Melanocytic nevi in pregnancy are associated with higher mitotic rates but with no increase in recurrence rates or malignant transformation.

**Background:** Melanocytic lesions in pregnancy are controversial and changes in pre-existing melanocytic lesions may raise the clinical suspicion of a melanoma. Few articles have examined the histopathologic changes of melanocytic nevi in pregnancy.

**Objective:** To examine the histopathological changes of melanocytic nevi occurring during pregnancy.

**Design:** Retrospective study.

**Participants:** 11 pregnant women from all 3 trimesters with melanocytic nevi.

**Methods:** Non-dysplastic dermal nevi (16 cases) were compared to 15 cases of dermal nevi from 13 non-pregnant women. Histopathologic sections were assessed for: dermal mitotic figures, prominent multinucleated melanocytes, pigmentation, and irritation changes. The percentage of Ki-67 staining melanocytes was determined and the distribution of HMB45 examined.

**Results:** Rounded clusters of 3 to 20 large epithelioid melanocytes with prominent nucleoli and fine melanin cytoplasmic pigmentation were confined to the superficial dermis and were termed superficial micronodules of pregnancy (SMOPs), identified in 81.3% (13 of 16) in the nevi of pregnancy and 26.7% (4 of 15) control nevi. HMB45 staining was consistent throughout the SMOPs. Mitotic figures were more frequent and with a higher rate than controls (62.5% vs 13.3%). No atypical mitotic figures were noted. Ki-67 proliferation index was slightly higher in nevi of pregnancy than controls (3% vs 1%). Multinucleated melanocytes were only seen in control cases. No significant difference in pigmentation or irritation was noted. Clinical follow-up exhibited a benign behavior. Two cases were re-excised because of increased mitotic figures and were free of recurrence or progression.

**Conclusions:** Melanocytic nevi of pregnancy may show increased mitotic figures and superficial SMOPs, raising the suspicion of malignant transformation. To date, however, all of these melanocytic nevi have behaved in a benign fashion warranting a conservative approach when diagnosing melanotic nevi of pregnancy.

**Reviewer's Comments:** The entity the authors describe as SMOP is an important addition to the diagnostic lexicon of melanocytic nevi. If the overall histopathologic architecture is a benign melanocytic nevus, no atypical mitotic figures are identified and the SMOP is localized to the superficial dermis, a conservative approach is warranted. These melanocytic proliferations are frequently encountered in a busy dermatopathology practice and the histopathologic criteria identified in this paper will assist in arriving at a correct diagnosis. Increasingly, fluorescent in situ hybridization probes are being utilized on small and focused sections of melanocytic proliferations arising in otherwise banal melanocytic nevi and it would be interesting to see if these SMOPs exhibit any molecular aberrations. Dysplastic nevi were not included in this study and a future study examining histopathologic changes may also be instructive. (Reviewer-Paul K. Shitabata, MD).

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Keywords: Melanocytic Nevi, Pregnancy, Proliferation Index, Ki-67

Print Tag: Refer to original journal article
A failure to transcribe the words "no" or "not" in the final pathology report may lead to medical errors and misinterpretation of the final diagnosis.

Background: The Centers for Medicare and Medicaid Services designates “never events” as preventable occurrences that may directly harm or lead to harm of patients. Suggestions have included a list of “do not use” abbreviations, symbols, or acronyms that may lead to misinterpretation of the medical report. In the author’s institution, a pathology report was released that was missing the word "no," resulting in the phrase "lymph node with carcinoma seen" instead of "lymph node with NO carcinoma seen."

Objective: To determine whether the words "no" or "not" should be a never event in the final pathology report.

Design: Retrospective review.

Methods: All pathology reports were reviewed during a 5-year period (172,548 cases). Amendments were identified in 0.8% of total cases (1371); of these, 28% (383) were amendments to the final diagnosis. One author attempted to diagnose cases for a 4-month period without using the word "no" or "not" in the final diagnosis. Alternative terminology included words such as negative or benign, unremarkable, and qualifiers such as absent. The results were compared to the author’s efforts over the previous 4 months.

Results: 8 cases were identified where the word "no" or "not" failed to be transcribed. The intended diagnoses ranged from "no specific pathologic change," "no carcinoma seen," and "diagnostic features of celiac disease are not seen." During the 4-month period where one author attempted to decrease the use of the words, the words were used 6 times in 1398 cases (0.4%) compared to the previous 4 months utilizing the words 133 times in 1433 cases (9.3%). The difference was statistically significant (P <0.001).

Conclusions: Using the words "no" or "not" in the final diagnosis is dangerous and should be classified as a never event in anatomic pathology.

Reviewer’s Comments: This intriguing article presents an issue that is rarely discussed. An editorial response to this article contended that the reasons stated were insufficient to support "such a draconian step." In my own practice, I have been burned by the rare transcription error of leaving out a "no" or "not." Therefore, for many years, I have been utilizing some of the practices outlined in this article inserting terms such as "negative" so if this modifier is left out, the diagnosis is nonsensical. While the use of malignancy summary checklists, which are common with malignant melanoma, may reduce potential errors, ultimately, the final report may still contain typographical errors. Whether one agrees with the authors’ conclusions to designate the words "no" or "not" as a never event is debatable, but every dermatopathologist should open a dialogue with their client dermatologists to agree upon precise terminology with minimal confusion. (Reviewer-Paul K. Shitabata, MD).

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Keywords: Anatomic Pathology Report, Never Events, Error Reduction

Print Tag: Refer to original journal article
Is Adalimumab the Answer for Psoriasis?

Efficacy and Safety of Adalimumab Across Subgroups of Patients With Moderate to Severe Psoriasis.

Menter A, Gordon KB, et al:

J Am Acad Dermatol 2010; 63 (September): 448-456

While a consistent improvement of ≥75% in PASI scores was observed in the majority of patient subgroups, these results must be interpreted with great care and with knowledge of the limitations of post-hoc subgroup analyses.

**Objective:** To determine the efficacy and safety of adalimumab for various subgroups of patients with moderate to severe psoriasis and to determine whether these profiles were consistent with the overall results.

**Design/Methods:** This study is a post-hoc subgroup analysis based on the week 16 data from the adalimumab phase III randomized control trial, also known as the REVEAL trial. This post-hoc subgroup analysis was conducted to determine relationships between adalimumab efficacy and/or safety and age group, sex, race, baseline weight intervals, baseline body mass index, disease duration, baseline severity, prior treatments, and comorbidities.

**Results:** Consistent Psoriasis Area and Severity Index (PASI 75) improvements were seen in all patient subgroups. However, moderately reduced responses were noted for patients in the greater weight and body mass index categories. Adalimumab treatment, weight, and age were the most important factors influencing mean percentage change in PASI scores at week 16. The authors did not observe any significant differences in the risk of serious adverse events in adalimumab versus placebo-treated patients across weight categories.

**Conclusions:** While a consistent improvement of ≥75% in PASI scores was observed in the majority of patient subgroups, these results must be interpreted with great care and with knowledge of the limitations of post-hoc subgroup analyses.

**Reviewer's Comments:** Several questions will need to be addressed with any subgroup analysis. First, were the subgroup analyses planned before the start of the study? In general, subgroup analysis should be defined a priori based either on results of prior studies or plausible biological mechanisms. Preferably, the choice of subgroups, the expected magnitude and direction of the subgroup differences, and power calculations were designed into the original trial. The present study is a post-hoc subgroup analysis, which refers to examining data after the trial has concluded for patterns that were not specified a priori. This type of analysis will need to be interpreted with caution. Second, most studies have just enough patients to adequately test the primary hypothesis. When the study population is divided into subgroups, the analyses may no longer be powered to detect clinically meaningful differences. Third, findings from post-hoc subgroup analyses must be analyzed with special attention. An important test to use when analyzing the differences in treatment response between the different subgroups is an "interaction" test. This test evaluates whether the observed treatment response is different in the various categories of subgroups. For example, to determine whether there is differential response to adalimumab based on whether a patient is normal weight or obese, results from interaction tests would be helpful on multivariate analysis. Results of interaction tests between the treatment group and the various choices of subgroups on multivariate analyses would also be important to include. (Reviewer-April W. Armstrong, MD).

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Keywords: Psoriasis, Biologics, Adalimumab, Subgroup Analysis

Print Tag: Refer to original journal article
Bone Marrow Transplantation for Recessive Dystrophic Epidermolysis Bullosa.
Wagner JE, Ishida-Yamamoto A, et al:

Clinical improvement of recessive dystrophic epidermolysis bullosa lesions is seen between 30 and 130 days after bone marrow transplantation in certain subsets of patients.

**Objective:** To determine whether allogeneic marrow contains stem cells capable of ameliorating the manifestations of recessive dystrophic epidermolysis (DE) bullosa in humans.  

**Participants/Methods:** The authors reported 7 children with recessive DE bullosa treated with immunomyceloablative chemotherapy using busulfan, fludarabine, and cyclophosphamide followed by allogeneic stem cell transplantation. Patients were treated at the University of Minnesota between October 2007 and August 2009 with follow-up data reported through January 2008. Main outcomes included expression of Collagen VII as determined by immunofluorescence stains, visualization of anchoring fibrils with transmission electron microscopy, healing of blisters as per digital photography, and degree of chimerism by competitive polymerase chain-reaction assay.  

**Results:** One patient died of cardiomyopathy before bone marrow transplant. The remaining 6 patients had improved healing and reduced number of blisters between 30 and 130 days after transplant. They also had substantial proportions of donor cells in the skin and no evidence of anti-Collagen VII antibodies. Five of 6 patients showed increased deposition of Collagen VII at the dermal-epidermal junction but there were no normal anchoring fibrils. One patient died of graft rejection and infection at 183 days. Five patients were alive at 130 to 799 days after bone marrow transplant.  

**Conclusions:** Increased Collagen VII deposition and a sustained presence of donor cells were found in the skin of children with recessive DE bullosa after allogeneic bone marrow transplantation. Further studies are needed to assess the long-term risks and benefits of such therapy in patients with this disorder.  

**Reviewer's Comments:** The paper under review today is very important as it describes a potential cure for a dismal disease. The authors designed a phase 1-phase 2 study in humans based on encouraging findings in mouse studies showing increased survival in 15% of treated mice. They demonstrated that clinical improvement of blisters parallels Collagen VII levels in the skin. Their results, however, showed that improvement can be quick and dramatic in some patients but slow and barely significant in others. Also, one of their patients had a period without blisters followed by recurrence after 60 days. It is not clear yet which factors are predictors of a good response but it seems that there are certain subsets of recessive DE bullosa patients that respond better than others. Future research should clarify some of these unknowns, and as dermatologists, we should try our best to keep updated on potential future therapies for patients with epidermolysis bullosa. (Reviewer-Carlos Garcia, MD).

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Keywords: Recessive Dystrophic Epidermolysis Bullosa, Bone Marrow Transplant

Print Tag: Refer to original journal article
In this study, the incremental increased risk for inflammatory bowel disease was modest (hazard ratio, 1.19 to 1.63), but the numbers of patients affected were very small compared to the number treated.

**Background:** There is a resurgence of concern over a potential association between use of isotretinoin and risk of inflammatory bowel disease (IBD). Many of these patients have also received oral systemic tetracyclines.

**Objective:** To evaluate the risk of development of IBD relative to tetracycline exposure.

**Design:** Retrospective cohort study.

**Participants:** Patients registered in The Health Improvement Network database of the United Kingdom felt to be generally representative of the population of England and Wales in terms of age, sex, and geographical distribution.

**Methods:** From the database, the authors extracted data from 94,487 individuals with acne followed up by a general practitioner for 406,294 person-years.

**Results:** The authors found that prescriptions for minocycline were received by 24,085 individuals, for tetracycline/oxytetracycline by 38,603 individuals, and for doxycycline by 15,032 individuals. IBD was noted in 41 individuals exposed to minocycline, 79 individuals exposed to tetracycline/oxytetracycline, 32 individuals exposed to doxycycline, and 55 individuals not exposed to any of these antibiotics. On the basis of these numbers, they calculated hazard ratios for developing IBD ranging from 1.19 for minocycline to 1.43 for tetracycline/oxytetracycline, and 1.63 for doxycycline. The risks were higher for Crohn’s disease than for ulcerative colitis.

**Conclusions:** Tetracycline antibiotics, particularly doxycycline, may be associated with the development of IBD, particularly Crohn’s.

**Reviewer’s Comments:** The numbers of affected patients are quite small compared to the whole total treated, so basically, assuming there really is any increased risk, it is a small incremental increase of risk over a very small population. Coincidentally, the same journal published an article in the August print version by Toshifumi Ohkusa et al, titled, “Newly Developed Antibiotic Combination Therapy for Ulcerative Colitis: A Double-Blind Placebo-Controlled Multicenter Trial.” The article described an improvement over placebo in ulcerative colitis patients treated with oral amoxicillin, metronidazole, and tetracycline, 1.5 grams a day. (Reviewer-David L. Swanson, MD).
What Are the Most Common Culprit Drugs in DRESS?

Drug Reaction With Eosinophilia and Systemic Symptoms: A Retrospective Study of 60 Cases.

Chen YC, Chiu HC, Chu CY:

Arch Dermatol 2010; August 16 (): epub ahead of print

DRESS or SCAR (severe cutaneous adverse reactions to drugs) is a heterogenous entity associated with significant morbidity and mortality.

**Background:** Drug reaction with eosinophilia and systemic symptoms (DRESS) is characterized by systemic manifestations that can encompass multiple organ systems.

**Objective:** To better characterize the characteristics and outcomes of patients with DRESS/SCAR (severe adverse cutaneous reactions).

**Design/Methods:** The authors performed a retrospective chart review between 1998 and 2008. Inclusion criteria required 3 of 7 findings: rash, fever >38°C, lymphadenopathy, involvement of at least 1 internal organ, abnormal lymphocyte count, eosinophilia, and thrombocytopenia. Patients with Stevens-Johnson syndrome or toxic epidermal necrolysis were excluded.

**Results:** There were 60 patients, with a mean age of 51 years (6 to 90 years, median 54.5). The most common drugs identified were: allopurinol (32%), phenytoin (18%), dapsone (17%), carbamazepine (5%), cotrimoxazole (5%), NSAIDs (5%), lamotrigine (3%), antituberculosis drugs (3%), and unknown chinese medicines (3%). The average drug reaction latency period was 20.7 days, and 48% of patients had mucosal involvement. All patients presented with a diffuse exanthematous eruption. In total, 80% of patients had elevated liver function test results, and renal involvement was present in 40%. Lung complaints were present in 20% and cardiomuscular system complaints without elevation of myocardial enzymes were present in 15%. In total, 5% had pancreatic involvement. Hematologic abnormalities included lymphocytosis (25%), lymphocytopenia (45%), atypical lymphocytes (67%), eosinophilia (52%), and thrombocytopenia (25%). Skin biopsies were available in 17 cases, and 77% of cases demonstrated various degrees of basilar vacuolization, dyskeratosis, lymphocyte exocytosis, dermal edema, and superficial perivascular inflammation; the remaining biopsies demonstrated lymphocytic vasculitis or mixed perivascular inflammation.

**Conclusions:** According to the authors, drug reaction with eosinophilia and systemic symptoms has a variable clinical presentation, and its definition requires clarification. It may be a heterogeneous syndrome with some particular patterns related to different drugs. Early diagnosis and prompt discontinuation of offending drug regimens are essential.

**Reviewer's Comments:** DRESS syndrome is a heterogenous disorder with a constellation of findings. Allopurinol, anticonvulsants, and sulfonamides are the most common culprits, but other drugs can lead to the disorder as well. It is important to identify this disorder in a patient, and eosinophilia and liver involvement is not necessarily in every case. In biopsy findings, the DRESS can be nonspecific, and can be suggestive of erythema multiforme. The suspicion for DRESS syndrome usually occurs with systemic findings on clinical and laboratory evaluation. Usually, patients with DRESS appear ill, and an important clue is a relatively late onset of the disorder several weeks after the start of the culprit medication. Significant mortality can occur, and hepatic failure can occur, and it had occurred in 4 patients in this case series. The most important treatment is likely to stop the offending medication and offer supportive care. (Reviewer-Amy Cheng, MD).

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Keywords: Drug Reactions, Eosinophilia

Print Tag: Refer to original journal article
Patients with a new diagnosis of dermatomyositis should be considered for a pulmonary work-up even in absence of complaints on review of systems.

**Background:** Dermatomyositis (DM) is a connective tissue disease (CTD) that can be associated with internal malignancies along with other systemic manifestations such as interstitial lung disease (ILD).

**Objective:** To determine the prevalence of ILD and isolated low diffusing capacity for carbon monoxide (DLCO) in a large cohort of outpatients with dermatomyositis.

**Design/Participants:** In this study, the authors performed a retrospective chart review of patients with adult onset dermatomyositis diagnosed between May 2006 and May 2009. Patients with juvenile DM or those with pre-existing chronic lung disease were excluded.

**Results:** There were 91 patients who fulfilled the criteria, and were categorized as classic DM (CDM) or skin-predominant DM (SDM). Seven of the patients (3 SDM, 4 CDM) had overlap with other CTDs. Positive antinuclear antibodies were present in 51% of patients, with no difference between CDM and SDM groups. Internal malignancy rate was 13% in the CDM group, and no patients in the SDM had an internal malignancy on chart review. Seventy-one of 91 patients had DLCO and/or thin-section chest CT performed for pulmonary testing. Of these 71 patients, 23% (16) were considered to have ILD based on CT scan, and there was no difference in the prevalence of ILD in SDM versus CDM patients. All the patients with CT scans compatible with ILD had a reduced DLCO, and 11 of 16 also had restrictive impairment on pulmonary function testing (PFTs). Overall, 52% of patients who underwent pulmonary testing had at least one normal test by DLCO or CT scanning or both, with no difference in the 2 DM groups. A total of 25% (18) of patients testing had lung diffusion abnormalities of uncertain significance, and had reduced DLCO without findings of ILD on CT scan; and the number of patients in this group was similar for SDM and CDM.

**Conclusions:** According to the authors, radiologic ILD and isolated DLCO reductions, which may signify early ILD or pulmonary hypertension, are common in dermatology outpatients with both classic and skin-predominant dermatomyositis. Because DLCO testing is both inexpensive and sensitive for pulmonary disease, it may be appropriate to screen all patients with dermatomyositis with serial DLCO measurements and base further testing on DLCO results.

**Reviewer’s Comments:** Patients with dermatomyositis should have PFTs, as symptoms of ILD can be subtle and difficult to detect. Furthermore, musculoskeletal symptoms from dermatomyositis may mask the findings of lung disease. Not all patients in this study with evidence of ILD had restrictive impairment on regular PFTs (69%). DLCO is a relatively sensitive test that can be utilized to monitor and screen patients for ILD, and serial DLCOs may also be beneficial. CT scanning should be considered for patients with significantly low DLCO or decreasing DLCO on serial exams. Limitations of this study included the retrospective nature and the short duration of follow-up. (Reviewer-Amy Cheng, MD).
20% arnica cream may reduce bruising more effectively than placebo or combination vitamin K and retinol cream.

**Background:** Preliminary evidence has shown that oral arnica and topical vitamin K with retinol might help reduce bruising intensity and accelerate its resolution.

**Participants/Methods:** 16 patients were enrolled to have their lower inner arm treated with purpuric doses from a pulsed dye laser (PDL). Patients were randomized to receive 4 different topical preparations consisting of: 5.0% vitamin K, 1.0% vitamin K and 0.3% retinol, 20.0% arnica, or white petrolatum. Medications were applied twice daily under occlusion. A blinded dermatologist rated the bruising severity immediately following treatment and after 2 weeks of treatment.

**Results:** Significant changes were seen in all 4 rater-observer scores at the 2-week assessment interval. There was also a significant difference between rater scores for the arnica-treated bruise and those treated with petrolatum and combination vitamin K and retinol cream. Though the improvement with arnica was greater than that of vitamin K only cream, the difference was not significant. Side effects were not serious in nature. Bruising and excessive redness were reported in 25% of enrolled patients, but were associated with all tested medications and the placebo. Blisters were reported in one patient, presumably due to the high fluence necessary to achieve ecchymosis for the study.

**Conclusions:** 20% arnica cream may reduce bruising more effectively than placebo or combination vitamin K and retinol cream.

**Reviewer's Comments:** Though the number of patients enrolled was small, the authors still achieved statistical significance in terms of efficacy of arnica over placebo. This is impressive given there were only 16 patients in this study. While I don't usually give much consideration to the use of herbal medicines, this well-designed trial may make me consider using arnica cream for patients undergoing cosmetic laser procedures. A natural extension would be the use of this agent to reduce the duration of bruising from senile purpura or perhaps other cosmetic procedures such as fillers. If you're wondering what the mechanism of action of this medication is, some studies suggest it inhibits NF-κB, which results in reduced expression of inflammatory mediators. Other purported benefits of arnica are the reduction of stiffness and muscle soreness. These benefits were not studied in this paper. (Reviewer-Daniel Eisen, MD).

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Keywords: Arnica, Herbal, Ecchymosis, Bruising

Print Tag: Refer to original journal article
Non-mycosis fungoides primary cutaneous T-cell lymphomas have a more favorable outcome than secondary cutaneous T-cell lymphomas; these lymphomas can be separated into indolent and aggressive groups.

**Background:** Non-mycosis fungoides (non-MF) primary cutaneous T-cell lymphomas (PCTCL) represent a heterogeneous group with variable clinical presentation, histology, immunophenotype, and prognosis. These are very rare lymphomas, which has made classification and study difficult. The current classification is a compilation of the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classifications.

**Objective:** To evaluate non-MF PCTCL in terms of the classification system, comparison with the European literature, and grouping based on indolent and aggressive clinical behavior.

**Methods:** Skin biopsies diagnosed as lymphoma were identified from the Cleveland Clinic pathology archives. All cases were stained and evaluated for T-cell receptor (TCR) gamma gene rearrangements. Clinical follow-up was obtained when possible, and overall survival was evaluated. Based on the results, the cases were classified according to the WHO-EORTC classification.

**Results:** In total, 44 cases were identified with a mean age range at diagnosis of 52 to 65 years. Most subgroups had a male predominance. Ten cases of secondary T-cell lymphoma secondarily involving the skin were also identified. The authors discussed each entity, and only a brief summary will be described here with a more extensive review discussed in the audio portion. The studied entities include: primary cutaneous anaplastic large cell lymphoma (PC-ALCL), subcutaneous panniculitis-like T-cell lymphoma (SPTCL), cutaneous gamma/delta T-cell lymphoma (CGD-PTL), primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (AECD8), primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (CTLCG4), unspecified, primary cutaneous peripheral T-cell lymphoma (PC-PTCL, unspecified, and secondary CTCL. Non-MF PCTCL tended to have a longer median overall survival (OS) (approximately, 14 years) compared with SCTCL (2.5 years). PC-ALCL had the longest median OS of the entities with a large enough sample size (14 years). Both PC and SC-PTCLs had short OS. WHO-EORTC non-MF CTCL entities were able to be statistically significantly divided into 2 groups based on indolent and aggressive behavior.

**Conclusions:** The case series described correlates well with the current WHO-EORTC classification. PC-ALCL represents the most common distinct entity. Currently, the entities can be divided into clinically indolent and aggressive groups.

**Reviewer's Comments:** This is a challenging and evolving topic, with much of the knowledge coming from Europe. This is the first North American series that supports the previous findings and current classification system. (Reviewer-William A. Kanner, MD).

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Keywords: T-Cell Lymphoma, Skin, WHO-EORTC

Print Tag: Refer to original journal article
Desmoplastic Melanoma -- Identifying Type May Help With Prognosis

Murali R, Shaw HM, et al:
Cancer 2010; June 8 (): epub ahead of print

Pure desmoplastic melanomas were significantly associated with longer time to disease recurrence than combined desmoplastic melanomas.

**Background:** Desmoplastic melanoma (DM) is characterized by malignant spindle cells embedded in a fibrocollagenous stroma. DMs are uncommon and most often occur in the head and neck region. However, criteria defining how much desmoplasia is required to diagnose DM are still unclear. Previous studies have shown that patients with DMs present less frequently with sentinel lymph node (SLN) metastasis than patients with conventional melanoma.

**Objective:** To evaluate the prognostic value of various clinicopathologic factors in patients with DM, including extent of desmoplasia.

**Participants:** 252 patients with DM who underwent SLN biopsy.

**Methods:** Patients with a diagnosis of primary cutaneous melanoma which was at least partially desmoplastic were included in the study. All patients underwent SLN biopsy and complete excision. Melanomas were classified as pure DM if ≥90% of the invasive tumor was desmoplastic and as combined DM if <90% of the invasive tumor was desmoplastic. Clinical and pathologic parameters, as well as follow-up data, were obtained from the pathologic report and medical records.

**Results:** Mean patient age was 60.5 years, and the most common site was head and neck. Of tumors, 123 (49%) were pure DM and 129 (51%) were combined DM. Pure DMs were significantly associated with location in the head and neck, thicker depth of invasion, and neurotropism. SLN biopsies were positive in 7% of patients. SLN-positive patients were significantly associated with increasing tumor thickness. There was a trend for SLN metastasis to be less frequent in patients with pure DM-type tumors (5%) compared to combined DM-type tumors (8.5%). On multivariate analysis, increasing tumor thickness and positive SLN status were independent predictors of shorter disease-free survival. Combined DM type, ulceration, and positive SLN status were independently associated with shorter time to locoregional recurrence.

**Conclusions:** This study confirms the reduced rate of SLN metastasis in patients with DM. In addition, type of DM was significantly and independently associated with length of time to recurrence. The presence of a desmoplastic component in malignant melanomas should be identified and reported, as well as the type (pure or combined).

**Reviewer's Comments:** This is the largest study to date which examines patients with DM and SLN biopsy. It is interesting that although pure DMs were more commonly neurotrophic, they were less likely to develop lymph node metastasis and had a longer period to locoregional recurrence. This supports the notion that reporting of DM type may be helpful in predicting patient outcome. (Reviewer-Deborah J. Chute, MD).

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Keywords: Desmoplastic Melanoma, Diagnosis, Melanoma, Pathology, Prognosis, Sentinel Lymph Node Biopsy, Skin

Print Tag: Refer to original journal article
Merkel Cell Carcinoma Related to Sun Exposure

Merkel Cell Carcinoma: Incidence, Mortality, and Risk of Other Cancers.

Kaae J, Hansen AV, et al:

J Natl Cancer Inst 2010; 102 (June 2): 793-801

Merkel cell carcinoma occurs mostly in elderly individuals in sun-exposed skin.

**Background:** Merkel cell carcinoma (MCC) is an aggressive neuroendocrine carcinoma of the skin. Recently, it was shown to be related to infection with a virus, the Merkel cell polyomavirus (MCV). The tumors occur in sun-exposed individuals and are more likely to occur in individuals who are immunocompromised. It has also been noted that they are more likely to occur in individuals with hematologic malignancies.

**Objective/Design:** This study used a population database to study the incidence, mortality, and risk for other cancers in patients who develop MCC.

**Methods:** Nearly 30 years of results were collected from the Danish Cancer Register, which is believed to capture between 90% and 95% of all incident cancers in Denmark. All MCCs and other skin cancers were identified, and HIV/AIDS status was also gathered. Incidence rates and mortality rates were calculated. Incidence of other cancers was gathered.

**Results:** 185 diagnoses of MCC were made over nearly 30 years. More than 90% of patients were >65 years of age, and almost 60% were at least 75 years old. Nearly 50% of the tumors occurred in the head, and the remaining tumors were relatively evenly distributed on the upper limbs, lower limbs, and trunk. More than half of the patients had localized disease, 20% had metastases, and 25% were not staged. No patients had HIV or AIDS, but the incidence of this disease in Denmark is very low. The incidence rate of MCC was 2.0 and 2.4 per million people-years for men and women, respectively. The increased incidence in women was found to be secondary to longer life spans. Male patients were twice as likely as female patients to die of disease. Matched for age, 33% of patients without MCC were expected to die within 5 years compared to 55% and 84% of patients with localized and nonlocalized MCC, respectively. Patients diagnosed with MCC were more likely to have been diagnosed with squamous cell carcinoma of the skin, basal cell carcinoma, melanoma, chronic lymphocytic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma. Patients with MCC were also more likely to be diagnosed with squamous cell carcinoma and chronic lymphocytic leukemia after their diagnosis than other people of the same age.

**Conclusions:** MCC is a disease of older individuals that occurs mostly in sun-exposed skin, often with other skin cancer. Its relationship to hematologic malignancy is interesting and may be secondary to immunocompromised states.

**Reviewer’s Comments:** This paper shows the advantages of a national cancer database for epidemiologic studies. In spite of the association with viral infection, it is interesting to note how related to sun exposure MCC appears to be. (Reviewer-Edward B. Stelow, MD).

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Keywords: Merkel Cell Carcinoma, Incidence, Mortality, Comorbidity

Print Tag: Refer to original journal article
The false-negative rate for sentinel lymph node biopsy for melanoma is approximately 11%.

**Objective:** To determine factors and outcomes associated with the occurrence of a false-negative sentinel lymph node biopsy for melanoma.

**Design:** Retrospective analysis of a prospective randomized clinical trial.

**Participants:** Eligible patients for this study included those aged 18 to 70 years with melanoma >1 mm who lacked clinical evidence of lymph node or distant metastases. All patients underwent wide local excision of the primary melanoma and sentinel lymph node biopsy. Sentinel lymph node biopsy was performed using technetium-99 sulfur colloid with lymphoscintigraphy and vital blue dye. All patients with sentinel lymph node metastases underwent complete lymph node dissection. A false-negative result was defined as a tumor recurrence in a previously mapped nodal basin in which the sentinel node was negative.

**Results:** 2451 patients with cutaneous melanoma were included in this analysis. The median follow-up was 61 months. Sentinel lymph nodes were tumor negative in 80% of patients. Among all patients with a negative sentinel lymph node biopsy, 3% developed tumor recurrence in the previous mapped lymph node basin. The overall false-negative rate was 10.8%. The false-negative rate after excluding patients who developed local tumor recurrence was 7.6%. Factors significantly associated with a false-negative sentinel lymph node included lower tumor thickness, increased patient age, and less lymphovascular invasion. Patients with a false-negative sentinel node had a higher incidence of local/in-transit recurrence. The presence of a false-negative sentinel node was associated with a significantly higher rate of distant recurrence compared to patients with a true-positive sentinel node or a true-negative sentinel node. The overall survival rate was not significantly worse in the false-negative versus the true-positive groups.

**Conclusions:** The false-negative rate for sentinel lymph node biopsy for melanoma is about 11%.

**Reviewer's Comments:** The reasons for false-negative sentinel lymph node biopsy for melanoma may be due to surgeon or pathology error. Avoidance of a false-negative sentinel lymph node biopsy is important because it is associated with an increased risk of distant metastases. (Reviewer-Todd M. Tuttle, MD).

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Keywords: Lymph Node Biopsy, Melanoma, Occurrence

Print Tag: Refer to original journal article
Expert Pathology Review Leads to Changes in Melanoma Treatment

Pathology Review of Thin Melanoma and Melanoma in Situ in a Multidisciplinary Melanoma Clinic: Impact on Treatment Decisions.

Santillan AA, Messina JL, et al:

J Clin Oncol 2010; 28 (January 20): 481-486

Expert pathology review frequently leads to restaging in patients with early-stage melanoma.

Objective: To determine the impact of expert pathology review on the staging and treatment of early-stage melanoma.

Design: Retrospective, single-institutional study.

Participants: The authors identified patients at their institution who had biopsy-proven melanoma in situ (MIS) and thin melanoma (≤1 mm) at outside facilities. All medical records, pathology reports, and slides were reviewed. Pathologic staging was performed according to American Joint Commission for Cancer (AJCC) guidelines. Treatment recommendations were based on the National Cancer Comprehensive Cancer Network (NCCN) guidelines.

Results: The authors reviewed 424 lesions from 420 patients referred to their institution from outside facilities. Key pathological findings (recommended by the NCCN) were frequently not included in outside pathology reports including mitotic rate (47%), ulceration status (13%), deep margin status (29%), and Clark level (2%). After expert pathology review, major changes in diagnosis occurred in 15 (4%) of the patients. Among patients with an outside diagnosis of thin melanoma, 26% were restaged after expert pathology review; 13% were upstaged and 13% were downstaged. Among patients with an outside diagnosis of MIS, 11% were upstaged to thin melanoma. Expert pathology review led to changes in recommended surgical excision margins of the primary lesion in 12% of patients, based on NCCN guidelines. Using the AJCC guidelines, expert pathology review led to changes in the recommendations of sentinel lymph node biopsy in 16% of patients.

Conclusions: The authors conclude that expert pathology review of early-stage melanoma and MIS changes the diagnosis in 4% of patients and leads to pathology restaging in 24% of patients.

Reviewer’s Comments: This important study demonstrates that expert pathology review frequently leads to changes in melanoma treatment. It is not clear from this study whether changes were more likely to occur if the original biopsies were reviewed by a general pathologist or a dermatopathologist. (Reviewer-Todd M. Tuttle, MD).

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Keywords: Pathology, Staging, Treatment

Print Tag: Refer to original journal article
Conditional survival estimates provide useful quantitative prognostic information for melanoma survivors.

**Objective:** To determine melanoma-specific survival rates among patients who have survived a certain period of time after initial melanoma treatment.

**Design:** Population-based study.

**Participants:** The authors used the Surveillance, Epidemiology and End Results database to identify patients diagnosed with melanoma from 1988 to 2000. All patients were manually restaged, using the 6th edition of the American Joint Committee on Cancer staging manual. Survival estimates were determined at year 1 through 10. For patients with at least 5 years of follow-up, 5-year condition survival estimates were calculated for each stage. Additional estimates were adjusted for age, race, marital status, tumor location, and gender.

**Results:** Most patients were diagnosed with stage I melanoma (80%). Nodular melanoma was most commonly associated with stage II and III disease, whereas superficial spreading melanoma was most commonly associated with stage I disease. The 10-year disease-specific survival rate was 94% for stage I, 62% for stage II, 44% for stage III, and 16% for stage IV melanoma. The 5-year conditional survival rate for stage I disease remained at 97%. For stage II disease, the 5-year conditional survival rates increased from 72% at time 0 to 86% for those surviving 5 years. For stage III, the 5-year conditional survival rates increased from 51% at time 0 to 87% for those surviving 5 years. For stage IV, 5-year conditional survival estimates increased from 19% at time 0 to 84% for those surviving 5 years. Overall, patients who were <50 years of age had higher estimated survival rates at the time of diagnosis than patients who were aged ≥50 years. When stage-specific subgroups were stratified by age, males had a lower 5-year disease-specific survival rate; however, the conditional survival rates for both genders increased over time.

**Conclusions:** Conditional survival estimates provide more relevant quantitative information for melanoma survivors as their risk profiles change over time.

**Reviewer’s Comments:** These data provide useful information for counseling surviving patients and providing surveillance recommendations. Surviving to a given period of time is a powerful prognostic factor, even for patients with stage IV disease. (Reviewer-Todd M. Tuttle, MD).

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Keywords: Advanced Melanoma, Survival

Print Tag: Refer to original journal article
The number of tumor-containing lymph nodes is the most significant prognostic factor for patients with stage III melanoma.

**Objective:** To determine the survival rates and predictors of survival among patients with stage III melanoma.

**Design:** Prospective multi-institutional database.

**Participants/Methods:** The authors used the American Joint Committee on Cancer staging database to identify patients with stage III melanoma. This database was created in 1999 and is composed of prospective databases from major cancer centers and clinical trial cooperative groups. The database included 2,313 patients with stage III melanoma who had complete clinical and pathologic data on the primary melanoma and regional nodal metastases. Most (90%) of the micrometastases were detected by sentinel lymph node biopsy. Survival curves were calculated from time of diagnosis of primary melanoma. Multivariate Cox models were used to identify independent predictors of survival.

**Results:** As compared to patients with macrometastases, micrometastases were associated with fewer positive lymph nodes. The 5-year survival rates were significantly better for those patients with micrometastases compared to those with macrometastases (67% vs 43%). On multivariate analysis of patients with micrometastases, age, tumor thickness, mitotic rate, anatomic site, and number of involved lymph nodes were independent predictors of survival. On multivariate analysis of patients with macrometastases, only age and number of tumor-containing lymph nodes were independent predictors of survival. The number of tumor-containing lymph nodes was the most significant prognostic factor in this study. Among patients with micrometastases, the 5-year survival rate was 74% for those <50 years of age, 65% for those between 50 and 69 years of age, and 47% for those ≥70 years of age.

**Conclusions:** There is a substantial variation in survival rates for patients with stage III melanoma. The number of nodal metastases was the most significant predictor of survival.

**Reviewer's Comments:** Although we are clearly improving our ability to provide accurate prognostic information for melanoma patients, we have not identified more effective adjuvant therapies. (Reviewer-Todd M. Tuttle, MD).

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Keywords: Stage III Melanoma, Micrometastases, Macrometastases, Prognostic Factors

Print Tag: Refer to original journal article