductal carcinoma of the prostate (IDC-P) is a new and important entity. It is defined as “malignant epithelial cells filling large acini and prostatic ducts with at least partial preservation of basal cells forming either solid or dense cribriform patterns or loose cribriform/micropapillary patterns with either marked nuclear atypia or comedonecrosis.” There is currently no standard reporting format, but at a minimum, this entity should be reported due to its association with high-grade invasive cancer. Finally, the grading of unusual subtypes of prostate adenocarcinoma is discussed.

**Reviewer's Comments:** This article summarizes the current state of practice as well as the issues that we currently face in prostate biopsies in terms of Gleason grading and reporting. (Reviewer-Stacey E. Mills, MD).
Background: In recent years, sentinel lymph node (SLN) biopsy has become standard of care in select breast cancer patients to replace axillary lymph node dissection (ALND). Pathologists have intensified the protocols for handling these nodes, including serial sectioning, multiple levels, and immunohistochemical staining. One concern is that this may result in increased detection of tumor-affected lymph nodes and a resultant stage migration of these patients.

Objective: To evaluate the lymph node status of patients undergoing current therapy compared to a historic group from before SLN biopsy.

Methods: Breast cancer patients were prospectively enrolled during an 18-month study interval. Patients underwent SLN biopsy if there was clinical tumor size <5 cm, no clinical evidence of nodal disease, and no preoperative therapy. The control group consisted of a historical group treated for breast carcinoma in 1994 that underwent ALND. In both groups, women with T4 or M1 disease were excluded. SLNs were examined by multiple H&E sections and CAM5.2 staining. Completion ALND was performed in all women with a positive SLN biopsy. Positive lymph nodes were classified as isolated tumor cells (ITCs; <0.2 mm), micrometastasis (0.2–2.0 mm), or macrometastasis (>2.0 mm). For statistical analysis, the final lymph node stage was simplified to N0 and N1 disease. ITCs were classified as N0 disease (according to the 2002 staging criteria) or as N1 disease (according to the 1997 staging criteria).

Results: 284 patients underwent SLN biopsy, and an additional 76 underwent immediate ALND due to contraindications for SLN biopsy. The control group consisted of 88 historical patients who underwent ALND. When ITCs were considered N1 disease, 185 patients (51%) in the SLN group and 39 patients (44%) in the historical group had N1 disease (P=0.04). However, when ITCs were considered N0 disease, there was no significant difference in N1 disease between the 2 groups (SLN group, 43%; controls, 39%). After correcting for age, tumor size, and histologic grade, the difference remained nonsignificant. Conclusion: Introduction of the SLN biopsy in breast cancer patients with intensified workup by pathologists has led to the detection of more tumor-affected lymph nodes. However, using the 2002 staging criteria, there has been no stage migration, as isolated tumor cells are categorized as node-negative disease.

Reviewer's Comments: The clinical significance of isolated tumor cells in axillary lymph nodes remains uncertain. Currently, data are conflicting on whether these cells are an independent predictor of outcome. (Reviewer—Deborah J. Chute, MD).

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Keywords: Sentinel Lymph Node, Micrometastasis

Print Tag: Refer to original journal article
Nodular fasciitis (NF) is a benign reactive process composed of fibroblasts/myofibroblasts in a haphazard pattern.

**Objective:** To present a clinicopathologic description of NF in the head and neck region.

**Methods:** 30 cases of NF diagnosed in the head and neck region were culled from 3 medical centers, and the clinicopathologic features were reviewed.

**Results:** 18 patients were male. The mean patient age was 37 years (range 3-71 years), and 25 patients were older than age 18 years. The median lesion size was approximately 1 cm. The lesions occurred predominantly in the neck, forehead, cheek, and lip. No cases had an antecedent history of trauma. Most cases consisted of incomplete biopsies or excisions. Half the cases had clinical follow-up (range, 3 months to 2 years), and only 1 documented recurrence was noted. On microscopic examination, the lesions varied from hypocellular with myxoid change to hypercellular with varying amounts of collagen production. A zonated architectural pattern was also present in many cases. Cytologically, these cells were spindled to stellate in shape with moderate amounts of cytoplasm. The nuclei were not irregular, and they demonstrated pale chromatin and small nucleoli. In all cases, there was at least focal myxoid change, often with cystic spaces. Mitotic figures were rare, and no atypical mitotic figures were noted. The vascular findings included fine capillaries lined by plump endothelial cells (no staghorn pattern) and extravasated red blood cells. In 2 cases, the lesion was completely intravascular. Osteoclast-type giant cells and ganglion cells were present in most cases. Two cases were adjacent to salivary glands with the lesion appearing to entrap the normal glands. Importantly, one-third of cases demonstrated focal and superficial involvement of skeletal muscle. All tested cases demonstrated strong and diffuse reactivity to smooth muscle actin. Negative markers included S-100, desmin, CD34, CD68, and Factor XIIIa.

**Differential diagnoses:** The various differential diagnoses include leiomyosarcoma, low-grade myofibroblastic sarcoma, salivary gland tumors, chronic sclerosing sialadenitis, benign fibrous histiocytoma, schwannoma, DFSP, desmoid fibromatosis, tumefactive fibroinflammatory lesions, inflammatory myofibroblastic tumor, and myofibroma.

**Conclusions:** While NF has a similar histologic presentation as in other areas, NF in the head and neck region is distinctive for being smaller in size, having more prominent skeletal muscle invasion and demonstrating strong and diffuse actin positivity.

**Reviewer’s Comments:** This article is important and practical since its authors thoroughly discuss a benign reactive lesion that is often not considered in the head and neck region. (Reviewer-William A. Kanner, MD).

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Keywords: Nodular Fasciitis, Head & Neck

Print Tag: Refer to original journal article
The authors have identified a new antibody that may be useful in the diagnosis of autoimmune pancreatitis.

**Background:** Autoimmune pancreatitis, a rare disorder, is an inflammatory condition of the pancreas that leads to organ dysfunction. In some cases, autoimmune pancreatitis may mimic pancreatic carcinoma.

**Objective:** To identify a serum biomarker that can distinguish autoimmune pancreatitis from pancreatic adenocarcinoma using a molecular biology approach.

**Methods:** The authors screened a random peptide library with pooled IgG obtained from 20 patients with autoimmune pancreatitis. Testing and validation were also performed on other patient groups, including 40 patients with histologically confirmed pancreatic adenocarcinoma, 18 patients with intraductal papillary mucinous neoplasms (IPMNs), 21 patients with alcohol-related pancreatitis, 1 patient with systemic sclerosis, and 1 patient with rheumatoid arthritis. The control group consisted of 40 healthy age- and gender-matched adults. Peptide-specific antibodies were then measured in serum specimens obtained from the study patients.

**Results:** A protein called autoimmune pancreatitis peptide (AIP1-7) was recognized in serum specimens from 18 of 20 patients with autoimmune pancreatitis and in the serum from 4 of 40 patients with pancreatic cancer. This protein was not found within serum from the healthy controls. The AIP peptide showed homology with a protein called ubiquitin-protein ligase E3 component n-recognin 2 (UBR2), which is an acinar cell enzyme highly expressed in pancreatic acinar cells, as well as with an amino acid sequence of plasminogen-binding protein (PBP) of *Helicobacter pylori*. Anti-PBP antibodies were detected in 19 of 20 patients with autoimmune pancreatitis (95%) and in 4 of 40 patients with pancreatic cancer (10%). This reactivity was not detected in patients with IPMNs or with alcohol-related chronic pancreatitis. The above results were then validated in a second series of patients with either autoimmune pancreatitis or pancreatic cancer. When results from the initial test group and following validation groups were combined, the test was positive in 33 of 35 patients with autoimmune pancreatitis (94%) and in 5 of 110 patients with pancreatic cancer (5%).

**Conclusions:** One of the identified antibodies, AIP1-7, is detectable in about 95% of patients with autoimmune pancreatitis. Since the antibody is also seen in approximately 5% of patients with pancreatic adenocarcinoma, it does not perfectly discriminate between these 2 conditions.

**Reviewer's Comments:** This topic is relevant to laboratorians and anatomic pathologists since initial testing from the clinical lab, in combination with the medical history and imaging findings, may occasionally prompt pancreatic fine-needle aspiration biopsy. Even now, some cases of probable autoimmune pancreatitis are referred to as sclerosing or tumefactive pancreatitis. (Reviewer-T. David Bourne, MD).

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Keywords: Autoimmune Pancreatitis

Print Tag: Refer to original journal article
Background: Criteria for evaluation of malignancy in smooth muscle tumors is site-specific and can be especially difficult in primary gynecological lesions, which are allowed more mitotic activity than their soft tissue counterparts. Some smaller reports have described the use of estrogen receptor (ER) and WT-1 for smooth muscle tumors, with positive reactions supporting a gynecological (GYN) site of origin. And once determined to be arising from the GYN tract, p16, p53 and Ki-67 have been proposed as biomarkers supportive of malignancy.

Objective: To evaluate the use of antibodies in the assessment of site of origin and malignancy in a large series of smooth muscle tumors.

Methods: 245 leiomyosarcomas (LMS), including 102 from the GYN tract, were incorporated into a tissue microarray (TMA) and subjected to immunohistochemistry. In addition, 49 uterine leiomyomas were evaluated. ER and WT-1 were positive if at least 5% of cells stained, while p16 and p53 were positive if at least 50% were moderately to strongly reactive.

Results: ER was positive in 50% of the GYN LMS and only 3% of the non-GYN LMS. Of the 4 positive non-GYN cases, 2 were pelvic and a GYN origin was not entirely excluded. The other 2 occurred in males in the recto-genital region. Of the GYN leiomyomas, 100% were ER-positive. Weak to moderate nuclear WT-1 staining was observed in 8% of GYN LMSs and none of the non-GYN LMSs. Cytoplasmic staining was observed in both groups, but without significant differences. Of the uterine leiomyomas, 67% were WT-1 positive. Specimens were positive for p53 in 23% of GYN LMSs, 17% of non-GYN LMSs, and none of the uterine leiomyomas. Positivity for p16 was seen in 87% of GYN LMSs, 90% of non-GYN LMSs, and 2% of the uterine leiomyomas. Visual analysis of Ki-67 staining (>10%) was observed in 65% of GYN LMSs, 71% of non-GYN LMSs, and none of the uterine leiomyomas.

Conclusions: Diffuse p16 and p53 staining with a 10% Ki-67 index is a sensitive and specific panel for confirming malignancy in smooth muscle tumors of the GYN tract. ER positivity is more helpful than WT-1 in demonstrating the origin as the GYN tract.

Reviewer's Comments: These biomarkers should be rigorously studied in the smooth muscle tumors of uncertain malignant potential (STUMP) with follow-up data to confirm their utility in histologically borderline lesions. (Reviewer-Mary T. Galgano, MD).

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Keywords: Smooth Muscle Tumors, Immunohistochemistry

Print Tag: Refer to original journal article
Detailed histologic typing of lung cancers can help distinguish second primary tumors from metastases.

**Background:** Non-small cell carcinomas are very heterogeneous, and most adenocarcinomas show diverse growth patterns with acinar, papillary, bronchioloalveolar, and solid growth. Recently, it has been shown that some of these growth patterns have particular molecular abnormalities. For example, the papillary and bronchioloalveolar patterns are more likely to be associated with epidermal growth factor receptor (EGFR) mutations. The histologic typing of tumors may be helpful for distinguishing second primary lung cancers from pulmonary metastases.

**Objective:** To discuss the use of current histologic subtyping for distinguishing these lesions and to compare this to molecular/mutational profiling.

**Methods:** Patients with at least 2 lung cancers seen at a single institution with available frozen tissue were included. Mutational profiling was used for genes within the EGFR signaling pathway, and genomic profiling was performed using comparative genomic hybridization array technology. Mathematical models were then used to classify tumors as metastases or separate primaries. All histologic material was reviewed, and tumors were classified based on histologic subtype. Paired tumors with similar histology were considered metastases.

**Results:** 42 tumors from 20 patients were studied. Fourteen patients had metachronous tumors. Molecular profiling classified 14 cases as separate primaries, 4 as metastases, and 4 as equivocal. Mutational profiling showed matching mutation in 8 pairs, including the 4 classified as metastases by molecular profiling. Nine pairs had discordant mutations. Results were consistent with mutational profiling in all cases in which both tests were performed. Thus, overall, 8 pairs were considered metastases. About 75% of the tumors were adenocarcinomas, and of these, a slight majority was considered papillary. Using percentages of the various growth patterns as well as other histologic features, such as lymphoid background, 8 pairs of tumors were regarded as histologically similar. Histologic assessment was similar to mutational/molecular profiling in 91% of the cases. Discordant results were discussed.

**Conclusions:** Comprehensive histologic assessment allows for the distinction of second primary lung cancers from metastases with results similar to molecular/mutational profiling. The authors suggest that this histologic assessment can be used to assist in guiding therapy.

**Reviewer's Comments:** It is not infrequent that we see patients with multiple synchronous or metachronous lung cancers. I would suggest that pathologists signing out lung cancers check out this article and familiarize themselves with the different growth patterns of lung adenocarcinoma. (Reviewer-Edward B. Stelow, MD).

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**Keywords:** Multiple Primaries vs Metastasis

**Print Tag:** Refer to original journal article
Tumor Seeding Risk Not Increased by CT-Guided Biopsy

Percutaneous Computed Tomography-Guided Lung Biopsy and Pleural Dissemination: An Assessment by Intraoperative Pleural Lavage Cytology.

Sano Y, Date H, et al:

Cancer 2009; 115 (December 1): 5526-5533

In patients with lung nodules, CT-guided lung biopsy does not increase the risk for the development of pleural recurrence.

**Background:** Radiographic imaging of lung nodules continues to improve so that smaller and smaller lesions are detected. As such, these lesions are often very difficult to characterize, and benign and malignant diseases are often considered within the differential diagnosis. Because the lesions also are frequently peripheral, transbronchial biopsy may not be an option and CT-guided biopsy may be needed to obtain tissue. Some doctors may worry that such biopsy techniques carry risk for needle tract seeding or pleural dissemination.

**Objective:** To review the risk of pleural dissemination using pleural lavage cytology performed at the time of surgery for patients with lung cancer.

**Methods:** Nearly 500 patients with primary lung cancer underwent surgery at a single institution during a 4-year study interval. Patients with macroscopic pleural effusions, dissemination, or severe adhesions were excluded. All CT-guided biopsies were performed using a 19-gauge introducer and a 20-gauge core biopsy needle. Two to four biopsies were obtained per case. Pleural lavage cytology was performed in all cases with material collected immediately on gaining access to the pleural cavity. Cases were classified by cytology as either positive or negative. Results were compared for patients who had versus those who had not undergone percutaneous CT-guided biopsy prior to surgery.

**Results:** Pleural lavage was available for >400 patients. Patients not undergoing antecedent biopsy outnumbered those undergoing biopsy. No patients developed chest wall recurrence at a median of 20 months. Pleural lavage cytology was slightly more commonly positive in the non-biopsy group (5%) than in the biopsy group (3%), although this difference was not statistically significant. Patients not having undergone biopsy were also slightly more likely to develop pleural or other recurrences (difference not statistically significant). Patients with slightly larger tumors were less likely to have undergone biopsy prior to surgery, although there were no overall differences in stages between the 2 groups.

**Conclusions:** Using predominately pleural lavage cytology results, the authors concluded that percutaneous CT-guided lung biopsy does not result in increased risk for the development of pleural recurrence.

**Reviewer's Comments:** Given the rather limited sensitivity of pleural cytology, especially in situations such as this, the lavage data are less interesting than the follow-up data. As expected, even using this data, surgeons and others need not worry about biopsy "seeding" with CT-guided biopsies. (Reviewer-Edward B. Stelow, MD).

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Keywords: Lung Nodules, CT-Guided Biopsy, Tumor Seeding

Print Tag: Refer to original journal article
PLA2 May Help Diagnose Neurologic Disorders

Cerebrospinal Fluid Secretory Ca2+-Dependent Phospholipase A2 Activity Is Increased in Alzheimer Disease.

Chalbot S, Zetterberg H, et al:

Clin Chem 2009; 55 (December): 2171-2179

PLA2 may be a useful biomarker for diagnosing and monitoring various neuroinflammatory diseases. A new way to reliably measure PLA2 activity in the serum and CSF has been developed.

**Background:** Phospholipase A2 (PLA2) enzymes are involved in the production of free fatty acids and other phospholipid molecules. The excessive production of physiologically active metabolites resulting from PLA2 activity is believed to contribute to various pathologic states. Since the brain has such a relatively high concentration of lipid, dysregulation of lipid metabolism and upregulation of PLA2 may be important disease effectors. This PLA2 upregulation is of interest in the context of various central nervous system diseases, including Alzheimer disease (AD). As of yet, there has been no simple, reproducible, and sensitive assay for the detection of PLA2 activity in cerebrospinal fluid (CSF).

**Objectives:** To develop and validate an assay for measuring PLA2 isoenzymes in CSF.

**Methods:** Serum and CSF samples were collected from 42 healthy individuals and 33 AD patients. Apolipoprotein E isoform testing was performed on all serum samples. An assay to measure the secretory form of PLA2 (sPLA2) activity was developed using fluorescence-labeled liposomes and a previously reported PLA2-specific substrate. CSF or serum samples were placed in 96-well microplates, to which fluorescence-labeled liposomes were then added. PLA2 activity was determined by measuring the intensity of fluorescence, which was performed over a 90-minute period. PLA2 activity was also assessed in the presence of differing calcium concentrations as a way to further characterize the PLA2 subtype. Validation assessments of test linearity, precision, and repeatability were conducted. Statistical analysis of the data was performed.

**Results:** Compared with the normal control group, the AD patient group had significantly higher levels of sPLA2 activity. The AD group had lower Mini-Mental State Examination scores and had a percentage of subjects found to be ApoE4 carriers. No ApoE4 carriers were identified in the control group. PLA2 activity in CSF did not correlate with either age or gender.

**Conclusions:** A reliable, reproducible, and relatively simple microplate assay for measuring secretory PLA2 isoenzymes in CSF has been developed. Increased CSF sPLA2 levels were identified in patients with Alzheimer disease compared with healthy controls. This biomarker may be useful in diagnosing and monitoring various neurologic disorders, such as AD.

**Reviewer’s Comments:** The findings are likely to prompt further investigation into the utility of measuring PLA2 enzyme activity in a variety of disease states. Its diagnostic role in Alzheimer disease, however, may be limited due to lack of disease specificity. (Reviewer-T. David Bourne, MD).

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Keywords: Phospholipase A2 Assay

Print Tag: Refer to original journal article
RAD51, a protein involved in DNA repair, appears to show increased expression in high-grade prostate cancer. Elevated RAD51 expression may help identify patients requiring urgent treatment.

**Background:** RAD51 is an enzyme encoded by the *RAD51* gene, and it plays an important role in repairing breaks in double-stranded DNA. The activity of the RAD51 protein is also associated with BRCA1 and BRCA2 proteins. BRCA1 is thought to be necessary for shuttling the RAD51 protein into the nucleus to the site of DNA damage, while BRCA2 is thought to play a more direct role with RAD51 in the repair process itself. The expression of RAD51 in prostate cancers from patients with and without *BRCA1/2* mutations has not been extensively studied.

**Objective:** To test the hypothesis that expression of the RAD51 protein is associated with *BRCA1/2* mutation-carrier status or with an aggressive phenotype of sporadic prostate cancer.

**Methods:** Prostate tumor samples were collected from 17 men harboring germline *BRCA1* or *BRCA2* mutations and from 119 men who had a low-probability of germline mutations (control group). RAD51 expression was examined in tumor samples from each case by immunohistochemistry.

**Results:** In general, RAD51 expression was higher within the cytoplasm and nuclei of tumor cells compared with benign prostatic tissue. Within the 2 groups of tumor patients, RAD51 cytoplasmic expression was significantly higher in patients with tumors having Gleason scores >7 (high-grade tumors). This finding was observed irrespective of the patient’s underlying *BRCA* mutation status. Compared with benign prostatic tissue, strong nuclear RAD51 expression was seen in all but the low-grade *BRCA*-associated prostate cancers.

**Conclusions:** RAD51 protein expression is increased in tumor cells relative to benign prostatic tissue. Among tumors, RAD51 shows increased expression in high-grade compared to low-grade prostate cancers. This increased expression appears independent of underlying *BRCA* mutation status.

**Reviewer’s Comments:** The authors suggest that RAD51 expression may help identify those patients who might require more timely and/or aggressive treatment for prostate cancer. However, RAD51 expression does not appear to be a better prognostic factor than Gleason grading. (Reviewer-T. David Bourne, MD).

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Keywords: Cancer, RAD51 Expression

Print Tag: Refer to original journal article
The Patho-TB kit was 95% sensitive and 100% specific for the detection of *Mycobacterium tuberculosis*. In labs with limited resources, the kit could be extremely useful, particularly in endemic areas.

**Background:** Tuberculosis (TB) is a serious health problem worldwide. The gold standard for diagnosis is sputum culture, but this can take weeks to months to provide a result. Direct examination of sputum smears stained with Ziehl-Neelsen (ZN) stain is the most commonly used rapid technique, but it is less sensitive when compared to culture. A sensitive and specific diagnostic test for the rapid detection of active TB infection would facilitate early treatment and prevent transmission. The Patho-TB™ kit is an antibody-based test for the detection of TB which is simple to perform, rapid, and inexpensive.

**Objective:** To evaluate the usefulness of the Patho-TB test in the diagnosis of active pulmonary TB compared with conventional techniques.

**Methods:** 79 patients with clinically diagnosed active TB and 21 non-TB control patients (admitted for asthma or chronic obstructive pulmonary disease) were enrolled. Sputum was obtained from each patient and direct smear examination, culture, and Patho-TB testing were performed. The bacilli load in ZN-stained smears was semiquantitated according to the American Thoracic Society’s recommendations (0–4+). Specimens were cultured on Löwenstein-Jensen media at 37°C for 16 weeks. The Patho-TB test used 200 µL of decontaminated sputum which was solubilized for 20 minutes and then passed through a filter. *Mycobacterium tuberculosis* (MT) antigens were immobilized on the filter, and rabbit anti-MTa IgG was added. A conjugate revealed a positive reaction by a red-pink color in the middle of the filter.

**Results:** All 79 clinical TB patients were positive by both smear examination and culture for MT. Of these patients, 75 (95%) were positive using the Patho-TB test. The 4 false-negative samples ranged from 1 to 4+ on the ZN smears. All control patients were negative for MT by smear, culture, and Patho-TB test. The sensitivity and specificity of the Patho-TB test were 95% and 100%, respectively. **Conclusion:** Patho-TB is a simple, rapid, and highly sensitive and specific test for the diagnosis of MT. The few false-negative results did not appear to be due to bacilli load, but may be due to poor solubilization of the MT antigen or mutation of the targeted antigen.

**Reviewer's Comments:** Accurate sputum examination by microscopy requires significant time, technician training, and sophisticated equipment. In laboratories where resources are limited, the Patho-TB test could be extremely useful, particularly in endemic areas. (Reviewer-Deborah J. Chute, MD).

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Keywords: Tuberculosis, Rapid Detection

Print Tag: Refer to original journal article
Most organ-confined Gleason score 6 prostate cancers that progress are initially inaccurately graded or staged. Careful attention to pathologic grading and staging is critically important.

**Background:** Radical prostatectomy (RP) is the treatment of choice for men with clinically localized prostate cancer (PC). Men with organ-confined (OC) disease and a low Gleason score (score ≤6) have a favorable overall prognosis after RP. However, a small subset of these patients will have recurrence.

**Objective:** To examine a large cohort of patients with PC coded by the urologist as OC Gleason score ≤6, with specific attention to the subset of patients with biochemical recurrence after RP.

**Methods:** 2551 patients with OC Gleason score 6 PC were identified with at least 1 year of follow-up. The median follow-up was 3 years. Clinical follow-up data were obtained, and biochemical recurrence was defined as a single PSA level of ≥0.2 ng/mL after RP. All patients with biochemical recurrence were re-examined histologically; the prostates were initially serially sectioned and totally submitted for evaluation. Cases were reviewed for Gleason score, Gleason grade, extra-prostatic extension (EPE), and margin status.

**Results:** 38 patients (1.5%) developed biochemical recurrence during follow-up. Histopathologic examination demonstrated that 27 of these cases with recurrence (71%) were incorrectly scored or staged according to the urologists' coding. The most common error was a missed component of Gleason grade 4 disease: 15 tumors were re-classified as Gleason score 7, 5 of which also had EPE. An additional 9 tumors were primarily Gleason score 6, with a tertiary component of Gleason grade 4. One tumor was Gleason score 6 with EPE, and 2 tumors were Gleason score 6 with OC disease but positive margins due to an intra-prostatic incision. Finally, 11 patients with recurrence (29%) had confirmed OC and low Gleason score disease; most of these patients had very low PSA levels and/or >8 years to progression. Of note, the correct information was contained in the pathology report in 6 cases and incorrectly coded by the urologists (4 cases with tertiary grade 4 and both cases with positive margins).

**Conclusions:** Most cases of organ-confined, Gleason score ≤6 prostatic carcinomas with progression are under-graded, under-staged, or suffer from situations with ambiguous staging. True organ-confined Gleason score 6 tumors have a low likelihood of progression (0.4%).

**Reviewer's Comments:** The clinical significance of low-level biochemical progression is uncertain. None of the true OC Gleason score 6 tumors showed other clinical evidence of progression. However, this study highlights that careful attention to pathologic grading and staging is critically important in appropriately treating patients and providing prognostic information. (Reviewer-Deborah J. Chute, MD).

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Keywords: Radical Prostatectomy, Progression

Print Tag: Refer to original journal article
CISH and SISH are two emerging technologies in evaluating HER2 amplification. With these tests, histologic features and HER2 status of a specimen can be evaluated in parallel.

**Background:** Overexpression of human epidermal growth factor 2 (HER2) in breast cancer patients is associated with aggressive disease and shorter survival. Trastuzumab targets HER2 and confers a significant survival benefit in these patients. The likelihood of response is directly related to the level of HER2 overexpression. Only patients with tumors with an immunohistochemical (IHC) score of 3+ and/or showing HER2 gene amplification (FISH) benefit from trastuzumab therapy.

**Objective:** To review current and new methods to assess HER2 amplification. **Current and Emerging Technologies:** Currently, 2 technologies are validated and in broad clinical use: IHC and FISH. Emerging methods now include chromogenic in situ hybridization (CISH), dual-color CISH (dc-CISH), and silver-enhanced in situ hybridization (SISH). CISH is a modification of the FISH method that uses a HER2 probe. In this method, labeled nucleic acid probes hybridize to specific complementary nucleic acids in the tissue. A peroxidase enzyme-labeled probe is used for chromogenic detection. Formalin-fixed paraffin-embedded tissue can be used, and the slide can be evaluated using a standard bright-field microscope. CISH scoring is based on evaluating the number of copies of the HER2 gene in a nucleus in >50% of tumor cells. Five or fewer copies constitute no amplification, 6 to 10 copies indicate low amplification, and >10 copies indicate high amplification. dc-CISH uses HER2 and a CEP17 probes, enabling exclusion of chromosome 17 polysomy. dc-CISH is based on the same principle as 2-color FISH and is reported as a HER2/CEP17 ratio (>2 indicates amplification). Silver-enhanced in situ hybridization (SISH) is a fully automated technique to detect chromogenic signals. It is scored similarly to CISH, is faster to perform than FISH, and can be used with a conventional light microscope.

**Advantages and Disadvantages:** The advantages with bright-field ISH are as follows: gene copy number and tissue histopathologic features can be evaluated simultaneously; the signal does not decay; a conventional bright-field microscope can be used; and processing costs are less when compared to FISH. Disadvantages include that, until recently, a validated intrinsic control was lacking and that the technology is still new with little experience in practice. **Comparisons (IHC, FISH, Bright-Field ISH):** Numerous studies have compared these methods. Most of these studies report high rates of concordance. Discrepancies arise with samples having low-level amplification by FISH. When implementing, the CISH/SISH results should be compared with IHC or FISH.

**Reviewer's Comments:** CISH and SISH are likely to become routine tests, and the authors of this article summarize the current studies regarding these tests. (Reviewer-William A. Kanner, MD).

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Keywords: HER2 Overexpression, Assessing Amplification

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Pretransfusion Warming of PLTs Does Not Improve Viability

Effects of Pretransfusion Warming of Platelets to 35°C on Posttransfusion Platelet Viability.

Slichter SJ, Christoffel T, et al:

Transfusion 2009; 49 (November): 2319-2325

At least in normal subjects, warming of platelets prior to transfusion offers no measurable benefit in terms of platelet survival and recovery.

Background: Three prior studies have shown significant improvement in posttransfusion corrected count increments (CCI) for platelets (PLTs) incubated at 37°C compared to PLTs that remained at 22°C prior to transfusion. One study did not show a significant difference. It was postulated by 1 author that the PLTs incubated at 37°C restored their disk shape, which led to improved in vivo responses.

Objective: To determine the recoveries and survivals of warmed versus nonwarmed PLTs.

Methods: Apheresis PLTs were obtained and pooled from 18 normal subjects. Each bag was then divided into 2 bags. After 5 days at 22°C, 1 bag was warmed to 35°C and the other left at 22°C. There were 3 methods of warming the PLTs. Experiments 1 and 2 consisted of warming the PLTs to 35°C for 10 minutes and 60 minutes, respectively, radiolabeling, and then transfusing the PLTs. Because it takes 2 hours to radiolabel the PLTs, by the time of transfusion, the PLTs had returned to 22°C. In experiment 3, the PLTs were first radiolabeled and then warmed (60 minutes) to 35°C prior to transfusion. The last experiment most closely simulated those experiments done in prior studies. In vitro measurements were evaluated prior to transfusion, including PLT morphology score, pH, hypotonic shock response, extent of shape change, and annexin V binding.

Results: In the in vivo studies, there were no significant differences in either the PLT recovery or survival measurements between PLTs that were warmed and those that remained at 22°C. Further, there were no significant differences between the 3 experiments. The same held true for in vitro studies. Discussion: The authors demonstrate that prewarming PLTs prior to transfusion does not lead to significant gains in PLT recovery or survival. Radiolabeling PLTs before transfusion permits precise measurements. A weakness of this study is the small sample size.

Reviewer's Comments: This study shows that, at least in normal subjects, warming of platelets prior to transfusion offers no measurable benefit in terms of platelet survival and recovery. (Reviewer-William A. Kanner, MD).

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Keywords: Platelet Transfusion, Warming

Print Tag: Refer to original journal article
In patients with esophageal adenocarcinoma, tumor regression after neoadjuvant chemotherapy has prognostic significance, and standardized methods for assessment are recommended.

**Background:** Esophageal adenocarcinoma is commonly treated with neoadjuvant chemotherapy followed by surgical resection. While this regimen has improved patient survival overall, many patients do not appear to respond to the chemotherapy. It is generally accepted that those who respond will have an improved survival over those who do not respond. However, response to therapy has not been clearly defined nor has the method for evaluation been standardized.

**Objective:** To set forth a proposed procedure for evaluating response to neoadjuvant therapy with correlation to clinicopathological features and outcome.

**Participants:** 92 patients had biopsy confirmed esophageal adenocarcinoma for which they received neoadjuvant chemotherapy followed by surgical resection.

**Methods:** The macroscopic tumor or tumor bed was submitted entirely in 5-mm sections and then otherwise routinely assessed by standard methods. VVG, PAS, and immunohistochemistry for pankeratin were used to define tumor and tumor desmoplasia (versus chemotherapy-related scar) as needed. In the absence of residual tumor, 3 additional levels were obtained for confirmation. Regression was graded as volume of tumor compared to the tumor bed (described as having scarry fibrosis, histiocytic foamy cells, acellular mucus lakes, and reactive vascular changes). The grading scores were 1 (no residual tumor per tumor bed), 2 (1%-50% residual tumor per tumor bed), and 3 (>50% residual tumor per tumor bed).

**Results:** 7 patients (7.6%) had no residual tumor (grade 1), 49 (53%) were partially responsive to therapy (grade 2), and 37 (40%) had minimal or no response to therapy (grade 3). Neither tumor subtype nor grade was associated with extent of response. There was an association between grade 1-2 response and downstaging to ypT0-2, while most ypT3 were grade 3 responders. Responders were also more likely to lack lymph node metastases and lymphovascular invasion. Minimal response to therapy was associated with lack of complete tumor resection. With follow-up intervals exceeding 6 years, the 5-year survival rate was 42% overall. All those with grade 1 response were alive. The median survival rate was 51 months for grade 2 responders and 16 months for grade 3 responders. By multivariate analysis, tumor regression grade was the only independent prognostic variable.

**Conclusions:** Thorough evaluation of tumor regression in esophageal adenocarcinoma after neoadjuvant chemotherapy has significant prognostic value and should be standardized in pathological assessments.

**Reviewer’s Comments:** The guidelines set forth in this manuscript provide a standardized manner for evaluating the response to therapy that has clear prognostic value. (Reviewer-Mary T. Galgano, MD).

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Keywords: Adenocarcinomas, Documenting Regression

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Counting mitotic figures in a single set of 10 HPFs has too much variability for clinical utility and 5 sets of 10 HPFs is recommended for cases with low mitotic rates.

**Background:** The Nottingham grading system relies on the mitotic index (MI) as determined by a count of 10 HPFs as 1 of 3 factors. While the histologic grade of breast carcinoma correlates to clinical outcome, there is a concern over suboptimal reproducibility among reviewers.

**Objective:** To examine the precision and accuracy of evaluating MI using a coefficient of variation (CV).

**Methods:** Breast carcinoma from routine service and from a cooperative tissue bank (weighted for node-negative cancers) were included for review if at least 2 sets of 10 HPFs were present for formal evaluation. Mitotic counts were determined in >1 and up to 6 sets of 10 HPFs. While cellular and well-preserved areas were selected at low power, no effort was made to begin in a hot spot of mitotic figures. The fields were systematically counted with manual mechanical stages, but any field with poor cellularity was skipped. The MI represented the average across the sets of 10 HPFs, and then the tertial cutoffs were established by finding equal thirds by magnitude of the MI. Standard error and CVs were compared with expected results.

**Results:** The tertial cutoff values for MI were 1.14 and 5.33. The mean CV was 147% for the lowest third, 72% for the middle, and 34.6% for the highest. Binomial probability accurately predicted the standard errors and CV, indicating poor reproducibility of mitotic counts in tumors with low MI. There was also a strong negative skew, indicating tertiary cutoffs that were incompatible with the established systems.

**Conclusions:** MI based on mitotic count from a single set of 10 HPFs has too broad of a standard of error and too large of a coefficient of variation for clinical utility. Five sets of 10 HPFs should be considered in lesions with low mitotic rates.

**Reviewer’s Comments:** This study was weighted with node-negative carcinomas and may be biased toward lower grade tumors with a lower MI. The authors’ conclusions of the Nottingham cutoff values being too high and 1 set of 10 HPFs being inefficient may be influenced by the population studied. (Reviewer-Mary T. Galgano, MD).

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Keywords: Carcinoma, Mitotic Counts

Print Tag: Refer to original journal article
Rectal Lymph Nodes Prognostic After Neoadjuvant Therapy

Lymph Node Status After Neoadjuvant Radiotherapy for Rectal Cancer is a Biologic Predictor of Outcome.

Chang GJ, Rodriguez-Bigas MA, et al:

Cancer 2009; 115 (December 1): 5432-5440

Lymph node status after neoadjuvant therapy for rectal adenocarcinoma is predictive of survival.

Background: Preoperative chemoradiotherapy is now used for most patients diagnosed with rectal adenocarcinomas. Compared to postoperative therapy, preoperative therapy allows for improved local control and sphincter preservation. Furthermore, patients experience less toxicity from the therapy. A number of studies have shown that the pathologic assessment of resected rectal adenocarcinomas is important because the treatment effect is predictive of outcome, especially the degree of down-staging. Patients with greater treatment effect tend to fare better. Some have suggested that patients with less down-staging should receive additional postoperative chemotherapy.

Objective: To determine the prognostic value of the pathologic presence of lymph node metastases in these rectal specimens that have had neoadjuvant therapy.

Methods: The Surveillance Epidemiology and End Results database that collects approximately 25% of cancer cases in the United States was used. Only patients with first-time tumors and without distant metastatic disease were included. Type of surgery, use of radiation therapy, and when radiation therapy was used were recorded. Pathologic data, including staging data, were recorded and compared to survival results.

Results: Of nearly 24,000 cases, about 50% received radiation therapy and, of these, nearly 50% received their therapy prior to surgical resection. Younger patients and those with higher-grade tumors were more likely to undergo therapy preoperatively. Patients undergoing preoperative therapy were found to be lower stage at the time of resection. Furthermore, fewer lymph nodes were found with these patients. Patients found to have positive lymph nodes after preoperative therapy fared worse than patients with positive lymph nodes who had radiation therapy after surgery and those with negative lymph nodes.

Conclusions: The staging of lymph nodes after neoadjuvant radiation therapy is an important predictor of outcome for patients with rectal adenocarcinomas. The authors suggest that these patients should be selected for expanded therapy.

Reviewer’s Comments: Although not as exciting to look at, careful inspection of tumors that have undergone neoadjuvant therapy is important. We need to be as diligent with these specimens as we are with those that have not undergone neoadjuvant therapy, especially as systemic therapy may be based on our findings. (Reviewer-Edward B. Stelow, MD).

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Keywords: Rectal Cancer, Staging, Prognosis

Print Tag: Refer to original journal article
**Background:** A number of head and neck squamous cell carcinomas (SCCs) have been shown to be secondary to infection by high-risk human papillomavirus (HR-HPV). Most of these tumors occur within the oropharynx, and the tumors are typically nonkeratinizing (“basaloid”). Papillary SCC of the upper aerodigestive tract (UADT) is characterized by numerous exophytic papilla that are lined by a dysplastic, typically nonkeratinizing SCC in situ that appears similar to SCC in situ of the uterine cervix.

**Objective:** To review the relationship of head and neck papillary SCC and HR-HPV infection.

**Methods:** A single institution’s surgical pathology database was searched for all cases of papillary SCC of the UADT. Cases were reviewed, and demographic and clinical data were collected. The presence of definitive stromal invasion or the development of invasion or lymph node metastases was recorded. Immunohistochemistry was performed with antibody to p16, and in situ hybridization was performed for HR-HPV.

**Results:** There were 31 cases of papillary SCC identified from 11 women and 20 men (mean age, 62.5 years). Most tumors were from the oropharynx or larynx. No patients had a history of papillomatosis. Nearly 75% of the tumors showed strong and diffuse immunoreactivity with antibodies to p16. Of these, nearly 70% were positive for HR-HPV. Of tumors that were nonreactive with antibodies to p16, none were HPV-positive. All oropharyngeal tumors were immunoreactive with antibodies to p16, and >80% of these were HPV-positive. Only 2 of 11 laryngeal tumors were HPV-positive. Two of the 4 sinonasal tumors were positive for HPV. Patients with HPV-positive papillary SCCs were younger and less likely to have a history of smoking. Approximately one-third of patients had stromal invasion, and >50% of these patients had metastases. Metastatic disease was typically nonkeratinizing.

**Conclusions:** UADT SCCs are frequently associated with HPV infection and occur in similar patients and at similar sites with other HPV-associated SCCs of the UADT.

**Reviewer’s Comments:** The data regarding HPV and head and neck SCCs continue to accumulate. Multiple histologic variants of SCC and sites of the UADT can be associated with infection. (Reviewer-Education B. Stelow, MD).

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Keywords: Squamous Cell Carcinoma, Human Papillomavirus

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