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GUIDELINES

Guidelines for the diagnosis and treatment of cutaneous squamous cell carcinoma and precursor lesions

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Carcinomas are malignant tumours of epithelial origin. Cutaneous carcinomas are primarily of keratinocytic origin (epidermal or follicular keratinocytes) or of adnexal glandular origin. Keratinocytic carcinomas include basal cell carcinomas (BCC) and *cutaneous squamous cell carcinomas (SCC)*. BCC and SCC are by far the most common forms of cancer in humans. Paradoxically, as they are not generally recorded in cancer registers, their importance in terms of public health and their economic impact on healthcare systems are widely underestimated.

These professional recommendations have received the joint INCA-HAS guarantee of quality, which signifies that the guidelines have been created according to the procedures and methodological rules recommended by the INCA and the HAS. Any queries regarding the content should be addressed to the sponsor.

These guidelines have been drawn up at the request of the French Dermatology Society (SFD).

*These guidelines were first published in *Annales de Dermatologie et de Venereologie*[1].

The relative incidences of BCC and SCC differ according to whether SCC is grouped among lesions with the same oncogenesis or not, namely *actinic keratosis (AK)* and *Bowen's disease (BD)* (see below). If AK is included in this group, SCC is the most common form of human cancer. If it is excluded, while being responsible for the majority of deaths attributable to non-melanoma skin cancers (NMSC), SCC is the second most important form of cancer in terms of frequency. Although the majority of SCC cases are not life-threatening, this carcinoma is likely to metastasize, particularly if initial treatment was inadequate.

The SFD has drawn up guidelines for the treatment of BCC (2004) and melanoma (2005). The present work is the logical continuation of this initiative. It aims to provide practitioners treating skin cancer patients with a series of recommendations based on scientific evidence or, when this was not available, on expert consensus.

Medical textbooks refer to a wide array of clinical and histological forms of SCC. The prognosis for these different forms varies

according to whether therapy has been specifically codified or not. In addition, the terminology used to describe these lesions varies, which may lead to confusion and prevent use of a clear decision-making tree.

The TNM classification, developed by AJCC/IUAC/UICC, which is used for all skin cancers except melanoma, is not suitable for SCC. It does not take into account the multiple prognostic criteria identified in the literature.

Many treatments are currently available, in particular, for SCC precursor lesions, but the criteria of choice and the methods of application are generally far from clear for practitioners. This results in major disparities in terms of therapeutic management.

The present guidelines deal with the treatment of SCC and precursor lesions in immunocompetent adults in France, in both ambulatory and hospital settings. The aims are as follows:

- to clarify the terminology used to describe the different forms of SCC and of their precursors AK and BD;
- to propose a prognostic classification of SCC that takes into account various clinical and histological factors;
- to recommend diagnostic and therapeutic measures for SCC based on previously identified prognostic factors;
- to optimize diagnostic and therapeutic management of AK and BD in accordance with recent data in the literature;
- to provide an overview of the principles for primary prevention of SCC and precursor lesions (based on the same methods), and for screening of subjects identified as at risk for SCC (other than genodermatosis and immunosuppression).

Due consideration has been given to the fact that patients with SCC, AK or BD are generally (very) elderly. This creates problems in terms of screening for lesions, and for amenability to care and treatment (poor compliance to certain treatments, difficulty in carrying out sequential physical treatments, refusal of onerous surgery, or surgery requiring multiple operations). The oncogeriatric dimension of therapy has thus been taken into account. These guidelines do not address the following issues:

- SCC of the nails or the genital and anal mucosa;
- SCC in immunosuppressed patients, particularly transplanted patients;
- SCC in the context of certain genodermatoses.

The levels of evidence and grades used are those defined by the HAS [*French Health Authority*] (Annex 1). The literature on SCC generally carries low levels of evidence and, except where otherwise stated, the recommendations included in these guidelines are of grade C.

I. Method

I.1. General remarks

These guidelines have been created in the form of Recommendations for Clinical Practice in accordance with the ADAPTE method.[2] As its name suggests, this method advocates the adaptation to a particular situation – in this case, medical practice in France in 2008 – of one or more guidelines on the same theme, drawn up previously or in other countries.

Medical societies concerned with SCC were consulted on the initiative of the French Dermatology Society (SFD), the sponsor, to define the scope of the guidelines, identify work performed on the subject and recommend professional members for the organizing committee (OC), the working group (WG) and the reading group (RG). Mention must be made of the difficulty of recruiting general practitioners to these groups, despite the fact that, in view of the subject, their assistance is vital.

In the Spring of 2007, the Dermatology Recommendations Association (aRED), a subgroup of the SFD, created a multidisciplinary OC on behalf of the SFD, comprising doctors in private and public practice, both university and non-university practitioners, from a variety of geographic origins. The OC then set up a WG using the same criteria of professional diversity. Members of the OC and WG were asked to complete a form indicating any conflict of interest regarding management of SCC (Annex 2). The members of the RG were recommended by medical societies, once again with the aim of reflecting the diversity of professional practice.

The overall arguments, key points and recommendations were drafted by the WG following the identification and selection of previous guidelines on SCC, contextualization (occasionally critical) of recommendations contained therein and a synthetic update of the literature.

Practitioners in the reading group were sent a letter asking for their opinion on the topic, including presentation of the key points and recommendations, in particular, regarding clarity and applicability. The comments made by the RG were analysed by the WG and, whenever possible, taken into consideration in the final draft. Lastly, on the 11 December 2008, the main recommendations were presented and discussed publicly in the presence of practitioners to whom the guidelines were addressed during the *Journées Dermatologiques de Paris*, the main French national dermatology congress.

The low level of evidence in the existing literature underscores the continuing lack of knowledge about optimal management of patients with SCC. These areas represent subjects for future work by the OC and WG (see *Perspectives* section).

I.2. Details of the drafting process for the guidelines

I.2.1. ADAPTE method This rigorous and explicit method, recently described and published by an international group,[2,3] is designed to enable the adaptation of existing guidelines, and to reduce the time, effort and cost required to create a fresh set of guidelines. Methodological guidelines concerning the use of this method were published online by HAS in March 2007.[3]

I.2.2. Choice of method for drafting guidelines In the spring of 2007, the SFD *Bureau* and the aRED decided that the ADAPTE method could be used to draft French guidelines for the management of SCC. Foreign guidelines on this topic, some of them fairly

old, were already known, and ADAPTE contextualization was entirely possible, as these guidelines had been published by agencies or medical societies for populations and levels of health infrastructure and organization comparable with those in France. However, as the literature used for the drafting of these guidelines was deemed to be of mediocre quality, the ADAPTE method presented a number of limitations. In addition to this, several questions that have subsequently come to the fore (e.g. the nature of AK or the place of new medical treatments) occupied little or no place in the existing guidelines. Therefore, in addition to adaptation, updating of the literature proved necessary.

I.2.3. Definition of the scope of the guidelines The limits of the SCC topic were discussed in conference calls between members of the OC in July 2007. The PIPOH checklist[3] used to define the scope and target audience of the guidelines was as follows:

- P (patient population) = French population of both sexes;
- I (interventions) = prevention, screening, diagnosis, treatment and monitoring;
- P (professionals) = specialists responsible for diagnostic and therapeutic management of SCC, general practitioners (GPs), occupational therapists as well as specialists involved in the screening and follow-up;
- O (outcomes, the evaluation criteria used for the recommendations) = levels of treatment response in terms of remission, local relapse, remote metastasis and mortality, when these parameters were available;
- H (healthcare setting) = ambulatory or hospital.

In addition to diagnosis and curative treatment of SCC, it was decided to include:

- screening of subjects identified as at risk for SCC (excluding genodermatosis and immunodepression);
- cutaneous or cutaneous-mucosal sites on the borderline of dermatology: eyelids and vermilion border of the lips;
- lesions considered precancerous and keratoacanthoma. These lesions are histogenetically related to SCC and have been dealt with in several recent studies of medical and surgical therapies.

However, genital and anal sites in both genders were ruled out as these are normally dealt with by gynaecological surgeons, urologists, gastroenterologists or digestive surgeons. Ungual sites were similarly ruled out. In addition, it was decided not to include SCC observed in immunosuppressed organ transplant recipients, as guidelines for the management of these patients were being drawn up under the auspices of the HAS.[4]

I.2.4. Documentary research In late June to early July 2007, Mrs J. Brugneaux performed a literature search for practical guidelines on SCC and precursor lesions using systematic surveys of medical bibliography databanks (Annex 3) and looking out for guidelines, consensus conferences, articles on decision-making process, systematic reviews, meta-analyses and other national and international evaluation studies. Relevant websites (government agencies, medical societies, etc.) were also explored. Documents not accessible by the standard diffusion circuits ('grey literature') were consulted using every available means. Legal and regulatory texts on this subject were also consulted. Only English- and French-language articles were considered eligible. Initially, the selected references were screened by L. Martin and J.-J. Bonerandi to eliminate all texts unrelated to the subject on the basis of their titles, (e.g. non-cutaneous CE of the head and neck; genital CE) and irrelevant literature (guidelines currently at project level, etc.). The remaining texts (n = 58) were submitted to all CO members in July 2007 to ensure that they were authentic guidelines, didactic articles or authors' opinions.

I.2.5. Determination of questions to be covered in the guidelines At a plenary session of the OC held on 19 September 2007, the scope of the guidelines was definitively agreed upon, as were the various topics to be covered therein:

- clinical, pathological and epidemiological forms of SCC and precursor lesions;
- prognostic factors for SCC;
- treatment methods for SCC and precursor lesions;
- patient management.

At 19 September 2007 meeting, a list with the following documents, theoretically amenable to adaptation, was established:

1 Non-melanoma skin cancer: guidelines for treatment and management in Australia.
National Health and Medical Research Council. 2002 (NHMRC, Australia).
2 Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma.
British Association of Dermatologists/British Association of Plastic Surgeons. 2002 (BAD/BAPS, UK)
3 Guidelines for management of Bowen's disease: 2006 update.
British Association of Dermatologists. 2006 (BAD, UK).
4 Guidelines for the management of actinic keratosis.
British Association of Dermatologists. 2007 (BAD, UK).
5 Basal cell and squamous cell skin cancers.
National Comprehensive Cancer Network. 2007 (NCCN, US).
6 Multiprofessional guidelines for the management of the patient with primary squamous cell carcinoma.
N**ational Guideline Clearinghouse. 2007** (NGC, US).
7 Green A, Marks R. Squamous cell carcinoma of the skin (non-metastatic). ***Clin Evid*** 2005; 4: 2086–2090.

I.2.6. Selection of guidelines for adaptation The suitability of these seven guidelines for adaptation in different areas of practice was assessed by five WG, using the simplified AGREE appraisal instrument[5] (Annex 4).

The NGC guidelines and the *Clinical Evidence* article were not used, as the former is a retranscription of the BAD 2002

guidelines, whereas the latter gives no indication of the method used for the bibliography search, and was thus deemed inconsistent with the scope of the present guidelines.

The following three SCC guidelines were ultimately selected:

- Basal cell and squamous cell skin cancers, 2007 (NCCN);
- Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma, 2002 (BAD 2002);
- Non-melanoma skin cancer: guidelines for treatment and management in Australia, 2002 (NHMRC), together with Guidelines for the management of actinic keratoses, 2007 (BAD 2007) and Guidelines for management of Bowen's disease: 2006 (BAD 2006).

I.2.7. Layout of the guidelines, key points and recommendations Each section was divided into 'items', some of which contained one or more 'key points' or 'recommendations'. An item was comprised of a topic concerning epidemiology, diagnosis or treatment amenable to targeted documentary research (e.g. prevalence of SCC among the French population; use of imiquimod in the treatment of AK). Each item was assigned to a group comprising two or three WG members, based on their experience or interest in the topic. Individual items were either identified as existing in one or more adapted guidelines, or were created anew by the WG. Items are summarized at the end of this section in a summary table showing the adapted guideline(s), where they are also discussed (Table 1).

Key points comprise information items of cultural relevance which are possibly not directly related to day-to-day practice. Recommendations refer to the diagnostic or therapeutic management of patients. Key points and, wherever possible, recommendations were graded using the HAS method (Annex 1).

In accordance with the ADAPTE method,[6] items identified in previous guidelines were evaluated by WG members to determine the degree of concordance between the data analysed and the conclusions set out in the arguments, and between these conclusions and the recommendations proposed. Any divergence with regard to prior guidelines is indicated at the start of the paragraph. In most cases, updating of bibliographical references proved necessary, and this was carried out by Mrs J. Brugneaux (January 2008) (Annex 3).

Finally, actual adaptation (drafting of the arguments, key points and recommendations) involved summarizing the proposals set out in the various guidelines and drafting the arguments suitable for medical practice in France in 2008.

An initial version of the arguments and the proposed recommendations was reread and discussed in plenary sessions by the WG on 11 March 2008 and by the OC on 25 March 2008.

Updating of the bibliography was suspended at this point. Opinions differed within the WG regarding a number of relevant items (prognostic classification of primary SCC, value of routine histological analysis of excision margins and hierarchical classification of therapeutic choices for precancerous lesions). In the absence of consensus within the adapted guidelines and of literature providing an adequate level of evidence, these divergent opinions gave rise to numerous e-mail exchanges and meetings until a pragmatic consensus was reached within the WG and the CO. The successive versions of the arguments attest to changes in viewpoints regarding these items. The WG stressed the need for clinical trials designed to obtain factual information which would settle these divergences.

A complete argumentation framework and an initial version of the short text comprising the key points and recommendations were sent to readers during summer 2008. Final versions of the documents and of a highly synthetic pocket-sized flyer were prepared in autumn 2008.

The CO and the WG are well aware that their editorial choices simply reflect medical and scientific knowledge concerning SCC and precursor lesions up to spring 2008. Follow-up on bibliography data and annual meetings of the WG are scheduled to ensure prompt modification of the guidelines following the publication of relevant diagnostic, prognostic or therapeutic information regarding SCC and precursor lesions (see *Perspectives*).

I.2.8. Abbreviations 5-FU: 5-fluorouracil; AK: actinic keratosis; BAD: British Association of Dermatologists; SCC: squamous cell carcinoma; BCC: basal cell carcinoma; BD: Bowen's disease; CT: computed tomodensitometry; CMM: Mohs micrographic surgery; DPT: dynamic phototherapy; HAS: *French Health Authority* (*Haute Autorité de Santé*); HPV: human papillomavirus; IDC: interdisciplinary consultation; IFN-γ: interferon gamma; INCA: *French National Cancer Institute*; KIN: keratinocytic intraepithelial neoplasia; LE: level of evidence; MRI: magnetic resonance imaging; NCCN: *National Comprehensive Cancer Network* NHMRC: *National Health and Medical Research Council*; OC: Organisation Committee; OGE: Overall geriatric evaluation scale; ORL: otorhinolaryngology; PDT: Photodynamic therapy; PET: positron emission tomography; PNI: perineural invasion; RT: radiotherapy; SFD: *French Dermatology Society (Société Française de Dermatologie)*; TNF-α: tumour necrosis factor alpha; TNM: tumour, node, metastasis staging system; UVA/UVB: ultraviolet A, ultraviolet B; WG: Working Group; AFSSE French Environmental Health Safety Agency

II. Clinico-anatomical forms and epidemiology of SCC and precursor lesions

The term squamous cell carcinoma encompasses all malignant epithelial tumours with predominantly malpighian differentiation. SCCs include primary malignant skin tumours with malpighian differentiation, and are distinct from other primary epithelial skin tumours such as BCC. The term thus covers a number of different clinico-anatomical entities, some of which only differ in terms of clinical presentation or degree of aggressiveness.

The inclusion of AK and keratoacanthoma under SCC by some authors and in certain reference works is currently disputed.[6] The

Table 1 Synopsis: items included in adapted guidelines

Bibliographical references	BAD 2002	NHMRC 2002	NCCN 2007	BAD 2006 BD	BAD 2007 AK
	1947–2001	1951–2001	1964–2006	1961–2005	1968–2006
Clinical features of AK		X		X	
Histology of AK		X		X	
Nosology of AK					
Epidemiology of AK		X		X	
Clinical features of BD		X			X
Histology of BD		X			X
Nosology of BD					X
Epidemiology of BD					X
Prevention of AK and BD		X		X	X
Surgery for AK and BD				X	X
Cryotherapy		X	X	X	X
Curettage		X	X	X	X
Laser CO2		X		X	X
5-FU		X	X	X	X
Imiquimod		X	X	X	X
Diclofenac				X	
Photodynamic therapy (PDT)		X	X	X	X
Retinoids	X	X	X		
Radiotherapy for AK, BD	X	X			
Epidemiology of SCC	X	X			
Clinical features of SCC	X	X			
Variants of SCC			X		
Clinical prognosis of SCC	X	X	X		
Histological prognosis of SCC	X	X	X		
Prognostic classification			X		
Metastases of SCC		X	X		
Prevention of SCC	X	X	X		
Surgery for SCC	X	X	X		
Micrographic surgery for SCC	X	X	X		
Curettage for SCC	X	X			
Surgery for SCC metastases	X	X	X		
Radiotherapy for SCC	X	X	X		
Chemotherapy for SCC		X			
Screening for AK, BD, and SCC	X		X	X	
Histopathology of SCC	X	X			
Standardized histology report		X			
Histopathology of lymph nodes					
Initial staging of SCC			X		
Investigation methods					
Monitoring of SCC	X	X			
Treatment of SCC according to prognosis					
Treatment of lymph node metastasis			X		
Treatment of remote metastasis			X		
Keratoacanthoma		X			
Histology of keratoacanthoma		X			
Nosology of keratoacanthoma		X			
Epidemiology of keratoacanthoma					
Surgery for keratoacanthoma		X			
Medical treatment for keratoacanthoma		X			

adapted guidelines, i.e. the three guidelines dedicated to SCC (NHMRC,[7] NCCN[8] and BAD[9]) and those specifically focused on AK and BD,[10,11] restrict themselves to a summary description of these entities without discussing clinico-anatomical forms and nomenclature. The WG felt it was necessary to adopt a position on this subject and therefore, the ADAPTE method was not used in drafting this chapter, for which a specific bibliographical analysis was performed. This chapter contains epidemiological overviews and proposals with regard to terminology and classification. It also describes the populations targeted by these guidelines.

II.1. Risk factors for SCC and precursor lesions

II.1.1. Environmental factors Exposure to sun Sunlight is the principal environmental factor, and evidence for its role in SCC relies on the appearance of lesions on the areas of skin most exposed to sun, a greater prevalence of lesions among fair-skinned subjects, a latitude gradient for populations with the same skin phototype and a higher incidence of the disease among patients working outdoors.[12] The occurrence of SCC is associated with total cumulative lifetime UV dose. The most commonly affected sites include the face, back of the hands and forearms. In a Spanish study, more than 92% of SCC cases occurred in these areas.[13] UVB (290–320 nm) and UVA (320–400 nm) play a role in carcinogenesis. For most SCC, UV-induced mutations are observed in the *P53* gene.[14]

Artificial sources of UV have also been incriminated.[15] PUVA therapy in excess of 200 sessions is associated with the onset of SCC. Sources of this type of radiation in tanning salons are not harmless and must be added to other risk factors.[16] According to the 2005 report by the French Environmental Health Safety Agency (AFSSE), 'Evaluation of risks associated with exposure to UV radiation', the risk of skin cancer (carcinoma or melanoma) is increased by a factor 1.10 with 30 sessions per year over a 10-year period and by 1.39 with 100 sessions.

Other exogenous risk factors include arsenic, pesticides, hydrocarbons, tobacco (lower lip), ionizing radiation, prolonged local chemotherapy, etc.[17]

II.1.2. Constitutional factors The main constitutional factor is the skin phototype, which is genetically determined: The risk is higher in patients with a poor capacity for tanning.[18]

In *xeroderma pigmentosum*, a hereditary recessive disorder, a deficiency in enzymes that repair photoinduced damage to DNA is associated with a high risk of SCC, AK and keratoacanthoma.

II.1.3. Other risk factors The following factors are involved in less than 1% of SCC: iatrogenic immunosuppression, chronic inflammation, chronic leg ulcers and scarring.[19]

Human papillomavirus (HPV) infections have been incriminated, particularly in the genital and anal areas, but HPV also occurs in extragenital regions in the case of BD, in areas that are both exposed and unexposed to sunlight and in immunodepressed and immunocompetent patients alike.[20–23] However, the presence of HPV alone is insufficient to induce cellular proliferation. Three risk factors are found in organ grafted patients: sun exposure, immunodepression and HPV.

Key points

- Squamous cell carcinoma subsumes a number of malignant primary epithelial skin tumours with malpighian differentiation, and is distinct from BCC.
- The key factor favouring onset of SCC, Bowen's disease (BD) or actinic keratosis (AK) is the total lifetime dose of UV received, whether natural or artificial.
- The risk of developing AK, BD or SCC is affected by skin phototype, which is genetically determined.
- A number of co-carcinogens, which may be specific to particular sites, have been identified, such as tobacco for actinic cheilitis and SCC of the lower lip, as well as HPV for genital or anal SCC.
- Certain medical diseases also predispose to SCC: chronic inflammation, chronic wounds and immunodepression.

II.2. Precursors of SCC

II.2.1. Actinic keratosis

II.2.1.1. Clinical, histological, epidemiological aspects and natural history

Clinical aspects

Actinic keratosis consists of common lesions, particularly among light-skinned subjects, found in areas exposed to the sun such as the face, the back of the hands and the scalp in balding subjects, and is often associated with other signs of helioderma (e.g. wrinkles, freckles, etc.). Diagnosis is usually based on the clinical setting, and is suggested by flat, rough lesions of varying thickness, occasionally more apparent to the eye than to the touch, with a diameter of around 1 cm or less, with varying degrees of erythema, occasionally pigmented and adhesive yellowish or brownish keratin coating.

In practice, isolated AK or small numbers of AK are distinguished from multiple AK, which occasionally come together to form plaques (scalp). On the lower lip, actinic cheilitis is the labial equivalent of AK. This particular disorder is characterized by the presence of tobacco smoking as a second carcinogenic factor and by the marked metastatic potential of SCC in this area.

Histological aspects

There is no single histological aspect of AK. There may be thinning or hyperplasia of the epidermis. The corneal layer is proportional to epidermal thickness, and is occasionally very thick (corn or callous). An inflammatory reaction develops on contact with the epidermis, and there is frequently a lichenoid appearance.

Diagnosis is based on the presence of various keratinocytic abnormalities: loss of polarity accompanied by changes in the epidermal architecture, atypical cytonuclear features, dyskeratotic cells, acantholysis or acanthokeratolysis. In AK, these abnormalities occur in isolation and do not involve the entire epidermis or the skin appendages. The term carcinoma *in situ* is only used when these abnormalities occur together in a pronounced fashion and affect the entire epidermal lining. Most reference works mention morphological variants of AK: pigmented, atrophic, hypertrophic, acantholytic and lichenoid. The WG considers that these variants are simply minor variations of the same entity and, as such, do not merit classification as distinct forms.

Prevalence, incidence and natural history

These figures are not known for France. The published prevalence for adults aged over 40 ranges between 11% and 25% in populations of the northern hemisphere, but between 40% and 60% in populations of the southern hemisphere.[19] In Great Britain, around 3–6% of men aged between 40 and 49, and 20% of patients over 60, have at least one AK.[20,21] If left untreated, AK may remain unchanged, regress spontaneously or progress to SCC. The probability of spontaneous regression of such lesions over a 1-year period has been estimated to be between 15% and 25% of cases.[22] A mathematical model devised in this particular study suggests that a patient presenting with 7.7 AK has a 10% risk of one of these AK developing into SCC within 10 years.[24] According to several studies, from 5% to 20% of AK progress to SCC within 10–25 years.[10]

II.2.1.2. Nosological discussion

AK and epithelial dysplasias of the genital area: semantics

Epithelial dysplasias of the genital area form a separate group of AK due to their site and the role of HPV in their aetiopathogenesis.

A wealth of gynaecological literature has established the concept of *vulvar* (and subsequently *penile*) *intraepithelial neoplasia* (VIN and PIN) as well as *cervical intraepithelial neoplasia* (CIN). Atypical cases observed are semi-quantified under the term VIN (or PIN or CIN) I, II or III, according to whether they involve the lower third, two-thirds or more than two-thirds of the epithelial thickness. When the entire epithelium is involved, the term intraepithelial SCC or Bowen's disease is used.

Cockerell *et al.*[25,26] stress the analogy between AK and cervical dysplasia lesions and suggest that the nomenclature of epidermal lesions (AK and BD) should be handled in the same way as their counterparts in the genital mucosa or semi-mucosa, using the term KIN (i.e. *keratinocytic intraepidermal neoplasia*).

The WG felt that there was little value in seeking to unify histopathological criteria for entities with divergent aetiopathogenesis and clinical aspects. It therefore considered that there were no grounds for replacing the clinical name of AK, recognized by the entire medical community, with a histopathological name that is less clear to practitioners. Histopathologists may nevertheless continue to grade the level of epithelial dysplasias in their reports.

AK: precursor or squamous cell carcinoma?[7,8,10,25–28]

This distinction might appear to be purely academic, were it not for its significant impact in terms of treatment and health insurance (social security reimbursement, life insurance premiums, etc.).

Proponents of a unified term[29] consider that all forms of AK are in fact SCC, together with BD, Bowenoid papulosis, giant condyloma, verrucous carcinoma, keratoacanthoma and proliferating trichilemmal cysts. Among other shared features, these entities are characterized by the existence of mutations in oncogene *P53*.

However, a number of epidemiological studies have established that the course of AK may take three different forms: spontaneous disappearance, persistence, or progression to SCC. The progression rate for AK is low: In the Australian cohort study by Marks *et al.*, cited in the NHMRC, the progression rate over a 5-year follow-up period was lower than 1/1000 per year.[30]

The NCCN guidelines consider AK as photoinduced precancerous lesions. However, the NHMRC and BAD guidelines do not adopt a position concerning the nature of AK, simply noting that most SCC appear subsequent to AK, but that the risk of progression of AK to SCC is low, thus justifying the choice of non-invasive topical therapy for most AK cases.

Cancerization field

Initially described in relation to carcinomas of the oral cavity, a cancerization field denotes a region containing pretumoural abnormalities, and subclinical and multifocal genetic mutations constituting the site of new primary tumours and of local relapse.

Regarding the skin, it has been clearly established that UV radiation is associated with the initiation, promotion and proliferation stages of carcinogenesis. Oncogenetic abnormalities have been shown to be more common in sun-exposed areas than in non-exposed areas. Furthermore, genetic alterations have been detected at AK excision margins. These molecular findings confirm long-standing clinical notions, namely the frequent co-existence of SCC and small AK, occasionally invisible and only detectable through slight roughness evident on palpation, and the possible development of large numbers of occasionally confluent AK in certain areas (e.g. scalp).

In practice, these finding could motivate preventive treatment of the entire surface of the affected area rather than individual treatment of each lesion. However, no studies have, as yet, demonstrated the value of such an approach.[31–33]

II.2.2. Bowen's disease Bowen's disease is an intraepithelial SCC. The prevalence and incidence of this disease in France and elsewhere are unknown.[7] Patients most affected by the disease in published cases are in the 7th decade of life and are predominantly women (70% of cases).[7]

Clinically, the cutaneous lesion appears as a clearly delimited discoid, erythematous-squamous plaque, which is generally keratotic or with a crust. It is generally found in areas of covered skin. Such lesions progress slowly. In the mucosa and semi-mucosa, BD may be smooth or weeping, and erythroplastic (Queyrat's

erythroplasia of the penis) or leukoplastic. Genital forms are closely associated with HPV.

Histopathology

The epidermis is hyperplastic, with a disorganized architecture and atypical keratinocytes (loss of normal polarity, hyperchromatic nuclei, anisonucleosis, mitoses and dyskeratosis), present at all levels, although by definition, they do not cross the basal membrane. Variants of BD with clear, pagetoid or pigmented cells have been described, and immunohistochemistry may be required to determine whether they are malpighian.

In the perineal areas, differential diagnosis with Bowenoid papulosis (VIN 3, PIN 3) is based primarily on time of onset, clinical appearance, medical history, presence of histological signs of viral cytopathogenic effect and, in certain cases, identification of any associated HPV.

Risk of progression of BD to invasive SCC

This risk of progression has been calculated in a very approximate and necessarily biased fashion based on several retrospective studies. The risk appears to be between 3% and 5% for cutaneous BD, and around 10% for Queyrat's erythroplasia.[7] Progression occurs after varying times, and clinical presentation involves the appearance on the flat plaque of an often ulcerated tumour. The metastatic risk seems to be greater than that of the common SCC form.[34,35]

Key points

- AK is an epidermal dysplasia.
- Onset of AK is associated with chronic exposure to UV.
- The prevalence of AK is estimated at 11–25% in adults over 40 years in the northern hemisphere, and increases with age.
- AK is considered to be a precancerous lesion with a low risk of progression to malignancy and a high probability of spontaneous regression.
- The WG considers that AK meets the clinical definition of a precursor of SCC, with which it shares a number of physiopathological factors, but as there is no obligatory transition from one to the other, the distinction between AK and SCC should be maintained.
- BD is an intraepidermal *(in situ)* SCC most commonly seen in the lower limbs.
- The prevalence of BD is unknown.
- The rate of progression of BD to invasive SCC has not been accurately determined.
- AK and BD may be likened to low-grade and high-grade intraepithelial neoplasias (or SCCs *in situ*), respectively, found at other sites. However, their clinical and aetiological features are sufficiently distinct from these lesions for them to be considered as separate.
- To date, no studies have demonstrated the value of treatment based on the notion of cancerization fields.

II.3. Invasive cutaneous squamous cell carcinomas

The adjectives 'infiltrating' and 'invasive' used with SCC are synonymous and refer to any SCC crossing the basal layer of the epithelium and invading the dermis, regardless of the depth of invasion.

II.3.1. Definition, epidemiology and natural history The vast majority of SCC cases are found in sun-exposed areas, starting from an AK, with which they share numerous risk factors. The prevalence of SCC increases as latitude decreases. The risk of developing SCC is also influenced by skin phototype, which is genetically determined.

A number of co-carcinogens, which may be fairly site-specific, have been identified, e.g. tobacco and SCC of the lower lip; genital or anal HPV and SCC. More rarely, SCC occurs in BD, chronic ulceration, scars, chronic cutaneous inflammation (e.g. hidradenitis suppuritiva radiodermatitis) or *de novo*.

Squamous cell carcinoma is also more common in immunodepressed patients (e.g. transplant patients, AIDS patients, etc.) and in the course of certain genodermatoses. These particular situations are outside the scope of the present guidelines.

The prevalence and incidence of SCC in France are not precisely known, as SCC is not routinely declared as a specific entity in cancer records. Two French departmental cancer registers have kept records on SCC, one since 1983 (Doubs region), and the other since 1991 (Haut-Rhin region).

The data in the Doubs register[36] revealed a far higher incidence in men (sex ratio around 2). The mean age at diagnosis (74.4 years in men and 77 years in women) was almost 10 years higher than for BCC. Between 1983 and 2002, the incidence rose from 18.48 to 31.47 in men and from 6.26 to 16.87 in women, making SCC one of the most rapidly increasing cancer forms in this French department. The Haut-Rhin data[37] confirmed the predominance of the disease in men, as well as the trend towards an increasing incidence as noted in the Doubs department. A standardized increase in incidence for the world population was observed, rising from 15.8 to 22.3 in men, and from 7.5 to 8.4 in women, between 1988 and 1999. According to a prospective study in the Champagne-Ardenne region of France,[38] the raw annual incidence of SCC was 30/100 000 in the general population, which was at least four times lower than that of BCC. The prevalence and incidence of SCC are increasing as a result of ageing of the population and increased sun exposure in the second half of the 20th century. The use of UV radiation in solariums is a cause for future concern.

Squamous cell carcinoma may cause considerable morbidity and quality-of-life impairment, particularly when lesions occur on the face.

Key points

- The importance of SCC in terms of public health is doubtlessly underestimated.
- In view of the ageing of the French population, the WG recommends the adoption of epidemiological tools enabling a more accurate determination of the frequency and cost of SCC.

Squamous cell carcinomas progress gradually along fascias, periostea, perichondria and neural sheaths.

They may give rise to local, regional or distant metastases, which may eventually result in death. Overall, 80% of metastases spread via the lymphatic system. As the cervical-cephalic region is the principal site of SCC, the lymph nodes most frequently involved are the lateral-cervical (jugular-carotid), submandibular, submental and intraparotid nodes. The risk of metastases (roughly assessed in the literature using the ratio of number of metastases/number of cases described) is 2.3% at 5 years, and 5.2% after a follow-up of more than 5 years for SCC in sun-exposed skin.

The occurrence of relapse or metastasis, and the mortality associated with SCC are, in most cases, due to late or inappropriate treatment of the tumour or to aggressive histopathological forms (*level of evidence 4*).

II.3.2. Clinico-anatomical forms of SCC The term SCC covers a wide variety of subtypes which differ in terms of morphology and mode of progression. The classifications in the literature correspond to authors' descriptions. There is a general consensus regarding the most frequently used terms, but terminology diverges with regard to rarer forms, the morphology of which is not always clearly defined.

Of the three guidelines, BAD 2002, NHMRC and NCCN,[7–9] only the NCCN guidelines deal with the various clinico-anatomical forms of SCC.

These latter guidelines recommend the following classification:

1 Metatypical or mixed carcinoma (*basosquamous carcinoma*) should be considered as SCC rather than a variant of BCC on account of its metastatic risk.
2 Acantholytic, mucoepidermoid[39,40] and desmoplastic[41] forms should be considered as separate entities as these well-differentiated tumours have an aggressive character that may be underestimated if the histological criteria of cellular differentiation alone are used.

In the absence of any specific literature permitting classification of the various clinico-anatomical forms to be based on actual evidence, the WG has opted to describe these forms on the basis of chapters dedicated to SCC in reference works[6,42–44] and in four reviews on the clinico-anatomical and histoprognostic grading of SCC.[45–49] Of these, Cassarino *et al.*[46,47] conducted a large review of the literature and proposed histoprognostic grading of SCC based on the percentage of metastasis cases in relation to the number of published cases.

Table 2 provides an overview of the SCC variants identified by the WG in the literature.

For five of these variants (pigmented SCC, clear cell SCC, signet-ring cell SCC, SCC of trichilemmal differentiation and lymphoepithelioma-like SCC), the WG decided to report their existence, but declined to consider them as separate forms of SCC owing to the scarcity of reported cases and to uncertainty concerning their prognosis and histogenesis.

Regarding a sixth form (SCC as a complication of Bowen's disease), the WG considered the arguments given in the literature as insufficient to warrant its distinction from standard SCC.

The other variants are classified under seven distinct forms in three separate sections based on rough estimates of their aggressiveness.

II.3.2.1. Common form of SCC

This form, known as common SCC, comprises the majority of SCC cases. It is mainly seen in abnormal skin showing signs of helioderma, stemming from AK. It may also appear in BD, chronic ulceration, scars, radiology-induced lesions or may even occur *de novo*.

Three other components are also observed to varying degrees: budding, ulceration and infiltration.

The most common form, the ulcerovegetative form, presents as a raised, infiltrating tumour with an irregular surface and the morphology of an ulcer with a budding and bleeding centre. Infiltration extends beyond the visible borders of the lesion.

This form carries a low metastatic risk: Cassarino *et al.*[47] estimated the risk of metastases for invasive carcinomas stemming from AK at around 0.5% (*level of evidence 4*).

Histologically, these lesions generally involve the epidermis and form irregular buds comprising atypical keratinocytes that infiltrate the dermis. Squamous differentiation is responsible for cell morphology (large, polygonal, with abundant eosinophilic cytoplasm), the presence of intercellular 'bridges' and corneal maturation: formation of corneal globes at the centre of the tumour globules or dyskeratosis. The degree of tumour differentiation is a key factor for prognosis (see above).

II.3.2.2. Variants of SCC with low metastatic risk

***Verrucous carcinomas*[54,55,73–75]**

The adapted guidelines are in agreement on the grouping together of a number of similar entities under this classification, distinguished by site: *carcinoma cuniculatum* (legs and feet), oral papillomatosis (oral mucosa and pharyngeal mucosa) and Buschke–Lowenstein tumour (genital or perianal region). These tumours of low-grade malignancy share their common association with HPV infection, slow progression, vegetative, exophytic clinical presentation and slow infiltrating spread.

Table 2 Clinico-anatomical forms of squamous cell carcinoma: literature analysis

	No. published series*	Largest no. cases	Weedon	McKee	Elder	WHO	Cassarino	Maguire	Kane
Metatypical	2 [49,50]	35 [49]	+§	+§	+§	+§	–	–	–
Verrucous	4 [39,51–54]	46 [54]	+	+	+	+	+	+	+
Acantholytic/adenoid/ pseudovascular	4 [38,55–57]	155 [56]	+	+	+	+	+	+	+
Fusiform/pleomorphous/ sarcomatoid cells	3 [58–60]	38 [58]	+	+	+	+	+	+	+
Pigmented¶	1 [61]	5	+		–	–	+	–	+
Desmoplastic	1 [40]	44	+	+	–	–	+	–	+
Mucoepidermoid	1 [39]	10	+	+	+	+	+	–	–
Clear cell**	0	NE	+	+	–	–	+	+	–
Signet ring cells	0	NE	+	‡	–	–	+	–	–
Trichilemmal	3 [62–64]	13 [64]	+	‡	–	–	+	–	–
Inflammatory	0	NE	+	–	–	–	–	–	–
Lymphoepithelioma-like	4 [65–68]	40 [67]	+	†	–	–	+	–	–
Basaloid	1	20 [69]	+	–	–	–	–	–	–
Carcinosarcoma/metaplastic	1	4 [70]	+	+	–	–	–	–	–
Papillary	1	3 [71]	–	–	–	–	+	–	–
Invasive Bowen's disease			–	–	–	–	+	–	–

*Only studies with a minimum of three cases were considered as series.

†This form is mentioned, but is not considered by the author as a SCC variant.

‡McKee grouped together clear cell SCC, signet ring SCC and trichilemmal SCC as a single entity.

§In these references, metatypical carcinoma was associated with BCC.

¶Associated melanocytic-dendritic contingent.

**Heterogeneous form comprising tumours with trichilemmal differentiation and cases in which cellular clarification was caused by degenerative phenomena (hydropic appearance of cytoplasm or accumulation of lipid vacuoles).

NE, Not evaluable.

Histologically, these SCC appear as a well-differentiated proliferation of cells over a long period, combining acanthosis and papillomatosis, with no cytological or architectural anomalies. Their proliferation seems to push back rather than invade underlying tissue. At this point, the clinical presentation and site may prompt a diagnosis of SCC.

This stage is followed by marked deep infiltration, but with none of the normal criteria of malignancy. The latter are seen only later and in certain cases, thus accounting for occasionally extensive local invasion at the time of diagnosis. The risk of metastasis is low (*level of evidence 4*).

These cases are similar to SCC occurring in verruciform epidermal dysplasia, a hereditary disease associated with HPV infection. The risk of such lesions progressing to SCC is very high, but the lesions' aggressiveness does not appear to be greater than that of common SCC.[47]

Metatypical (or intermediate) carcinoma and mixed carcinoma

These ambiguous names are used for rare tumours, described for the most part in guidelines and reference books under the section on BCC. They may be described separately or in some cases together. One common feature is their association with epidermal and basaloid proliferation, both of which carry metastatic risk. In the WG's opinion, this justifies their association with SCC.[51] The term *metatypical* (or *intermediate*) refers to basaloid tumours, but the tumours do not present standard peripheral palisading and are composed of larger cells that are clearer than those seen in common BCC.[51]

Mixed carcinoma (basosquamous carcinoma), proposed in the NHMRC guidelines[7] as a variant of SCC, is defined as a form of BCC with squamous carcinomatous differentiation, comprising three cell types: basaloid, squamous and intermediate, with each component being clearly identifiable.

Fusiform (sarcomatoid) epidermoid carcinoma

This relatively rare form[59–61] is observed in sun-exposed areas in elderly patients. Diagnosis is straightforward when part of the tumour expresses keratinizing differentiation or dyskeratosis, or is contiguous with the epidermis.[59]

In the absence of the above histological signs, distinction from mesenchymatous tumours or melanoma is based on immunohistochemical analysis, which shows expression of cytokeratin (CK) and epithelial membrane antigen (EMA) by tumour cells. The most frequently expressed keratins are high molecular weight keratins such as CK5-6 and 34βE12. However, certain fusiform SCC may express both cytokeratin and vimentin.

The progression of fusiform SCC on sun-exposed skin tends to be non-aggressive. However, fusiform SCC occurring after irradiation carries a different prognosis. Given that this entity is

well-characterized in the literature in a number of significant patient series, and because of the importance of distinguishing aggressive SCCs, radio-induced SCC and relatively undifferentiated and non-differentiated SCC (together with the associated problems of histological differential diagnosis), the WG decided to maintain this variant as a distinct form of SCC.

II.3.2.3. Variants of SCC likely to have greater metastatic risk

While these forms merit differentiation in terms of morphology, it is difficult to assess their level of aggressiveness accurately, given the small number of studies available and the retrospective nature of published series (*level of evidence 4*).

Acantholytic epidermoid carcinoma

This form accounts for 2–4% of SCC, particularly of the head and neck, where it generally appears following acantholytic AK.[39,56–58]

As a result of focal or extensive acantholysis, tumoural lobules create pseudoglandular (adenoid) structures. These cavities may contain amorphous, basophile matter of secretory appearance, but do not contain any mucinous secretion identifiable using the usual staining methods (periodic acid-Schiff, alcian blue, mucicarmine, etc.). The lumens of these cavities contain atypical and occasionally multinucleate dyskeratotic cells.

In some cases, the formation of intratumoral cavities is such that the tumour may suggest angiosarcoma at the histological level. Diagnosis of this pseudovascular form may require immunohistochemical analysis.

The two main series published (level of evidence *4*) yielded contradictory results regarding prognosis.[57,58] In the oldest series comprising 155 patients, there were five cases of death associated with distant metastases or local invasion. In the most recent series involving 55 cases in 49 patients, metastases were observed in 19% of cases and followed by death, the latter outcome correlating with a tumour size in excess of 1.5 cm.

Adenosquamous carcinoma[40,76]

This lesion is characterized by the co-existence of SCC-type proliferation expressing keratin 7 and mucosecretory tubular structures with a content positive for mucicarmine and alcian blue. The tubular structures are bordered by atypical cuboidal cells expressing carcinoembryonic antigen.

Differential diagnosis must be made with a pseudoglandular acantholytic SCC and metastases, particularly mucoepidermoid carcinoma of the salivary glands.

In a review of 13 cases, tumour diameter was between 0.5 and 5 cm (mean: 2.2 cm) with marked aggressiveness and a high rate of relapse (6/13) and death (5) (*level of evidence 4*) after a follow-up ranging from 2 months to 6 years (mean: 32 months). Consequently, the WG decided to classify this entity as a separate variant of SCC.

Desmoplastic epidermoid carcinoma

This form is defined histologically by the following criteria: tumour cells comprising squamous differentiation and forming more or less branched chains within an abundant 'desmoplastic' fibrous stroma, which by definition occupies at least 30% of the entire tumour. The prospective study by Breuninger *et al.*[41] involving 594 SCC cases, with a follow-up ranging from 4 to 10 years (median: 5.3 years), comprised 44 cases meeting these criteria. No differences were observed between desmoplastic SCC and common SCC regarding gender, age or distribution in sun-exposed areas, but the number of cases of metastatic progression was six times higher and was dependent on tumour thickness (*level of evidence 4*). This study led the WG to consider the entity as a variant of SCC.

II.3.3. Immunohistochemical markers Although there are as yet no prognostic markers or molecular markers (translocation or recurrent genetic anomaly) specific for SCC and precursor lesions, immunohistochemical markers of differentiation can be used to resolve several problems regarding differential diagnosis (Table 3).

The use of immunohistochemical markers is at the discretion of the pathologist, based on the appearance of the individual lesion. No individual markers may be recommended for routine practice. Immunohistochemistry can aid the differential diagnosis between fusiform SCC, atypical fibroxanthoma, cutaneous sarcoma or fusiform melanoma by demonstrating the expressionby tumour cells of epithelial markers: cytokeratins (CK), notably high molecular weight cytokeratins (CK5-6, 34αE12 and MNF116), epithelial membrane antigen (EMA) and p63.[77] Certain fusiform SCC may nevertheless express both cytokeratins and vimentin.[61]

For the differential diagnosis between acantholytic SCC and vascular tumours, it may be useful to demonstrate positivity of tumour cells for cytokeratins and negativity for vascular markers (CD 34, factor VIII and CD31).[78]

Key points

The clinico-anatomical variants of SCC adopted by the WG, and well-characterized in terms of morphological presentation and prognosis, are as follows:

- common SCC;
- verrucous SCC, fusiform SCC, metatypical (or intermediate) SCC and mixed SCC which, together with the common form of SCC, have a low risk of metastasis;
- acantholytic SCC, mucoepidermoid SCC and desmoplastic SCC, which appear to carry greater metastatic risk.

Within the fusiform SCC group, it is important to distinguish SCC on irradiated areas which, despite their fusiform cell morphology, have a poor prognosis.

For the differential diagnosis of SCC, use of immunohistochemical markers is at the discretion of the pathologist, depending on the appearance of the lesion. No markers can be recommended for routine use.

Table 3 Differential diagnosis between SCC and precursor lesions: immunohistochemical markers

	Differential diagnosis	Useful histochemical markers*
Keratoacanthoma	Well-differentiated SCC	None
Actinic keratosis	Dubreuilh melanoma	Melanocytic markers
	Seborrheic keratosis	None
Bowen's disease	*In situ* melanoma	Cytokeratin+
		Melanocytic markers
	Paget's disease	Cytokeratin 20±; cytokeratin 7–
Poorly differentiated fusiform SCC	Atypical fibroxanthoma	Epithelial markers+
		(CK5-6, 34βE12, MN116, and p63)
	Cutaneous sarcoma	Epithelial markers+
		(CK5-6, 34βE12, MN116, and p63)
	Fusiform melanoma	Epithelial markers+
		(CK5-6, 34βE12, MN116, and p63),
		Melanocytic markers
		(PS100, MelanA)
Verrucous SCC	Epidermal hyperplasia	None
Acantholytic SCC	Angiosarcoma	Epithelial markers +
		Vascular markers–
	Adenocarcinoma I or II	Profile of cytokeratin expression
Adenoid-epidermoid SCC	Adenocarcinoma I (adnexal) or II	None
Mixed SCC	BCC	None
Desmoplastic SCC	Sclerodermiform BCC	None

*The results shown are those normally found in SCC and precursor lesions.

I = primary tumour, II = secondary tumour.

II.4. Keratoacanthoma

Diagnosis of keratoacanthoma is classically based on the association of clinical and histopathological criteria:

- tumour of rapid onset, centred around a keratotic crater;
- symmetrical general organization of the lesion around the central crater occupied by keratin;
- tumour 'hooked' to surrounding epidermis on either side of the crater;
- large keratinocytes with clear cytoplasm;
- low mitotic index;
- spontaneous regression within 2–4 months.

The nature of keratoacanthoma and its relationship with SCC have been debated by numerous authors, including NHMRC experts, who consider keratoacanthoma to be a generally regressive form of SCC.[6,7] The two tumour forms share a number of epidemiological factors, in addition to age at onset and topography. There are no biological markers allowing for the two forms to be distinguished. Certain antigens appear to be expressed differently in keratoacanthomas and SCC, supporting the notion that keratoacanthoma should be considered as a separate entity.[79–81] None of these markers, however, is sufficiently sensitive or specific to constitute an authentic diagnostic tool. Furthermore, a small number of tumours, initially believed to be keratoacanthomas, subsequently progressed in the same way as SCC, in spite of having a seemingly characteristic clinico-anatomical appearance.[29,82]

While these facts remain too rare to rule out the existence of keratoacanthoma and its favourable prognosis, a number of arguments must be taken into account for therapeutic management:

- spontaneous regression may take more than 4 months;
- extensive ulcerous progression is possible, particularly on the nose and eyelids;
- scars that remain following spontaneous regression are frequently unsightly;
- histological distinction between keratoacanthoma and the crateriform architecture of SCC may be difficult or even impossible,[81] as far as biopsies or partial resections are concerned.

The WG thus recommends that pathologists should only make a diagnosis of keratoacanthoma when they are able to assess the architecture of the entire lesion in the biopsy sample. The WG considers that, in atypical cases, excision of the carcinoma is warranted. In typical cases, surgical excision is preferable to the standard 'wait and see' approach (see section V.6).

Key points

Keratoacanthoma should be considered as a separate entity from SCC.

The clinical and histological features of keratoacanthoma, as well as its progression, allow it to be distinguished from SCC, provided the architecture of the entire lesion can be evaluated on the biopsy sample. Partial biopsy does not normally enable formal differentiation between keratoacanthoma and SCC.

III. Prognostic factors for SCC

Prognosis is good for the majority of SCC. The metastatic risk (roughly estimated in the literature using the ratio of number of metastases/number of cases described) is 2.3% at 5 years and 5.2% after follow-up of over 5 years for SCC on sun-exposed skin.

The frequency of relapse or metastasis and of mortality associated with SCC is generally due to late or inappropriate initial treatment of the tumour or to the existence of aggressive clinico-anatomical forms.

While the adapted guidelines provide a number of fairly coherent elements concerning prognostic factors for SCC, the evidence is rarely of level 2 and generally of level 4. The various prognostic factors have been investigated mainly in retrospective studies, which differed in terms of both analytical methods and

criteria used, and of practice and recruitment of teams. The three adapted practice guidelines[83] provide details of the large review by Rowe,[83] which covers a selection of retrospective studies published between 1940 and 1992, as well as several more recent retrospective series, three cohort studies, a prospective study evaluating the definition of at-risk patients[84–87] and another study designed to assess the histoprognostic value of tumour thickness.[88]

The NHMRC guidelines[83] list seven risk factors:

1 TNM classification stage. This is used in the absence of any better classification, although poor suitability for SCC has been pointed out. With regard to T, priority is given to external diameter to define stages T1 to T3, irrespective of the degree of dermal and hypodermal invasion, whereas T4 is defined as invasion of deep muscle and bone layers.
2 Presence of local lymphatic metastases or perineural propagation.
3 Local recurrence or incomplete treatment, grouped together as they are interdependent.
4 Histological grade (well differentiated, fairly well differentiated, poorly differentiated or undifferentiated) and invasive potential, with the emphasis put on 'aggressiveness of fusiform cells', which is contested by several studies.
5 Primary tumour site: SCC with the highest loco-regional risk are those found on the scalp, ear and vermilion border of the lip;
6 Non-photo-induced SCC in immunocompetent patients (SCC on chronic osteomyelitis fistulas, burn scars or radiotherapy areas);
7 SCC in immunodepressed subjects (not dealt with in these guidelines).

- The BAD guidelines[83] further add two criteria for poor prognosis: microscopic measurement of tumour thickness greater than 4 mm and level V hypodermic invasion, with reference to Clark's melanoma classification.
- The NCCN guidelines[83] distinguish the clinical and pathological risks listed in the following table.

In reality, while the majority of criteria listed in this table refer to SCC, the definition of risk associated with site (in three areas: H, I and B) cannot be accepted, as the NCCN experts have defined these risk factors based on relapse rates in a series of BCC. The four articles published by the same team (Silverman *et al.*) were based on a retrospective study involving 5,755 BCC cases, 2,314 of which were treated by curettage and cautery, 862 by radiotherapy and only 588 by surgery. Site was a risk factor independent of relapse, only in the BCC group treated by curettage and cautery. In the surgery group, the only risk factors independent of recurrence were location in the cephalic extremity (in the absence of any further information) and male gender. Consequently, the WG decided not to follow the NCCN proposal of distinguishing three cutaneous areas with different risk levels for SCC (Table 4).

Table 4 Prognostic factors for SCC according to NCCN

	Low risk	High risk
Clinical		
Site/size	Zone B <20 mm	Zone B ≥20 mm
	Zone I <10 mm	Zone I ≥10 mm
	Zone H <6 mm	Zone H ≥6 mm
Edges	Well defined	Poorly defined
Primary vs. recurrence	Primary carcinoma	Recurrence
Immunodepression	No	Yes
SCC on radiolesion or inflammatory lesion	No	Yes
Rapid-growing SCC	No	Yes
Neurological symptoms	No	Yes
Histological		
Degree of differentiation	Well differentiated	Moderately or poorly differentiated
Forms: adenoid (acantholytic), adenosquamous (mucosecretory) or desmoplastic	No	Yes
Depth: Clark level or thickness	I, II, III or <4 mm	IV, V or ≥4 mm
Perineural or vascular invasion	No	Yes

Low-risk area (B): trunk and limbs.
Intermediate-risk area (I): cheeks, forehead, scalp, and neck.
High-risk area (H): central facial region (eyelids, eyebrows, periorbital region, nose, lips, chin and jaw), ear and periauricular region, temples, genital regions as well as hands and feet.

III.1. Clinical prognostic factors in primary SCC

III.1.1. Tumour site The risk of local recurrence and metastasis varies according to the initial tumour site, but this risk is difficult to evaluate as the conducted studies either involve small numbers of cases or do not report correlations with tumour thickness and depth of invasion.[7,9,83]

Lesions occurring in sun-exposed areas (other than the lips and ears) carry the lowest risk of recurrence.

Sites reported as carrying the highest risk of relapse or metastasis are:

- periorificial areas (nose, lips, outer ear and eyelids) and scalp;
- carcinomas originating in non-sun-exposed areas (perineum, sacrum and soles of the feet) or on radiodermatitis, burn scars, chronic inflammation or chronic ulcers (*level of evidence 4*).

III.1.2. Lesion diameter Although this parameter may be considered to be an imprecise reflection of actual tumour volume, it is presented as a prognostic factor in the NHMRC, 2002 BAD and NCCN guidelines. It is the sole criterion employed in the TNM

skin cancer classification, which uses two thresholds to classify tumour diameter: 2 and 5 cm (T1 to T3). This classification makes no reference to depth of invasion other than for the most advanced tumours (T4: infiltration of muscle, bone or cartilage).

In the review by Rowe,[83] tumours with a diameter of 2 cm or more are considered to carry a twofold risk of local relapse and a threefold risk of distant metastases at 5 years in comparison to tumours with a diameter of less than 2 cm. The 5-year relapse and metastasis rates for the latter are nevertheless 7.4% and 9.1%, respectively, which is far from negligible. Several more recent retrospective studies and one prospective study show similar findings[84–93] *(level of evidence 2)*.

A tumour size of 2 cm may thus be considered as a significant prognostic factor, but the aforementioned relapse figures suggest that in terms of tumour size, the safety threshold is in fact lower, particularly at-risk sites (*level of evidence 4*).

As we shall see at at-risk sites, other studies suggest that lesion diameter is probably not the most relevant predictive factor, and that other factors must be taken into account.

III.1.3. Local recurrence Local recurrence is a significant risk factor for lymph node or distant metastases. It is the result of either non-compliance with the rules concerning excision margins or histological verification of these margins or, more rarely, local lymphotropic micrometastases. In a prospective study involving 193 patients with head and neck SCC, a significant correlation was observed between lymph node metastases and relapse.[85] Other studies indicate high rates of metastasis following relapse, ranging from 25% to 45% according to the region.[83,89,92] The risk of local recurrence, however, is not independent of tumour size or initial tumour spread, as the latter factors determine the difficulty of excision *in sano,* and thus of satisfactory local control (*level of evidence 4*).

III.1.4. Immunodepression Increased incidence of SCC following organ transplantation has been widely demonstrated,[94] although opinions on this subject differ. In a cohort study involving 5,356 transplant patients, the risk of skin cancer (non-melanoma and non-BCC) was 100 times greater than in the general population[94] *(level of evidence 2)*.

In addition, the risk of a transplant patient developing SCC is associated with the degree of long-term iatrogenic immunosuppression. After age adjustment, renal transplant patients receiving cyclosporine, azathioprine and prednisolone are at significantly higher (×2.8) risk than those receiving dual therapy with azathioprine and prednisolone. Following adjustments for age and therapeutic regimen, heart transplant patients have a significantly higher risk than renal transplant patients (×2.9).[95,96] The aggressiveness of SCC in transplant patients appears to be higher than in the immunocompetent population. A case/control study involving 60 SCC cases in transplant patients and 40 SCC cases in immunocompetent patients revealed a worse prognosis for SCC in transplant patients[97] *(level of evidence 3)*.

III.2. Histoprognostic factors for primary SCC

III.2.1. Thickness and depth of invasion Tumour thickness and depth of invasion appear to have the best predictive value, but this information is often absent from histopathology reports, and is therefore not taken into consideration in all studies.

In the review by Rowe,[83] tumours thicker than 4 mm and those with invasion or extension beyond the reticular dermis (Clark level IV or V) were three times more likely to recur locally at 5 years and six times more prone to metastasis than tumours with a lower thickness or Clark level. Recurrence and metastasis rates at 5 years for the latter are nevertheless 5.3% and 6.7%, respectively, which is far from negligible, suggesting that the safety threshold is in fact lower, particularly for the aforementioned at-risk sites.

In the largest retrospective series with histoprognostic analysis involving 673 cases of SCC and carcinoma of the lower lip,[88] no metastasis was seen 3 years after surgery for SCC of a thickness <2 mm ($n = 325$). The metastasis rate was 4.5% for tumour thickness between 2 and 6 mm and 12% for tumour thickness >6 mm. An equivalent correlation was found with the level of invasion: No metastasis was recorded when invasion involved only half of the dermis thickness, 4.1% in the event of hypodermic invasion and 12.5% in the case of muscle or bone invasion *(level of evidence 2)*.

Several retrospective series and two prospective series[41,96] reached similar conclusions, although the thresholds selected in each case were not the same, thus enabling the WG to adopt the following principles:

Tumours of thickness ≤2 (or 3) mm or of Clark level ≤III or IV metastasize only rarely. Tumours of thickness >2 (or 3) mm and ≤5 mm may be considered presenting a moderate risk (3–5% metastasis rate) with certain exceptions such as a metastasis rate of 21% (6/28) for the desmoplastic SCC group in the Breuninger series.[98] At thicknesses above 4 or 5 (or 6) mm and at Clark level ≥V, risk may exceed 15% and be as much as 45%[83,86,91–93] *(level of evidence 2)*.

The term 'Breslow thickness' refers to melanoma and was therefore not adopted. The WG notes that determination of the thickness of vegetative tumours must exclude parakeratosis, which is often thick. The thickness of ulcerated tumours must be measured from the base of ulceration.[98]

III.2.2. Perineural invasion (neurotropism) Perineural invasion (PNI) of SCC occurs occasionally, with an estimated prevalence of 2.5–14%. When associated with facial tumours, it results in a risk of symptomatic intracranial carcinomatous neuropathy, which is generally observed at the trigeminal nerve (V) and facial nerve (VII), as well as at other sites, with high levels of relapse and

metastasis. In a study involving 967 SCC cases in 520 patients, PNI was detected in 14% of patients. In the latter group, an increase in rates of both lymph node metastasis (35% vs. 15%; $P < 0.0005$) and distant metastasis (15% vs. 3%; $P < 0.0005$) was observed in comparison with patients without PNI.[99] A recent Australian study included 1,177 patients undergoing Mohs surgery for SCC, 336 of whom were followed over a 5-year period. PNI was reported in 70 SCC cases (5.95%), 25 of which were followed over 5 years, the percentage relapse rate in the PNI group being 8% vs. 3.7% in the group without PNI ($P = 0.02$)[98] *(level of evidence 2)*.

III.2.3. Degree of cytological differentiation Classification of SCC according to the degree of differentiation was taken as a prognostic factor in the three adapted guides. The four broadest classification grades, based on the ratio of differentiated to undifferentiated cells (grade 1 = 3:1, grade 2 = 1/1, grade 3 = 1/3 and grade 4 = no tendency towards differentiation) are rarely used in practice. The majority of pathologists nevertheless use a simplified classification involving description of tumour differentiation as 'well differentiated', 'slightly differentiated' or 'undifferentiated'.

In the review by Rowe, in the event of both relatively undifferentiated or undifferentiated tumours, SCC carries a twofold risk of local relapse and a threefold risk of metastasis in comparison to well-differentiated tumours[83,88,89] (*level of evidence 4*).

III.2.4. Histological type Distinction between certain histological forms of SCC was made only in the NCCN guidelines, which differentiate between mixed, acantholytic, mucoepidermoid and desmoplastic forms.[8]

The study of histoprognostic SCC classification by Cassarino *et al.*[46,47] was based upon a large literature review. It used the percentage of metastasis cases in relation to the number of published cases, without specifying the duration of observation. According to this method of calculation, the group of low-risk SCC (metastatic risk ≤2%) included the common SCC form, verrucous carcinomas, fusiform SCC (except for fusiform SCC in irradiated areas), as well as mixed and metatypical carcinomas. The intermediate-risk group (3–10% risk of metastasis) consisted of the acantholytic form, whereas the high-risk group (metastatic risk >10%) comprised the invasive form of Bowen's disease and desmoplastic and mucoepidermoid SCC (*level of evidence 4*).

Table 5 Clinical TNM classification of non-melanoma skin cancers

Primary tumour (T)			
TX: primary tumour cannot be evaluated			
T0: no identifiable primary tumour			
Tis: carcinoma *in situ*			
T1: tumour ≤2 cm across largest diameter			
T2: tumour 2 cm ≤ T ≤ 5 cm across largest diameter			
T3: tumour >5 cm across largest diameter			
T4: tumour invading deep structures: cartilage, bone or striated muscle			
NB: multiple simultaneous tumours are classified under the highest T with the number of tumours indicated in brackets			
Regional lymph nodes (N)			
NX: regional lymph nodes cannot be evaluated			
N0: no regional lymph node metastasis			
N1: regional lymph node metastasis			
a) micrometastasis			
b) single macrometastasis in the homolateral area, diameter <3 cm			
N2:			
a) single metastasis in the homolateral area, diameter >3 cm <6 cm			
b) multiple metastases in the homolateral area, diameter ≥6 cm			
c) regional intralymphatic metastases (in-transit or satellite)			
N3:			
a) bilateral or contralateral metastases			
b) lymph node metastases with invasion of the facial region or base of skull			
Distant metastases (M)			
MX: distant metastases cannot be evaluated			
M0: no distant metastases			
M1: distant metastases			
Staging			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T4	N0	M0
	all T	N1	M0
Stage IV	all T	all N	M1

Histopathological classification pTNM.
The categories pT, pN and pM correspond to categories T, N and M.
pN0: Histological examination of lymph node curettage samples must include six or more lymph nodes.

III.3. Prognostic classification of primary SCC

To date, no satisfactory prognostic classification exists for primary SCC. The TNM classification developed by AJCC/IUAC/UICC (Table 5) and applied to all forms of non-melanoma skin cancer, is not suitable for SCC. It uses tumour size at its greatest diameter as the sole criterion for T1 to T3, with thresholds at 2 and 5 cm, and defines stage T4 in terms of invasion of deep subdermal structures: cartilage, striated muscle or bone.

While these shortcomings were regretted by the authors of the adapted guidelines, no alternatives were suggested. A more precise prognostic classification would permit better evaluation of risk level, identification of patient groups with comparable risk and improved selection of therapeutic options. Such a classification would require results from a prospective study involving a large patient cohort, with multivariate analysis of multiple potential factors.

The WG felt that because retrospective studies of patient series provided no indication as to whether morphological variants were a discriminating prognostic parameter, independently of tumour thickness and depth of invasion in particular, it would be difficult to adopt this classification as it stands.

The best established variants may nevertheless be classified into two groups:

- four variants of SCC with low metastatic risk: common, verrucous, fusiform (except for those involving irradiated areas) as well as mixed and metatypical SCC;
- three forms that are likely to be more aggressive: acantholytic SCC, desmoplastic SCC and mucoepidermoid SCC.

Recommendations

The WG suggests using a prognostic classification that distinguishes between two SCC groups on the basis of six clinical and five histological criteria (*professional consensus*).

Two of these criteria, clinical size and site, are related: tumour size threshold is dependent on site (Table 6).

Group 1: SCC with low risk of recurrence and/or metastasis

This comprises only SCC with good prognostic criteria. Treatment for these SCC is easy to codify and may be decided upon without needing a multidisciplinary consultation (IDC).

Group 2: other SCC with significant risk of recurrence and/or metastasis

A single criterion in the 'at significant risk' column is sufficient for SCC to be included in this group, but it must be stressed that this group is highly heterogeneous in terms of prognosis for the following reasons:

- Firstly, the risk associated with each of these criteria varies. While five are intrinsically negative (immunodepression, recurrence, adhesion to deep structures indicating a high level of invasion, neurological symptoms of invasion and perineural histological invasion), for each of the six others, the associated risk must be evaluated on a case-by-case basis (tumour size, tumour thickness, site, level of invasion, degree of differentiation and histological form);
- Secondly, the association of several independent criteria may denote increased risk.

In conclusion, the prognostic criteria for SCC in this group should be evaluated individually on a scale ranging from 'moderate risk' to 'very high risk'. Consequently, the procedure to be followed for investigations and treatment should be discussed in IDC.

The WG is fully aware of the relatively low level of evidence for this proposal. It calls on clinicians and histopathologists to routinely record the abovementioned prognostic factors to allow for more conclusive studies to be envisaged subsequently.

Table 6 Prognostic classification of SCC

Criteria	Group 1: low risk	Group 2: significant risk
Clinical		
Primary vs. recurrence	Primary	Recurrence
Degree of clinical infiltration	Absence	Adhesion to deep structures
Neurological symptoms of invasion	No	Yes
Immune status	Immunocompetent	Immunodepressed
Size (diameter) depending on site	<10 mm in area R+† <20 mm in area R−*	≥10 mm in area R+* ≥20 mm in area R−†
Histopathological		
Perineural invasion	No	Yes
Degree of cellular differentiation	Good	Moderate to undifferentiated
Histological forms	Common, verrucous, fusiform (outside irradiated areas), mixed or metatypical SCC	Desmoplastic > mucoepidermoid > acantholytic SCC
Tumour depth (Clark level) Thickness	Level ≤III thickness ≤3 mm	Level ≥IV thickness >3 mm

*Areas at low risk (R−): other sites on the top of the head, trunk and limbs (sun-exposed areas).

†Areas at significant risk (R+): periorificial areas (nose, lips, outer ear[48] and eyelids), non-sun-exposed areas (perineum, sacrum, soles of the feet and nails) radiodermatitis, burn scars, chronic inflammation or chronic ulcers.

III.4. Classification of metastatic stage

Squamous cell carcinoma may be associated with local, regional or distant metastasis, potentially leading to death. Lymphatic dissemination is responsible for 80% of metastases.

III.4.1. Intralymphatic metastases Distinction is made between:

- Local intralymphatic metastases: these are microscopic emboli occasionally seen in dissected tissues taken from near the primary tumour. When they go unnoticed and are not initially treated, they may lead to local recurrence and satellite metastases;
- Intransit metastases (i.e. occurring upstream of the first lymph node): the prognosis is similar to that of lymph node metastases.[7]

III.4.2. Lymph node metastases As the principal site of SCC is the head and neck region, the lymph nodes most often involved are the lateral cervical (jugular-carotid), submandibular, submental and intraparotid nodes.

The NHMRC guidelines[7] are the only ones to offer a prognostic classification of the status of lymph node areas and to devote a

chapter to SCC metastases. Lymph node area status has a strong bearing on prognosis, as the probability of 5-year survival for lymph node metastasis is of the order of 40%, whereas relapse at a lymph node site following radical lymphatic curettage is fatal in most cases.

The Australian authors stress the over-simplified nature of the TNM classification of skin cancers, which distinguishes only between N0 and N1, without taking into consideration the two significant histopathological factors predictive for risk of regional recurrence following radical lymphadenectomy, namely the number of metastatic lymph nodes and perinodal invasion (capsule rupture).[7]

These criteria may be evaluated to some extent using imaging methods during the preoperative work-up, but they are eventually based upon histopathological examination of the surgical curettage tissue sample.

Knowledge of these factors can be used to more accurately determine the prognosis of lymph node involvement.

Number of N invaded	Survival at 5 years
1	49%
2	30%
3 or more	13%
Extracapsular extension	
Absent	47%
Present	23%

The 2002 BAD guidelines, dedicated to primary tumours, do not deal with this topic.

The NCCN guidelines accept the TNM classification content and recommend management by a specialized team at the metastatic stage.

Published literature on head and neck SCC also adopts the AJCC TNM classification for skin cancers.

Thus, based on a prospective study involving 87 patients with parotid metastasis of SCC followed up for a minimum of 2 years, O'Brien[100] performed a multivariate analysis demonstrating that patients with cervical and parotid (P) metastases had a worse prognosis than those with parotid metastases alone, that parotid invasion was an independent predictive criterion for local recurrence, and that stage N was an independent predictive parameter for survival *(level of evidence 2)*.

O'Brien proposed the following classification, taking into account parotid gland status:

Parotid: P1 node metastatic ≤3 cm in diameter;

- P2: 3 cm <metastatic node ≤6 cm in diameter;
- P3: metastatic node >6 cm, paralysis of facial nerve, or invasion of base of skull.

Neck: N0: no cervical site;

- N1: homolateral metastatic lymph node ≤3 cm in diameter;
- N2: metastatic lymph node >3 cm in diameter or multiple or contralateral.

Recommendations

Prognostic evaluation of lymph node status must take into account:

- the number and size of lymph nodes invaded;
- the presence or absence of extracapsular invasion.

As the majority of lymph node metastases seen are associated with head and neck SCC, the WG proposes to adopt, in these cases, the classification criteria (number, size and site of metastases) for head and neck carcinomas.

III.4.3. Distant metastases The onset of distant metastases carries a fatal prognosis in the short- to medium-term.

IV. Treatment methods for SCC and precursor lesions

IV.1. Treatment methods for precursor lesions of SCC

IV.1.1. Surgery In theory, surgical treatment of SCC precursors may be envisaged, and is based on standard surgery with minimal margins. It is used extensively in Bowen's disease, where it has the advantage of enabling histopathological verification of the diagnosis and the absence of invasion. However, there is a strong preference in some quarters for medical and physical methods, particularly in the treatment of AK. The value of surgery has not been evaluated in comparison with the latter methods.

IV.1.2. Description of medical and physical treatment methods

IV.1.2.1. Cryotherapy and cryosurgery

These methods involve tissue destruction by application of extreme cold using liquid nitrogen. In the English scientific literature, the terms 'cryotherapy' and 'cryosurgery' are often used interchangeably without specifying the actual method used.

Cryotherapy involves vaporizing liquid nitrogen on a lesion to freeze it. This approach destroys superficial tissue. Cryotherapy is a simple, rapid and inexpensive method, provided there is easy access to a practitioner (in general, a dermatologist). The optimum duration of freezing is not known, but the lowest rates of recurrence are obtained using 'aggressive' protocols. Several cryotherapy sessions may be needed.

Cryotherapy requires routine control of therapeutic efficacy, and carries a risk of deep pigmented scars.

Cryosurgery is used for deeper lesions. To this end, cold is diffused across the thickness of the skin following application of a cold electrode under local anaesthesia. The degree of freezing is controlled using an impedance metre. However, there are very few studies in which the value of this therapeutic approach for AK and BD has been assessed.

IV.1.2.2. Curettage and cautery

This destructive technique, performed under local anaesthesia, combines curettage of the lesion and coagulation with an electric scalpel. The technique is rapid and allows for haemostasis, even in patients on anticoagulant drugs. In France, this method is used infrequently.

IV.1.2.3. CO_2 laser

CO_2 laser causes non-selective tissue vaporization by a thermal effect, with loss of substance and cautery necrosis of edges, thus providing a cutting effect. It has been used in combination with curettage as an alternative to electrocautery. This technique has no advantages in comparison to the previously described methods.

IV.1.2.4. Fluorouracil (5-FU)

Fluorouracil, a cytotoxic antimetabolite belonging to the antipyrimidine group, acts by inhibiting RNA messenger synthesis.

Five per cent 5-FU cream (Efudix®) has been approved for the treatment of AK and BD. Recommended are one to two applications per day on the lesions, in a thin layer and in a small quantity. The area of treated skin must not exceed 500 cm^2 (approximately 23×23 cm). Treatment must be continued for several weeks (mean: 3–4 weeks).

Therapeutic response comprises an inflammatory reaction (erythema, burning sensation and oedema), erosions and scaly crusts, followed by renewed epithelial growth. These secondary effects, although frequent, are tolerable in most cases.

IV.1.2.5. Imiquimod

Imiquimod is an imidazoquinoline, an immunostimulatory molecule, which induces synthesis and release of cytokines, exerting antiviral and antitumour activities. Aldara®, 5% cream, is marketed in 250-mg sachets of cream, sufficient to cover a skin area measuring 10–20 cm^2 (maximum: two sachets/day). The indications in the marketing authorization are clinically typical, non-hyperkeratotic AK of the face or scalp, in immunocompetent adults, when the size and number of lesions restrict the efficacy and/or safety of cryotherapy.

The cream is applied by the patient in the evening, three times weekly for 4 weeks. The product is left in place for 8 hours and then washed off with copious rinsing. The maximum recommended duration of treatment is 8 weeks. Checks to ensure that the AK has subsided are carried out 4 weeks following treatment discontinuation. Local reactions are common, and may require increased spacing between applications. Due to its immunostimulatory properties, imiquimod cream must be used with caution in patients on immunosuppressant drugs (e.g. transplant patients).

IV.1.2.6. Diclofenac disodium

Solaraze® gel is a non-steroidal anti-inflammatory gel combined with sodium hyaluronate which, by inhibiting cyclooxygenase, reduces the synthesis of prostaglandins and arachidonic acid, involved in epithelial tumour growth. Diclofenac, used in the treatment of AK as two applications per day for 2–3 months, is well tolerated.

IV.1.2.7. Photodynamic therapy (PDT)

PDT involves administration of a photosensitizing product by the topical route. This results in the accumulation of photoreactive porphyrins in tumour cells. Photoactivation of these cells, using a suitable light source, leads to apoptosis and selective necrosis of tumour cells, with sparing of healthy adjacent tissue.

One tube of 5-methylaminolevulinate (MAL) Metvixia® 168 mg/g cream is sufficient to treat an area of around 22 cm^2. In practice, the topical cream is used after curettage. The photosensitizing preparation is applied to the region to be treated 3 hours prior to irradiation and then placed under occlusive bandaging. Irradiation may be administered using various types of lamp, most commonly a red laser at 635 nm. Following irradiation, the treated region is once again covered with occlusive bandaging for 24 h to avoid any further interaction between light and the photosensitizing agent. Several lesions located in the same region may be treated during a single session. The cost of PDT comprises the price of the therapeutic act itself, and of the photosensitizing agent.

One session is generally needed for AK, and two (1 week apart) are needed for BD.

Unwanted effects include primarily pain, which may be severe, and varies from patient to patient and depending on the site. Ventilation with air pulverization of water using a vaporizer or with liquid nitrogen vapour has been proposed to reduce pain, but none of these methods is completely effective.

IV.1.3. Evaluation of local treatments for SCC precursors

IV.1.3.1. Actinic keratosis

According to the 2007 BAD guidelines,[10] there is insufficient evidence to warrant routine treatment of AK as a means to preventing risk of progression.

However, according to Braathen LR *et al.*[104] and Stocketh *et al.*,[105] as progression of AK is not always clinically predictable, effective treatment of all AK cases is necessary.

In practice, common sense suggests that although there is insufficient evidence to warrant mandatory treatment in all instances, there is, however, justification for treating all cases of AK which have become problematic, due to their size, thickness or unsightliness.

Cryotherapy

Cryotherapy is a rapid and inexpensive method, and access to this technique depends in practice on the possibility of a consultation with a dermatologist. The 2007 BAD guidelines[10] recommend cryotherapy, while insisting on its ease of use. According to the NHMRC guidelines,[7] cryotherapy is a simple and effective treatment for AK. In a randomized study[112] comparing imiquimod (applied three times weekly for 4 weeks), cryosurgery (20–40 s per lesion) and 5-FU (twice daily for 4 weeks) in 75 patients, efficacy

was inferior, and the 1-year relapse rate was higher in the cryotherapy group (*level of evidence 2*).

Key points

Cryotherapy is the reference treatment for AK in dermatological practice, despite the existence of very few comparative studies on this topic.

Cryotherapy is a simple, rapid and inexpensive method, provided a specialist is at hand.

It may be used as first-line treatment, despite the fact that its efficacy, which is largely operator-dependent, may be inferior to that of chemical treatments.

CO2 laser

According to the 2007 BAD guidelines, CO_2 laser, like other sources of destructive energy, can be used for AK treatment, although there is little data as to the efficacy of this treatment (*level of evidence 4*).

In a retrospective study involving 31 patients, 58% presented no recurrence during a mean follow-up period of 2 years.[120]

Fluorouracil (5-FU)

According to the 2007 BAD guidelines, the efficacy of 5-FU in the treatment of AK has an evidence level of 1. The efficacy of this treatment when given as two applications per day for 6 weeks has been known since the 1970s. In addition to multiple open studies of this therapeutic approach, several double-blind placebo-controlled randomized studies are available, with a follow-up period of at least 1 year. Dosages involving wider intervals (one application/day) or over shorter time intervals (3–4 weeks) to limit topical side-effects may also be effective, but have been less extensively evaluated.

Key points

Topical 5-FU is an efficient therapeutic method, which allows for treatment of isolated AK, as well as large areas of AK. It may be applied by the patient, and is inexpensive compared with the new therapies (*level of evidence 1*).

Imiquimod

According to the 2007 BAD guidelines, the adverse effects of imiquimod 5% cream, which are similar to those of 5-FU, are difficult to predict and may differ widely from one patient to another. Clinical response appears to be proportional to these side-effects. No data concerning possible long-term recurrence is available. However, efficacy has been demonstrated for a 16-week therapy, but with only a short 8-week follow-up period following treatment discontinuation *(level of evidence 1)*.

Further bibliography includes recent randomized studies,[106–108] an open study[109] and two pivotal studies.[110,111]

Recent studies (Table 7) appear to indicate that reducing duration (to 4 weeks) and rate of application (two to three time-

Table 7 Imiquimod study results

Author Year	Study type	*N* total *N*/group	Treatment modality	Withdrawal Imiquimod/placebo	CR ≥ 75% Imiq/PLB	PR < 75% Imiq/PLB	Local reaction Imiq/PLB	Follow-up relapse
Chen 2004	RCS vs. PLB	*n* = 44 33 Imiq/11 placebo	3/wk/3 wk 2nd session 7 wk if PR	4/1	72% of 29/30% of 10 at 14 wk	28% of 29 70% of 10 at 14 wk	93% of 2/40% of 10	14 wks?
Lebwohl 2004	RCS vs. PLB multicentre	*n* = 436 215 Imiq/221 PLB	2/wk/16 wk	7.9% of 215 6.8% of 221	45% of 215 3.2% of 221 at 20 wk	59% of 215 12% of 221 at 20 wk	34.4% of 215/15% of 221	24 wks?
Korman 2005	RCS vs. PLB multicentre	*n* = 492 242 Imiq/250 PLB	3/wk/16 wk	13.2% of 242 5.2% of 250	48% of 242 7% of 250 at 24 wk	64% of 242 13.6% of 250 at 24 wk	% severe reactions greater with Imiq	24 wks?
Stockfieth 2007	Open multicentre	*n* = 829	3/wk/4 wk 2nd session 4 wk (S2) if RP at 8 wk	29 at S1 and 13 at S2	68.9% (571/829)	80.2% (665/829)	More severe in patients in CR	4 wks?
Alomar 2007	RCS vs. PLB multicentre	*n* = 259 129 Imiq/130 PLB	3/wk/4 wk 2nd session 4 wk if PR	3 in S1 and 1 in S2/0 in S1 and 3 in S2	Histo control 55% of 129 2.3% of 130	Histo control 66% of 129 3.8% of 130	% higher with Imiq	8 wks?
Jorizzo 2007	RCS vs. PLB multicentre	*n* = 246 123 Imiq/123 PLB	3/wk/4 wk 2nd session 4 wk if PR	2 in S1 and 2 in S2/1 in S1 and 2 in S2	26.9% (S1) and 53.7% (total)/4.1% and 14.6%	36.6% (S1) and 61.0% (total)/7.2%	% higher with Imiq	84 followed up at 1 year (59 Imiq/14 PLB) relapse: 39% Imiq/57% PLB

RCS: randomized controlled study; *n*: total number of patients in study; PLB: placebo; PR: partial response; CR: complete response; wk: week; /d or wk: per day or week; /x wk: for x weeks; Imiq: imiquimod.

s/week) does not diminish efficacy. Krawtchenko *et al.*,[112] comparing imiquimod (applied three times per week for 4 weeks), cryosurgery (20–40 s per lesion) and 5-FU (twice daily for 4 weeks) in 75 patients in three identical groups over a 1-year period, observed that reduction in histological signs and aesthetic outcome were in favour of imiquimod compared with 5-FU, followed by cryosurgery. The 5-FU and cryosurgery groups showed a high rate of relapse at 12 months.

Key points

Imiquimod cream 5% is at least as effective against AK as 5-FU and cryotherapy, with equally good aesthetic results, but at a higher cost *(level of evidence 1)*.

Local skin reactions such as irritation are common.

Of note is that the safety of use of imiquimod has not been evaluated in organ transplant patients.

Diclofenac sodium (Solaraze®)

- According to the 2007 BAD guidelines, this treatment displays moderate efficacy, along with a good safety profile.
- Four randomized double-blind studies have demonstrated the superiority of Solaraze® over placebo.[113–115] In 96 eligible patients, Solaraze® exhibited complete resolution of clinical lesions in 47% of patients compared with 19% in the placebo group at 4 months (level of evidence 2). Clinical safety was excellent, comparable to that of placebo. The follow-up period, however, was only 30 days after the end of treatment, and the rate of recurrence is unknown.
- However, another placebo-controlled study in 20 patients showed more modest results with a clear decrease in the number of AK, but a clinical cure rate of only 9%.[116] Solaraze® (twice daily for 90 days) was compared with 5-FU cream (twice daily for 28 days) in 30 patients, with patients acting as their own controls. Half of the cases of keratosis were treated with Solaraze® and the other half with 5-FU. Efficacy was comparable for the two treatments, but safety was clearly better for Solaraze®.[117] There is no data available concerning recurrence *(level of evidence 2)*.

Key points

Solaraze® gel, used for AK treatment at a dosage of two applications per day for 2–3 months, is well tolerated, but data in the literature are insufficient to confirm equivalent efficacy compared with other topical agents.

As yet, there is no data on recurrence rates. In practice, the efficacy of diclofenac appears less favourable than that of other topical treatments.

Photodynamic therapy (PDT)

The NHMRC and BAD guidelines, published in 2002, present PDT as a treatment promising good aesthetic results, which is primarily of interest in the case of multiple lesions or lesions in poorly healing areas. However, its place in the therapeutic arsenal for AK remains to be defined.

Additional bibliography

Kurwa *et al.*[118] compared the efficacy of topical 5-FU and PDT: The backs of the left and right hands of 17 patients were randomized to receive either 3 weeks of treatment with topical 5-FU twice daily or treatment with PDT. Patients were followed up at 1, 4 and 24 weeks. Fourteen of the 17 patients completed the study. The mean reduction in lesions at 6 months was 70% for regions treated with topical 5-FU and 73% for regions treated with PDT, with no significant between-group difference observed. Furthermore, no difference was noted in pain scores *(level of evidence 2)*. The guidelines of Braathen LR *et al.*[104] were devised by international experts from the *International Society for Photodynamic Therapy in Dermatology* in January 2005. According to these authors, PDT was highly suited for AK treatment, leading to high cure rates (complete response of around 90% after 2 sessions) as well as good-to-excellent aesthetic results (≥84%). In general, this treatment is well tolerated by patients.

In the open, multicentre, clinical trial by Morton *et al.*,[119] 1,501 AK cases of the face and scalp in 119 patients were treated, and intra-individual MAL-PDT was compared with cryotherapy. The percentage rate of complete AK regression at 12 weeks in the *per protocol (PP)* population was better for PDT (86.9%) than for cryotherapy (76.2%), with similar results observed at 24 weeks (89.1% vs. 86.1%). Cosmetic results for PDT in the PP population were also better according to patients and assessors alike (results were 'excellent' at 12 and 24 weeks: 70.8% and 77.2% vs. 57.4% and 49.7% for cryotherapy). Safety was considered good for both treatments (Table 8).

Key points

The efficacy of PDT is globally comparable with that of cryotherapy and 5-FU in the treatment of AK *(level of evidence 2)*.

Aesthetic results are good.

Generally, this treatment is well tolerated except for local pain during irradiation. Further studies are required to assess long-term efficacy.

PDT is costly and can only be carried out in hospital settings for the moment.

Recommendations

Once the decision has been taken to treat AK, the choice between cryotherapy with liquid nitrogen and other topical treatments, such as 5-FU, imiquimod, PDT and diclofenac, must take into account the individual patient's situation *(professional consensus)*.

5-FU, imiquimod and PDT are effective treatments, and while local side-effects may be severe, they are generally tolerable.

These therapies may be considered as first-line treatments for multiple AK or AK in areas of skin with poor healing *(grade B)*.

Table 8 Diclofenac study results

Author year	Study type	No. subjects/group	Treatment modality	PR: diclo/PLB or other	Safety
Wolf 2001	RCS vs. PLB	96 (46 diclo/52 PLB)	2×/d for 90 d	47/19% at 4 months	Comparable
Fariba 2006	RCS vs. PLB	20	2×/d for 3 months	9/0% at 3 months	
Rivers 2002	RCS vs. PLB, multicentre	195	2×/d for 30 d: 49 PLB/49 diclo 2×/d for 60 d: 49 PLB/48 diclo	17/5% at 30 d 31/10% at 60 d	
Gebauer 2003	RCS vs. PLB	115 (50 diclo/65 placebo)	2×/d for 90 d	38/10% at 4 months	
Smith 2007	Comparative diclo/5-FU	30	diclo: 2×/d for 90 d 5-FU: 2×/d for 28 d	Comparable efficacy	Superior for diclo

RCS: randomized controlled study; PLB: placebo; PR: partial response; /d or wk.: per day or week; /x d, wk., or month: for x days, weeks or months; diclo: diclofenac.

Due to its immunostimulatory properties, imiquimod cream must be used with caution in patients on immunosuppression therapy (transplant patients).

IV.1.3.2. Bowen's disease

Surgery

This is a simple, rapid and effective treatment for BD of limited size, located in suitable areas. It allows for verification of the diagnosis and of the intraepithelial nature of the lesion.

Cryotherapy

According to the 2006 BAD guidelines,[11] highly variable results have been reported by different authors following application of liquid nitrogen to destroy Bowen's disease lesions. However, when 'adequate' cryotherapy was used (one 30-s freezing cycle of an area exceeding the lesion perimeter by 3 mm or two freeze-defrost cycles lasting 20 s), and at the expense of perioperative discomfort and postoperative ulceration, the 1-year relapse rate was lower than 10% *(level of evidence 2)*.

The study by Morton[123] demonstrated the superiority of PDT over cryotherapy in terms of efficacy, with fewer infectious and cosmetic complications.

Key points

In the treatment of BD, cryotherapy is associated with relapse rates of around 10% at 1 year, which is slightly higher than those seen with 5-FU and PDT *(level of evidence 2)*.

This approach is not recommended for BD in areas with poor wound healing.

Curettage and cautery

According to the 2006 BAD,[11] curettage and cautery under local anaesthesia are a relatively painless and effective method *(level of evidence 2)*.

In a prospective study involving 67 patients, Ahmed[124] compared the efficacy of cryotherapy with that of curettage and cautery. Cryotherapy consisted of vaporization of liquid nitrogen for 5–10 s in two applications to 36 AK lesions; curettage and cautery was carried out on 44 lesions following local anaesthesia. In the cryotherapy group, the median clinical healing time was 46 days (90 days for 12 lesions); four patients presented superinfection and 13 lesions recurred at 2 years. In the curettage group, median healing time was 35 days (90 days for 6 lesions); two patients presented superinfection and four lesions recurred at 2 years. The authors concluded that the benefit/risk ratio was greater for curettage than for cryotherapy (which is not a reference treatment for BD).

Key points

Curettage and cautery are used infrequently in France, and the data in the literature are insufficient to draw firm conlusions on the efficacy of this approach in BD.

Laser

According to the NHMRC guidelines,[7] laser may be useful in the treatment of BD (*level of evidence 4*), but it must be performed by a trained specialist and is expensive. According to the 2006 BAD guidelines,[11] the laser types used in the treatment of BD lesions include CO_2, argon and Nd-YAG. The lesion is destroyed by vaporization following local or general (for extensive lesions) anaesthesia. While the results obtained with this method are excellent, those published in the literature involve only small series of patients (*level of evidence 4*).

Key points

Laser is a costly and relatively inaccessible method. The data in the literature are insufficient to draw firm conclusion on its efficacy.

Fluorouracil

According to the 2006 BAD guidelines,[121] local 5-FU is an effective treatment in BD *(level of evidence 2)*. As with AK, the dosage consists of one to two applications per day in a thin layer and in a small quantity, solely on the lesions, and this is carried out for several weeks (mean: 3–4 weeks) under medical supervision.

Bargman[121] demonstrated the long-term efficacy of local 5-FU, with biopsy-confirmed resolution of all lesions in 26 patients. At 10 years, only two patients presented local recurrence.

Key points

Topical 5-FU is an effective treatment for histologically confirmed Bowen's disease.

It may be applied to the patient, providing the best cost/efficacy and efficacy/safety ratios in BD for extensive or multiple lesions, or for lesions in areas with poor wound healing (*level of evidence 2*).

PDT

According to the 2006 BAD guidelines,[121] PDT yields equivalent or superior results to cryotherapy and 5-FU, regarding efficacy or quality of wound healing, according to the controlled randomized studies reported therein (*level of evidence 1)*. It is particularly useful in the treatment of large lesions, lesions on the lower part of the limb or lesions in other areas with poor healing.

According to Braathen LR *et al.*,[104] topical PDT is a non-invasive treatment for BD with high efficacy and good safety. It is suitable for BD, which is often found in areas with poor healing, and produces good cosmetic results. PDT is at least as effective as cryotherapy and 5-FU, yet with fewer side-effects. It may be considered the treatment of choice in BD *(level of evidence 1)*.

Key points

PDT is effective in the treatment of BD and produces good cosmetic results *(level of evidence 1)*. Results following this treatment are equivalent or superior to those obtained with cryotherapy and 5-FU, but due to the price of the act and the photosensitization agent, this method is costly.

Imiquimod

Few studies have been conducted on the treatment of BD with imiquimod. The NHMRC guidelines[7] report a small open study by Mackenzie-Wood A *et al.*,[122] without providing any conclusion. Treatment of 16 BD patients with 5% imiquimod cream for 16 weeks resulted (14/15) in complete clinical and histological response in 93% of the cases. Local reactions were common.

According to the 2007 BAD guidelines,[11] imiquimod may be used in BD, particularly for lesions in areas with poor wound healing *(level of evidence 2)*. According to the NCCN guidelines,[8] when surgery or radiotherapy is contraindicated or unfeasible, treatment with imiquimod may be envisaged, despite its lower cure rates.

Key points

Imiquimod appears to be efficacious in the treatment of BD, but it is expensive compared with 5-FU.

It has not obtained marketing authorization in this indication, and therapeutic modalities are yet to be optimized.

Recommendations

5-FU or PDT may be proposed in BD when surgery is complicated due to extensive or multiple lesions, or when lesion sites are in areas with poor wound healing *(grade B)*.

There is insufficient data to recommend cryotherapy, particularly as far as areas with poor wound healing are concerned.

No recommendations can be formulated regarding the use of laser, curettage and cautery in BD.

IV.2. Surgical treatment of infiltrating SCC

Surgery is unanimously recognized in the adapted BAD, NCCN and NHMRC guidelines as the treatment of choice for these tumours. It has the advantage of providing excision tissue, which enables histological confirmation of diagnosis and verification of excision quality, as well as achieving extremely high rates of local control and cure in the vast majority of patients.

It remains the gold standard against which all non-surgical treatments for SCC must be compared.[125]

IV.2.1. Standard surgery

IV.2.1.1. Aims of treatment

The main aim of surgical treatment for SCC is to obtain complete and histologically confirmed tumour excision.

There are two other relevant goals:

- maintenance of normal function as far as possible;
- satisfactory cosmetic results.

This requirement of resection *in sano* followed by functional and cosmetic reconstruction is particularly important for the face, especially for lesions near natural orifices.

Primary excision, when performed properly, results in cure rates in excess of 90%.[83,126]

IV.2.1.2. General principles of surgical treatment

These are set out in detail by the NHMRC,[125] and the WG adopted the following recommendations:

- Patients must be fully informed prior to all surgical acts. This information comprises therapeutic options, both surgical and non-surgical, the risks and potential sequelae involved, as well as the benefits and results expected in the short- and long-term with respect to functional and cosmetic outcomes. The patient must be informed that tissue removed during excision will undergo histopathological analysis, and that further surgery may be necessary depending on the results of this analysis in the event of incomplete excision.
- If there are clinical doubts about the diagnosis, histological confirmation is necessary. This will require a biopsy (by punch biopsy or surgery) before the main excision, or complete excision in the case of small lesions that are easy to remove and repair.

- By definition, biopsies only allow for partial study of lesions, and any data must be completed by analysis of tissue removed during surgery.
- The surgical procedure must be planned in accordance with tumour parameters. The lateral and deep borders (degree of infiltration) of the lesion must undergo careful clinical evaluation. Excision margins must be marked prior to the injection of local anaesthetic agents, as the latter could make tumour margins more difficult to discern.
- Extensive tumour resection involving cosmetically or functionally sensitive areas (partial sacrifice of an eyelid or tear duct, operations involving the face, lips, nasal pyramid and generally any operation resulting in extensive loss of flesh followed by reconstruction) requires surgical expertise in skin cancer management.
- Surgery on periorificial SCC of the face, lips and ears, as well as SCC with perineural invasion should be undertaken following IDC, whenever it is difficult to ensure sparing of the standard margins without affecting cosmetic or functional prognosis *(professional consensus)*.
- Postoperative radiotherapy is occasionally necessary (*see below*).

IV.2.1.3. Excision margins

The margin of healthy skin that needs to be removed to ensure complete tumour eradication is the crucial question in surgical treatment and the main topic of discussion.[125,127]

The 2002 BAD and NCCN guidelines refer to Brodland and Zitelli[125] who, based on a prospective study involving 141 cases of primary SCC removed by Mohs surgery, noted that:

- a 4-mm margin is sufficient to eradicate 95% of tumours measuring less than 2 cm in diameter;
- a margin >6 mm is necessary to obtain the same result for tumours of diameter >2 cm or for tumours associated with risk factors, such as poorly differentiated SCC, SCC invading subcutaneous tissue or SCC located in areas at risk *(level of evidence 2)*.

It is important to note that the excision margin should be increased to 10 mm or more to obtain similar levels of local control under certain circumstances: further excision following positive postoperative control of the margins or tumour characteristics associated with risk of subclinical extension, such as high histological grade, invasion of the hypodermis, location in areas at risk and, *a fortiori*, in cases of perineural invasion. For very large lesions, wider margins may be proposed.

Recommendations

Given that excision margins must be adapted to the degree of aggressiveness of the SCC, that tumour size is only an approximate reflection of the actual degree of aggressiveness, and that excision margins are insufficient in 5% of cases, the WG recommends:

- a standardized margin of 4–6 mm for tumours in Group 1 of the prognostic classification proposed in these guidelines, with standard histological examination and macroscopic sampling to provide as much information as possible about the margins;
- an extended margin ≥6 mm or even 10 mm or more, for Group 2 tumours, particularly in the case of tumours with several risk factors for subclinical extension *(professional consensus)*.

There have been fewer evaluations concerning **excision depth**. Excision must involve the hypodermis, while sparing aponeuroses, periostium and perichondrium, provided that these structures have not been in contact with or invaded by the tumour. The methods used to study margins on excised tissue are not all equally reliable.

- Extemporaneous examination is of real value if conducted by the surgeon on one or more areas at risk for invasion and performed as exhaustively as possible in these areas.[128] It should be borne in mind that only a small percentage of margins can be examined, and that further postoperative studies must be performed on the fragment examined extemporaneously and on the remainder of the tissue removed at surgery.
- Two-stage surgical excision constitutes an alternative to extemporaneous examination, as it enables control of margins in paraffin blocks, which in theory provide higher quality than frozen slices. No studies have been performed comparing these two approaches, but for extemporaneous examination, the value of histopathological analysis depends on the exact direction of excision used by the surgeon for the excised tissue and, where possible, for the areas at risk for invasion. Methods involving the exhaustive study of margins offer greater security, particularly regarding high-risk carcinomas (see Micrographic surgery).

IV.2.2. Micrographic surgery Micrographic surgery comprises a range of techniques permitting complete viewing of the excision margins (100% of peritumoral borders).

IV.2.2.1. Surgical technique

The micrographic surgery technique described by F. Mohs in 1941 has evolved considerably since its first use.[129] It is usually carried out under local anaesthesia with extemporaneous analysis of frozen sections. The tumour is first removed by curettage or surgical excision. A thin section (approximately 2 mm) is then taken of the entire peritumoral surface. This section is marked, oriented and flattened to allow the outer part to be sliced horizontally following freezing, ensuring that all peritumoral borders are visible in a single plane. After extemporaneous histological verification, if

there are no further tumoural foci, the margins are considered to be healthy. Otherwise, the residual tumour is marked to allow for further excision, which is carried out in parallel to the area from which tissue has been removed. Such excision in successive slices requires close co-ordination between surgery, section preparation and histological analysis. However, it increases operating times and involves more staff, thereby increasing treatment costs.

With other types of micrographic surgery, Mohs Micrographic Surgery (MMS) with inclusion in a paraffin block (slow Mohs) or similar approaches (Breuninger and others), histology results are not immediately available, as the tissue is included in paraffin. Although the absence of extemporaneous histological analysis reduces the cost, this remains a complex operation involving minute examination of the excised tissue by the histopathologist.

IV.2.2.2. Bibliographical analysis

BAD guidelines[9]

MMS ensures complete excision of a tumour expanding from a single site by adjusting tissue removal in accordance with subclinical spread. MMS should be considered in the treatment of high-risk SCC. It is particularly recommended in cases where the unavoidable creation of broad excision margins could cause functional impairment. The best cure rates for high-risk SCC have been obtained in patient series treated with MMS.[82]

If MMS is not available in these indications, the surgical alternative is standard excision with a margin ≥6 mm, with histopathological control of the peritumoral edges.[129]

However, there are no prospective randomized studies comparing the results of standard excision to those of MMS.

NCCN guidelines[8]

MMS must be carried out by a trained team. It is indicated in both high-risk SCC, where it is the treatment of choice, and low-risk SCC, when the margin tests positive after standard excision of 4–6 mm. The alternatives to MMS are surgical excision followed by complete circumferential, peripheral and deep margin assessment, or standard surgery with standard margins of 10 mm.

NHMRC guidelines[7]

MMS is especially suitable in cases where complete excision is difficult to achieve, and in cases with a higher than normal risk of recurrence. The indications adopted are SCC located on the central facial region or periorificial areas, as well as recurrence or incomplete excision, with clinical and histological characteristics of high-risk tumour.

The advantages of MMS lie in the sparing of healthy tissue, its very high cure rate, the certainty of complete excision allowing for confident reconstruction as well as the option of operating under local anaesthesia.

The drawbacks of MMS include the duration and cost of the procedure, as well as the need for trained and experienced staff.

Analysis of additional publications

Leibovitch I *et al.*[131] reported the results of a prospective multicentre study involving 1,263 SCC cases (1993–2002), of which 61.1% were primary and 38.9% recurrences. Following MMS, the 5-year rate of recurrence for 381/1,263 patients was 2.6% for primary SCC and 5.9% for recurrent SCC *(level of evidence 2)*.

In another prospective series, Malhotra R *et al.*[132] reported a relapse rate of 3.64% (2/56) in 71 patients undergoing MMS for periocular SCC. This rate is lower than that of all other therapeutic alternatives for these tumours with poor prognosis.

Key points

The advantages of micrographic surgery are:

- sparing of healthy tissue (tissue removal is adjusted in accordance with subclinical extension), with better functional and cosmetic prognosis;
- a very high cure rate (the best cure rates for high-risk SCC are reported in patient series treated with MMS), although no controlled studies have been performed comparing the efficacy of this approach with that of other surgical techniques.

Drawbacks: duration and cost of the procedure, which requires the presence of both a surgeon and a histopathologist.

Recommendations

Most SCC lesions are small at the time of diagnosis, with a favourable prognosis, and may be removed by excision with direct primary closure *(grade C)*.

As the excision margin must be adjusted for the aggressiveness of the SCC, defined by numerous clinical and histological factors, a standardized margin of 4–6 mm is recommended for tumours of Group 1 in the prognostic classification proposed in these guidelines, and a wider margin, ≥6 mm or even 10 mm or more, is recommended for Group 2 tumours, particularly when there is a risk of subclinical extension *(professional consensus)*.

Deep excision must comprise removal of the hypodermis *(professional consensus)*.

Specialist treatment is necessary for SCC in the central facial region, the lips and the ears, owing to the difficulty involved in achieving standard excision margins without impairment of aesthetic or functional prognosis.

For patients presenting SCC with perineural invasion, specialist therapy is necessary. Wide excision margins and postoperative radiotherapy are recommended *(grade C)*.

The WG would like to see use of micrographic methods extended to the treatment of Group 2 SCC, in which control of peritumoral margins is important *(professional consensus)*. However, for this to be achieved, it would be necessary to secure a higher remuneration rate for these procedures under the histopathology fee schedule.[133]

IV.2.3. Curettage and cautery This destructive technique is based on the difference in consistency between normal friable

tumour tissue and normal adjacent tissue resistant to curettage. It comprises one or more cycles of scraping using a curette, under local anaesthesia, followed by freezing with an electric scalpel. The procedure is rapid, spares skin tissue, enables haemostasis, even in patients on anticoagulant therapy and is inexpensive.

A study of curettage shavings can provide histological confirmation of diagnosis, but does not allow for margin control. This approach requires certainty of clinical diagnosis, well-delineated tumour edges, surface extension as well as a trained operator.

The NCCN guidelines list two provisos for using this technique: Pilar regions are not suitable as tumours spreading along pilar sheaths are not always caught by the curette; the technique is inappropriate for lesions involving the hypodermis, because in this area, the operator is unable to distinguish between the consistency of tumours and that of healthy tissue.

The NHMRC guidelines simply note that little data are available in the literature concerning the value of this method, but point out (without proposing any recommendations on this subject) that the technique is used in the treatment of SCC, BD and keratoacanthoma.

In France, this method is infrequently used. The data given in the literature are insufficient to allow for any recommendations to be made.

IV.2.4. Surgical treatment of metastases

IV.2.4.1 Local (in-transit) metastases

The presence of clinically observable metastases around primary or recurrent SCC warrants surgical excision if the number, size, spread and location of lesions are consistent with the ability to achieve healthy clinical macroscopic margins. Additional adjuvant radiotherapy is desirable.[9]

IV.2.4.2 Lymph node metastases

The survival of patients presenting lymph node metastases is in the order of 30% at 5 years.

Routine lymph node curettage

This is currently performed in SCC affecting mucous membrane of the head and neck with a high risk of lymph node metastasis (risk of occult metastasis >20%), although in terms of survival, the value of routine curettage has not been demonstrated.

It has been proposed for lip lesions of a thickness >6 mm and for other sites where thickness exceeds 8 mm, although the level of evidence is low.[9,134]

It should be noted that ENT data are not automatically transposable to SCC, as they have a better prognosis and lower metastatic risk. Routine curettage for SCC would result in unnecessary surgery in a high number of patients, while only benefiting a small number. In the case of SCC, first-line lymphadenectomy is not recommended due to its unfavourable benefit/morbidity ratio.[135]

Selective curettage

This approach is also proposed for high-risk head and neck carcinomas with no palpable adenopathy. Curettage is restricted to the site of the lymph nodes draining the initial lesion[9] with extemporaneous control of the distal lymph nodes, with complete curettage performed only if the latter examination proves positive.

Selective lymph node curettage using the sentinel node technique has no proven value, and is not currently recommended.[85,136,137] The sentinel node technique may be envisaged in the event of very high-risk SCC in the context of controlled studies.

Mandatory curettage

This is performed in the case of clinically apparent adenopathies or histologically confirmed adenopathies detected by imaging. The choice of surgical method and the anatomical extent of curettage are beyond the scope of the present guidelines. The mean numbers of lymph nodes involved in the surgical field are:

- ≥15 lymph nodes in the axillary region (three levels in all);
- ≥10 lymph nodes in the inguinal region;
- ≥15 lymph nodes in the cervical–facial regions.

These figures provide an approximate idea of the anatomical extent of lymph node curettage, but they may vary according to individuals and to the degree of screening for lymph nodes in excised tissue.

Recommendations

Routine lymph node curettage is not recommended due to the poorly evaluated benefit/morbidity ratio *(professional consensus)*.

Selective curettage using the sentinel node technique is of no proven value, and patient groups that could potentially be benefitted have not been identified. This type of curettage cannot be recommended.

The sentinel node technique may be envisaged in clinical trials *(professional consensus)*. Lymph node metastasis of SCC requires histological confirmation.

First-line treatment of lymph node metastases consists of surgical curettage. Combination with adjuvant radiotherapy may be envisaged in IDC *(grade C)*.

IV.3. Radiotherapy

IV.3.1. Presentation of the technique Radiotherapy (RT) consists of the use of ionizing radiation in the treatment of cancer via two main modalities: external radiotherapy and interstitial curietherapy.

IV.3.1.1. External radiotherapy

This modality uses low-energy X photons (contact X-ray therapy), high-energy X photons, gamma rays (telecobalt) or electron beams (linear accelerators). It is a non-invasive form of treatment that may be used in SCC irrespective of size or depth. A number of sessions (mean: 10–30) are required over a period of 3–6 weeks. Dose fractionation achieves better cosmetic results while increasing treatment time. This factor must be taken into account in elderly

patients or patients living far from the treatment centre. The practitioner must take into consideration the radiation curve regarding depth and for the penumbra around the actual radiation field, depending on the type of energy used.

A safety margin of 1–1.5 cm around the tumour is recommended because of the risk of microscopic dissemination and uncertainty about patient movement throughout delivery.

Acute secondary effects such as epidermitis occur 2–3 weeks after the start of treatment sessions and are reversible within several days to several weeks.

Late side-effects occurring several months or years after treatment are irreversible and include cutaneous atrophy with hair loss, reduction of sweat and sebaceous secretion, dyschromia (hypopigmentation or hyperpigmentation), telangectasia as well as dermal or hypodermal sclerosis. These effects are continually evolving, but due to computerized dose calculation, it should be possible to avert the phenomenon of radionecrosis.

Radiotherapy exposes patients to the risk of a second carcinoma in the irradiated area, and is contraindicated in very rare cases of genodermatosis predisposing to skin cancer.

Factors affecting the cosmetic outcome include type of RT, volume and area treated, site, extent of tumoural tissue destruction, individual susceptibility, dose delivered per session and duration of treatment. Complications tend to occur more in flat areas of the face (forehead, temples), the back and relatively non-vascularized areas, as well as in cartilaginous areas.

IV.3.1.2 Interstitial curietherapy

This approach consists of implanting plastic tubes – through which iridium192 (lr192-main gamma transmitter) wires may be loaded – into the tumour, generally under local anaesthesia. During treatment, the patient is hospitalized for 3–4 days in a specialized unit. This information must be borne in mind for elderly patients.

IV.3.2. Indications for radiotherapy All indications were drawn from a comparative study of the three guidelines, BAD, NHRMC and NCCN, along with an updated bibliography. The only data available in the literature concerns retrospective studies, presenting overall coherence (*level of evidence 4*).

IV.3.2.1 Recommendations of the guidelines consulted

***NHMRC guidelines*[7]**

Radiotherapy has been used in all forms of SCC, and has displayed efficacy comparable to that of surgery, but as the majority of SCC consist of small lesions, surgery has the advantage of ease of use, rapid wound healing, along with good cosmetic results. The NHMRC guidelines thus recommend RT solely as second-line treatment, based on specialist advice, and in the following cases only:

- a minority of primary SCC, where the patient's condition contraindicates surgery, the patient refuses surgery or surgery would result in unacceptable morbidity;
- recurring or advanced SCC where RT may be combined with surgery to improve tumour control;
- residual tumours where surgical treatment is unfeasible;
- management of metastases.

The contraindications for radiotherapy listed by the NHMRC are as follows:

- patients aged under 60 years where the lesion is operable;
- lesions on the scalp or in contact with the tear duct;
- advanced lesions invading tendons, joints or bone;
- lesions in poorly vascularized and easily injured areas (e.g. pretibial lesions);
- lesions in areas already irradiated;
- lesions covering bone exposed to trauma, lower limbs, upper eyelid or where radiotherapy is poorly tolerated;
- genodermatosis predisposing to skin cancer, basal cell nevus syndrome and *xeroderma pigmentosum*.

***NCCN guidelines*[8]**

Excellent results may be obtained with RT in terms of cure rates and cosmetic outcome, provided the method is fully mastered, and appropriate training has been given. The recommendations are as follows:

- RT may be indicated as first-line treatment in patients aged over 60 years for small primary SCC at sites other than the hands, feet or genital organs (with the exception of curietherapy for penile SCC);
- RT is indicated in addition to incomplete excision of low-risk SCC;
- RT is an effective therapeutic alternative for large BD or in patients refusing surgery;
- RT may be considered an adjuvant to Mohs surgery in the event of extensive perineural invasion of a large nerve;
- RT is not recommended in verrucous SCC as the literature indicates increased risk of metastasis in patients undergoing radiotherapy for this type of tumour, which is normally of low-grade malignancy.

It is also contraindicated in genetic diseases predisposing to cancer such as *xeroderma pigmentosum* and connective tissue disease.

The recommended safety margins for RT are 5–10 mm for SCC <0 mm, and 15–20 mm for SCC >20 mm. The recommended doses are 45–50 Gy in fractions of 2.5–3 Gy for tumours measuring less than 2 cm, and of 60–66 Gy by fraction of 2 Gy or 50–60 Gy by fraction of 2.5 Gy for tumours measuring more than 2 cm. For adjuvant postsurgical RT, the total recommended dose is 45–55 Gy in fractions of 2.5–3 Gy.

***2002 BAD guidelines*[9]**

The results of RT alone in SCC are comparable to those of the most successful surgical treatment. In some circumstances, good cosmetic and functional results may be obtained with RT. This is often the case, for example, with regard to lesions of the lip, the nasal vestibule and the ear. RT may also offer the best therapeutic solution in certain highly advanced tumours where postsurgical morbidity would be too extensive.

IV.3.2.2 Indications for radiotherapy according to clinical situation

Previously untreated SCC

External radiotherapy[7–9,138–141] and interstitial curietherapy[142–154] yield results comparable with those of surgery, with levels of local control at 5 years of:

- 92–97% for T1 tumours;
- 65–85% for T2 tumours;
- 50–60% for T3-4 tumours on the TNM classification.

For external radiotherapy, the WG has adopted the NCCN recommendations:

- recommended safety margins of 5–10 mm for SCC of diameter <20 mm and of 15–20 mm for SCC >20 mm;
- proposed (recommended) algorithms: doses of 45–50 Gy in fractions of 2.5–3 Gy for tumours of >2 cm, doses of 60–66 Gy in fractions of 2 Gy or 50–60 Gy in fractions of 2.5 Gy for tumours of >2 cm.

For adjuvant postsurgical radiotherapy, the total recommended dose is 45–55 Gy in fractions of 2.5–3 Gy.

There have been numerous retrospective series[143,144,148,150,153,154] assessing interstitial curietherapy alone in the treatment of SCC of the lip. The largest study[153] involved 2,274 tumours, 1,276 of which were treated with Ir192 wire sources. Rates of local control for stages T1, T2 and T3 were 98.5%, 96.5% and 90%, respectively, at 5 years.

Radiotherapy is not indicated for SCC of the hands, legs, feet, genitals or upper eyelids due to the presence of critical organs in adjacent areas (tendons, articulations, testicles, eyes, etc.) and because of the risk of secondary necrosis.

However, when surgery is not possible or has failed, interstitial curietherapy may be proposed for the treatment of penile SCC T1–T2, for which local control at 5 years was between 85% and 91%.[145–149] When using transfixing needles, prior circumcision may be carried out.

Recurring SCC

Recurrence of SCC is an indicator of poor prognosis. When further surgery is impossible, the rate of local control following irradiation is estimated to be between 65% and 80% at 5 years.[7,8]

Incomplete excision and PNI are factors for relapse, and the prognosis is poorer for recurring forms than for primary forms.[6,7,130]

To date, there is insufficient bibliographical data assessing the role of adjuvant radiotherapy vs. further surgery alone. Consequently, in the event of microscopic residual tumours, adjuvant radiotherapy is indicated only when further surgery is not possible.

Levels of local control attained following treatment of SCC with microscopic PNI or extensive (clinical) relapse are 78–87% and 50–55% respectively.[7,155]

Adjuvant radiotherapy may be envisaged in the case of extensive PNI, principally around the base of the skull.[7,8,155]

Metastatic SCC

In the case of lymph node involvement, surgical resection may be proposed as first-line treatment (BAD 2002, NHRMC, NCCN). The level of local control following combined treatment (surgery–adjuvant external RT) in the event of parotid lymph node invasion is around 80% vs. 30–50% following single-modality treatment (surgery or external RT (with relapse-free survival at 5 years of 70% vs. 50%.[156–161]

Recommendations

Histological confirmation of diagnosis is required before beginning RT management of SCC.

Radiotherapy should be used only for a minority of primary SCC which pose special problems with regard to standard surgery, and for SCC with poor prognosis (recurring SCC or advanced SCC), where surgical treatment may be combined with radiotherapy to improve tumour control *(grade B)*.

When radiotherapy is indicated, it must be adjusted and modulated in accordance with:

- patient age, autonomy and distance from treatment centre;
- SCC site and size;
- availability and type of technical equipment provided by the radiotherapy unit.

Radiotherapy is not recommended as first-line treatment in the following cases (*professional consensus*):

- where surgical excision is possible;
- in certain areas such as hands, feet, legs or genital organs (with the sole exception of curietherapy for penile SCC).

Radiotherapy may be discussed in due course and proposed as first-line treatment in the following cases *(grade B)*:

- where surgery is not possible (contraindication, patient refusal);
- where surgery could cause major functional or morphological problems (nasal amputation, surgery of the internal ocular canthus, labial resection, commissural labial resection and extensive facial SCC with loss of substance or sacrifice of facial nerve), after the patient has been informed, and the advantages and disadvantages of each method have been discussed in terms of oncological, functional and morphological results.

Adjuvant radiotherapy is indicated in the following cases *(grade B)*:

- incomplete microscopic excision with no possibility of further surgery;
- SCC with extensive perineural invasion;
- metastatic lymph node invasion.

IV.4. Systemic chemotherapy in SCC

Chemotherapy is of limited value, being used only in cases of failed surgery or radiotherapy, where these treatments are

inadequate or have been undertaken too late. In the NHRMC guidelines, cisplatin is the reference chemotherapy. The literature on this subject is very scant and contains only a few small series along with numerous isolated cases.[162–163] The only controlled studies concern head and neck SCC (mouth, pharynx and larynx), but these cannot be fully assimilated to SCC.

Several different types of chemotherapy options exist.

IV.4.1. Preoperative (neoadjuvant) chemoreduction Neoadjuvant chemotherapy has been used in very large tumours to render them amenable to surgery. As the majority of studies have shown no improvement in tumour control or survival, this treatment method is rarely used.

Thermochemotherapy of an isolated limb has been proposed as neoadjuvant therapy instead of palliative systemic chemotherapy in advanced carcinomas of the limbs. The substances used are melphalan and doxorubicin, either alone or in combination with cisplatin. This method, that is technically very demanding, is possible only for highly trained teams, as it involves non-negligible regional risks (lymphoedema, phlebitis) that may on occasion be serious (arterial dissection, extensive cutaneous necrosis or super-infection). Combination of TNF-α and of IFN-γ with melphalan has produced spectacular improvement in response rates, allowing for local control and obviating amputation,[165] but with no improvement in overall survival.

IV.4.2. Adjuvant chemotherapy and chemo-radiotherapy Postoperative radiotherapy is a standard procedure for primary mucosal SCC of the head and neck with a poor prognosis (post-surgical residual tumour, multiple lymph node metastases, lymph node metastases measuring >3 cm or vascular/nervous invasion). It has resulted in high rates of local control and improved 5-year survival.

The results of studies involving combined treatment are not concordant. In a recent randomized controlled study, combined postoperative radiotherapy-cisplatin resulted in improved progression-free and global survival compared with radiotherapy alone.[166]

Recommendations

The literature contains insufficient data to allow for any recommendation to be made concerning the use of neoadjuvant chemotherapy or adjuvant chemotherapy in the treatment of SCC. Adjuvant thermochemotherapy by regional infusion in an isolated limb may be given for advanced SCC at treatment centres where this approach is possible, following discussion in IDC of the benefit/risk ratio, and once the patient has been fully informed *(professional consensus)*.

IV.4.3. Palliative chemotherapy and chemo-radiotherapy Palliative chemotherapy is reserved for forms of the disease which are inoperable from the outset due to loco-regional extension, and for metastatic forms. It may also be used in combination with radiotherapy, provided the patient's general health, which is often highly compromised, allows for this.

Drugs considered active in this case are cisplatin,[164] bleomycin, 5-fluorouracil, methotrexate and adriamycin. The highest response rates (around 80%) have been obtained with combined treatments such as combined cisplatin (D1, 100 mg/m^2), 5-fluorouracil (D1 to D5, 650 mg/m^2/d) and bleomycin (D1 to D5, 16 mg/m^2/d). Comparable results have been obtained by combining cisplatin or carboplatin with taxanes, gemcitabine or ifosfamide. Complete remission is rare and frequently transient. No studies have demonstrated increased survival for polychemotherapy compared with cisplatin alone.

Several studies and meta-analyses of combined therapy involving palliative chemotherapy-radiotherapy in mucosal SCC of the head and neck have exhibited superior survival rates in relation to radiotherapy alone, but at the price of increased toxicity (mucosal, neurological, gastrointestinal, medulla and renal). The drugs used were cisplatin alone, 5-FU/cisplatin, 5-FU/carboplatin and paclitaxel/carboplatin.[162,164,167–169]

IV.4.4. New therapies: cetuximab EGFR *(epidermal growth factor receptor)* is expressed in SCC of the face and trunk, as well as in lymph node metastases of SCC. Overexpression appears to worsen the prognosis. Cetuximab is a chimeric human and murine monoclonal antibody with strong affinity for EGFR, and inhibits cell maturation. Used in cancers of the respiratory/digestive tract and in metastatic colorectal cancer, the product is relatively well tolerated.

A randomized phase III study[170] involving 117 patients with metastasizing SCC of the oropharynx, lip, or face showed superior efficacy of combined cetuximab-cisplatin compared with cisplatin alone, but with no significant increase in duration of survival and at the price of inferior skin tolerability. In a non-controlled phase II study involving 103 patients with metastatic or recurring SCC of the head and neck, treated with cetuximab alone, the response rate was 13%.[171] More recently, an unpublished phase II study was presented at ASCO 2008 (Maubec *et al.* abstract no. 9042). In this trial, cetuximab monotherapy was used as first-line treatment in 31 patients (more than half of whom were aged over 60 years) presenting locally advanced or metastatic head and neck SCC expressing EGFR. The response rate was around 30%, with acceptable safety.

It is not currently possible to confirm that cetuximab represents a valuable therapeutic option, notably in patients for whom chemotherapy cannot be envisaged. It would be useful to assess the value of this drug in controlled studies.

Recommendations

The data in the literature are insufficient to allow for recommendation of palliative chemotherapy in advanced SCC other than in controlled clinical trials.

It may be proposed in IDC for inoperable forms from the outset due to loco-regional spread, and in metastatic forms, possibly in combination with radiotherapy, provided the patient's general health, which is usually highly compromised, permits this (*professional consensus*).

The use of monoclonal antibodies may constitute an interesting therapeutic option, but this approach is currently under evaluation.

V. Management of SCC and precursor lesions

V.1. Prevention

V.1.1. Primary prevention Onset of SCC is directly associated with sun exposure and is therefore dependent on latitude and lifestyle. The study of Australian immigrants showed that exposure during childhood and adolescence played an important role in the emergence of SCC. This underscores the significance of protection against sun exposure at these stages of life, although it is still necessary to limit sun exposure in adults. Prevention programmes must target school children and adolescents with emphasis on damage caused to the skin rather than on the risk of cancer.

As for the prevention of melanoma, information and advice aim to promote reasonable behaviour with regard to sun exposure along with suitable photoprotection,[101,102] which should be continued throughout life, particularly in patients at risk (light skin phototype, and professional or recreational sun exposure), by:

- avoiding exposure to the midday sun (between 11.00 am and 3.00 pm): 60% of the sun's daily energy reaches the earth during these times;
- remaining in the shade as much as possible;
- wearing protective clothing such as broad-brimmed hats, T-shirts, sunglasses, etc.

Sunscreens constitute a last line of protection: index higher than 20, broad-spectrum, water-resistant and applied every 2 hours. Sunscreens do not allow for exposure times to be increased.

Window glass of a thickness of 3 mm provides a protective index of 14 for UVB, but not against UVA.

The use of sun lamps and tanning cabins should be limited, as this does not reduce the risk, but rather increases the amount of radiation received.

V.1.2. Secondary prevention There is no consensus on routine screening in the general population, as this strategy has not been shown to reduce morbidity or mortality.

Patients with SCC form a group at high risk for further SCC. Fifty-two per cent of these patients will present another skin cancer in the ensuing 5 years. Thus, Trakatelli[101] recommends a 5-year monitoring in these at-risk patients, without providing information on monitoring intervals.

In Australia, it has been shown that promotion of strict sun protection reduces the appearance of AK and the risk of a new SCC (but not of BCC) in patients having already developed a SCC *(level 1)*.[103]

Recommendations (*professional consensus*)

Prevention of SCC and precursor lesions involves the following measures:

- protection of the skin by use of appropriate clothing and sunscreens during outdoor activities;
- spending as much time as possible in the shade at midday (11.00 am to 3.00 pm);
- wearing of broad-brimmed hats outdoors;
- avoidance of sunbeds, lamps and cabins;
- use of sunscreens does not allow for increased sun exposure times.

V.2. Screening and clinical diagnosis

Due to the frequency of SCC, doctors should be familiar with the clinical presentations of these tumours and should be attentive to their possible onset. We have no figures concerning accuracy of diagnosis by French doctors with regard to SCC. The NHMRC guidelines cite a study of Australian dermatologists indicating 39% accuracy for SCC,[6] which is far below that of 59% for BCC. The NHRMC guidelines conclude that diagnosis of SCC, particularly with regard to distinction from AK, appears clinically complex.

Most cases of SCC are observed in AK, with 50–60% occurring on the head and neck, and the rest distributed across sun-exposed areas in particular. Cases of SCC on chronic ulcers, scars, radiography lesions, in a setting of hidradenitis suppritiva[172] or even *de novo*, are rare.

Signs indicative of AK progression to SCC include sensitivity to palpation, appearance of an erosion or readily bleeding ulceration, extension and budding on the surface as well as deep infiltration. These changes are normally gradual and occur over a period of several months. Lesions appearing *de novo* have the appearance of a keratotic plaque, but on a previously normal area of skin.

Key points

If a lesion clinically evocative of AK is found, the therapeutic attitude may be resumed in the following four points:

- inform the patient that the lesion is considered to be a precursor of SCC, but that the risk of progression to SCC is very low;
- inform the patient that the lesion may be treated on an outpatient basis by means of simple, short-lasting, relatively non-invasive, inexpensive and effective therapy;

- inform the patient that the presence of this AK indicates a risk of skin cancer at the same site or on other skin areas, and that it is consequently necessary to examine the entire skin surface to ensure that there are no further suspect lesions;
- advise the patient to be attentive to the condition of their skin and to the appearance of any new lesions.

Recommendations

Screening for SCC is recommended after the age of 50, particularly in patients at risk as defined by the following criteria: light skin, high level of sun exposure, helioderma, previous history of skin cancer, radiotherapy, chronic ulceration, old scars, hidradenitis suppuritiva, etc. *(professional consensus)*.

The skin can be examined at any medical consultation, but the optimal frequency of such examination is not known.

Clinical diagnosis of incipient SCC is difficult: All AK showing signs of extension or persistence following adequate treatment should be investigated by histopathological examination *(professional consensus)*.

V.3. Role of biopsy

According to the NHMRC guidelines,[7] prior biopsy is useful in cases of clinically uncertain diagnosis where the choice of treatment may be guided by histological subtype or depth of invasion, and prior to extensive surgery in areas of cosmetic concern, to determine the spread of a clinically poorly delimited tumour (multiple biopsies).

Scalpel or punch biopsy should be performed to assess tumour depth (particularly before radiotherapy). Fragments obtained by curettage are less reliable indicators due to the destruction of tumoural architecture by this method.

When several biopsies are performed, samples should be clearly identified and forwarded to the laboratory in separate containers. The histological analysis of the biopsy sample should be compared with the study of resected tissue to establish the definitive result.

The BAD guidelines[9] recommend biopsy when there are clinical doubts or when specialized treatment is envisaged. The authors note that biopsy provides information on the histological subtype, which is of great value with regard to the prognosis.

According to the NCCN guidelines,[8] biopsy may be performed for all suspect lesions, as histological analysis is the only reliable basis for an unequivocal diagnosis.

Recommendations (*professional consensus*)

Histopathological examination is essential for diagnosis of SCC.

For clinically characteristic Group 1 SCC, excision may be performed at the outset, and histological confirmation be obtained on the excised tissue.

Biopsy is essential when:

- the clinical diagnosis is uncertain;
- the proposed treatment is not surgical;
- the envisaged surgery requires extensive reconstruction.

Partial scalpel or punch biopsy may be performed (professional consensus) and must be sufficiently deep so as to include the reticular dermis to allow for detecting any infiltration.

V.4. Treatment of SCC precursor lesions

V.4.1. Actinic keratosis (Table 9) Routine treatment of all AK to improve global survival or quality of life has not been shown to be universally advantageous. The WG nevertheless considers that patients should be offered treatment and be informed of the natural history of AK and of the different available therapies (depending on the specific medical setting).

The possibility of therapeutic abstention may be discussed for one or more typical forms of AK, depending on the patient's wishes, intercurrent medical or social difficulties, life expectancy and distance from treatment facilities *(professional consensus)*.

V.4.2. Bowen's disease (Table 10) For small lesions, surgical excision with minimal margins and histological control of the excision are recommended.

Where surgery is complex (extensive or multiple lesions or involving poorly healing areas), local chemotherapy with 5-FU cream, imiquimod cream or PDT may be envisaged, following verification of the diagnosis by means of biopsy.

Cryotherapy may be given on two conditions: verification of the diagnosis by prior biopsy and avoidance of poorly healing areas (legs and all other areas with precarious trophicity). Annual posttherapeutic clinical monitoring is recommended.

V.5. Management of infiltrating SCC

V.5.1. Histopathological analysis of samples Diagnosis of SCC may be made upon biopsy fragments or excised tissue. The histopathologist is responsible for processing of samples and confirmation of diagnosis.

V.5.1.1. Standard procedure

Macroscopic sampling of excised tissue is a compromise which provides acceptable reliability within the limits of feasibility, and at a reasonable cost. For this reason, techniques differ from one team to another. As no recommendations on this subject are given in the literature, the following proposals are based on a technical note published in 1997 by three French authors specializing in dermatopathology,[173] and concern macroscopic procedures for skin tumours.

Table 9 Summary of indications for AK treatment

	First-line	Second-line	Comments
Characteristics of AK			
Isolated or scant AK	Cryotherapy or PDT	5-FU, imiquimod, or diclofenac Diclofenac not reimbursed	Classification by unit cost
Multiple or confluent AK	5-FU	Imiquimod or PDT	Cryotherapy often poorly tolerated
Fine AK	Cryotherapy or diclofenac	5-FU, imiquimod, or PDT	Diclofenac not reimbursed
Hypertrophic AK	Biopsy recommended	Cryotherapy, where follow-up and biopsy are possible in the case of failure	
AK not responding to adequate treatment	Biopsy or excision recommended		
Site			
Crown, ears, nose, cheeks, and forehead	Cryotherapy, 5-FU	Imiquimod, PDT	
Periorbital areas	Diclofenac or cryotherapy	5-FU, imiquimod, or PDT	Inflammatory oedema with most treatments. Diclofenac not reimbursed
Confluent AK on crown	5-FU	Imiquimod or PDT	
Patient characteristics			
Patient with little autonomy	Cryotherapy	5-FU, imiquimod, or PDT, if nursing care available	Follow-up and care to be conducted by paramedical team
Single-phase treatment	Cryotherapy		
Patient far from monitoring treatment centre	Cryotherapy	5-FU, diclofenac, imiquimod	Paramedical desirable
Medico-economic considerations Cost/efficacy ratio by unit cost	Cryotherapy, 5-FU	Imiquimod, diclofenac, PDT	Classification by unit cost

This table summarizes the therapeutic options as a function of disease characteristics and lesions.
In the absence of comparative studies on the different treatments, the choices proposed below are based on the setting and on authors' evaluation of efficacy, ease of use, side-effects and treatment cost.

Table 10 Summary of indications for BD treatment

	First-line	Second-line	Comments
Characteristics of BD			
Isolated BD	Surgical excision	Cryotherapy, 5-FU, imiquimod or PDT	Surgery and cryotherapy should be avoided in poorly healing areas or areas of precarious trophicity. Post-therapeutic monitoring should be carried out for treatment when there is no histological verification of results
Multiple BD	5-FU, imiquimod or PDT	Surgical excision cryotherapy	
Large BD	Surgical excision	5-FU, imiquimod or PDT	Histological analysis of the whole lesion provides assurances on absence of invasive character
Hypertrophic BD	Surgical excision		
Site			
Poorly healing region	5-FU, imiquimod or PDT		Treatments without histological verification of the result require post-therapeutic surveillance. Cryotherapy should be avoided
Patient characteristics			
Patient with little autonomy	Cryotherapy	5-FU, imiquimod,or PDT	Surveillance and care by a paramedical team
Single-phase treatment	Surgical excision	Cryotherapy	
Far from care centre	Cryotherapy	5-FU, imiquimod	Surveillance by a paramedical team is desirable

This table summarizes the therapeutic options available as a function of patient and lesion characteristics.
In the absence of comparative studies on the different treatments, the choices expressed are based on the setting and upon the authors' evaluation of efficacy, ease of use, side-effects and treatment costs.

Role of the surgeon

The practitioner taking the sample must provide the following essential clinical information: patient gender and age, lesion site and information on progression and/or previous treatment (primary tumour, repeat surgery, local recurrence, etc.).

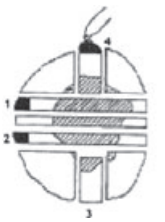
The orientation of the section must be indicated (suture, ink, incisions, etc.), and immediately forwarded to the histopathology laboratory, fresh and with a diagram. If the sample cannot be submitted immediately, it must be fixed. The best fixative is formaldehyde, which results in better preservation than alcohol-based fixatives with regard to proteins and nucleic acids.

Of note is that formaldehyde is a toxic product classified as a Group 1 carcinogen by the WHO. In France, since the 13 July 2006 Decree, all work involving exposure to formaldehyde is considered carcinogenic, and pathology laboratories must thus choose between using alternative fixatives (none of which are as effective as formaldehyde) and introducing extremely costly protective equipment and prevention policies.

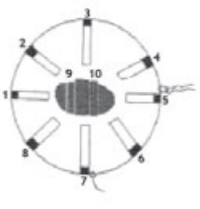
Role of the histopathologist

The histopathologist and laboratory technicians must work in compliance with good laboratory practice. Excised tissue must be described and measured (measurements made after fixation, are always lower than the actual dimensions due to tissue retraction). If the lesion is visible, it should be described or photographed and measured. The smallest macroscopic safety margin must be determined, with precise details of its site. Deep and lateral resection margins must be marked in ink. The orientation of samples must be indicated and may be represented in a diagram. Macroscopic sampling methods vary according to the size and topography of the biopsy sample or excised tissue:

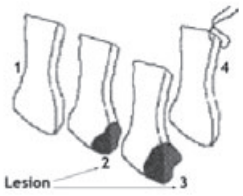
- size <0.5 cm: sample cut in half perpendicularly along the main axis of the piece, or included as a whole;
- size 0.5–3 cm: parallel sections perpendicular to the main axis of the piece. To view the extremities, each side may be finished with one or more sections perpendicular to the other sections (cruciform sample);
- size >3 cm: tumour sample perpendicular to the main axis, and samples radiating out from the centre in areas with narrow safety margins;
- excision of a lesion along a free edge (ear helix, eyelid, nostril or lip): cutting into parallel sections, perpendicular to the free edge with control of the outer face of the two distal sections.



Sections of excised tissue measuring between 0.5 and 3 cm



Sections of excised tissue > 3 cm



Sections of lesion located on an outer edge

V.5.1.2. Histopathology for exhaustive verification of margins

While standard macroscopic sample preparation in perpendicular sections provides adequate information when there is a standardized excision margin and the standard procedure has been followed, it enables viewing of only a small proportion of the surgical margin.

Micrographic surgery (MS) seeks to overcome this problem and allows for an exhaustive study of the margins by providing sectional planes parallel to the actual surgical section. F. Mohs was the first to describe this procedure involving extemporaneous examination of frozen sections (see section IV.2.2.1.).

Variations on the Mohs technique may be adapted for use by dermatologists, surgeons and pathologists in France, provided these acts, which are time-consuming for doctors, nurses and technicians, are better remunerated within the histopathology fee schedule. The technique in question is that of 'slow Mohs', in which peripheral skin is fixed (and not frozen), and exhaustive verification of the margins is carried out by sampling sections of the excised tissue, itself fixed or unfixed (Moehrle and Breuninger).[174] In all cases, a cardinal requirement of this method is close coordination between the operating theatre and the laboratory. Excision samples must be marked accurately using coloured ink markers. The orientation of the piece can be indicated in a drawing to aid communication between surgeon and pathologist. In the laboratory, the fragments are placed in a cassette with the information-bearing side (outer edge) facing downwards. The cassettes, carefully spatially identified, are labelled and, on inclusion, the orientation of the sample is scrupulously respected, so that all edges are represented in the section.

Recommendations

Histopathological analysis may be carried out on biopsy fragments or excised tissue.

Excised SCC matter must be labelled, and preferably accompanied by a diagram prior to submission to the histopathology laboratory.

Macroscopic analysis must provide details on sample size, tumour size and excision margins, whereas edges must be inked.

The reference fixative is formaldehyde, but careful consideration of procedures is necessary when using this product because of its carcinogenic potential.

In classical surgery, macroscopic sampling depends on sample size and should seek to provide as much information as possible.

The WG would like to see micrographic methods used in the management of Group 2 SCC, where verification of the peritumoral edges is essential *(professional consensus)*, but this would imply higher remuneration for these procedures in the medical fee schedule.

V.5.1.3. Histopathology report

No standardized report format is given in the NHMRC, NCCN or BAD guidelines. The purpose of this section is to propose a standardized report format containing the items essential for good patient management (Table 11).

The need for standardization is demonstrated by a study showing (and confirming what is seen in common practice) that SCC histology reports do not always contain the information needed for prognostic assessment (size, thickness, level of invasion, cytological grade, morphological variants, etc.).[175] The method used to evaluate excision margins must be stated (specified) in the report. It is vital to indicate that excision is incomplete, should this be the case.

However, some discussion is needed concerning **measurement of histological margins**: The classical macroscopic sampling method does not allow surgeons to examine all edges, and this measurement could therefore lull surgeons into a false sense of security. The term 'complete excision' should in any case not be used in histopathology reports, and measurement of margins, which is in all probability underestimated due to retraction caused by excision and fixation, should be accompanied by a statement that this measurement concerns only the sections examined and nothing else.

V.5.2. Initial staging

Staging is carried out following diagnosis of malignant tumour to ascertain locoregional and distant disease spread.

V.5.2.1. Issues at stake

The risks of progression to which patients are exposed following initial diagnosis are of two types:

- local recurrence or regional or distant metastasis, where risk depends on different prognostic criteria;
- appearance of another SCC or another tumour, such as BCC or melanoma.

The incidence of metastatic SCC is low. In the study by Rowe *et al.*[83] involving 71 published series from various disciplines (dermatology, ENT, plastic surgery and oncological surgery, pathology and radiology), the rate of metastases was 2.6% for studies with a follow-up of less than 5 years and 5.2% for studies with follow-up of more than 5 years. The higher figures, of 7.4% and 9.9%, respectively, quoted by two surgical teams, one carrying out Mohs micrographic surgery,[92] and the other involved in ORL operations,[176] are attributable to the fact that these teams treated patients with a higher risk for metastasis.

Extension of SCC may occur locally by adjacent spread along fascias, periostea, perichondria or vascular and neuronal sheaths. Locoregional dissemination (lymph node metastases or in-transit metastases) accounts for 80% of metastatic sites.[92] Mean time to onset after initial therapy is 12–24 months.[9] As the main site of SCC is the head-and-neck region, the local lymph nodes most often involved are the submental, submandibular and intraparotid lymph nodes, and it is therefore essential to ensure that methods are in place for early detection of lymph node metastases in patients with high-risk SCC.

The **key questions** are:

1 Is staging necessary at the time of diagnosis?
2 If so, how should staging be carried out?
3 What type of follow-up is required, at what intervals and with what aims?

The answers to these questions suppose determination of the diagnostic value of the various clinical and laboratory examination methods employed.

V.5.2.2. Diagnostic value of examination methods

Clinical examination

Clinical examination is of limited efficacy in the detection of lymph node metastases. In the study of advanced SCC by Friedman *et al.*,[177] the sensitivity of clinical examination was 71.7% compared with 91.1% for computerized tomography (CT) and magnetic resonance imaging (MRI).

Imaging methods

While undeniable progress has been made in the detection of SCC metastases, the choice of the most effective examination continues to be debated.

Ultrasound is the least costly examination, and has been shown to be superior to clinical examination in terms of sensitivity and specificity. The efficacy of ultrasound is strictly dependent on the operator, as well as the equipment and analytical criteria used. In a study comparing the criteria of ultrasound analysis [lymph node size, ratio of longitudinal/transversal size (L/T), presence or absence of echogenic hilum and cortical appearance], the combination of absence of hilum with a high L/T ratio exhibited the greatest specificity (97%), with a positive predictive value of 93%.[178]

However, the results of comparative studies on the efficacy of different examination techniques are not unanimous. Several studies have shown ultrasound to be superior or equivalent to CT and superior to MRI in detecting subclinical lymph node metastases in head and neck SCC. Current ultrasounds combining Doppler function (for assessment of vascularization) and 3D greyscale imaging have an advantage over other methods, as they allow physicians to detect metastatic lymph nodes of 3–4 mm.[179,180]

In a prospective study, CT, MRI, positron emission tomography (PET) and ultrasound, all carried out in association with systematic curettage, were compared in terms of sensitivity, specificity, positive predictive value, negative predictive value and reliability with regard to histopathological analysis of curettage shavings. No significant difference was observed between ultrasound and CT. Ultrasound was superior to MRI and PET, but the negative predictive value for all four techniques was too low (75.6% for ultrasound) to be considered reliable.[181]

Table 11 Proposed standardized report format *(professional consensus)*

MACROSCOPY						
Sample:	Orientation	...	suture ...,	cork ...,	diagram ...,	other ...
	No orientation	...				
	Sample size: ... cm		not evaluable ...			
Lesion:	Flat ..., nodular/in relief ..., verrucous ..., ulcerated...			ulcerovegetative ...		
	Lesion size (largest diameter):		... cm			
Macroscopic margins:	Minimum lateral margin:		... mm	not evaluable ...		
	Minimum margin area (diagram): not evaluable ...					
Macroscopic sample method for edges:						
- Standard: ...						
If yes, number of transverse/longitudinal sections (diagram):						
- Circumferential: Breuninger: ...; ''*slow* Mohs'': ...						
If yes, was exhaustive measurement made of tumour depth?: yes ..., no ..., (diagram) - Mohs surgery...						
Frozen in tumour sample library:		yes ..., no ...				
HISTOPATHOLOGY Free description:						
Histological type:	Common SCC	...				
	Verrucous	...				
	Mixed (basosquamous)	...				
	Spindle	...				
	Acantholytic	...				
	Mucoepidermoid (adenosquamous) ... Desmoplastic					
Differentiation:	Well differentiated	...				
	Moderately differentiated...					
	Poorly differentiated	...				
	Undifferentiated	...				
Maximum tumour thickness		... mm				
Level of dermal invasion: <4 ..., 4 ..., 5 ... or more ...						
Vascular emboli:		present ...	absent ...			
Perineural sheaths:		present ...	absent ...			
Associated with: Keratosis:			yes ...	no ...		
Carcinoma *in situ* (Bowen's disease):			yes ...	no ...		
Excision includes healthy tissue:			yes ...	no ...	Not evaluable ...	
Margins: Minimum lateral margin			... mm			
Minimum deep margin			... mm			
Conclusion						

For standard macroscopic sampling of margins, specify that the stated margin measurements refer only to the sections actually examined.

In another comparative study,[124] 60 patients with head-and-neck SCC were investigated using PET, MRI, CT and ultrasound, in association with cervical curettage. Histopathological analysis was carried out on 1,294 lymph node biopsy samples, of which 117 were metastatic. Upon verification of these results against those obtained with imaging, PET exhibited significant advantages in terms of sensitivity (90%) and specificity (94%), revealing smaller metastases than CT, MRI or ultrasound.

A recent review[182] recommends PET for monitoring of head-and-neck carcinomas, 1–2 months following surgery and 2–6 months after chemotherapy to detect, and possibly assess persistence of tumours or relapse, either locally or remotely.

Global figures are affected by variations in efficacy according to the different tissues and lesion types explored. In a study comparing MRI and CT scans in patients with cervical lymph node metastasis[183,184] from SCC, CT appeared to be the best method for detecting central lymph node necrosis, extracapsular spread, invasion of the base of the skull and cartilage involvement, whereas MRI was more effective in screening for neurotropism and in distinguishing between different levels of tissue involvement. In another study, PET resulted in better detection of metastases within areas of necrosis or of scar fibrosis following radiotherapy, whereas CT and MRI were more sensitive in detecting bone erosion and mild soft tissue infiltration.[185]

Sentinel lymph node detection and biopsy

This method has been dealt with in only a few retrospective publications and in two recent systematic reviews,[186,187] one of which

included 85 patients, and the other 83 patients (incorporating 22 previously unpublished cases). These studies show that the method allows for diagnosing subclinical lymph node metastases with few false negatives and low morbidity. In the case of a positive result, so-called selective lymph node curettage is performed, but there is as yet, no clear evidence of the survival value of selective curettage guided by sentinel node biopsy.

Recommendations (*professional consensus*)

Initial work-up.

The majority of patients treated for SCC are cured by initial therapy.

For *in situ* carcinomas and low-risk SCC (Group 1 of the prognostic classification), no laboratory examinations are warranted.

Clinical examination must include inspection of the entire skin surface to screen for further carcinomas, along with evaluation of phototype and helioderma, palpation of drainage lymph node areas, and a general clinical evaluation.

For primary carcinomas considered at risk (Group 2 of the prognostic classification): Complete clinical examination must be performed (see above). Locoregional ultrasound examination of the drainage area (echogenicity study of the hilum) should be performed (*professional consensus*).

Other examinations are only warranted in the event of evocative clinical signs or upon IDC decision due to the presence of certain risk criteria.

The sentinel node procedure may be envisaged for clinical trials and evaluation studies.

V.5.3. Therapeutic management of SCC

V.5.3.1. Geriatric aspects of management

The vast majority of SCC cases are seen in elderly patients. The elderly population is heterogeneous, and chronological age alone does not constitute a decisive criterion on which to base diagnostic and therapeutic decisions. For elderly patients, an overall evaluation is essential to ensure proper adaptation of anti-cancer treatment to individual patients.

Overall geriatric evaluation (OGE),[188] which should in practice be carried out by a multidisciplinary team, is a standardized and valid evaluation scale that takes into consideration the patient's somatic, psychological and social status.[189] Versions of this scale more specifically for use in oncology have been proposed, but have not yet been validated.[188]

This evaluation takes into account the following parameters: concomitant diseases (high incidence of chronic diseases; risk factors for organ failure on initiation of chemotherapy), physical and mental independence, mobility (relating to both motor autonomy and patient's social and familial environment, with potential impact on treatment compliance), existence of cognitive disorders, nutritional status as well as laboratory status (hypoalbuminaemia; anaemia).

The OGE scale allows for classifying patients into three groups based on fragility criteria[188,190–192]:

- patients ageing well, who are totally independent, with little or no detrimental effect of ageing on functional capacity. These patients represent over half of patients aged between 70 and 75 years, and almost a quarter of those aged 80–85 years. Their life expectancy is higher than that of their age group, and they are likely to benefit from optimal cancer management to a comparable extent than young adults (Group 1);
- 'fragile' patients in terms of geriatric evaluation. Such patients have a lower life expectancy than their age group and are at high risk of poor treatment tolerability as a result of impaired organ function (Group 3). In most cases, treatment should focus on patient comfort and short-term quality-of-life goals;
- an intermediate group of vulnerable patients in whom geriatric evaluation is essential to ensure suitable and effective cancer therapy (Group 2).

For elderly cancer patients, the choice of treatment and treatment modalities should be based upon prior evaluation of the patient's somatic, psychological and social status and on any fragility criteria detected during this evaluation.

V.5.3.2. Primary forms of infiltrating SCC

Any attempt to derive therapeutic guidelines from the literature concerning SCC faces two problems:

- the low number of controlled clinical trials;
- the lack of precision, in many studies, as to the prognostic data from the cases analysed.

The following proposals are based on *professional consensus:*

- *Patients should be informed,* prior to any surgical act, by means of a preoperative visit that must meet the criteria for an information consultation;
- *SCC with Group 1 clinical criteria* (low risk of recurrence or metastasis).

The recommended treatment is surgical resection of the lesion with a *standardized lateral margin of 4–6 mm from the clinical borders and a deep hypodermic margin*, followed by standard histopathological control of the edges of an oriented tissue section removed during surgery.

If there is any uncertainty concerning the diagnosis, a prior biopsy sample of adequate size for diagnostic confirmation (punch ≥4 mm) is recommended. Surgical excision of the lesion may be carried out subsequently with margins suitable for Group 1.

In the event of positive margins (incomplete excision), further surgery comprising either standard surgery under the same conditions (margin: 5 mm) or micrographic surgery is essential.

If the sample obtained during surgery shows *histological criteria suggesting reclassification of the carcinoma as Group 2*, subsequent therapy should be discussed with IDC.

• *SCC with Group 2 clinical criteria* (significant risk of recurrence or metastasis): discussion with IDC is recommended.

The following algorithm is proposed:

Prior partial biopsy of adequate size (punch ≥4 mm) for diagnostic confirmation.

Surgical excision is the reference treatment with standardized lateral margins ≥6 mm (or even ≥10 mm) and a deep margin within the area not infiltrated by the tumour.

For reconstruction with closure involving a skin flap, it is advisable to ensure prior confirmation of complete excision by means of histological examination of the excised lesion, whether extemporaneous or delayed (two-stage surgery), using standard or micrographic techniques.

An IDC opinion may be requested, either preoperatively, to decide on the therapeutic approach to be adopted, or following surgery (and after histology results have been obtained), to validate the therapeutic approach.

When prognosis is poor, IDC discussion is recommended so as to determine margin size, histological control procedure for lesion edges (standard or micrographic), the type of reconstruction needed and whether additional treatment is required or not, and if so, the modalities thereof.

When surgery is impossible (medical contraindication or patient refusal) or carries a risk for functional disorders or major morphological problems due to the lesion site and size:

The therapeutic approach should be discussed in IDC after the patient has been fully informed of the advantages and disadvantages of the available therapeutic options:

- high-energy external radiotherapy: electron therapy;
- interstitial curietherapy with iridium192 in regions of complex geometry, e.g. periorificial (lips or eyelids), nasal groove or retroauricular groove;
- combined radiotherapy–chemotherapy;
- thermochemotherapy of a single limb as neoadjuvant or palliative treatment.

Post-therapeutic monitoring: see section V.5.4.

- SCC with residual tumour or low probability of complete tumour control by surgery.

First ensure that further surgery is not possible.

Additional treatment should be discussed in IDC:

- radiotherapy;
- tumour reduction chemotherapy followed by surgery and/or radiotherapy;
- cetuximab.

V.5.3.3. Treatment of metastatic SCC

Local (in-transit) metastases

The presence of clinically observable metastases around primary or recurring SCC warrants surgical excision when the number, size, extension and site of lesions are all consistent with the use of macroscopically healthy clinical margins. The possibility of adjuvant radiotherapy should be discussed (*see below*) *(professional consensus)*.

Lymph node involvement

Lymph node involvement is seen in high-risk SCC as defined earlier.[39,55–57,59,60]

Routine preoperative screening should be performed for lymph node involvement in the event of SCC with poor prognosis.

Ultrasound and/or CT examination are essential when there is clinical suspicion of lymph node metastasis.

Histological control of a surgical biopsy sample is required for all cases of suspected adenomegaly, whether clinically evident or identified using imaging techniques[193] *(professional consensus)*.

N- SCC: the WG advises against routine lymph node curettage if clinical extension results are negative.

Options for high-risk SCC that may be discussed in IDC:

- ultrasound analysis of drainage regions by an experienced radiologist;
- sentinel lymph node procedure in controlled studies;
- selective curettage for positive sentinel lymph nodes.

N+ SCC: **curative treatment consists of complete lymph node curettage** followed by histological analysis of all lymph nodes detected macroscopically in the excised tissue.

The report must indicate the total number of lymph nodes examined, and both of the following relevant prognostic factors:

- number and size of infiltrated lymph nodes;
- presence or absence of ruptured capsules.

Adjuvant radiation therapy may be discussed in IDC following deliberation of the curettage histopathology report:

- moderate metastatic invasion (single micrometastasis or macrometastasis) without ruptured capsule: no additional treatment other than complete curettage;
- extensive metastatic invasion () when curettage appears incomplete or doubtful: adjuvant radiotherapy of the sentinel lymph node is indicated (*professional consensus*).

Distant metastasis

Palliative treatment should be given.

The following therapeutic options should be discussed in IDC: surgery, when the metastasis is accessible, radiotherapy or chemotherapy.

V.5.4. Post-therapeutic monitoring

Selecting a monitoring strategy

The purpose of monitoring SCC patients is to ensure the earliest possible diagnosis of either curable recurrences or of further *de novo* SCC. There is no evidence that regular monitoring of high-risk SCC, allowing for early detection of metastases, results in early treatment and thus better survival. There have been no studies specifying optimal monitoring strategy, and there is no data defining the profile of patients likely to derive benefit from such monitoring. However, as 95% of local recurrences and 95% of metastases are detected within 5 years,[9,83] it seems reasonable to monitor patients with SCC at risk for recurrence throughout this period.

In the absence of studies dealing specifically with the format, value and frequency of monitoring, no evidence-based conclusions may be drawn from the literature, and the following recommendations are thus based solely on expert consensus.

Clinical examination

Clinical examination is the fundamental method: It may be repeated at all medical visits. It is straightforward and allows for detecting locoregional recurrence. Ideally, it should be supplemented by patient self-examination.

There is no justification for routine recourse to more sophisticated examinations in the absence of clinical signs in the majority of patients following excision of an SCC carrying a good prognosis.

In these circumstances, it is reasonable to restrict monitoring chiefly to clinical examination and patient instruction in self-examination.

Lymph node ultrasound

This risk-free and relatively inexpensive technique is warranted for the monitoring of high-risk SCC due to its high sensitivity and specificity when carried out by an experienced radiologist. Repeated CT and MRI investigations to identify occult metastases are of little value, and the WG suggests that these investigations be performed only in patients with factors indicating poor prognosis or in the event of suspect clinical signs.

Cervical-thoracic-abdominal-pelvic CT

Due to cost and availability, this is the fundamental examination for tumour-spread carried out in the event of recurrence and before inclusion of patients in clinical trials. It allows for detecting parenchymatous and lymph node involvement (provided lymph node sites to be investigated are included in the scanned area).

MRI

This method is superior to CT for the detection of cerebral, hepatic and bone metastases.

PET-FDG

The efficacy of this technique, which is increased by combining PET-FDG with CT (with or without injection), is superior to that of standard imaging in the detection of distant metastases, except for cerebral metastases (where MRI is superior) and pulmonary metastases (where CT is superior). It enables appropriate treatment of patients at high and very high risk, as it allows for more reliable staging, with only one staging examination required for the entire body. For instance, it allows for lymph node surgery to be ruled out in the case of remote metastases.

Recommendations

Monitoring.

***In situ* carcinoma and prognostic *Group 1 SCC*.**

Clinical examination once yearly.

Patient instruction in self-examination and detection of recurrence.

No laboratory tests or additional imaging in the absence of suspect signs.

Prognostic Group 2 SCC

Clinical examination, every 3–6 months for 5 years, according to prognostic criteria, and then for a period determined in relation with severity criteria.

Patient instruction as for prognostic Group 1 SCC.

Loco-regional ultrasound of the drainage area by an experienced radiologist every 6 months for 5 years.

For suspect clinical signs: cervical-thoracic-abdominal-pelvic CT + lymph node areas ± cerebral or PET/CT and/or cerebral MRI.

***N+ SCC*:** postsurgical or post-therapeutic monitoring combined with screening for loco-regional recurrence or distant metastases using ultrasound, PET, CT or MRI. The type and frequency of examinations should be deliberated in IDC depending on the clinical context.

V.6. Management of keratoacanthoma

V.6.1. Surgery The recommended surgical treatment upon detection of a lesion clinically evocative of keratoacanthoma is complete excision *(professional consensus)*.

Recommendations

The WG recommends that pathologists should only make a diagnosis of keratoacanthoma when they are able to evaluate the architecture of the entire lesion in the excision sample. The WG considers oncological excision to be justified in atypical cases. In typical cases, surgical excision is preferable to a wait-and-see approach *(professional consensus)*.

In clinically atypical cases (deep infiltration, central ulceration or absence of regression) or histologically atypical cases (difficulty in distinguishing from well-differentiated SCC; crateriform architecture), oncological excision is justified when any doubt exists.

V.6.2. Medical or physical treatment The treatment of choice for keratoacanthoma is surgical excision, but alternative approaches have been suggested in several publications. Chemotherapy involving intralesional injection of methotrexate, 5-fluorouracil or even interferon-α II, was successfully used in open studies in small patient series.[194–198] While such injections are apparently painful,

in these series of patients, regression occurred after a mean of three sessions, with high-quality cosmetic results obtained on lesions in sensitive sites (nose or lips). The retrospective study by Annest *et al.* in 38 patients treated by intralesional methotrexate injection showed a 92% success rate following a mean of 2.1 injections.[195]

Recommendations

The current data are insufficient to support any recommendations concerning local chemotherapy for keratoacanthoma.

The WG advises against any treatment for keratoacanthoma which does not allow for histological control in the absence of certainty as to the clinical criteria required for diagnosis.

VI. Quality criteria for improved practice

In a bid to improve quality, the WG proposes quality criteria for one of the key aspects of these recommendations, notably the management of primary SCC (comprising both prognostic classification and treatment).

Evaluation may consist of either targeted clinical audit or monitoring of indicators using randomized records of patients treated for primary SCC.

Assessment should be based on the risk criteria set out in Table 6 for the prognostic classification of SCC.

VI.1. Evaluation of prognostic classification of primary SCC

Traceability of the five clinical risk criteria in the patient's medical file.

Traceability of the five histopathological risk criteria in the histopathology report.

Traceability of classification of Group 1 SCC (low risk) or Group 2 (significant risk).

Degree of correspondence between classification of the patient in Group 1 or 2 with the classification recommended in the present guidelines (Table 6).

Number of cases of Group 2 SCC examined in IDC.

VI.2. Evaluation of management of primary SCC

Traceability of the excision margin in the patient file. Coherence between the margin recorded in the file and that recommended in this guideline (Group 1: margin >4 mm; Group 2: margin >6 mm).

VII Perspectives

VII.1. Updating of the guidelines

The use of the ADAPTE method did not enable the WG to significantly reduce the amount of time needed to prepare these guidelines. The drafting time included relatively constant times required for administrative and labelling steps. The latest bibliographical update will therefore be 1-year old upon publication of these guidelines. Such difficulties are frequently encountered in the drafting of papers of this kind, and the WG is fully aware of the need to reassess the literature concerning SCC and precursor lesions in the months following publication of the guidelines to ensure continuing scientific relevance.

The method selected by the WG is as follows:

- updating of bibliographical and documentary sources in the autumn of 2009 (then once yearly at the same period);
- critical review of the recent literature by a WG subgroup comprising a representative of each of the medical and surgical specialties involved;
- the impact of these guidelines on practice must be evaluated at the same time (modifications resulting from this text, intentions regarding practice, assessment of diagnostic procedures, etc.), and the SFD is able to carry out such evaluations.

VII.2. Perspectives for future studies

The creation of these recommendations has brought to the attention of the WG the mediocrity of medical and scientific literature on SCC, which is not a rare medical problem. In the body of the text, the WG has listed a number of crucial points that must be resolved through adequate studies to ensure improved management of patients with SCC or precursor lesions.

These various points are summarized below:

- the WG recommends the adoption of epidemiological tools enabling more precise evaluation of the incidence and cost of SCC;
- evaluation of morbidity and impairment of quality of life is needed regarding SCC patients;
- aspects of geriatric management require further development;
- the public health benefits of SCC screening must be evaluated;
- prospective studies are required to define independent predictive factors that may be used to adapt therapy to the intrinsic prognosis of each SCC. This requires systematic recording by clinicians and histopathologists of the prognostic factors set out in these guidelines;
- controlled prospective studies comparing the efficacy of standard surgery with that of micrographic surgery are required;
- the WG deeply regrets the fact that the low rate of remuneration for examination by histopathologists of excision samples from micrographic surgery currently prevents using this procedure in France in cases where it would be useful, namely in the treatment of Group 2 SCC and particularly in situations where compliance with the standard margins poses reconstruction problems;
- controlled studies are required to assess the value of the sentinel node technique, as well as the role of chemotherapy, particularly targeted chemotherapy.

VIII General conclusion

Squamous cell carcinoma and its precursor lesions (actinic keratosis and Bowen's disease) are extremely common in the French population, and their incidence is set to rise in coming years as a result of ageing of the population and increased sun exposure.

The WG's aim was to propose recommendations allowing for better management of these lesions throughout the course of therapy by insisting on the importance of diagnosis and optimal therapeutic management of the most aggressive types of potentially life-threatening SCC.

Primary prevention and screening of SCC and precursor lesions is incumbent on all doctors and, in particular, general practitioners, geriatricians, occupational therapists and dermatologists. It is based on identification of patients at most risk, on repeated explanation of simple measures to avoid excessive sun exposure, and on repeated examination of the skin. Secondary prevention of SCC and of precursor lesions is the duty of the same practitioners. Identification of any lesion thought to be an SCC precursor should prompt discussion with a dermatologist regarding treatment methods. When a lesion thought to be SCC is positively identified, a dermatologist or surgeon should be contacted to carry out a biopsy or an excision-biopsy to confirm the diagnosis and collect clinical and histological prognostic factors.

Treatment of actinic keratosis should be proposed routinely. The literature analysed for the present recommendations suggests no clear advantage of physical therapy over topical drug therapy. The choice must be based upon characteristics of the patient and the type of lesion(s) to be treated.

For Group 1 SCC (exhibiting all the clinical and histological criteria indicative of good prognosis), the dermatologist or surgeon must inform the patient of the diagnosis and of the proposed treatment, which generally involves surgery with excision margins of around 5 mm.

For Group 2 SCC (presenting at least one clinical or histological criterion of poor prognosis), following announcement of the diagnosis, it is recommended that the opinion of an IDC in skin cancer be sought. This opinion may be given after the start of treatment, particularly surgery. Again, surgical excision constitutes the first-line of therapy, with margins of 6–10 mm or more, possibly involving reconstruction surgery, either in a single stage or in two stages, once the definitive histology results have been received. Use of additional treatment (e.g. radiotherapy) should be discussed in IDC.

Monitoring of SCC under treatment is not only the responsibility of the dermatologist or surgeon but also of the treating physician, the geriatrician or any other doctors responsible for care of the patient. The aim is to ensure identification of any SCC relapse, whether local, affecting lymph nodes or distant.

Histological analysis of any relapse should be carried out, and treatment should be decided by the skin cancer IDC.

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X. Annexes

Annex 1: Levels of evidence and grades of recommendations (HAS)

Scientific levels of evidence provided by the literature (therapeutic studies)	Grade of recommendations
Level 1 A Established scientific proof (**LE1**)	
Randomized comparative studies of high statistical power	**A**
Meta-analysis of randomized comparative studies	Established scientific proof
Analysis of decisions based on well-conducted studies	
Level 2 B Scientific presumption (**LE2**)	
Randomized comparative studies with low power	**B**
Well-conducted, non-randomized comparative studies	Scientific presumption
Cohort studies	
Level 3 C Low level of evidence (**LE3**)	
Case control studies	**C**
Level 4 C Low level of evidence (**LE4**)	Low level of evidence
Comparative studies with marked bias	
Retrospective studies	
Case studies	

Annex 2: Summary table of declarations of conflicts of interest

	Presence of conflicts of interest	Absence of conflicts of interest
Prof. C. Beauvillain		X
Mrs J. Brugneaux		X
Prof.J.-F. Chassagne		X
Prof. P. Clavère		X
Prof. J.-L. Grolleau		X
Dr M. Grossin		X
Dr L. Martin		X
Dr J.-F. Sei		X
Prof. J.-J. Bonerandi		X
Dr L. Caquant		X
Dr V. Chaussade		X
Dr C. Desouches		X
Prof. F. Garnier		X
Dr A. Jourdain		X
Dr J.-Y. Lemonnier		X
Dr H. Maillard		X
Dr N. Ortonne		X
Dr E. Rio		X
Dr E. Simon		X

Annex 3: Search sources and strategy

Search sources *Bibliographical databases searched*

Medline (*National Library of Medicine*, US)

INIST (databases of the French *Institut de l'Information Scientifique et Technique*)

French public health databases (ENSP, France)

Other sources consulted

Useful websites (government agencies, learned societies, etc.) were consulted, but not all yielded useful results (*NB:* URLs were checked on 17 December 2008).

The Cochrane Library <http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/AccessCochraneLibrary.html> (consulted in June 2007)

NICE (National Institute for health and Clinical Excellence) <http://www.nice.org.uk/> (consulted in June 2007)

SIGN (Scottish Intercollegiate Guidelines Network) <http://www.sign.ac.uk/> (consulted in June 2007)

AFSSAPS (Agence Française de sécurité sanitaire des produits de santé) <http://agmed.sante.gouv.fr/> (consulted in June 2007)

ICSI (Institute for Clinical systems improvement) <http://www.icsi.org/guidelines_and_more/index.aspx?catID=12> (consulted in June 2007)

CADTH (Canadian Agency for Drugs and Technologies in Health) <http://www.cadth.ca/> (consulted in June 2007)

SCHIN (Sowerby Centre for Health Informatics at Newcastle) <http://www.schin.co.uk/> (consulted in June 2007)

Site of the AF Lemanissier medical library <http://www.bmlweb.org/consensus.html> (consulted in June 2007)

CMA Infobase – Clinical Practice Guidelines (Canadian Medical Association) <http://mdm.ca/cpgsnew/cpgs/index.asp> (consulted in June 2007).

NGC – National Guideline Clearinghouse <http://www.guideline.gov/> (consulted in June 2007)

Guidelines International Network <http://www.g-i-n.net/> (consulted in June 2007)

New Zealand Guidelines Group <http://www.nzgg.org.nz/index.cfm/> (consulted in June 2007)

Guidelines Advisory Committee <http://www.gacguidelines.ca/> (consulted in June 2007)

Reigister of good practice recommendations & French-language consensus conferences – Rouen University Hospital <http://www.chu-rouen.fr/cismefbp/> (consulted in June 2007)

ASCO (American Society of Clinical Oncology) <http://www.asco.org/portal/site/ASCO/> (consulted in June 2007)

Fédération Nationale des Centres de Lutte Contre le Cancer <http://www.fnclcc.fr/> (consulted in June 2007)

National Comprehensive Cancer Network <http://www.nccn.org/default.asp> (consulted in June 2007)

Anticancer department, Ministry of Health and Social Services of Quebec

EBM Online Review <http://ebm.bmj.com/> (consulted in June 2007)

''Clinical Evidence'' journal <http://clinicalevidence.bmj.com/ceweb/index.jsp> (consulted in June 2007)

Search strategy The Medline search strategy gives the search terms used for each subject and the date of the search. The terms are either those used in a thesaurus (MeSH descriptors) or terms used in titles or abstracts (free text). They were combined using the operands ''AND'' and ''OR''. The different searches and the number of references found are shown in tabulated form. The languages used were French and English.

Recommendations for squamous cell carcinomas and cutaneous keratoses	
(''Keratosis'' [MeSH] OR actinic keratos* [All Fields] OR ''Carcinoma, Squamous Cell'' [MeSH]) AND (''Skin'' [MeSH] OR ''Skin Diseases'' [MeSH])	July 2007 79 ref.
AND (practice guideline [Publication Type] OR practice guidelines [MeSH Terms] OR guideline [Publication Type] OR guidelines [MeSH Terms] OR guideline* [Title] OR recommendation* [Title] OR recommandation* [Title] OR ''Evidence-Based Medicine'' [MeSH] OR ''Consensus'' [MeSH] OR ''Consensus Development Conferences'' [MeSH] OR ''Consensus Development Conference'' [Publication Type]	
OR ''meta-analysis'' [Publication Type])	
Recommendations for squamous cell carcinoma of the lips and eyelids	
(Epidermoid* [All Fields] OR actinic keratos* [All Fields] OR ''Carcinoma, Squamous Cell'' [MeSH] OR ''Keratosis'' [MeSH])	July 2007 79 ref.
AND (''Lip'' [MeSH] OR ''Lip Diseases'' [MeSH] OR ''Eyelids'' [MeSH] OR ''Eyelid Diseases'' [MeSH])	
AND (practice guideline [Publication Type] OR practice guidelines [MeSH Terms] OR guideline [Publication Type] OR guidelines[MeSH Terms] OR guideline*[Title] OR recommendation*[Title] OR recommandation* [Title] OR ''Evidence-Based Medicine'' [MeSH] OR ''Consensus'' [MeSH] OR ''Consensus Development Conferences'' [MeSH] OR ''Consensus Development Conference'' [Publication Type]	
OR ''meta-analysis'' [Publication Type]) July 2007 7 ref.	
Epidemiological data on cutaneous squamous cell carcinoma	
(''Carcinoma, Squamous Cell/epidemiology'' [MeSH] OR ''Carcinoma, Squamous Cell/mortality'' [MeSH] OR ''Carcinoma, Squamous Cell/statistics and numerical data'' [MeSH]) AND (''Skin'' [MeSH] OR ''Skin Diseases'' [MeSH])	Dec. 2007 315 ref.
Limits: Publication Date from 2000/01/01, English, French	
Therapeutics	
Keratosis/diclofenac and keratosis	
(''Keratosis'' [MeSH] OR keratosis[All Fields])	Dec. 2007 51 ref.
AND (''Diclofenac'' [MeSH] OR diclofenac [All Fields] OR solaraze [All Fields]) Limits: English, French	
Fluorouracil/Epidermal Growth Factor Receptor for squamous cell carcinoma and keratosis	
(''Fluorouracil'' [MeSH] OR ''Receptor, Epidermal Growth Factor'' [MeSH])	Dec. 2007 483 ref.
AND (''Keratosis'' [MeSH] OR ''Carcinoma, Squamous Cell'' [MeSH])	
AND (''Skin'' [MeSH] OR ''Skin Diseases'' [MeSH])	
AND (English [lang] OR French [lang])	
Mohs Surgery/imiquimod/photochemotherapy for squamous cell carcinoma, keratoacanthoma and keratosis	
(''Carcinoma, Squamous Cell'' [MeSH] OR ''Keratoacanthoma'' [MeSH] OR ''Keratosis'' [MeSH]) AND (''Skin Diseases'' [MeSH] OR ''Skin'' [MeSH])	Dec. 2007 651 ref.
AND (''Mohs Surgery'' [MeSH] OR ''imiquimod'' [Substance Name] OR ''Photochemotherapy'' [MeSH]) AND (English [lang] OR French [lang])	
To refine the previous strategy somewhat and limit the number of returns, we qualified and capitalized certain key words	
(''Keratoacanthoma/drug therapy'' [Majr] OR ''Keratoacanthoma/therapy'' [Majr] OR ''Keratosis/drug therapy'' [Majr] OR ''Keratosis/therapy'' [Majr] OR ''Carcinoma, Squamous Cell/drug therapy'' [Majr] OR ''Carcinoma, Squamous Cell/therapy'' [Majr]) AND (''Skin Diseases'' [Majr] OR ''Skin'' [Majr])	Dec. 2007 294 ref.
AND (''Mohs Surgery'' [MeSH] OR ''imiquimod'' [Substance Name] OR ''Photochemotherapy'' [MeSH]) AND (''1997/12/21'' [EDat]: ''2007/12/18'' [EDat]	
AND (English [lang] OR French [lang])	
Therapeutic recommendations for squamous cell carcinoma, keratoacanthoma and keratosis	
(''Keratoacanthoma/drug therapy'' [MeSH] OR ''Keratoacanthoma/therapy'' [MeSH] OR ''Keratosis/drug therapy'' [MeSH] OR ''Keratosis/therapy'' [MeSH] OR ''Carcinoma, Squamous Cell/drug therapy'' [MeSH] OR ''Carcinoma, Squamous Cell/therapy'' [MeSH]) AND (''Skin Diseases'' [MeSH] OR ''Skin'' [MeSH])	Dec. 2007 52 ref.
AND (''practice guideline'' [Publication Type] OR ''practice guidelines'' [MeSH Terms] OR ''Guidelines as Topic'' [MeSH] OR ''Practice Guidelines as Topic'' [MeSH] OR ''guideline''[Publication Type]	
OR ''Health Planning Guidelines'' [MeSH] OR ''guidelines'' [MeSH Terms] OR guideline* [Title]	
OR recommendation* [Title] OR recommandation* [Title] OR ''Evidence-Based Medicine'' [MeSH] OR ''Consensus'' [MeSH] OR consensus [Title] OR ''Consensus Development Conferences'' [MeSH]	

OR ''Consensus Development Conference'' [Publication Type] OR ''Consensus Development Conference, NIH'' [Publication Type] OR ''Consensus Development Conferences as Topic'' [MeSH]	
OR ''Consensus Development Conferences, NIH as Topic'' [MeSH] OR ''meta-analysis'' [Publication Type])	
Prognosis for squamous cell carcinoma and precursor lesions	
(''Carcinoma, Squamous Cell'' [MeSH] OR ''Keratosis'' [MeSH] OR ''Keratoacanthoma'' [MeSH] OR ''Carcinoma, Adenosquamous'' [MeSH] OR ''Carcinoma, Verrucous'' [MeSH] OR ''spindle cell carcinoma'' [All Fields]) AND (''Skin'' [MeSH] OR ''Skin Diseases'' [MeSH])	Jan. 2008 344 ref.
AND (''Prognosis'' [MeSH] OR ''Risk Factors'' [MeSH] OR ''Age Factors'' [MeSH] OR ''Population Characteristics'' [Mes h] OR ''high-risk'' OR ''high risk'' OR ''low risk'' OR ''low-risk'')	
AND (''Practice Guideline'' [Publication Type] OR ''Practice Guidelines as Topic'' [MeSH] OR ''Guideline'' [Publication Type] OR ''Guidelines as Topic'' [MeSH] OR ''Guideline Adherence'' [MeSH] OR ''Health Planning Guidelines»[MeSH] OR «Consensus»[MeSH] OR «Consensus Development Conferences as Topic»[MeSH] OR ''Consensus Development Conferences, NIH as Topic'' [MeSH] OR ''Consensus Development Conference, NIH'' [Publication Type] OR ''Consensus Development Conference'' [Publication Type] OR ''Evidence-Based Medicine'' [MeSH] OR ''Review Literature as Topic'' [MeSH] OR ''Review'' [Publication Type] OR ''Randomized Controlled Trial'' [Publication Type] OR ''Randomized Controlled Trials as Topic'' [MeSH] OR ''Meta-Analysis as Topic'' [MeSH] OR ''Meta-Analysis'' [Publication Type] OR guideline* [Title] OR consensus [Title] OR recommendation* [Title] OR recommandation* [Title])) AND (English [lang] OR French [lang])	
AND Publication Date from 1998/01/01	

Clinical and histological diagnosis of squamous cell carcinoma and precursor lesions	
Step 1	
(''Carcinoma, Squamous Cell/classification'' [MeSH] OR ''Carcinoma, Squamous Cell/diagnosis'' [MeSH] OR ''Carcinoma, Squamous Cell/pathology'' [MeSH] OR ''Keratosis/classification'' [MeSH]	
OR ''Keratosis/diagnosis'' [MeSH] OR ''Keratosis/pathology'' [MeSH] OR ''Keratoacanthoma/classification'' [MeSH] OR ''Keratoacanthoma/diagnosis'' [MeSH] OR ''Keratoacanthoma/pathology'' [MeSH] OR ''Carcinoma, Adenosquamous/classification'' [MeSH] OR ''Carcinoma, Adenosquamous/diagnosis'' [MeSH] OR ''Carcinoma, Adenosquamous/pathology'' [MeSH] OR ''Carcinoma, Verrucous/classification'' [MeSH] OR ''Carcinoma, Verrucous/diagnosis'' [MeSH] OR ''Carcinoma, Verrucous/pathology'' [MeSH])	
Step 2	
(''Carcinoma, Squamous Cell'' [MeSH] OR ''Keratosis'' [MeSH] OR ''Keratoacanthoma'' [MeSH] OR ''Carcinoma, Adenosquamous'' [MeSH] OR ''Carcinoma, Verrucous'' [MeSH] OR ''spindle cell carcinoma'') AND ''Immunohistochemistry''[MeSH]	
Strategy used	Jan. 2008 322 ref.
Step 1 OU Step 2	
AND (''Skin''[MeSH] OR ''Skin Diseases''[MeSH])	
AND (''Practice Guideline ''[Publication Type] OR ''Practice Guidelines as Topic''[MeSH] OR ''Guideline ''[Publication Type] OR ''Guidelines as Topic''[MeSH] OR ''Guideline Adherence''[MeSH] OR ''Health Planning Guidelines''[MeSH] OR ''Consensus''[MeSH] OR ''Consensus Development Conferences as Topic''[MeSH] OR ''Consensus Development Conferences, NIH as Topic''[MeSH] OR ''Consensus Development Conference, NIH ''[Publication Type] OR ''Consensus Development Conference ''[Publication Type] OR ''Evidence-Based Medicine''[MeSH] OR ''Review Literature as Topic''[MeSH] OR ''Review ''[Publication Type] OR ''Randomized Controlled Trial ''[Publication Type] OR ''Randomized Controlled Trials as Topic''[MeSH] OR ''Meta-Analysis as Topic''[MeSH] OR ''Meta-Analysis ''[Publication Type] OR guideline*[Title] OR consensus[Title] OR recommendation*[Title] OR recommandation*[Title]))	
AND (English[lang] OR French[lang])	
AND Publication Date from 2003/01/01	
Update of the strategy of July 2007: the terms defining ''guidelines'' in Medline were modified in the second half of 2007 by the NLM	
(''Keratosis''[MeSH] OR ''Carcinoma, Squamous Cell''[MeSH])	Dec. 2008 82 ref.
AND (''Skin''[MeSH] OR ''Skin Diseases''[MeSH])	
AND (''Guideline ''[Publication Type] OR ''Guidelines as Topic''[MeSH] OR ''Guideline Adherence''[MeSH] OR ''Health Planning Guidelines''[MeSH] OR ''Consensus''[MeSH] OR ''Consensus Development Conferences as Topic''[MeSH] OR ''Consensus Development Conference ''[Publication Type] OR ''Evidence-Based Medicine''[MeSH] OR ''Meta-Analysis ''[Publication Type] OR ''Meta-Analysis as Topic''[MeSH] OR guideline*[Title] OR consensus[Title] OR recommandation*[Title] OR recommendation*[Title])	
AND ((English[lang] OR French[lang]))	

Annex 4: AGREE analysis of guidelines to be adapted

The five guidelines ultimately selected as source guidelines for clinical practice were as follows:

- The National Health & Medical Research Council: Non-melanoma skin cancer: Guidelines for treatment and management in Australia 2002.
- The British Association of Dermatologists, the British Association of Plastic Surgeons & the Faculty of Clinical Oncology of the Royal College of Radiologists: Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *British Journal of Dermatology* 2002; 146: 18–25.
- National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology: Basal Cell and Squamous Cell Skin Cancer. 2007.
- The British Association of Dermatologists: Guidelines for management of Bowen's disease: 2006. *British Journal of Dermatology* 2007; 156: 11–21
- The British Association of Dermatologists: Guidelines for the management of actinic keratoses. *British Journal of Dermatology* 2007; 156: 222–230

The following tables summarize the AGREE scores attributed by the six appraisers to the various items for each of these five guidelines.

Collated results of AGREE assessment of BAD SCC guidelines 2002

Domain	Items	Appraiser 1	Appraiser 2	Appraiser 3	Appraiser 4	Appraiser 5	Appraiser 6
Domain 1	Item 1	3	4	4	4	4	3
	Item 2	3	3	4	3	4	3
	Item 3	3	3	1	3	3	1
Domain 2	Item 4	3	4	4	4	3	1
	Item 5	2	2	1	2	2	1
	Item 6	3	3	2	3	3	1
	Item 7	4	2	1	2	3	1
Domain 3	Item 8	3	3	4	3	3	1
	Item 9	3	3	2	3	3	2
	Item 10	4	3	2	3	3	1
	Item 11	3	1	1	2	3	1
	Item 12	3	4	4	3	4	3
	Item 13	4	4	4	2	1	1
	Item 14	3	2	3	2	2	1
Domain 4	Item 15	3	4	4	4	2	2
	Item 16	3	3	3	3	4	3
	Item 17	3	4	4	3	4	2
	Item 18	2	2	2	1	4	1
Domain 5	Item 19	2	2	1		4	1
	Item 20	2	2	1	3	3	1
	Item 21	2	1	2	1	2	1
Domain 6	Item 22	4	3	3	2	2	1
	Item 23	3	2	1	4	2	4
Overall assessment		Recommend	Strongly recommend	Recommend with provisos or alterations	Recommend with provisos. Good for tt and prognosis	Strongly recommend	Would not recommend

Collated results of AGREE assessment of NHMRC 2002 guidelines

Domain	Items	Appraiser 1	Appraiser 2	Appraiser 3	Appraiser 4	Appraiser 5	Appraiser 6
Domain 1	Item 1	3	4	4	4	4	4
	Item 2	3	4	4	4	4	4
	Item 3	3	4	4	3	4	4
Domain 2	Item 4	3	4	4	4	4	4
	Item 5	2	3	3	3	2	2
	Item 6	3	2	4	3	3	3
	Item 7	2	1	1	2	3	1
Domain 3	Item 8	3	3	4	4	3	1
	Item 9	3	3	4	4	3	4
	Item 10	3	3	3	4	3	2
	Item 11	3	4	3	3	4	4
	Item 12	3	4	4	4	3	4
	Item 13	2	1	1	3	3	4
	Item 14	2	1	1	2	2	1
Domain 4	Item 15	3	3	4	4	4	4
	Item 16	3	3	4	3	4	4
	Item 17	3	4	4	3	4	4
	Item 18	2	3	2	1	4	2
Domain 5	Item 19	2	3	2	3	4	1
	Item 20	3	4	3	4	2	3
	Item 21	2	1	2	3	2	1
Domain 6	Item 22	3	4	3	3	3	1
	Item 23	2	2	1	3	3	1
Overall assessment		Recommend	Recommend	Strongly recommend	Strongly recommend May 2002 (no diclofenac or anti-EGFR)	Strongly recommend (basis of efforts of the WG)	Recommend with provisos or alterations

Collated results of AGREE assessment of NCCN 2007 guidelines

Domain	Items	Appraiser 1	Appraiser 2	Appraiser 3	Appraiser 4	Appraiser 5	Appraiser 6
Domain 1	Item 1	4	4	4	4	4	4
	Item 2	4	4	4	4	4	4
	Item 3	3	3	4	3	4	4
Domain 2	Item 4	4	4	4	3	4	4
	Item 5	3	2	2	2	1	1
	Item 6	3	3	3	2	3	4
	Item 7	3	3	1	2	3	3
Domain 3	Item 8	4	3	2	3	3	4
	Item 9	4	3	3	3	2	4
	Item 10	3	3	2	3	2	4
	Item 11	3	3	3	3	3	4
	Item 12	3	2	4	4	2	4
	Item 13	3	4	1	3	2	4
	Item 14	4	4	4	1	2	4
Domain 4	Item 15	3	4	4	4	4	4
	Item 16	3	4	4	3	4	4
	Item 17	3	3	4	4	4	4
	Item 18	3	4	3	4	4	4

Domain 5	Item 19	3	3	1	3	3	2
	Item 20	3	4	1	2	3	1
	Item 21	3	2	3	2	2	2
Domain 6	Item 22	4	4	2	3	2	4
	Item 23	3	2	1	3	2	4
Overall assessment		Strongly recommend	Strongly recommend	Recommend with provisos (e.g. indication of interstitial curietherapy	Strongly recommend. Good for decision trees, surgery, prog factors	Recommend with alterations Essential decision trees	Strongly recommend

Collated results of AGREE assessment of BAD Bowen's disease guidelines 2006

Domain	Items	Appraiser 1	Appraiser 2	Appraiser 3	Appraiser 4	Appraiser 5	Appraiser 6
Domain 1	Item 1	4	4	4	4	4	4
	Item 2	3	4	4	4	4	4
	Item 3	3	2	2	3	4	3
Domain 2	Item 4	3	4	3	2	3	2
	Item 5	2	2	2	2	2	2
	Item 6	3	3	4	3	3	3
	Item 7	4	1	1	3	3	1
Domain 3	Item 8	3	3	4	4	3	3
	Item 9	4	4	4	4	3	4
	Item 10	4	3	3	4	3	4
	Item 11	3	3	3	3	4	4
	Item 12	4	4	4	4	2	4
	Item 13	4	3	1	3	2	2
	Item 14	4	2	3	2	2	2
Domain 4	Item 15	3	3	2	4	4	4
	Item 16	3	3	4	4	4	4
	Item 17	4	3	2	4	4	2
	Item 18	4	3	2	1	4	2
Domain 5	Item 19	3	2	2	2	2	1
	Item 20	3	2	1	3	2	1
	Item 21	4	1	1	2	2	1
Domain 6	Item 22	3	3	3	1	3	2
	Item 23	4	4	4	4	3	4
Overall assessment		Strongly recommend	Recommend	Recommend with provisos or alterations	Strongly recommend. Good for medical tt	Recommend with alterations	Recommend with provisos or alterations

Collated results of AGREE assessment of BAD actinic keratosis guidelines 2007

Domain	Items	Appraiser 1	Appraiser 2	Appraiser 3	Appraiser 4	Appraiser 5	Appraiser 6
Domain 1	Item 1	4	4	4	4	4	4
	Item 2	3	4	4	4	4	4
	Item 3	3	1	2	3	4	4
Domain 2	Item 4	3	4	3	2	3	3
	Item 5	3	2	2	2	2	1
	Item 6	3	4	4	3	3	4
	Item 7	4	2	1	3	2	2
Domain 3	Item 8	4	4	4	4	3	4
	Item 9	4	4	4	4	3	4
	Item 10	4	3	3	4	3	4
	Item 11	4	3	3	3	4	3
	Item 12	4	4	4	4	2	4
	Item 13	4	2	1	3	2	2
	Item 14	3	3	3	2	2	1
Domain 4	Item 15	3	3	2	4	4	4
	Item 16	4	4	4	4	4	4
	Item 17	4	3	2	4	4	4
	Item 18	4	2	2	1	3	4
Domain 5	Item 19	3	2	2	2	2	1
	Item 20	4	2	1	3	1	2
	Item 21	3	4	1	2	1	1
Domain 6	Item 22	3	3	3	1	2	4
	Item 23	3	4	4	4	2	4
Overall assessment		Recommend	Recommend	Recommend with provisos or alterations	Strongly recommend Good for medical tt	Recommend with alterations	Recommend with provisos or alterations

Choice of selected guidelines:

The following table provides a summary of the scores by AGREE domain for each of the five guidelines ultimately selected as sources for the SDF guidelines.

Summary table of scores by domain and by guideline

Domain		BAD SCC 2002	NHMRC 2002	NCCN 2007	BAD Bowen 2006	BAD AK 2007
Domain 1	Scope	70%	96%	94%	85%	85%
Domain 2	Stakeholder involvement	46%	58%	60%	51%	57%
Domain 3	Rigour	56%	64%	69%	75%	75%
Domain 4	Clarity	67%	76%	90%	74%	79%
Domain 5	Applicability	24%	50%	46%	31%	35%
Domain 6	Editorial independence	53%	47%	61%	72%	69%
Decision		Recommend with provisos	Recommend	Recommend	Recommend	Recommend