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

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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 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 micrographic 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).
Superficial 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 15–50% (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/noduloculcerative BCCs (Glas I A). 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 I B). 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, Bertill Persson, Mikael Tarstedt, Susanne Uddström and Ann-Marie Wennberg. We also acknowledge all previous contributors to this living document.

References


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Comments to guidelines - edited by Tomas Norman Dam

Specific comments to this guideline 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 criteria 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.