ment modalities in uveitis, in addition to immunosuppressive drugs.

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REFERENCES

- Gordon KB, Langley RG, Leonardi C, *et al*. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006;**55**:598–606.
- Suhler EB, Smith JR, Wertheim MS, *et al*. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. *Arch Ophthalmol* 2005;**123**:903–12.
- Mushtaq B, Saeed T, Situnayake RD, *et al*. Adalimumab for sight-threatening uveitis in Behcet's disease. *Eye*. Published Online First: 7 April 2006. doi: 10.1038/sj.eye.6702352.
- Galar A, Perez VL, Hammel JP, *et al*. Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. *Ophthalmology* 2006;**113**(12):2317–23.
- Vazquez-Cobian LB, Flynn TJ, Lehman TJ. Adalimumab therapy for childhood uveitis. *J Pediatr* 2006;**149**:572–5.
- Kump LI, Cervantes Castaneda RA, Androud SN, *et al*. Visual outcomes in children with juvenile idiopathic arthritis-associated uveitis. *Ophthalmology* 2006;**113**:1874–7.
- Saurenmann RK, Levin AV, Rose JB, *et al*. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology* 2006;**45**:982–9.
- Biester S, Deuter C, Michels H, *et al*. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007;**91**:319–24.
- Kotaniemi K, Savolainen A, Karma A, *et al*. Recent advances in uveitis of juvenile idiopathic arthritis. *Surv Ophthalmol* 2003;**48**:489–502.
- Gale S, Lightman S. Anti-TNF therapies in the management of acute and chronic uveitis. *Cytokine* 2006;**33**:231–7.
- Guignard S, Gossec L, Salliot C, *et al*. Efficacy of tumor necrosis factor blockers in reducing uveitis flares in spondylarthropathy patients: a retrospective study. *Ann Rheum Dis* 2006;**65**:1631–4.
- Weisman MH, Moreland LW, Furst DE, *et al*. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. *Clin Ther* 2003;**25**:1700–21.
- Haraoui B. Differentiating the efficacy of tumor necrosis factor inhibitors. *J Rheumatol Suppl* 2005;**74**:3–7.
- Anderson PJ. Tumor necrosis factor inhibitors: clinical implications of their different immunogenicity profiles. *Semin Arthritis Rheum* 2005;**34**(5 Suppl 1):19–22.
- Nestorov I. Clinical pharmacokinetics of TNF antagonists: how do they differ? *Semin Arthritis Rheum* 2005;**34**(5 Suppl 1):12–18.
- Kamal KM, Madhavan SS, Hornsby JAA, *et al*. Use of tumor necrosis factor inhibitors in rheumatoid arthritis: a national survey of practicing United States rheumatologists. *Joint Bone Spine* 2006;**73**(6):718–24.
- Tauber T, Turetz J, Barash J, *et al*. Optic neuritis associated with etanercept therapy for juvenile arthritis. *J AAPOS* 2006;**10**:26–9.
- Chung JH, Van Stavern GP, Frohman LP, *et al*. Adalimumab-associated optic neuritis. *J Neurol Sci* 2006;**244**:133–6.
- Woolley JM. Comparison of costs associated with the use of etanercept, infliximab, and adalimumab for the treatment of rheumatoid arthritis. *Manag Care Interface* 2006;**19**:47–53.
- Mansour AM. Infliximab treatment of posterior uveitis. *Ophthalmology* 2004;**111**:197–8.

All skin cancers are not created equal

All skin cancers are not created equal

Jeffrey A Nerad

The diagnosis of squamous cell carcinoma deserves a high degree of respect and care in confirming complete excision.

Gokmen Soysal and Markoc,¹ in their paper titled, Invasive squamous cell carcinoma of the Eyelids and Periorbital Region, remind us of the serious nature of squamous cell carcinoma (SCC) and its potential for devastating consequences (*see page 325*). Early diagnosis remains an important feature of treatment. Aggressive surgical excision, especially when the lesion is small, offers the highest cure rate. Preventative measures and newer treatment modalities may offer some prophylaxis.

How serious is cutaneous SCC? 60 000 new cases of skin cancer are diagnosed each year in the UK.² Over one million new cases of skin cancer are diagnosed each year in the United States.³ These include basal cell carcinoma (BCC), SCC, melanoma and sebaceous cell carcinoma. BCC and SCC, both having a similar etiologic relationship to actinic damage, are collectively, referred to as nonmelanotic skin cancers (NMCC) and represent the most common form of cancer today. UV exposure has been shown to be a risk factor for cutaneous melanoma also. It is

estimated that 50% of adults will have a NMCC by age 65.⁴ BCC represent more than 90% of these tumors. SCC, however, is a much more aggressive and potentially invasive neoplasm.

Gokmen Soysal and Markoc report on 76 patients with periorbital SCC. Orbital invasion was present in a large percentage of patients: 33/76 patients (43.4%). Of these 7/33 had paranasal sinus extension as well. Intracranial involvement was present in 1 patient. Lymph node involvement was seen in 6.6% of patients. Other recent reports show high morbidity, although not as high as shown by Gokmen Soysal and Markoc. Donaldson *et al*⁵ reported on 50 cases of SCC of the eyelids. Orbital invasion was found in three patients (6%) and treated with exenteration in two. The third patient died as a result of local extension of the tumor. No distant or regional metastases were identified over a 31 month follow up period. Faustina *et al*⁶ reported that 7/111 (6.3%) required orbital exenteration. 27 (24.3%) eventually had regional spread and 6.2% had distant metastases.

Although the exact percentage and pattern of local spread varies among these individual studies, likely due to referral pattern, and perhaps follow up length, it is clear that SCC is associated with a high level of morbidity and sometimes mortality.

What histopathologic characteristics suggest an aggressive nature of these tumors? The manuscript illustrates three characteristics known to be associated with aggressive behavior: subtype, perineural invasion (PNI), and associated inflammation. SCC is categorised histopathologically by subtype ranging from well differentiated to poorly differentiated. In the study by Gokmen Soysal and Markoc, 11.9% of tumors considered poorly differentiated, and all of these demonstrated orbital extension. In the study by Malhotra,⁷ 38% of recurrent tumors were either moderately or poorly differentiated. Perineural invasion (PNI) is associated with the higher morbidity of SCC. Gokmen Soysal and Markoc had a high rate of PNI (23.8%), perhaps consistent with the high percentage of patients with orbital invasion (43.4%). Bowyer *et al*⁸ described the management of perineural spread in 17 patients with SCC. Numbness and pain were the most common symptoms, whereas ophthalmoplegia, ptosis and facial nerve palsy were the most common signs. Six of 17 had recurrent tumor and the disease progression resulted in death in four of these six patients. Four of 50 patients in Donaldson's study had PNI. Faustina's study did not discuss PNI. Of the 79 patients in Malhotra's study three had PNI and two of the three were recurrent

lesions. McNab reported that the presence of PNI was highly correlated with the recurrence and metastasis rates. In his series, 14/21 patients with PNI died within 5 years.⁹

The presence of an inflammatory infiltrate surrounding a tumor suggests that there is a host defense response to the tumor. Likely tumor cells are forming spontaneously in all patients and being destroyed as a matter of normal immunosurveillance. The high rates of SCC in immunosuppressed patients or those patients with Xeroderma Pigmentosa are indirect evidence for this. SCC is a disease of older patients with normal declining immune response. A lack of inflammation is a potential indicator that the tumor growth may be preceding with less host defense response, and a more invasive growth pattern or a higher recurrence rate.

Are we treating periocular squamous cell carcinoma effectively? It is difficult to say.

Markoc report a 22.4% recurrence rate, which appears unacceptably high, although none of the recurrences occurred with tumors less than 1 cm without orbital exenteration. The Malhortra and the Donaldson studies reported 3.6% and 2% recurrence rates respectively (follow up periods were 73 and 31 months respectively). Interestingly, in these studies series, 27% and 28% of the tumors were initially referred for recurrence.

When viewing all SCC a recurrence rates less than 5% for SCC seems reasonable.

Although most of us reading this are likely playing the role of diagnosing and treating lesions we should continue to point to the role of prevention of skin cancer, especially in children and young adults. Individuals with light skin and prone to sunburn, need to be extra cautious. This is easier said than done, especially in our society where the "bronzed body" is considered a requisite by many fair skinned young people. This topic has received some recent attention in the pediatric literature where The Nurses Health Study showed that frequent sunburns, suboptimal sunscreen use, and high rates of tanning bed use are commonplace even among the children of health professionals who are at risk for developing skin cancer themselves as a result of personal or family history.¹⁰ Sunscreens that reduce the amount of UV damage without avoiding outdoor activities should be promoted. An alternative to tanning salons, "spray on" tans, do not add to natural UV damage.

As practitioners, our best chance at decreasing the morbidity of SCC (and all cutaneous cancers) is early diagnosis when the lesion is small. BCC and SCC

share many of the same clinical characteristics: scalloped contours, asymmetric shape, induration, ulceration and a lack of tenderness. Pearly margins and telangiectasia suggest a diagnosis of BCC, but may be present in either lesion. Hyperkeratosis is associated with SCC. The diagnosis is easier by recognising the "company that these tumors keep"—signs of sun damaged skin. The presence of telangiectasis due to dermal atrophy, loss of skin elasticity, wrinkling, solar lentigines and actinic keratoses suggest that a small suspicious lesion is likely to be a malignancy. A history of excessive sun exposure is common.

Gokmen Soysal and Markoc showed that 61.8% patients had a history of chronic sun exposure and actinic skin changes were present in 32/76 patients. On histopathological examination, 35% of tumors were associated with areas of actinic keratosis near the tumor. We should be especially suspicious when a previous diagnosis of NMCC has been made. In Donaldson's paper 64% of patients had a history of previous skin cancer.

At the first suspicion of malignancy, a simple incisional biopsy should be performed.

Excision and repair is easiest when the lesion is small. In selected cases, premalignant skin changes and inconspicuous malignancies may disappear with topical 5 FU (Effudex) or imiquimod (Aldara) cream.

It is accepted that complete tumor excision with confirmation of free surgical margins is the best treatment for SCC. Some surgeons recommend additional radiation therapy in cases with PNI. The original reports by Mohs showed a recurrence rate of 2% for SCC.¹¹ The Malhortra and the Donaldson studies reported 3.6% and 2% recurrences using different techniques, Mohs micrographic surgery (MMS) and frozen section respectively. The role of MMS compared with more traditional frozen section or permanent section monitoring has been the subject of some recent debate with proponents on both sides. For an excellent perspective, I refer you to the articles by Cook and Bartley,¹² Bartley¹³ and Rapini.¹⁴

As surgeons who treat 10–20 times more BCC than SCC we may have a tendency for complacency due to the high cure rate associated with most skin cancers. However, all skin cancers are not created equal. The best recommendation is to individualise tumor excision from patient to patient. First, we must remember that most skin cancers are BCC, not SCC. A diagnosis of SCC should be cause for alarm. Aggressive subtypes of SCC, the presence of PNI, or lack of

inflammation are additional warning signs that we dealing with aggressive tumors. Whether the surgeon acts as the pathologist or not, some consideration of these, and other factors such as tumor size, location and previous recurrence, should be considered in the ultimate degree of "free" margins. As is often the case, the first attempt at a surgical cure is the most likely to succeed. Lastly, patients must be followed closely for a minimum of 5 years.

These papers serve as a reminder to us that the diagnosis of SCC carcinoma deserves a high degree of respect and care in confirming complete excision. Increasing public awareness of the harmful effects of UV radiation, use of sunscreens, topical treatments and early diagnosis and appropriately aggressive resection are all a part of the successful treatment of squamous cell carcinoma.

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REFERENCES

- 1 Gokmen Soysal H, Markoc F. Invasive Squamous Cell Carcinoma of the Eyelids and Periorbital Region. *Br J Ophthalmol* 2007;**91**:325–9.
- 2 Association for International Cancer Research. Skin Cancer FAQs, <http://www.aicr.org.uk/SkinCancerFAQs.stm> (accessed 23 October 2006).
- 3 Skin Cancer Foundation. Skin Cancer Facts, <http://www.skincancer.org/skincancerfacts.php> (accessed 23 October 2006).
- 4 National Cancer Institute. U.S. National Institutes of Health. Cancer Statistics, <http://www.cancer.gov/statistics> (accessed 23 October 2006).
- 5 Donaldson MJ, Sullivan TJ, Whitehead KJ, et al. Squamous cell carcinoma of the eyelids. *Br J Ophthalmol* 2002;**86**:1161–5.
- 6 Faustina M, Diba R, Ahmadi MA, et al. Patterns of regional and distant metastasis in patients with eyelid and periocular squamous cell carcinoma. *Ophthalmology* 2004;**111**:1930–2.
- 7 Malhortra R, Huilgol SC, Huynh NT, et al. The Australian Mohs database: periocular squamous cell carcinoma. *Ophthalmology* 2004;**111**:617–23.
- 8 Bowyer JD, Sullivan TJ, Whitehead KJ, et al. The management of perineural spread of squamous cell carcinoma to the ocular adnexae. *Ophthalm Plast Reconstr Surg* 2003;**19**:275–81.
- 9 McNab AA, Francis IC, Benger R, et al. Perineural spread of cutaneous squamous cell carcinoma via the orbit. Clinical features and outcome in 21 cases. *Ophthalmology* 1997;**104**:1457–62.
- 10 Geller AC, Brooks DR, Colditz GA, et al. Sun protection practices among offspring of women with personal or family history of skin cancer. *Pediatrics* 2006;**117**:e688–94.
- 11 Mohs FE. Micrographic surgery for the microscopically controlled excision of eyelid cancers. *Arch Ophthalmol* 1986;**104**:901–9.
- 12 Cook BE Jr, Bartley GB. Epidemiologic characteristics and clinical course of patients with malignant eyelid tumors in an incidence cohort in Olmsted County, Minnesota. *Ophthalmology* 1999;**106**:746–50.
- 13 Bartley GB. Mohs surgery: proclamation, proof, principles, and promise. *Ophthalmology* 2004;**111**:615–6.
- 14 Rapini RP. On the definition of Mohs surgery and how it determines appropriate surgical margins. *Arch Dermatol* 1992;**128**:673–8.