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Mellerio, J. E.; Robertson, S. J.; Bernardis, C.; Diem, A.; Fine, J. D.; George, R.; Goldberg, D.; Halmos, G. B.; Harries, M.; Jonkman, M. F.

Published in:
The British journal of dermatology

DOI:
10.1111/bjd.14104

Publication date:
2016

BJD
British Journal of Dermatology

Management of cutaneous squamous cell carcinoma in patients with epidermolysis bullosa: best clinical practice guidelines

J.E. Mellerio,[1,2] S.J. Robertson,[3] C. Bernardis,[4] A. Diem,[5] J.D. Fine,[6] R. George,[7] D. Goldberg,[8] G.B. Halmos,[9] M. Harries,[10] M.F. Jonkman,[11] A. Lucky,[12] A.E. Martinez,[2] E. Maubec,[13] S. Morris,[10] D.F. Murrell,[14] F. Palisson,[15] E.I. Pillay,[1] A. Robson,[16] J.C. Salas-Alanis[17] and J.A. McGrath[18]

[1]St John's Institute of Dermatology, [4]Department of Plastic Surgery, [7]Department of Palliative Care, [10]Department of Oncology and [16]Department of Dermatopathology, Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, U.K.

[2]Department of Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, U.K.

[3]Department of Dermatology, The Royal Melbourne Hospital, The Royal Children's Hospital and Monash Medical Centre, Melbourne, Australia

[5]Department of Dermatology, Paracelsus Medical University, Salzburg, Austria

[6]Division of Dermatology, Vanderbilt University School of Medicine, Nashville, TN, U.S.A.

[8]Division of Dermatology, University of Massachusetts, Worcester, MA, U.S.A.

[9]Department of Otorhinolaryngology, Head and Neck Surgery and [11]Department of Dermatology, University Medical Centre Groningen, Groningen, the Netherlands

[12]Department of Dermatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, U.S.A.

[13]Department of Dermatology, APHP, Avicenne Hospital, Bobigny, France

[14]Department of Dermatology, St George Hospital, University of New South Wales, Sydney, Australia

[15]Facultad de Medicina, Clínica Alemana, Santiago, Chile

[17]Basic Sciences Department, Universidad de Monterrey, Monterrey, Mexico

[18]St John's Institute of Dermatology, King's College London (Guy's Campus), London, U.K.

Linked Comment: Krupiczojc and O'Toole. *Br J Dermatol* 2016; **174**: 15

Summary

This article summarizes recommendations reached following a systematic literature review and expert consensus on the diagnosis and management of cutaneous squamous cell carcinomas in people with epidermolysis bullosa. The guidelines are intended to help inform decision making by clinicians dealing with this complex complication of a devastating disease.

Correspondence

Jemima E. Mellerio.
E-mail: jemima.mellerio@kcl.ac.uk

Accepted for publication

13 August 2015

Funding sources

None.

Conflicts of interest

None declared.

DOI 10.1111/bjd.14104

What's already known about this topic?

- Some subtypes of epidermolysis bullosa (EB), particularly severe generalized recessive dystrophic EB, are associated with the development of mucocutaneous squamous cell carcinomas (SCCs).
- These tumours behave aggressively and are a leading cause of morbidity and mortality in at-risk patients with EB.

What does this study add?

- These guidelines will assist clinicians in the diagnosis, management and staging of EB-associated cutaneous SCCs based on available evidence and expert consensus.
- They highlight the importance of a holistic multidisciplinary approach to the management of EB-associated SCCs, where patient involvement in decision making is paramount.

Some forms of epidermolysis bullosa (EB) are associated with the development of cutaneous or, more rarely, mucosal squamous cell carcinoma (SCC). Unlike cutaneous SCCs occurring in the general population where chronic ultraviolet exposure predisposes to the development of tumours on sun-exposed sites, EB-associated SCCs tend to arise at sites of chronic skin blistering, wounds and scarring. In addition, multiple primary SCCs often occur, tumours generally behave more aggressively than conventional SCCs, and they carry a very significant morbidity and mortality for those affected. EB cancers are the leading cause of death in patients with recessive dystrophic EB (RDEB), particularly the severe generalized form (RDEB-SG).

The cumulative risk of developing SCC in EB increases with age: for patients with RDEB-SG, the cumulative risk of having at least one SCC is 7·5% at age 20 years, 67·8% at 35 years and 90·1% by 55 years.[1] This increased risk is paralleled by an increased cumulative risk of death from SCC in this type of EB: 38·7% by age 35 years, 70·0% by 45 years and 78·7% by 55 years. These deaths occur despite aggressive tumour resection. The risks for patients with other forms of EB prone to SCC are lower, with tumours occurring later in life and tending to be less aggressive. It is also important to acknowledge that many EB subtypes, especially EB simplex, are not associated with an increased SCC risk.[1]

Clinical detection of SCCs in patients with EB on a background of chronic ulceration may be particularly challenging, and therefore the possibility of malignancy should be borne in mind, with suspicious lesions biopsied for histological evaluation. Hitherto, there have been many case reports in the literature describing EB SCCs and a variety of approaches towards investigation, monitoring and treatment. However, given the rarity of EB and the occurrence of cancer in a subset of patients only, there has been no prospective work or trials looking at how these tumours should best be managed.

DEBRA International is a worldwide network of national groups working on behalf of those affected by EB. In order to improve the diagnosis and management of SCCs arising in people with EB, they commissioned these guidelines, which have been drawn up from a systematic review of the available literature and guided by expert consensus. They are divided into sections on monitoring and surveillance for EB cancers, diagnosis, and surgical and nonsurgical treatments. Sections on putative preventative measures and palliative care have also been included.

Aim

To provide the user with information on the diagnosis and management of SCCs in people with EB so as to improve patient outcomes and quality of life.

Users

Dermatologists, paediatricians, plastic surgeons, dermatological surgeons, oncologists, dermatopathologists, palliative care physicians, nurses and people living with EB.

Target group

This guideline is aimed at adolescent and adult patients with forms of EB associated with the development of mucocutaneous SCCs, notably those with RDEB, dominant dystrophic EB, generalized intermediate junctional EB and Kindler syndrome.

Methods

In 2010, an international multidisciplinary working group was established to undertake a systematic review of the literature pertaining to the development, investigation and management of SCCs in people with EB, and to develop clinical recommendations based on the literature and their own expert opinions. This group included the following specialties: dermatology, plastic surgery, medical oncology, surgical oncology, dermatopathology, specialist nursing and palliative care.

The systematic literature searches were conducted using Medline, CINAHL, Allied and Complimentary Medicine Database, British Nursing Index, Embase and PsychINFO using the search terms 'epidermolysis bullosa', 'cancer' and 'squamous cell carcinoma'. The search was limited to articles about humans in English or French with no other restrictions. The literature review was updated in April 2014 with new publications incorporated into the review.

Topics for the guidelines, which had been determined by the group prior to the systematic review, were used to formulate initial recommendations that then formed the basis for subsequent iterations based on review and consensus by the expert collaborators. Importantly, particular regard was made in ensuring that the guidelines were clinically relevant and applicable to practice throughout the world, where the availability of various diagnostic and therapeutic modalities may be limited. The draft guidelines were then circulated for comments from people with EB, their families and a lay person.

In order to formulate the recommendations from the selected studies, the Scottish Intercollegiate Guidelines Network guidelines were used (Appendix 1). These detail the strength of recommendations and quality of evidence used herein.

Search results

In total 376 papers or conference abstracts meeting the search criteria were identified. Of these, 300 were discarded as they were not relevant (e.g. they did not pertain to inherited forms of EB), they comprised duplicate material or did not contain information concerning screening, diagnosis or management of EB-associated SCCs. Most articles were single case reports or small series of patients with EB with cutaneous SCCs, with no clinical trials identified in this group of patients. Additional references relating to other aspects of EB care or therapies for non-EB-related SCCs were added during the iterative process of guideline development from expert consensus.

Plans for updating the guidelines

It is anticipated that a literature search for new evidence pertaining to the management of SCCs in EB will be undertaken every 3 years after publication in order to update the guidelines. These revised guidelines will be hosted by the DEBRA International website (http://www.debra-international.org/homepage.html) to ensure their availability and dissemination to clinicians and people living with EB.

Implementation of the guideline

As this guideline is intended for international use, it is not possible to formulate a strategy for its implementation in all clinical centres. However, the activities of DEBRA International will aid in dissemination of the guidelines and facilitate adoption by the proposed user groups.

Table 1 Summary of key recommendations

	Strength of recommendation	Quality of evidence	Key references
Surveillance and diagnosis			
At-risk patients with EB should have regular clinical surveillance for SCC	D	III–IV	11–13
Areas of skin clinically suspicious for SCC should be biopsied for histological evaluation	D	III–IV	12,14,17,22
Tumour evaluation and staging			
All patients with EB presenting with an SCC should have multidisciplinary review	☑		
SCCs ≥ 5 cm diameter or overlying difficult anatomical sites should be imaged with magnetic resonance imaging or computed tomography to assess tumour extent	D	III	15,16,27
Lymphadenopathy should be assessed for potential metastatic SCC	D	III	2,4,9,13,15–33
Patients with EB diagnosed with an SCC may require staging	D	III	4,13,20,22,24,27,34,35
Surgical treatment			
Wide local excision is the treatment of choice for EB SCCs	D	III	2–6,8,9,13–16,18–22,24–27,30,32,33,36–60
Where an EB SCC excision is not possible, amputation of the digit or limb may be needed	D	III	3,9,10,13,14,17,18,20,22,23,25–27,29,30,34,38,40,42,44,49,51,58,61–70
Regional lymph node dissection should be offered if nodal SCC is identified by fine-needle aspiration or surgical biopsy	☑		
In some cases amputation may be favoured over wide excision where it is believed that a more aggressive surgical approach may reduce recurrence risk. Functional considerations and patient preference should inform treatment decisions	☑		
The choice of wound closure may be guided by anatomical considerations and availability of suitable donor skin or alternatives	☑		
Nonsurgical treatment			
Radiotherapy may be a useful palliative modality for inoperable EB SCCs or for subcutaneous, lymph node and distant metastases	D	III	12–14,17,19,20,26,30,34,38,40,66,71,76
Radiotherapy may need to be delivered in smaller fractions to minimize risk of severe skin desquamation in patients with EB	☑		
Conventional chemotherapy may be of some benefit used palliatively in EB SCCs, but risks may outweigh benefits	☑		
EGFR antagonists and tyrosine kinase inhibitors may be useful for palliation in advanced EB SCCs	☑		
Prosthetics			
Limb prostheses may be used successfully in EB following limb amputation	D	III	61–63
End-of-life care			
Appropriate analgesia should be prescribed to patients with EB towards the end of life. A number of different routes of administration of opioid analgesia may be used safely	C	1–	88–90
Psychological support of the patient with EB and family/carers is vital after a diagnosis of SCC and as end-of-life care approaches	☑		

EB, epidermolysis bullosa; SCC, squamous cell carcinoma; EGFR, epidermal growth factor receptor.

Surveillance and monitoring

SCCs may arise at a young age in patients with EB, particularly those with RDEB-SG. This complication has been described in a child as young as 6 years of age,[2] and has been reported frequently in patients aged < 20 years.[3–10] As the incidence of SCC increases with age in at-risk forms of EB, and patients frequently develop multiple primary tumours,[1] ongoing monitoring for patients with previous SCCs becomes even more important (Table 1).

Clinical evaluation

SCCs may be difficult to identify clinically in patients with EB because they frequently resemble areas of nonmalignant EB ulceration and wounds. Indicators of SCC in patients with EB include the following: (i) a nonhealing wound, lasting longer than normal EB wounds (e.g. 4 weeks or more); (ii) a rapidly growing wound, especially one that is heaped up, resembling exuberant granulation tissue; (iii) a deep, punched-out ulcer, especially if it has a raised or rolled edge; (iv) an area of hyperkeratosis, especially if surrounded by a shoulder of raised skin; and (v) a wound with altered sensation relative to normal EB wounds (e.g. tingling or increased pain).

☑ There should be a high index of suspicion for atypical wounds. Regular skin checks should be performed in all at-risk EB patient groups. (Strength of recommendation: good practice point, GPP) (see Appendix 1).

D The risk of developing SCC in some subtypes of EB, and the aggressive nature of these tumours, calls for vigilance and clinical surveillance in these patients.[11–13] (Strength of recommendation D, quality of evidence III–IV.)

1 Patients with RDEB-SG have a very high risk of developing SCC and should have a full skin examination every 3–6 months from age 10 years. For other groups (dominant dystrophic EB, generalized intermediate RDEB, RDEB inversa, pretibial dystrophic EB, EB pruriginosa, generalized intermediate junctional EB and Kindler syndrome), the risk of malignancy is not as high and it does not usually occur as early. Clinical screening for these lower-risk groups should usually commence from age 20 years and take place every 6–12 months, although if an SCC is diagnosed, 3-monthly screening should be undertaken subsequently.
2 Clinical screening should be undertaken by a dermatologist and/or specialist nurse with experience of EB wounds, where possible. All areas of a patient's skin should be examined and any relevant history about the duration and symptoms from clinically suspicious wounds should be sought. If it is not possible to examine all of the skin in one sitting (due to constraints of dressing changes), the skin should be examined serially over the course of a few days to 1–2 weeks so that all areas are examined. Photography of wounds at baseline for later comparison may be helpful, especially when other eroded and crusted lesions may arise in adjacent areas. Serial photography of suspicious areas that will not undergo immediate sampling or excision may be helpful, whenever possible and practical.
3 As they are responsible for day-to-day evaluation and management of the skin, patients and families should be educated about the risk of SCC and clinical features and symptoms that might indicate malignancy. This is imperative so that they are aware of the need to contact their medical team as soon as possible if they have concerns.
4 Six-monthly dental review of at-risk patients with EB is recommended so that the oral mucosae can be examined and any areas of chronic ulceration or leucoplakia can be biopsied. Patients should be advised to present sooner if there are nonhealing areas.
5 Patients with a history of SCC should be clinically evaluated at 3-monthly intervals. There is no evidence to advocate the use of routine imaging for local or systemic spread, but clinical examination (e.g. enlarged regional lymph nodes) or symptoms (e.g. bony pain) may guide further investigations, including fine-needle aspiration (FNA) of lymph nodes, fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning and computerized tomography (CT) scanning.

Biopsy of clinically suspicious lesions

D Areas of skin clinically suspicious for SCC should be biopsied for histological evaluation.[14] (Strength of recommendation D, quality of evidence III–IV.)

1 Diagnostic biopsies (e.g. 3–4-mm punch biopsies) should be taken from suspicious areas of skin for histopathological examination. To minimize the risk of sampling error, multiple biopsies around the edge of the lesion should be taken. The position of each biopsy within the lesion should be carefully recorded with clinical diagram(s) or digital photograph(s).
2 Biopsies can generally be taken under local anaesthesia, but occasionally they may need to be taken under general anaesthesia if multiple sites are to be sampled, especially in children or anxious adults. Undertaking biopsies at the time of a general anaesthetic for another procedure may be possible. Alternatively, a regional nerve block or oral anxiolytic may be utilized to minimize pain and anxiety when taking biopsies.
3 Reporting of biopsies from clinically suspicious EB wounds should ideally be undertaken by a pathologist experienced in examining EB biopsies, as there may be difficulties in distinguishing SCC from granulation tissue or pseudoepitheliomatous hyperplasia.

Tumour evaluation and staging

Once an SCC has been identified by diagnostic biopsies, further evaluation may be necessary to stage the patient to make the most appropriate management plan. Imaging of the primary tumour may guide surgical management, specifically the feasibility of excision vs. the need for more radical surgery

such as amputation. Assessment of regional lymph node involvement and possible distant metastatic spread may also be required.

Evaluation of the primary tumour

☑ All patients with EB presenting with an SCC should be discussed at a multidisciplinary meeting, where possible, with relevant specialists: dermatologist, plastic surgeon, histopathologist and oncologist. This allows for review of the histology and planning of staging and treatment. (Strength of recommendation GPP.)

D Larger SCCs (≥ 5 cm in diameter) or those overlying difficult anatomical sites should be imaged to assess their extent, particularly whether they involve underlying structures such as tendons, nerves and vessels.[15,16] Magnetic resonance imaging would be the investigation of choice, but where this is not available, CT scanning may be undertaken. (Strength of recommendation D, quality of evidence III.)

Evaluation of regional lymph nodes

D Patients with EB often have enlarged lymph nodes secondary to inflammation and colonization or infection of skin wounds. However, it is important to assess lymphadenopathy for potential metastatic SCC to plan treatment appropriately. (Strength of recommendation D, quality of evidence III.)

1 If regional lymph nodes are clinically palpable at the time of presentation of the SCC, ultrasound-guided FNA (or, in the case of inconclusive results at repeated FNA, surgical biopsy) should be undertaken to look for the presence of SCC.[4,13,17–25] If negative, no further evaluation is necessary, although lymph nodes should be examined every 3 months and rebiopsied if there is evidence of further enlargement. It should be noted that clinical evaluation may be difficult if there is significant axillary scarring making lymph node palpation difficult, in which case ultrasound evaluation may be helpful.
2 If lymph node biopsy is positive for metastatic SCC, regional lymph node dissection should be considered.[2,9,13,15,19,21,25–30] This can usually be carried out at the time of surgical excision of the primary SCC.
3 Sentinel lymph node biopsy (SLNB) may be undertaken in patients with EB presenting with SCC.[30] However, all reports of SLNB in patients with EB have so far been negative for nodal SCC.[20,31–33] As yet, there is no evidence that SLNB results inform prognosis in EB SCCs, nor that undertaking regional lymph node clearance in SLNB-positive patients influences the eventual clinical outcome.
4 Regional lymph node clearance should be undertaken if there is evidence of nodal disease on FNA or biopsy, although there is no evidence that it affects prognosis. However, removal of nodal SCC deposits may reduce subsequent problems from ulceration and local complications of secondary tumour deposits.
5 Regional lymph node dissection without proven nodal SCC (elective nodal dissection) should not be undertaken due to the morbidity associated with regional lymphoedema, which may exacerbate blistering, chronic wounds and exudate levels in patients with EB.

Staging for distant metastases

D Patients with EB diagnosed with an SCC may require staging to determine the presence and extent of distant metastases, as this will have a bearing on subsequent management.[4,13,20,22,24,27,34,35] (Strength of recommendation D, quality of evidence III.)

1 Patients with a primary SCC ≥ 5 cm in maximum diameter, or those with symptoms suggestive of metastatic spread (e.g. localized bony pain, deranged liver function tests, breathlessness), should undergo staging.
2 Where available, FDG-PET with CT scanning should be undertaken. In interpreting the results, it should be noted that in EB there may be nonspecific uptake of isotope on PET scanning from chronic skin wounds, reactive lymph nodes, the oesophagus and bone marrow, but combination with CT scanning can help to clarify the significance of increased uptake.[10,23,25,36,37]
3 Where PET scanning is not available, a CT or magnetic resonance imaging scan of the chest, abdomen and pelvis may identify systemic or lymph node metastases.
4 If CT scanning is unavailable, abdominal ultrasonography and/or bone scanning may help to identify systemic metastases.

Surgical treatment

Surgical excision is the standard treatment for EB SCCs, although the techniques used may vary depending on the site and size of the primary tumour. A number of approaches, including wide local excision, Mohs micrographic surgery and amputation are described, although evidence of the superiority of one modality over another is lacking and, in practice, it may be that one technique is preferred over another on anatomical or functional grounds. Open discussion of surgical options with the patient is paramount to ensure that the need for extensive or potentially radical surgery is balanced with the patient's functionality and ability to carry out activities of daily living.

In addition to various techniques of tumour resection, a number of different approaches to wound closure have also been used for EB SCCs, including partial or full-thickness skin grafting, the use of allografts or artificial skin equivalents, and healing by secondary intention. However, there is no clear evidence for the superiority of one modality over another, and the choice may depend, therefore, on the size and anatomical location of the wound, the availability of intact skin for autografting, and the availability of alternative graft materials.

If there is evidence of regional lymph node involvement, block dissection should be undertaken, ideally at the same

time as excision of the primary tumour to minimize the number of anaesthetic procedures. Regional nodal disease or subcutaneous metastases presenting after surgical excision of the primary tumour may be amenable to surgical excision to provide palliative, symptomatic relief.

Wide local excision

D Wide local excision is considered the treatment of choice for EB SCCs.[2–6,8,9,13,15,18–22,24–27,30,32,33,36–60] However, if imaging demonstrates involvement of underlying structures such as vessels, nerves or tendons, this approach may not be possible and more radical surgery (generally amputation) may be needed. (Strength of recommendation D, quality of evidence III.)

Consideration should be given to the following.

1. Ideally there should be a 2-cm excision margin around the tumour as assessed clinically. However, in practice it may be difficult to define the extent of the tumour clinically, and the margin may be limited by anatomical considerations.
2. Marker sutures should be used so that the specimen can be orientated for histopathological evaluation.
3. Ideally, the resection specimen should be mounted/pinned to a board and photographed prior to sampling, with clear labelling of blocks taken, allowing easy identification of the origin of subsequent slides. This facilitates successful orientation of histological abnormalities. Discussion between the surgeon and histopathologist prior to prosection also aids appropriate sampling and interpretation. Histopathological evaluation should determine whether the lateral and deep margins of the wound are clear of tumour, and if so state the distance of clearance. If the margins are not clear, the report should state which margin(s) is/are involved.
4. The histopathology report should comment on the thickness and differentiation of the SCC (although in practice all EB SCCs have the potential to behave aggressively independently of histological grade) and whether vascular or neural invasion is seen.
5. If there is evidence of residual tumour at a margin, re-excision of that portion of the wound should be considered. Where anatomical or functional considerations mean that this is not possible, amputation of an affected digit or limb may need to be considered.

Amputation

D Where the size or anatomical location of an EB SCC means that excision is not possible, it may be necessary to consider amputation of the digit or limb.[3,9,10,13,14,17,18,20,22,23,25–27,29,30,34,38,40,42,44,49,51,58,61–70] (Strength of recommendation D, quality of evidence III.)

☑ Local recurrence of SCCs may render further local excision impossible and leave amputation as the treatment of choice. In some cases amputation may be favoured over wide excision where it is believed that a more aggressive surgical approach may reduce the risk of recurrence; however, there is currently no evidence to support this. Functional considerations should also be borne in mind and discussed fully with the patient: amputation with the prospect of using a prosthesis may be preferable to wide excision leaving a painful wound and functional impairment. (Strength of recommendation GPP.)

1. Amputation may be necessary if a tumour or recurrence of a tumour is not amenable to wide local excision.
2. In some circumstances, amputation may be chosen in preference to excision for functional reasons, particularly if consideration is being given to subsequent use of a prosthesis.
3. There is no evidence that amputation gives any survival advantage over wide local excision.
4. Involvement of the patient in decisions about whether to opt for amputation or not is vital; some may prefer to avoid amputation to preserve function and independence, even it if means that the SCC may cause more morbidity and, perhaps, earlier mortality in the longer term.

Minimally invasive surgical techniques

A number of different techniques of minimally invasive surgery have been used in EB SCCs, including Mohs micrographic surgery, rush paraffin sections ('slow Mohs') and chemosurgery.[13,14,35,62,66,71–75]

There are some advantages of this approach: (i) examination of all of the excised tissue margin for histological evaluation; (ii) confirmation of histological clearance in clinically difficult-to-delineate EB SCCs and (iii) preservation of uninvolved tissue (particularly when the location and size of the tumour may compromise function and/or aesthetics).

However, a number of other factors should be considered. Firstly, interpretation of frozen sections in EB SCCs may be difficult; differentiating SCC from pseudoepitheliomatous hyperplasia may be challenging, even for a histopathologist experienced in these tumours. Secondly, EB skin is fragile so excision by minimally invasive surgical techniques needs a sharp surgical blade, a sharp cryostat blade and complete freezing of the tissue prior to sectioning. Thirdly, if conventional Mohs micrographic surgery with frozen sections is difficult, rush paraffin sections ('slow Mohs') may be used. However, the extent of EB SCCs may mean that it is not feasible for the patient to have potentially large excision wounds left unclosed pending results from each excision stage. Finally, EB SCCs may be aggressive and have a high local, regional and distant recurrence rate. It could be argued that getting a wider excision margin is preferable to minimize the risks of recurrence.

☑ Despite the use of minimally invasive surgical techniques in a number of EB SCCs, there is no evidence that they are beneficial or detrimental in terms of further management, morbidity or mortality. (Strength of recommendation GPP.)

1 Minimally invasive surgical techniques may have a role in the management of EB SCCs where the primary tumour is difficult to define clinically, and therefore it is difficult to be sure of excision margins at the time of surgery.
2 Minimally invasive surgical techniques may have a role in the management of EB SCCs where preservation of normal tissue is imperative for functional or aesthetic reasons.
3 There is no evidence that the use of minimally invasive surgery with clear margins for an EB SCC has any influence on the subsequent risk of recurrence.

Closure of surgical wounds

Different approaches to wound closure following excision of EB SCCs have been employed, including healing by secondary intention,[13,24,34,35,60,75] autologous split skin,[3–5,9,13–16,18–22,24,33,39,41,43,44,48,49,53,55,57,59,73] epidermal[39] or full-thickness grafting,[2,32,40,48,50,58] allogeneic skin grafting,[28,38,58] cadaveric skin grafting,[58] artificial skin equivalents,[28,57,59] flaps,[28,50,73–75] application of autologous or allogeneic keratinocyte suspensions,[27,28,59] or combinations of the above.[28,57] Of these techniques, split-skin grafting has been most frequently employed, usually with meshing, although donor sites in EB may be complicated by delayed healing.

☑ Many different techniques of wound closure have been used in EB SCC wounds. The choice of closure may be guided by anatomical considerations and the availability of suitable donor skin (for autografts), or the availability of alternatives such as skin equivalents. (Strength of recommendation GPP.)

☑ There is insufficient evidence to indicate that any one modality is associated with better healing than another, although meshed split-skin grafts are the technique most commonly employed. (Strength of recommendation GPP.)

☑ Autologous skin grafting may be complicated by delayed healing of donor sites and may be inappropriate if there are large or multiple sites requiring closure. (Strength of recommendation GPP.)

Nonsurgical treatment

While surgery is the first-line treatment for the majority of SCCs in EB, some clinical situations, notably when there has been local recurrence of disease, or regional or distant metastasis, may call for consideration of nonsurgical treatment such as radiotherapy or chemotherapy. Topical modalities including photodynamic therapy and 5-fluorouracil have also been used in small numbers of patients, particularly for early, *in situ* disease.

Radiotherapy

Radiotherapy has been used widely in the treatment of EB SCCs, as either a definitive or palliative treatment of a primary tumour[13,14,20,26,34,38,40,76] or, more commonly, to palliate local, regional or distant metastases, or following regional lymph node dissection.[12,17,19,30,66,71] Larger total radiation doses appear to be associated with severe desquamation and skin breakdown in patients with EB,[66,71] although in other cases radiotherapy has been well tolerated, particularly if delivered in smaller fractions. Radiotherapy has also been used as a primary treatment for mucosal SCCs in Kindler syndrome and RDEB.[76,77]

☑ Radiotherapy may be useful to reduce the primary tumour size prior to surgical excision, but evidence that it is effective as a definitive treatment is lacking. (Strength of recommendation GPP.)

D Radiotherapy may be a useful palliative modality for locally recurrent EB SCCs as an alternative to surgical resection, where surgery is not possible, or after regional lymph node dissection. (Strength of recommendation D, quality of evidence III.)

D Radiotherapy may be useful in palliation of subcutaneous, lymph node and distant (e.g. bony) metastases. (Strength of recommendation D, quality of evidence III.)

☑ Care should be given in planning radiotherapy in patients with EB to minimize the risk of inducing severe desquamation of overlying skin. The use of lower doses (e.g. 2 Gy) per fraction may help to minimize toxicity to the surrounding or overlying skin. (Strength of recommendation GPP.)

Conventional chemotherapy

There are only a few case reports describing the use of conventional chemotherapy for palliation of advanced EB SCCs.[12,18,30,36,78,79] Agents used include cisplatin, carboplatin, taxol, carboplatin, fluorouracil, doxorubicin and methotrexate. Some reports describe partial remission, although this has usually been reserved for use in patients with very advanced disease, and there is little or no follow-up data available. Concerns about septicaemia from indwelling vascular catheters for delivering chemotherapeutic drugs, particularly when therapy may cause neutropenia, should be taken into account when considering conventional chemotherapy in EB SCCs.

D Conventional chemotherapy may be of some benefit when used palliatively in EB SCCs, but the risk of septicaemia due to indwelling vascular catheters and neutropenia may outweigh the potential benefits. (Strength of recommendation GPP.)

Alternative biologic approaches

A raft of new biologic agents, notably epidermal growth factor receptor (EGFR) antagonists and tyrosine kinase inhibitors, have been used in non-EB SCCs.[80–85] There are limited case reports of favourable results with cetuximab (a monoclonal antibody that binds the extracellular domain of EGFR) in metastatic EB SCCs strongly expressing EGFR.[30,36] The oral tyrosine kinase inhibitor erlotinib may be another putatively use-

ful agent for advanced disease in this patient group. Both of these classes of drug are associated with a frequent incidence of acneiform rash and gastrointestinal disturbances.

☑ EGFR antagonists and tyrosine kinase inhibitors may prove useful palliatively in advanced EB SCCs, although at present, evidence for their benefit is limited. (Strength of recommendation GPP.)

Other nonsurgical techniques

A number of other nonsurgical modalities have been used in EB SCCs, although most comprise single case reports with scant information about response and outcome. These include dermabrasion,[14] cryotherapy,[3] tubercidin, topical 5-fluorouracil and injected purified protein derivative therapy,[18] and CO_2 laser.[22] Photodynamic therapy with topical 5-aminolaevunlinic acid has been used successfully in a single case report of Bowen disease on the finger in a patient with RDEB.[86] Recently, favourable responses of EB SCCs to electrochemotherapy have been published.[87] Hyperthermic isolated limb perfusion is a modality used in advanced nonmelanoma cancers; although not reported in EB, this may be a potentially useful therapy.[88]

☑ Electrochemotherapy may be a potential treatment for EB SCCs. (Strength of recommendation D, quality of evidence III.)

☑ Single case reports of other nonsurgical treatments for EB SCC do not provide evidence that they are beneficial. (Strength of recommendation GPP.)

☑ PDT may be efficacious in Bowen disease in EB, although the relative rarity of *in situ* disease relative to invasive SCC may limit its application. (Strength of recommendation GPP.)

Prosthetics

Many patients with EB SCCs affecting limbs undergo amputation when the patient presents with advanced primary or recurrent disease not suitable for wide local excision. Functionally, the effect of losing part of a limb can be devastating, especially where function or mobility is already compromised by scarring and contractures in other limbs. Although the skin of an amputation stump in EB is fragile, prostheses have been used with success, enabling patients to transfer, ambulate and use their arms.[61–63] Generally, using lightweight prosthetic materials and soft padding (e.g. silicone inserts or pads) will reduce trauma to the stump and facilitate weight bearing.

D Limb prostheses may be used successfully in EB following limb amputation, with appropriate care to minimize trauma or friction to the stump. (Strength of recommendation D, level of evidence III.)

Prevention

SCCs arising in EB occur early, are often multiple and have a very poor prognosis. In addition, even early detection and aggressive surgical excision do not appear to influence survival outcomes, nor do they prevent further primary tumours from developing. Experience in other conditions with a predisposition to cutaneous SCCs, such as xeroderma pigmentosum and solid organ transplantation, has suggested benefit from use of systemic retinoids to reduce the incidence of new tumours arising.[89,90] Other modalities, for example photodynamic therapy or topical imiquimod, which might treat neoplastic change early on before invasive SCC has developed, might also be of benefit in EB. This is especially so where detection of *in situ* SCC may be difficult on a background of scarred, inflamed or eroded skin.

Systemic retinoids

There has been only one phase I clinical trial of systemic retinoids in patients with RDEB, in which isotretinoin was given in doses of up to 0·5 mg kg^{-1} per day for 8 months.[31] This was well tolerated, although some patients experienced increased skin fragility on treatment. A single case report also describes systemic etretinate (1 mg kg^{-1} per day) in a patient with large keratoacanthomas in generalized intermediate junctional EB; there was no effect on the growth of the keratoacanthomas and therapy was stopped after 2 months due to side-effects.[43] Further work to explore whether systemic retinoids might be effective in chemoprevention of EB SCCs has not been undertaken to date.

D Systemic retinoids may be well tolerated and safely administered in EB.[31] (Strength of recommendation D, quality of evidence III.)

☑ Although there have been no trials to explore whether systemic retinoids are effective for primary or secondary chemoprevention of SCCs in EB, experience in other conditions in which there is an increased risk of cutaneous SCC indicates that there may be some benefit for patients with EB at high risk for these tumours. (Strength of recommendation GPP.)

Other approaches

Photodynamic therapy with 5-aminolaevulinic acid has been used to treat Bowen disease in a single patient with RDEB,[86] and may be a modality that could be used to target subclinical foci of *in situ* disease in EB before the development of invasive SCC. Similarly, other topical measures such as 5-fluorouracil or imiquimod may be potential treatments for early disease. However, at present there is no evidence to support their use.

End-of-life care

Due to the very aggressive nature of SCCs in EB, many patients with these tumours reach the point at which their disease is no longer 'curative', and efforts must be directed towards palliation and providing the best quality of life for that individual. Ideally, management should take place within a multidisciplinary team of health professionals including a dermatologist, specialist nurse, surgeon, oncologist, psycholo-

gist and pain or palliative care specialist. However, central to any holistic decision-making processes are the patient themselves and their family/carers. There may be situations in which the patient opts not to have particular treatments, even when the medical advice they are receiving suggests that it could be to their benefit. Making sure that the patient is informed of all possible options, the pros and cons of each, and supporting them in their decision as to which (if any) they would like to pursue is paramount. The patient's and family's wishes should also be listened to in making decisions about, for example, where they wish to die, and feeding and hydration.[91]

Pain management

Patients with EB with advanced SCCs may experience pain from their primary tumour, locoregional spread or distant metastases. Towards the end of life, efforts should focus on alleviating this pain,[92] without the usual concerns of tolerance of or addiction to opioid analgesics, although it is important to be mindful that using larger doses of opioids may make the patient less alert and responsive. Opioids may be given by a variety of routes to cover background, acute or procedural pain. Topical morphine in a hydrogel can be applied directly to a painful malignant wound and replaced at each dressing change.[93,94] Subcutaneous opioids can be delivered by a syringe driver with the cannula held in place with soft silicone tape to facilitate removal.[94,95] Opioid patches may also be helpful in delivering sustained-release analgesia, and can be taken off atraumatically with a medical adhesive-removal spray.[94,95] Radiotherapy may be used to alleviate pain from bony metastases.

C Appropriate analgesia should be prescribed to alleviate pain in patients with EB with SCC towards the end of life. A number of different routes of administration of opioid analgesia may be used safely in patients with EB, including topical morphine gel. (Strength of recommendation C, quality of evidence 1−.)

Wound management

Malignant EB wounds are often complicated by significant exudate and odour.[94,95] Low-air-loss mattresses can help to redistribute pressure to aid patient comfort and help deal with high volumes of exudate. A number of dressings are also specially designed to absorb and hold exudate away from the skin to minimize maceration of surrounding tissues. Charcoal, honey or silver dressings may reduce odour, and deodorizers may be helpful to mask it.[94] When EB SCCs or metastases overlie blood vessels, especially larger arteries and veins, such as in the groins or axillae, there is a risk of tumour invasion and catastrophic bleeding. In these situations, it may be possible to ensure that there are dark-coloured towels at hand to absorb and cover the blood loss, and to administer a fast-acting benzodiazepine such as midazolam subcutaneously or buccally to reduce patient anxiety.[94]

☑ A variety of dressings designed to cope with wounds that have high exudate levels or odour may be helpful in managing EB SCC wounds. (Strength of recommendation GPP.)

☑ Where an EB SCC or metastasis overlies blood vessels, consideration should be made of the risk of potentially catastrophic bleeding and how to alleviate anxiety in the patient and family should this happen. (Strength of recommendation GPP.)

Psychological support

Psychological support of a patient with EB should ideally be part of holistic, multidisciplinary care throughout life, although following the diagnosis of SCC the psychological needs of the patient and their family/carers may increase greatly. Towards the end of life, this is particularly important to help the patient and family adjust to the situation and to help communicate concerns and wishes. Following death, ongoing bereavement support of the family should be offered.

☑ Psychological support of the patient with EB and family/carers is important throughout life, but particularly vital after a diagnosis of SCC and as end-of-life care approaches. (Strength of recommendation GPP.)

☑ Support following bereavement may also be welcome for the family/carers. (Strength of recommendation GPP.)

Additional measures

During end-of-life care, patients with EB may be in great discomfort when moved for dressing changes or for personal care. In some situations, it may be reasonable to insert a small soft silicone urinary catheter to reduce the need for toileting and to reduce soiling of dressings.[94,95] Whereas catheterization is generally avoided in EB when not essential, due to the risk of urethral stricturing, in the context of being close to dying this is not a consideration. Where oral intake has reduced significantly, patients may be thirsty. It is reasonable to consider giving nasogastric or subcutaneous fluids (with the nasogastric tube cannula secured with soft silicone tape), so long as this does not cause undue distress to the patient. In patients with EB who are close to death, the benefits of undertaking dressing changes (comfort, and exudate and odour control) should be weighed against the discomfort that the dressings may entail. Ideally, the patient and/or family/carers should be involved in deciding how and when to carry out dressing changes.

☑ Urinary catheterization and giving nasogastric or subcutaneous fluids towards the end of life in EB may be beneficial in some cases if they outweigh discomfort. Similarly, patients may be more comfortable having less frequent dressings or even forgoing dressing changes completely at this stage. The patient and family/carers should be central to this decision making. (Strength of recommendation GPP.)

Acknowledgments

The generous assistance of Michael Jaega, Annette Wiles and Hannah Bujic is gratefully acknowledged in providing patient

or lay input to these guidelines. All authors volunteered their time and no source of funding was provided for any aspect of this guideline.

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Appendix 1

Levels of evidence

1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Nonanalytical studies, e.g. case reports, case series
4	Expert opinion

RCT, randomized controlled trial.

Grades of recommendation

A	At least one meta-analysis, systematic review or RCT rated as 1++, directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

RCT, randomized controlled trial. The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

Good practice points

☑	Recommended best practice based on the clinical experience of the guideline development group

Adapted from the *SIGN 50 Guideline Developer's Handbook*, NHS Scottish Intercollegiate Guidelines Network, revised edition January 2014.