



## Overview

# Electrochemotherapy and Ablative Therapies in Non-melanoma Skin Cancer



N. O'Donoghue<sup>\*</sup>, D. Mowatt<sup>†</sup>, A.J. Sykes<sup>†</sup>

<sup>\*</sup>Salford Royal NHS Foundation Trust Hospital, Salford, UK

<sup>†</sup>The Christie NHS Foundation Trust Hospital, Manchester, UK

Received 14 June 2019; received in revised form 2 August 2019; accepted 21 August 2019

## Abstract

Although surgery and radiotherapy remain the most commonly used treatments for non-melanoma skin cancer, there are a variety of alternatives. Here we discuss the use of electrochemotherapy and ablative treatments and examine the evidence for their effectiveness against a number of non-melanoma skin cancers.

© 2019 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.

**Key words:** Ablative; electrochemotherapy; keratinocyte tumours; non-melanoma; skin cancer

## Statement of Search Strategies Used and Sources of Information

Search strategies included searching online sources using internet search engines and searches on PubMed.

## Introduction

Non-melanoma skin cancers (NMSC) together are the most common tumour worldwide. In the UK, the age-standardised incidence rates increased by 147% in the 20 years up to 2013–2015 [1]. Most NMSC are keratinocyte cancer, basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). This overview looks at the role of electrochemotherapy (ECT) and ablative therapies in their treatment. NMSC also includes Merkel cell carcinoma, lymphomas and other rarer tumours. These are discussed below.

## Electrochemotherapy

ECT is a type of chemotherapy that relies on the use of short, but intense, electrical pulses to increase cell membrane permeability (electroporation). This allows the entry of very high doses of cytotoxic chemotherapy. Bleomycin, either systemically or intralesionally, is most commonly used, although cisplatin is also used intralesionally.

ECT was first used with cisplatin in 1991 [2], but its adoption was slow until the publication of a set of standard operating procedures in 2006 [3]. Since then many units around the world have used ECT to treat a variety of different tumours. In the UK, the National Institute of Health and Care Excellence (NICE) has approved the use of ECT for the treatment of metastases in the skin from tumours of non-skin origin and melanoma (IPG466, March 2013) and issued guidance for the treatment of primary BCC and primary SCC (IPG478, February 2014). An international register, the InspECT register, was set up in 2008 to collect treatment data from centres around the world with the aim of publishing research into the use of ECT.

There are few contraindications to ECT. Treatment should be avoided in pregnant or lactating females or patients with a history of hypersensitivity to bleomycin or cisplatin. A history of symptomatic pulmonary disease or renal

Author for correspondence: A.J. Sykes, The Christie Hospital NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX, UK. Tel: +44-161-446-3354; Fax: +44-161-446-3478.

E-mail address: [andrew.sykes@christie.nhs.uk](mailto:andrew.sykes@christie.nhs.uk) (A.J. Sykes).

impairment may require a dose reduction. A pacemaker does not contraindicate ECT as long as electricity is not delivered directly to the pacemaker, although patients with an implantable cardioverter defibrillator should have this temporarily deactivated for delivery of the treatment. Patients usually require a general anaesthetic when multiple lesions are treated, but local anaesthesia may be possible for small numbers of lesions.

Intravenous bleomycin is given 8 min before electroporation to allow drug distribution. Electroporation should be completed within a 40-min window, during which time the bleomycin concentration is at its peak. This allows adequate time to treat large lesions or multiple small lesions. A variety of electrodes are available for tumours of different sizes and geometries, but in our experience an applicator that can be adjusted to treat tumours of varying depth is most commonly used (Figure 1). The effect of the electrical pulse falls off rapidly outside the area of the electrodes and the entire lesion to be treated must be encompassed, including where feasible a margin of about 1 cm of apparently normal tissue.

Acute toxicity is minimal, with no acute chemotherapy side-effects. There may be some pain at the electroporation site, which can normally be managed with paracetamol or other simple analgesia. Some sites, including those close to the periosteum, such as the pre-sternum and pre-tibia, can experience moderate postoperative pain and it is our practice to commence appropriate patients on a gabapentinoid 48 h before treatment. Patients can expect treated nodules to form an eschar as tumour necrosis occurs about 10–14 days after treatment. Late effects are seen, with commonly hyperpigmentation at the electroporation site. Bleomycin pulmonary fibrosis is a recognised but rare complication. The dose of bleomycin, 15 000 IU/m<sup>2</sup>, is low and multiple treatments can be given. It is recommended that the cumulative lifetime dose of bleomycin is kept below 400 000 IU.

ECT is a safe, well-tolerated treatment that is effective against a variety of tumour types. It is especially useful for treating multiple metastatic lesions that would be very difficult to manage surgically or with radiotherapy and can be used where previous surgery or radiotherapy has failed. For this reason, centres performing ECT are being referred patients with primary skin or non-skin cancers arising in or metastasising to skin. This may follow extensive standard treatment, including surgery, radiotherapy, chemotherapy, targeted systemic therapy or immunotherapy, where disease has become resistant to, or is not suitable for, further standard treatments. This section will consider those diseases that have shown complete or partial responses to ECT.

### Basal Cell Carcinoma

BCC is the most common NMSC [4]. A variety of treatments are available, including curettage, cryotherapy, photodynamic therapy (PDT), radiotherapy and surgery (either conventional or Mohs). ECT adds another option, particularly for patients where surgery or radiotherapy is contraindicated. A multicentre retrospective analysis of data from the InsPECT database [5] of 277 patients who underwent ECT for BCC found that of 246 evaluable patients with a total of 466 lesions there was an objective response rate (complete and partial) of 93.8% per patient and 95.2% per lesion (complete response of 79.2% and 81.5%, respectively). Responses were higher in patients with a primary presentation ( $P = 0.0035$ ), smaller nodules <3 cm ( $P = 0.0009$ ), no previous treatment ( $P = 0.0003$ ) and no previous irradiation ( $P = 0.0001$ ). The data suggest that ECT is a safe and effective treatment, particularly in the elderly, or where standard treatments are contraindicated.

### Squamous Cell Carcinoma

Cutaneous SCC is the second most common form of NMSC. Tumours are conventionally treated by surgical excision with appropriate margins. There are circumstances, however, where surgical excision is not feasible, either due to the extent of surgical resection, lack of reconstructive options or comorbidities excluding anaesthesia. Likewise, when radiotherapy as either a curative or a palliative option may not be feasible and in advanced cases with palliative intent where chemotherapy may be contraindicated due to comorbidities, ECT may be an effective alternative. A retrospective series of 22 cases published by Di Monta *et al.* [6] showed a 23% complete response rate and a 59% partial response rate 4 weeks after treatment. A prospective study by Bertino *et al.* [5] in 2016 reported a 55% complete response rate and a 24% partial response rate in 50 cutaneous head and neck SCC, noting that lesions <3 cm had a significantly better response than lesions >3 cm.

### Malignant Adnexal Tumours of the Skin

This is a heterogeneous group of rare tumours including eccrine porocarcinoma accounting for less than 1% of all skin cancers. Given their small numbers, there is no consensus on management guidelines. Wide surgical resection is generally considered the primary treatment of choice, however it is recognised that some have a propensity for local recurrence. The successful treatment of locally recurrent porocarcinoma with ECT obtaining a



Fig 1. Variable applicator for electrophoresis (reproduced with permission of IGEA).

complete response for local control has been reported [7]. At the Christie Hospital we have successfully managed a case of widespread, locally recurrent porocarcinoma in a lower limb where below knee amputation was considered the only alternative.

#### *Merkel Cell Carcinoma*

Merkel cell carcinoma is a rare and aggressive cancer whose incidence is rising. It occurs most frequently in the head and neck area (41–50%), followed by the upper and lower limbs (32–38%) and trunk (12–14%) [8]. This neuro-endocrine tumour arises from the Merkel cell cutaneous mechanoreceptor, located in the basal layer of the epidermis, and the tumour is associated with the Merkel cell polyomavirus in about 80% of cases. Merkel cell carcinoma has a poor prognosis; the National Cancer Intelligence Network, UK found that 79% of patients with Merkel cell carcinoma died within 2 years of diagnosis, for the period between 1999 and 2008. Standard treatment consists of radical surgery and/or radiotherapy. Local recurrences are common and although published literature is restricted to case reports, ECT has been reported to be effective in inducing complete and partial remission of tumours [9,10].

#### *Dermatofibrosarcoma Protuberans*

Dermatofibrosarcoma protuberans is a rare, slowly growing spindle cell neoplasm usually arising in the dermis with low grade to intermediate malignant potential. It presents as an indurated plaque on which multiple reddish purple, firm nodules arise, sometimes in association with ulceration. It most commonly appears on the trunk and extremities of young adults. In most cases it is associated with a translocation that fuses part of the COL1A1 gene from chromosome 17 with part of the PDGFB gene from chromosome 22. The tumour is usually slow growing, sometimes developing over several years, and there is often a history of repeated local excisions followed by recurrence. About 5% of cases will undergo high-grade sarcomatous transformation. Standard treatment involves wide surgical excision, or excision under Mohs micrographic control. Cases of effective control of advanced disease with ECT have been reported [11,12].

#### *Angiosarcoma*

Angiosarcoma is a rare, but often aggressive, vascular neoplasm with a high propensity for local recurrence, characterised by rapidly proliferating, extensively infiltrating anaplastic cells derived from blood vessels. These tumours are either primary, with a propensity for the head and neck, secondary to chronic lymphoedema or radiation induced, most commonly after breast irradiation. Where radical treatment with curative intent has failed and radiotherapy or chemotherapy are no longer palliative options, a good local response to ECT has been reported. According to a retrospective multicentre study including 19 patients with superficially metastatic angiosarcoma treated

by ECT between 2007 and 2014, the objective response rate was 63% and 1-year local progression-free survival was 68% [13–15].

#### *Kaposi's Sarcoma*

Kaposi's sarcoma is caused by infection with the Kaposi sarcoma-associated herpes virus, also known as human herpesvirus 8. Viral infection is needed to cause Kaposi's sarcoma but only a small proportion of those infected will develop Kaposi's sarcoma, usually associated with some other weakness of the immune system, such as HIV infection or anti-rejection immune suppression. We have found that ECT is a highly effective treatment for localised areas of Kaposi's sarcoma and particularly in anatomical areas such as the hands and feet where surgery or radiotherapy would be difficult [16,17].

#### *Cutaneous Metastases*

Any non-skin malignancy can theoretically metastasise to the skin. Cutaneous metastases might cause bleeding, oozing, disfigurement, pain and sometimes social embarrassment. Treatment of cutaneous metastases can reduce or eliminate these symptoms and improve quality of life. Most commonly, patients are referred with metastatic breast disease, for which ECT has been shown to be an effective option [18,19], and less frequently with renal, lung and gastrointestinal cancer. ECT is an effective option that can combine with other palliative modalities such as surgery, chemotherapy or radiotherapy. ECT can be appropriate at any stage in the disease process, either for local control before the start of systemic therapy, or during or after systemic therapy when resistance to treatment has developed. Similarly, ECT can be sequenced before or after treatment with radiotherapy, although data would suggest that the technique is more effective in non-irradiated tissues [5].

## **Ablative Therapy**

The first choice for the management of 'keratinocyte cancers', considered by many to be the favoured term for BCC and SCC [20], remains surgery [21,22]. A limitation with all other treatments is the difficulty in assessing the completeness of treatment. When surgery is not possible, radiotherapy is often the preferred management [23,24]. However, as discussed in another article in this special issue [25], there are a number of situations when these options are either not possible or preferable.

Tumours deemed low risk for recurrence or metastasis (as outlined in Table 1) in particular may be considered appropriate for treatments with ablative therapies.

BCC is rarely associated with metastasis [26]. Given this, less aggressive management is more likely to be considered, especially where excision may result in significant cosmetic impairment. SCC, however, is associated with the majority of NMSC deaths [27], so in considering non-standard management, care must be taken to assess the risk of

**Table 1**  
Low risk features for BCC and SCC

Features	Low-risk BCC	Low-risk SCC
Clinical		
Location*/size†	Area L < 20 mm Area M < 10 mm	Area L < 20 mm Area M < 10 mm
Borders	Well defined	Well defined
Primary versus recurrent	Primary	Primary
Immunosuppression	No	No
Site of prior radiation therapy	No	No (nor previous chronic trauma)
Rapidly growing tumour	(n/a to BCC, which is always slow growing)	No
Neurological symptoms	(n/a to BCC)	No
Pathological		
Growth pattern/histological subtype	Nodular, superficial§	Not a high-risk histological subtype§
Perineural involvement	No	No (nor lymphatic or vascular involvement)
Degree of differentiation	n/a	Well or moderately differentiated
Depth of invasion/thickness	n/a	<2 mm, and not beyond subcutaneous fat

Adapted from the National Comprehensive Cancer Network Guidelines 2019 [8,9,22,23]. BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

\* Area L: trunk and extremities (excluding hands, feet, pretibial skin and ankles); area M: cheeks, forehead, scalp, neck and pretibial skin; area H: 'mask area' of face, i.e. central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, preauricular and postauricular skin, temple, ear, genitalia, hands and feet.

† Greatest tumour diameter, including peripheral rim of erythema.

§ Adenoid (acantholytic), adenosquamous (showing mucin production), desmoplastic or metaplastic (carcinosarcomatous) subtypes.

recurrence and metastasis. The characteristics of the tumour that are associated with low risk are outlined in [Table 1](#). In addition to tumour features, patient characteristics and preferences need to be considered, such as comorbidities, concerns regarding scarring/wound healing and cosmesis, in creating an individual's treatment plan. Furthermore, patients may prefer or expect to actively participate in the decision-making process, particularly for managing BCC [28].

Treatments for keratinocyte tumours can broadly be categorised as physically destructive (including radiotherapy, curettage and electrodesiccation, lasers and cryotherapy); chemically destructive [including PDT, 5-fluorouracil (5-FU) and ECT, as discussed above]; and immunomodulatory (including imiquimod) [29]. For this special issue, the discussion below focuses on treatments with higher-quality evidence from studies with longer-term follow-up, together with some key emerging treatments and controversies. Treatments for BCC, then SCC, have been considered, grounding the discussion in current clinical dermatological practice. Less commonly used novel therapies of particular note from all of these categories have been tabulated ([Table 2](#)).

### Physically Destructive Treatments

Radiotherapy is considered in a separate article in this special issue (see [43]).

### Curettage and Electrodesiccation

This method (curettage/scraping off the lesion, then performing electrodesiccation to the wound base and margins) is a longstanding, commonly used treatment for low-risk primary BCC and can yield high cure rates, with historical recurrence rates of 4.3–18.1% [44] at 5 years for

BCC. The choice of site is important. There are high recurrence rates when mid-facial BCC are treated compared with BCC elsewhere on the head and neck [45] and it should not be used at sites that bear terminal hairs [27], given the risk of follicular extension of tumour and the theoretically higher risk of recurrence at these sites, as well as disfiguring postoperative alopecia within the scar.

Although one, two or even three [46] cycles of curettage then electrodesiccation have been established as the standard of care, given the relatively large scars that result from this process and the longer healing time, an approach regaining interest in the recent past is performing curettage alone, with reports of 5-year cure rates of the order of 96% for BCC [47] and 97% in a small series of SCC [48]. This is in keeping with historical recurrence rates of 3.4–4.5% [49] at 2 or more years for (mostly small) SCC. Recurrence rates have been found to be highly histological subtype [50] and operator [51] dependent, and recurrence of SCC after curettage and electrodesiccation from the pinna resulted in death for 2/15 patients in one study [52].

As curettage (with or without electrodesiccation) is relatively easily delivered, quick and therapeutic, as well as diagnostic, it is cost-effective and so will probably remain a key approach in selected NMSC where excision is not feasible or desirable.

### Cryotherapy/Cryosurgery

In cryotherapy, liquid nitrogen at a temperature of  $-196^{\circ}\text{C}$  is applied by either direct contact or open spray to the skin surface to induce tissue necrosis. One difficulty with this modality is that any regimen aggressive enough to adequately treat NMSC is usually also associated with significant adverse effects and poor cosmetic outcomes [53]. Where expertise is available, however, results with cryotherapy have been reported as equivalent to PDT, with

**Table 2**  
Additional and emerging treatments for keratinocyte tumours

Treatment	(Putative) mechanism of action	Further details
Ingenol mebutate (topical gel)	Ingenol rapidly induces necrosis specifically targeted to dysplastic cells and causes neutrophil-mediated immunostimulatory effects [30]	Currently approved only for use in field cancerisation with actinic keratosis. Evidence of efficacy in superficial BCC is limited to case reports/small series [31] and an early randomised dose-finding trial [32], but this may prove a useful option
5-fluorouracil (intralesional injections)	Fluorouracil reduces cell proliferation and induces cell death, particularly in cells with high cell division rates and combinations	Data are scarce; however, it may be useful in low-risk SCC [33,34]
Interferon $\alpha$ 2b (perilesional injections)	Immune modulator effect on tumour cells	96% cure rate reported in a series of superficial and nodular BCC after 10 years of follow-up; however, nine treatment visits are typically required and flu-like side-effects were reported in all patients [35]
Solasodine glycoalkaloids (topically)	Not fully understood: may disrupt the cell membrane, resulting in cell lysis or causes TNF receptor activation and binding to TNF leading to cancer cell death by apoptosis	78% response rate in a study of 98 patients with BCC after 1 year of follow-up [36]
Non-ablative laser: pulsed dye laser	BCC has a clinically visible telangiectatic vascular network, amenable to treatment with a vascular-specific 595 nm pulsed dye laser, resulting in selective damage of these vessels, rather than an unspecific effect through bulk heating	Pulsed dye laser has been used to good effect in managing small BCC [37] but caution is advised with larger tumours: in a case series where both superficial and nodular lesions were treated on four occasions, those less than 1.5 cm had a 91.7% complete response rate, compared with only 25% for larger lesions [38]. Small studies, including some BCC at high-risk sites, showed a complete clinical response of 75–78.6% [39,40]. Dyspigmentation was a significant risk, with hypopigmentation and hyperpigmentation rates of 93% and 37%, respectively [39]. Overall, pulsed dye laser is thought to be a moderately effective treatment, but its use is recommended largely in small well-defined superficial and/or nodular BCC in low-risk areas
Non-ablative laser: Nd:YAG	As above, targets a BCC's vascular network	One small retrospective study showed 100% clearance after an average of 9 months of follow-up, a larger prospective study of 33 BCC on the trunk and extremities reported a histological clearance rate of 90% and no scarring was observed [41], so this may be a treatment option with good potential
Combination therapy: nanoparticle technology for PDT	Nanoparticles may help deliver aminolevulinic acid in topical PDT by stabilising aminolevulinic acid and improving cutaneous penetration	In mouse studies, the volume of SCC tumours reduced 68% 2 weeks after four treatments with nanoparticle PDT [42]

BCC, basal cell carcinoma; PDT, photodynamic therapy; SCC, squamous cell carcinoma; TNF, tumour necrosis factor.

similar clearance rates [54,55], especially for elderly patients with low-risk, small, superficial BCC on the trunk and extremities. However, the procedure is not standardised and meta-analyses have shown that recurrence rates when treating BCC are less favourable than surgery or radiotherapy at 21.0% compared with 3.3% and 3.2%, respectively [28,56].

Pooled average recurrence rates for SCC after cryotherapy have been calculated at 0.8% in the eight reported studies (of 273 patients) that describe recurrence after cryotherapy [19], but there was variability in the number of freeze–thaw cycles used.

Given this, at present, cryotherapy is rarely used to treat NMSC in dermatological practice. More recently, intralesional cryotherapy (where a probe is used to introduce liquid nitrogen directly into the tumour tissue so that freezing is initiated in its core) has been trialled. A study of eight patients with superficial and nodular BCC of the lower

limbs showed a 100% histological clearance rate at 85 days, although the mean recovery time was notably long at 80 days [57]. Another group showed that 45/46 (97.8%) patients with facial superficial and nodular BCC had a complete response after one treatment, with 69.6% patients describing a good to excellent cosmetic result [58]. Larger studies are needed to investigate a possible place for intralesional cryosurgery in managing BCC.

#### Ablative Lasers

Carbon dioxide and erbium yttrium aluminium garnet (Er:YAG) lasers work by ablating tissue through the vaporisation of tissue water. Both achieve similarly good therapeutic and aesthetic results in the management of BCC, with the carbon dioxide laser showing 63–100% complete response rates [59,60] and Er:YAG lasers achieving results comparable with PDT (91.75%) in one study [61]. Data are

relatively scarce for laser treatment, so in practice their use is typically limited to centres with ease of access.

#### *Ablative Fractional Lasers plus Topical Treatments*

This is an area of increasing interest. Fractionation of a laser beam of energy into multiple microbeams produces skip columns of thermal injury to the epidermis and dermis, known as microthermal zones. This significantly enhances the uptake of topically applied therapeutic agents [62].

Several studies have shown that pretreatment with ablative fractional lasers (AFXL) increases aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) induced fluorescence, improving the effectiveness of PDT in patients with nodular BCC: 12 months after two treatment cycles, clearance rates were 63–92.9% [63,64] in the pretreated arms compared with 56–80.4% in the non-pretreated arms.

Given the literature showing ablative laser treatment for SCC *in situ* [65], a single-blind comparative trial of patients with microinvasive SCC (i.e. SCC limited to papillary dermis) was carried out, comparing (Er:YAG) AFXL treatment then PDT (single treatment) with two treatments with MAL-PDT. This showed a complete response rate 3 months after treatment of 84.2% for the combined arm and 52.4% for MAL-PDT alone ( $P = 0.03$ ). After 24 months, the recurrence rate was significantly lower with AFXL-PDT (12.5% versus 63.6%) ( $P = 0.006$ ). Given the shallow depth of penetration of lasers, and the biology of SCC, care must be taken before this treatment is considered.

#### *Chemically Destructive Treatments*

##### *Photodynamic Therapy*

PDT uses visible light (blue or red) and a light-sensitive topical compound, commonly either 5-ALA or MAL, to induce a photodynamic reaction through enhanced light absorption by protoporphyrin IX, resulting in destruction of malignant keratinocyte cells. Protocols for PDT vary with regards to the photosensitiser used (although efficacy is equivalent) [66], the duration of application of the photosensitiser and the number of treatment sessions. The main side-effect is localised pain. Good response rates at 5 years of follow-up are seen with low-risk superficial and nodular BCC with PDT (53–62.7%) [67–70]. The main advantage of PDT is cosmetic outcome, which has been repeatedly shown to be superior to both surgery and cryotherapy [71]. PDT is therefore recommended as a treatment of choice for patients with multiple superficial BCC, particularly if located at cosmetically important locations, especially if the patient is unable to apply a topical treatment. Given the risks of incomplete ablation, the role of PDT (as with all topical treatments) in managing nodular BCC is less clear, but it may be considered for small lesions where other treatments are not suitable.

Recently, daylight PDT, in which natural sunlight is the light source, has been used very successfully to treat non-hyperkeratotic actinic keratoses on the face and scalp [72]. A pilot study of primary superficial and small nodular BCC treated with daylight PDT cleared 74% at 12 months [73]. Penetration of topically applied photosensitisers through

keratinised tumour surfaces will probably be less effective in thicker tumours, so there has recently been a focus on delivering both ALA and the light source intra-tumourally. One small study showed promising results in patients with nodular BCC, with no clinical recurrence observed (mean follow-up 19.5 months) [74]. Larger studies are necessary before daylight PDT or intra-tumoural PDT may be recommended as a treatment alternative for BCC.

A few studies have confirmed the histological clearance of SCC after PDT; one small study showed complete response rates at 2 years of 25.8% and 57.5% for invasive and micro-invasive SCC, respectively [75]; another study of 25 patients (treated with an intravenous photosensitiser) showed recurrence or metastatic disease in four patients [76]. Given this (albeit limited) data, PDT is not currently recommended to treat invasive SCC [5].

##### *Fluorouracil*

5-FU is a thymidylate synthase inhibitor that blocks the synthesis of pyrimidine thymidine, a nucleoside required for DNA replication, so rapidly replicating malignant cells undergo cell cycle arrest and apoptosis [77]. Topical 5% 5-FU is a long-established treatment for superficial BCC. At 3 years it showed a complete response rate equivalent to imiquimod; however, after 5 years of follow-up this dropped to 70%, compared with 80.5% [69] with imiquimod. Nodular BCC treatment has been disappointing, with a 21.4% recurrence rate in one 10-year follow-up study [78]. Local skin reactions are very common (erythema, pruritus, burning sensation, inflammation), although systemic toxicity is rare; use of 5-FU cream is usually limited to the treatment of small and superficial BCC.

Topical 5-FU is not recommended for use in invasive SCC [20], although intralesional 5-FU has been used to good effect in a small number of case reports (see Table 2) and so may be an emerging therapeutic option.

#### *Immunomodulatory Treatments*

##### *Imiquimod*

Imiquimod is an immune-response modifier. It stimulates Toll-like receptors expressed on dendritic cells and monocytes, increasing the production of cytokines and chemokines, which promote T-helper-1 innate and adaptive cell-mediated immune responses to make tumour cells more susceptible to apoptosis [79]. High-level evidence from a randomised controlled trial of 601 superficial BCC showed that 5% imiquimod cream was superior when compared with PDT and topical 5-FU, with a clinical clearance of 80.5% 5 years after treatment [69]. Cosmetic appearance was graded as better for imiquimod when reviewed independently [69]. Further case series of superficial BCC and small nodular BCC have shown clearance rates of 87% [54] and 65% [80], respectively. Especially where scarring or cosmesis is a concern, imiquimod may be considered the treatment of choice for superficial BCC at low-risk sites.

There have been a small number of case reports and two case series of the use of imiquimod in treating SCC on thin

periorbital skin [81–83]. Recently, however, there has been a report describing the development of SCC in three patients after treatment of *in situ* SCC with imiquimod [84]. Given the risk of metastasis, the use of imiquimod for the treatment of confirmed SCC is not recommended [20].

## Conclusions

The use of either ECT or one of a variety of different ablative therapies offers many non-surgical, non-radiotherapy options for the treatment of NMSC. Great care should be given to deliver the 'right treatment to the right lesion' [85] for any given patient. The area of greatest controversy with keratinocyte tumour management is the decision about which treatment would be optimal for the given situation. The ablative therapies outlined above may be suitable when managing low-risk lesions, such as small or superficial BCC, particularly when the risk to benefit ratio from complex surgery or radiotherapy is increased. The variety of treatment options allow for the approach to be tailored to the lesion and individual patient preference.

Increasing numbers of studies are being carried out in which various therapies are combined, in an effort to maximise the tolerability of treatments for patients. Combined approaches, such as combinations of PDT with other topical treatments, show promise, and warrant further exploration in managing BCC. Caution is needed in assessing novel treatments for SCC, given its more aggressive biology.

Clinicians will be supported in assessing treatment options if in future studies, diagnosis, treatment courses and outcomes are standardised, using a core outcome set [86], and, ideally, recurrence, adverse events and cosmetic outcomes recorded, as well as details of healthcare costs. The InspECT register, an international register dedicated to ECT, is a valuable step in this direction.

## Conflict of interest

The authors declare no conflicts of interest.

## References

- [1] Cancer Research UK, <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-melanoma-skin-cancer/incidence#ref-2019>; 2019.
- [2] Mir LM, Belehradec M, Domenge C, Orlowski S, Poddevin J, Schwab G. Electrochemotherapy, a new antitumour treatment: first clinical trial. *C R Acad Sci* 1991;313(13):613–618.
- [3] Mir LM, Gehl J, Sersa G, Collins CG, Garbay JR, Gillard V, et al. Standard operating procedures of the electrochemotherapy: instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the Cliniporator™ by means of invasive or non-invasive electrodes. *Eur J Cancer Suppl* 2006;4:14–25.
- [4] Ghandi SA, Kamp J. Skin cancer epidemiology, detection, and management. *Med Clin North Am* 2015;99(6):1323–1335.
- [5] Bertino G, Sersa G, De Terlizzi F. European Research on Electrochemotherapy in Head and Neck Cancer (EURECA) project: results of the treatment of skin cancer. *Eur J Cancer* 2016;63:41–52.
- [6] Di Monta G, Caracò C, Simeone E, Grimaldi AM, Marone U, Di Marzo M, et al. Electrochemotherapy efficacy evaluation for treatment of locally advanced stage III cutaneous squamous cell carcinoma: a 22-cases retrospective analysis. *J Transl Med* 2017;15(1):82. <https://doi.org/10.1186/s12967-017-1186-8>.
- [7] Maorne U, Caraco C, Anniciello A, DiMonta G, Chiofalo M, Di M, et al. Metastatic eccrine porocarcinoma: report of a case and review of the literature. *World J Surg Oncol* 2011;9:32. <https://doi.org/10.1186/1477-7819-9-32>.
- [8] Tello TL, Cogshall K, Yom SS, Yu SS. Merkel cell carcinoma: an update and review: current and future therapy. *J Am Acad Dermatol* 2018;78(3):445–454.
- [9] Scelsi D, Mevio N, Bertino G, Occhini A, Brazzelli V, Morbini P, et al. Electrochemotherapy as a new therapeutic strategy in advanced Merkel cell carcinoma of head and neck region. *Radiol Oncol* 2013;47(4):366–369.
- [10] Curatolo P, Mancini M, Clerico R, Ruggiero A, Frascione P, Di Marco P, et al. Remission of extensive Merkel cell carcinoma after electrochemotherapy. *Arch Dermatol* 2009;145(4):494–495.
- [11] Bonadies A, Elia F, Solivetti FM, Vidiri A, Muscardin L, Bucher S. Electrochemotherapy of a multirecurrent dermatofibrosarcoma protuberans of the orbital margin: a case report. *Anticancer Res* 2015;35(11):6121–6126.
- [12] Wiater K, Zdzienicki M, Morysiński T, Koseta H, Klimczak A, Obrebski M, et al. Effective treatment of recurrent, advanced dermatofibrosarcoma protruberans by electrochemotherapy. *Eur J Dermatol* 2013;23(2):260–261.
- [13] Guida M, Campana LG, Curatolo P, Strippoli S, Bonadies A, Grilz G, et al. Local treatment with electrochemotherapy of superficial angiosarcomas: efficacy and safety results from a multi-institutional retrospective study. *J Surg Oncol* 2016;114(2):246–253.
- [14] Guida M, Ruggieri E, Fucci L, Ressa M, D'Aluisio L, Fanelli G, et al. A case of cutaneous giant angiosarcoma treated successfully with electrochemotherapy. *Br J Dermatol* 2017;177(2):e27.
- [15] Al-Hadithy N, Dehnel A, George A, Kisiel R, Lunt C, Stone C. Patient reported outcomes in prospective cohort study of electrochemotherapy. *Int J Surg* 2018;52:110–119.
- [16] Starita N, Di Monta G, Cerasuolo A, Marone U, Anniciello A, Botti G, et al. Effect of electrochemotherapy on human herpesvirus 8 kinetics in classic Kaposi sarcoma. *Infect Agent Cancer* 2017;12:35.
- [17] Curatolo P, Quaglino P, Marengo F, Mancini M, Nardò T, Mortera C, et al. Electrochemotherapy in the treatment of Kaposi sarcoma cutaneous lesions: a two-center prospective phase II trial. *Ann Surg Oncol* 2012;19(1):192–198. <https://doi.org/10.1245/s10434-011-1860-7>.
- [18] Matthiessen LW, Keshtgar M, Curatolo P, Kunte C, Grischke EM, Odili J, et al. Electrochemotherapy for breast cancer - results from the INSPECT database. *Clin Breast Cancer* 2018;18(5):e909–e917.
- [19] Bourke M, Soden D, Clover AJP. Effective treatment of intractable cutaneous metastases of breast cancer with electrochemotherapy: a useful contributor to cutaneous disease control. *Breast Cancer Res Treat* 2017;164(1):251.
- [20] Karimkhani C, Boyers LN, Dellavalle RP, Weinstock MA. It's time for "keratinocyte carcinoma" to replace the term "non-melanoma skin cancer". *J Am Acad Dermatol* 2015;72:186–187.
- [21] Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Dermatol* 2002;146:18–25.

- [22] Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 2008;159:35–48.
- [23] NCCN clinical practice guidelines in oncology; squamous cell skin cancer 2019. Available at: [www.nccn.org](http://www.nccn.org).
- [24] NCCN clinical practice guidelines in oncology; basal cell skin cancer 2019. Available at: [www.nccn.org](http://www.nccn.org).
- [25] Kosutic D, Haw W, Ghura V. Current concepts in the surgical management of non-melanoma skin cancers. *Clin Oncol* 2019;31:738–748.
- [26] Wysong A, Aasi SZ, Tang JY. Update on metastatic basal cell carcinoma: a summary of published cases from 1981 through 2011. *JAMA Dermatol* 2013;5:615–616.
- [27] Barton V, Armeson K, Hampras S, Ferris LK, Visvanathan K, Rollison D, et al. Nonmelanoma skin cancer and risk of all-cause and cancer-related mortality: a systematic review. *Arch Dermatol Res* 2017;309:243–251.
- [28] van Egmond S, Wakkee M, Droger M, Bastiaens MT, van Rengen A, de Roos KP, et al. Needs and preferences of patients regarding basal cell carcinoma and cutaneous squamous cell carcinoma care: a qualitative focus group study. *Br J Dermatol* 2019;180:122–129.
- [29] Griffin LL, Ali FR, Lear JT. Non-melanoma skin cancer. *Clin Med* 2016;16:62–65.
- [30] Alchin DR. Ingenol mebutate: a succinct review of a succinct therapy. *Dermatol Ther* 2014;4:157–164.
- [31] Izzi S, Sorgi P, Piemonte P, Carbone A, Frascione P. Successfully treated superficial basal cell carcinomas with ingenol mebutate 0.05% gel: report of twenty cases. *Dermatol Ther* 2016;29:470–472.
- [32] Siller G, Rosen R, Freeman M, Welburn P, Katsamas J, Ogbourne SM. PEP005 (ingenol mebutate) gel for the topical treatment of superficial basal cell carcinoma: results of a randomized phase IIa trial. *Australas J Dermatol* 2010;51:99–105.
- [33] Dando EE, Lim GFS, Lim SJM, Kim C, Pugliano-Mauro M. Intralesional 5-fluorouracil for the nonsurgical management of low-risk, invasive squamous cell carcinoma. *Dermatol Surg* 2018. <https://doi.org/10.1097/DSS.0000000000001740>.
- [34] Metterle L, Nelson C, Patel N. Intralesional 5-fluorouracil (FU) as a treatment for nonmelanoma skin cancer (NMSC): a review. *J Am Acad Dermatol* 2016;74:552–557.
- [35] Tucker SB, Polasek JW, Perri AJ, Goldsmith EA. Long-term follow-up of basal cell carcinomas treated with perilesional interferon alfa 2b as monotherapy. *J Am Acad Dermatol* 2006;54:1033–1038.
- [36] Punjabi S, Cook LJ, Kersey P, Marks R, Cerio R. Solasodine glycoalkaloids: a novel topical therapy for basal cell carcinoma. A double-blind, randomized, placebo-controlled, parallel group, multicenter study. *Int J Dermatol* 2008;47:78–82.
- [37] Konnikov N, Avram M, Jarell A, Tannous Z. Pulsed dye laser as a novel non-surgical treatment for basal cell carcinomas: response and follow up 12–21 months after treatment. *Lasers Surg Med* 2011;43:72–78.
- [38] Shah SM, Konnikov N, Duncan LM, Tannous ZS. The effect of 595 nm pulsed dye laser on superficial and nodular basal cell carcinomas. *Lasers Surg Med* 2009;41:417–422.
- [39] Minars N, Blyumin-Karasik M. Treatment of basal cell carcinomas with pulsed dye laser: a case series. *J Skin Cancer* 2012;286480.
- [40] Karsai S, Friedl H, Buhck H, Jünger M, Podda M. The role of the 595-nm pulsed dye laser in treating superficial basal cell carcinoma: outcome of a double-blind randomized placebo-controlled trial. *Br J Dermatol* 2015;172:677–683.
- [41] Ortiz AE, Anderson RR, DiGiorgio C, Jiang SIB, Shafiq F, Avram MM. An expanded study of long-pulsed 1064 nm Nd:YAG laser treatment of basal cell carcinoma. *Lasers Surg Med* 2018. <https://doi.org/10.1002/lsm.22803>.
- [42] Wang X, Shi L, Tu Q, Wang H, Zhang H, Wang P, et al. Treating cutaneous squamous cell carcinoma using 5-aminolevulinic acid poly(lactide-co-glycolic acid) nanoparticle-mediated photodynamic therapy in a mouse model. *Int J Nanomed* 2015;10:347–355.
- [43] Veness MJ, Delishaj D, Barnes EA, Bezugly A, Rembielak A. Current role of radiotherapy in non-melanoma skin cancer. *Clin Oncol* 2019;31:749–758.
- [44] Thissen MR, Neumann MH, Schouten LJ. A systematic review of treatment modalities for primary basal cell carcinomas. *Arch Dermatol* 1999;135:1177–1183.
- [45] Salasche SJ. Curettage and electrodesiccation in the treatment of midfacial basal cell epithelioma. *J Am Acad Dermatol* 1983;8:496–503.
- [46] Suhge d'Aubermont PC, Bennett RG. Failure of curettage and electrodesiccation for removal of basal cell carcinoma. *Arch Dermatol* 1984;120:1456–1460.
- [47] Barlow JO, Zalla MJ, Kyle A, DiCaudo DJ, Lim KK, Yiannias JA. Treatment of basal cell carcinoma with curettage alone. *J Am Acad Dermatol* 2006;54:1039–1045.
- [48] Yakish K, Graham J, Hossler EW. Efficacy of curettage alone for invasive cutaneous squamous cell carcinoma: a retrospective cohort study. *J Am Acad Dermatol* 2017;77:582–584.
- [49] Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. *BMJ* 2013;347:f6153.
- [50] Sheridan AT, Dawber RP. Curettage, electrosurgery and skin cancer. *Australas J Dermatol* 2000;41:19–30.
- [51] Goldman G. The current status of curettage and electrodesiccation. *Dermatol Clin* 2002;20:569–578:[ix].
- [52] Shiffman NJ. Squamous cell carcinomas of the skin of the pinna. *Can J Surg* 1975;18:279–283.
- [53] Hall VL, Leppard BJ, McGill J, Kessler ME, White JE, Goodwin P. Treatment of basal-cell carcinoma: comparison of radiotherapy and cryotherapy. *Clin Radiol* 1986;37:33–34.
- [54] Kufflik EG. Cryosurgery for skin cancer: 30-year experience and cure rates. *Dermatol Surg* 2004;30:297–300.
- [55] Bath-Hextall F, Bong J, Perkins W, Williams H. Interventions for basal cell carcinoma of the skin: systematic review. *BMJ* 2004;329:705.
- [56] Drucker AM, Adam GP, Rofeberg V, Gazula A, Smith B, Moustafa F, et al. Treatments of primary basal cell carcinoma of the skin: a systematic review and network meta-analysis. *Ann Intern Med* 2018;169:456–466.
- [57] Har-Shai Y, Sommer A, Gil T, Krausz J, Gal-Or N, Mettanes I, et al. Intralesional cryosurgery for the treatment of basal cell carcinoma of the lower extremities in elderly subjects: a feasibility study. *Int J Dermatol* 2016;55:342–350.
- [58] Weshahy AH, Abdel Hay RM, Metwally D, Weshahy OA, Gad Z. The efficacy of intralesional cryosurgery in the treatment of small- and medium-sized basal cell carcinoma: a pilot study. *J Dermatolog Treat* 2015;26:147–150.
- [59] Horlock N, Grobbelaar AO, Gault DT. Can the carbon dioxide laser completely ablate basal cell carcinomas? A histological study. *Br J Plast Surg* 2000;53:286–293.
- [60] Campolmi P, Brazzini B, Urso C, Ghersetich I, Mavilia L, Hercogova J, et al. Superpulsed CO<sub>2</sub> laser treatment of basal cell carcinoma with intraoperative histopathologic and cytologic examination. *Dermatol Surg* 2002;28:909–911. discussion 912.
- [61] Smucler R, Vlk M. Combination of Er:YAG laser and photodynamic therapy in the treatment of nodular basal cell carcinoma. *Lasers Surg Med* 2008;40:153–158.

- [62] Lee WR, Shen SC, Wang KH, Hu CH, Fang JY. The effect of laser treatment on skin to enhance and control transdermal delivery of 5-fluorouracil. *J Pharm Sci* 2002;91:1613–1626.
- [63] Haak CS, Togsverd-Bo K, Thaysen-Petersen D, Wulf HC, Paasch U, Anderson RR, et al. Fractional laser-mediated photodynamic therapy of high-risk basal cell carcinomas – a randomized clinical trial. *Br J Dermatol* 2015;172:215–222.
- [64] Lippert J, Smucler R, Vlk M. Fractional carbon dioxide laser improves nodular basal cell carcinoma treatment with photodynamic therapy with methyl 5-aminolevulinate. *Dermatol Surg* 2013;39:1202–1208.
- [65] Covadonga Martínez-González M, del Pozo J, Paradelo S, Fernández-Jorge B, Fernández-Torres R, Fonseca E. Bowen's disease treated by carbon dioxide laser. A series of 44 patients. *J Dermatolog Treat* 2008;19:293–299.
- [66] Morton CA, Dominicus R, Radny P, Dirschka T, Hauschild A, Reinhold U, et al. A randomized, multinational, non-inferiority, phase III trial to evaluate the safety and efficacy of BF-200 aminolaevulinic acid gel vs. methyl aminolaevulinate cream in the treatment of nonaggressive basal cell carcinoma with photodynamic therapy. *Br J Dermatol* 2018;179:309–319.
- [67] Mosterd K, Thissen MR, Nelemans P, Kelleners-Smeets NW, Janssen RL, Broekhof KG, et al. Fractionated 5-aminolaevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial. *Br J Dermatol* 2008;159:864–870.
- [68] Basset-Seguín N, Ibbotson SH, Emtestam L, Tarstedt M, Morton C, Maroti M, et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. *Eur J Dermatol* 2008;18:547–553.
- [69] Rhodes LE, de Rie MA, Leifsdottir R, Yu RC, Bachmann I, Goulden V, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. *Arch Dermatol* 2007;143:1131–1136.
- [70] Jansen MHE, Mosterd K, Arits AHMM, Roozeboom MH, Sommer A, Essers BAB, et al. Five-year results of a randomized controlled trial comparing effectiveness of photodynamic therapy, topical imiquimod, and topical 5-fluorouracil in patients with superficial basal cell carcinoma. *J Invest Dermatol* 2018;138:527–533.
- [71] Collier NJ, Haylett AK, Wong TH, Morton CA, Ibbotson SH, McKenna KE, et al. Conventional and combination topical photodynamic therapy for basal cell carcinoma: systematic review and meta-analysis. *Br J Dermatol* 2018;179:1277–1296.
- [72] Shive ML, Coakley BJ, Bierman DF, Serowka Lane KL, Wiegell SR, Haedersdal M, et al. Use of 5-aminolevulinic acid and daylight photodynamic therapy for the treatment of actinic keratoses. *Dermatol Surg* 2019;45:529–535.
- [73] Wiegell SR, Skodt V, Wulf HC. Daylight-mediated photodynamic therapy of basal cell carcinomas – an explorative study. *J Eur Acad Dermatol Venereol* 2014;28:169–175.
- [74] Rodríguez-Prieto MÁ, González-Sixto B, Pérez-Bustillo A, Alonso-Alonso T, Ortega-Valín L, Martínez-Valderrábano V, et al. Photodynamic therapy with intralesional photosensitizer and laser beam application: an alternative treatment for nodular basal cell carcinoma. *J Am Acad Dermatol* 2012;67:e134–e136.
- [75] Calzavara-Pinton PG, Venturini M, Sala R, Capezzer R, Parrinello G, Specchia C, et al. Methylaminolaevulinate-based photodynamic therapy of Bowen's disease and squamous cell carcinoma. *Br J Dermatol* 2008;159:137–144.
- [76] Kübler AC, de Carpentier J, Hopper C, Leonard AG, Putnam G. Treatment of squamous cell carcinoma of the lip using Foscan-mediated photodynamic therapy. *Int J Oral Maxillofac Surg* 2001;30:504–509.
- [77] Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. *Nat Rev Cancer* 2003;3:330–338.
- [78] Reymann F. Treatment of basal cell carcinoma of the skin with 5-fluorouracil ointment. A 10-year follow-up study. *Dermatologica* 1979;158:368–372.
- [79] Dummer R, Urosevic M, Kempf W, Hoek K, Hafner J, Burg G, et al. Imiquimod in basal cell carcinoma: how does it work? *Br J Dermatol* 2003;149(Suppl. 66):57–58.
- [80] Sterry W, Ruzicka T, Herrera E, Takwale A, Bichel J, Andres K, et al. Imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinoma: randomized studies comparing low-frequency dosing with and without occlusion. *Br J Dermatol* 2002;147:1227–1236.
- [81] Ross AH, Kennedy CT, Collins C, Harrad RA. The use of imiquimod in the treatment of periocular tumours. *Orbit* 2010;29:83–87.
- [82] Singh M, Singh H, Kakkar N, Zadeng Z, Gupta P. Treatment of squamous cell carcinoma of the eyelid with imiquimod 5% cream. *Can J Ophthalmol* 2019;54:e24–e27.
- [83] Todorovic-Zivkovic D, Zalaudek I, Longo C, De Pace B, Albertini G, Argenziano G. Successful treatment of two invasive squamous cell carcinomas with topical 5% imiquimod cream in elderly patients. *Eur J Dermatol* 2012;26:579–580.
- [84] Dika E, Fanti PA, Lambertini M, Scarfi F, Ravaioli GM, Veronesi G, et al. Cutaneous squamous cell carcinoma progression during imiquimod treatment. *J Am Acad Dermatol* 2018;79:e11–e12.
- [85] Lear JT. Evidence-based treatment for low-risk basal cell carcinoma. *Lancet Oncol* 2014;15:12–13.
- [86] Schlessinger DI, Iyengar S, Yanes AF, Lazaroff JM, Godinez-Puig V, Chen BR, et al. Development of a core outcome set for clinical trials in basal cell carcinoma: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials* 2017;18:490.