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Classic diseases revisited

Basal cell carcinoma

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Summary

Basal cell carcinoma is the commonest malignancy in Caucasians with incidence rates of 300 per 100 000 reported in the USA. Rates are increasing at over 10% per year leading to a lifetime risk of 30%. Although mortality is low, the disease is responsible for considerable morbidity and places a substantial burden on health service provision in the UK. Furthermore, lesions may recur and patients often develop multiple tumours giving major implications for treatment and follow-up. Four main types of basal cell carcinoma are seen: nodulo-ulcerative; pigmented; morpheaform and superficial. Diagnosis is by histological evaluation although many tumours have a characteristic clinical appearance. The differential diagnosis is large. Identified risk factors include male gender, skin type 1, red/blonde hair and increasing age. Patients with basal cell carcinoma are more likely to develop malignant melanoma and squamous cell carcinoma but it is still unclear whether there is a link with internal malignancy. The main treatment modalities are surgery and radiotherapy. Each has advantages and disadvantages. The choice of treatment depends on many factors. Principles of treatment include identification of high-risk patients to enable early detection, complete removal of the lesion, and careful follow-up to detect recurrence or new lesions. Approximately 10% of tumours recur, depending on site, size and treatment modality. Metastatic basal cell carcinoma and the association of ultraviolet radiation to basal cell carcinoma risk are reviewed.

Keywords: basal cell carcinoma, ultraviolet radiation, skin cancer

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Incidence and mortality

Basal cell carcinoma is the commonest skin cancer and is the most common malignancy in Caucasians. Squamous cell carcinoma (often grouped with basal cell carcinoma under the title non-melanoma skin cancer) and malignant melanoma are the two other main forms of skin cancer. Basal cell carcinoma is composed of cells similar to those found in the basal areas of the epidermis and appendages, hence its name. It is rare in black-skinned individuals. Incidence rates of 300 per 100 000 people in 1977 in the USA have been described, with rates up to 1000 per 100 000 seen near the equator in Australia.[1] The lifetime risk of a basal cell carcinoma for a child born in 1994 in the USA is 28–33%. Non-melanoma skin cancer will affect approximately a million people in the USA in 1994, leading to predictions that incidence will become similar in magnitude to the total incidence of all malignancies,[2] thus placing a significant burden on health service provision.

Incidence rates are highest in Australia and are increasing in many countries. Depletion of stratospheric ozone leading to increased ultraviolet (UV) radiation is predicted to further increase rates.[3] There is evidence from four sources, with different ascertainment methods, of a striking increase in incidence of non-melanoma skin cancer in North America during the past two decades.[1] Population-based estimates of non-melanoma skin cancer in 1977–78 revealed rates are higher for men.[4] When compared with a previous study by the same group in 1971–72 an increase of 15–20% had occurred. In Australia, the incidence of basal cell carcinoma increased by 11% between 1985 and 1990.[5] Similar increases have been shown in Tasmania,[6] UK,[7] Sweden,[8] and The Netherlands.[9]

Mortality data is more accurate in most countries.[5] Recent estimates suggest a rate of 0.5 per 100 000 whites/year in 1987–88 (0.67 for men and 0.30 for women). These rates have been dropping with a 20–30% decrease from 1969 through to 1988. Although mortality is lower than malignant melanoma, morbidity and cosmetic deformity are important for basal cell carcinoma, although there is no good quantitative assessment of the degree of disability or handicap.

Clinical features

Early basal cell carcinomas are translucent or pearly, with raised, rounded areas covered by thin epidermis through which dilated vessels may show. Occasionally pigment can be seen. As they advance they can have a wide variety of patterns (box 1, figures 1–4), which may make classification difficult. Telangiectasia are characteristically seen, especially in the morpheaform variety. The majority of tumours (80%) occur on the head and neck, particularly the upper central part of the face. The superficial type, however, is found mainly on the trunk.[10] Importantly, multiple tumours often occur. The role of a family

Types of basal cell carcinoma

- nodulo-ulcerative (rodent ulcer)
- pigmented (more common in dark skinned people)
- morpheaform (ulceration rare)
- superficial (found mainly on the trunk)
- premalignant fibroepitheliomas (flesh coloured, sessile lesions)

Box 1

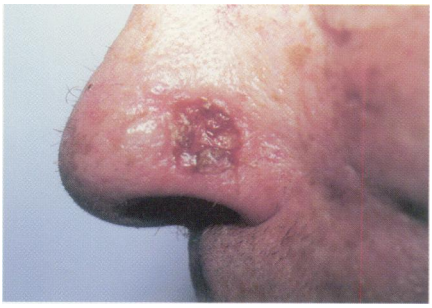

Figure 1 Rodent ulcer

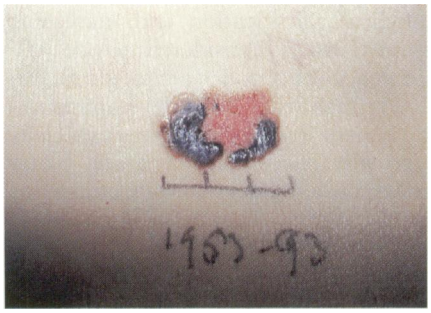

Figure 2 Pigmented basal cell carcinoma

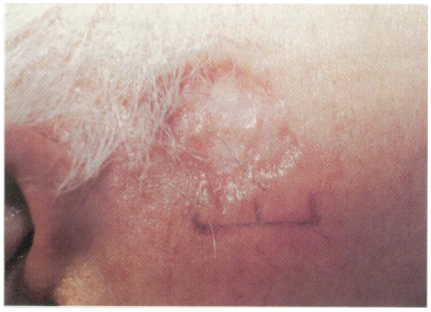

Figure 3 Morphoeic basal cell carcinoma

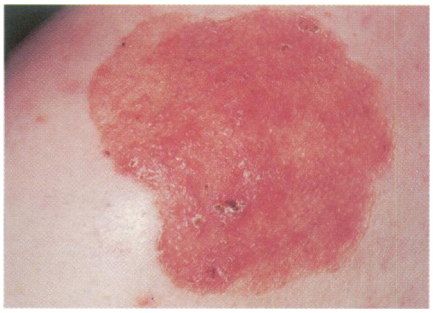

Figure 4 Superficial basal cell carcinoma on the trunk

Basal cell carcinoma: differential diagnosis

- other cutaneous malignancies: Bowen's disease, squamous cell carcinoma, malignant melanoma
- eczema
- psoriasis
- naevi
- seborrhoeic and viral warts
- sebaceous hyperplasia
- solar keratosis
- molluscum contagiosum
- granulomatous reactions, eg, sarcoid

Box 2

Basal cell carcinoma: risk factors

- increasing age
- red/blonde hair
- blue/green eyes
- male gender
- skin type 1
- freckling
- actinic keratoses
- UV exposure
- outdoor occupation
- low socio-economic status (giant lesions)

Box 3

history in non-melanoma skin cancer is unclear, with some supportive data[11] and other suggestions that inheritance of complexion may explain familial clustering.[12] Typical basal cell carcinomas are indolent with a slow progression, although spontaneous fluctuations in size can occur. Diagnosis is based on histological examination of biopsy specimens but many tumours have a characteristic clinical appearance. Differential diagnoses are shown in box 2.

Predisposing factors

Patients with albinism and xeroderma pigmentosum are at increased risk. In the naevoid basal cell carcinoma syndrome (Gorlin's syndrome), multiple basal cell carcinomas at an early age (<30 years) are found, together with other manifestations including: milia; punctate hyperkeratosis and circular pits on the hands and feet; dental cysts; spina bifida, bifid ribs; hypertelorism; syndactyly and cataracts. This is inherited in an autosomal dominant fashion with a linked locus on chromosome 9q.[13] Although UV radiation is considered to be the major factor predisposing to basal cell carcinoma, exogenous chemicals have also been associated. Arsenic toxicity predisposes to the development of multiple basal cell carcinoma, particularly the superficial type on the trunk, illustrating that exogenous factors can be important, possibly via interactions with UV radiation.[14]

Risk factors and associations with other malignancies (see box 3)

The study of risk factors enables identification of at-risk individuals in the hope of preventing or modifying the natural history of the condition. This is of great importance in basal cell carcinoma as smaller tumours are more easily dealt with. In the UK there have been relatively few case-control studies on risk factors in basal cell carcinoma.[15] It was shown that actinic keratoses, freckling and the number of hours spent outdoors after the age of 60 years were important. Other recognised risk factors include increasing age, red/blonde hair, blue/green eyes and fair skin.[16] Outdoor occupation and family history may also be important.[17] Smoking, although a risk factor for cutaneous squamous cell carcinoma, has not been consistently associated with basal cell carcinoma.[18] The paucity of data on risk factors in the UK indicates that further large studies are needed in the British population.

Low socio-economic status and infrequent physician visits have been shown to be associated with very large basal cell carcinomas. Such patients are less concerned about their general health and pose a significant management problem. Patients with basal cell carcinoma are at high risk of suffering further primary lesions.[19] Importantly, this risk depends on the number of lesions present. Thus, in subjects with one lesion the five-year risk is 27%, while in those with 10 or more tumours the risk is 90%, suggesting accrual of lesions is not just dependent on time but that some subjects have an increased susceptibility. Male gender, age over 60 years, burning easily and sun-damaged skin were also associated with an increased risk of subsequent new tumours.

It is interesting to note whether patients with basal cell carcinoma are at increased risk of other skin cancers or internal malignancies. Such observations will have implications for follow-up and give insights into the pathogenesis of this tumour. Several studies show that patients with basal cell carcinoma are at an increased risk of both squamous cell carcinoma[18] and malignant melanoma. One study found a relative risk of 17 for the development of malignant melanoma in patients with a prior basal cell carcinoma.[20] Other studies have found relative risks between 2.8 to 6.6.[21,22] Differences between these rates may

be explained by recruitment bias, histological classification and increasing incidence. The link between these associations is considered to be UV radiation, as in both diseases UV is considered to be a major aetiologic factor. Thus, patients with basal cell carcinoma are at high risk for the development of malignant melanoma and could potentially benefit from surveillance, especially as early melanomas in the horizontal growth phase have a much better prognosis than later lesions in a vertical growth phase.[23] Regular total cutaneous examinations have been advocated as a useful, noninvasive, quick surveillance technique to detect new tumours in at-risk individuals.[24] However, a physician skilled in the detection of skin cancers is needed to give the best results and such people are in relatively short supply in the UK.

The association with internal malignancy remains unclear, with some studies suggesting no association[25,26] and another study suggesting that men with basal cell carcinoma have an increased risk of cancer of the lung and thyroid gland and women an increased risk of cancer of the uterine cervix.[21] The explanation for these observations is not clear but exposure to carcinogens such as arsenic were suggested. Renal transplant recipients are at increased risk of both skin cancer, particularly squamous cell carcinoma, and lymphomas, illustrating the role of the immune system in cancer prevention.[27]

Treatment, recurrence and metastasis

Basal cell carcinomas can grow very large, become locally invasive, and can metastasise. Therefore treatment is almost always indicated. The principles of management include identifying high-risk patients for prevention and early detection, complete removal of the lesion, careful follow-up to detect local recurrence and new tumours. Available treatment modalities include curettage, primary resection with closure of defect (including flaps and grafts), Mohs' micrographic surgery (see below), radiotherapy, cryotherapy, and laser excision. Some preliminary evidence suggests that vitamin supplementation may reduce the risk of basal cell carcinoma[28] and that interferon reduces recurrence.[29] Further studies are required to confirm these observations. The choice of treatment depends on the size and site of tumour, age of patient, efficacy of treatment modality, cosmetic considerations, and the preferences of patient and physician. In general, the smaller the tumour the easier it is to treat, with minimal morbidity and a favourable outcome.[30] There have been no large randomised prospective studies comparing one treatment modality with another. An ideal treatment would be one with a high cure and low recurrence rate; quick, cheap and easy to perform and with good cosmetic results.

Surgical resection is the commonest form of treatment used in the UK. Removal can be performed easily, usually in an out-patient setting; 80% of lesions can be removed with primary closure but larger, more complex lesions require grafts or rotational skin flaps to close the defect and may need general anaesthesia. The simplest surgical procedure is curettage. It is quick, sutures are not required (haemostasis is achieved via electrodessication) and cosmetic results can sometimes be better than resection. However, recurrence rates can be higher than resection especially with inexperienced individuals. Many physicians prefer to use this technique although it seems most suitable in small lesions (<6 mm) at any site, any lesions on the neck, trunk and limbs and in elderly patients.[31] Cure rates of 90–95% can be achieved with selection of patients who fit into the above categories. Primary surgical excision is associated with a 90–95% cure rate in most studies. Ideally the margin of resection should be at least 5mm because as closer margins are obtained, local recurrences are increased.[32] Bigger tumours often need more sophisticated techniques to achieve complete excision. In 1939, Frederick E Mohs developed a technique to fix skin cancer *in situ* and a method of systematically excising and pathologically mapping the excised tumour to obtain margins of normal skin. Since 1970, the technique has evolved so that chemical fixation is no longer needed.[33] The technique is, however, slow and tedious, but cure rates of 97% can be achieved, even in large tumours. This method is particularly useful for morphoeic basal cell carcinoma where the margins of the lesion are unclear to the naked eye. Grafts or flaps may be needed after Mohs' resection to reconstruct the defect. Mohs' surgery is a highly specialised technique and there are few trained individuals in the UK.

Radiotherapy is a useful and effective treatment modality.[30] Better cosmetic results are achieved by fractionation of dose (10–16 fractions for small tumours (<5 cm) and in 15–30 divided doses for larger tumours). Therefore multiple sessions over a period of weeks are required. However, because of time constraints, often one to three fractions are used. The main advantages and disadvantages of radiotherapy are given in box 4. Radiotherapy is contra-

Advantages and disadvantages of radiotherapy

Advantages
- no anaesthesia or surgery needed
- 95% effective
- effective in troublesome areas (nose, eyes, ears)
- margins not critical
- useful in elderly patients

Disadvantages
- time consuming for patient and radiotherapist
- expensive
- no histological specimen
- radiation necrosis to skin
- ? carcinogenesis

Box 4

indicated in those with Gorlin's syndrome as recurrence is high. Patients in whom radiotherapy is particularly useful are the elderly and those with lesions in difficult anatomical sites, such as eyes and ears. However, after radiotherapy, subsequent surgery can be more difficult.

Clinical trials are currently underway to assess the effect of photodynamic therapy in basal cell carcinoma. This makes use of the tumour cell's ability to take up a haematoporphyrin derivative in higher concentrations than the surrounding tissue.[34] This makes the cells photosensitive to light of wavelengths 514.5, 488 and 625–30 nm. The tumour is then exposed to laser light which destroys selectively the tumour cells. Intralesional interferon-alfa-2b, 1.5 million units three times a week for three weeks gave a cure rate of 85% with excellent cosmetic results.[35] However, large or recurrent lesions were not treated. Further work is needed to establish the role of this therapy in clinical practice. Oral retinoids can produce regression but not cure. They have a role in prevention of lesions in patients with xeroderma pigmentosum or Gorlin's syndrome.

Factors affecting recurrence

- tumour size
- location (tumours on eyes, nose and ears more likely to recur)
- deep or marginal invasion on histology
- resection margin <5 mm
- growth pattern (morphoeic more likely to recur)
- initial treatment modality

Box 5

Depending on site, size of tumour and treatment modality, up to 10% of tumours recur, making the treatment of recurrent lesions a common problem. Surgical resection of recurrent tumours gives a cure rate of 65% whereas Mohs' procedure gives 94% cure rates.[36] Factors influencing recurrence are listed in box 5.[30,37] Treatment of choice for recurrent basal cell carcinoma is therefore Mohs' surgery but access to this facility is extremely limited in the UK and recurrences are usually re-excised via non-Mohs' techniques. Radiotherapy has also been shown to be effective.[38]

Metastatic basal cell carcinoma (box 6) is rare. The reported rate of incidence ranges from 0.0028% to 0.55%.[39] The typical metastatic tumour begins as a neglected, large, ulcerated, locally invasive neoplasm that recurs despite repeated treatment.[40] Tumours greater than 3 cm have a higher incidence of metastasis.[41] The average age of onset is 48 years which is lower than non-metastatic tumours.[42] The interval from onset to metastasis ranges from one to 45 years with a median of nine years.[43] Anatomical location of tumour is no different between metastatic and non-metastatic lesions. Morpheaform and adenocystic types are more aggressive than other variants.[42] Survival after metastasis ranges from one to 192 months with 10% surviving five years.[43] Why basal cell carcinoma metastasises so rarely is not clear. However, its dependence on its surrounding tissue (or stroma) is important. This concept is supported by failed attempts to transplant human basal cell carcinoma without surrounding tissue into other animals or humans.[43]

Features of metastatic basal cell carcinoma

- large size (>3cm)
- long time to first presentation with primary tumour
- locally ulcerative
- recurrent
- younger age of onset
- morpheaform/adenocystic types more common
- median time to metastasis nine years
- 10% five-year survival

Box 6

The role of UV radiation exposure

UV radiation is considered the major aetiological agent in the pathogenesis of basal cell carcinoma. UV causes mutagenesis in mammalian cells, induces pyrimidine dimers in human skin and is photocarcinogenic in mice.[44] UV has also been shown to invoke a degree of immunosuppression in both animals and humans. Thus, both UV-induced DNA alterations as well as immune modulation are important in cutaneous carcinogenesis. Risk has traditionally been thought to be related solely to cumulative dose received, with a monotonic relationship between cumulative dose and basal cell carcinoma risk. One of the main problems in this area is that information relies on the accurate memory of an often elderly patient to recall exposures from many years previously. The evidence for the relationship between UV and skin cancer has arisen from animal experiments[45] and observations that incidence can be related to occupational sun exposure.[46] However, more recent research has cast doubts on this monotonic relationship between dose and risk. Two studies have found little evidence of increasing risk of basal cell carcinoma with increasing UV exposure and postulated a plateau in risk at higher doses.[47,48] There is also evidence of higher rates of basal cell carcinoma in North America and Europe than more southerly regions of these continents.[46] The anatomical location of basal cell carcinoma is now seen to increasingly favour sites, mainly trunk, that are not regarded as continuously exposed to the sun when outdoors.[46] Thus, it seems that cumulative dose does not entirely explain basal cell carcinoma risk. Further research is needed to confirm this plateau effect: its implications are that substantial reductions in exposure may be necessary if heavily exposed populations are to reduce their risk of basal cell carcinoma.[49]

The effect of intermittent exposure is still unclear but it was found that a significant increase in risk occurred with increased exposure at the weekend, especially in late teenage years,[49] suggesting infrequent, probably intense increments will increase risk of basal cell carcinoma more than a similar dose delivered continuously. Another study found an increased risk with recreational

sunlight exposure from the ages of 0 to 19 years and no association with mean annual cumulative exposure.[50] These results suggest that childhood may be a critical period for establishing adult risk. Freckling, light skin colour and severe sunburn in childhood were also associated with an increased risk. Therefore, freckling may be a marker for UV damage to the skin. It was suggested that, by extension of these results, sun-avoidance behaviour in adulthood may not markedly reduce risk for this tumour.[50] The usefulness of sunscreens with high protection factors has caused much debate. It seems that sunscreens are associated with a decreased risk of solar keratoses and current trials are assessing the effects on skin cancer incidence.[51]

Prevention

As UV is considered the major aetiological agent, prevention focuses on reducing exposure to this, both in childhood and in later life. Much effort has addressed these issues in public health campaigns. Sunscreens have been advocated but there is no hard evidence that they prevent basal cell carcinoma. They do suppress actinic keratoses, a possible precursor to squamous cell carcinoma.[51] Trials are currently underway to assess the effect of sunscreens in basal cell carcinoma prevention.

1 Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. J Am *Acad Dermatol* 1994; **30:** 774–8.
2 Boring CC, Squires TS, Tong T. Cancer statistics, 1993. *CA Cancer J Clin* 1993; 43: 7–26.
3 Russell-Jones R. Ozone depletion and cancer risk. *Lancet* 1987; **2:** 443–6.
4 Scotto J, Fears TR, Fraumeni JF. *Incidence of non-melanoma skin cancer in the United States.* National Cancer Institute: NIH Publ No 83–2433, 1983.
5 Marks R. An overview of skin cancers. *Cancer* 1995; **75:** 607–12.
6 Kaldor J, Shugg D, Young B, Dwyer T, Wang YG. Non-melanoma skin cancer: ten years of cancer-registry-based surveillance. *Int J Cancer* 1993; **53:** 886–91.
7 Ko CB, Walton S, Keczes K, Bury HPR, Nicholson C. The emerging epidemic of skin cancer. *Br J Dermatol* 1994; **130:** 269–72.
8 Dahl E, Aberg M, Rausing A, Rausing EA. Basal cell carcinoma. *Cancer* 1992; **70:** 104–8.
9 Coebergh JWW, Neumann HAM, Vrints LW, Van Der Heijden L, Meijer WJ, Verhagen-Teulings MTh. Trends in the incidence of non-melanoma skin cancer in the SE Netherlands 1975–1988: a registry based study. *Br J Dermatol* 1991; **125:** 353–9.
10 Betti R, Inselvini E, Carducci M, CrostiC. Age and site prevalence of histologic subtypes of basal cell carcinomas. *Int J Dermatol* 1995; **34:** 174–6.
11 Czarnecki D, Zalcberg J, Meehan C, *et al.* Familial occurrence of multiple nonmelanoma skin cancer. *Cancer Genet Cytogenet* 1992; **61:** 1–5.
12 Belisano JC. The malignant tumours of the skin. *Aust J Dermatol* 1954; **1:** 179–206.
13 Wicking C, Berkman J, Wainwright B, Chenevix-Trench G. Fine genetic mapping of the gene for naevoid basal cell carcinoma syndrome. *Genomics* 1994; **22:** 505–11.
14 Yeh S, How SW, Lin CS. Arsenical cancer of the skin. *Cancer* 1968; **21:** 312–39.
15 McHenry PM, Aitchison T, MacKie RM. Risk factors for basal cell carcinoma and squamous cell carcinoma. *Br J Dermatol* 1995; **133** (suppl 45): 29.
16 Lin AN, Carter DM. Skin cancer in the elderly. *Dermatol Clin* 1986; **4:** 467–71.
17 Hogan DJ, To T, Gran L. Risk factors for basal cell carcinoma. *Int J Dermatol* 1989; **28:** 591–4.
18 Karagas MR, for the Skin Cancer Prevention Study Group Occurrence of cutaneous basal cell and squamous cell malignancies among those with a prior history of skin cancer. *J Invest Dermatol* 1994; **102:** 10S–13S.
19 Karagas MR, Greenberg ER. Unresolved issues in the epidemiology of basal cell and squamous cell skin cancer. In: Mukhtar H, ed, *Skin cancer: mechanisms and human relevance.* Boca Raton, Florida: CRC Press, 1995; pp79–86.
20 Marghoob AA, Slade J, Salopek TG, Kopf AW, Bart RS, Rigel DS. Basal cell and squamous cell carcinomas are important risk factors for cutaneous malignant melanoma. *Cancer* 1995; **75:** 707–14.
21 Lindelhof B, .Sigurgeirsson B, Wallberg P, Eklund G. Occurrence of other malignancies in 1973 patients with basal cell carcinoma. *J Am Acad Dermatol* 1991; **25:** 245–8.
22 Holman CDJ, Armstrong BK. Pigmentary traits, ethnic origin, benign naevi and family history as risk factors for cutaneous malignant melanoma. *JNCI* 1984; **72:** 257–66.
23 Koh HK, Geller AC, Miller DR, Lew RA. Early detection of melanoma: an ounce of prevention may be a ton of work. *J Am Acad Dermatol* 1993; **28:** 645–7.
24 Lookingbill DP. Yield from a complete skin examination: findings in 1157 new dermatology patients. *J Am Acad Dermatol* 1988; **18:** 31–7.
25 Sandstrom A, Larsson LG, Damber L. Occurrence of other malignancies in patients treated for basal cell carcinoma of the skin. *Acta Radiol Oncol* 1984; **23:** 227–30.
26 Mellor R, Nielsen A, Reymann F. Multiple basal cell carcinoma and internal malignant tumours. *Arch Dermatol* 1975; **111:** 584–5.
27 Boyle J, MacKie RM, Briggs JD, Junior BJR, Aitchison TC. Cancer, warts and sunshine in renal transplant patients: a case control study. *Lancet* 1984; **1:** 702–5.
28 Wei Q, Mutanoski GM, Farmer ER, Hedayati MA, Grossman L. DNA repair related to multiple skin cancers and drug use. *Cancer Res* 1994; **54:** 437–40.
29 Ikic D, Padovan I, Pipic N, *et al.* Interferon reduces recurrences of basal and squamous cell cancers. *Int J Dermatol* 1995; **34:** 58–60.
30 Fleming ID, Amonette R, Monaghan T, Fleming MD. Principles of management of basal and squamous cell carcinoma of the skin. *Cancer* 1995; **75:** 699–704.
31 Silverman MK, Kopf AW, Grin CM, Bart RS, Levenstein MJ. Recurrence rates of treated basal cell carcinomas. Part 2: Curettage-electrodessication. *J Dermatol Surg Oncol* 1991; **17:** 720–6.
32 Chandrasekhar S, Terry JJ. Non-melanoma skin cancer. In: McMurray RJ, Murphy GP, eds, *Cancer surgery.* Philadelphia: Lippincott, 1994; pp 537–49.
33 Mohs FE. *Chemosurgery; microscopically controlled surgery for skin cancer.* Springfield (IL): Chas A Thomas, 1978.
34 Svanberg K, Andersson T, Killander D, *et al.* Photodynamic therapy on non-melanoma malignant tumours of the skin using topical delta-amino laevulinic acid sensitisation and laser irradiation. *Br J Dermatol* 1994; **30:** 743–51.
35 Cornell RC, Greenway HT, Tucker S. Treatment of basal cell carcinoma with intralesional interferon. *J Am Acad Dermatol* 1990; **23:** 694–701.
36 Zitelli JA. Mohs micrographic surgery for skin cancer. *Principles Problems Oncol* 1992; **6:** 1–10.
37 Dixon AY, Lee SH, McGregor DH. Histologic features predictive of basal cell carcinoma recurrence: results of a multivariate analysis. *J Cutan Pathol* 1993; **20:** 137–42.
38 Wilder RB, Shimm DS, Kittelson JM, Rogoff EE, Cassady R. Recurrent basal cell carcinoma treated with radiation therapy. *Arch Dermatol* 1991; **127:** 1668–72.
39 Scanlon EF, Volkmer DD, Oveido MA. Metastatic basal cell carcinoma. *J Surg Oncol* 1980; **5:** 171–80.
40 Amonette RA, Salasche SJ, Chesney TM, Clarendon CC. Metastatic basal cell carcinoma. *J Dermatol Surg Oncol* 1981; **7:** 397–400.
41 Snow SN, Sahl W, Lo JS, *et al.* Metastatic basal cell carcinoma. *Cancer* 1994; **73:** 328–35.
42 Lo JS, Snow SN, Reizner GT, Mohs FE, Larson PO, Hruza GJ. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. *J Am Acad Dermatol* 1991; **24:** 715–9.
43 Von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. *J Am Acad Dermatol* 1984; **10:** 1043–60.
44 Strickland PT. Photocarcinogenesis by near UVA radiation in Sencar mice. *J Invest Dermatol* 1986; **87:** 272–5.
45 De Gruijl FR, Van Der Meer JB, Van DER Leun JC. Dose-time dependency of skin tumour induction by chronic UV exposure. *Photochem Photobiol* 1983; **37:** 53–62.
46 Kricker A, Armstrong BK, English DR. Sun exposure and non-melanocytic skin cancer. *Cancer Causes Control* 1994; **5:** 367–92.
47 Vitasa BC, Taylor HR, Strickland PT, *et al.* Association of non-melanoma skin cancer and actinic keratoses with cumulative solar UV exposure in Maryland watermen. *Cancer* 1990; **65:** 2811–7.
48 Hunter DJ, Colditz GA, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Risk factors for basal cell carcinoma in a prospective cohort of women. *Ann Epidemiol* 1990; **1:** 13–23.
49 Kricker A, Armstrong BK, English DR, Heenan PJ. Does intermittent sun exposure cause basal cell carcinoma? *Int J Cancer* 1995; **60:** 489–94.
50 Gallagher RP, Hill GB, Bajdik CD, *et al.* Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I Basal cell carcinoma *Arch Dermatol* 1995; **131:** 157–63.
51 Naylor MF, Boyd A, Smith DW, *et al.* High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol* 1995; **131:** 170–5.