

## Journal Watch

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### **Excision margins in high-risk malignant melanoma**

Thomas JM, Newton-Bishop J, A'Hern R, et al., for the United Kingdom Melanoma Study Group; British Association of Plastic Surgeons; Scottish Cancer Therapy Network.  
*N Engl J Med* 2004;350:757-66.

It was a multicenter randomised clinical trial investigating the effect of the excision margin on the outcome of patients with malignant melanoma of 2 mm or greater in thickness.

Nine hundred patients were recruited and randomised to undergo primary excision surgery with a 1-cm (n=453) or 3-cm surgical margin (n=447), and followed up for a median of 60 months. The median tumour thickness was 3.0 mm for the 1-cm margin group and 3.1 mm for the 3-cm margin group. Only tumours on the trunk or limbs were included. No elective lymph-node dissection, sentinel-node biopsy or adjuvant therapy was performed in either group.

The risk of local regional recurrence was higher in the group with 1-cm excision margin (168 versus 142; hazard ratio, 1.26; 95% confidence interval 1.00-1.59;  $p=0.05$ ). There were more deaths from melanoma in the 1-cm margin as compared to the 3-cm margin (128 versus 105; hazard ratio, 1.24; 95% confidence interval 0.96-1.61;  $p=0.1$ ). The overall survival rate was similar between the two groups (hazard ratio, 1.07; 95% confidence interval, 0.85-1.36;  $p=0.6$ ).

Many international guidelines prefer the use of 2-cm margin while some allow the use of a

minimal of 1-cm margin for tumours between 2 and 4 mm thickness. This study suggested that the risk of local recurrence and death from melanoma were greater when melanomas of at least 2 mm thickness were excised with a 1-cm margin. However, the outcome difference between 2-cm and 3-cm margin was not investigated in this study. Nevertheless, a wider excision margin may be justified in patients with tumours of increasing thickness.

### **Treatment of photoaging**

Stern RS.

*N Engl J Med* 2004;350:1526-34.

Photoaging manifests by wrinkles, skin roughness, mottled hyperpigmentation, telangiectasia, and sallowness. Both ultraviolet A and B radiation contribute to photoaging, though their relative contributions are controversial. Photoprotection at any age may retard and slightly diminish the sign of photoaging, and decreases the incidence of actinic keratosis and squamous cell cancer. However, the risk of basal cell carcinoma depends on the amount of sun-exposure during childhood. Patients with substantial photoaging should be evaluated for actinic keratosis and skin cancers.

Sun-protection is the key step to reduce photoaging. The author recommended routine daily use of sunscreen with sun protection factor 15 or higher. Non-opaque sunscreens claimed to block ultraviolet A radiation, cannot be consistently quantified. Both artificial and natural tanning are discouraged.

The Food and Drug Administration has approved topical retinoids for the treatment of fine wrinkles and irregular pigmentation of photoaging. Over-the-counter preparations that contain hydroxyl acids also have small beneficial effects on roughness, sallowness, and pigmentary changes. However, skin that has been treated with hydroxyl acids is more sensitive to sunlight and concomitant sunscreen use is essential. Finally, a number of surgical procedures such as laser, intense pulsed light, radiofrequency, dermabrasion, botulinum toxin type A, fillers and chemical peels may improve facial appearance. People should understand the associated costs, possible risks, and temporary nature of the effects. There are not enough evidence to support the use of vitamins C and E, co-enzyme Q10, kinerase, beta-carotene, green-tea extract for the treatment or prevention of photoaging.

### **Number of acquired melanocytic naevi in patients with melanoma and control subjects in Japan: naevus count is a significant risk factor for nonacral melanoma but not for acral melanoma**

Rokuhara S, Saida T, Oguchi M, Matsumoto K, Murase S, Oguchi S.  
*J Am Acad Dermatol* 2004;50:695-700.

This study aimed at obtaining the epidemiologic data of acquired melanocytic naevi in Japanese population and evaluating the number of naevi as a risk factor for melanoma development.

Six hundred control subjects and 82 patients with malignant melanoma (50 acral lentiginous and 25 nonacral melanoma) were included in this study. Each subject was examined to determine the number of acquired melanocytic naevi of 2 mm or greater in size, in the whole body other than the scalp and genital area.

In the control subjects, the highest number of acquired melanocytic naevi occurred in the 20- to 39-year-old group, reaching  $6.7 \pm 8.1$ /person. The nonacral melanoma patients had a significant higher number of acquired melanocytic naevi than the control subjects for the 40- to 59- ( $20.1 \pm 25.3$  versus  $4.3 \pm 3.9$ ;  $p < 0.001$ ) and the 60- to 79-year-old groups ( $10.7 \pm 8.3$  versus  $3.8 \pm 5.0$ ;  $p < 0.0001$ ). The number of naevi in the acral area was similar between the control and the patients with acral melanoma. The proportion of participants having more than 20 naevi was significantly higher in the nonacral melanoma patients than the control for the 40- to 59- (25.0% versus 1.4%;  $p = 0.0146$ ) and the 60- to 79-year-old group (18.2% versus 1.9%,  $p = 0.0340$ ). In contrast, no difference was found between the acral melanoma group and control.

This study concluded that a large number of melanocytic naevi is a risk factor for developing nonacral melanoma in the Japanese population, as in the Caucasian population.

### **Predictors of atopic dermatitis severity over time**

Ben-Gashir MA, Seed PT, Hay RJ.  
*J Am Acad Dermatol* 2004;50:349-56.

This was a longitudinal observational study on atopic dermatitis in a community-based design. The primary aim was to investigate the risk factors affecting the disease severity of atopic dermatitis over time.

A total of 137 children (65 boys, 72 girls; age 5 to 10 years) were recruited from general practices in the United Kingdom. The children were interviewed and examined every six months for up to four times, during the study period starting March 1998. The follow-up rate was 88%. The disease severity distribution according to the

SCORAD index at the third visit was: 80% mild, 18% moderate and 2% severe. In addition, a piloted questionnaire was completed by the parents at the first interview, investigating potential risk factors of severity including age of onset, social class, ethnic group, child's atopy, family history of atopy and others. The observer remained blinded to the results of the questionnaires.

The independent risk factors for developing more severe disease were identified as followed: onset during first year of life (adjusted odds ratio 2.1; 95% CI 1.2-3.2;  $p=0.008$ ), child's atopy including hay fever (adjusted odds ratio 2.42; 95% CI 1.39-4.2;  $p=0.002$ ) and asthma (adjusted odds ratio 2.0; 95% CI 1.1-3.6;  $p=0.021$ ), living in an urban area (adjusted odds ratio 2.15; 95% CI 1.12-4.1;  $p=0.021$ ).

The authors suggested that clinicians should be aware that patients exposed to these risk factors may have a different disease outcome.

### Strategies for skin cancer prevention

Harris RB, Alberts DS.

Int J Dermatol 2004;43:243-51.

Over the past three decades, more about the underlying pathways for the development of various cancers have been learnt. This has led to the development of potential cancer preventive and chemopreventive agents and strategies. Since solar ultraviolet (UV) exposure is the most important aetiologic factor for both non-melanoma skin cancers and melanoma, limiting UV exposure has been the aim of primary skin cancer prevention. It has been shown that daily use of a broad-spectrum sunscreen decreased the number of actinic keratosis. However, in a recent randomised controlled trial, routine daily use of a sunscreen made squamous cell carcinoma, but not basal cell carcinoma, amenable to prevention.

Addition of beta-carotene to the sunscreen does not confer any beneficial or harmful effect. The role of sunscreen to prevent melanoma remains questionable. Dysplastic naevi have been proposed to be important risk markers and potential precursors of melanoma. Identification of patients having dysplastic naevi occupies an important role in the prevention of skin melanoma.

The use of systemic retinol has been shown to be effective for both reduction of actinic keratosis and the inhibition of progression to squamous cell carcinoma. However, it is not effective for the reduction of subsequent skin tumours in those already have a history of non-melanoma skin cancers. Moreover, epigallocatechin gallate, a green tea polyphenolic compound, has been shown to inhibit the growth of different tumour cell lines, including a recent report showing that hot tea consumption reduces the risks of squamous cell carcinoma.

### 0.03% tacrolimus ointment applied once or twice daily is more efficacious than 1% hydrocortisone acetate in children with moderate to severe atopic dermatitis: results of a randomised double-blind controlled trial

Reitamo S, Harper J, Bos JD, et al., for the European Tacrolimus Ointment Group.

Br J Dermatol 2004;150:554-62.

This was a randomised double blind controlled study recruiting 624 patients aged 2-15 years with the diagnosis of atopic eczema to compare the efficacy of 0.03% tacrolimus ointment once ( $n=207$ ) or twice ( $n=210$ ) daily with 1% hydrocortisone acetate ointment twice daily ( $n=207$ ). The patients are randomised to apply the ointment for a minimum of 2 weeks and 1 more week post-clearance.

After 3 weeks of treatment, the median percentage decreased from baseline in modified Eczema Area and Severity Index was 78.7%, 70.0% and 47.2% for twice daily and once daily 0.03% tacrolimus ointment and 1% hydrocortisone acetate group respectively. For patients with moderate atopic dermatitis, there was little difference in the efficacy between once daily and twice daily tacrolimus, whereas patients with severe baseline atopic dermatitis responded significantly better to twice daily application of tacrolimus. Transient mild to modified skin burning were more common among the tacrolimus group, but usually resolved within three to four days.

Thus, tacrolimus is more effective in the treatment of atopic dermatitis than 1% hydrocortisone acetate and it is appropriate to adjust the frequency of application of tacrolimus ointment according to the severity of the disease. The major drawback in this study was the failure to compare tacrolimus ointment with more potent topical steroids commonly used in the treatment of atopic dermatitis.

This study was supported by Fujisawa GmbH, Munich, Germany.

### **Seborrhoeic keratoses: a study comparing the standard cryosurgery with topical calcipotriene, topical tazarotene, and topical imiquimod**

Herron MD, Bowen AR, Krueger GG.  
Int J Dermatol 2004;43:300-2.

Cryosurgery is the standard treatment for seborrhoeic keratoses. This was a non-randomised open-label study comparing the efficacy of cryosurgery, topical calcipotriene ointment, tazarotene cream, and imiquimod cream on truncal seborrhoeic keratoses. Fifteen patients, 13 women and two men, were enrolled

in this study. Nine seborrhoeic keratoses on each patient were assigned. The size of the seborrhoeic keratoses ranged from 5 to 15 mm. Each seborrhoeic keratosis received one of the following nine treatment options: single treatment cryosurgery, four-month treatment of the followings: tazarotene cream 0.1% daily and twice daily, calcipotriene ointment 0.005% daily and twice daily, imiquimod cream 5% daily and twice daily, Vanicream daily and twice daily. Vanicream represented a negative control.

The patients were evaluated monthly for six months after completion of treatment. It was found that one treatment of cryosurgery and twice daily application of tazarotene cream resulted in complete clinical and histological clearance of all and seven of 15 seborrhoeic keratoses respectively. Ten patients experienced initial irritation after applying tazarotene which improved with continuous use. None of the other treatment options resulted in complete clearance, either clinically or histologically.

This study confirmed that cryosurgery is effective in the treatment of seborrhoeic keratoses and tazarotene cream 0.1% twice daily may be considered if topical treatment is requested. The small number of patients in this study is one major drawback and the authors did not mention how the cryosurgery was performed.

### **Prevalence of dermatological disorders in Thai HIV-infected patients correlated with different CD4 lymphocyte count statuses: a note on 120 cases**

Wiwanitkit V.  
Int J Dermatol 2004;43:265-8.

Dermatological diseases are one of the important conditions of patients infected with Human

Immunodeficiency Virus (HIV). This was a cross-sectional descriptive study that reviewed 120 HIV infected patients in Bangkok, Thailand in 2000. All subjects received a complete physical examination to detect cutaneous disorders. Procedures like skin scrapings or biopsies were taken when necessary. Patients were categorised according to their CD4 counts.

There were 42 patients with CD4 counts >500/ul, 41 with CD4 counts at 200-499/ul and 37 with CD4 counts <200/ul. Ninety-six of 120 patients had cutaneous disease, including 28, 32 and 36 patients for the respective CD4 count groups. The overall prevalence of each dermatological condition were xerosis (73.33%), oral candidiasis (54.17%), seborrhoeic dermatitis (46.67%), pruritic papular eruption (36.67%), oral hairy leucoplakia (12.50%), folliculitis (11.67%), herpes zoster (9.17%), and alopecia (6.67%). The three most common skin disorders in patients with CD4 >500/ul were xerosis (64.29%), seborrhoeic dermatitis (30.95%), and oral candidiasis (19.04%); and that for patients with CD4 at 200-499/ul, were xerosis (73.17%), oral candidiasis (53.66%), and seborrhoeic dermatitis (51.22%); and that for patients with CD4 <200/ul were oral candidiasis (94.59%), xerosis (83.78%), and pruritic papular eruption (81.08%).

Patients with CD4 counts <200/ul were found to have significantly more skin disorders. There were no cases of Kaposi's sarcoma reported in this study, which might be due to the lower prevalence of human herpesvirus 8 in Asians or the fewer homosexual cases in the present study. There were also less drug eruption seen in this study for which no explanation was given.

## **Sentinel node biopsy for high-risk non-melanoma cutaneous malignancy**

Wagner JD, Evdokimow DZ, Weisberger E, Morre D, Chuang TY, Wenck S, et al.  
Arch Dermatol 2004;140:75-9.

This study evaluated the effectiveness of sentinel lymph node biopsy (SNB) in the detection of occult metastases in high-risk, non-melanoma cutaneous malignancies.

Twenty-four patients (9 women, 15 men, average age 61.4 years) with squamous cell carcinoma (n=17), adenocarcinoma (n=2) and Merkel cell carcinoma (n=5) were studied. Patients underwent lymphatic mapping and affected sentinel lymph nodes were removed and analysed. Complete lymphadenectomy was performed in nine patients and in those with a positive sentinel lymph node. SNB alone was done in a second group of patients with no palpable lymph node. Those with a positive SNB were offered complete lymphadenectomy or radiation therapy. Those with a negative SNB were followed clinically. The incidence of micrometastases in the SNB was compared to those who underwent lymphadenectomy.

SNB and complete lymphadenectomy was performed in 12 patients and SNB alone in 12 patients. Seven (29%) patients had at least one positive lymph node. There was one false-negative result in which tumour was detected in a non-sentinel lymph node in one SNB negative patient (12%). At a median follow-up time of 11 months (range 4-41 months) for ten patients with negative sentinel node, there were no recurrences in a sentinel node basin. The sensitivity for SNB was 88% and specificity was 100%. Its positive and negative predictive value were respectively 1.0 (7/7) and 0.94 (16/17).

SNB has a potential to detect occult lymph node disease in non-melanoma cutaneous malignancies. Larger trials are required. However, SNB is a labour-intensive process, requiring expertise and careful patient selection.

### **Number of satellite naevi as a correlate for neurocutaneous melanocytosis in patients with large congenital melanocytic naevi**

Marghoob AA, Dusza S, Oliveria S, Halpern AC. *Arch Dermatol* 2004;140:171-5.

An analysis of patients from an Internet Web-based registry for large congenital melanocytic naevus (LCMN) was performed to determine risk factors for developing neurocutaneous melanocytosis (NCM). LCMN referred to those naevus that is or can be expected to measure at least 20 cm in adulthood. The following parameters of the naevus were studied by questionnaire: size, distribution, site, change in character, number of satellite lesions. The NCM status of the naevus was assessed by noting any neurological conditions, symptoms, MRI findings, personal or family history of melanoma.

A total of 379 patients with LCMN were analysed (mean age 8 years, 75% < 10 years of age). There were 159 (42%) males and 220 (58%) females. Most (72%) of the LCMN were located on the posterior axis (head, neck, paraspinal), while 7% were found on the extremities. The mean and median number of satellite naevi was 81.5 and 20 respectively. There were 26 cases of NCM (median age at diagnosis 2.4 years, range birth-24.5 years). Patients with LCMN on the posterior axis were more likely to have a NCM (crude odds ratio 5.1, 95% confidence interval 1.2-22.2) when compared to those with LCMN elsewhere. However, its significance was attenuated when the number of satellite lesions was added to the multivariate analysis. The number of satellite

lesions was the main factor associated with the development of NCM. Those who had more than 20 satellite naevi had a 5.1-fold increased risk of NCM when compared to those with fewer than 20 satellite naevi. Logistic regression analysis of age, sex, location of LCMN did not identify any other significant factors.

### **UV radiation exposure related to age, sex, occupation, and sun behaviour based on time-stamped personal dosimeter readings**

Thieden E, Philipsen PA, Heydenreich J, Wulf HC. *Arch Dermatol* 2004;140:197-203.

The ultraviolet radiation (UVR)-exposure pattern in volunteers (golfers, gardeners, rangers, sun worshippers, indoor workers, children) was assessed. The time-related UVR exposure was measured in standard erythema doses (SEDs) by a personal electronic UVR dosimeter worn on the wrist and recording their sun-behaviour in a diary. Ambient solar UVR was measured by a biometer.

The median annual estimated UVR dose received was 173 SEDs. The median percentage of the ambient UVR dose received on working days was 2.2% (range 0-29%) and 5.5% (range 0.2-22.4%) during off days. When on vacation in southern Europe, 29% of the ambient UVR dose was received. The gardeners (outdoor workers) received most (55%) of their UVR dose on working days and received 6.6% of ambient UVR. A median of 2.5 SEDs was received when sunbathing or exposing the shoulders outside the beach in northern Europe and 3.2 SEDs/day in southern Europe. A median of 4.6 SEDs/day and 6.9 SEDs/day were received at the beach in northern and southern Europe respectively.

In children, girls received more UVR than boys (median SEDs 175 vs 116). The estimated UVR

dose increased by 5 SEDs per year among subjects young than 20 years. Adolescents received 11 SEDs/day at the beach in southern Europe and children received 44% of the total UVR dose at the beach. For all groups, approximately 50% of the total UVR dose was received between noon and 3 pm.

Decreasing the number of days of risk behaviour will substantially reduce the total UVR dose. However, due to different cultural habits and climate, UVR exposure patterns will vary between different regions.

### **Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomised prospective trial**

Rhodes LE, de Rie M, Enström Y, Groves R, Morken T, Goulden V, et al.

Arch Dermatol 2004;140:17-23.

The efficacy of photodynamic therapy (PDT) in the treatment of nodular basal cell carcinoma (BCC) was compared to surgery. Patients with previously untreated nodular BCC were randomised to either treatment. The following were excluded: face or scalp lesions smaller than 6 mm diameter or greater than 15 mm, extremities or neck lesions over 20 mm diameter, truncal lesions over

30 mm diameter. Fifty-two patients were treated with two PDT sessions (methyl aminolevulinate cream 160 mg/g, 75 J/cm<sup>2</sup> red light, 570-670 nm) given seven days apart and 49 patients received surgery. Thirteen patients with a non-complete response to PDT at three months were retreated. The patients were assessed at 3, 12 and 24 months.

Ninety-seven patients were assessed. There was no significant difference in clinical response between the two treatments (surgery 51/52 lesions, 98%; PDT 48/53, 91%) when assessed at three months. At 12 months, the total disease-free response rates were 44 (83%) of 53 lesions with PDT versus 50 (96%) of 52 lesions in those treated with surgery. Two lesions cleared by PDT had relapsed at 12 months while none had relapsed in the surgical group. At 24 months, three more lesions relapsed in the PDT group compared to one more lesion in the surgical group. However, PDT was associated with a significantly better cosmetic outcome at three, 12 and 24 months. Reported side-effects were erythema, burning sensation, and pain. One patient withdrew from PDT because of side-effect.

The authors concluded that PDT is an effective treatment for nodular BCC resulting in a better cosmetic result. However, as there is a higher relapse rate, long-term follow-up was recommended. This study was sponsored by Photocare.