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GUIDELINES

# Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma

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**Summary** These guidelines for management of primary cutaneous squamous cell carcinoma present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of epidemiological aspects, diagnosis and investigation.

## Disclaimer

These guidelines, prepared on behalf of the British Association of Dermatologists, the British Association of Plastic Surgeons and in consultation with members of the Faculty of Clinical Oncology of the Royal College of Radiologists, reflect the best published data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not be necessarily deemed negligent.

## Definition

Primary cutaneous squamous cell carcinoma (SCC) is a malignant tumour that may arise from the keratinizing cells of the epidermis or its appendages. It is locally invasive and has the potential to metastasize to other organs of the body. These guidelines are confined to the treatment of SCC of the skin and the vermilion border of the lip, and exclude SCC of the penis, vulva and anus, SCC *in situ* (Bowen's disease), SCC arising from mucous membranes, and keratoacanthoma.

## Incidence, aetiology and prevention

SCC is the second most common skin cancer and, in many countries, its incidence is rising.[1–5] Its occurrence is usually related to chronic ultraviolet light exposure and is therefore especially common in the sun-damaged skin of fair-skinned individuals, in albinos and in those with xeroderma pigmentosum. It may develop *de novo*, as a result of previous exposure to ionizing radiation or arsenic, within chronic wounds, scars, burns, ulcers or sinus tracts, and from pre-existing lesions such as Bowen's disease ('intraepidermal SCC').[6–14] Individuals with impaired immune function, for example those receiving immunosuppressive drugs following allogeneic organ transplantation or those with lymphoma or leukaemia, are at increased risk of this tumour; some SCCs are associated with human papillomavirus infection.[15–23] There is good evidence linking SCCs with chronic actinic damage and to support the use of sun avoidance, protective clothing and effective sunblocks in the prevention of actinic keratoses and SCCs; this is particularly important for patients receiving long-term immunosuppressive medication.[24–27]

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## Clinical presentation

SCC usually presents as an indurated nodular keratinizing or crusted tumour that may ulcerate, or it may present as an ulcer without evidence of keratinization.

## Diagnosis

The diagnosis is established histologically. The histology report should include the following: pathological pattern (e.g. 'adenoid type') cell morphology (e.g. 'spindle cell SCC'), degree of differentiation ('well differentiated' or 'poorly differentiated)', histological grade (as described by Broders, Appendix 2), depth (thickness in mm), the level of dermal invasion (as Clark's levels, excluding layers of surface keratin), and the presence or absence of perineural, vascular or lymphatic invasion. The margins of the excised tissue should be stained prior to tissue preparation to allow their identification histologically and comment should be made on the lateral and deep margins of excision.[28–40]

## Prognosis

The accumulated experience of treating cutaneous SCC by various methods has allowed some generalizations to be made about prognosis based on the original lesion. Factors that influence metastatic potential include anatomical site, size, rate of growth, aetiology, degree of histological differentiation and host immunosuppression. These details are frequently omitted from reported series of treated SCC and the conclusions of such series must therefore be interpreted with caution. Patient referral patterns may influence local experience of this condition, and series reported from office practices tend to suggest a more favourable prognosis than cases reported from hospital and tertiary centres.[41–48]

## Factors affecting metastatic potential of cutaneous squamous cell carcinoma (SCC)

*Site*

Tumour location influences prognosis: sites are listed in order of increasing metastatic potential.[30,41,49–52]

**1** SCC arising at sun-exposed sites excluding lip and ear.
**2** SCC of the lip.
**3** SCC of the ear.
**4** Tumours arising in non-sun-exposed sites (e.g. perineum, sacrum, sole of foot).
**5** SCC arising in areas of radiation or thermal injury, chronic draining sinuses, chronic ulcers, chronic inflammation or Bowen's disease.

*Size: diameter*

Tumours greater than 2 cm in diameter are twice as likely to recur locally (15·2% vs. 7·4%), and three times as likely to metastasize (30·3% vs. 9·1%) as smaller tumours.[41]

*Size: depth*

Tumours greater than 4 mm in depth (excluding surface layers of keratin) or extending down to the subcutaneous tissue (Clark level V) are more likely to recur and metastasize (metastatic rate 45·7%) compared with thinner tumours.[29,35,41] Recurrence and metastases are less likely in tumours confined to the upper half of the dermis and less than 4 mm in depth (metastatic rate 6·7%).[31,32,35,41]

*Histological differentiation*

Poorly differentiated tumours (i.e. those of Broders' grades 3 and 4; Appendix 2) have a poorer prognosis, with more than double the local recurrence rate and triple the metastatic rate of better differentiated SCC.[33,34,41] Tumours with perineural involvement are more likely to recur and to metastasize.[39,53] It seems logical that lymphatic or vascular invasion might imply a poor prognosis, but there is no evidence to support this as an independent risk factor.

*Host immunosuppression*

Tumours arising in patients who are immunosuppressed have a poorer prognosis. Host cellular immune response may be important both in determining the local invasiveness of SCC and the host's response to metastases.[22,23,28]

*Previous treatment and treatment modality*

The risk of local recurrence depends upon the treatment modality. Locally recurrent disease itself is a risk factor for metastatic disease. Local recurrence rates are

considerably less with Mohs' micrographic surgery than with any other treatment modality.[41,50–52,54,55]

## Treatment

In interpreting and applying guidelines for treatment of SCC, three important points should be noted:

- There is a lack of randomized controlled trials (RCTs) for the treatment of primary cutaneous SCC.
- There is widely varying malignant behaviour in those tumours that fall within the histological diagnostic category of 'primary cutaneous SCC'.
- There are varied experiences among the different specialists treating these tumours; these are determined by referral patterns and interests. Plastic and maxillofacial surgeons may encounter predominantly high-risk, aggressive tumours, whereas dermatologists may deal predominantly with smaller and less aggressive lesions.

However, there are three main factors that influence treatment, which are:

- the need for complete removal or treatment of the primary tumour;
- the possible presence of local 'in transit' metastases;
- the tendency of metastases to spread by lymphatics to lymph nodes.

The majority of SCCs are low risk and amenable to various forms of treatment, but it is essential to identify the significant proportion that are high-risk. These may be best managed by a multiprofessional team with experience of treating the most malignant tumours.[42,43,45,48,56–59]

The goal of treatment is complete (preferably histologically confirmed) removal or destruction of the primary tumour and of any metastases. In order to achieve this the margins of the tumour must be identified. The gold standard for identification of tumour margins is histological assessment, but most treatments rely on clinical judgement. It must be recognized that this is not always an accurate predictor of tumour extent, particularly where the margins of the tumour are ill-defined.[40,60–63]

SCC may give rise to local metastases, which are discontinuous with the primary tumour. Such 'in-transit' metastases may be removed by wide surgical excision or destroyed by irradiation of a wide field around the primary lesion. Small margins may not remove metastases in the vicinity of the primary tumour. Locally recurrent tumour may arise either due to failure to treat the primary continuous body of tumour, or from local metastases.[28,32,42,43,45,54,57,64,65]

SCC usually spreads to local lymph nodes and clinically enlarged nodes should be examined histologically (for example by fine needle aspiration or excisional biopsy). Tumour-positive lymph nodes are usually managed by regional node dissection, but detailed discussion of the management of metastatic disease is beyond the scope of these guidelines.[49,66–69]

In the absence of clinically enlarged nodes, techniques such as high resolution ultrasound-guided fine needle aspiration cytology may be useful in evaluating regional lymph nodes in patients with high risk tumours.[70–73] The role of sentinel lymph node biopsy has not been established.

Although there are many large series in which long-term outcome after treatment for cutaneous SCC has been reported (comprehensively summarized in Rowe *et al.* [41]), there are no large prospective randomized studies in which different treatments for this tumour have been compared.[42,63,74–76]

### *Guidelines for patient treatment*

Conclusions from population-based studies do not necessarily indicate the best treatment for an individual patient. In particular, when choosing a treatment modality it is important to be aware of the factors that may influence success. Curettage and cautery, cryosurgery, and to a lesser degree radiotherapy, are all techniques in which the outcome depends of the experience of the physician. Although the same could be said of surgical excision and Mohs' micrographic surgery, these two modalities provide tissue for histological examination that allows the pathologist to assess the adequacy of treatment and for the physician to undertake further surgery if necessary. For this reason, where feasible, surgical excision (including Mohs' micrographic surgery where appropriate) should be regarded as the treatment of first choice for cutaneous SCC. The other techniques can yield excellent results in experienced hands, but the quality of treatment cannot be assured or audited contemporaneously by a third party.[28,41,46,61,62,67,69,74,77–79]

### *Surgical excision*

Surgical excision is the treatment of choice for the majority of cutaneous SCC. It allows full characterization of the tumour and a guide to the adequacy of treatment through histological examination of the margins of the excised tissue.[32,41]

When undertaking surgical excision a margin of normal skin is excised from around the tumour. For clinically well-defined, low risk tumours less than 2 cm in diameter, surgical excision with a minimum 4-mm margin around the tumour border is appropriate and would be expected to completely remove the primary tumour mass in 95% of cases[61] (*Strength of Recommendation A, Quality of Evidence II-iii*). Narrower margins of excision are more likely to leave residual tumour. In order to maintain the same degree of confidence of adequate excision, larger tumours, high risk tumours of Broders' grade 2, 3 or 4, tumours extending into the subcutaneous tissue and those in high-risk locations (ear, lip, scalp, eyelids, nose) should be removed with a wider margin (6 mm or more) and the tissue margins examined histologically, or with Mohs' micrographic surgery.[50–52,61]

It is only meaningful to consider such margins when the peripheral boundary of the tumour appears clinically well-defined. The concept of a 'surgical margin' (i.e. normal-appearing tissue around the tumour) is based upon an assumption that the clinically visible margin of the tumour bears a predictable relationship to the true extent of the tumour, and that excision of a margin of clinically normal-appearing tissue around the tumour will encompass any microscopic tumour extension. The wider the surgical margin, the greater the likelihood that all tumour will be removed. Large tumours have greater microscopic tumour extension and should be removed with a wider margin. This concept is equally valid for non-surgical treatments such as radiotherapy and cryotherapy in which a margin of clinically normal-appearing tissue is treated around the tumour. Mohs' micrographic surgery does not make this assumption but displays the margins of the tissue for histological examination, and allows a primary tumour mass, growing in-continuity to be excised completely with minimal loss of normal tissue. There are important lessons to be learned from the experiences of micrographic surgery in treating cutaneous SCC (see below).[40,41,50–52,54,62]

### *Local metastases*

Microscopic metastases may be found around high-risk primary cutaneous SCC.[43,65,68] Under these circumstances a 'wide' surgical margin extending well beyond the primary tumour may include such metastases and thus have a higher cure rate than a narrower margin. Mohs' micrographic surgery removes tumour growing in continuity but does not identify in-transit micrometastases. For this reason some practitioners of Mohs' micrographic surgery will excise a further surgical margin when treating high risk tumours after the Mohs' surgical wound has been histologically confirmed to be clear of the primary tumour mass.[43,68]

### *Histological assessment of surgical margins*

Conventional histological examination of one or more transverse sections of excised tissue displays a cross-section of the tumour and tissue margins. This is the best way of assessing and categorizing the nature of the tumour, and it is usual to comment on whether the tumour extends to the tissue margin, or if not, to record the margin of uninvolved skin around the tumour.[40] The value of such comments depends on how closely the section examined reflects the excised tissue in general. If SCC appears to extend to the margin of the examined tissue, then it should be assumed, particularly if the true margin of the tissue has been stained prior to sectioning, that excision is incomplete. Orientating markers or sutures should be placed in the surgical specimen by the surgeon to allow the pathologist to report accurately on the location of any residual tumour. A pathologist, using the conventional 'breadloaf' technique for examining tissue, typically views only a small sample of the specimen microscopically,[40] and this may allow incompletely excised high-risk tumour to go undetected. There are several alternative tissue preparations that allow the peripheral margins of the excised tissue to be more comprehensively examined.[60] The clinician and pathologist must work closely together in order to ensure appropriate sampling and microscopic examination of excised tissue, particularly with high-risk tumours.[40,60]

Mohs' micrographic surgery differs because the tissue is not displayed in cross-section and, if the first level of excision is adequate, tumour may not be seen at all in the microscopic sections. There are technical factors that may occasionally hamper identification of SCC in frozen sections and under these circumstances final histological examination should be undertaken on formalin-fixed tissue.[80,81]

### *Mohs' micrographic surgery*

Mohs' micrographic surgery allows precise definition and excision of primary tumour growing in-continuity, and as such would be expected to reduce errors in

primary treatment that may arise due to clinically invisible tumour extension. There is good evidence that the incidence of local recurrent and metastatic disease are low after Mohs' micrographic surgery and it should therefore be considered in the surgical treatment of high-risk SCC, particularly at difficult sites where wide surgical margins may be technically difficult to achieve without functional impairment[32,41] (*Strength of Recommendation B, Quality of Evidence II-iii*). The best cure rates for high risk SCCs are reported in series treated by Mohs' micrographic surgery.[41] Where Mohs' micrographic surgery is indicated but not available then one of the other histological techniques to examine the peripheral margin of the excised tissue should be employed.[60]

However, there are no prospective randomized studies comparing therapeutic outcome between conventional or wide surgical excision vs. Mohs' micrographic surgery for cutaneous SCC.

It is firmly established that incomplete surgical excision is associated with a worse prognosis and, when doubt exists as to the adequacy of excision at the time of surgery, it is desirable, where practical, to delay or modify wound repair until complete tumour removal has been confirmed histologically.[28,41–45,53]

### *Curettage and cautery*

Excellent cure rates have been reported in several series[41,63,74,78] and experience suggests that small (< 1 cm) well-differentiated, primary, slow-growing tumours arising on sun-exposed sites can be removed by experienced physicians with curettage. There are few published data relating outcome after curettage of larger tumours and different clinical tumour types.

The high cure rates reported following curettage and cautery of cutaneous SCC (*Quality of Evidence II-iii*) may reflect case selection, with a greater proportion of small tumours treated by curettage than by other techniques, but also raise the question as to whether curettage *per se* has a therapeutic advantage. The experienced clinician undertaking curettage can detect tumour tissue by its soft consistency and this may be of benefit in identifying invisible tumour extension and ensuring adequate treatment. Conventionally, cautery or electrodesiccation is applied to the curetted wound and the curettage–cautery cycle then repeated once or twice. In principle, curettage could be combined with other treatments such as surgical excision, cryotherapy or radiotherapy; it is routinely undertaken to 'debulk' the tumour prior to Mohs' micrographic surgery. Curettage provides poorly orientated material for histological examination and no histological assessment of the adequacy of treatment is possible. Curettage and cautery is not appropriate treatment for locally recurrent disease.

### *Cryosurgery*

Good short-term cure rates have been reported for small histologically confirmed SCC treated by cryosurgery in experienced hands. Prior biopsy is necessary to establish the diagnosis histologically. There is great variability in the use of liquid nitrogen for cryotherapy and significant transatlantic variations in practice. For this reason caution should be exercised in the use of cryotherapy for SCC, although it may be an appropriate technique for selected cases in specialized centres.[41,77] Cryosurgery is not appropriate for locally recurrent disease.

### *Radiotherapy*

Radiation therapy alone offers reported short- and long-term cure rates for SCC that are comparable with other treatments.[32,41,74] Radiotherapy will, in certain circumstances, give the best cosmetic and/or functional result. This will often be the case for lesions arising on the lip, nasal vestibule (and sometimes the outside of the nose) and ear, among others. Certain very advanced tumours, where surgical morbidity would be unacceptably high may also be best treated by radiotherapy.

### *Elective prophylactic lymph node dissection*

Elective prophylactic lymph node dissection has been proposed for SCC on the lip greater than 6 mm in depth and cutaneous SCC greater than 8 mm in depth, but evidence for this is weak[46,49] (*Strength of Recommendation C, Quality of Evidence II-iii*). Elective lymph node dissection is not routinely practised and there is no compelling evidence of benefit over morbidity.[29,30,36]

### *The multiprofessional oncology team*

Patients with high risk SCC and those presenting with clinically involved lymph nodes should ideally be reviewed by a multiprofessional oncology team which includes a dermatologist, pathologist, appropriately

trained surgeon (usually a plastic or maxillofacial surgeon), clinical oncologist and a clinical nurse specialist in skin cancer. Some advanced tumours are not surgically resectable and these should be managed in a multiprofessional setting in order that other therapeutic options are considered. Patients should be provided with suitable written information concerning diagnosis, prognosis and follow-up support, local and national support organizations and, where appropriate, access to a multiprofessional palliative care team.

## Follow-up

Early detection and treatment improves survival of patients with recurrent disease. Ninety-five percent of local recurrences and 95% of metastases are detected within 5 years.[32,41] It would therefore seem reasonable for the patient who has had a high-risk SCC to be kept under observation for recurrent disease for this period of time (*Strength of Recommendation A, Quality of Evidence II-ii*). Patients should be, as far as possible, instructed in self-examination. Observation for recurrent disease may be undertaken by the specialist, primary care physician or by patient self-examination. The decision as to who follows the patient will depend upon the disease risk, local facilities and interests.[32,41]

## Summary of treatment options for primary cutaneous squamous cell carcinoma

Please see Table 1 for recommendations.

## Appendix 1

Full details of the British Association of Dermatologists' guidelines process are published in a previous edition of the journal.[82]

*Strength of recommendations*

**A** There is good evidence to support the use of the procedure.
**B** There is fair evidence to support the use of the procedure.
**C** There is poor evidence to support the use of the procedure.
**D** There is fair evidence to support the rejection of the use of the procedure.
**E** There is good evidence to support the rejection of the use of the procedure.

*Quality of evidence*

**I** Evidence obtained from at least one properly designed, randomized control trial.
**II-I** Evidence obtained from well-designed controlled trials without randomization.
**II-ii** Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one centre or research group.
**II-iii** Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
**III** Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
**IV** Evidence inadequate owing to problems of methodology (e.g. sample size, or length or comprehensiveness of follow-up or conflicts in evidence).

**Table 1.** Summary of treatment options for primary cutaneous squamous cell carcinoma

| Treatment | Indications | Contraindications | Notes |
|---|---|---|---|
| Surgical excision | All resectable tumours | Where surgical morbidity is likely to be unreasonably high | Generally treatment of choice for SCC<br>High risk tumours need wide margins or histological margin control |
| Mohs, micrographic surgery/ excision with histological control | High risk tumours, recurrent tumours | Where surgical morbidity is likely to be unreasonably high | Treatment of choice for high risk tumours |
| Radiotherapy | Non-resectable tumours | Where tumour margins are ill-defined | |
| Curettage and cautery | Small, well-defined low-risk tumours | High risk tumours | Curettage may be useful prior to surgical excision |
| Cryotherapy | Small, well-defined, low risk tumours | High risk tumours, recurrent tumours | Only suitable for experienced practitioners |

## Appendix 2

*Broders' histological classification of differentiation in squamous cell carcinoma*

Broders devised a classification system in which grades 1, 2 and 3 denoted ratios of differentiated to undifferentiated cells of 3 : 1, 1 : 1 and 1 : 3, respectively. Grade 4 denoted tumour cells having no tendency towards differentiation.

## References


1 Marks R. Squamous cell carcinoma. *Lancet* 1996; **347**: 735–8.
2 Bernstein SC, Lim KK, Brodland DG, Heidelberg KA. The many faces of squamous cell carcinoma. *Dermatol Surg* 1996; **22**: 243–54.
3 Glass AG, Hoover RN. The emerging epidemic of melanoma and squamous cell skin cancer. *JAMA* 1989; **262**: 2097–100.
4 Gray DT, Suman VJ, Su WP *et al.* Trends in the population-based incidence of squamous cell carcinoma of the skin first diagnosed between 1984 and 1992. *Arch Dermatol* 1997; **133**: 735–40.
5 Weinstock MA. The epidemic of squamous cell carcinoma. *JAMA* 1989; **262**: 2138–40.
6 Baldursson B, Sigurgeirsson B, Lindelof B. Leg ulcers and squamous cell carcinoma. An epidemiological study and review of the literature. *Acta Derm Venereol* 1993; **73**: 171–4.
7 Bosch RJ, Gallardo MA, Ruiz del Portal G *et al.* Squamous cell carcinoma secondary to recessive dystrophic epidermolysis bullosa: report of eight tumours in four patients. *J Eur Acad Dermatol Venereol* 1999; **13**: 198–204.
8 Keefe M, Wakeel RA, Dick DC. Death from metastatic cutaneous squamous cell carcinoma in autosomal recessive dystrophic epidermolysis bullosa despite permanent inpatient care. *Dermatologica* 1988; **177**: 180–4.
9 Chang A, Spencer JM, Kirsner RS. Squamous cell carcinoma arising from a nonhealing wound and osteomyelitis treated with Mohs' micrographic surgery: a case study. *Ostomy Wound Manage* 1998; **44**: 26–30.
10 Chowdri NA, Darzi MA. Postburn scar carcinomas in Kashmiris. *Burns* 1996; **22**: 477–82.
11 Dabski K, Stoll HL Jr, Milgrom H. Squamous cell carcinoma complicating late chronic discoid lupus erythematosus. *J Surg Oncol* 1986; **32**: 233–7.
12 Fasching MC, Meland NB, Woods JE, Wolff BG. Recurrent squamous cell carcinoma arising in pilonidal sinus tract – multiple flap reconstructions. Report of a case. *Dis Colon Rectum* 1989; **32**: 153–8.
13 Lister RK, Black MM, Calonje E, Burnand KG. Squamous cell carcinoma arising in chronic lymphoedema. *Br J Dermatol* 1997; **136**: 384–7.
14 Maloney ME. Arsenic in dermatology. *Dermatol Surg* 1996; **22**: 301–4.
15 Moy R, Eliezri YD. Significance of human papilloma-induced squamous cell carcinoma to dermatologists. *Arch Dermatol* 1994; **130**: 235–8.
16 Bens G, Wieland U, Hofmann A *et al.* Detection of new human papillomavirus sequences in skin lesions of a renal transplant recipient and characterization of one complete genome related to epidermodysplasia verruciformis-associated types. *J Gen Virol* 1998; **79**: 779–87.
17 Harwood CA, McGregor JM, Proby CM, Breuer J. Human papillomavirus and the development of non-melanoma skin cancer. *J Clin Pathol* 1999; **52**: 249–53.
18 Harwood CA, Surentheran T, McGregor JM *et al.* Human papillomavirus infection and non-melanoma skin cancer in immunosuppressed and immunocompetent individuals. *J Med Virol* 2000; **61**: 289–97.
19 Glover MT, Niranjan N, Kwan JT, Leigh IM. Non-melanoma skin cancer in renal transplant recipients: the extent of the problem and a strategy for management. *Br J Plast Surg* 1994; **47**: 86–9.
20 Liddington M, Richardson AJ, Higgins RM *et al.* Skin cancer in renal transplant recipients. *Br J Surg* 1989; **76**: 1002–5.
21 Ong CS, Keogh AM, Kossard S *et al.* Skin cancer in Australian heart transplant recipients. *J Am Acad Dermatol* 1999; **40**: 27–34.
22 Veness MJ, Quinn DI, Ong CS *et al.* Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience. *Cancer* 1999; **85**: 1758– 64.
23 Weimar VM, Ceilley RI, Goeken JA. Aggressive biologic behaviour of basal and squamous cell cancers in patients with chronic lymphocytic leukaemia or chronic lymphocytic lymphoma. *J Dermatol Surg Oncol* 1979; **5**: 609–14.
24 Green A, Williams G, Neale R *et al.* Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 1999; **354**: 723–9.
25 Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma in the skin: a prospective study. *Lancet* 1988; **9**: 795–7.
26 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.
27 Thompson SC, Jolley D, Marks R. Reduction of solar keratosis by regular sunscreen use. *N Eng J Med* 1993; **329**: 1147–51.
28 Barksdale SK, O'Connor N, Barnhill R. Prognostic factors for cutaneous squamous cell and basal cell carcinoma. Determinants of risk of recurrence, metastasis and development of subsequent skin cancers. *Surg Oncol Clin N Am* 1997; **6**: 625–38.
29 Breuninger H, Black B, Rassner G. Microstaging of squamous cell carcinomas. *Am J Clin Pathol* 1990; **94**: 624–7.
30 Breuninger H, Hawlitschek E. Das Mikrostaging des Plattenepithelkarzinoms der Haut und Lippen – lichtmikroskopisch erfasste Pronosenfaktoren. In: *Fortschritte der Operativen und Onkologischen Dermatologie* (Tilgen W, Petzoldt D, eds). Berlin, Heidelberg, New York: Springer, 1995; 110–15.
31 Breuninger H, Langer B, Rassner G. Untersuchungen zur Prognosebestimmung des spinozellularen karzinoms der Haut und Unterlippe anhand des TNM-Systems und zusatzlicher Parameter. *Hautarzt* 1988; **39**: 430–4.
32 Breuninger H. Diagnostic and therapeutic standards in interdisciplinary dermatologic oncology. German Cancer Society, 1998.
33 Broders AC. Squamous cell epithelioma of the lip. *JAMA* 1920; **74**: 656–64.
34 Broders AC. Squamous cell epithelioma of the skin. *Ann Surg* 1921; **73**: 141–60.
35 Friedman HI, Cooper PH, Wanebo HJ. Prognostic and therapeutic use of microstaging in cutaneous squamous cell carcinoma of the trunk and extremities. *Cancer* 1985; **56**: 1099–105.
36 Frierson HF, Cooper PH. Prognostic factors in squamous cell carcinoma of the lower lip. *Hum Pathol* 1986; **17**: 346–54.
37 Heenan PJ, Elder DJ, Sobin LH. *WHO International Histological Classification of Tumors* Berlin, Heidelberg, New York: Springer, 1993.

38 Hermanek P, Heuson DE, Hutter RVP, Sobin LH. *UICC (International Union Against Cancer) TNM Supplement*. Berlin, Heidelberg, New York: Springer, 1993.
39 Mendenhall WM, Parsons JT, Mendenhall NP *et al.* Carcinoma of the skin of the head and neck with perineural invasion. *Head Neck* 1989; **11**: 301–8.
40 Abide JM, Nahai F, Bennett RG. The meaning of surgical margins. *Plast Reconstr Surg* 1984; **73**: 492–6.
41 Rowe DE, Carroll RJ, Day CL. Prognostic factors for local recurrence, metastasis and survival rates in squamous cell carcinoma of the skin, ear and lip. *J Am Acad Dermatol* 1992; **26**: 976–90.
42 Dzubow LM, Rigel DS, Robins P. Risk factors for local recurrence of primary cutaneous squamous cell carcinomas. *Arch Dermatol* 1982; **118**: 900–2.
43 Epstein E, Epstein NN, Bragg K, Linden G. Metastases from squamous cell carcinomas of the skin. *Arch Dermatol* 1968; **97**: 245–51.
44 Epstein E. Malignant sun-induced squamous cell carcinoma of the skin. *J Dermatol Surg Oncol* 1983; **9**: 505–6.
45 Eroglu A, Berberoglu U, Berberoglu S. Risk factors related to locoregional recurrence in squamous cell carcinoma of the skin. *J Surg Oncol* 1996; **61**: 124–30.
46 Friedman NR. Prognostic factors for local recurrence, metastases and survival rates in squamous cell carcinoma of the skin, ear and lip. *J Am Acad Dermatol* 1993; **28**: 281–2.
47 Katz AD, Urbach F, Lilienfeld AM. The frequency and risk of metastases in squamous cell carcinoma of the skin. *Cancer* 1957; **10**: 1162–6.
48 Kwa RE, Campana K, Moy RL. Biology of cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 1992; **26**: 1–26.
49 Afzelius LE, Gunnarsson M, Nordgren H. Guidelines for prophylactic radical lymph node dissection in cases of carcinoma of the external ear. *Head Neck Surg* 1980; **2**: 361–5.
50 Mohs FE, Snow SN. Microscopically controlled surgical treatment for squamous cell carcinoma of the lower lip. *Surg Gynecol Obstet* 1985; **160**: 37–41.
51 Mohs FE. Chemosurgical treatment of cancer of the ear: a microscopically controlled method of excision. *Surgery* 1947; **21**: 605–22.
52 Mohs FE. Chemosurgical treatment of cancer of the lip. *Arch Surg* 1944; **48**: 478–88.
53 Cottel WI. Perineural invasion by squamous cell carcinoma. *J Dermatol Surg Oncol* 1982; **8**: 589–600.
54 Glass RL, Spratt JS, Perez-Mesa C. The fate of inadequately excised epidermoid carcinoma of the skin. *Surg Gynecol Obstet* 1966; **122**: 245–8.
55 Mohs FE. Chemosurgery. *Clin Plast Surg* 1980; **7**: 349–60.
56 Immerman SC, Scanlon EF, Christ M, Knox KL. Recurrent squamous cell carcinoma of the skin. *Cancer* 1983; **51**: 1537–40.
57 Kraus DH, Carew JF, Harrison LB. Regional lymph node metastasis from cutaneous squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg* 1998; **124**: 582–7.
58 Petter G, Haustein UF. Histologic subtyping and malignancy assessment of cutaneous squamous cell carcinoma. *Dermatol Surg* 2000; **26**: 521–30.
59 Tavin E, Persky M. Metastatic cutaneous squamous cell carcinoma of the head and neck region. *Laryngoscope* 1996; **106**: 156–8.
60 Rapini RP. Comparison of methods for checking surgical margins. *J Am Acad Dermatol* 1990; **23**: 288–94.
61 Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 1992; **27**: 241–8.
62 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.
63 Knox JM, Freeman RG, Duncan WC, Heaton CL. Treatment of skin cancer. *Southern Med J* 1967; **60**: 241–6.
64 Lund HZ. Metastasis from sun-induced squamous cell carcinoma of the skin: an uncommon event. *J Dermatol Surg Oncol* 1984; **10**: 169–70.
65 Dinehart SM, Pollack SV. Metastases from squamous cell carcinoma of the skin and lip. *J Am Acad Dermatol* 1989; **21**: 241–8.
66 Nicolson GL. Organ specificity of tumor metastasis: role of preferential adhesion, invasion and growth of malignant cells at specific secondary sites. *Cancer Metastasis Rev* 1988; **7**: 143–88.
67 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.
68 Brodland DG & Zitelli JA. Mechanisms of metastasis. *J Am Acad Dermatol* 1992; **27**: 1–8.
69 Geohas J, Roholt NS, Robinson JK. Adjuvant radiotherapy after excision of cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 1994; **30**: 633–6.
70 van den Brekel MWM, Stel HV, Castelijns JA *et al.* Lymph node staging in patients with clinically negative neck examinations by ultrasound and ultrasound-guided aspiration cytology. *Am J Surg* 1991; **162**: 362–6.
71 Vassallo P, Wernecke K, Roos N, Peters PE. Differentiation of benign from malignant superficial lymphadenopathy: the role of high resolution US. *Radiology* 1992; **183**: 215–20.
72 Knappe M, Louw M, Gregor RT. Ultrasonography-guided fine-needle aspiration for the assessment of cervical metastases. *Arch Otolaryngol Head Neck Surg* 2000; **126**: 1091–6.
73 Sumi M, Ohki M, Nakamura T. Comparison of sonography and CT for differentiating benign from malignant cervical lymph nodes in patients with squamous cell carcinoma of the head and neck. *AJR Am J Roentgenol* 2001; **176**: 1019–24.
74 Freeman RG, Knox JM, Heaton CL. The treatment of skin cancer. A statistical study of 1341 skin tumours comparing results obtained with irradiation, surgery and curettage followed by electrodesiccation. *Cancer* 1964; **17**: 535–8.
75 Macomber WB, Wang MKH, Sullivan JG. Cutaneous epithelioma. *Plast Reconst Surg* 1959; **24**: 545–62.
76 Stenbeck KD, Balanda KP, Williams MJ *et al.* Patterns of treated non-melanoma skin cancer in Queensland – the region with the highest incidence rates in the world. *Med J Aust* 1990; **153**: 511–15.
77 Kuflik EG, Gage AA. The five-year cure rate achieved by cryosurgery for skin cancer. *J Am Acad Dermatol* 1991; **24**: 1002–4.
78 Tromovitch TA. Skin cancer. Treatment by curettage and desiccation. *Calif Med* 1965; **103**: 107–8.
79 Karagas MR. Occurrence of cutaneous basal cell and squamous cell malignancies among those with a prior history of skin cancer. *J Invest Dermatol* 1994; **102**: 10–13S.
80 Telfer NR. Mohs' micrographic surgery for cutaneous squamous cell carcinoma: practical considerations. *Br J Dermatol* 2000; **142**: 631–3.
81 Turner RJ, Leonard N, Malcolm AJ *et al.* 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.
82 Griffiths CEM. The British Association of Dermatologists guidelines for the management of skin disease. *Br J Dermatol* 1999; **141**: 396–7.