Melanoma Prognosis Based on Anatomic Site

Melanoma prognosis is usually based on Breslow thickness, Clark level, presence of ulceration or nodal and distant metastases, and lactic dehydrogenase level. The influence of anatomic site is less certain. In this retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER) melanoma database, the authors analyzed survival rates by anatomic site in 51,704 white, non-Latino patients with a first invasive melanoma diagnosed from 1993 through 2003. To isolate the effect of anatomic site, the authors used multivariate analysis to eliminate the effects of age, sex, Breslow thickness, ulceration, and lymph node status.

On average, compared with melanomas situated elsewhere, lesions of the scalp and neck occurred in older patients (59 vs. 55 years), were thicker (0.80 vs. 0.63 mm), were more likely to be ulcerated (7% vs. 5%), and were more likely to be associated with positive nodes at presentation (7% vs. 4%). Kaplan-Meier survival rates were significantly lower in patients with scalp and neck lesions than in those with lesions elsewhere (83% vs. 92% at 5 years, and 76% vs. 89% at 10 years). Scalp and neck melanomas accounted for 6% of the melanomas in the database but 10% of the melanoma deaths. After multivariable adjustment, patients with scalp and neck lesions were 1.84 times more likely to die from their melanomas, and patients with melanomas on the trunk were 1.27 times more likely to die from their melanomas, than were patients with melanomas located elsewhere.

Comment:
Independent of other known prognostic factors, location on the scalp and neck, and, to a lesser degree, on the trunk, seems to predict more-aggressive melanoma than location at other sites. There is no satisfactory explanation for this difference. Clearly, careful scalp examination with the help of a comb or other aid during skin examination is important for early diagnosis in high-risk patients.
— George J. Hruza, MD

Lachiewicz AM et al. Survival differences between patients with scalp or neck melanoma and those with melanoma of other sites in the Surveillance, Epidemiology, and End Results (SEER) program. Arch Dermatol 2008 Apr; 144:515.

Shedding Light on Perceptions of Indoor Tanning

Indoor tanning has been estimated to increase the risk for melanoma by 75%. Still, the use of tanning beds has increased dramatically over the years: 50% of teens and young adults use tanning beds. To determine knowledge and attitudes about indoor tanning in this age group, researchers in Chicago questioned beachgoers between the ages of 18 and 30 and compared their answers with responses to similar surveys conducted in 1988 and 1994. Awareness of the relation between tanning and skin cancer increased from 42% of responders in 1988 to 87% in 2007. From 1988 to 2007, the percentage of respondents who knew that avoiding tanning helps to prevent skin cancer substantially increased (the percentage rose from 25% in 1988 to 77% in 1994, but fell to 67% in 2007). Despite knowledge of these health consequences, the percentage of respondents who reported that they looked better with a tan increased from 69% in 1994 to 81% in 2007. Use of indoor tanning beds grew from 1% in 1988 to 27% in 2007.

People received information about indoor tanning most often from the media, family, and friends. Relatively few were counseled by family physicians (28%) or dermatologists (31%). Although physicians were a less common source of information, they were
Illuminating the Relation Between Polymorphous Light Eruption and Lupus

Photosensitivity is a common feature of both polymorphous light eruption (PMLE) and cutaneous lupus. Of ongoing concern to dermatologists is that some PMLE patients might eventually develop cutaneous lupus. Dermatologists in Vienna examined the validity of this concern in 472 patients with moderate-to-severe PMLE requiring phototherapy.

The investigators identified 55 patients (11.7%) who had an antinuclear antibody (ANA) ≥1:80 on at least one occasion, 3 of whom also had SS-A/Ro antibodies (0.6%). Thirty-nine ANA-positive patients were reexamined after a mean of 8 years; ANA titters had returned to normal in 14 but remained elevated in the other 25 (median, 1:160; range, 1:80–1:640). However, no patients developed clinical, histopathologic, or laboratory evidence of lupus. The authors conclude that there is no evidence that patients with PMLE are at increased risk for developing lupus.

Comment:

Other studies of the relation between PMLE and lupus have had too few subjects or too short a follow-up. It is notable that, in this study, the percentage of positive ANAs among PMLE patients was no different from that in the general population. The take-home points for the practicing dermatologist are that (1) positive ANA and photosensitivity do not necessarily indicate lupus — these factors are also present in PMLE without lupus, and (2) patients with an unequivocal PMLE diagnosis (i.e., consistent history, physical examination, histopathology, and, in many cases, confirmatory photoprovocation testing) can be counseled that they have no greater likelihood of progression to cutaneous lupus than the general population. However, differentiating between PMLE and lupus in many patients with photosensitivity can be difficult. Careful follow-up and lupus reevaluation are advisable in such patients.

— Craig A. Elmets, MD


Vitamin D and Infections

The skin produces vitamin D after exposure to sunlight. Activated vitamin D₃ interacts with genes to regulate microbial recognition and defense. Specifically, vitamin D₃ upregulates genes that induce Toll-like receptor-2 (TLR-2) on keratinocytes and to increase the expression of antimicrobial peptides, such as cathelicidin. Cathelicidin activates innate immune mechanisms that protect and defend the skin against infecting and invading organisms.

Schauber and colleagues recently found that such activation also requires histone acetylation. They found that inhibitors of histone deacetylase increased epidermal cathelicidin and enhanced antimicrobial actions against Staphylococcus aureus. Blocking the vitamin D receptor or steroid receptor coactivator 3 (SRC3), which mediates histone acetyltransferase activity, blocked the induction of cathelicidin synthesis.

After activation in the liver and kidney, synthesized vitamin D₃ becomes
Kidney Failure After Unidentified Filler Injection

Use of fillers for cosmetic enhancement has become increasingly popular in the U.S., but bargain seekers should beware of unprincipled charlatans. The CDC has reported the cases of three patients who underwent buttoc enhancement on December 22, 2007, with a liquid silicone oil and saline mixture at a facility staffed by a radiology technician without any physician supervision or affiliation. The volumes injected were 400 mL, 800 mL, and an unknown amount. Within 1 hour of injection, all three patients developed headache, fatigue, nausea and vomiting, and burgundy-colored urine. On hospital admission several days later, the patients were found to have acute renal failure — in two cases, requiring hemodialysis. Renal function returned to normal within 1 month. No agent or chemical was identified as the cause of the renal failure; all three patients had received prior injections at the same facility without adverse events.

Investigators found multiple breaches of standard infection-control practice at the facility. Records often contradicted patient recollection. Consent forms were general, without reference to filler material. No samples of the injected substance — nor records, orders, or invoices regarding the filler — were available for inspection at the facility. The facility was referred to as a “family medical practice,” using the name of an MD not affiliated with the facility. Four other patients who had undergone the silicone injections were interviewed. One reported having pink urine after the procedure, but no other adverse events were reported. The operator was initially barred from performing any more injections and then arrested for practicing medicine without a license.

Comment:
The authors found that symptoms of cutaneous allodynia (CA; skin pain resulting from a stimulus that does not normally cause pain) were common during headache attacks in these patients, regardless of headache type (range, 36.7% with tension-type headaches to 68.3% with transformed migraines). Migraine headache of any type was associated with significantly higher CA prevalence and severity than other types. Among migraineurs, CA was positively associated with attack frequency, obesity, and disease duration. Depression was independently associated with higher CA scores for all headache types. CA was more common in women than in men, and relative frequency decreased with age.

Comment:

The skin is the most richly innervated organ in the human body and serves as an important sensory system for
maintaining overall homeostasis. Therefore, to find chronic headaches associated with skin hypersensitivity is not surprising. Central and peripheral sensitization is a common feature of chronic pain associated with C nerve fiber nociceptors and is the presumed basis for the cutaneous allodynia. The significantly higher CA prevalence and severity in migraineurs supports the notion that a neurogenic inflammation involving skin vasculature is implicated in migraines.

Small clinical trials have shown that CA develops during migraine attacks. This large population study further supports this concept. The authors do not provide data on the anatomic location of the allodynia. It would be critically important to know whether pain occurred in the face, scalp, or neck areas, suggesting the involvement of sensory cranial and cervical spinal nerves in peripheral sensitization. An interesting question for dermatologists is whether patients with chronic headaches are more prone to develop burning sensations related to the use of fragrances and soaps, the so-called sensitive skin syndrome. — Gil Yosipovitch, MD

Dr. Yosipovitch is Professor of Dermatology, Neurobiology & Anatomy, and Regenerative Medicine, Wake Forest University Health Sciences, Winston-Salem, NC.


PEComas: A Recently Described Tumor to Keep in Mind

Perivascular epithelioid cell tumors (PEComas) are apparently benign mesenchymal tumors that can easily be misdiagnosed as malignant melanoma. These authors performed a retrospective analysis and describe the clinicopathologic spectrum of 10 primary cutaneous PEComas.

Ten patients (8 female; age range, 15–82, none with tuberous sclerosis) presented with painless, slowly growing dermal nodules or plaques. Eight tumors were located on the legs and two on the back. Most tumors involved the dermis, with extension to the subcutis. The median size was 1.5 cm. The tumors had a nested or trabeculated growth pattern of epithelioid or epithelioid/spindle cells in a background rich in vessels. The proliferative cells ranged from clear to pale eosinophilic or granular cytoplasm. Mitotic activity was <1 per 10 high-powered fields. The cells were positive for HMB-45, Melan A and microphthalmia transcription factor. Epithelial markers (pan-keratin and epithelial membrane antigen) were negative. The investigators also noted smooth-muscle differentiation, with positive desmin and smooth-muscle actin.

In 20% of patients, the tumors had been misdiagnosed as malignant melanomas; eight tumors with positive margins were completely excised, and two were partially excised. One patient with a melanoma misdiagnosis underwent sentinel lymph node biopsy, with negative results. After a median follow-up of nearly 4 years, no recurrences were observed.

COMMENT:
Although PEComas are frequently identified in the retroperitoneum, abdominal viscera, and pelvic sites, only about 20 cases have been described in the literature. No definitive association of these neoplasms with the tuberous sclerosis complex has been made. PEComas and malignant melanomas may have overlapping histologic and immunohistochemical features. Awareness of primary cutaneous PEComas will increase the identification of this apparently benign entity and avoid inappropriate treatment. — Angelica Selim, MD


Childhood Rosacea: Look Them in the Eye

Although rare in pediatric practice, rosacea does occur in children and is probably underrecognized. Pediatric dermatologists and ophthalmologists in France performed a retrospective review of 20 children with rosacea (age range, 1–15 years). Six patients had family histories of rosacea; 6 had cutaneous disease, 3 had ocular disease, and 11 had both.

The researchers noted three dermatomic patterns, in descending order of frequency: papulopustular rosacea, facial erythema (with or without flushing), and granulomatous rosacea (perioral dermatitis). The latter was associated with previous use of topical steroids (JW Dermatol May 2008, p. 35, and Br J Dermatol 2008).

The ocular rosacea noted in 14 children appeared as chalazions in 10, blepharoconjunctivitis in 9, meibomitis in 6, keratitis in 4, and corneal ulcers in 2 (some children had more than 1 finding). Ocular hyperemia was common. Undiagnosed ocular rosacea preceded facial eruptions in 55%.

Mild cutaneous disease was treated with topical metronidazole or topical niacinamide. Mild ocular rosacea was treated with warm-water eyelid massage and saline solution instilled 3 to 4 times daily. Patients with severe ocular or cutaneous rosacea also received oral antibiotics: tetracyclines (e.g., doxycycline, for patients older than 12 years) or metronidazole (10 children received 1-month courses of 30 mg/kg/day without adverse effects). Remission occurred in all children within about 3 months. The authors propose diagnostic criteria; two features are required for diagnosis in children versus only one in adults.

COMMENT:
This excellent clinical review of childhood rosacea includes useful photographs and therapeutic information. In my experience, perioral dermatitis is far more common than the other two variants (and patients with darker skin are more likely to have the perioral subtype). In the U.S., oral erythromycin is the most widely prescribed oral agent for young children with severe disease. Oral metronidazole may be a good second-line agent, but its long-term use increases risk for peripheral neuropathy. Always consider an ophthalmology consultation in childhood rosacea. — Mary Wu Chang, MD


A Few More T-Cells and Cytokines to Investigate in Psoriasis

T cells have been subdivided into the subsets Th1 and Th2, depending on the cytokines that they produce. Th1 cells make interleukin (IL)-2 and
Can Money Buy Happiness?

Once daily needs are met, income has only a small effect on happiness, according to many studies. As income increases, people tend to spend it on things that don’t provide lasting happiness. Although happiness is fostered by helping and spending time with others and donating money, striving to increase wealth makes people less likely to engage in these activities.

Investigators examined the relation between happiness and prosocial spending (spending on others). First, they interviewed a representative sample of 632 Americans and found that personal spending was unrelated to happiness but greater prosocial spending was significantly associated with greater happiness. The researchers then studied 16 people before and after they received a profit-sharing windfall (about US$4900). Controlling for degree of happiness before the windfall, the investigators found that those who donated the money or spent it on others were significantly happier afterward than those who spent it on themselves.

Finally, the investigators asked 46 participants to rate their happiness in the morning, gave each one $5 or $20, and then randomly assigned them to spend the money on themselves or on others. In ratings at the end of the day, the amount of money received was unrelated to happiness. Those who spent on themselves had no increased happiness, but those who spent on others had significantly greater happiness.

Comment:

People (including, I propose, physicians) adapt quickly to increasing income and spending levels. Prosocial spending requires a choice, and that choice promotes happiness. It’s a win-win situation. Although gifts of time or assistance were not studied here, physicians may reap happiness from giving such “extra-mile” care. Let’s face it — there is a minimum level of care we must give, so extra efforts are gifts. I know that I am happier when I engage with patients and do the best job I can.

— Mark V. Dab, MD

Accutane: Thoughts and Ramblings

The Journal of Clinical Investigation recently published the results of an important clinical study on the mechanism of action of 13-cis retinoic acid in acne therapy. Of equal importance to the study’s scientific value is the question it raises of whether clinical research into the treatment of severe acne is stagnating.

First the facts: Investigators analyzed biopsy samples of the back skin of six patients receiving 0.50 or 0.67 mg/kg/day of 13-cis retinoic acid for severe acne; skin was biopsied before treatment and 1 week after the start of therapy. A reduction in the size of the sebaceous glands was of borderline significance (P=0.16), but apoptosis increased markedly in sebaceous cells (and not in epidermal cells). Using gene arrays, with data confirmed by real-time PCR, the investigators noted a sevenfold increase in messenger RNA for the lipocalin-2 gene (LCN2), which encodes the protein NGAL (neutrophil gelatinase-associated lipocalin) in the sebaceous glands and increases NGAL protein in sebocytes. NGAL initiates apoptosis in cultured sebocytes; in vitro, LCN2-induced changes can be abrogated by siRNA for LCN2.

Comment:

Let’s take as a given that oral 13-cis retinoic acid is a very effective treatment for severe cystic acne. I suggest that little is being done to optimize its clinical use. If apoptosis in the sebaceous glands eliminates sebaceous stem cells, or follicle-cell sebaceous-gland precursors, or both, this action could be the basis for 13-cis retinoic acid’s long-term effects. Better clinical optimization of 13-cis retinoic acid is needed, but how will it be possible in the current climate for clinical research and the I-Pledge program? The manufacturers of 13-cis retinoic acid are unlikely to fund serious studies; they will be satisfied with the 5-month courses currently in use. If apoptosis is the key mechanism, studies to determine optimum treatment duration and dose for inducing apoptosis are important. The reported trials were short, with doses <1 mg/kg/day. Might quick bursts at higher dosages lead to shorter courses? Are inadequate doses necessitating longer or repeated
These summaries are reprinted from the Journal Watch family of medical literature surveillance newsletters.

**A Hidden Risk of “Lipotourism”: Mycobacterium Infection**

Patients who elect to undergo surgical procedures, including cosmetic surgery for removal of fat, are increasingly seeking care at hospitals and clinics outside the U.S. These authors report an unusual infection seen in “lipotourists.”

In 2004, the Centers for Disease Control and Prevention (CDC) investigated reports of unusual skin infections in patients who had undergone cosmetic surgery in the Dominican Republic. The CDC identified 20 cases of infection with *Mycobacterium abscessus* in patients who had undergone abdominoplasty; some patients also had undergone liposuction or breast augmentation or reduction surgery. The authors analyzed details of eight patients who underwent surgery at the same clinic and had related isolates. Symptoms began 2 to 18 weeks after the procedures, and most patients presented with skin abscesses. All eight patients required prolonged courses of antimicrobial therapy (clarithromycin alone or with azithromycin), and all but one were eventually cured. Patients who underwent breast augmentation required removal of the implants.

**First Do No Harm — Avoiding Medication Errors in Children**

Medication errors are among the most common causes of adverse events in hospitalized patients. The Joint Commission on Accreditation of Healthcare Organizations recently issued a Sentinel Event Alert (http://www.jointcommission.org/SentinelEvents/SentinelEventAlert/sea_39.htm) about the high risk for medication errors in children. Data reported in the April issue of *Pediatrics* demonstrated a mean of 11 adverse drug events per 100 randomly selected patients from 12 children’s hospitals, 16 events per 1000 patient-days, and 1 event per 1000 medication doses. Twenty-two percent of the errors were classified as preventable, and 2.5% led to patient harm. Medication errors are especially problematic in children for a variety of reasons, including that many drugs are formulated for adults, many healthcare settings do not have reference materials or safeguards designed specifically for children, children have developmental differences in metabolism and excretion of drugs, proper dosing for children often requires additional calculation and fractional dosing with decimal points, and children might not be able to communicate adverse effects.

Recommendations from the Joint Commission to prevent pediatric medication errors include standardizing protocols for pharmacy ordering and timing of medications, ensuring equivalent home and hospital dosing of medications, using oral syringes for oral medications to avoid inadvertent intravenous administration, weighing patients in kilograms only, avoiding administering drugs based on estimated weight, and using error-proofing technology (e.g., bar coding, computer order entry).

**COMMENT:**

These recommendations are relevant for both inpatient and outpatient settings. Among hospital therapies, chemotherapy and total parenteral nutrition pose particular challenges because of the complexity of the protocols. Not mentioned, but another important source of errors is illegible handwriting. All prescriptions should be printed by hand or computer.

— F. Bruder Stapleton, MD

**More Evidence That Gabapentin Works for Hot Flashes**

In the search for alternatives to hormone therapy for controlling menopause-related vasomotor symptoms, gabapentin has shown some promise. Now, in a randomized, double-blind, placebo-controlled trial, Canadian investigators assessed the efficacy of gabapentin for treating hot flashes occurring with natural menopause. Community-dwelling, symptomatic, postmenopausal women (197; age range, 45–65) recruited by family physicians or through advertisements were randomized to either manufacturer-supplied gabapentin (300 mg, 3 times daily) or placebo for 4 weeks. Participants maintained hot-flash diaries so that hot-flash scores, which incorporate frequency and severity, could be calculated.

Ten of the 99 women receiving gabapentin and 6 of the 98 receiving placebo discontinued treatment because of adverse effects. Results of intention-to-treat analysis at 4 weeks showed that, relative to baseline, mean daily hot-flash scores decreased by 51% (from 19.6 to 9.5) in the gabapentin group and by 26% (from 18.3 to 13.5) in the placebo group (*P*<0.001). Mean daily hot-flash frequency dropped from 8.5 to 4.5 (a decrease of 46%) and 8.5 to 6.5 (a decrease of 25%), respectively (*P*<0.001). Dizziness, unsteadiness, and drowsiness were significantly reduced.

— Diane M. Birnbaum, MD, FACEP
Monozygotic Twins Are Not Genetically Identical

Comparisons of monozygotic (identical) and dizygotic (fraternal) twins have been used in genetic studies for more than 100 years to distinguish between genetic and environmental causes of disease. In this study, researchers examined DNA copy-number variations (CNVs) using white blood cells from 19 monozygotic twin pairs that were phenotypically concordant or discordant for neurodegenerative disease. The researchers found evidence of somatic changes in both concordant and discordant twin pairs that must have occurred during development and that affected both chromosomal architecture and CNV of DNA segments.

CNVs were found between the members of discordant pairs (which explained the discordance), but CNVs were also found between discordant unaffected pairs. The authors call for future studies that examine DNA from more than one tissue in larger cohorts of monozygotic twins.

**Comment:**
Monozygotic twins have genetic differences that arise from changes during their individual in utero (and postbirth) development. Growing evidence suggests that somatic changes in the genetic information occur in all individuals. For instance, we know that cancers arise from somatic changes in cancer-causing genes and have suspected for a long time that neurodegenerative diseases arise from somatic genetic changes in nervous tissue. Future research might help identify specific areas of the genome that are at increased risk for somatic changes. In the meantime, it is clear that monozygotic twins are not genetically identical.

— Judith G. Hall, OC, MD


Self-Criticism and CBT

Individuals with major depression have heterogeneous cognitive schemas, personality traits, and life histories. Some depressed patients who experienced rejection and criticism from early caregivers have become competitive, judgmental, and self-critical adults. These individuals are prone to depression relapse after an achievement-related stressor. By contrast, individuals with intrusive, controlling early caregivers tend to be more agreeable and more demanding of emotional support. They are sensitive to interpersonal stressors that activate fears of abandonment. Proven approaches to treatment of depression could vary in effectiveness for patients with these differing personality traits.

This research group undertook a comparative study of cognitive-behavioral therapy, interpersonal therapy (IPT), and pharmacotherapy for depressed patients. They had previously reported that attachment style predicted differential response to CBT and IPT (*J Consult Clin Psychol* 2006; 74:1041). The current analysis focused on differential results based on levels of self-criticism and dependency in a subgroup of 102 patients.

Greater self-criticism before treatment predicted significantly poorer response among IPT recipients and marginally better response among pharmacotherapy recipients. Among CBT recipients, greater dependency showed a trend toward predicting poorer response.

**Comment:**
Depressed patients are served best by practitioners who make use of the full range of treatment tools. To do so most effectively, we need to know which methods best suit which patients. This research suggests that highly self-critical individuals with depression may benefit more from CBT or medication than from IPT. This may be especially true if the depressive episode is triggered by a threat to personal achievement.

— M. Katherine Shear, MD

Looking Far Afield . . .

Human Skin Is Operating at an Extremely High Frequency

Physical Review Letters is where Albert Einstein published five seminal papers, including the one that spelled out the mass–energy relation (E=mc²). What might Einstein think of the journal’s recent report on human skin functioning as antennae for millimeter and submillimeter waves? He was the master of thought experiments, interested in practical implications of arcane research; I’m guessing he would enjoy it immensely.

Optical coherence tomography revealed eccrine ducts to be helical coils in the stratum corneum, inside which sweat functions as a conductive aqueous solution. These authors measured spectral reflectance from skin, which increased during induced sweating and physiological stress. Inhibiting sweating decreased the amplitude of the reflected waves. The researchers found that the sweat glands operate as low-electric-charge (low-Q) antennae. Human skin contains approximately 3×10⁶ eccrine sweat glands, each connected to the skin surface by a helical sweat duct. The authors suggest that the skin in its entirety, therefore, can be regarded as an array of helical antennae operating at extremely high frequency, the range used in radio astronomy and remote sensing.

Comment:
A consulting dermatologist might have added an essential experiment, determining the effect on transmission when males with X-linked anhidrotic dysplasia (who lack eccrine structures and cannot sweat) were studied. The presence of endogenous antennae in humans raises many questions: Can we communicate with others via waves aimed at the skin? Is this a potential mechanism for ESP? Might this discovery lead to security technologies, tracking of individuals, or even electrical evaluation of another’s mental state? If you get unusual sensations from your skin, your receiver might be picking up interesting incoming messages. Pay attention!

— Lowell A. Goldsmith, MD, MPH
