Actinic Keratosis, Squamous Cell Carcinoma and Basal Cell Carcinoma
Clinical Guidelines, Sweden

Presented by John Paoli and Olle Larkö
Department of Dermatology, Sahlgrenska University Hospital, Göteborg, Sweden. E-mail: john.paoli@vgregion.se

These guidelines are a shortened version of the national guidelines adopted in Sweden in 2008 by the Section for Dermatologic Surgery and Oncology, Swedish Society for Dermatology and Venereology.

The guidelines are based largely on material that was used in connection with the development of guidelines for the Stockholm-Gotland region. The Section for Dermatologic Surgery and Oncology has revised the recommendations. This is intended as a living document.

SQUAMOUS CELL CARCINOMA

This section refers to squamous cell carcinoma (SCC) arising in sun-damaged skin. Facts and guidelines presented here should not be applied to similar tumours localized ano-genitally or in mucous membranes, or to SCC in chronic ulcers, inflamed skin, burns, etc.

Epidemiology

The incidence of SCC in sun-damaged skin is increasing rapidly in Sweden and accounts for 9.0% of all infiltrative cancer forms in men, excluding basal cell carcinoma. The corresponding figure in women is 7.5%. The annual increase in incidence in the last 20 years has been 3.2% for men and 4.0% for women. SCC is the second most common skin tumour after basal cell carcinoma. In 2006, 4,192 new cases of invasive SCC and 5,524 cases of SCC *in situ* were registered in Sweden. The incidence is 62.6/100,000 person years for men and 32/100,000 person years for women. The highest incidence is seen in persons over the age of 60 years in chronically sun-damaged skin in the head and neck area. SCC on the scalp and ears is much more common in men than in women, while women have more tumours on the lower legs (1).

Aetiology

A high cumulative dose of chronic exposure of sunlight is probably the most important risk factor for the development of SCC. Seventy-five to 80% of SCC are localized on sun-exposed areas, such as the head and neck region or dorsum of the hands. Persons with a light complexion and sun-sensitive skin run the highest risk of developing SCC (2–4). A clearly increased risk has also been seen in immunosuppressed patients (5–10), for example in kidney transplant recipients who run a 100 times risk increase (11). Other causes of SCC in the skin are radiation treatment, chronically inflamed skin, chronic ulcers, burns and arsenic (12–20). Patients with xeroderma pigmentosum have a clearly increased risk of developing SCC (21). Genital SCC is strongly associated with infections with human papilloma virus (HPV) and in some cases with lichen sclerosus (22–29).

Definition

Primary SCC of the skin arises from keratin-producing cells in the epidermis. Its growth is locally invasive and has a potential to spread to regional lymph nodes as well as to other parts of the body. Keratoacanthoma seems to be a more benign form of SCC. It also has a much faster growth (30) and can be described as an exophytically growing tumour with a central keratin plug. Keratoacanthomas often regress spontaneously after several months, but cases that metastasize have been described (31, 32).

Premalignant lesions

Actinic keratosis (AK) is a premalignant lesion. There are several histopathological types. Actinic keratoses (AK) have a low risk of progression to invasive SCC and may even regress spontaneously (33, 34). The risk of a single AK to progress to SCC might be 10% in 10 years (35).

SCC *in situ* (Mb Bowen) is an intraepidermal SCC. SCC in situ occurring ano-genitally is often associated with high risk-HPV.

Field cancerization is used to describe atypical histology in sun-damaged skin, occasional premalignant areas or invasive SCCs in extensive skin areas (36–39). It is commonly seen in heavily sun-damaged skin in older patients and in chronically immunosuppressed organ transplant recipients.

Prognosis and treatment

The risk of metastases to regional lymph nodes has been estimated to be 2–5% (40–42). SCC on the ears and the scalp may even metastasize to the parotid gland (42). The rate of metastasis is dependent on the site of the tumours, size, growth rate, histological differentiation and degree of immunosuppression. The risk of local recurrences is affected by the treatment method (4, 41, 43–48).

If major surgery is needed, a plastic surgeon or an Ear-, Nose-, Throat- (ENT) specialist should be involved. Palpation of regional lymph glands should always be performed (49). There are no current controlled studies showing any effect of sentinel lymph node biopsy (50, 51). If signs of regional metastasis

or a local recurrence of the head and neck presents, an ENT specialist should be consulted. When signs of regional metastasis outside the head and neck area are evident a surgeon or oncologist should be consulted.

Premalignant lesions should be treated in order to stop development to infiltrative SCC (34, 52). The methods of treatment are many. The choice depends on the experience of the doctor, the number of lesions, lesion site, the age of the patient, etc. Also, cosmetic outcome should be considered.

For single AKs, cryosurgery with liquid nitrogen is well suited (33, 34, 53–55). Previous curettage of hyperkeratosis should be performed.

Multiple AKs should preferably be treated with photodynamic therapy (PDT) (54, 56–58), imiquimod (59–61) or 5-fluorouracil (33, 53, 62, 63). Diclofenac is moderately effective and the treatment time of several months increases the risk of inadequate compliance (64, 65). Curettage and electrodessication (C&E) is a superficially destructive treatment that may give rise to scarring (34, 53, 66). Seldom used alternatives include ablative laser treatments, chemical peels or dermabrasion, but evidence for recommending these modalities is lacking (33, 34).

Primary care physicians, who have the skills to diagnose AKs, either clinically or with the help of a biopsy, may treat these with imiquimod, for example. If the diagnosis is unclear, or if the treatment is insufficient, the patient should be referred to a dermatologist.

SCC *in situ* in the face should preferably be excised in order to achieve radicality. Other treatment options in the face include PDT (×2) and cryosurgery (67–69). SCC in situ on the trunk and extremities excluding the lower legs may be treated with excision, cryosurgery, C&E and PDT (×2) (68, 69). Ablative laser treatment cannot be recommended since only case reports (70) and dubious results have been published (71).

SCC *in situ* on the lower legs may be treated with excision, PDT (×2), C&E or 5-fluorouracil topically (68, 69, 72). Cryosurgery is probably effective, but may give rise to ulcers that heal slowly.

Ano-genital SCC *in situ* should be treated by excision, Mohs micrograsphic surgery (MMS) or ablative laser therapy although several other alternatives are possible (68, 69, 73, 74). The risk of recurrence is high with all treatment modalities (73, 74).

Invasive SCC. Excision with at least a 4 mm margin on low-risk tumours and a minimum of 6 mm on high-risk SCCs is the treatment of choice. MMS has been shown to be highly effective (2, 4, 47, 75–77). For complicated tumours localized in the head and neck area a plastic surgeon should be consulted.

As a second choice of therapy for low-risk tumours, C&E or curettage and cryosurgery may be used (2, 4, 49).

Radiation therapy for SCC should rarely be used (2, 4, 75, 78).

Metastasizing disease. If metastasizing disease is suspected, a fine needle aspiration biopsy is advocated (2). Widespread disease should be discussed with specialists in ENT, oncology, surgery or plastic surgery.

Follow-up

Actinic keratosis. Not generally necessary.

Invasive SCC. High-risk tumours should be followed for at least 2 years. Individual follow-up routines with controls 1–4 times yearly should be used for selected immunosuppressed patients. Follow-up of low-risk patients is not considered necessary.

BASAL CELL CARCINOMA

Epidemiology

Basal cell carcinoma (BCC) is the most common malignancy of the skin. In 2006, 39,000 new cases were reported in Sweden (79). The tumour is usually seen in patients over the age of 50 years. In an epidemiological study of the incidence of BCC, an annual incidence rise of 12% during a 10-year period was reported (80). It appears that the incidence has risen 10-fold during the last 30 years. Since 2003, BCCs are reported to the Swedish national cancer registry by pathologists.

Aetiology

Intense, intermittent sun exposure, but also a high cumulative dose of sunlight seems to be the major cause of BCC. Most cases are localized to sun-exposed areas. Immunosuppressed patients run a 6–10 times higher risk of developing BCC (7, 81). Arsenic is a well-known risk factor (20) and BCCs can sometimes occur in chronic ulcers (82).

Definition

BCCs develop from pluripotent cells in the basal layer, most often in the epidermis, but also in hair follicles and sweat glands (81–91). The tumour seems to be dependent on its specialized stroma for its growth, which limits its metastatic potential (87, 92). The risk of developing a new BCC appears to be high (93, 94). Nodular and morpheiform BCC occur more often in the head and neck region, while superficial BCCs (sBCCs) are more common on the trunk (88). In Sweden, BCCs are classified histopathologically following the classification proposed by Jernbeck et al. ("Sabbatsbergsmodellen") (95).

Nodular or noduloulcerative BCC (Glas I *A*). Well-defined tumours most often localized in the face but also the trunk (88, 96).

Superfical BCC (Glas I B). Accounts for 20–25% of all BCCs (92, 107). Mainly localized to the trunk, more seldom in the face (88).

Infiltrative, moderately aggressive BCC (Glas II). Approximately 10–20% of all BCCs (95, 97).

Morpheiform, highly aggressive BCC (Glas III). Invades subcutaneous tissue, cartilage and bone. The tumour borders are hard to delineate (95). Most common in the face (88, 96).

Micronodular BCCs may be regarded as highly aggressive BCCs. **Metatypic or basosquamous cancer** is not very common, but is aggressive with differentiation towards SCC (98–100).

Prognosis and treatment

The risk of recurrence for primary BCC is 1–10%, whereas for recurrent tumours it is 15–30% (5). High-risk factors are growth on the nose, nasolabial folds, ears and eyelids, tumour diameter > 2 cm and an aggressive growth pattern (2, 89, 101). Metastasis to regional lymph nodes is very rare (2, 101).

A punch biopsy is generally recommended in cases of unclear clinical diagnosis. Surgical excision is the gold standard of treatment (2, 90, 101, 102). The excision margin should be at least 3–4 mm for small BCCs.

Nodular/noduloulcerative BCCs (Glas IA). Excision is usually recommended for facial lesions (89, 97). Curettage and cryosurgery may also be used as a first-line therapy if the tumour is localized on the nose (103), the ears (104) or the eyelids (105).

In other areas of the body, excision (89), curettage plus cryosurgery (89, 106–108) or C&E (89, 109) may be recommended alternatives. Curettage and cryosurgery should be avoided on the lower legs due to the risk of ulcers (101). PDT (× 2) after curettage has been shown to be relatively effective, but cannot be recommended as a first-line therapy. The single study published so far was a 5-year follow-up that showed markedly better results with surgery compared with PDT (110).

Superficial BCCs (Glas IB). Excision is the first line of treatment if localized in the face (2, 97). Cryosurgery may be an alternative but should be avoided if the tumour is localized to the eyebrows or nasolabial folds (89, 101, 111). PDT (× 2) has been reported to be effective for superficial BCCs (2, 36, 89, 101). Topical imiquimod has been shown to be efficient in 73–90% of cases when treating small superficial BCCs (112–114), and in one study, 79% of the patients were free of recurrence after 2 years (113). Also, 5-fluorouracil topically might be useful and has shown histological clearance in 28/31 patients in a small study (115).

For tumours localized outside the head and neck area, several therapeutic modalities may be used, excision, cryosurgery, PDT and topical treatments such as imiquimod and 5-fluorouracil (2, 89, 101, 109).

Infiltrative moderately aggressive BCCs (Glas II). Excision is usually the therapy of choice regardless of site (2, 89, 101). Curettage and cryosurgery may be a second-line therapy (2, 89, 101). MMS might be an alternative in selected cases.

Morpheiform, highly aggressive BCCs (Glas III), micronodular, metatypic, and recurrent BCCs. MMS is the internationally recommended alternative (2, 90, 101, 116–118). The method is unfortunately not easily accessible in the Nordic countries. Complete excision is encountered in only 82% of cases if ordinary excision is performed (119). Hence, advanced reconstruction with flaps should be avoided if completeness of excision is unknown.

On other parts of the body, at least a 5 mm excision margin is recommended for highly aggressive BCCs and recurrences (89, 120). Smaller, lowly aggressive BCCs that recur may, as an alternative, be treated with curettage and cryosurgery or C&E (89). However, these alternatives and medical treatments (imiquimod, 5-fluorouracil, PDT) should generally be considered as contraindicated for highly aggressive and recurrent BCCs (2).

Incomplete excision

If the excision is incomplete, re-excision is recommended (2, 89, 101, 121–124). The risk of recurrence after an incomplete excision is 38–42% within 5 years and can be more than 50% within 10 years after treatment (122). When incompletely excised BCCs are re-excised, tumour residues are found in 41–54% of the histopathological slides (122).

Advanced reconstruction after surgical excision

Defects after excision of BCCs where you have no histopathological confirmation of complete excision should mainly be primarily sutured or left to heal secondarily. In these cases, flaps distorting the skin should be avoided as they increase the difficulty of re-excising potential tumour residues after incomplete excisions (101, 125).

Follow-up

One-third of all patients diagnosed with BCC encounter a new tumour within 2 years and 36% have another BCC after 5 years (94). Potential recurrences are discovered in 33% of cases within one year, 50% within 2 years and 66% within 3 years (116).

- Patients treated for BCC should be informed about the disease and regarding self-control and prevention.
- We recommend patients having more than one high-risk factor for BCC are followed up by a dermatologist for 2 years.

- Individual follow-up routines with follow-up controls 1–4 times yearly are recommended for selected immunosuppressed patients and patients with Gorlin's syndrome as long as new tumours develop.
- Follow-up for low-risk patients is not necessary.

RADIOTHERAPY FOR SCC AND BCC

Radiotherapy is effective for both SCC and BCC but should be considered only in very selected cases regarding primary tumours. For metastasizing SCCs radiotherapy may be a choice (41, 75, 78, 101). Radiotherapy is not recommended for patients with Gorlin's syndrome (2, 84, 86, 87).

This document is intended as a living document.

Acknowledgements

We would like to thank the other authors of the Section for Dermatologic Surgery and Oncology's latest version of the "Guidelines for the management of SCC and BCC": Mats Bjellerup, Bertil Persson, Mikael Tarstedt, Susanne Uddströmer and Ann-Marie Wennberg. We also acknowledge all previous contributors to this living document.

References

1. The Swedish Cancer Registry. National Board of Health and Welfare. Cancer incidence in Sweden 2006. 2007. Available from: http://www.socialstyrelsen.se/Publicerat/2007/9850/2007-42-16.htm. Accessed July 2009.
2. National Health & Medical Research Council. Non-Melanoma Skin Cancer: Guidelines for treatment and management in Australia. 2002. Available from: http:dd//www.nhmrc.gov.au.
3. Lindelöf B, Dal H, Wolk K, Malmborg N. Cutaneous squamous cell carcinoma in organ transplant recipients: a study of the Swedish cohort with regard to tumor site. Arch Dermatol 2005; 141: 447–451.
4. Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. Br J Dermatol 2002; 146: 18–25.
5. Blohme I, Larkö O. Skin lesions in renal transplant patients after 10–23 years of immunosuppressive therapy. Acta Derm Venereol 1990; 70: 491–494.
6. 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: 574–579.
7. Espana A, Redondo P, Fernandez AL, Zabala M, Herreros J, Liorens R, et al. Skin cancer in heart transplant recipients. J Am Acad Dermatol 1995; 32: 458–465.
8. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med 2003; 348: 1681–1691.
9. Jensen P, Hansen S, Moller B, Leivvestad T, Pfeffer P, Geiran O, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol 1999; 40: 177–186.
10. Naldi L, Fortina AB, Lovati S, Barba A, Gotti E, Tessari G, et al. Risk of nonmelanoma skin cancer in Italian organ transplant recipients. A registry-based study. Transplantation 2000; 70: 1479–1484.
11. Lindelöf B, Sigurgeirsson B, Gabel H, Stern RS. Incidence of skin cancer in 5356 patients following organ transplantation. Br J Dermatol 2000; 143: 513–519.
12. Baldursson B, Sigurgeirsson B, Lindelöf B. Leg ulcers and squamous cell carcinoma. An epidemiological study and a review of the literature. Acta Derm Venereol 1993; 73: 171–174.
13. Baldursson BT, Hedblad MA, Beitner H, Lindelöf B. Squamous cell carcinoma complicating chronic venous leg ulceration: a study of the histopathology, course and survival in 25 patients. Br J Dermatol 1999; 140: 1148–1152.
14. Bosch RJ, Gallardo MA, Ruiz del Portal G, Snchez P, Arce MF, Herrera E. 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.
15. Chowdri NA, Darzi MA. Postburn scar carcinomas in Kashmiris. Burns 1996; 22: 477–482.
16. Dabski K, Stoll HL, Jr., Milgrom H. Squamous cell carcinoma complicating late chronic discoid lupus erythematosus. J Surg Oncol 1986; 32: 233–237.
17. 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: 153–158.
18. Karagas MR, Nelson HH, Zens MS, Linet M, Stukel TA, Spencer S, et al. Squamous cell and basal cell carcinoma of the skin in relation to radiation therapy and potential modification of risk by sun exposure. Epidemiology 2007; 18: 776–784.
19. Lister RK, Black MM, Calonje E, Burnand KG. Squamous cell carcinoma arising in chronic lymphoedema. Br J Dermatol 1997; 136: 384–387.
20. Maloney ME. Arsenic in dermatology. Dermatol Surg 1996; 22: 301–304.
21. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. Arch Dermatol 1987; 123: 241–250.
22. Barbagli G, Palminteri E, Mirri F, Guazzoni G, Turini D, Lazzeri M. Penile carcinoma in patients with genital lichen sclerosus: a multicenter survey. J Urol 2006; 175: 1359–1363.
23. Madsen BS, Jensen HL, van den Brule AJ, Wohlfahrt J, Frisch M. Risk factors for invasive squamous cell carcinoma of the vulva and vagina – population-based case-control study in Denmark. Int J Cancer 2008; 122: 2827–2834.
24. Nasca MR, Innocenzi D, Micali G. Penile cancer among patients with genital lichen sclerosus. J Am Acad Dermatol 1999; 41: 911–914.
25. Perceau G, Derancourt C, Clavel C, Durlach A, Pluot M, Lardennois B, Bernard P. Lichen sclerosus is frequently present in penile squamous cell carcinomas but is not always associated with oncogenic human papillomavirus. Br J Dermatol 2003; 148: 934–938.
26. Powell J, Robson A, Cranston D, Wojnarowska F, Turner R. High incidence of lichen sclerosus in patients with squamous cell carcinoma of the penis. Br J Dermatol 2001; 145: 85–89.
27. Tornesello ML, Duraturo ML, Losito S, Botti G, Pilotti S, Stefanon B, et al. Human papillomavirus genotypes and HPV16 variants in penile carcinoma. Int J Cancer 2008; 122: 132–137.
28. Velazquez EF, Cubilla AL. Lichen sclerosus in 68 patients with squamous cell carcinoma of the penis: frequent atypias and correlation with special carcinoma variants suggests a precancerous role. Am J Surg Pathol 2003; 27: 1448–1453.
29. Velazquez EF, Cubilla AL. Penile squamous cell carcinoma: anatomic, pathologic and viral studies in Paraguay (1993–2007). Anal Quant Cytol Histol 2007; 29: 185–198.
30. Rinker MH, Fenske NA, Scalf LA, Glass LF. Histologic variants of squamous cell carcinoma of the skin. Cancer Control 2001; 8: 354–363.
31. Hodak E, Jones RE, Ackerman AB. Solitary keratoacanthoma is a squamous-cell carcinoma: three examples with metastases. Am J Dermatopathol 1993; 15: 332–342; discussion 343–352.
32. Requena L, Romero E, Sanchez M, Ambrojo P, Sanchez Yus E. Aggressive keratoacanthoma of the eyelid: "malignant" keratoacanthoma or squamous cell carcinoma? J Dermatol Surg Oncol

1990; 16: 564–568.
33. de Berker D, McGregor JM, Hughes BR. Guidelines for the management of actinic keratoses. Br J Dermatol 2007; 156: 222–230.
34. Stockfleth E, Kerl H. Guidelines for the management of actinic keratoses. Eur J Dermatol 2006; 16: 599–606.
35. Dodson JM, DeSpain J, Hewett JE, Clark DP. Malignant potential of actinic keratoses and the controversy over treatment. A patient-oriented perspective. Arch Dermatol 1991; 127: 1029–1031.
36. Braathen LR, Szeimies RM, Basset-Seguin N, Bissonnette R, Foley P, Pariser D, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. J Am Acad Dermatol 2007; 56: 125–143.
37. Paoli J, Halldin C, Ericson MB, Wennberg AM. Nerve blocks provide effective pain relief during topical photodynamic therapy for extensive facial actinic keratoses. Clin Exp Dermatol 2008; 33: 559–564.
38. Ulrich M, Maltusch A, Rowert-Huber J, Gonzalez S, Sterry W, Stockfleth E, Astner S, et al. Actinic keratoses: non-invasive diagnosis for field cancerisation. Br J Dermatol 2007; 156 Suppl 3: 13–17.
39. Vatve M, Ortonne JP, Birch-Machin MA, Gupta G. Management of field change in actinic keratosis. Br J Dermatol 2007; 157 Suppl 2: 21–24.
40. Czarnecki D, Staples M, Mar A, Giles G, Meehan C. Metastases from squamous cell carcinoma of the skin in southern Australia. Dermatology 1994; 189: 52–54.
41. Joseph MG, Zulueta WP, Kennedy PJ. Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of metastases and their outcome. Aust N Z J Surg 1992; 62: 697–701.
42. Veness MJ, Porceddu S, Palme CE, Morgan GJ. Cutaneous head and neck squamous cell carcinoma metastatic to parotid and cervical lymph nodes. Head Neck 2007; 29: 621–631.
43. Cherpelis BS, Marcusen C, Lang PG. Prognostic factors for metastasis in squamous cell carcinoma of the skin. Dermatol Surg 2002; 28: 268–273.
44. Dinehart SM, Pollack SV. Metastases from squamous cell carcinoma of the skin and lip. An analysis of twenty-seven cases. J Am Acad Dermatol 1989; 21: 241–248.
45. Dzubow LM, Rigel DS, Robins P. Risk factors for local recurrence of primary cutaneous squamous cell carcinomas. Treatment by microscopically controlled excision. Arch Dermatol 1982; 118: 900–902.
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: 281–282.
47. Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol 1992; 26: 976–990.
48. Veness MJ. High-risk cutaneous squamous cell carcinoma of the head and neck. J Biomed Biotechnol 2007; 2007: 80572.
49. Drake LA, Dinehart SM, Goltz RW,Graham GF, Hordinsky MK, Lewis CW, et al. Guidelines of care for Mohs micrographic surgery. American Academy of Dermatology. J Am Acad Dermatol 1995; 33: 271–278.
50. Ross AS, Schmults CD. Sentinel lymph node biopsy in cutaneous squamous cell carcinoma: a systematic review of the English literature. Dermatol Surg 2006; 32: 1309–1321.
51. Wagner JD, Evdokimow DZ, Weisberger E, Moore D, Chuang TY, Wenck S, et al. Sentinel node biopsy for high-risk nonmelanoma cutaneous malignancy. Arch Dermatol 2004; 140: 75–79.
52. Anwar J, Wrone DA, Kimyai-Asadi A, Alam M. The development of actinic keratosis into invasive squamous cell carcinoma: evidence and evolving classification schemes. Clin Dermatol 2004; 22: 189–196.
53. McIntyre WJ, Downs MR, Bedwell SA. Treatment options for actinic keratoses. Am Fam Physician 2007; 76: 667–671.
54. Szeimies RM, Karrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. J Am Acad Dermatol 2002; 47: 258–262.
55. Thai KE, Fergin P, Freeman M, Vinciullo C, Francis D, Spelman L, et al. A prospective study of the use of cryosurgery for the treatment of actinic keratoses. Int J Dermatol 2004; 43: 687–692.
56. Freeman M, Vinciullo C, Francis D, Spelman L, Nguyen R, Fergin P, et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. J Dermatolog Treat 2003; 14: 99–106.
57. Morton CA, Brown SB, Collins S, Ibbotson S, Jenkinson H, Kurwa H, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. Br J Dermatol 2002; 146: 552–567.
58. Pariser DM, Lowe NJ, Stewart DM, Jarret MT, Lucky AW, Pariser RJ, et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. J Am Acad Dermatol 2003; 48: 227–232.
59. Korman N, Moy R, Ling M, et al. Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. Arch Dermatol 2005; 141: 467–473.
60. Stockfleth E, Sterry W, Carey-Yard M, Bichel J. Multicentre, open-label study using imiquimod 5% cream in one or two 4-week courses of treatment for multiple actinic keratoses on the head. Br J Dermatol 2007; 157 Suppl 2: 41–46.
61. Szeimies RM, Gerritsen MJ, Gupta G, Ortonne JP, Serresi S, Bichel J, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. J Am Acad Dermatol 2004; 51: 547–555.
62. Jury CS, Ramraka-Jones VS, Gudi V, Herd RM. A randomized trial of topical 5% 5-fluorouracil (Efudix cream) in the treatment of actinic keratoses comparing daily with weekly treatment. Br J Dermatol 2005; 153: 808–810.
63. Kurwa HA, Yong-Gee SA, Seed PT, Markey AC, Barlow RJ. A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. J Am Acad Dermatol 1999; 41: 414–418.
64. Tarstedt M, Larkö O, Molin L, Wennberg AM. [Increasing number of skin cancer cases – also among the younger]. Läkartidningen 2005; 102: 1972–1975.
65. Wolf JE, Jr., Taylor JR, Tschen E, Kang S. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. Int J Dermatol 2001; 40: 709–713.
66. Dinehart SM. The treatment of actinic keratoses. J Am Acad Dermatol 2000; 42: 25–28.
67. Cox NH, Eedy DJ, Morton CA. Guidelines for management of Bowen's disease. British Association of Dermatologists. Br J Dermatol 1999; 141: 633–641.
68. Cox NH, Eedy DJ, Morton CA. Guidelines for management of Bowen's disease: 2006 update. Br J Dermatol 2007; 156: 11–21.
69. Moreno G, Chia AL, Lim A, Shumack S. Therapeutic options for Bowen's disease. Australas J Dermatol 2007; 48: 1–8; quiz 9–10.
70. Fader DJ, Lowe L. Concomitant use of a high-energy pulsed CO2 laser and a long-pulsed (810 nm) diode laser for squamous cell carcinoma in situ. Dermatol Surg 2002; 28: 97–99; disc. 100.
71. Humphreys TR, Malhotra R, Scharf MJ, Marcus SM, Starkus L, Calegari K. Treatment of superficial basal cell carcinoma and squamous cell carcinoma in situ with a high-energy pulsed carbon dioxide laser. Arch Dermatol 1998; 134: 1247–1252.
72. Ahmed I, Berth-Jones J, Charles-Holmes S, O'Callaghan CJ, Ilchyshyn A. Comparison of cryotherapy with curettage in the treatment of Bowen's disease: a prospective study. Br J Dermatol 2000; 143: 759–766.
73. Paoli J, Ternesten Bratel A, Lowhagen GB, Stenquist B, Forslund O, Wennberg AM. Penile intraepithelial neoplasia: results of photodynamic therapy. Acta Derm Venereol 2006; 86: 418–421.

74. von Krogh G, Horenblas S. The management and prevention of premalignant penile lesions. Scand J Urol Nephrol Suppl 2000; 205: 220–229.
75. Albright SD, 3rd. Treatment of skin cancer using multiple modalities. J Am Acad Dermatol 1982; 7: 143–171.
76. An KP, Ratner D. Surgical management of cutaneous malignancies. Clin Dermatol 2001; 19: 305–320.
77. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. J Am Acad Dermatol 1992; 27: 241–248.
78. Goldman GD. Squamous cell cancer: a practical approach. Semin Cutan Med Surg 1998; 17: 80–95.
79. The Swedish Cancer Registry. National Board of Health and Welfare. [Basal Cell Carcinoma – Statistics for 2006] 2008. Available from: http: //www.socialstyrelsen.se/Publicerat/2008/9965/2008-125-2.htm. Accessed July 2009.
80. Wallberg P, Skog E. The incidence of basal cell carcinoma in an area of Stockholm County during the period 1971–1980. Acta Derm Venereol 1991; 71: 134–137.
81. Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation 1990; 49: 506–509.
82. Combemale P, Bousquet M, Kanitakis J, Bernard P. Malignant transformation of leg ulcers: a retrospective study of 85 cases. J Eur Acad Dermatol Venereol 2007; 21: 935–941.
83. Diaz-Fernandez JM, Infante-Cossio P, Belmonte-Caro R, Ruiz-Laza L, Garcia-Perla-Garcia A, Gutierrez-Perez JL. Basal cell nevus syndrome. Presentation of six cases and literature review. Med Oral Patol Oral Cir Bucal 2005; 10 Suppl 1: E57–66.
84. Evans DG, Birch JM, Ramsden RT, Sharif S, Baser ME. Malignant transformation and new primary tumours after therapeutic radiation for benign disease: substantial risks in certain tumour prone syndromes. J Med Genet 2006; 43: 289–294.
85. Gorlin RJ, Goltz RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome. N Engl J Med 1960; 262: 908–912.
86. Howell JB. Nevoid basal cell carcinoma syndrome. Profile of genetic and environmental factors in oncogenesis. J Am Acad Dermatol 1984; 11: 98–104.
87. Miller SJ. Etiology and pathogenesis of basal cell carcinoma. Clin Dermatol 1995; 13: 527–536.
88. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol 2002; 147: 41–47.
89. Telfer NR, Colver GB, Bowers PW. Guidelines for the management of basal cell carcinoma. British Association of Dermatologists. Br J Dermatol 1999; 141: 415–423.
90. Thissen MR, Neumann MH, Schouten LJ. A systematic review of treatment modalities for primary basal cell carcinomas. Arch Dermatol 1999; 135: 1177–1183.
91. Zackheim HS. Origin of the human basal cell epithelioma. J Invest Dermatol 1963; 40: 283–297.
92. Pinkus H. Epithelial and fibroepithelial tumors. Arch Dermatol 1965; 91: 24–37.
93. Marghoob A, Kopf AW, Bart RS, Sanfilippo L, Silverman MK, Lee P, et al. Risk of another basal cell carcinoma developing after treatment of a basal cell carcinoma. J Am Acad Dermatol 1993; 28: 22–28.
94. Robinson JK. Risk of developing another basal cell carcinoma. A 5-year prospective study. Cancer 1987; 60: 118–120.
95. Jernbeck J, Glaumann B, Glas JE. [Basal cell carcinoma. Clinical evaluation of the histological grading of aggressive types of cancer]. Läkartidningen 1988; 85: 3467–3470.
96. Heckmann M, Zogelmeier F, Konz B. Frequency of facial basal cell carcinoma does not correlate with site-specific UV exposure. Arch Dermatol 2002; 138: 1494–1497.
97. Kuijpers DI, Thissen MR, Berretty PJ, Ideler FH, Nelemans PJ, Neumann MH. Surgical excision versus curettage plus cryosurgery in the treatment of basal cell carcinoma. Dermatol Surg 2007; 33: 579–587.
98. Costantino D, Lowe L, Brown DL. Basosquamous carcinoma – an under-recognized, high-risk cutaneous neoplasm: case study and review of the literature. J Plast Reconstr Aesthet Surg 2006; 59: 424–428.
99. Leibovitch I, Huilgol SC, Selva D, Richards S, Paver R. Basosquamous carcinoma: treatment with Mohs micrographic surgery. Cancer 2005; 104: 170–175.
100. Martin RC, 2nd, Edwards MJ, Cawte TG, Sewell CL, McMasters KM. Basosquamous carcinoma: analysis of prognostic factors influencing recurrence. Cancer 2000; 88: 1365–1369.
101. Kuijpers DI, Thissen MR, Neumann MH. Basal cell carcinoma: treatment options and prognosis, a scientific approach to a common malignancy. Am J Clin Dermatol 2002; 3: 247–259.
102. Bath-Hextall F, Leonardi-Bee J, Somchand N, Webster A, Delitt J, Perkins W. Interventions for preventing non-melanoma skin cancers in high-risk groups. Cochrane Database Syst Rev 2007: CD005414.
103. Nordin P, Larkö O, Stenquist B. Five-year results of curettage-cryosurgery of selected large primary basal cell carcinomas on the nose: an alternative treatment in a geographical area underserved by Mohs' surgery. Br J Dermatol 1997; 136: 180–183.
104. Nordin P, Stenquist B. Five-year results of curettage-cryosurgery for 100 consecutive auricular non-melanoma skin cancers. J Laryngol Otol 2002; 116: 893–898.
105. Lindgren G, Larkö O. Long-term follow-up of cryosurgery of basal cell carcinoma of the eyelid. J Am Acad Dermatol 1997; 36: 742–746.
106. Kokoszka A, Scheinfeld N. Evidence-based review of the use of cryosurgery in treatment of basal cell carcinoma. Dermatol Surg 2003; 29: 566–571.
107. Kuflik EG. Cryosurgery for skin cancer: 30-year experience and cure rates. Dermatol Surg 2004; 30: 297–300.
108. Kuflik EG, Gage AA. The five-year cure rate achieved by cryosurgery for skin cancer. J Am Acad Dermatol 1991; 24: 1002–1004.
109. Sheridan AT, Dawber RP. Curettage, electrosurgery and skin cancer. Australas J Dermatol 2000; 41: 19–30.
110. Rhodes LE, de Rie MA, Leifsdottir R, Yu RC, Bachmann I, Goulden V et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch Dermatol 2007; 143: 1131–1136.
111. Zacarian SA. Cryosurgery of cutaneous carcinomas. An 18-year study of 3,022 patients with 4,228 carcinomas. J Am Acad Dermatol 1983; 9: 947–956.
112. 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: 722–733.
113. Gollnick H, Barona CG, Frank RG, Ruzicka T, Megahed M, Tebbs V, et al. Recurrence rate of superficial basal cell carcinoma following successful treatment with imiquimod 5% cream: interim 2-year results from an ongoing 5-year follow-up study in Europe. Eur J Dermatol 2005; 15: 374–381.
114. Schulze HJ, Cribier B, Requena L, Reifenberger J, Ferrandiz C, Garcia Diez A, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. Br J Dermatol 2005; 152: 939–947.
115. Gross K, Kircik L, Kricorian G. 5% 5-Fluorouracil cream for the treatment of small superficial basal cell carcinoma: efficacy, tolerability, cosmetic outcome, and patient satisfaction. Dermatol Surg 2007; 33: 433–439; discussion 440.
116. Rowe DE, Carroll RJ, Day CL, Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. J Dermatol Surg Oncol 1989; 15: 315–328.
117. Rowe DE, Carroll RJ, Day CL, Jr. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. J Dermatol Surg Oncol 1989; 15: 424–431.
118. Wennberg AM, Larkö O, Stenquist B. Five-year results of Mohs'

micrographic surgery for aggressive facial basal cell carcinoma in Sweden. Acta Derm Venereol 1999; 79: 370–372.
119. Breuninger H, Dietz K. Prediction of subclinical tumor infiltration in basal cell carcinoma. J Dermatol Surg Oncol 1991; 17: 574–578.
120. Burg G, Hirsch RD, Konz B, Braun-Falco O. Histographic surgery: accuracy of visual assessment of the margins of basal-cell epithelioma. J Dermatol Surg 1975; 1: 21–24.
121. 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: 549–553.
122. Griffiths RW. Audit of histologically incompletely excised basal cell carcinomas: recommendations for management by re-excision. Br J Plast Surg 1999; 52: 24–28.
123. Nagore E, Grau C, Molinero J, Fortea JM. Positive margins in basal cell carcinoma: relationship to clinical features and recurrence risk. A retrospective study of 248 patients. J Eur Acad Dermatol Venereol 2003; 17: 167–170.
124. Su SY, Giorlando F, Ek EW, Dieu T. Incomplete excision of basal cell carcinoma: a prospective trial. Plast Reconstr Surg 2007; 120: 1240–1248.
125. Cook J, Goldman G. Random pattern cutaneous flaps. In: Surgery of the skin – Procedural Dermatology 2005: 311–344.

Comments to guidelines - edited by Tomas Norman Dam

Specific comments to this guidline were given by Robert Gniadecki, Petter Gjersvik and Per Helsing and "acceptance without comments were recieved from the other Forum for NDV Editors have been compiled into a summary edited by CME editor Tomas Norman Dam. Further comments to the guidelines from Forum readers can be mailed to cme@medicaljournals and will be presented open for discussion in the next issue of the CME section.

In general

It has been commented by all the editors that it is very valuable that different guidelines referring to the same disease are published showing the whole palette of treatments and recommendations available in Nordic countries. The Swedish guidelines can now be compared to the Danish guidelines published recently. It appears from the comments that there are discrepancies in the definition of both BCC, SCC and the definition of actinic keratosis (AK) as a premalignant lesion also accommodated for some of the comments received.

Danish guidelines define the clinically more aggressive forms of both BCC and SCC, dividing the tumors into low-malignant and highly-malignant ones. In particular, tumor thickness has been shown to be the most important predictive factor in SCC and the pathologists is asked to measure it for SCC to better assess patient's risk. It appears that the Swedish guideline does not include a clear definition of the risk of invasion from SCC and this could be a problem during follow-up.

Epidemiological data from Norway has suggested possible differences in the histopathological criterias for SCC. They suspect that some lesions that might be diagnosed as keratoacanthomas are included in the Swedish numbers for SCC, and that the incidence of SCC would have been lower if keratoacanthomas had been excluded. In their opinion, the authors also overestimate the risk of AKs developing into a SCC by simply stating that the "risk of a single AK to progress to SCC might be 10% in ten years" – with only one reference (from 1991). There are a number of studies indicating a much lower risk; some authors have suggested the risk to be as low as 0.1%.

The definition of AK as a pre-malignant lesion has been discussed by Dr. R. Gniadecki: "Histopathologically and biologically, both actinic keratoses and Bowen's disease represent a SCC in situ. This is often a matter of a personal judgement of the histopathologist whether to classify a lesion as early SCC or AK. In contrast to Swedish guidelines the treatment of AK is not compulsory in Denmark due to a very low of progression towards clinically infiltrative stage". It has therefore been argued that the wait-and-see approach is fully justifiable unless the patients requires the treatment due to cosmetic or other reasons.

Comments regarding treatment

The center responsible for these guidelines is oriented towards surgery and has a unique position in Nordic countries having access to Mohs surgery whereas in Danish tradition, there has been more focus on non-surgical treatments. Treatment options for low-malignant tumours are more liberal and although differences in recurrence rate exist, the clinical documented difference between the options, such as curettage, PDT, radiation and surgery is low and all options are allowed as a first-line. Radiotherapy has received special interest as the preferred mode of treatment for facial, low-risk tumours in elderly population.

Comments regarding follow-up

For the treatment of multiple AKs the authors recommend photodynamic therapy (PDT), imiquimod or 5-fluorouracil. This last option, 5-fluorouracil, is seldom used in Norway (not recommend) due to their experience with risk of complications and low compliance.

It was commented that in the department in Oslo they consult both an ear-nose-throat specialist and an oncologists when a patient has regional metastasis from a SCC.