Nonmelanoma skin cancer

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INTRODUCTION

According to statistics from the American Cancer Society, the annual incidence of nonmelanoma skin cancer (NMSC) in the United States is now estimated at over one million cases and thus approximately equals all other cases of human malignancies combined (www.cancer.org, Cancer Facts and Figures). The overwhelming majority of NMSC cases are basal cell and squamous cell carcinomas (BCCs and SCCs, respectively) in a ratio of approximately 4:1. A wide variety of additional nonmelanoma skin tumors arise from other cell types present in skin, such as lymphocytes, vascular endothelial cells, Merkel cells, mesenchymal stromal cells, and cells forming the adnexal structures. These entities are quite rare relative to BCC and SCC and will not be discussed herein.

Not surprisingly, given the large number of NMSC cases, there is a correspondingly large body of literature addressing various aspects of epidemiology, pathogenesis, and treatment. It is impossible in this format to present a completely comprehensive synopsis that includes all manuscripts relating to this very broad topic. Articles presented herein were chosen in an effort to give a reasonably comprehensive representation of the many lines of active inquiry currently advancing our understanding of NMSC. Selection of specific articles was based on the author's clinical and scientific experience with the published literature, literature review conducted specifically for this synopsis, and consultation with dermatology colleagues. Valuable work from many distinguished authors was unable to be included directly in this article, but is cited within references from papers highlighted herein. This synopsis focuses primarily on those contributions published in English since the turn of the millennium that are believed to be of greatest interest to the majority of currently practicing dermatologists.

Abbreviations used:

AK:	actinic keratosis
ALA:	5-aminolevulinic acid
BCC:	basal cell carcinoma
5-FU:	5-fluorouracil
FasR:	Fas receptor
HPV:	human papillomavirus
MC1R:	melanocortin-1 receptor
MMS:	Mohs micrographic surgery
NMSC:	nonmelanoma skin cancer
PDT:	photodynamic therapy
PUVA:	psoralens plus UVA
RCM:	reflectance confocal microscopy
SCC:	squamous cell carcinoma
SLN:	sentinel lymph node
UV:	ultraviolet
XP:	xeroderma pigmentosum

GENERAL REVIEWS

Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med 2001;344:975-83.

Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med 2005;353:2262-9.

This is a pair of well-written, comprehensive general reviews with value for both the dermatologist and general practitioner.

EPIDEMIOLOGY

It is difficult to obtain accurate epidemiological data on NMSC as cases are frequently specifically excluded from state and national cancer registries. Furthermore, incidence rates vary significantly depending on the ethnicity and geographic location of the study population. Despite this variability, most studies show that rates are increasing significantly worldwide, generally thought to be a result of increased cumulative ultraviolet (UV) exposure. This is in large measure an inevitable consequence of an increasingly elderly population, with additional contribution from changes in outdoor activities,

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This report reflects the best data available at the time the report was prepared, but caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations set forth in this report.

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clothing styles, atmospheric ozone, and environmental pollutants. Highest incidence rates continue to be in populations with light skin types living in regions of high UV exposure.

Diepgen TL, Mahler V. The epidemiology of skin cancer. Br J Dermatol 2002;146(Suppl 61):1-6.

This is a frequently cited, concise comprehensive review of many epidemiologic studies between 1990 and 2000 detailing NMSC rates in various regions within Europe, the United Kingdom, and the United States. The highest incidence rates by far were seen in Australia, with between 1% and 2% of the population developing NMSC per year.

Tran H, Chen K, Shumack. S. Epidemiology and aetiology of basal cell carcinoma. Br J Dermatol 2003;149(Suppl 66):50-2.

This brief review compiles data from many studies demonstrating a general increase in the incidence of BCC and cites additional studies on age, gender, and other factors contributing to BCC, including specific gene mutations caused by UV damage.

Housman TS, Feldman SR, Williford PM, Fleischer AB Jr, Goldman ND, Acostamadiedo JM, et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. J Am Acad Dermatol 2003;48:425-9.

Medicare claims data were studied from 1992 to 1995. Although the cost of treatment per individual case of NMSC was significantly less than that of many other cancers with higher morbidity and mortality, the large number of cases makes NMSC the fifth most costly cancer, accounting for 4.5% of all Medicare cancer costs. Further, the costs increased 41% between 1992-1993 and 1994-1995.

Athas WF, Hunt WC, Key CR. Changes in nonmelanoma skin cancer incidence between 1977-1978 and 1998-1999 in north central New Mexico. Cancer Epidemiol Biomarkers Prev 2003;12:1105-8.

Czarnecki D, Sutton T, Czarnecki C, Culjak G. A 10-year prospective study of patients with skin cancer. J Cutan Med Surg 2002;6: 427-9.

Harris RB, Griffith K, Moon TE. Trends in the incidence of nonmelanoma skin cancers in southeastern Arizona, 1985-1996. J Am Acad Dermatol 2001;45:528-36.

Karagas MR, Greenberg ER, Spencer SK, Stukel TA, Mott LA. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. Int J Cancer 1999;81:555-9.

Koh D, Wang H, Lee J, Chia KS, Lee HP, Goh CL. Basal cell carcinoma, squamous cell carcinoma and melanoma of the skin: analysis of the Singapore Cancer Registry data 1968-97. Br J Dermatol 2003;148:1161-6.

Wassberg C, Thorn M, Johansson AM, Bergstrom R, Berne B, Ringborg U. Increasing incidence rates of squamous cell carcinoma of the skin in Sweden. Acta Derm Venereol 2001;81: 268-72.

These 6 individual studies describe NMSC incidence rates and trends in diverse geographic locations from within the United States (New Hampshire, New Mexico, Arizona), as well as from Singapore, Sweden, and Australia. In New Hampshire, age-adjusted incidence rates of SCC increased by 235% in men and by 350% in women between 1979 and 1993, while incidence rates of BCC increased by more than 80% in both men and women. Similarly, age-adjusted SCC incidence rates for non-Hispanic white residents in New Mexico doubled between 1977 and 1998 with BCC incidence increasing by 50% in males and 20% in females. In contrast to these studies, data from the Southeastern Arizona Skin Cancer Registry between 1985 and 1996 demonstrates that while the incidence rates of NMSC are among the highest in the world, they do not appear to have steadily increased over the study period. In fact, the incidence of SCC demonstrated a slight decline. Reasons for this are not immediately clear, but may result in part from increased physician awareness and treatment of precursor actinic keratoses and from increased photoprotection among an increasingly informed public.

Data presented from the Singapore Cancer Registry from 1968-1997 also showed a slight annual decrease (0.9%) in SCC, while BCC increased 3% annually. In Sweden, SCC is one of the most rapidly increasing malignancies. In general, Swedish medical records are very thorough and extremely well organized, facilitating national epidemiologic studies. A total of 39,805 SCC cases were registered in the Swedish Cancer Registry between 1961 and 1995. Incidence rates for SCC increased substantially in both men (+425%) and women (+146%) in this predominantly fair-skinned Nordic population. In Australia, 300 NMSC patients were followed up for 10 years for development of additional skin cancers. New skin cancers developed in 67.8%, and multiple skin cancers (≥ 3) in 51.8%. The main risk factors for new skin cancer formation were male sex and prior multiple skin cancers. Men who had an NMSC were 8 times more likely than the general population to develop a melanoma, while women with NMSC were 4 times more likely.

Pearce MS, Parker L, Cotterill SJ, Gordon PM, Craft AW. Skin cancer in children and young adults: 28 years' experience from the Northern Region Young Persons' Malignant Disease Registry, UK. Melanoma Res 2003;13:421-6.

NMSC is rare in young populations, with correspondingly little epidemiologic data. In this study, the Northern Region Young Persons' Malignant Disease Registry was used to identify 200 cases of melanoma and NMSCs in patients younger than 25 years old from northern England between 1968 and1995. The incidence was 1.2 cases per million per year for children (0-14 years of age) and was 13 cases per million per year for young adults (15-24 years). Melanoma accounted for 138 cases, of

which 16 were in subjects younger than 15 years old at diagnosis. Of the 62 patients with NMSC, 66% were diagnosed with primary BCC, 13% with dermatofibrosarcoma protuberans, 10% with SCC and 11% with other tumors. The incidence of NMSC was significantly higher during the period 1982-1995 than during 1968-1981. The concerning increasing incidence parallels that seen in other studies of older adult populations and is presumably due to similar etiologic factors, highlighting the need for vigorous UV protection and skin cancer screening in the pediatric and young adult population.

Christenson LJ, Borrowman TA, Vachon CM, Tollefson MM, Otley CC, Weaver AL, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA 2005; 294:681-90.

Retrospective chart review was used to determine incidence of NMSC in persons younger than 40 years in Olmsted County, Minnesota, between 1976 and 2003. Overall, the age-adjusted incidence of BCC per 100,000 persons was 25.9 for women and 20.9 for men. The SCC incidence was similar in men and women, with an average age- and sex-adjusted incidence per 100,000 persons of 3.9. Importantly, the incidence of BCC increased significantly during the study period among women (but not men), while the incidence of SCC increased significantly among both women and men. These increases may translate into markedly increased NMSC cases as the population ages, emphasizing the need for early skin cancer prevention education in young adults.

EFFECTS OF UV RADIATION, SMOKING, DIET, AND TANNING BED USE ON NMSC

Armstrong BK, Kricker A: The epidemiology of UV induced skin cancer. J Photochem Photobiol 2001;63:8-18.

This review summarizes epidemiological evidence supporting a causal role for sun exposure in development of SCC, BCC, and melanoma. Data from many primary articles is synthesized to establish that (1) the incidence rate of each skin cancer type is higher in fairer skinned, sun-sensitive individuals; (2) risk increases with increasing ambient solar radiation; (3) the highest densities are on the most sun-exposed parts of the body; (4) cutaneous malignancies are increased in individuals with total (mainly SCC), occupational (mainly SCC), and recreational sun exposure (mainly melanoma and BCC), and in individuals with a history of sunburn and presence of benign sun damage in the skin. These epidemiologic data, coupled with additional studies in which sun-exposed human keratinocytes and melanocytes are found to harbor signature UVA and UVB mutations in known oncogenes, strongly support the premise that UV radiation is causally associated with NMSC. Additional evidence is provided by animal models in which UV radiation is employed to drive SCC and melanoma formation.

De Hertog SA, Wensveen CA, Bastiaens MT, Kielich CJ, Berkhout MJ, Westendorp RG, et al. Relation between smoking and skin cancer. J Clin Oncol 2001;19:231-8.

Smoking is an obvious risk factor for several malignancies, although little is known about its effect on skin cancer risk. Authors employed a hospital-based case-control study including 161 patients with cutaneous SCC, 301 with nodular BCC, 153 with superficial multifocal BCC, 125 with melanoma, and 386 control subjects. Information on smoking history was collected during personal interviews. After adjustment for age, sex, and sun exposure, tobacco smoking was an independent risk factor for SCC with a relative risk twice that of control subjects. There appeared to be a higher risk for current smokers than for former smokers. Interestingly, no significant association was found between smoking and BCC or between smoking and malignant melanoma. This lack of association with cutaneous melanoma is consistent with the typical oral findings in smokers. The oral cavity, which is obviously exposed to the highest concentrations of smoke, typically also develops oral SCC; however, there appears to be no increased risk of oral melanoma.

Fung TT, Spiegelman D, Egan KM, Giovannucci E, Hunter DJ, Willett WC. Vitamin and carotenoid intake and risk of squamous cell carcinoma of the skin. Int J Cancer 2003;103:110-5.

This study looked for the effect of differential dietary intake of vitamins A, C, and E; folate; total carotene; and several individual carotenoids on SCC incidence in two large cohorts of men and women without a history of cancer from the Nurses' Health Study and the Health Professionals Follow-up Study in the United States, in 1982 (N = 85,944 women) and 1986 (N = 43,867 men). Follow-up was for 14 years in women and 10 years in men. Diet was measured with food-frequency questionnaires every 2 to 4 years. A total of 369 cases of SCC in women and 305 cases in men were identified. After multivariate adjustment for various known behavioral, sun-exposure, and sun-sensitivity risk factors for SCC, no evidence was found that vitamins A, C and E; folate; or carotenoids are protective against SCC.

Duffield-Lillico AJ, Slate EH, Reid ME, Turnbull BW, Wilkins PA, Combs GF Jr, et al. Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. J Natl Cancer Inst 2003;95:1477-81.

The Nutritional Prevention of Cancer Trial was a double-blind, randomized, placebo-controlled, clinical trial designed to test whether selenium could prevent NMSC among 1312 patients from the eastern

United States who had prior NMSC. Selenium supplementation was found to be ineffective at preventing BCC and actually increased the risk of SCC and total NMSC.

Black HS, Herd JA, Goldberg LH, Wolf JE Jr, Thornby JI, Rosen T, et al. Effect of a low-fat diet on the incidence of actinic keratosis. N Engl J Med 1994;330:1272-5.

Black HS, Thornby JI, Wolf JE Jr, Goldberg LH, Herd JA, Rosen T, et al. Evidence that a low-fat diet reduces the occurrence of non-melanoma skin cancer. Int J Cancer 1995;62:165-9.

In these two complementary studies, patients with NMSC were randomized to either a control group, which made no dietary changes and consumed approximately 40% of daily caloric intake as fat, or to an intervention group that reduced dietary fat to approximately 20% of total caloric intake during the 24-month study period. Patients were examined at 4-month intervals by dermatologists blinded as to their dietary assignments. Nutrient analyses, conducted at each of the 4-month follow-up visits, indicated that the percentage of calories from fat consumed in the intervention groups had been reduced to about 20% and remained at this level throughout the study. The percentage of calories as fat in the control groups remained above 36%. There were no significant differences in total calories consumed or mean body weights, between control and intervention groups. After 2 years, the groups receiving a low-fat diet displayed significantly lower incidences of both actinic keratoses and NMSC.

Davies TW, Treasure FP, Welch AA, Day NE. Diet and basal cell skin cancer: results from the EPIC-Norfolk cohort. Br J Dermatol 2002;146:1017-22.

To examine the effect of dietary fat on NMSC incidence in a European population, patients enrolled in the European Prospective Investigation into Cancer and Nutrition—Norfolk study were followed up for development of NMSC. Dietary assessment was via a self-reported food diary. Between 1993 and 1998, 109 new cases of BCC were identified. The calculated odds ratios corresponded to an increase in consumption of one standard deviation (25.5 g) of fat. This level of increased fat consumption was not found to be a risk factor for BCC. In further analysis of additional diet components and food groups, a modest protective effect was found for increased vitamin E consumption. There was no evidence of a generalized healthy eating effect. Unfortunately, the number of SCC cases in this study was too small to make meaningful comparisons.

Karagas MR, Stannard VA, Mott LA, Slattery MJ, Spencer SK, Weinstock MA. Use of tanning devices and risk of basal cell and squamous cell skin cancers. J Natl Cancer Inst 2002;94:224-6.

A population-based, case-control study that included 603 BCC patients, 293 SCC patients, and 540 control subjects was used to evaluate NMSC risk from UV tanning beds. Personal interviews were used to obtain information on tanning device use, sun exposure history, sun sensitivity, and other risk factors for skin cancer. Use of tanning devices was associated with odds ratios of 2.5 for SCC and 1.5 for BCC. Adjustment for history of sunburns, sunbathing, and sun exposure did not affect results. In response to an association between tanning bed use and skin cancer, many states now prohibit, or require parental consent for, minors wishing to use tanning beds.

HERITABLE RISK FACTORS FOR NMSC

Box NF, Duffy DL, Irving RE, Russell A, Chen W, Griffyths LR, et al. Melanocortin-1 receptor genotype is a risk factor for basal and squamous cell carcinoma. J Invest Dermatol 2001;116:224-9.

Melanocortin-1 receptor (MC1R) is a 7-pass transmembrane G-protein coupled receptor expressed by melanocytes which regulates eumelanogenesis through activation by the proopiomelanocortin-derived peptides α-melanocyte-stimulating hormone and adrenocorticotropic hormone. Specific MC1R gene variants Arg151Cys, Arg160Trp, and Asp294His are associated with red hair, fair skin color, increased ultraviolet sensitivity, and increased risk of melanoma. In this study, authors examined 220 individuals from Queensland, Australia, 111 of whom were at high risk (based on previous SCC, BCC or AKs) and 109 at low risk (no prior NMSC or AKs) for NMSC. As with melanoma, there was an association between MC1R variants Arg151Cys, Arg160Trp, and Asp294His, and the development of NMSC. Other commonly occurring variant alleles were identified as having a minimal impact on pigmentation and NMSC risk.

Carless MA, Lea RA, Curran JE, Appleyard B, Gaffney P, Green A, et al. The GSTM1 null genotype confers an increased risk for solar keratosis development in an Australian Caucasian population. J Invest Dermatol 2002;119:1373-8.

The glutathione-S-transferase genes play a part in detoxification of carcinogens and mutagens, including some produced by UV radiation. This study examined the role of glutathione-S-transferase gene polymorphisms in susceptibility to development of solar keratoses. A significant association between glutathione-S-transferase M1 genotypes and solar keratoses development was detected, with null individuals having an approximate two-fold increase in risk for solar keratoses, and a significantly higher risk increase in combination with high outdoor exposure and other known risk factors including fair skin and poor tanning ability.

Hemminki K, Zhang H, Czene K. Familial invasive and in situ squamous cell carcinoma of the skin. Br J Cancer 2003;88:1375-80.

The national Swedish Family-Cancer Database was used to compare the incidence rates of NMSC among

children of NMSC patients with that expected for the general population. Analysis of data from 1961 to 1998 showed 1252 invasive and 2474 in situ SCC among offspring and over 10 times more among parents. In 259 families, a parent and an offspring had SCC. The familial standardized incidence ratios were 2.72 for invasive and 2.40 for in situ skin cancers in offspring. Expectedly, multiple skin cancers in parents were associated with increased standardized incidence ratios for invasive SCC in offspring, being 2.55 for one and up to 14.93 for two invasive and two in situ cancers in parents. Results provide evidence that there is an underlying hereditary susceptibility for at least part of the familial SCC clustering.

Milan T, Verkasalo PK, Kaprio J, Koskenvuo M, Pukkala E. Malignant skin cancers in the Finnish Twin Cohort: a population-based study, 1976-97. Br J Dermatol 2002;147:509-12.

To dissect hereditary and environmental factors in the etiology of NMSC, the Finnish Twin Cohort, comprising 25,882 adult twins with established zygosity, was linked with the Finnish Cancer Registry to identify malignant skin cancers in a prospective follow-up from 1976 to 1997. Sixty twins were diagnosed with melanoma and 49 twins with NMSC during the follow-up. While these numbers seem low, they did not differ from the risk in the matched population at large. There was only one pair where both twins had a malignant skin cancer (dizygotic male twins both with SCC). Authors concluded that the near-total lack of concordance for skin cancer in twin pairs suggests that environmental rather than hereditary factors are most important for development of malignant skin cancers in this white population with low levels of sun exposure. This conclusion differs from that of the Swedish study above, which found that hereditary factors were important for defining NMSC risk. It is unlikely that the Finns and Swedes are really that different. It seems that these results may be in part a consequence of the low incidence of NMSC in the Finnish study population.

SPECIAL CASES: TRANSPLANT, PUVA, UVB, AND IMMUNOSUPPRESSED POPULATIONS

Over the past two decades there has been a dramatic increase in the number of patients living with chronic immune suppression. This results largely as an unfortunate consequence of the antirejection regimens associated with organ transplantation. The immunosuppressed population is also augmented by an increase in the number and efficacy of immunosuppressive pharmacologic agents used not only in transplant medicine, but also in rheumatologic and autoimmune diseases. These factors coupled with the concurrent AIDS epidemic has contributed to the establishment of a large immunosuppressed population, and comprehensive dermatologic management of these high-risk transplant patients has become a difficult clinical problem. These vulnerable patients have a markedly increased risk of both typical and highly invasive NMSC. It is also of interest to note that while the BCC/SCC incidence ratio is approximately 4:1 in the general population, SCCs become more prevalent in the transplant population with a BCC/SCC ratio of approximately 1:2. Reasons for this change are not completely clear, although human papillomavirus is most likely at least one etiologic factor, with decreased immune surveillance leading to a relative inability to clear infected keratinocytes. These persistent HPV infected cells may thus create a population of epidermal keratinocytes highly susceptible to malignant degeneration due to inactivation of cell cycle G1 regulatory constraints by HPV E6 and E7 proteins. Additional mutations through UV damage may then rapidly lead to SCC development. That UV radiation is still a driving factor in these patients is highlighted by the fact that transplant patients with darker skin are relatively resistant to SCC compared with transplant patients with lighter skin types.

With DNA damage secondary to UV exposure as the primary etiologic factor driving tumorigenesis in skin, it may come as no surprise that an additional, especially vulnerable population is created in dermatology offices through the use of UV light therapy. Psoralens plus UVA radiation (PUVA) has been clearly linked to significantly increased SCC risk. Given its known mutagenic effects, it is possible that UVB treatment also increases NMSC, although not to the same degree as with PUVA. While the risk/benefit ratio may come down in favor of these treatment modalities for select patients, meticulous follow-up is essential to ensure that the potential for significant treatment-associated morbidity and mortality is not worse than the primary condition.

Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. J Am Acad Dermatol 2002;47:1-17.

This continuing medical education article is a well-written, very comprehensive review of skin cancer in transplant recipients, including epidemiology, clinical presentation, pathogenic cofactors, and options for management. Physicians interested in this subject should start by reviewing this article.

Bordea C, Wojnarowska F, Millard PR, Doll H, Welsh K, Morris PJ. Skin cancers in renal-transplant recipients occur more frequently than previously recognized in a temperate climate. Transplantation 2004;77:574-9.

This is a comprehensive epidemiologic review of skin cancers occurring in a population of 979 patients receiving kidney transplants in Oxford between 1975 and 1996. One hundred eighty-seven (19.1%) transplant patients developed at least one skin malignancy, at a rate of 141 per 1000 person years at risk. Sixty-four percent of patients with skin cancer had multiple lesions. SCC was the most common skin cancer, and the mean time to presentation of the first skin cancer was 8 years. Risk factors identified include increasing age at transplantation, male sex, total time of immunosuppression, elevated creatinine levels, and graft relation. The cumulative incidence of skin cancer reached 61% at 20 years after transplantation.

Carroll RP, Ramsay HM, Fryer AA, Hawley CM, Nicol DL, Harden PN. Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: a prospective study in Queensland, Australia. Am J Kidney Dis 2003;41:676-83.

A single-center prospective study of 310 kidney transplant recipients in Queensland established an overall NMSC incidence of 28.1%, which increased with duration of immunosuppression therapy. Incidence was 47.1% in patients with more than 20 years of immunosuppression.

Ramsay HM, Fryer AA, Hawley CM, Smith AG, Harden PN. Non-melanoma skin cancer risk in the Queensland renal transplant population. Br J Dermatol 2002;147:950-6.

Authors studied records from 398 kidney transplant recipients in Queensland Australia between July 1999 and April 2000 to determine the risk of NMSC following kidney transplantation. One hundred eighty-seven of 361 (51.8%) transplant recipients of Fitzpatrick skin types I-IV developed 3979 NMSCs since first transplantation. The ratio of SCC/BCC was reversed from 1:3.7 before transplantation to 2:1 after transplantation. NMSC increased with duration of immunosuppression; 29.1%, 52.2%, 72.4% and 82.1% of those immunosuppressed for less than 5, 5-10, 10-20, and more than 20 years, respectively.

Mithoefer AB, Supran S, Freeman RB. Risk factors associated with the development of skin cancer after liver transplantation. Liver Transpl 2002;8:939-44.

Authors surveyed 151 liver transplant recipients for NMSC history and potential risk factors associated with cutaneous malignancies. There were 86 documented skin cancers in 34 patients: 56 SCCs, 23 BCCs, and 7 melanomas with a median follow-up of 1490 days. In a multivariate model, age, male gender, red hair, brown eyes, sclerosing cholangitis, and use of cyclosporine are the strongest predictors. Authors note that the incidence of skin cancer after liver transplantation is typically underestimated, and that like other solid organ transplants, SCC incidence is significantly higher than in the general population.

Lindelof B, Granath F, Dal H, Brandberg Y, Adami J, Ullen H. Sun habits in kidney transplant recipients with skin cancer: a case-control study of possible causative factors. Acta Derm Venereol 2003;83:189-93.

A case-control study was carried out on 95 kidney transplant recipients who developed SCC after the transplant and on a matched control population of 154 kidney transplanted patients. Compared with patients with Fitzpatrick skin type IV, the cutaneous SCC odds ratio was 3.0 for skin types I and II. Patients with light blond or red hair also had a higher odds ratio (3.2) than those with dark hair, and patients with warts after transplant had a higher odds ratio (2.2) than those without.

Katz KA, Marcil I, Stern RS. Incidence and risk factors associated with a second squamous cell carcinoma or basal cell carcinoma in psoralen + ultraviolet A light-treated psoriasis patients. J Invest Dermatol 2002;118:1038-43.

The PUVA Follow-up Study enrolled 1380 psoriasis patients at 16 centers in the United States in 1975 and 1976 and the cohort has been analyzed multiple times since its inception. It is well established that psoralen plus ultraviolet A (PUVA)—treated psoriasis patients are at increased risk for SCC and BCC. Incidence and risk factors for second SCCs and BCCs were studied in the initial cohort of 1380 patients followed up for more than 20 years. Two hundred sixty-four (19%) had an SCC and 258 (19%) had a BCC after starting PUVA therapy. After a first SCC, the risk of a second SCC was 26% at 1 year, 62% at 5 years, 75% at 10 years, and 91% at 15 years. These rates are significantly higher than for non-PUVA treated control patients after an initial SCC diagnosis. Risk increased with high PUVA exposure. Risk of a second BCC was 21% at 1 year, 49% at 5 years, 61% at10 years, and 70% at 15 years. The first 5 years of BCC data are similar to those of other control studies.

Nijsten TE, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. J Invest Dermatol 2003;121:252-8.

In an extension of the prior study, the 1380 PUVA-treated psoriasis patients were studied to determine skin cancer risk among patients who have discontinued PUVA. A total of 27,840 person-years were observed, of which 59.4% were years without psoralen and UV. No significant decrease in risk was noted during the first 15 years after PUVA was discontinued. Subsequently, SCC risk was somewhat reduced. However, after 25 years, about 7% of patients with less than 200 PUVA treatments, and more than half of the patients with more than 400 treatments developed at least one SCC. After 25 years, almost one third of the patients exposed to

more than 200 treatments developed at least one BCC. Authors therefore conclude that NMSC risk remains elevated in PUVA-treated patients, even those more than two decades removed from their last treatment, highlighting the need for close follow-up examinations for prolonged time periods.

Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. J Invest Dermatol 2005;124:505-13.

In an additional extension of the studies described above, the 1380 PUVA patients were examined to determine the relation of skin cancer incidence to UVB treatment. This was possible, because over the 28 years of the study, the majority of the patients also had a history of at least some UVB therapy. The data indicate that the risks of UVB therapy are only significant after high cumulative exposure (>300 treatments) and after sufficient time has elapsed from exposure for the development of tumors. After controlling for possible confounders, authors conclude that in comparison to patients with low-dose UVB exposure, high-dose UVB exposure increases the risk of developing an SCC or BCC in a given year by about 40%. The increase in relative risk is most apparent among individuals previously treated with smaller amounts of PUVA, on anatomic sites typically exposed during phototherapy, but only rarely or intermittently exposed to environmental sunlight. However, since the underlying tumor incidence on these anatomic sites is relatively small, the increased risk of NMSC translates into a relatively small increase in the absolute number of tumors. UVB is much less carcinogenic than PUVA, and the modest risks associated with UVB therapy must be viewed within the overall context of the patient's baseline skin cancer risk, and potential benefits of therapy.

Lee E, Koo J, Berger T. UVB phototherapy and skin cancer risk: a review of the literature. Int J Dermatol 2005;44:355-60.

In an effort to synthesize the available data on UVB and NMSC, authors identified all studies between 1966 and 2002 that attempted to quantify the skin cancer risk of UVB phototherapy. Eleven studies (10 of which concerned psoriasis patients), involving approximately 3400 participants, were included. None of the studies showed a statistically significant increase in the risk of NMSC, with the exception of one PUVA cohort which displayed an increased rate of genital tumors associated with UVB phototherapy. The more recent reference by Lim and Stern (cited immediately above) was published later and was thus not included in this study.

Karagas MR, Cushing GL Jr, Greenberg ER, Mott LA, Spencer SK, Nierenberg DW. Non-melanoma skin cancers and glucocorticoid therapy. Br J Cancer 2001;85:683-6.

A population-based case-control study in New Hampshire was used to determine whether patients taking glucocorticoids for reasons other than organ transplant are at an increased risk of skin malignancies. Logistic regression analysis was used to compute odds ratios associated with glucocorticoid use for 1 month or longer while controlling for potential confounding factors. SCC risk was increased among patients who were treated with glucocorticoids for at least 1 month (adjusted odds ratio = 2.31) with risk of BCC elevated modestly (adjusted odds ratio = 1.49). Inhaled steroid use did not have any effect of NMSC incidence.

Nguyen P, Vin-Christian K, Ming ME, Berger T. Aggressive squamous cell carcinomas in persons infected with the human immunodeficiency virus. Arch Dermatol 2002;138:758-63.

These authors relate their clinical experience with 10 consecutive patients infected with HIV who had aggressive SCCs. Despite treatment, 5 patients died of metastatic SCC within 7 years of their initial diagnosis. Clearly, these SCC patients with HIV infection had much more aggressive and lethal tumors than the general SCC patient population. Surprisingly, HIV stage and the degree of immunosuppression were not associated with increased morbidity and mortality. Patients initially undergoing combination surgery and radiation therapy or radical neck dissection had the best outcomes. Authors concluded that high-risk SCCs should be managed aggressively rather than palliatively in patients infected with HIV.

Sanchez-Palacios C, Guitart J. Hydroxyurea-associated squamous dysplasia. J Am Acad Dermatol 2004;51:293-300.

Hydroxyurea therapy has been associated with increased risk of AKs and SCCs, especially on sun-exposed surfaces. This report describes two cases of squamous dysplasia associated with long-term hydroxyurea therapy and reviews 17 additional cases from the literature. Authors discuss possible pathogenetic mechanisms of carcinogenicity.

ON THE RELATIONSHIP BETWEEN AK AND SCC

Recent debate has been directed at establishing a relationship between SCC and AK. At the center of this discussion is whether the AK is in fact an in situ SCC, or rather, an early, precancerous UV-induced epidermal atypia. Answering the question, of course, depends on how one defines cancer. Employing the use of standard experimental criteria for malignant transformation, including indefinite proliferative capacity in cell culture (immortalization), colony growth in soft agar, and ability to develop tumors after introduction into immunodeficient mice, is

currently not possible as human cell lines have not been established from any nonmucosal, nongenital cutaneous SCC or AK. Reasons for this technical difficulty are not clear, but while normal primary keratinocytes are easily isolated and grow well in culture, keratinocytes isolated from cutaneous SCCs do not grow in vitro. There are most likely factors present in the local tumor environment (possibly from stromal fibroblasts, surrounding keratinocytes, or immune cells) necessary for supporting growth of the malignant keratinocytes that are lacking in keratinocyte culture media.

As it is currently not possible to establish that AKs are in situ SCCs using standard laboratory definitions, defining the relationship for now depends on clinical behavior and analysis of histopathological patterns. AKs are clearly induced by UV damage, are a risk factor for development of classically defined SCC, and, in some cases, appear to develop directly into full-blown SCC. That many AKs spontaneously resolve may represent immune system clearing of atypical cells. Relative deficiency in this clearing may be a driving factor underlying the high SCC rates in immunosuppressed patients. This AK versus SCC distinction is meaningful only if it affects prognosis, management, or therapy. For now, most would agree that managing AKs with the same methods employed to treat traditionally defined SCC in situ is not only financially prohibitive, but also poses excessive risk and morbidity to patients. This is not to say however, that the common AK should be dismissed as a banal and inconsequential triviality; rather, it should be afforded the attention deserving of a keratinocytic neoplasia harboring UV-induced DNA mutations driving altered cellular signaling, which results in significantly aberrant cellular growth and differentiation.

Lebwohl M. Actinic keratosis: epidemiology and progression to squamous cell carcinoma. Br J Dermatol. 2003;149(Suppl 66):31-3.

This article and the references cited therein constitute a thorough review of the epidemiology of AK and the histopathological and molecular evidence for its close relationship with SCC.

Brand D, Ackerman AB. Squamous cell carcinoma, not basal cell carcinoma, is the most common cancer in humans. J Am Acad Dermatol 2000;42:523-6.

If BCC is widely recognized to have a superficial variant, why does no one refer to "superficial SCC"? This piece is a lively argument making the case for considering the solar keratosis as a subtype of SCC. At the risk of adding confusion to the semantic argument, the author of this synopsis would posit that the cellular atypia in a "superficial SCC" is confined to the basal layer, while atypia extending to the most superficial layers of the epidermis is recognized as SCC in situ—in situ meaning the "natural or original place." Therefore, if a solar keratosis is the original initiating manifestation in an SCC spectrum, it seems that its most appropriate designation would be SCC in situ too.

Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol. 2000;42:4-7.

This literature review identifies the frequency, distribution, and determinants of AKs and SCC. The epidemiology and risk factors for AK and SCC were virtually the same. However, SCC occurred most frequently on the head, with AKs most frequently on the upper extremities. AKs were found to be the most important risk factor identifying those most predisposed to the development of SCC.

RISK FACTORS AND PROGNOSIS FOR RECURRENT, INVASIVE, AND METASTATIC SCC

In addition to immunosuppression, several studies have identified other factors that correlate with increasing likelihood of recurrent, invasive, or metastatic disease. It should be recognized, however, that the literature on this topic is not definitively clear, as studies examining the complete complement of known potential risk factors with cohorts large enough to perform statistically meaningful multivariate analysis are lacking. Nonetheless, these findings have implications for patient education regarding prognosis as well as for establishing the most appropriate treatment and follow-up surveillance plan.

Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol 2000;136:1524-30.

This study was designed to assess the risk of developing a BCC, SCC, and/or Bowen's disease after development of an NMSC of a specific type. Authors identified and reviewed 17 studies that included data for 26 tumor combinations. Overall, the 3-year cumulative risk of a subsequent SCC after an index SCC is 18%, at least a 10-fold increase in incidence compared with the incidence of first tumors in a comparable general population. For BCCs, the 3-year cumulative risk is 44%, also at least a 10-fold increase in incidence compared with the rate in a comparable general population. The risk of developing a BCC in patients with a prior SCC is about equal to the risk among persons with a prior BCC, but the risk of developing an SCC in patients with a prior BCC is relatively low (6%). Authors conclude that the risk of developing a subsequent skin cancer of a specific type depends on the type of prior NMSC and the number of prior skin tumors of that type. On the

basis of these findings, follow-up strategies for patients with BCC and SCC are suggested.

Griffiths RW, Feeley K, Suvarna SK. Audit of clinical and histological prognostic factors in primary invasive squamous cell carcinoma of the skin: assessment in a minimum 5-year follow-up study after conventional excisional surgery. Br J Plast Surg 2002;55:287-92.

A 6-year (1990-1995) cohort of SCC patients was used to evaluate prognostic factors for primary SCC treated by conventional surgery. Of the 93 evaluable patients, 85 lived without recurrence or metastasis for at least 5 years after treatment, and 8 died of their disease. Comparing the groups who were alive or had died of disease at 5-year follow-up, the tumor diameter and tumor thickness were significantly greater in the 8 patients who died, but there were no significant differences with regard to age, deep resection margin clearance, lateral epidermal resection margin clearance, lymphocyte response, or degree of tumor differentiation.

Cherpelis BS, Marcusen C, Lang PG. Prognostic factors for metastasis in squamous cell carcinoma of the skin. Dermatol Surg 2002;28:268-73.

Using a tumor registry from the Dermatologic Surgery Unit at the Medical University of South Carolina, 25 cases of metastatic SCC were compared with 175 cases of nonmetastasizing SCC treated by Mohs surgery. Tumor size, Clark level, degree of differentiation, the presence of small tumor nests, infiltrative tumor strands, single-cell infiltration, perineural invasion, acantholysis, and recurrence all correlated strongly with metastasis. Location, ulceration, inflammation, and Breslow depth did not correlate with metastasis.

Martinez JC, Otley CC, Stasko T, Euvrard S, Brown C, Schanbacher CF, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. Arch Dermatol 2003;139:301-6.

An international, multicenter, collaborative group retrospectively analyzed data from 68 organ transplant recipients with 73 distinct metastatic skin cancers to evaluate the demographic characteristics, clinical course, and outcome in organ transplant recipients with metastatic skin cancer. Metastasis from skin cancer in organ transplant recipients was most commonly SCC in regional lymph nodes. By 1 year after metastasis, the cumulative incidence of relapse was 29%, and the 3-year disease-specific survival rate was 56%. Not surprisingly, patients whose initial metastases were distant or systemic had a significantly poorer disease-specific survival than those whose initial metastases were in-transit or regional. Authors concluded that metastatic skin cancer in organ transplant recipients has a poor prognosis necessitating preventive, early, and aggressive therapeutic interventions to minimize this serious complication of transplant-associated immunosuppression.

MOLECULAR MECHANISMS DRIVING NMSC

Sunlight is the primary etiologic agent driving both SCC and BCC formation. UV radiation leads directly to characteristic DNA mutations that can be identified within tumor tissue as being caused specifically by UV. While these mutations occur throughout the genome, SCC and BCC tumor cells frequently harbor characteristic mutations in specific pathways. The p53 tumor suppressor protein is mutated in the majority of both SCC and BCC, while mutations in the Patched pathway are frequently encountered in BCC. Mouse and human model systems for experimentally controlled NMSC have recently been developed that may significantly advance our understanding of the complex interplay between aberrant specific cellular signaling pathways driving epidermal tumorigenesis.

Brash DE. Sunlight and the onset of skin cancer. Trends Genet 1997;13:410-4.

Cleaver JE, Crowley E. UV damage, DNA repair and skin carcinogenesis. Front Biosci 2002;7:d1024-43.

Leffell DJ, Brash D. Sunlight and skin cancer. Sci Am 1996;275:52-3, 56-9.

These 3 readily approachable reviews highlight the primary mechanisms through which UV radiation leads to DNA mutation and clonal expansion of malignant cell populations resulting in NMSC.

Kreimer-Erlacher H, Seidl H, Back B, Cerroni L, Kerl H, Wolf P. High frequency of ultraviolet mutations at the INK4a-ARF locus in squamous cell carcinomas from psoralen-plus-ultraviolet-A-treated psoriasis patients. J Invest Dermatol 2003;120:676-82.

Kreimer-Erlacher H, Seidl H, Back B, Kerl H, Wolf P. High mutation frequency at Ha-ras exons 1-4 in squamous cell carcinomas from PUVA-treated psoriasis patients. Photochem Photobiol 2001;74:323-30.

Wolf P, Kreimer-Erlacher H, Seidl H, Back B, Soyer HP, Kerl H. The ultraviolet fingerprint dominates the mutational spectrum of the p53 and Ha-ras genes in psoralen + ultraviolet A keratoses from psoriasis patients. J Invest Dermatol 2004;122:190-200.

This set of articles explores possible mechanisms through which PUVA increases SCC risk. Squamoproliferative lesions from these patients frequently exhibit mutations in the p53 tumor suppressor gene (57%), the Ha-ras proto-oncogene (44%-76%), and at the INK4a-ARF locus (42%), whose two overlapping genes code for critical proteins which indirectly regulate p53 and Rb. These mutations can be organized into 3 groups based on the type of mutations identified: (1) UVB resulting in C-to-T or CC-to-TT transitions at dipyrimidine sites; (2) PUVA and/or UVB resulting in C-to-T transitions at dipyrimidine

sites opposite a 5′TpG sequence (a potential psoralen binding site); and (3) other mutations without a characteristic signature. In these studies, the majority of the SCC mutations were of the UVB type, suggesting that PUVA itself may not be playing a direct causal role in many of these tumors. Mutations were identified in several regions of these genes where their functional consequence is not always known, making it unclear whether these mutations are actually contributing to the malignant phenotype. Some recurrent mutations do, however, occur at hot spots known to affect protein function. In particular, frequent mutations (33%) were seen at Ras amino acid 12. Mutations at this location frequently result in a constitutively active Ras protein, immune to normal counter-regulatory mechanisms, which in cooperation with additional aberrant cellular signaling is a dominant force driving malignant transformation.

Cairey-Remonnay S, Humbey O, Mougin C, Algros MP, Mauny F, et al. TP53 polymorphism of exon 4 at codon 72 in cutaneous squamous cell carcinoma and benign epithelial lesions of renal transplant recipients and immunocompetent individuals: lack of correlation with human papillomavirus status. J Invest Dermatol 2002;118:1026-31.

The p53 codon 72 encoding either arginine or proline has been shown to confer a susceptibility to the development of skin tumors in renal transplant recipients. This study analyzed HPV presence and p53 allele distribution in SCCs from kidney transplant recipients and immunocompetent patients. Fifty-three SCCs from 40 kidney transplant recipients, 50 benign epithelial skin lesions from 50 kidney transplant recipients with no history of skin cancer, 51 SCCs from immunocompetent patients, and 29 blood samples from immunocompetent individuals without skin cancer were investigated. HPV DNA was detected in 64% of SCCs and 79% of benign epithelial lesions from renal transplant recipients and in only 37% of SCCs from immunocompetent patients. Mucosal oncogenic HPV types were predominant in SCC from both renal transplant recipients and immunocompetent patients. Rate of arginine homozygosity in SCC from renal transplant recipients was significantly higher (83%) than in immunocompetent patients with or without SCC (60% and 59%, respectively). The TP53 arginine/arginine genotype may therefore represent a potential risk factor for the development of SCC in kidney transplant recipients compared with immunocompetent patients.

McGregor JM, Harwood CA, Brooks L, Fisher SA, Kelly DA, O'Nions J, et al. Relationship between p53 codon 72 polymorphism and susceptibility to sunburn and skin cancer. J Invest Dermatol 2002;119:84-90.

The relationship between the p53-position 72 allelic forms and NMSC was examined by determining the correlation with susceptibility to sunburn and by p53 sequence analysis of a series of tumors. A positive association was found between p53-72R and susceptibility to sunburn, as assessed by skin phototype and minimal erythema radiation dose. A significant association was also found between p53-72R homozygosity and both SCC and BCC in kidney transplant recipients but not in immunocompetent patients. p53 sequence data revealed mutations in 30 of 70 (42.9%) NMSCs, 28 (93%) of which were in the p53-72R allele. Loss of heterozygosity occurred more frequently in p53-72RP than in p53-72RR tumors with preferential loss of p53-72P in heterozygotes, independent of the mutant status of the concomitant allele. These data suggest functional differences between polymorphic forms of p53 that are likely to be relevant to skin carcinogenesis and are consistent with results above.

Dajee M, Lazarov M, Zhang JY, Cai T, Green CL, Russell AJ, et al. NF-kappaB blockade and oncogenic Ras trigger invasive human epidermal neoplasia. Nature 2003;421:639-43.

Mechanistic research into human cutaneous SCC has been difficult for two main reasons. First, there have been no successful attempts to establish human SCC cell lines from nonmucosal spontaneously occurring human SCC. Second, cell lines that have been established from mucosal tumors are heterogeneous and carry an unknown number of genetic mutations. Furthermore, these highly passaged lines are frequently genetically unstable and often contain one or more viral oncogenes (frequently from HPV). Studying epidermal tumorigenesis in mouse systems is also problematic as the medical relevance of murine studies is limited by differences between mouse and human skin, and by the greater ease of transforming murine cells. This article details the first human SCC model system employing defined genetic elements and, in so doing, represents a significant advance in the study of human epidermal tumorigenesis. Starting with normal human keratinocytes, authors introduced two mutant genes and used these transduced cells to reconstitute skin grafts, which were placed on immunodeficient mice. After growing for a few weeks, human grafts with the two mutant genes showed all of the hallmarks of naturally occurring invasive SCC with disordered epidermal hyperproliferation, cellular atypia, and invasion through basement membrane. Control grafts with normal human keratinocytes yielded normal-appearing skin. The two mutant genes were oncogenic Ras and a constitutively active form of IκBα, which inhibits signaling through the NF-κB pathway. These proteins had previously been implicated in epidermal SCC in mice and were also shown in this article to be relevant to naturally occurring human SCC. Also

important, development of SCC in this model system was shown to be dependent on intact laminin 5 and $\alpha 6\beta 4$ integrin, indicating that these basement membrane components may be doing more than simply anchoring epidermis to dermis and may also play a role in regulating growth and differentiation of the proliferating basal keratinocytes.

Chiles MC, Ai L, Zuo C, Fan CY, Smoller BR. E-cadherin promoter hypermethylation in preneoplastic and neoplastic skin lesions. Mod Pathol 2003;16:1014-8.

E-cadherin is an intercellular adhesion molecule specifically expressed in epithelial tissues that is important for maintaining epithelial stability. E-cadherin inactivation is linked to increased potential for tumor invasiveness and distant metastasis in many human cancers, including SCC. Inactivation of E-cadherin is known to occur via mutation in E-cadherin itself as well as by hypermethylation of the promoter region, a mechanism for gene silencing which leads to decreased transcription. Analysis of AK, SCC in situ, invasive SCC, and uninvolved control skin demonstrated that E-cadherin promoter hypermethylation increased in parallel with tumor invasiveness.

Lacour JP. Carcinogenesis of basal cell carcinomas: genetics and molecular mechanisms. Br J Dermatol. 2002;146(Suppl 61):17-9.

This comprehensive review details the major signaling pathways known to drive BCC formation. Like SCC, they are also largely induced by UV damage, but data suggest that some differences may exist in the mechanisms of their UV induction. The originating cells likely arise from deeper interfollicular basal cells, hair follicles, or sebaceous glands, which seems to suggest exposure to different doses or wavelengths of UV radiation. The *P53* gene and the *patched* gene (*PTCH*) are major targets of UV radiation for BCC induction with frequent observation of the UV signature. As well as these inhibiting mutations in *P53* and *PTCH*, activating mutations in Smoothened, another downstream element in the Patched pathway, are also involved in BCC formation. Mouse models are consistent with this, as transgenic mice overexpressing Smoothened or Sonic hedgehog in the skin spontaneously produce skin lesions resembling human BCCs.

Fan H, Oro AE, Scott MP, Khavari PA. Induction of basal cell carcinoma features in transgenic human skin expressing Sonic Hedgehog. Nat Med 1997;3:788-92.

This article describes a human model for human BCC. Retroviral transduction of normal human keratinocytes was used to constitutively express Sonic hedgehog (SHH). These keratinocytes were then used to generate transgenic human skin grafts on immune-deficient mice. These grafts consistently displayed the abnormal histologic features seen in BCCs, including down-growth of epithelial buds into the dermis, basal cell palisading, and separation of epidermis from the underlying dermis. In addition, SHH skin displays the gene expression abnormalities previously described for human BCCs, including decreased BP180/BPAG2 and laminin 5 adhesion proteins and expression of basal epidermal keratins. Thus expression of SHH in human skin recapitulates features of human BCC in vivo, suggesting that activation of this conserved signaling pathway contributes to the development of epithelial neoplasia.

Xie J, Murone M, Luoh SM, Ryan A, Gu Q, Zhang C, et al. Activating Smoothened mutations in sporadic basal-cell carcinoma. Nature 1998;391:90-2.

Activating mutations in the *Smoothened* gene were identified in sporadic BCCs from 3 patients. Expression of active mutant Smoothened in transgenic murine skin resulted in skin abnormalities similar to BCC. These findings support the role of Smoothened protein as a signaling component of the SHH pathway and provide direct evidence that mutated Smoothened protein can function as an oncogene driving formation of BCC.

Chen JK, Taipale J, Cooper MK, Beachy PA. Inhibition of Hedgehog signaling by direct binding of cyclopamine to Smoothened. Genes Dev 2002;16:2743-8.

The plant-derived steroidal alkaloid cyclopamine specifically blocks the Hedgehog signaling pathway via direct binding of cyclopamine to Smoothened. In addition to BCC, the hedgehog pathway has been shown to be important in many gastrointestinal malignancies, and cyclopamine is now being aggressively developed as a potential antitumor agent for use in humans.

Couve-Privat S, Bouadjar B, Avril MF, Sarasin A, Daya-Grosjean L. Significantly high levels of ultraviolet-specific mutations in the *smoothened* gene in basal cell carcinomas from DNA repair-deficient xeroderma pigmentosum patients. Cancer Res 2002; 62:7186-9.

To elucidate the role of UV radiation in the deregulation of the SHH pathway, BCCs and SCCs from UV-hypersensitive patients with xeroderma pigmentosum (XP) were analyzed for alterations of the *Smoothened* gene. UV-specific *Smoothened* mutations were identified in 30% of XP patients' BCCs, 3 times higher than those in sporadic Caucasian BCCs, confirming the high rate of UV-induced mutations in DNA repair–deficient XP patients. No alteration was found in XP SCCs, indicating the involvement of the *smoothened* gene specifically in the development of BCC.

Hutchin ME, Kariapper MS, Grachtchouk M, Wang A, Wei L, Cummings D, et al. Sustained Hedgehog signaling is required for basal cell carcinoma proliferation and survival: conditional skin tumorigenesis recapitulates the hair growth cycle. Genes Dev 2005;19:214-23.

Transgenic mice were generated that allowed for doxycycline-regulated expression of Gli2 in mouse keratinocytes. With forced Gli2 expression, mice formed BCCs that were dependent on continued Gli2 expression, as transgene inactivation led to BCC regression. In that regard, the tumors were "addicted" to the activity of the *gli2* oncogene, suggesting that inhibitors of this pathway may be useful as therapeutic agents for BCC. However, after tumor regression, a small population of nonproliferative cells remained, and these again formed tumors upon transgene reactivation. This indicates that hedgehog pathway inhibitors may be useful only as long-term suppressive therapy for BCC. However, there are many differences between defined genetic murine cancer models and the corresponding spontaneously occurring human malignancies, and the potential utility of anti-hedgehog pathway therapies in humans remains to be determined.

Ratner D, Peacocke M, Zhang H, Ping XL, Tsou HC. UV-specific p53 and *PTCH* mutations in sporadic basal cell carcinoma of sun-exposed skin. J Am Acad Dermatol 2001;44:293-7.

This case report describes an 80-year-old patient in whom 3 novel p53 mutations, as well as UV-specific *PTCH* mutations, were detected in two BCC samples from sun-exposed skin. This is the first report of simultaneous UV-specific p53 and *PTCH* mutations in the same BCC sample.

SURGICAL TREATMENT

Brodland DG, Amonette R, Hanke CW, Robins P. The history and evolution of Mohs micrographic surgery. Dermatol Surg 2000; 26:303-7.

This thorough history details the development of Mohs micrographic surgery from its conceptual beginnings in a zoology laboratory where zinc chloride—treated rat tumors were sectioned horizontally, to the early days of chemosurgeons, and the recent establishment of accredited fellowship programs.

McGovern TW, Grossman D, Fitzgerald D, Glusac EJ, Leffell D. Status of residual tumor in patients with squamous cell carcinoma referred for Mohs micrographic surgery. Arch Dermatol 1999;135:1557-9.

To determine the likelihood of residual SCC in patients without clinical evidence of residual tumor, 30 of 139 SCC patients referred for Mohs micrographic surgery (MMS) were analyzed, while patients with clinical evidence of residual tumor, such as nodulation, induration, ulceration, crusting, oozing, or tenderness, were excluded. The MMS procedure was performed, with only the outermost margin from the initial stage examined by frozen section. Tissue specimen blocks were then fixed in formalin and serially sectioned to assess the presence of residual tumor. Of 30 patients, only 3 (10%) had microscopic evidence of residual tumor. Results suggest that there is a subset of SCC that may not require significant therapy after adequate biopsy of the tumor. There is certain to be significant variation between practitioners with respect to their assessment of clinical evidence of residual tumor. Also in this setting, the potential for later recurrence remains an open question.

Ratner D, Lowe L, Johnson TM, Fader DJ. Perineural spread of basal cell carcinomas treated with Mohs micrographic surgery. Cancer 2000;88:1605-13.

Perineural spread is a well-documented feature of cutaneous tumors and may be predictive of an aggressive clinical course. Prospective evaluation of 434 patients with BCC treated with MMS assessed the presence or absence of perineural inflammation and invasion in 78 tumors requiring more than one stage of surgery. Also noted were demographic features, clinical characteristics, histologic subtype, and operative data. Perineural inflammation, perineural tumor invasion, or both were present in 29 of the 78 tumors (37%), or 6.7% of all 434 prospectively evaluated cases. Twenty-one of the 78 tumors (26.9%) exhibited perineural inflammation, 3 (3.8%) demonstrated perineural invasion, and 5 (6.4%) exhibited both. Tumors with perineural invasion required 5.3 surgical stages on average for clearance, in contrast to tumors without perineural invasion, which required 2.2 stages. Tumors with perineural inflammation, inflammation plus tumor invasion, or invasion alone were larger in area preoperatively than tumors without perineural involvement.

Turner RJ, Leonard N, Malcolm AJ, Lawrence CM, Dahl MG. A retrospective study of outcome of Mohs' micrographic surgery for cutaneous squamous cell carcinoma using formalin fixed sections. Br J Dermatol 2000;142:752-7.

MMS with formalin fixation was performed on 61 SCC patients with a median follow-up of 4 years. In two cases there was local recurrence and in 3 others, metastasis to local lymph nodes. The overall cure rate was 92%. Authors demonstrate that this technique can be a cost-effective alternative to conventional frozen-section techniques in the treatment of SCC in regions where the technical expertise required for high-quality frozen sections may not be available. Furthermore, the formalin-fixed tissue method has the advantage of providing high-quality permanent histological sections using conventional pathology services.

Madani S, Huilgol SC, Carruthers A. Unplanned incomplete Mohs micrographic surgery.J Am Acad Dermatol 2000;42:814-9.

The high patient tolerability and efficacy of MMS is demonstrated in this retrospective review of

10,346 MMS procedures. Only 15 (0.15%) were identified as incomplete MMS in which the procedure was halted with the tumor margins known to be still positive. Two procedures were terminated because the patient could not tolerate additional surgery. Of the 12 unresectable cases with complete records, MMS was terminated because of ongoing multifocal positive skin margins, bony invasion, or extension of tumor to other locations. Surgical defects were repaired, with residual disease managed through a variety of methods.

Cook JL, Perone JB. A prospective evaluation of the incidence of complications associated with Mohs micrographic surgery. Arch Dermatol 2003;139:143-52.

All patients presenting for outpatient Mohs micrographic surgery at Duke University Medical Center during the year 2000 (1358 MMS cases) were prospectively enrolled in this study to evaluate the incidence of surgical complications including: postoperative hemorrhage, hematoma formation, wound infection, wound dehiscence, and flap/graft necrosis. All procedures were performed by a single attending surgeon. Complications were rare, with an overall complication incidence of 1.64%, most of which involved difficulties with hemostasis. No complications necessitated the assistance of another specialist or inpatient hospitalization. This extremely low complication rate likely reflects the inherent safety of the MMS technique when performed by an experienced surgeon, coupled with several preoperative precautions including discontinuation or limitation of anticoagulant therapy and nonsteroidal anti-inflammatory drugs (when medically appropriate), and use of empiric antibiotics for high-risk locations and complicated repairs.

Weisberg NK, Bertagnolli MM, Becker DS. Combined sentinel lymphadenectomy and Mohs micrographic surgery for high-risk cutaneous squamous cell carcinoma. J Am Acad Dermatol 2000;43:483-8.

When cutaneous SCC metastasizes, it typically spreads first to local lymph nodes. This case report demonstrates the feasibility of combining sentinel lymph node biopsy and MMS. The described patient had a high-risk recurrent SCC on the forehead. A preauricular sentinel lymph node (SLN) was localized by lymphoscintigraphy and excised. Subsequent pathologic evaluation of the SLN was negative for evidence of metastatic SCC. The day after SLN excision, the tumor was removed via Mohs micrographic surgery. Formal studies will need to be conducted on high-risk cases to identify any additive benefit of SLN and MMS. Additionally, it may be more practical to simply perform a local excision at the time of the SLN biopsy, and follow up with a Mohs procedure only if the margins on the excisional specimen are positive.

Robinson JK, Fisher SG. Recurrent basal cell carcinoma after incomplete resection. Arch Dermatol 2000;136:1318-24.

Over a 20-year period, 994 patients with incompletely excised BCC of the head referred for subsequent MMS were studied to determine factors associated with the interval to tumor recurrence, interval to MMS, and extent of MMS required to clear recurrent tumor. The interval to signs or symptoms of recurrence and to MMS from incomplete resection was greater for men, patients older than 65 years, those having a tumor on the nose or cheek, those with aggressive or fibrosing BCC, and those who underwent flap reconstruction. The extent of MMS resection was greater for those with flap and split-thickness skin graft repairs. The number of tumor nests identified by MMS was significantly greater in those treated with split-thickness skin graft and flap.

Thissen MR, Neumann MH, Schouten LJ. A systematic review of treatment modalities for primary basal cell carcinomas. Arch Dermatol 1999;135:1177-83.

All studies published in English, French, German, Dutch, Spanish, or Italian between 1970 and 1997 that prospectively examined recurrence rates for at least 50 patients with primary BCCs observed for at least 5 years after treatment with Mohs micrographic surgery, surgical excision, curettage and electrodesiccation, cryosurgery, radiotherapy, immunotherapy with interferon or fluorouracil, or photodynamic therapy were included. Of 298 studies found in several electronic databases, only 18 met the requirements for this analysis. Tumors treated with MMS show the lowest recurrence rates after 5 years, followed in order by those treated with surgical excision, cryosurgery, and curettage and electrodesiccation. However, recurrence rates for different therapies could not be compared directly because of a lack of uniformity in reporting methods, with the result that evidence-based guidelines could not be developed.

Batra RS, Kelley LC. Predictors of extensive subclinical spread in nonmelanoma skin cancer treated with Mohs micrographic surgery. Arch Dermatol 2002;138:1043-51.

This study was designed to identify predictive risk factors for extensive subclinical tumor spread for NMSC by using a retrospective analysis of 1131 Mohs micrographic surgical cases. Variables analyzed included patient age, sex, and immune status and lesion size, location, histologic subtype, and recurrence. Necessity for 3 or more Mohs layers was defined as extensive subclinical spread. The highest-risk tumors, with odds ratios greater than 6.0, were basal-squamous and morpheaform BCC on the nose, morpheaform BCC on the cheek, and those with a

preoperative size larger than 25 mm. Other important risk factors were recurrent and nodular BCC on the nose; location on the eyelid, temple, or ear helix; neck tumors and recurrent BCC in men; and tumor size greater than 10 mm. Patients younger than 35 years were at lower risk of extensive subclinical spread.

Smeets NW, Kuijpers DI, Nelemans P, Ostertag JU, Verhaegh ME, Krekels GA, et al. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face—results of a retrospective study and review of the literature. Br J Dermatol 2004;151:141-7.

Records for 620 patients with 720 BCCs treated by MMS over a 7-year period were reviewed. The 5-year recurrence rates estimated from this study were 3.2% for primary BCC and 6.7% for recurrent BCC. Increased recurrence rates were seen with aggressive histopathological subtype, more than 4 Mohs' stages, a large defect size, and a recurrent BCC.

Bialy TL, Whalen J, Veledar E, Lafreniere D, Spiro J, Chartier T, et al. Mohs micrographic surgery vs. traditional surgical excision: a cost comparison analysis. Arch Dermatol 2004;140:736-42.

This clever study was designed to compare the cost and margin adequacy of Mohs micrographic surgery with traditional surgical excision for the treatment of facial and auricular NMSC. Although each patient ultimately underwent an actual Mohs procedure, they were initially evaluated by an ear-nose-throat surgeon who outlined a proposed traditional surgical excision by drawing the theoretical margin for the procedure on each patient prior to the Mohs procedure. The actual tumor margin as assessed by Mohs surgery was compared with the ear-nose-throat surgeon's proposed margin to assess the adequacy of the theoretical traditional surgical excision. In this study, more than 30% of the traditional excision procedures would have resulted in positive surgical margins necessitating a second surgical procedure. Mohs surgery was comparable in cost to traditional surgical excision when the subsequent procedure for inadequate margins with the traditional excision procedure after permanent sectioning was Mohs surgery or a subsequent traditional surgical excision. When facility-based frozen sections were requested for traditional excision, Mohs surgery was significantly less costly. Results should be interpreted in light of the observation that cost conclusions were affected significantly by the choice of repair.

Essers BA, Dirksen CD, Nieman FH, Smeets NW, Krekels GA, Prins MH, et al. Cost-effectiveness of Mohs Micrographic Surgery vs Surgical Excision for Basal Cell Carcinoma of the Face. Arch Dermatol 2006;142:187-94.

Smeets NW, Krekels GA, Ostertag JU, Essers BA, Dirksen CD, Nieman FH, et al. Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial. Lancet 2004;364:1766-72.

This pair of articles from the Netherlands first details a randomized controlled trial of surgical excision versus Mohs surgery for both primary and recurrent BCC on the face. The primary outcome was BCC recurrence. Three hundred ninety-seven primary tumors (198 MMS, 199 surgical excision) and 201 recurrent tumors (99 MMS, 102 surgical excision) were treated. Of the primary carcinomas, 3% recurred after surgical excision compared with 2% after MMS during 30 months of follow-up. Of the recurrent carcinomas, 3% recurred after surgical excision and none after MMS during 18 months of follow-up. Although both differences favored MMS, the differences were not statistically significant, and follow-up periods were relatively short.

In the follow-up study based on the randomized trial, the authors attempted to determine the relative cost-effectiveness of each surgical treatment by calculating an incremental cost-effectiveness ratio. This value represents the financial premium necessitated by the more costly (yet presumably more effective) MMS to avoid one BCC recurrence in the study population. For primary BCC, the incremental cost-effectiveness ratio was determined to be about $33,000, while that for recurrent BCC was about $9,000. Authors therefore concluded that it does not seem cost effective to introduce MMS on a large scale for both primary and recurrent BCC.

There are a number of potential limitations to this set of studies, many of which are illustrated in the thoughtful comments and author replies published in response to these references. First among these is the short follow-up period. Additionally, there are a number of confounding factors, as there were a significant number of patients who dropped out or were lost to follow-up. Also, because of the specifics of the study design, there were additional potential complications resulting from referral and enrollment bias. These studies were conducted in the Netherlands, and results may not be directly applicable to medical care systems in other countries that utilize different billing and reimbursement structures. Additionally, there appear to be some technical differences between the surgical procedures employed in the study and those typically used in the United States.

Berlin J, Katz KH, Helm KF, Maloney ME. The significance of tumor persistence after incomplete excision of basal cell carcinoma. J Am Acad Dermatol 2002;46:549-53.

Charts and pathology slides of all incompletely excised BCCs from 1991 to 1994 were examined. On surgical reexcision, tumor persistence was found in 28% of cases. However, incompletely excised BCCs of superficial or nodular subtype, less than 1 cm in diameter, located anywhere except the nose or ears, with less than 4% marginal involvement on the initial

inadequate excision, had no evidence of tumor persistence, indicating that close clinical follow-up rather than surgery may be a reasonable management option for these select patients.

Swetter SM, Boldrick JC, Pierre P, Wong P, Egbert BM. Effects of biopsy-induced wound healing on residual basal cell and squamous cell carcinomas: rate of tumor regression in excisional specimens. J Cutan Pathol 2003;30:139-46.

To determine the extent to which wound healing and inflammation following a partial biopsy of BCC or SCC may induce tumor regression, NMSC biopsy and re-excision specimens from 1994 to 2001 were reviewed for histologic evidence of scar and presence of residual tumor. Regressed and nonregressed tumors were analyzed to assess influence of anatomic location, biopsy technique, histologic tumor subtype, time interval between biopsy and excision, and patient age. Nine hundred ten excisions were performed for transected BCC or SCC, 217 (24%) of which showed scar with no residual tumor. SCCs were more likely to regress than BCCs (40% vs 20%). Independent of the NMSC type, tumors regressed more often following shave rather than punch biopsy, as did tumors on the trunk and extremities compared with those from the head and neck.

Nordin P, Stenquist B. Five-year results of curettage-cryosurgery for 100 consecutive auricular non-melanoma skin cancers. J Laryngol Otol 2002;116:893-8.

This 5-year follow-up attempts to evaluate whether curettage-cryosurgery could be an alternative to MMS for selected auricular NMSCs. One hundred auricular NMSCs were treated by curettage, followed by cryosurgery. Seventy-seven BCCs, 13 SCCs, 6 SCCs in situ, and 4 basosquamous carcinomas were included. Morpheaform BCCs, recurrent BCCs with fibrotic component, and most of the SCCs were selected for MMS. Seventy-one patients with 81 tumors were followed up for at least 5 years with only one recurrence. Cosmetic results were good or acceptable in most patients suggesting that thorough curettage followed by liquid nitrogen may be a safe and inexpensive therapy for some NMSCs of the external ear.

CONFOCAL MICROSCOPY

Nori S, Rius-Diaz F, Cuevas J, Goldgeier M, Jaen P, Torres A, et al. Sensitivity and specificity of reflectance-mode confocal microscopy for in vivo diagnosis of basal cell carcinoma: a multicenter study. J Am Acad Dermatol 2004;51:923-30.

While not a treatment for NMSC per se, reflectance-mode confocal microscopy (RCM) is a rapidly developing technology which allows for noninvasive high-resolution imaging of human skin in vivo and may be used as an additional tool to both diagnose NMSC as well as guide surgical treatment procedures. This multicenter retrospective study employed blinded retrospective analysis of images from both pathologically conformed BCC and control tissues to determine the sensitivity and specificity of 5 RCM criteria for diagnosing BCC. These 5 criteria included: elongated monomorphic basaloid nuclei; polarization of these nuclei along the same axis of orientation; prominent inflammatory infiltrate; increased dermal vasculature; and pleomorphism of the overlying epidermis indicative of actinic changes. The presence of 4 or more criteria yielded a specificity of 95.7% and sensitivity of 82.9%. Addition of RCM to standard photography-based predictions of clinical probability of BCC significantly improved the accuracy for noninvasive diagnosis of BCC over clinical assessment alone.

5-FLUOROURACIL

Kraus S, Miller BH, Swinehart JM, Shavin JS, Georgouras KE, Jenner DA, et al. Intratumoral chemotherapy with fluorouracil/epinephrine injectable gel: a nonsurgical treatment of cutaneous squamous cell carcinoma. J Am Acad Dermatol 1998;38:438-42.

A fluorouracil/epinephrine injectable gel (5-FU/epi gel) was used once weekly for up to 6 weeks to treat 25 patients with biopsy-proven SCC. On follow-up histologic examination, 96% (22 of 23) tumors had complete tumor clearing. There were no clinically significant systemic reactions and the cosmetic results were good to excellent.

Morse LG, Kendrick C, Hooper D, Ward H, Parry E. Treatment of squamous cell carcinoma with intralesional 5-Fluorouracil. Dermatol Surg 2003;29:1150-3.

This case report details the complete clearing of a facial SCC with 8 weekly injections of 5-FU. These reports together suggest that this modality may provide a nonsurgical option for SCC in cosmetically sensitive locations or for patients in whom surgery may be otherwise problematic.

Bargman H, Hochman J. Topical treatment of Bowen's disease with 5-Fluorouracil. J Cutan Med Surg 2003;7:101-5.

To evaluate the long-term efficacy of topical 5-FU in treating SCC in situ, 24 patients with 26 biopsy-confirmed lesions of SCC in situ were treated with topical 5-FU cream and were followed up to 10 years. Two of the 26 lesions treated topically recurred at some point. The rest were apparently cured leading to the conclusion that treatment of SCC in situ with topical 5-FU cream can be effective and lasting.

IMIQUIMOD

Imiquimod is an immunomodulating imidazoquinoline amine approved initially in 1997 by the U.S. Food and Drug Administration for treating external genital and perianal warts. The Food and Drug Administration has also now granted approval for treatment of AKs and superficial BCC, although cure

rates for superficial BCC are still generally higher with surgery. Limited data suggest that imiquimod may also have some efficacy against nodular and infiltrative BCC, although clearance rates are less for these deeper tumors, and standard surgical treatments are preferred. Attempts to treat deeper or invasive NMSCs with imiquimod should be discussed clearly with the patient as an off-label use of the medication. Unfortunately, comparative randomized trials with imiquimod versus 5-FU or surgical treatments are lacking. Additionally, there is a need for longer follow-up studies (5-10 years) with imiquimod for NMSC.

Lebwohl M, Dinehart S, Whiting D, Lee PK, Tawfik N, Jorizzo J, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. J Am Acad Dermatol 2004; 50:714-21.

In this multicenter trial, 436 AK patients were randomized to either imiquimod 5% or vehicle cream, applied one time per day, 2 days per week for 16 weeks. Clearance of AK lesions was clinically assessed at an 8-week posttreatment visit. The complete clearance rate was 45.1% for the imiquimod group and 3.2% for the vehicle group. The median percent reduction in AK lesions was 83.3% for the imiquimod group and 0% for the vehicle group. Local skin reactions were common. Severe erythema was reported by 17.7% of participants who received imiquimod and 2.3% of participants who received vehicle.

Geisse J, Caro I, Lindholm J, Golitz L, Stampone P, Owens M. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatol 2004;50:722-33.

The efficacy and safety of imiquimod 5% cream for treating superficial BCC was evaluated in more than 700 patients with superficial BCC. Subjects were treated with imiquimod or vehicle cream once daily 5 or 7 times a week for 6 weeks. The lesion site was clinically examined 12 weeks posttreatment and excised for histologic evaluation. Histologic clearance rates for the 5 and 7 times per week imiquimod groups were not significantly different, with both at approximately 80%. Clearance rate in the vehicle only group was only 3%. Increasing severity of erythema, erosion, and scabbing/crusting was associated with higher clearance rates.

Marks R, Gebauer K, Shumack S, Amies M, Bryden J, Fox TL, et al. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multicenter 6-week dose-response trial. J Am Acad Dermatol 2001;44:807-13.

A multicenter, randomized, open-label dose-response trial of imiquimod 5% cream in the treatment of primary superficial BCC was designed to assess the efficacy and safety of different dose regimens. Ninety-nine patients were randomized to 6 weeks of imiquimod application in 1 of 4 treatment regimens: twice every day, once every day, twice daily 3 times per week, once daily 3 times per week. The treatment site was excised and examined histologically 6 weeks after cessation of imiquimod. Intention-to-treat analysis revealed 100% histologic clearance in the twice-daily regimen, 87.9% clearance in the once-every-day regimen, 73.3% clearance in the twice-daily 3 times per week regimen, and 69.7% clearance in the once-daily 3 times per week regimen. Dose-related inflammatory skin reactions at the site of application were common. The majority were well tolerated and only one patient withdrew from the trial as a result of a medication-related skin reaction. Authors concluded that imiquimod 5% cream has therapeutic potential as a patient-administered treatment option for superficial BCC.

Huber A, Huber JD, Skinner RB Jr, Kuwahara RT, Haque R, Amonette RA. Topical imiquimod treatment for nodular basal cell carcinomas: an open-label series. Dermatol Surg 2004;30:429-30.

Imiquimod was used successfully to treat 15 nodular BCCs, with all 15 showing complete histologic regression at week 15, following 12 weeks of topical treatment. At the 18-month follow-up, no patients had recurrent tumor, indicating that imiquimod may be useful for more than only superficial BCC.

Vidal D, Alomar A. Efficacy of imiquimod 5% cream for basal cell carcinoma in transplant patients. Clin Exp Dermatol 2004;29: 237-9.

To determine the efficacy of imiquimod in treating BCC in transplant patients, 10 BCCs (4 superficial, 3 nodular, 3 infiltrative) from 5 solid-organ transplant patients received imiquimod 5% cream for 5 to 6 weeks. Biopsy specimens taken 6 weeks after the end of treatment showed no tumor in 7 of 10 cases. All 4 superficial BCCs, 2 of 3 nodular lesions, and only 1 of 3 infiltrative cases had completely cleared. Therefore the suppressed immune system is still capable responding to imiquimod and completely clearing superficial BCC tumors. Whether the decreased efficacy for the deeper tumors reflects a deficiency in drug penetration, or an intrinsic resistance among the deeper cancer cells, is not immediately clear.

Smith KJ, Germain M, Skelton H. Bowen's disease (squamous cell carcinoma in situ) in immunosuppressed patients treated with imiquimod 5% cream and a cox inhibitor, sulindac: potential applications for this combination of immunotherapy. Dermatol Surg 2001;27:143-6.

Combination therapy using topical imiquimod and the oral cyclooxygenase inhibitor sulindac proved useful in the therapy of SCC in situ in immunosuppressed patients with long-standing chronic lymphocytic leukemia. Five patients with cutaneous

SCC in situ were treated for 16 weeks with complete clinical and histologic clearing of the tumors.

Smith KJ, Germain M, Skelton H. Squamous cell carcinoma in situ (Bowen's disease) in renal transplant patients treated with 5% imiquimod and 5% 5-fluorouracil therapy. Dermatol Surg 2001;27:561-4.

Combined therapy with 5-FU and imiquimod was shown to be effective in clearing SCC in situ from 5 immunosuppressed kidney transplant patients.

Mackenzie-Wood A, Kossard S, de Launey J, Wilkinson B, Owens ML. Imiquimod 5% cream in the treatment of Bowen's disease. J Am Acad Dermatol 2001;44:462-70.

This was a phase II, open-label study in 16 patients, treating a single biopsy-proven plaque of Bowen's disease that was 1 cm or larger in diameter, with once-daily self-application of imiquimod 5% cream for 16 weeks. A biopsy was performed on the treated area 6 weeks after the end of treatment, with patient follow-up at 3 and 6 months. Fourteen of the 15 patients had no residual tumor present in their 6-week posttreatment biopsy specimens. The 93% positive treatment response in biopsy-proven cases compares favorably with other current treatment modalities.

Hengge UR, Schaller J. Successful treatment of invasive squamous cell carcinoma using topical imiquimod. Arch Dermatol 2004; 140:404-6.

This case report demonstrated the complete clearing of invasive SCC on the temple of a 65-year-old severely compromised patient after 12 weeks of 3 times weekly imiquimod. This patient was on dialysis after a failed transplant and also suffered from metastatic prostate cancer, indicating that the skin-derived immune system was functional under these poor general health conditions.

Arlette JP. Treatment of Bowen's disease or erythroplasia of Queyrat Br J Dermatol 2003;149(Suppl 66):43-9.

Schroeder TL, Sengelmann RD. Squamous cell carcinoma in situ of the penis successfully treated with imiquimod 5% cream. J Am Acad Dermatol 2002;46:545-8.

Surgery and destructive treatment modalities for SCC in situ on the penis have significant risk of scarring, deformity, and impaired function. These two articles describe a total of 6 cases of SCC in situ on the penis, each of which appeared to regress completely after topical imiquimod treatment. Despite these successes, some physicians may be hesitant to rely on topical treatment given the relatively high metastatic rate for penile SCC.

Sauder DN. Imiquimod: modes of action. Br J Dermatol 2003; 149(Suppl 66):5-8.

This is a well-written, readily accessible review outlining the known mechanisms through which imiquimod induces production of multiple cytokines which activate both the innate and acquired arms of the immune system. Highlighted are the cellular signaling pathways activated after imiquimod binds to its cellular target (the Toll-like receptor TLR7), which results in downstream activation of AP-1 and nuclear factor-κB transcription factors.

Dummer R, Urosevic M, Kempf W, Hoek K, Hafner J, Burg G. Imiquimod in basal cell carcinoma: how does it work? Br J Dermatol 2003;149(Suppl 66):57-8.

Superficial BCCs were treated with imiquimod 5% cream daily for 5 to 8 days with lesions biopsied before and after treatment. Analysis of routine histology, immunohistochemistry, and gene array profiling demonstrated that imiquimod-induced BCC regression is associated with activation of the innate immune response, mediated by cells of macrophage-monocyte origin, and is associated with the induction of apoptosis.

Berman B, Sullivan T, De Araujo T, Nadji M. Expression of Fas-receptor on basal cell carcinomas after treatment with imiquimod 5% cream or vehicle. Br J Dermatol 2003;149(Suppl 66):59-61.

Imiquimod induced up-regulation of Fas receptor (FasR) expression in BCCs is identified as a possible mechanism through which imiquimod exerts its therapeutic effect. Expression of FasR leads to apoptosis after binding to Fas ligand. BCC cells do not usually express FasR, which may be responsible for the longevity of the tumor cells by preventing them from undergoing 'suicidal' apoptosis, as well as apoptosis induced by neighboring BCC cells and/or by infiltrating T lymphocytes. Imiquimod treatment induces interferon, which induces expression of FasR. FasR expression within BCCs was examined after exposure to imiquimod or vehicle. BCC cells expressed FasR in 3 of 4 imiquimod-treated BCCs but in none (0/5) of the vehicle-treated tumors. T lymphocytes apposed to BCC cells were evident in all 3 imiquimod-treated BCCs expressing FasR and in none of the FasR-negative, vehicle-treated BCCs, suggesting that FasR up-regulation may be mechanistically important for drug efficacy.

PHOTODYNAMIC THERAPY AND LASER

Marmur ES, Schmults CD, Goldberg DJ. A review of laser and photodynamic therapy for the treatment of nonmelanoma skin cancer. Dermatol Surg 2004;30:264-71.

The authors review the past 40 years of English-language medical literature and identify 20 articles pertaining to the use of laser and light source therapy for the treatment of NMSC with significant patient numbers and follow-up periods to merit inclusion in their study. Clearance rates were reported up to 100% for superficial BCCs, AKs, and SCC in situ; however, rates were dramatically lower (8%) for more invasive SCC. Recurrence rates ranged from 0% to 31% for superficial BCCs, 16% to 31% for AKs,

0% to 52% for SCC in situ, and an extremely high 82% for invasive SCC. However, the authors concluded from the data that the generally higher recurrence and clearance rates, coupled with the metastasis risk of SCC, limits the utility of laser based treatments for NMSC, and that they should be considered primarily for patients unable to undergo surgical therapy.

Varma S, Wilson H, Kurwa HA, Gambles B, Charman C, Pearse AD, et al. Bowen's disease, solar keratoses and superficial basal cell carcinomas treated by photodynamic therapy using a large-field incoherent light source. Br J Dermatol 2001144:567-74.

This study investigated the safety and efficacy of a large-field light source, along with application of 5-aminolevulinic acid (5-ALA) in the treatment of Bowen's disease, superficial BCCs, and AKs. Within two treatments, 88% of Bowen's disease lesions, 95% of BCCs, and 99% of AKs showed complete clinical clearance. At 12 months the complete response rates were 69% for Bowen's disease, 82% for BCC, and 72% for AK. Photodynamic therapy (PDT) can therefore be effective in the treatment of some cases of NMSC where existing surgical or topical treatments may be problematic.

Salim A, Leman JA, McColl JH, Chapman R, Morton CA. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. Br J Dermatol 2003;148:539-43.

Forty patients with SCC in situ from two centers were randomized to either topical PDT or 5-FU. The PDT group was treated with 20% ALA applied 4 hours before illumination with 100 J/cm^2 narrowband red light. 5-FU was applied to lesions for 4 weeks. A repeat treatment cycle was performed after 6 weeks if required. Twenty-nine of 33 (88%) lesions treated with PDT initially responded completely, compared with 22 of 33 (67%) after 5-FU. After 12 months, two recurrences in the PDT group and 6 in the 5-FU group reduced complete clinical clearance rates to 82% and 48%, respectively making PDT significantly more effective. There was no difference in overall pain experienced during each therapy. Authors conclude therefore, that topical ALA-PDT can be more effective than topical 5-FU in the treatment of BD, with fewer adverse events. However, clearance rates with MMS are still generally higher.

RETINOIDS

De Graaf YG, Euvrard S, Bouwes Bavinck JN. Systemic and topical retinoids in the management of skin cancer in organ transplant recipients. Dermatol Surg 2004;30:656-61.

This relatively comprehensive review summarizes many of the clinical trials using topical and oral retinoid therapy for prevention of NMSC in both normal immunocompetent individuals as well as in immunosuppressed transplant patients. While there is variation between studies, some general trends can be established. For immunocompetent individuals, oral retinoids seem to treat AKs and SCC in situ while having no effect on established invasive SCC or BCC. Oral retinoid treatment does seem to decrease the risk of SCC development in patients with AKs. While topical retinoids decrease the incidence of AKs, no formal studies have explored topical retinoids for prevention of SCC/BCC in immunocompetent patients.

In the transplant population, oral retinoid therapy generally decreases incidence of AK and SCC, although the effect is only observed during therapy, indicating the need for long-term treatment. Similar to the immunocompetent population, topical retinoid therapy also decreased the incidence of AKs. No studies have yet examined the effect of topical treatment on prevention of SCC/BCC in the transplant population.

Nijsten TE, Stern RS. Oral retinoid use reduces cutaneous squamous cell carcinoma risk in patients with psoriasis treated with psoralen-UVA: a nested cohort study. J Am Acad Dermatol 2003; 49:644-50.

During the study period from 1985 to 2000, 135 psoriasis patients being treated with psoralen plus UVA used oral retinoids for at least 26 weeks during one or more years. The incidence of SCC and BCC during years of substantial oral retinoid use was compared with other years. In a paired analysis, which compared each patient's own tumor experience while using and not using retinoids, retinoid use was associated with a 30% reduction in SCC incidence. Oral retinoid use and BCC incidence were not significantly associated.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Rivers JK, Arlette J, Shear N, Guenther L, Carey W, Poulin Y. Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. Br J Dermatol 2002;146:94-100.

There are no reported studies using topical nonsteroidal anti-inflammatory drugs for SCC or BCC; however, there is evidence showing efficacy against AKs. This double-blind, placebo-controlled study used 195 AK patients to evaluate the efficacy of 3.0% diclofenac in 2.5% hyaluronan topical gel. Treatment efficacy was assessed by using multiple indices, all of which generally showed improved efficacy in the treatment groups compared with placebo. Thirty-one percent of patients given active treatment for 60 days had a cumulative lesion number score equaling 0 (vs 8% for placebo). Treatments were generally well tolerated.