

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of electrochemotherapy for primary basal cell carcinoma and primary squamous cell carcinoma

Treating basal cell carcinoma and squamous cell carcinoma using pulses of electricity together with chemotherapy

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common types of skin cancer. They are generally slow-growing but can cause extensive tissue destruction if not treated, and SCC can spread to other parts of the body.

In electrochemotherapy an anticancer drug is given by injection either into a vein or directly into a tumour. Short, powerful pulses of electricity are then applied to the tumour. The electrical energy opens the membranes (outer coverings) of the tumour cells, allowing the anticancer drug to pass through into the cells and have a more damaging effect.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2012.

Procedure name

Electrochemotherapy for primary basal cell carcinoma and primary squamous cell carcinoma

Specialist societies

- British Association of Dermatologists

- British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)
- Faculty of Clinical Oncology, Royal College of Radiologists.

Description

Indications and current treatment

Basal cell carcinoma (BCC) is the most common type of skin cancer in the UK. It is generally a slow-growing, locally invasive epidermal skin tumour that rarely spreads to other parts of the body. Although it is not usually life-threatening, the tumour can cause extensive tissue destruction if it is not treated. Squamous cell carcinoma (SCC) is the second most common type of skin cancer in the UK. It may spread into local lymph nodes and metastasise to other parts of the body.

Current treatments for BCC and SCC include surgical excision and radiotherapy, and less commonly curettage, cryotherapy and chemotherapy.

What the procedure involves

Electrochemotherapy (ECT) is a local treatment that aims to enhance the effects of chemotherapy. The procedure is performed with the patient under general or local anaesthesia with or without sedation. Chemotherapy drugs are given first, either intravenously or directly into the tumour. Drug dose is individualised based on either body surface area or tumour volume. Shortly after drug administration, brief and intense electric pulses are delivered around or directly into the tumour using either surface plates or needle electrodes. This makes the cell membranes more permeable to the chemotherapy drugs so that their cytotoxic effect is more potent. Different-shaped electrodes or plates are used depending on the tumour size, extent, shape and location. Treatment duration may vary depending on the number and size of tumours. Larger tumours may need several applications to cover the entire surface. Repeated treatments can be performed if necessary (within the lifetime dose limits of the chemotherapy drugs).

The European Standard Operating Procedures for Electrochemotherapy (ESOPE), produced by the manufacturer, provides a set of guidelines for this procedure. ESOPE states that potential contraindications to ECT include poor renal function, manifest arrhythmia or pacemaker, pulmonary fibrosis or previous lifetime exposure to bleomycin above a stated threshold dose.

Outcome measures

The World Health Organization criteria for tumour response assessment are:

- complete response (CR): disappearance of target tumour
- partial response (PR): more than 50% reduction in tumour size

- no response (NR) or stable disease (SD): less than 50% reduction in tumour size and less than 25% increase in tumour size
- progressive disease (PD): more than 25% increase in tumour size.

Objective response (OR) is the aggregation of complete response and partial response results.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to electrochemotherapy for primary basal cell carcinoma and primary squamous cell carcinoma. Searches were conducted of the following databases, covering the period from their commencement to 3 April 2012: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good-quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, an editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with primary basal cell carcinoma and primary squamous cell carcinoma.
Intervention/test	Electrochemotherapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This IP overview is based on approximately 326 patients from 2 non-randomised comparative studies^{1, 2} and 6 case series^{3, 4, 5, 6, 7, 8}.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on electrochemotherapy in primary basal cell carcinoma and primary squamous cell carcinoma

Abbreviations used: BCC, basal cell carcinoma; CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOP, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; IU, international units; IV, intravenous; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease.																																																									
Study details	Key efficacy findings																																																								
Peycheva E (2004)¹ Non-randomised comparative study (compares 2 pulse sequences) Bulgaria Recruitment period: not reported. Study population: patients with primary early-stage non-melanoma skin tumours: BCC and SCC. n=113 patients (113 lesions) 85 BCC, 28 SCC (59 sequence A vs. 54 sequence B) Age: 64.2 years (mean) Sex: 31% (28/113) male Patient selection criteria: clinical stage T1 disease. No lesions on the thoracic cardiac region for patients with pacemakers/defibrillators. Minimum 12 months follow-up. Technique: Intratumoural bleomycin of 0.5–0.8 U dependent on lesion size. Electric pulses of 900 or 1200 V/cm for SCC and BCC respectively. Sequence A: 16 biphasic pulses of 25+25 microseconds duration, spaced at 0.6 ms (1667 Hz); duration-number product 0.8 ms; total sequence duration 9.6 ms. Sequence B: 8 biphasic pulses of 50+50 microseconds duration, spaced at 1.0 ms (1000 Hz); duration-number product 0.8 ms; total sequence duration 7.1 ms. Follow-up: 12 months Conflict of interest/source of funding: not reported.	Number of patients analysed: 113 (113 lesions) Lesion response rates by electric pulse sequence (at 12 months) <table border="1"> <thead> <tr> <th>Sequence</th><th>Tumour type</th><th>No. patients</th><th>No. lesions</th><th>CR (%)</th></tr> </thead> <tbody> <tr> <td rowspan="2">A</td><td>BCC</td><td>45</td><td>45</td><td>80.0</td></tr> <tr> <td>SCC</td><td>14</td><td>14</td><td>71.4</td></tr> <tr> <td rowspan="2">B</td><td>BCC</td><td>40</td><td>40</td><td>100.0</td></tr> <tr> <td>SCC</td><td>14</td><td>14</td><td>78.6</td></tr> <tr> <td colspan="2">Total</td><td>113</td><td>113</td><td></td></tr> </tbody> </table> Recurrence between 2 and 6 months Initially 100% CR was achieved in all groups, but 16 patients had recurrence between 2 and 6 months post-treatment. <table border="1"> <thead> <tr> <th>Sequence (tumour type)</th><th>2 months % (n)</th><th>4 months % (n)</th><th>5 months % (n)</th><th>6 months % (n)</th></tr> </thead> <tbody> <tr> <td>A (BCC)</td><td>7 (3/45)</td><td>-</td><td>13 (6/45)</td><td>-</td></tr> <tr> <td>A (SCC)</td><td>21 (3/14)</td><td>7 (1/14)</td><td>-</td><td>-</td></tr> <tr> <td>B (BCC)</td><td>-</td><td>-</td><td>-</td><td>-</td></tr> <tr> <td>B (SCC)</td><td>-</td><td>-</td><td>-</td><td>21 (3/14)</td></tr> </tbody> </table>				Sequence	Tumour type	No. patients	No. lesions	CR (%)	A	BCC	45	45	80.0	SCC	14	14	71.4	B	BCC	40	40	100.0	SCC	14	14	78.6	Total		113	113		Sequence (tumour type)	2 months % (n)	4 months % (n)	5 months % (n)	6 months % (n)	A (BCC)	7 (3/45)	-	13 (6/45)	-	A (SCC)	21 (3/14)	7 (1/14)	-	-	B (BCC)	-	-	-	-	B (SCC)	-	-	-	21 (3/14)
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	Key safety findings None reported.																																																								
	Comments Follow-up issues: - Monthly follow-up for at least 12 months. - No report of loss to intended follow-up. Study design issues: - Purpose of the study is to compare 2 pulse protocols – long versus short pulses. - No randomisation of patients between pulse protocols. - No description of electrodes - Difference in response rates is not tested or discussed. - No statistical basis for conclusion regarding the relative effectiveness of the 2 pulse sequences. Study population issues: - No assessment of patient group baseline differences. Mean age and lesion size appear similar, but mean bleomycin dose appears larger in the B sequence group (750/800 vs. 500 IU). Other issues: - Mean electric field strength was higher in BCC treatments.																																																								

Abbreviations used: BCC, basal cell carcinoma; CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; IU, international units; IV, intravenous; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease.																																															
Study details	Key efficacy findings			Key safety findings																																											
Heller R (1998)² Non-randomised comparative study USA Recruitment period: 1995–1996 Study population: patients with cutaneous malignancies n=34 patients (169 lesions) 20 BCC (65 lesions), 1 SCC (1 lesion), 12 melanoma (96 lesions), 1 Kaposi (7 lesions) IT bleomycin ECT (143 lesions) vs. IT bleomycin alone (20 lesions) vs. pulses alone (6 lesions) Age: 59.6 years (mean) Sex: 85.3% (29/34) male Patient selection criteria: patients with BCC, advanced melanoma metastatic to local or distant soft tissue and skin sites, SCC or Kaposi's sarcoma, even if standard therapies had failed. Technique: IT bleomycin administered at a concentration of 5000 IU/ml dependent on tumour volume (500 IU <100mm³ up to 4000 IU >5000mm³). Electric pulses administered using a BTX T820 Electro Square Porator (Genetronics) and plate or needle electrodes. Approximately 25% of patients were randomly selected for post-treatment biopsies. 11 lesions were selected for bleomycin-only or EPT-only treatment. Follow-up: 20 months (mean) (BCC only) Conflict of interest/source of funding: Supported by a grant from Genetronics Inc. Heller is scientific adviser for Genetronics Inc. and received stock options.	Number of patients analysed: 21 patients with BCC or SCC (66 lesions) Mean diameter: BCC (65 lesions) – 8.1 (3–21) mm SCC (1 lesion) – not known ECT lesion response rates (at 12 weeks) <table border="1"> <thead> <tr> <th>Tumour type</th><th>No. patients</th><th>No. lesions</th><th>NR % (n)</th><th>PR % (n)</th><th>CR % (n)</th></tr> </thead> <tbody> <tr> <td>BCC</td><td>20</td><td>54</td><td>0</td><td>5.6 (3/54)</td><td>94.4 (51/54)</td></tr> <tr> <td>SCC</td><td>1</td><td>1</td><td>0</td><td>100.0</td><td>0</td></tr> <tr> <td>Total</td><td>21</td><td>55</td><td>0</td><td>7.3 (4/55)</td><td>92.7 (51/55)</td></tr> </tbody> </table> Comparators (BCC) <table border="1"> <thead> <tr> <th>Comparator</th><th>No. patients</th><th>No. lesions</th><th>NR % (n)</th><th>PR % (n)</th><th>CR % (n)</th></tr> </thead> <tbody> <tr> <td>EPT</td><td></td><td>3</td><td>100.0</td><td>0</td><td>0</td></tr> <tr> <td>Bleomycin</td><td></td><td>8</td><td>87.5% (7/8)</td><td>12.5% (1/8)</td><td>0</td></tr> </tbody> </table> PR (BCC) – 2/3 were retreated and CR achieved, resulting in a final CR of 98% (53/54) Tumour control (after 12 weeks) Random biopsies in 25% (9/34) of study patients reported 100% correlation between histopathological results and clinical observations. PR lesions in ECT group showed necrosis along with small areas of viable tumour cells. Lesions treated with only bleomycin or EPT showed no significant histological changes. Recurrence (at 20 months) All tumours with a CR at 12 weeks (51/54) reported no recurrence.			Tumour type	No. patients	No. lesions	NR % (n)	PR % (n)	CR % (n)	BCC	20	54	0	5.6 (3/54)	94.4 (51/54)	SCC	1	1	0	100.0	0	Total	21	55	0	7.3 (4/55)	92.7 (51/55)	Comparator	No. patients	No. lesions	NR % (n)	PR % (n)	CR % (n)	EPT		3	100.0	0	0	Bleomycin		8	87.5% (7/8)	12.5% (1/8)	0	Procedural complications Muscle contractions were observed during each pulse but subsided after the pulse in all patients. Discomfort was reported by the 'majority' of patients at the treatment site during each pulse but disappeared immediately after pulsing. Greater intensity was at the extremities with plate electrodes and with larger gaps between the plate electrodes. Post-procedural complications Slight burning of the skin from the plate electrodes that healed in 6–8 weeks was reported in 87% (7/8) of patients. Muscle fatigue for 24 hours in treated limbs was reported by 'a few' patients. No further details reported. Slight nausea for 24–48 hours was reported in 6% (2/34) patients and 'may' have been related to the chemotherapy drug. No further details reported.	
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			Comments Follow-up issues: - Patients questioned about symptoms after 24 and 48 hours and lesions observed periodically for 12 weeks. - Longer-term observation must have taken place, but was not described. Study design issues: - Prospective study. - Randomisation and distribution of lesions is not described. Inpatient comparisons are not performed. - The choice of plate or needle electrodes was not described. - The distribution of biopsies between the lesion types is not described. Other issues - All BCCs treated were diagnosed as a nodular subtype. No superficial aggressive growth or BCC subtypes were included. 13 patients (103 lesions, melanoma and Kaposi) are not within the scope of this report. - The IT chemotherapy doses appear to be much higher than those recommended in the ESOPE guidelines. - There may be some overlap of patients with Mir LM (1998)⁴.																																												

Abbreviations used: BCC, basal cell carcinoma; CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; IU, international units; IV, intravenous; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease.																																			
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Peycheva (2001)³ Case series Bulgaria Recruitment period: not reported. Study population: patients with cutaneous malignant tumours n=127 patients (160 lesions) 99 BCC (126 lesions), 23 SCC (23 lesions), 5 mycosis fungoides (11 lesions) Age: 68.9 years (BCC), 67.4 years (SCC) (mean) Sex: not reported. Patient selection criteria: patients attending as outpatients in dermatology oncology clinic, confirmed diagnosis (BCC, SCC or mycosis fungoides), T1N0M0 stage disease, no cardiac arrhythmia or pacemakers. Technique: intratumoural bleomycin at dose 0.5 to 3.5 U depending on mean tumour diameter. EPT was delivered in runs of 8 biphasic pulses (50+50 microseconds). Mean electric field strength was 1400 V/cm for BCC and 860 V/cm for SCC. Suspected persistence checked by cytology/histology. Follow-up: up to 3 years Conflict of interest/source of funding: not reported.	Number of patients analysed: 122 patients with BCC or SCC (149 lesions) Mean lesion size: BCC: 16.4±1.2 mm SCC: 12.1 ±1.1 mm Lesion response rates (evaluation time point uncertain) <table border="1"> <thead> <tr> <th></th><th>No. patients</th><th>No. lesions</th><th>CR %</th></tr> </thead> <tbody> <tr> <td>BCC</td><td>99</td><td>126</td><td>96.4</td></tr> <tr> <td>SCC</td><td>23</td><td>23</td><td>95.7</td></tr> </tbody> </table> 3 patients with BCC had 3 lesions with SD at 3 months. Of these, 1 patient received a second treatment and remained CR at 12 months. 3 patients with SCC had 3 lesions with SD at 3 months. Of these, 2 patients received a second treatment and reported CR at 15-month follow-up. Survival <table border="1"> <thead> <tr> <th>Patients</th><th>1 year</th><th>2 years</th><th>3 years</th></tr> </thead> <tbody> <tr> <td>BCC (n)</td><td>92/99</td><td>87/92</td><td>81/87</td></tr> <tr> <td>SCC (n)</td><td>19/23</td><td>17/19</td><td>14/17</td></tr> <tr> <td>Total (n)</td><td>111</td><td>104</td><td>95</td></tr> <tr> <td>Rate* (%)</td><td>90.9</td><td>85.2</td><td>77.9</td></tr> </tbody> </table> * The survival rate here is calculated by the reviewer, not that reported in the paper which was an actuarial rate.		No. patients	No. lesions	CR %	BCC	99	126	96.4	SCC	23	23	95.7	Patients	1 year	2 years	3 years	BCC (n)	92/99	87/92	81/87	SCC (n)	19/23	17/19	14/17	Total (n)	111	104	95	Rate* (%)	90.9	85.2	77.9	1 BCC patient had allergic reaction to bleomycin that resolved in 10 days. No further details reported.	Follow-up issues: - Assessment at 3 days, 1 and 3 months. Follow-up every 6 months, up to 3 years. 9% (9/99, 9 lesions) of patients with BCC lost to follow-up. - Lesion response appears to be determined at 3 months. - Unclear which patients (90 or 99) contribute to the quoted response rates and whether this includes second treatment. - The survival rates reported in the article are actuarialised, i.e. they represent the percentage of patients surviving in each year. This produces inflated survival rates. Study design issues: - Prospective study. - No description of device used. 5 patients with mycosis fungoides were additionally given intratumoural interferon-α. Population issues: - Patients with BCC had 75.4% (95/126) of lesions on the face. Patients with SCC had 74% lesions on the lip. Other issues: 5 patients (11 lesions, mycosis fungoides) were outside the scope of this report. 1 SCC patient with stable disease was given near-focus X-ray therapy.
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Mir LM (1998)⁴ Case series France (3 centres), USA, Slovenia. Recruitment period: not reported. Study population: patients with cutaneous and subcutaneous tumours. n=50 patients (291 tumours) 10 BCC (32 tumours), 20 melanoma (142 tumours), 3 metastases of adenocarcinoma (30 tumours), 17 metastases of head and neck SCC (87 tumours). Age: 55.8 years (mean) BCC; 54.6 years (mean) all patients Sex: not reported. Patient selection criteria: patients with primary BCC of skin had previous surgery or multiple lesions and refused further standard treatments. Technique: European centres: IV bleomycin was administered at either 18 units m⁻² (10 mg m⁻²) or 27 units m⁻² (15 mg m⁻²). Pulses delivered using PS 15 Jouan electropulsator and plate electrodes. US centre: IV bleomycin at 0.25 to 1.0 U per tumour. Pulses delivered using Genetronics BTX T820 generator and plate or needle electrodes. Follow-up: 15 months (mean) (BCC only) Conflict of interest/source of funding: some funding provided from Genetronics Inc.		Number of patients analysed: 10 patients with BCC (32 tumours) BCC mean diameter 7.7 mm. <table><tr><th>Response rates (at ≥30 days)</th><th>No. patients</th><th>No. tumours</th><th>PR % (n)</th><th>CR % (n)</th></tr><tr><td>IV bleomycin</td><td>2</td><td>6</td><td>83.3 (5/6)</td><td>16.7 (1/6)</td></tr><tr><td>IT bleomycin</td><td>8</td><td>26</td><td>11.5 (3/26)</td><td>88.5 (23/26)</td></tr><tr><td>All tumours</td><td>10</td><td>32</td><td>25.0 (8/32)</td><td>75.0 (24/32)</td></tr><tr><td>Per patient</td><td></td><td>10</td><td>30 (3/10)</td><td>70 (7/10)</td></tr></table> The first 2 patients (6 tumours) received IV bleomycin, which produced unacceptable response rates; 8 subsequent patients (26 lesions) were treated with IT bleomycin. Comparisons: 15 additional tumours were treated with either bleomycin or EPT alone; resulted in 100% PD. In the IT bleomycin patients, 2/3 PRs were retreated and CRs were obtained. The 8 PRs occurred in 3 patients: 1/3 also had 1 CR tumour, 1/3 also had 7 CR tumours. ‘Several’ cases reported reduced tumour pain. Recurrence (15 months) The 24 tumours (24/32; 75%) that disappeared within 1 month did not recur during follow-up.			Response rates (at ≥30 days)	No. patients	No. tumours	PR % (n)	CR % (n)	IV bleomycin	2	6	83.3 (5/6)	16.7 (1/6)	IT bleomycin	8	26	11.5 (3/26)	88.5 (23/26)	All tumours	10	32	25.0 (8/32)	75.0 (24/32)	Per patient		10	30 (3/10)	70 (7/10)	Procedural complications Muscle contractions during ECT disappeared immediately after pulsing. Numbers not reported. Erythema and slight oedema at tumour site (transient and resolved within 24 hours). Numbers not reported. Transient electrode marks were often visible. Further details not reported. Post-procedural complications Superficial leukonecrosis reported in large tumours in which the skin was altered before ECT. Further details not reported.	Follow-up issues: - Clinical outcome determined at least 30 days after treatment. Actual time point of assessment is unclear. Study design issues: - Prospective multicentre study. - The data are aggregated from independent trials at 5 centres. - The centres had different protocols for anaesthesia, chemotherapy administration and pulse delivery. - The selection of tumours for bleomycin-only treatment is not described. - No assessment of tumour size in response rates. Other issues 40 patients (259 tumours, melanoma and metastatic cancers) are not within the scope of this report. - The IV chemotherapy doses in the European centres are significantly larger than those recommended in ESOPE guidelines. - There may be some overlap of patients with Heller R (1998)².
Response rates (at ≥30 days)	No. patients	No. tumours	PR % (n)	CR % (n)																											
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Study details	Key efficacy findings	Key safety findings	Comments
Psycheva E (1999)⁹ Case series Bulgaria Recruitment period: not reported. Study population: patients with malignant tumours of the skin. n=24 patients (38 lesions) 16 BCC (20 lesions), 4 SCC (5 lesions), 4 melanoma (disseminated disease). Age: 71.4 years BCC, 72.0 years SCC (mean) Sex: 15% male BCC, 75% male SCC Patient selection criteria: not reported. Technique: intratumoural bleomycin 0.5–2.0 U dependent on lesion size. Electric pulses applied using custom-made device and surface electrodes formed from parallel wires. Electric fields strength varied from 500 to 2000 V/cm with a mean of 1400V/cm for BCC and 820 V/cm for SCC. Three sequences of electric pulses were used. (1) 8 monophasic rectangular pulses, 100 microseconds duration, spaced at 1 s (1 Hz) (2) 8 biphasic rectangular pulses, 50+50 microseconds duration, spaced at 1 s (1 Hz) (3) 8 biphasic rectangular pulses, 50+50 microseconds duration, spaced at 1.0 ms (1000 Hz) Follow-up: 6 months (mean) Conflict of interest/source of funding: not reported.	Number of patients analysed: 20 patients with BCC or SCC (25 lesions) Mean diameter: BCC (20 lesions) – 11.4 mm SCC (5 lesions) – 15.4 mm Lesion response rates (evaluation time point uncertain) 100% CR was reported – appears to be the response to 'total treatment' (including 2 patients with second treatments). 2 patients (1 BCC, 1 SCC) had 'persistence' at the lesion border (3 months and 2 months respectively). They received a second treatment and there was no further recurrence during about 5 months' follow-up. Taking these 2 patients into account as PRs, the first treatment response rate is: BCC: 5% PR 95% CR SCC: 25% PR 75% CR	1 patient had an allergic reaction to bleomycin. Further details not reported. Slight oedema and erythema were reported 72 hours post-treatment (numbers not reported). Patients tolerated the sequence with the faster repetition rate better, because they perceived all 8 as a single pulse. This is important because some patients perceive the sensation as a pain rather than a jolt.	Follow-up issues: - Follow-up procedure not reported, but appears to include a 6-day and 20-day review. - The time at which response is determined is not reported. Study design issues: - Prospective study. - Unclear whether lesions received 1 pulse sequence or all 3. - No inter-disease comparison. - Very poor reporting of study. Study population issues: - There is no assessment of patient group baseline differences. Mean age is similar, but lesion size and dose appear larger and electric field strength smaller in the SCC group than in the BCC group. Other issues - The electric field strength achieved is dependent on the lesion size and the 'voltage available from the pulse generator'. Values calculated from the tables differ from those in the text. 4 patients with melanoma were outside the scope of this report.

Abbreviations used: BCC, basal cell carcinoma; CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; IU, international units; IV, intravenous; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease.													
Study details	Key efficacy findings	Key safety findings	Comments										
Gargiulo M (2012)⁶ Case series Italy Recruitment period: 2007–2010 Study population: patients with primary or relapsed non-melanoma head and neck cancers n=25 patients (38 tumours) 9 BCC, 10 SCC, 3 recurrent SCC, 2 adenocarcinoma, 1 Bowen's disease Age: 73.9 years (mean) Sex: 68% male Patient selection criteria: based on ESOPE guidelines: life expectancy >6 months, measurable cutaneous lesions, offered ECT as a therapeutic option based on age, poor general condition, comorbidities, reduced lung performance, and cardiac deficit not related to electrical malfunction. Technique: procedure was based on ESOPE guidelines. Intravenous bleomycin at a dose of 15,000 IU/m² body surface area injected. EPT was delivered using a Cliniporator device and different types of electrodes at a frequency of 5000 Hz and 100µs duration. Follow-up: 18 months (median) Conflict of interest/source of funding: none	Number of patients analysed: 25 Tumour response at 6 weeks after first ECT OR: 100% CR: 72% (18/25) PR: 28% (7/25); 5 SCC and 2 adenocarcinomas CR was 89.5% for tumours of 4 cm or smaller and 16.7% for those larger than 4 cm. Recurrence None of the lesions that achieved a CR relapsed after a median follow-up of 18 months. 7 partial responders showed SD for the duration of follow-up. Survival at end of follow-up 22/25 patients were alive and free of disease and 3/25 patients were dead as a result of disease progression outside the treated area. Local control At a median follow-up of 18 months, ECT achieved a complete local control in 100% of patients with BCC and 65% of patients with SCC. ECT proved to be palliative to 15% SCCs and neoadjuvant in 20% SCCs.	<table><tr><th colspan="2">Adverse events</th></tr><tr><td>Serious adverse events</td><td>0</td></tr><tr><td>Haematological toxicity due to bleomycin</td><td>0</td></tr><tr><td>Unpleasant sensation due to muscle contraction with electric pulses</td><td>20% patients treated with local anaesthesia</td></tr><tr><td>Local tumour necrosis due to delayed wound healing and local erythema (resolved spontaneously)</td><td>2/38 (parotid tumours)</td></tr></table>	Adverse events		Serious adverse events	0	Haematological toxicity due to bleomycin	0	Unpleasant sensation due to muscle contraction with electric pulses	20% patients treated with local anaesthesia	Local tumour necrosis due to delayed wound healing and local erythema (resolved spontaneously)	2/38 (parotid tumours)	Follow-up issues: - Evaluation of response at 6 weeks after first ECT. Study design issues: - Retrospective study. - Second ECT treatment was given for partial responders. - ECT was done with palliative intent in 3 partial responders and as a neoadjuvant treatment (with surgical excision) in 4. Study population issues: 19/25 had T1 or T2 primary tumour stage, 6/25 had T3 or T4 primary tumour stage of which 5 had metastases. - Only 2 patients with oral cancer were treated under general anaesthesia. - Tumours were located at different sites: forehead, lips, scalp, cheeks, nose, tongue, parotid, temple, soft palate and canthus.
Adverse events													
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Study details	Key efficacy findings	Key safety findings	Comments											
Rodriguez-Cuevas S (2001)⁷ Case series Mexico Recruitment period: 1998–1999 Study population: patients with primary and metastatic skin cancers n=15 patients (38 tumours) 9 BCC (9 tumours), 2 SCC of the aerodigestive tract metastatic to the skin (2 tumours), 2 breast cancer (14 tumours), 2 melanoma (13 tumours) Age: 74.5 years (mean) (BCC patients) Sex: 40% male Patient selection criteria: patients without pacemakers. Technique: intratumoural bleomycin at 0.5–4 U dose depending on tumour volume (<100mm³ to >5000mm³). EPT was delivered using a custom-made device and needle electrodes. Patients with PR at 3 weeks had additional ECT treatments. Biopsies carried out on uncertain outcomes. Follow-up: 8.6 months (mean) Conflict of interest/source of funding: not reported.	Number of patients analysed: 9 patients with BCC (9 tumours) BCC mean diameter: 15.7 ± 4.3 mm Tumour response rates (evaluation time point uncertain) <table border="1"> <thead> <tr> <th>Type</th><th>No. patient s</th><th>No. tumour s</th><th>PR % (n)</th><th>CR %(n)</th></tr> </thead> <tbody> <tr> <td>BCC</td><td>9</td><td>9</td><td>22.3</td><td>77.7</td></tr> </tbody> </table> BCC patients were treated in an average of 1.3±0.5 sessions.	Type	No. patient s	No. tumour s	PR % (n)	CR %(n)	BCC	9	9	22.3	77.7	Muscle contractions due to electric pulses were 'well tolerated' in all patients but more intense in patients with facial tumours (further details not reported).	Follow-up issues: - Evaluation of response at 3 weeks. No other details reported. - It is unclear whether the quoted response rates relate to the 3-week evaluation or after PRs received additional treatment. Study design issues: - Prospective phase II study. - It is unclear whether the number of treatment sessions relates to repeated treatment of the same tumour or treatment of different tumours. The largest number of treatments was for single large SCCs. No assessment of tumour stage. Study population issues: - The authors state that better results are obtained in the primary BCC group; no statistical assessment of this is reported. Other issues: 6 patients (2 melanoma, 2 SCC from aerodigestive tract metastatic to skin, 2 breast) are outside the scope of this report. - The chemotherapy dose is higher than that recommended in the ESOPE guidelines.	
Type	No. patient s	No. tumour s	PR % (n)	CR %(n)										
BCC	9	9	22.3	77.7										

Abbreviations used: BCC, basal cell carcinoma; CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; IU, international units; IV, intravenous; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease.																													
Study details	Key efficacy findings			Key safety findings																									
Landström F (2010)⁸ Case series Sweden Recruitment period: 2005–2007 Study population: patients with skin cancer in the head and neck area. n=6 patients (6 tumours) 3 BCC, 3 SCC Age: 76.5 years (mean) Sex: 50% male Patient selection criteria: skin cancer of the head and neck area. Life expectancy >6 months. Technique: intratumoural bleomycin administered at a dose of 1000 IU/mL (0.25 mL/mL). EPT administered using Genetronics Medpulsar and needle electrodes. Multiple overlapping electric pulses applied from the outside of the tumour to the centre. Biopsies taken at 8 weeks. Follow-up: 24 months (median) Conflict of interest/source of funding: study initiated and sponsored by Genetronics Inc.	Number of patients analysed: 6 (6 tumours) Median diameter: 19 (10–35) mm Tumour response rates (at 24 months) <table border="1"> <thead> <tr> <th>Type</th><th>Patient s (n)</th><th>Tumour s (n)</th><th>NR % (n)</th><th>PR % (n)</th><th>CR % (n)</th></tr> </thead> <tbody> <tr> <td>BCC</td><td>3</td><td>3</td><td>0</td><td>0</td><td>100 (3/3)[‡]</td></tr> <tr> <td>SCC</td><td>3</td><td>3</td><td>33.3 (1/3*)</td><td>0</td><td>66.7 (2/3)</td></tr> <tr> <td>Total</td><td>6</td><td>6</td><td>16.7 (1/6)</td><td>0</td><td>83.3 (5/6)</td></tr> </tbody> </table> Tumour control at 8 weeks (biopsies) 67% (4/6) of patients with single treatment had complete tumour control. *1 patient with progressive SCC had a 'mild local reaction' and was retreated but failed to respond. (Allocated 'NR' by reviewer.) Recurrence [‡]1 patient with T4 staged metatypical BCC developed a recurrence 6 months after the final follow-up (24 months). Functional and cosmetic outcomes 67% (4/6) patients had tumours 'complicated' by proximity to facial nerve, parotid duct, eye muscles, external meatus of the ear or orbit of the eye. No damage to nerve or ocular function was observed. Cosmetic outcome at 6–12 months described as 'very satisfactory' (numbers not reported).			Type	Patient s (n)	Tumour s (n)	NR % (n)	PR % (n)	CR % (n)	BCC	3	3	0	0	100 (3/3) [‡]	SCC	3	3	33.3 (1/3*)	0	66.7 (2/3)	Total	6	6	16.7 (1/6)	0	83.3 (5/6)	1 patient with a tumour in the nasal vestibule developed a perforation of the septal cartilage following biopsy at 8 weeks. No further details reported. 2 patients with tumours in the medial canthus experienced increased tear fluid in the ipsilateral eye but no visual impairment. This resolved within 2 months. Post-treatment pain was described as 'moderate' and managed with acetaminophen and diclofenac for 5–7 days in all patients.	
Type	Patient s (n)	Tumour s (n)	NR % (n)	PR % (n)	CR % (n)																								
BCC	3	3	0	0	100 (3/3) [‡]																								
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Total	6	6	16.7 (1/6)	0	83.3 (5/6)																								
			Comments Follow-up issues: - Planned follow-up at 8 weeks with biopsies and clinically at 4, 6, 12, 15, 18 and 24 months. - A mean follow-up period of 18.5 months is quoted, but is inconsistent with data in the text and table indicating 5/6 patients were followed up for 24 months and 1 for 3 months. - One patient with progressive SCC underwent second treatment followed by surgery and RT and was excluded from follow-up after 3 months. Study design issues: - Prospective study. - Study intent was curative. - Very small study, results not generalisable. Study population issues 3 of the tumours were recurrences and had already been treated surgically.																										

Efficacy

Tumour response (clinical observation)

A non-randomised comparative study of 113 patients (85 BCC and 28 SCC) compared 2 different electric pulse sequences for ECT of stage I (T1N0M0) BCC and SCC tumours. The complete response was 83% at 12 months¹.

A non-randomised comparative study of 34 patients comparing ECT with either intratumoural bleomycin alone or electric pulse therapy included 21 patients with BCC or SCC (66 tumours). The study reported an objective response rate of 100% and a complete response of 94% (51/54) in BCC primary tumours treated with ECT at 12 weeks. The 1 SCC tumour treated with ECT had a partial response. There were no complete responses in the 11 BCC tumours treated with either intratumoural bleomycin alone (8 tumours) or electric pulse therapy alone (3 tumours)².

A case series of 127 patients (160 tumours) reported a complete response rate of 96% for BCC and SCC (122 patients, 149 tumours). Follow-up details are uncertain, but assessment seems to have been at 3 months after treatment. Of 6 patients who had stable disease at 3 months, 3 received a second ECT treatment. One of these (BCC) had a complete response at 12 months and 2 (SCC) had a complete response at 15 months' follow-up³.

A case series of 50 patients including 10 patients with BCC primary tumours (32 tumours) reported a complete response in 75% (24/32) of tumours and a partial response in 25% (8/32) of tumours at 30 days. The complete and partial response rates per patient were 70% and 30%⁴.

A case series of 24 patients including 20 patients with BCC or SCC (25 tumours) reported a 95% (15/16) complete response in BCC patients and a 75% (3/4) complete response in SCC patients after first treatment (evaluation time point unclear). Two patients (1 BCC, 1 SCC) with 'persistence' at the tumour border (at 3 and 2 months respectively) had a complete response after a second treatment with ECT and so a 100% complete response was reported⁵.

A case series of 15 patients including 9 patients with BCC (9 tumours) reported a 78% complete response and 22% partial response after a mean of 1.3 ECT treatments. Numbers not reported. The evaluation time point is uncertain⁷.

A case series of 6 patients (3 BCC and 3 SCC tumours) reported that 83% (5/6) of patients achieved a complete response at 24 months. The remaining patient's tumour (progressive SCC) remained non-responsive after a second treatment with ECT⁸.

Recurrence of tumours

The non-randomised comparative study of 113 patients (85 BCC and 28 SCC tumours) with an initial 100% complete response reported that 14% (16/113) of tumours recurred between 2 and 6 months after treatment (no further details reported)¹.

The non-randomised study of 34 patients (including 20 patients with 54 BCC tumours and 1 patient with an SCC tumour) with 93% (51/55) complete response at 12 weeks reported no recurrences during a mean follow-up of 20 months².

The case series of 50 patients including 10 patients with BCC primary tumours (32 tumours) reported that none of the tumours that disappeared within 1 month (75%, 24/32) had recurred at a mean follow-up of 15 months⁴.

The case series of 24 patients (including 16 BCC patients with 20 tumours and 4 SCC patients with 5 tumours) with 100% complete response to 'total treatment' (including second treatments) reported no recurrences during approximately 5 months' follow-up⁵.

The case series of 6 patients (6 tumours; 3 BCC and 3 SCC) reported that 1 patient (with T4 metatypical BCC in the medial canthus) developed a recurrence 6 months after the follow-up period of 24 months (no further details reported)⁸.

Effect on surrounding tissues or organs

The case series of 6 patients reported no damage to nerve or ocular function after ECT treatment in 4 patients with tumours close to the facial nerve, parotid duct, eye muscles, external meatus of the ear or orbit of the eye⁸.

Cosmetic outcome

The case series of 6 patients (3 BCC and 3 SCC tumours) reported a 'very satisfactory' cosmetic outcome at between 6 and 12 months after ECT treatment (no further details reported)⁸.

Safety

No study reported any adverse events that were life-threatening or required additional hospital stay.

Nasoseptal cartilage perforation

A septal cartilage perforation was reported in 1 patient receiving treatment in the right nasal vestibule in the case series of 6 patients. This occurred after a biopsy performed 8 weeks after treatment. No further details were reported⁸.

Adverse events considered to be related to chemotherapy drugs

Slight nausea for up to 48 hours thought to be associated with the chemotherapeutic drug was reported in 6% (2/34) of patients in the study of 34 patients. No further details were reported².

An allergic reaction due to the chemotherapeutic drug was reported in 1 patient in the case series of 127 patients³ and in 1 patient in the case series of 24 patients⁵. The former reaction subsided within about 10 days. No further details were reported in either study.

Muscle spasms

Localised involuntary muscle contractions and a sensation of a jolt or shock associated with the electric pulses were reported in 4 studies^{2, 4, 5, 7}. They stopped immediately when the electric pulses were discontinued.

Muscle fatigue

Muscle fatigue in treated limbs that lasted for 24 hours was reported by 'a few' patients in the study of 34 patients. No further details were reported².

Skin changes

Slight burning of the skin was reported in 87% (7/8) of patients on whom the plate electrodes were used in the study of 34 patients. This healed within 6–8 weeks. No further details were reported².

Erythema and oedema at treated areas which resolved within 24 hours was reported in the case series of 50 patients⁴. Another case series of 24 patients reported erythema and oedema 72 hours after treatment⁵. No further details were reported in either study.

Miscellaneous events

Increased tear production in the ipsilateral eye was reported in 2 patients who received treatment for tumours in the medial canthus in the case series of 6 patients. This caused no visual impairment and resolved within 2 months. No further details were reported⁸.

Validity and generalisability of the studies

- The evidence in all the studies identified in the literature review was of low quality and the studies had weaknesses in both methodology and reporting. Because of the quantity of case studies available, only peer-reviewed papers where BCC or SCC results could be separately identified were included in table 2. Following the publication of the ESOPE guidelines and the development of commercial purpose-designed ECT devices, the quality of later studies is expected to improve.

- The multicentre data reported in Mir (1998)⁴ may include patients from Heller (1998)².
- None of the studies in table 2 reported blinding of the response assessment or details of the patient recruitment procedures used.
- No studies compared ECT with other standard treatment modalities (such as radiotherapy, surgery or systemic chemotherapy).
- The point at which clinical response is evaluated is often unclear or inconsistent between patients. Patients may be evaluated at 1 time point but followed up for variable lengths of time afterwards.
- No studies investigated or tested the reported differences in response between BCC and SCC cancer types.
- All the studies used bleomycin as the chemotherapeutic agent. There was no explanation for the choice of drug. The ESOPE guidelines do not indicate a preference for either cisplatin or bleomycin.
- No studies appear to have explored the relationship between electric field strength, tumour size or chemotherapy dose and clinical response.

Existing assessments of this procedure

A Horizon Scanning Report update conducted for Australia and New Zealand in 2008 looked at ECT for the treatment of local malignant tumours. It is based mainly on studies involving patients with melanoma. The authors concluded that 'ECT showed moderately satisfying effectiveness and safety in the treatment of cutaneous or subcutaneous malignancies, during short follow-up period'. In addition, evidence from a cost-effectiveness analysis from the Italian National Healthcare System's perspective indicates that 'ECT was cost effective with an ICER of €1572 to achieve an additional tumour response'. It concludes that 'electrochemotherapy appears to be an effective method of treating subcutaneous melanomas'⁸.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions). NICE interventional procedures guidance 155 (2006). Available from www.nice.org.uk/guidance/IPG155

Medical technologies guidance

- Ambulight photodynamic therapy for the treatment of non-melanoma skin cancer. NICE medical technologies guidance 6 (2011). Available from www.nice.org.uk/guidance/MTG6

Cancer service guidance

- Improving outcomes for people with skin tumours including melanoma. NICE cancer service guidance CSGSTIM (2006). Available from www.nice.org.uk/guidance/CSGSTIM

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Christopher Bower, Carol Cuthbert (British Association of Dermatologists), Howard Peach, Barry Powell, (British Association of Plastic, Reconstructive and Aesthetic Surgeons).

- Two specialist advisers have performed this procedure regularly, and 1 Adviser has done it only twice in this group of patients. The other had never performed it. One specialist adviser stated that the procedure is carried out under general anaesthesia in most cases as the degree of sedation used with local anaesthetic is not acceptable for use in an outpatient setting in the UK.
- Two specialist advisers have experience in selecting patients for this procedure regularly.
- One specialist adviser suggested an alternative title: 'Role of ECT both in the management of primary disease and disseminated disease'. Another Adviser suggested: 'Electrochemotherapy for treatment of non-melanoma skin cancers'.
- One specialist adviser indicated that results were satisfactory in selected cases and patient selection is crucial for this procedure.
- One specialist adviser stated that repeated treatments are needed.
- Two specialist advisers stated that this procedure could be considered as novel practice, being performed by fewer than 10% of 'doctors. One specialist adviser stated that it is an established procedure performed by fewer than 10% of doctors. One specialist adviser stated that the evidence primarily involved recurrent disease.
- Two specialist advisers have undertaken bibliographic research and 1 Adviser has undertaken clinical research in ECT to treat patients with malignant melanoma.
- Two specialist advisers stated that there is no direct comparator because the procedure is used for patients for whom standard therapies have failed to control disease. One Adviser stated that isolated limb infusion/perfusion can be a comparator for multiple recurrences and surgical resection can be a comparator for isolated lesions.
- Reported adverse events included bleomycin-induced toxicity, pulmonary fibrosis as a result of bleomycin, muscle spasm, increase in wound exudate after the procedure, pain, nausea and lipothymia.

- Chemotherapy toxicity, nausea, pain, lipothymia and electrical burns were suggested as theoretical adverse events. One specialist adviser expressed concerns about adherence to chemotherapy policies.
- specialist advisers listed key efficacy outcomes as improvement in disease state or cure, control of disease tumour regression, duration of benefit, number of procedures needed, better quality of life (assessed using standard measures), control of bleeding and odour from fungating tumours, and reduction in pain from painful tumours. One Adviser noted that the procedure is not always successful.
- Two specialist advisers stated that there is an European registry (InspECT) for sharing and recording ECT information and a few European studies currently enrolling patients.
- One specialist adviser indicated the need for training in the procedure. One specialist adviser noted that patient selection is crucial and needs to be performed by someone trained to allow appropriate patients to be treated. He also suggested that the procedure should be considered as part of a multidisciplinary team, and is best performed by a surgeon because there will be cases where both ECT and surgical excision are needed and they can be done at the same time. He suggests that it can also be performed by a trained nurse specialist as the procedure does not require complex surgical skills. One specialist adviser noted that ongoing support is provided by the manufacturer.
- One specialist adviser stated that the procedure is performed in at least 10 hospitals in the UK and should be carried out by a specialist skin cancer multidisciplinary team including trained nurse practitioners; chemotherapy facilities and expertise are needed. Two specialist advisers stated that the procedure is likely to be performed in at least 10 specialist cancer units with chemotherapy facilities.
- Two specialist advisers said that the procedure would have a minor impact on the NHS but the impact might increase when it is well established. Only 1 specialist adviser stated that the procedure would have a moderate impact on the NHS, because it is currently used for recurrent disease. However, he thinks that if the indications for treatment change (for example complex primary non-melanotic skin malignancy, or other indications such as recurrent head and neck surgery or sterilising a tumour bed after tumour resection) then the impact would be greater.

Patient commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- Registry – an online registry for European ECT patients was instigated in 2008 and contains data on approximately 80 patients.

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8. Liufu V, Hiller JE (2008) Electrochemotherapy (ECT) for malignant tumours (update). Adelaide: Adelaide Health Technology Assessment (AHTA) on behalf of National Horizon Scanning Unit (HealthPACT and MSAC)

Appendix A: Additional papers on electrochemotherapy for the treatment of skin cancers

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non- inclusion in table 2
Asilian A, Momeni I., and Basiri A. (2013) Treatment of skin tumors with electrochemotherapy. Journal of Isfahan Medical School 31 (226)	Review	Among all available medicines, bleomycin and cisplatin have been widely studied in pre-clinical and clinical trials. In human clinical trials, electrochemotherapy has been an efficient method for treating advanced diseases with accessible malignant tumors of various types	Review
Fantini F, Gualdi G, Cimitan A et al. (2008) Metastatic basal cell carcinoma with squamous differentiation: report of a case with response of cutaneous metastases to electrochemotherapy. Archives of Dermatology 144 (9): 1186-1188	Single patient case study – metastatic BCC.	'Rapid clinical and histologic regression of the treated lesions'. No additional safety information in abstract.	Single patient. Table 2 contains information on patients with primary skin cancer.
Glass LF, Jaroszeski M, Gilbert R, et al. (1997) Intralesional bleomycin-mediated electrochemotherapy in 20 patients with basal cell carcinoma. Journal of the American Academy of Dermatology 37(4): 596-599.	BCC: 20 (54 lesions) Mean follow-up: 18 months	Additional safety information not reported in Heller (1998): 1 patient developed a wound infection on the ear, which responded to oral antibiotics.	These patients are included in Heller (1998).
Heller R, Jaroszeski MJ, Glass LF et al. (1996) Phase I/II trial for the treatment of cutaneous and subcutaneous tumors using electrochemotherapy. Cancer 77 (5): 964-971	6 case report: 2 patients with primary BCC (6 lesions) Follow-up of 90 days and 119 days .	Additional safety information: 2 of 6 patients reported that they had nausea, fever, chills, and general malaise for 24 to 48 hours after treatment, perhaps related to systemic chemotherapy. No further details reported.	Only 2 relevant patients with poor reporting of outcomes.

Kis E, Baltas E et al. (2012) Successful treatment of multiple basalomas with bleomycin-based electrochemotherapy: a case series of three patients with Gorlin-Goltz syndrome. Acta Dermato-Venereologica 92 (6) 648-651	Case series n=3 Patients with Gorlin-Goltz syndrome were treated with electrochemotherapy using intravenous bleomycin.	Gorlin-Goltz syndrome is a rare multisystemic disease, characterized by numerous basal cell carcinomas. Clinical response was obtained in 98 (99%) of the lesions, 86 (87%) of them showed complete response. In 2 tumours, regression was confirmed with histological examination. Long-term cosmetic results were excellent. We suggest using it as early as possible in selected patients to avoid disfiguring scarring.	Only 3 patients.
Mali B, Jarm T, Snoj M et al. (2013) Antitumor effectiveness of electrochemotherapy: a systematic review and meta-analysis. [Review]. European Journal of Surgical Oncology 39 (1) 4-16	Systematic review clinical effectiveness of electrochemotherapy, differences in effectiveness of electrochemotherapy with respect to tumor type, chemotherapeutic drug, and route of drug administration. n=44 studies Meta-analysis comparing responses of tumours of different histological types included in the systematic review.	In total, 44 studies involving 1894 tumors were included in the review. Data analysis confirmed that electrochemotherapy had significantly ($p < .001$) higher effectiveness (by more than 50%) than bleomycin or cisplatin alone. The effectiveness was significantly higher for intratumoral than for intravenous administration of bleomycin ($p < .001$ for CR%, $p = .028$ for OR%). Bleomycin and cisplatin administered intratumorally resulted in equal effectiveness of electrochemotherapy. Electrochemotherapy was more effective in sarcoma than in melanoma or carcinoma tumors. The results of this review shed new light on effectiveness of electrochemotherapy and can be used for prediction of tumor response to electrochemotherapy with respect to various treatment conditions.	Systematic Review is of poor quality as studies are not referenced properly and some of the key papers (on BCC and SCC) included in the meta-analysis are already in Table 2.
Mevino N, Bertino G et al (2012). Electrochemotherapy for the treatment of recurrent head and neck cancers: preliminary results. Tumori, 98:308-313.	Case series n=15 (33 lesions) 13 SCC, 1BCC, 1 Merkel cell carcinoma. Follow-up: 20 months	CR: 61.5% (19/31) lesions < 3cm. PR: 32.5% (10/31) SD: 3% (1/30) PD: 3% (1/30) OR at 2 months 94% at 20 months 29% were alive and free of disease, 50% alive with disease, 14% died of disease, 7% died of other causes.	Recurrent or extended primary head and neck cancer in patients not suitable for standard treatment options.

Pennacchioli E, Margarino C et al. (2011) Electrochemotherapy for treatment of locally advanced superficial cancer: Results from a single Institution. Pigment Cell and Melanoma Research 24 (5) 1074	Case series Electrochemotherapy in superficial spreading of different cutaneous and non-cutaneous diseases. n=179 Primary diseases (62 pts): SCC 40% (25/62), BCC 37% (23/62) and melanoma 8% (5/62). Metastatic disease 117 patients: 76% melanoma) 179 ECT treatments(iv Bleo 159 cases, local Bleo 20 cases) Follow-up: 1 year	Results at 1 month are: CR 12% of cases, PR 84% of cases; NR 4% of cases; at 3 months CR 14%; PR 47% PRO 26% and 5% DOD; 1 yr after treatment 18% CR; 25% PR 40% PRO and 10% DOD. The mean length of response in melanoma was 3 months (mean 2- 8 months). Concerning the histotype, CR was obtained in 57% cases of Kaposi sarcoma, 50% of BCC and 9% of melanoma. PR was obtained in melanoma in 89% of cases at 1 month, 35% at 6 months and 25% at 1 yr. The treatment was never used to obtain surgical operability. Local toxicity consist in mild pain, self-retaining serum effusion for at least couple of weeks and rare ulceration of treated nodules. In relation to the histotype it should be considered a palliative local treatment (melanoma, breast cancer) or a definitive curative treatment (Kaposi sarcoma and BCC).	Overall and BCC response rates were only reported. Full paper not available
Richetta AG, Curatolo P, D'Epiro S et al. (2011) Efficacy of electrochemotherapy in ulcerated basal cell carcinoma. La Clinica Terapeutica 162 (5): 443-445	Single patient case report – extensive and ulcerated BCC	'Successful' management where other approaches would have been 'dangerous and inappropriate'.	Single patient. English abstract, article in Italian.
Sersa G, Stabuc B, Cemazar M, et al. (1998) Electrochemotherapy with cisplatin: potentiation of local cisplatin antitumour effectiveness by application of electric pulses in cancer patients. European Journal of Cancer 34(8): 1213-1218.	4 case reports (cutaneous cancers) including 1 patient with recurrent BCC (9 lesions). Follow-up: 7-11 months.	Additional safety information: Note that this study does not report local or general anaesthesia. Reported pain of treatment is probably related to this. 1 patient with a lesion on the left side of the back at the level of the heart reported discomfort in the chest during treatment. No ECG abnormalities and no breathing disturbances.	Only 1 relevant patient.

Tassinari J, Orlandino G, and Fabrizio T. (2010) Electrochemotherapy in head and neck cancer. European Surgical Research 45 (3-4) 223-224	Case series n=10 Head and neck cancer patients (9 SCC and 1 metastases of SCC) Follow-up: not reported	The average age was 75,7 years. In all patients we found a reduced dimension of the tumour and bleeding stopped. In all patients after twenty days a reduction of the tumour with objective and documented clinical and radiological examinations was noted.	Only 9 patients with SCC. Full paper not available
Tavaniello B, Ceccone A et al. (2010) Electrochemotherapy for primary or metastatic skin tumours: A single institution experience. European Surgical Research 45 (3-4) 237	Case series n=26 patients (123 lesions) (in-transit metastases of melanoma: 22 pts (112 nodules), skin metastases from breast cancer: 1 pt (5 nodules), basal cell carcinoma: 1 pt (1 nodule), squamous cell carcinoma of the vulva: 1 pt (1 nodule), squamous cell carcinoma of the head skin :1 pt (4 nodules). Median follow-up was 14.1 months	After a median follow-up of 14.1 months, 3/26 patients were lost to follow-up, 15/23 (65.2 %) patients are alive in CR, in 3/23 patients we observed a progression of systemic disease after 2 months and 5/23 (21.7 %) patients are in PR; the local control rate is 86.9 %. No significant differences in response we observed comparing to the two drugs. No local and systemic toxicity was documented and the tolerance was adequate.	Only 3 relevant patients (1 BCC and 2 SCC).
Vitali GC, Verrecchia F et al. (2010) Electrochemotherapy with bleomycin: A local treatment with possible systemic implications. European Surgical Research 45 (3-4) 226-227	Case series n=73 patients with superficial cancer lesions; (55 had metastatic melanomas and 15 had squamous or large basal cell carcinomas). Follow-up: not reported	We observed an overall response (OR) rate of 90%; a complete response (CR) rate of 72% in melanoma patients and a CR rate of 65% in non-melanoma patients. Of the 73 patients, only 8 relapsed in the treatment field. The procedure, either under general or local anesthesia, was well tolerated with minimal side effects or discomfort for the patients. ECT is a safe and well tolerated procedure with quality of life improvement especially in a palliative setting.	15 patients with SCC or BCC. Full paper not available

Appendix B: Related NICE guidance for electrochemotherapy for the treatment of skin cancers

Guidance	Recommendations
Interventional procedures	Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions). NICE interventional procedures guidance 155 (2006) 1.1 Current evidence suggests that there are no major safety concerns associated with photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions). 1.2 Evidence of efficacy of this procedure for the treatment of basal cell carcinoma, Bowen's disease and actinic (solar) keratosis is adequate to support its use for these conditions, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.3 Evidence is limited on the efficacy of this procedure for the treatment of invasive squamous cell carcinoma. Recurrence rates are high and there is a risk of metastasis. Clinicians should ensure that patients understand these risks and that retreatment may be necessary. In addition, use of the Institute's information for the public is recommended (available from www.nice.org.uk/guidance/IPG155).
Medical technologies guidance	Ambulight photodynamic therapy for the treatment of non-melanoma skin cancer. NICE medical technologies guidance 6 (2011) Ambulight PDT offers a means of delivering photodynamic therapy (PDT) for patients with small non-melanoma skin cancers in an ambulatory care setting, including patients' homes, and its use may be associated with less pain than conventional PDT. However, the case for routine use of Ambulight PDT in achieving a more efficient service is not supported by the evidence submitted by the manufacturer. The quantity of clinical evidence on its use is limited and the cost consequences of adoption, when compared with conventional PDT, ranged from a saving (per patient) of £195 to a cost increase of £536. NHS organisations should take this into account, alongside other features of the technology, when considering whether to use Ambulight PDT.
Cancer service guidance	Improving outcomes for people with skin tumours including melanoma. NICE cancer service guidance CSGSTIM (2006)

	• Cancer networks should establish two levels of multidisciplinary teams – local hospital skin cancer multidisciplinary teams (LSMDTs) and specialist skin cancer multidisciplinary teams (SSMDTs). All health professionals who knowingly treat patients with any type of skin cancer should be members of 1 of these teams, whether they work in the community or in the hospital setting. • All patients with a suspicious pigmented skin lesion, with a skin lesion that may be a high-risk BCC, a squamous cell carcinoma (SCC) (see 'Glossary of terms', Appendix 6, for definitions) or a malignant melanoma (MM), or where the diagnosis is uncertain, should be referred to a doctor trained in the specialist diagnosis of skin malignancy, normally a dermatologist, who is a member of either an LSMDT or an SSMDT. • Cancer networks should ensure, through the skin cancer network site-specific group, that LSMDTs and SSMDTs work to network-wide agreed protocols for: – referral – review of patient care by the multidisciplinary team (MDT) management and audit of services for precancerous lesions and skin cancer services. They should also ensure provision of ongoing education for all healthcare professionals about this very common group of tumours. • The follow-up of patients after treatment should be jointly agreed between patient and doctor. After appropriate instruction, patients with low-risk disease will normally practise self-examination but follow-up may be offered in a community setting where appropriate. Patients with a high risk of recurrence of their skin cancer or of new primary cancers should normally be followed up in hospital but should still be instructed in self-examination and provided with written and photographic information. • All patients and carers should have access to high-quality information, in an appropriate style and format, about their condition and its management and about access to relevant support services. • Skin cancer network site-specific groups should follow protocols covering the management of high-risk groups or those with special needs such as transplant patients, those with genetic predisposition to skin cancer, patients with rare skin tumours (including cutaneous lymphoma), and children and young people. • Data collection on skin cancer including cancer
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	registration should be improved to adequately describe the epidemiology and service implications of the increasing incidence of skin cancer. This should be facilitated by new developments in information technology to enable more accurate and timely provision of this information. • Commissioners of cancer services should create an infrastructure for well-conducted research to take place in order to contribute to the skin cancer evidence base in epidemiology, treatment and management.
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Appendix C: Literature search for electrochemotherapy for the treatment of skin cancers

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	19/09/13	Issue 9 of 12, September 2013
Database of Abstracts of Reviews of Effects – DARE (WILEY)	19/09/13	Issue 3 of 4, Jul 2013
HTA database (CRD website)	19/09/13	Issue 3 of 4 Jul 2013
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	19/09/13	Issue 8 of 12, August 2013
MEDLINE (Ovid)	19/09/13	Ovid MEDLINE(R) 1946 to September Week 2 2013
MEDLINE In-Process (Ovid)	19/09/13	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations September 18, 2013
EMBASE (Ovid)	19/09/13	Embase 1974 to 2013 Week 37
CINAHL (NLH Search 2.0 or EBSCOhost)	19/09/13	-

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

- 1 Electrochemotherapy/
- 2 electrochemo*.tw.
- 3 CLINIPORATOR.tw.
- 4 Electroporation/
- 5 (electropor* or electro-por* or electropermeab* or electro-permeab*).tw.
- 6 (electric* adj3 (field* or pulse* or cell? or membrane* or pore?)).tw.
- 7 1 or 2 or 3 or 4 or 5 or 6
((skin* or Melanoma* or Cutaneous* or sarcoma* or "non melanoma") adj3
- 8 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metastas*)).tw.

9 exp Skin Neoplasms/

10 exp Melanoma/

11 Carcinoma, Squamous Cell/

12 Sarcoma, Kaposi/

13 Breast Neoplasms/

14 (breast* adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom*
or tumour* or tumor* or malignan* or metastas*)).tw.

15 "Head and Neck Neoplasms"/

16 ("head and neck" adj3 (secondar* or neoplasm* or cancer* or carcinoma* or
adenocarcinom* or tumour* or tumor* or malignan* or metastas*)).tw.

17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18 7 and 17

19 animals/ not humans/

20 18 not 19