

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of electrochemotherapy for metastases in the skin from tumours of non-skin origin

Treating metastases in the skin (of non-skin origin) using pulses of electricity together with chemotherapy

Cancer that starts in one part of the body can spread (metastasise) and form tumours on or below the skin elsewhere in the body, especially when the cancer is severe and widespread. These skin tumours can cause problems such as bleeding, pain or ulceration.

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 Clinical Excellence (NICE) has prepared this 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 metastases in the skin from tumours of non-skin origin

Specialist societies

- BASO – The Association for Cancer Surgery
- 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

Cutaneous and subcutaneous metastases of non-skin origin often occur in the setting of disseminated disease and cause significant clinical problems including bleeding, pain and ulceration. The primary aim of treatment is therefore palliative and includes modalities such as regional chemotherapy, curettage, cryotherapy and radiotherapy.

What the procedure involves

Electrochemotherapy aims to enhance the effects of chemotherapy and can be performed as an outpatient procedure. It can be used for local control of cancers that are unsuitable for surgery and resistant to radiotherapy or 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 increased. 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 electrochemotherapy 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 metastases in the skin from tumours of non-skin origin. 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 metastases in the skin from tumours of non-skin origin.
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 overview is based on approximately 182 patients from 3 non-randomised studies^{1, 2, 3} and 5 case series^{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 for metastases in the skin (of non-skin origin)

Abbreviations used: BCC, basal cell carcinoma; CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; HNC, head and neck cancer; IT, intratumoural; IU, international units; IV, intravenous; NR, no response; OR, objective response; PR, partial response; QoL, quality of life; SCC, squamous cell carcinoma; SD, stable disease.																																																						
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Marty M (2006)¹ Non-randomised comparative study France, Slovenia, Denmark, Ireland Recruitment period: 2003–2005 Study population: Patients with progressive cutaneous and subcutaneous metastases of any cancers n = 61 patients (290 tumours) for safety; 41 patients (171 tumours) for tumour response Of 61: 29 non-melanoma (100 tumours), 32 melanoma (190 tumours) Of 41: 21 non-melanoma (73 tumours: 58 breast cancer, 1 colon cancer, 3 cutaneous SCC, 2 SCC of the cervix, 9 Kaposi/ leiomyosarcoma), 20 melanoma (98 tumours) Age: 66 years (median) Sex: 33% (20/61) male Patient selection criteria: life expectancy >3 months, measurable cutaneous tumours ≤3 cm, treatment free for 2 weeks, Karnofsky performance ≥70% or WHO ≤2, progressive disease despite standard treatment, or refusal of standard treatment, no symptomatic or progressive visceral disease. Technique: Chemotherapy doses as ESOPE guidelines. Electric pulses delivered using IGEA Cliniporator with	Number of patients analysed: 41 patients (171 tumours), including 21 patient with non-melanoma metastases (73 tumours) Tumour response (at ≥60 days), absolute numbers not reported <table><tr><th>Tumour type</th><th>No. patients</th><th>No. tumours</th><th>CR %</th><th>OR %</th></tr><tr><td>MM</td><td>20</td><td>98</td><td>66.3</td><td>80.6</td></tr><tr><td>Non-melanoma</td><td>21</td><td>73</td><td>83.6</td><td>90.4</td></tr><tr><td>p value</td><td></td><td></td><td>0.018</td><td>0.07</td></tr></table> Tumour response (at end of follow-up), absolute numbers not reported <table><tr><th>Tumour type</th><th>PD %</th><th>NR %</th><th>PR %</th><th>CR %</th><th>OR %</th></tr><tr><td>All</td><td>4.7</td><td>10.5</td><td>11.1</td><td>73.7</td><td>84.8</td></tr></table> Tumour response according to drug delivery (at 150 days), absolute numbers not reported <table><tr><th>ECT method</th><th>No. tumours</th><th>CR %</th><th>OR %</th></tr><tr><td>IV bleomycin</td><td>86</td><td>88.2</td><td>89.5</td></tr><tr><td>IT bleomycin</td><td>41</td><td>73.1</td><td>80.5</td></tr><tr><td>IT cisplatin</td><td>44</td><td>75.4</td><td>79.5</td></tr></table>			Tumour type	No. patients	No. tumours	CR %	OR %	MM	20	98	66.3	80.6	Non-melanoma	21	73	83.6	90.4	p value			0.018	0.07	Tumour type	PD %	NR %	PR %	CR %	OR %	All	4.7	10.5	11.1	73.7	84.8	ECT method	No. tumours	CR %	OR %	IV bleomycin	86	88.2	89.5	IT bleomycin	41	73.1	80.5	IT cisplatin	44	75.4	79.5	Complications (61 patients, 290 tumours) Five serious adverse events were reported but not associated with ECT (death in 3 patients due to pulmonary metastases or disease progression; hypoxia and thoracic pain in another patient that spontaneously disappeared within 1 hour). Muscle contractions: 78% of patients demonstrated ‘no’ or ‘low’ level contractions. Contractions ceased immediately treatment was stopped. Hexagonal electrodes produced the least strong muscle contractions and surface electrodes the strongest.		Follow-up issues: • Patients followed-up at 2-week intervals for the first month and then monthly. • A minimum of 60 days was required to evaluate the tumour response. A minimum 4 week duration was required to qualify the response. 29.5% (18/61) patients (67 tumours) were lost to evaluation due to short follow-up, including 5 patients who died. Another 3% (2/61) patients did not attend for evaluation. Study design issues: • Prospective multicentre study. • There is likely to be some patient overlap with Larkin JO (2007). • No blinding of response assessment, but evaluations reviewed by the other centres. • Tumour size is not reported. • All patient tumours were treated but only a maximum of 7 were evaluated. The selection of tumours for evaluation is not described. • Details of the patient satisfaction interviews are not reported. Number of patients interviewed is unclear. • The χ^2 test used may be affected by non-independence (multiple tumours on the same patient) and
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Study details	Key efficacy findings	Key safety findings	Comments
surface (superficial tumours) or needle electrodes (deeper or larger tumours). Follow-up: 133 days (median) Conflict of interest/source of funding: Not reported, but the manufacturer of the Cliniporator was a partner in the EU-funded ESOPE project.	There was no significant difference in response rates between the 3 methods ($p=0.09$). Comparisons Tumour size: There was no relationship between tumour size and response to ECT except that IV bleomycin resulted in better OR than IT chemotherapy for the larger tumours ($>0.5\text{cm}^3$); OR 93.8% vs 75% ($p=0.047$). Absolute numbers not reported. Tumour location: Tumours on the trunk responded better to ECT than those on the head and neck or limbs – OR 92.6% vs 69.2% vs 79.2% respectively ($p=0.01$). Tumours on the limbs responded better to IV rather than IT drugs ($p=0.006$). Absolute numbers not reported. Previous irradiation: Tumours in previously irradiated areas did not respond differently to ECT than those in non-irradiated areas. Electrodes: There was no difference in response between the different electrodes used; however, treatment at a frequency of 5000 Hz was found to be more effective than 1 Hz – OR 87.2% vs 73.3% ($p=0.05$). Numbers not reported. Patient satisfaction 93% of patients interviewed would be willing to undergo the treatment again. Absolute numbers not reported.		small sample size (sub-groups with $n<20$). This seems like a post hoc 'fishing expedition' with multiple comparisons. This is a small study with a lack of critical examination of the results. Study population issues: - Patients with non-melanoma metastases are 47.5% (29/61) of the whole study population. Other issues: - Objective rate (OR) is not defined in the paper, although all other response criteria are. - The 20 melanoma patients are outside the scope of this report . - The 73 non-melanoma tumours include 3 metastases of SCC of the skin and between 1—8 metastases of Kaposi's sarcoma which are outside the scope of this report. This study is included because at least 84.9% (62/73) tumours are within scope. - The lack of effect of tumour size on response rate appears to be at odds with other studies. - Results are often reported as percentages only.

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Campana LG (2009)² Non-randomised comparative study Italy Recruitment period: 2006–2008 Study population: Patients with cutaneous and subcutaneous metastatic cancer (different histologies) unsuitable for conventional treatments. n = 52 patients (608 tumours) 11 breast cancer (174 tumours), 5 sarcoma (29 tumours), 1 SCC (31 tumours), 1 HNC (1 tumour), 34 melanoma (373 tumours). IV bleomycin (24 patients) vs IT bleomycin (6 patients) vs ECT IV and IT bleomycin (22 patients) Age: 67 years (median) Sex: 38% (20/52) male Patient selection criteria: derived from ESOPE, performance status ≤2 on Eastern Cooperative Oncology Group scale, no cancer treatment in preceding 2 weeks, inclusion of tumour nodules also >3 cm in size. Technique: Bleomycin injected IV and/or IT at a dose dependent on size of nodule. Electric pulses were given using the Cliniporator (IGEIA) and type II or type III needle electrodes. Patients with NR or PR at 4 weeks after 1 ECT session were re-treated.		Number of patients analysed: 52 (266 tumours), including 18 patients with non-melanoma (95 tumours) Per-patient response 50% (9/18) of non-melanoma patients had a CR at 4 weeks.			Adverse events in entire study		Follow-up issues • Tumour response evaluated at 2, 4, 8, 12 and 16 weeks and then according to standard follow-up. • Specifies response duration as time from achieving response to relapse/progression or last follow-up in case of disease free status. • The authors appear to use the terms ‘4 weeks’ and ‘1 month’ interchangeably. Design issues • Prospective phase II study • It appears that all tumours (608) were treated but that only up to 8 tumours per patient were measured (266); 95/266 non-melanoma tumours were evaluated. Numbers are not clearly reported. • Some patients had more than 2 treatment sessions (n=13).Tumour response was assessed using the Response Evaluation Criteria in Solid Tumours and toxicity according to Common Toxicity Criteria v2.0. • Quality of life was assessed pre-treatment and at 1 month and 2 months post-treatment using a non-validated 8 item questionnaire (bleeding, ulceration, aesthetics, activities of daily living, social																													
		<table><tr><th>Follow-up</th><th>NR % (n)</th><th>PR % (n)</th><th>CR % (n)</th><th>OR % (n)</th></tr><tr><td>4 weeks</td><td>4 (2/52)</td><td>46 (24/52)</td><td>50 (26/52)</td><td>96 (50/52)</td></tr><tr><td>9 months (median)</td><td>0</td><td>36 (19/52)</td><td>60 (31/52)</td><td>96 (50/52)</td></tr></table>			Follow-up	NR % (n)		PR % (n)	CR % (n)	OR % (n)	4 weeks	4 (2/52)	46 (24/52)	50 (26/52)	96 (50/52)	9 months (median)	0	36 (19/52)	60 (31/52)	96 (50/52)	<table><tr><th>Event</th><th>% (n)</th></tr><tr><td>Death due to disease progression</td><td>17% (9/52)</td></tr><tr><td>Episodes of lipothymia (postoperative syncope) with hospital discharge on the day after ECT</td><td>4% (2/52)</td></tr><tr><td>Postoperative nausea/vomiting</td><td>4% (2/52)</td></tr><tr><td>Inflammatory reaction in treated lesions (resolution at end of follow-up)</td><td>88% (46/52)</td></tr><tr><td>Mild local rash (grade I–II according to common toxicity criteria)</td><td>4% (2/52)</td></tr><tr><td>Gradel-II rash, desquamation or pigmentation at 4 weeks</td><td>12% (6/52)</td></tr></table>		Event	% (n)	Death due to disease progression	17% (9/52)	Episodes of lipothymia (postoperative syncope) with hospital discharge on the day after ECT	4% (2/52)	Postoperative nausea/vomiting	4% (2/52)	Inflammatory reaction in treated lesions (resolution at end of follow-up)	88% (46/52)	Mild local rash (grade I–II according to common toxicity criteria)	4% (2/52)	Gradel-II rash, desquamation or pigmentation at 4 weeks	12% (6/52)
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Study details	Key efficacy findings	Key safety findings		Comments																			
Follow-up: 9 months (median) Conflict of interest/source of funding: not reported.	Tumour response by tumour size Tumour diameter was inversely correlated with CR: 66% for ≤1.5 cm, 36% for 1.6-3 cm, 28% for >3 cm (p=0.0035). Recurrence 65% (17/26) of patients with CR at 4 weeks were disease free at a median follow-up of 9 months; 1 patient had a recurrence at 7 months. Survival At a median follow-up of 9 months 19% (10/52) of patients were alive and disease free, 63% (33/52) were alive with disease and 17% (9/52) died as a result of disease progression. Patient-reported quality of life – 6 items (36 patients)* <table><tr><td></td><td>Overall QOL score (range)</td><td>p value</td></tr><tr><td>Pre-treatment</td><td>46 (16–60)</td><td></td></tr><tr><td>1 month</td><td>52 (18–60)</td><td>0.004</td></tr><tr><td>2 months</td><td>55 (18–60)</td><td>0.004</td></tr></table> *On a scale of 0–10, higher scores indicating better QoL. P values vs pre-treatment score. 34/36 (94%) reported an improvement in 1 or more of the 6 parameters in the questionnaire. 9/22 (41%) patients with painful tumours reported better pain control after ECT. 34/36 (94%) of patients were amenable to further ECT.		Overall QOL score (range)	p value	Pre-treatment	46 (16–60)		1 month	52 (18–60)	0.004	2 months	55 (18–60)	0.004	<table><tr><td>Postoperative pain managed with minor analgesics</td><td>88% (46/52)</td></tr><tr><td>Ulceration in nodules at the time of accrual</td><td>42% (22/52)</td></tr><tr><td>Ulceration of nodules at end of study</td><td>10% (5/52)</td></tr><tr><td>Unpleasant sensation from electric pulses</td><td>15% (8/52)</td></tr></table>	Postoperative pain managed with minor analgesics	88% (46/52)	Ulceration in nodules at the time of accrual	42% (22/52)	Ulceration of nodules at end of study	10% (5/52)	Unpleasant sensation from electric pulses	15% (8/52)	relations, pain control, acceptance of retreatment and overall satisfaction). Study population issues - Some patients received locoregional chemotherapy. 27% of patients had nodules >3 cm in size. Other issues - The quality of life score is not validated and the authors do not report on what basis statistical significance was determined (i.e. in relation to defining a meaningful estimate of effectiveness from previous work or other quality of life scales). - A considerable number of patients experienced progression or the appearance of new lesions in new areas. 34 melanoma patients are not within the scope of this report.
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Rebersek M (2004)³ Non-randomised comparative study Slovenia Recruitment period: 1999–2002 Study population: Patients with cutaneous lesions of breast cancer n = 6 patients (26 lesions) 12 ECT vs 6 cisplatin only vs 8 control lesions Mean age: not reported Sex: 17% male Patient selection criteria: metastatic breast cancer with 1+ (sub)cutaneous lesion, exhausted possibility of standard treatment, >18 years, no local therapy within 4 weeks, no radiotherapy within 8 weeks, no systemic therapy within 2 weeks. Technique: Local anaesthesia with lidocaine spray followed by intratumoural cisplatin at 1 mg/100 mm³ tumour volume. Electric pulses were applied using a GHT 1287 Jouan electropulsator and surface electrodes. Two runs of 4 pulses were applied orthogonally. Patients were assessed 2 hours after treatment. Follow-up: up to 26 weeks Conflict of interest/source of funding: study supported by Ministry of education, science and sport, Slovenia.	Number of patients analysed: 6 (26 lesions) Lesion response rates after first treatment (at 4 weeks) <table border="1"> <thead> <tr> <th></th><th>No. lesions</th><th>Follow-up</th><th>PD % (n)</th><th>PR % (n)</th><th>CR % (n)</th></tr> </thead> <tbody> <tr> <td>ECT</td><td>12</td><td>26 weeks</td><td>0</td><td>67 (8/12)</td><td>33 (4/12)</td></tr> <tr> <td>Cisplatin alone</td><td>6</td><td>12 weeks</td><td>17 (1/6)</td><td>83 (5/6)</td><td>0</td></tr> <tr> <td>Control</td><td>8</td><td>9 weeks</td><td>75 (6/8*)</td><td></td><td></td></tr> </tbody> </table> * 2 patients exhibited no PD at death (4 and 10 weeks) Median duration of OR (until progression) ECT: CR – 10 (4–16) weeks PR – 5 (2–18) weeks Cisplatin: PR – 5 (2–10) weeks Median size of lesions achieving OR: ECT: CR – 72 mm³ PR – 192 mm³ Cisplatin: PR – 73 mm³ Difference in OR between ECT and cisplatin alone was not found to be significant (χ^2 test, p=0.26). This is ascribed to variability in lesion size, small sample size and short follow-up.				No. lesions	Follow-up	PD % (n)	PR % (n)	CR % (n)	ECT	12	26 weeks	0	67 (8/12)	33 (4/12)	Cisplatin alone	6	12 weeks	17 (1/6)	83 (5/6)	0	Control	8	9 weeks	75 (6/8*)			Procedural complications Muscle contractions in lesion area during application of electric pulses (resolved as soon as electric pulses were discontinued) – 100%. Post procedural complications Erythema and oedema at treatment area (disappeared within 2–4 weeks) – 100%. Crust at ECT site (persisted for 4–10 weeks) – 100% Itching around the crust at ECT site (resolved in 4 to 7 days) in 2 patients (7 lesions). Minimal scarring and depigmentation of skin at ECT site (persisted throughout observation period) – numbers not reported.	Follow-up issues: - Response evaluated at 4 weeks. - Patients followed up for up to 26 weeks (ECT), 12 weeks (cisplatin only) or 9 weeks (controls). 2 patients were followed up for 4 and 10 weeks, durations for the other 4 patients are not reported. Study design issues: - Prospective study. - Distribution of treatment groups between patients was not randomised or described. - The χ^2 test used may be affected by non-independence (multiple tumours on the same patient) and small sample size (sub-groups with n<20). - No statistical assessment of lesion size on response. - Duration of OR response indicates that all lesions eventually became progressive. - High variability in lesion volumes. 2 patients received systemic treatment with cisplatin before local treatment. Other issues - The cisplatin dose is large compared to ESOPE guidelines.
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Abbreviations used: BCC, basal cell carcinoma; CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; HNC, head and neck cancer; IT, intratumoural; IU, international units; IV, intravenous; NR, no response; OR, objective response; PR, partial response; QoL, quality of life; SCC, squamous cell carcinoma; SD, stable disease.																			
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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) 3 metastases of adenocarcinoma (30 tumours), 17 metastases of HNC SCC (87 tumours), 10 BCC (32 tumours), 20 melanoma (142 tumours) Age: 54.6 years (mean) Sex: Not reported. Patient selection criteria: Patients had recurrent tumours after several previous treatments by surgery, radiotherapy or chemotherapy. 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 on the skin surface. US centre: IV bleomycin at 0.25 to 1.0 U per tumour. Pulses delivered using a Genetronics BTX T820 generator and plate or needle electrodes. Follow-up: Not reported (for these patient groups) Conflict of interest/source of funding: Some funding provided from Genetronics Inc.	Number of patients analysed: 18 (99 tumours); including 2 with adenocarcinoma (22 tumours), 16 with head and neck SCC (77 tumours) Mean tumour diameter: HNC SCC: 17.5 (3–125) mm Adenocarcinoma: 8.5 (3–17) mm Response rates (at ≥30 days) <table><tr><th>Type</th><th>PD % (n)</th><th>SD % (n)</th><th>PR % (n)</th><th>CR % (n)</th></tr><tr><td>Adenocarcinoma (22 tumours)</td><td>0</td><td>0</td><td>0</td><td>100</td></tr><tr><td>HNC (77 tumours)</td><td>10 (8/77)</td><td>27 (21/77)</td><td>20 (15/77)</td><td>43 (33/77)</td></tr></table> Bleomycin only: 2 additional tumours that received bleomycin only (adenocarcinoma) achieved a PD response. HNC SCC: For the large nodules ‘massive necrosis and reduction in the height of the nodule was observed’, but the deepest parts were not thought to be effectively treated. Two tumours in 1 patient appear to have been treated in 2 sessions, but it is unclear whether this refers to treating different parts of the same tumours or to second treatments of the same area. ‘Several’ cases reported reduced tumour pain. Patients reported that they would undergo ECT treatment again. Further details were not reported.	Type	PD % (n)	SD % (n)	PR % (n)	CR % (n)	Adenocarcinoma (22 tumours)	0	0	0	100	HNC (77 tumours)	10 (8/77)	27 (21/77)	20 (15/77)	43 (33/77)	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 for which the skin was altered prior to ECT. Further details not reported.	Follow-up issues: - Clinical outcome determined at least 30 days after treatment. Actual time point of assessment is unclear. 2 additional patients (1 adenocarcinoma, 1 HNC) also treated but not evaluated because of too short a follow-up. Study design issues: - Prospective multicentre study. - The data is aggregated from independent trials at five centres. - The centres had different protocols for anaesthesia, chemotherapy and pulse delivery. Chemotherapy doses are larger than those recommended by ESOPE. - The selection of tumours for bleomycin only treatment is not described. - No assessment of tumour size on response rates. - The difference in response rates of the tumour types is not tested. Study population issues: - The tumour size in the HNC group is much larger than in the adenocarcinoma group (and also in the BCC and melanoma groups). Other issues 30 patients (154 tumours, melanoma and BCC) are not within the scope of this report.	
Type	PD % (n)	SD % (n)	PR % (n)	CR % (n)															
Adenocarcinoma (22 tumours)	0	0	0	100															
HNC (77 tumours)	10 (8/77)	27 (21/77)	20 (15/77)	43 (33/77)															

Abbreviations used: BCC, basal cell carcinoma; CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOP, European Standard Operating Procedures for Electrochemotherapy; HNC, head and neck cancer; IT, intratumoural; IU, international units; IV, intravenous; NR, no response; OR, objective response; PR, partial response; QoL, quality of life; SCC, squamous cell carcinoma; SD, stable disease.																													
Study details	Key efficacy findings			Key safety findings	Comments																								
Larkin JO (2007)⁵ Case series Ireland Recruitment period: 2003–2005 Study population: cutaneous or subcutaneous recurrences of inoperable or progressive tumours n = 30 patients (111 lesions) 14 metastatic breast cancer, 1 metastatic SCC, 1 synovial chondrosarcoma, 1 colon adenocarcinoma, 1 cervical SCC, 4 melanoma, 3 recurrent breast cancer, 3 recurrent SCC, 1 recurrent chest wall cancer Mean age: Not reported. Sex: Not reported. Patient selection criteria: progressive/metastatic cancer of any type, life expectancy >3 months, age >18 years, measurable cutaneous lesions, treatment free for 2 weeks, Karnofsky performance ≥70% or WHO ≥2. Progressive disease despite standard treatment or refusal of standard treatment, no symptomatic or progressive visceral disease. Technique: Intratumoural bleomycin for few lesions of ≤3 cm; IV bleomycin for large or numerous lesions (15,000 U/m² body surface area). Electric pulses were delivered using IGEA Cliniporator with plate electrodes for superficial lesions and needle electrodes for deeper lesions. Follow-up: 2–12 months Conflict of interest/source of funding: Not reported.	Number of patients analysed: 17 patients with skin metastases of non-skin origin (74 lesions); 12 with breast cancer (66 lesions), 1 with metastatic SCC (1 lesion), 1 with synovial chondrosarcoma (1 lesion), 1 with colon adenocarcinoma (2 lesions), 1 with cervical cancer (2 lesions), 1 metastatic HNC (2 lesions) Lesion response rates after first treatment (evaluation time point uncertain). Calculated by reviewer. <table border="1"> <thead> <tr> <th>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>All non-skin origin</td><td>17</td><td>74</td><td>15 (11/74)</td><td>23 (16/74)</td><td>62 (46/74)</td></tr> <tr> <td>Small lesions (<3cm)</td><td>11</td><td>60</td><td>5 (3/60)</td><td>20 (12/60)</td><td>75 (45/60)</td></tr> <tr> <td>Breast</td><td>12</td><td>66</td><td>9 (6/66)</td><td>23 (15/66)</td><td>68 (45/66)</td></tr> </tbody> </table> Breast cancer No tumour progression within the treated areas and amelioration of bleeding and pain. 4 breast cancer patients developed additional lesions outside the treated area; 2 of these had repeat treatment and regression of tumours was seen.			Type	No. patients	No. lesions	NR % (n)	PR % (n)	CR % (n)	All non-skin origin	17	74	15 (11/74)	23 (16/74)	62 (46/74)	Small lesions (<3cm)	11	60	5 (3/60)	20 (12/60)	75 (45/60)	Breast	12	66	9 (6/66)	23 (15/66)	68 (45/66)	2 patients reported mild pain which resolved within 48 hours.	Follow-up issues: - No response was reported for 2 additional breast cancer patients. 1 of these apparently did not receive treatment; no explanation is given. The response rates calculated here do not include these 2 patients. - No time point for response evaluation is reported but is taken to be the end of each patient's follow-up. Study design issues: - Prospective study. - Lesion size is not well described and no statistical assessment of size on response is made although the authors state that lesions <3 cm were 'more likely to respond'. Study population issues: - It is unclear from the data whether some patients have recurrent or metastatic disease therefore there is some difficulty with identifying which patients are within scope for this overview. Other issues 11 patients (4 melanoma, 7 recurrent SCCs or cancers of the breast or chest wall) are not included in the scope of this report.
Type	No. patients	No. lesions	NR % (n)	PR % (n)	CR % (n)																								
All non-skin origin	17	74	15 (11/74)	23 (16/74)	62 (46/74)																								
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Study details	Key efficacy findings	Key safety findings	Comments																		
Campana LG (2012)⁶ Case series Italy Recruitment period: 2006–2011 Study population: patients with progressive cutaneous chest wall recurrence after mastectomy with no further treatment options. n = 35 patients (516 metastases- median 15/patient; median size 20mm) Age: 67 years (median) Sex: 0% male Patient selection criteria: >18 years, previous mastectomy, chest wall metastases suitable for a needle electrode application, no anticancer treatments 4 weeks before and 8 weeks after ECT, contraindications to further chest wall irradiation and an Eastern Cooperative Oncology Group performance status of <2. Technique: Intravenous bleomycin at 15,000 I/m²U dose. EPT was delivered using a 2 cm hexagonal array needle electrode in each metastases connected to a Cliniporator pulse generator at a frequency of 5 kHz.. Treatment was individualised pulses delivered by multiple electrode insertions. ECT repeated after 8-12 weeks based on local response and occurrence of new lesions. Follow-up: 32 months (median) Conflict of interest/source of funding: None	Number of patients analysed: 35 (196 lesions) Tumour response rates at 2 months OR: 91.4% (31/35) CR: 54.3% (19/35) PR: 37.1% (13/35) NC: 8.6% (3/35) After a median follow-up of 32 months local tumour control was obtained in 85.7% (30/35) patients. Survival The 3 year local progression free survival was 81%, only 5/35 patients reported failure (median time 18 months). New Lesions 65.7% (23/35) patients developed new lesions after a median of 6.6 months, 1, 2, or 3 ECT cycles were required in 14, 15 and 6 patients respectively. Patients with fewer and less scattered and complete responding metastases are less likely to develop new lesions. Overall survival: the estimated overall survival rate at 3 years was 58%. It was significantly higher in patients with longer disease free interval from the primary breast cancer (P=0.047).	Adverse events <table><tr><th>Adverse events</th><th>% (n)</th></tr><tr><td>Death (at 9 weeks after 2nd ECT due to respiratory distress syndrome)</td><td>3%(1/35)</td></tr><tr><td>Fever</td><td>17% (6/35)</td></tr><tr><td>Nausea/ vomiting</td><td>(4/35)</td></tr><tr><td>Syncope</td><td>3%(1/35)</td></tr><tr><td>Urticaria</td><td>3%(1/35)</td></tr><tr><td>Skin ulceration 1 month after ECT</td><td>14% (5/35)</td></tr><tr><td>Skin ulceration 2 months after ECT</td><td>6% (2/35)</td></tr><tr><td>Transient alopecia due to systemic bleomycin</td><td>8.5% (3/35)</td></tr></table> Post treatment pain (4 point scale: no pain to severe pain) Pain increased after retreatments and was reported as severe/moderate by 6, 13 and 17% of patients 1 month after the first, second and third ECT treatments. Pain scores improved between 1 and 2 month follow-up.	Adverse events	% (n)	Death (at 9 weeks after 2 nd ECT due to respiratory distress syndrome)	3%(1/35)	Fever	17% (6/35)	Nausea/ vomiting	(4/35)	Syncope	3%(1/35)	Urticaria	3%(1/35)	Skin ulceration 1 month after ECT	14% (5/35)	Skin ulceration 2 months after ECT	6% (2/35)	Transient alopecia due to systemic bleomycin	8.5% (3/35)	Follow-up issues: - Tumour response evaluated at 1,4 and 8 weeks and every 3 months thereafter. Study design issues: - Single centre prospective phase II study. - Patients received a median of 2 ECT sessions. - Different types of systemic treatments given after ECT: endocrine therapy in 34%, chemotherapy in 60%, sequential chemo-and endocrine therapy in 6%. Study population issues: - Patients had previous re-irradiation and extensive systematic treatments. - Patients with different grades of tumours spread on the chest wall. 80% of patients had comorbidities such as pain, skin ulceration, oedema, hypertension and diabetes. Other issues Many patients received multiple ECT treatments.
Adverse events	% (n)																				
Death (at 9 weeks after 2 nd ECT due to respiratory distress syndrome)	3%(1/35)																				
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Abbreviations used: BCC, basal cell carcinoma; CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; HNC, head and neck cancer; IT, intratumoural; IU, international units; IV, intravenous; NR, no response; OR, objective response; PR, partial response; QoL, quality of life; SCC, squamous cell carcinoma; SD, stable disease.											
Study details	Key efficacy findings	Key safety findings	Comments								
Matthiessen LW (2012)⁷ Case series Denmark Recruitment period: 2008–10 Study population: patients with large cutaneous recurrence of breast cancer with no further treatment options. n = 17 patients (25 lesions) Mean age: 60years Sex: 100% male Patient selection criteria: histologically confirmed breast cancer cutaneous recurrences > 3cm, > 18 years, progressive/metastatic disease, patient declining or no further standard treatments, Eastern Cooperative Oncology Group performance status <2, life expectancy of at least 3 months, coagulation parameters within normal range, sexually active and had to use safe contraceptives up to 6 months after last treatment. Technique: IV bleomycin at a dose of 15,00 IU/m² or 1000 IU/ml intratumourally; Electric pulses delivered using Cliniporator pulse generator and electrodes with two parallel rows of needles or electrodes with a hexagonal array of needles at a frequency of 5 kHz. Patients were offered retreatments upto 3 times if lesions were not sufficiently treated or progression of treated lesions. Follow-up: 100 days (median) Conflict of interest/source of funding: None, study funded by investigators and different agencies; devices and database support provided by IGEA.	Number of patients analysed: 12 Tumour response at 8 weeks (PET/CT) CT showed that 33% (4/12) patients achieved over 50% tumour volume reduction, 67% (7/12) had less than 50% reduction, and 1 patient was not evaluable. Tumour response at 8 weeks (clinical examination) OR:17% (2/12) CR: 1 patient PR: 1 patient SD: 9 patients PD: 1 patient.	Adverse events (n=16) Procedural complications Contraction of muscles during pulse application caused minor displacement of the laryngeal mask in some patients. <table><tr><th>Adverse event</th><th>% (n)</th></tr><tr><td>Pain (grade 3 CTC)</td><td>44% (7/16)</td></tr><tr><td>Local infection (grade 3 CTC)</td><td>6% (1/16)</td></tr><tr><td>Lung toxicity/ decrease in diffusion capacity of the lung for carbon monoxide</td><td>0</td></tr></table> 10 patients had ulcerating tumours before treatment. They did not experience any worsening after treatment but 6 patients reported reduced exudates and 4 reported reduced bleeding, 5 reported improvement in odour after treatment. 4/16 patients reported decreased pain after treatment.	Adverse event	% (n)	Pain (grade 3 CTC)	44% (7/16)	Local infection (grade 3 CTC)	6% (1/16)	Lung toxicity/ decrease in diffusion capacity of the lung for carbon monoxide	0	Follow-up issues: 1 patient withdrew before evaluation; 12 patients had follow-up of more than 8 weeks. - Study was set at 1 year, but closed early as11/12 patients withdrew due to progressive disease or deteriorating status. Study design issues: - Prospective first Phase II study. - Small recurrences were treated but not included in analysis. 27 ECT sessions performed, a second ECT was given in patients with progressive disease or large size lesions. - IT bleomycin was given only in one session. - Safety assessed using Common Toxicity Criteria for Adverse Events (CTC 3.0) Study population issues: 22 tumours were on chest wall, 1 on abdominal wall, 1 on supraclavicular region. 15 tumours ulcerated and 10 were infiltrating the skin without ulceration. - Patients had extensive previous treatments including surgery, radiotherapy and several regimes of systemic therapy.
Adverse event	% (n)										
Pain (grade 3 CTC)	44% (7/16)										
Local infection (grade 3 CTC)	6% (1/16)										
Lung toxicity/ decrease in diffusion capacity of the lung for carbon monoxide	0										

Abbreviations used: BCC, basal cell carcinoma; CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOP, European Standard Operating Procedures for Electrochemotherapy; HNC, head and neck cancer; IT, intratumoural; IU, international units; IV, intravenous; NR, no response; OR, objective response; PR, partial response; QoL, quality of life; SCC, squamous cell carcinoma; SD, stable disease.			
Study details	Key efficacy findings	Key safety findings	Comments
Domenge C (1996)⁸ Case series France Recruitment period: 1992 Study population: Skin metastases of HNC or breast cancer n = 7 patients (2–20 nodules each) 5 HNC SCC, 1 adenocarcinoma of salivary gland, 1 breast cancer. Mean age: 51 years Sex: 71.4% (5/7) male Patient selection criteria: Recurrent/progressive HNC or breast cancer with measurable permeation nodules, pre-treated with conventional therapy (surgery, chemotherapy, radiotherapy), 18–70 years of age, 22 days of minimal washout period from other drugs, no previous bleomycin use. Technique: Patients treated in a surgical area; HR, BP and oxygenation monitored; kept as inpatients for 24 hours. Bleomycin administered as IV bolus (5 patients) or bolus plus infusion (2 patients) 10 or 15 mg/m²; 2 patients received intra-arterial drugs during secondary treatments. Electric pulses delivered by PS 15 Jouan electropulsator with surface electrodes. Not all nodules were treated with EPT. Follow-up: Not reported Conflict of interest/source of funding: Not reported.	Number of patients analysed: 7 (2-20 nodules each) Individual patient responses 1 – all treated nodules disappeared by day 18. Large recurrence in untreated area. 2 – long first treatment time: nodules treated before 28 mins responded to treatment with PR, maximum response for those treated at 15 mins. 30% response to second IV bleomycin treatment. 3rd treatment of large area produced better outcome for intra-arterial rather than IV chemotherapy. Overall minor response (thick tumour). 3 – smaller nodules disappeared and largest one reduced in thickness; overall 40% reduction at 2.5 weeks. Palliative treatment with Hydrea 2 months post-ECT. 5 – overall minor response. 6 – overall minor response, reduced nodule thickness but no change in diameter. PD after 2 months led to retreatment. Very deep tumour, not fully accessible to EPT; secondary treatment resulted in PD. 7 – rapidly proliferating disease and very thick nodule resulted in PD.	1 patient exhibited transient increase in HR and BP during treatment. Values returned to normal 'in a few seconds'. Amplitude of muscular contractions of the neck and shoulders increased with the proximity of the treatment area to nervous plexus. 2 patients exhibited 'slight hyperthermia' for several hours post-treatment. no further details reported. A statistically significant increase in neutrophils and platelets was noted on average at 40 days post-treatment in all patients Transient dyspnoea 5 days post-treatment, attributed to large bleomycin dose was reported in 1 patient.	Follow-up issues: - Patients examined at 5 days and every 15 days afterwards. - Patient 4 lost to follow-up due to rapid disease progression. Study design issues: - Prospective study. - Very early phase I trial in patients with advanced disease to assess treatment parameters. - Procedure and patient numbers for follow-up blood tests not reported. Study population issues: - Patients were suffering from advanced and sometimes aggressive disease. Large numbers of skin nodules and/or large total treatment areas. Other issues: - The authors noted the optimal treatment time for EPT post-bleomycin and the need to treat thick tumours at depth using needle electrodes.

Efficacy

Tumour response (clinical observation)

A non-randomised comparative study of 61 patients that evaluated electrochemotherapy efficacy in 21 patients (73 tumours) with mixed non-melanoma metastases and 20 patients (98 tumours) with melanoma metastases reported an 85% objective tumour response and a 74% complete tumour response at a median follow-up of 133 days regardless of tumour histology, drug used (bleomycin or cisplatin) or route of drug administration (intravenous or intratumoural). Numbers were not reported. At 60 days or more after treatment, an 84% complete response and a 90% objective response was reported in 21 patients with mixed non-melanoma metastases. Numbers were not reported. Tumours on the trunk responded better to electrochemotherapy than those on the head and neck or limbs (objective response 93% versus 69% and 79%, $p=0.01$)¹.

A non-randomised comparative study of 52 patients (608 tumours) including 18 patients with non-melanoma metastases of mainly breast cancer (95 tumours) reported a complete response of 50% (9/18) at 4 weeks².

A non-randomised comparative study of 6 patients with 26 cutaneous metastases of breast cancer origin, that compared electrochemotherapy (12 tumours), intratumoural chemotherapy alone (6 tumours) and 8 untreated control tumours, reported no significant difference in objective response (100% versus 83%) between electrochemotherapy and intratumoural chemotherapy alone at 26 weeks follow-up ($p=0.26$)³.

A case series of 50 patients including 18 patients (99 tumours) with metastases of adenocarcinoma and head and neck cancer reported a complete response in 56% (55/99) and a partial response in 20% (15/99) of tumours at 30 days⁴.

A case series of 35 patients with cutaneous chest wall recurrence from breast cancer reported 54% (19/35) complete response at 2 months follow-up⁶.

Tumour response by tumour size

The non-randomised comparative study of 61 patients (including 21 patients with mixed non-melanoma metastases) reported no significant relationship between tumour size and response to electrochemotherapy ($p=0.59$)¹. However, tumours greater than 0.5 cm³ responded better to systemic rather than intratumoural chemotherapy (objective response 94% versus 75%, $p=0.047$). Absolute numbers not reported¹.

The non-randomised study of 52 patients (including 18 with non-melanoma metastases), reported a significant inverse correlation between maximum tumour

diameter and complete response: 66% for tumours less than 1.5 cm, 36% for tumours between 1.6 cm and 3 cm and 28% for tumours larger than 3 cm ($p=0.0035$)².

Duration of response

The non-randomised comparative study of 6 patients treated by electrochemotherapy (12 tumours) reported a median duration of response of 10 weeks in 33% (4/12) of tumours that had a complete response and 5 weeks in 67% (8/12) of tumours that had a partial response at up to 26 weeks of follow-up. For 6 tumours treated by cisplatin alone the mean duration of partial response was 5 weeks at up to 12 weeks follow-up³.

Quality of life

The study of 52 patients with 18 non melanoma patients reported improvements in overall quality of life score (assessed in 36 patients) from a mean pretreatment score of 46 to mean scores of 52 and 55 at 1 and 2 months respectively ($p<0.005$). These were measured using a non-validated questionnaire with scores of 0 to 60, higher scores indicating better quality of life. In the study, 94% (34/36) of responding patients reported an improvement in 1 or more of the 6 parameters in the questionnaire assessed (bleeding, ulceration, aesthetics, activities of daily living, social relations and pain control)².

Patient satisfaction

In the non-randomised comparative study of 61 patients it was reported that 93% of those interviewed would be willing to undergo the treatment again; the number interviewed was not reported¹.

Safety

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

Muscle spasms

Localised involuntary muscle contractions and a sensation of a jolt or shock associated with the electric pulses are reported or referred to in all the studies. These stopped immediately after the electric pulses were discontinued.

The non-randomised comparative study of 61 patients reported that surface electrodes produced the strongest contractions and that 78% of patients exhibited 'no' or 'low'-level spasm¹.

Lipothymia (postoperative syncope)

Lipothymia occurred in 4% (2/52) of patients in the non-randomised comparative study of 52 patients⁴. Patients required no treatment and were discharged the day after electrochemotherapy².

Transient increase in heart rate and blood pressure

A transient increase in heart rate and blood pressure during treatment was reported in 1 patient in a case series of 7 patients. This returned to normal 'in a few seconds'⁸.

Hyperthermia

'Slight hyperthermia' was reported in 2 patients in the case series of 7 patients, persisting for several hours after treatment. No further details were reported⁸.

Dyspnoea

Transient dyspnoea 5 days after electrochemotherapy treatment was reported in 1 patient in the case series of 7 patients. This was attributed to the chemotherapy drug. No further details were reported⁸.

Nausea

Nausea and vomiting was reported in 4% (2/52) of patients in the non-randomised comparative study of 52 patients (no further details reported)².

Haematology

An increase in neutrophils and platelets was reported in the case series of 7 patients 40 days post-treatment⁸.

Skin changes

A mild injection site rash of grade I–II according to common toxicity criteria was reported in 8% (4/52) of patients treated with electrochemotherapy in the study of 52 patients with metastatic cancer (34 of whom had malignant melanoma). Grade I–II rash, desquamation or pigmentation were also reported at 4 weeks in 12% (6/52) of patients in this study².

Erythema and oedema at treated areas which resolved within 24 hours was reported in the case series of 50 patients⁴. The non-randomised comparative study of 6 patients reported erythema and oedema which resolved within 2–4 weeks. No further details were reported³.

A crust at the treatment site which persisted for 4–7 weeks was reported in all patients in the non-randomised comparative study of 6 patients. This was

followed by itching around the crust in 2 patients that resolved within 4–7 days. No further details were reported³.

‘Minimal scarring and depigmentation’ of the treatment site as a late effect was reported in the non-randomised comparative study of 6 patients. This persisted for the duration of follow-up (up to 26 weeks). No further details were reported³.

Validity and generalisability of the studies

- The evidence in all of the studies identified in the literature review was of low quality and the studies had weaknesses in both methodology and reporting. Following the publication of the ESOPE guideline and the development of commercial purpose-designed electrochemotherapy devices, the quality of later studies is expected to improve.
- None of the studies in table 2 reported blinding of the response assessment or details of patient recruitment procedures used.
- The point at which clinical response is evaluated is often unclear or inconsistent between patients. Patients may be evaluated at one time point but followed up for variable lengths of time afterwards.
- Recurrence is not systematically reported. Duration of follow-up in these studies is relatively short (up to 12 months), although treatment in patients with metastatic disease is most likely to be palliative in purpose and longer-term outcomes will be dependent on underlying disease progression.

Existing assessments of this procedure

A Horizon Scanning Report update conducted for Australia and New Zealand in 2008 looked at electrochemotherapy for the treatment of local malignant tumours. It is based mainly on studies involving patients with melanoma. The authors concluded that ‘electrochemotherapy 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 ‘electrochemotherapy 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’⁹.

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

Clinical guidelines

- Metastatic malignant disease of unknown primary origin: diagnosis and management of metastatic malignant disease of unknown primary origin. NICE clinical guideline 104 (2010). Available from www.nice.org.uk/guidance/CG104

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), Zenon Rayter (BASO – The Association for Cancer Surgery), Barry Powell, Howard Peach (British Association of Plastic, Reconstructive and Aesthetic Surgeons)

- Two Specialist Advisers had performed this procedure regularly, one Adviser has performed this at least once and the other 2 Advisers have never performed it. One Specialist Adviser stated that the procedure is carried out under general anaesthetic for most cases because the degree of sedation used along with local anaesthetic is not acceptable for use in an outpatient setting in the UK.
- One Specialist Adviser suggested an alternative title: 'Role of electrochemotherapy in disseminated disease'.
- One Specialist Adviser indicated that results were variable and that patient selection was critical. Two Specialist Advisers had experience in selecting patients for this procedure regularly.
- One Specialist Adviser stated that repeated treatments may also be needed and 1 stated that the number of optimal treatments is unknown.
- Two Specialist Advisers stated that this procedure could be considered as established practice, being performed by fewer than 10% or 10–50% of 'doctors'. The other 3 Specialist Advisers described it as the first in a new class of procedure being performed by a 'very small number of doctors', or fewer than 10% of specialists. One Specialist Adviser stated that the evidence primarily involved recurrent melanomas but it is also available for recurrent malignancy within the skin for other types of tumours, for example breast and sarcoma.

- 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. However, 1 Adviser wanted to see electrochemotherapy studied as a comparator to surgery or radiotherapy as a first-line treatment. 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. Another Adviser also suggested that it could be an alternative to isolate limb perfusion/infusion in the management of malignant melanoma.
- Reported anecdotal adverse events included chemotherapy-induced toxicity specifically pulmonary fibrosis, muscle spasm, increase in wound exudate after the procedure, pain, ulceration, nausea and lipothymia.
- Chemotherapy toxicity, nausea, pain, lipothymia and electrical burns were suggested as theoretical adverse events. A significant proportion of patients receive general anaesthesia to undergo electrochemotherapy. One Specialist Adviser expressed concerns about adherence to chemotherapy policies. He also stated that it should be used with caution in patients with impaired respiratory function or who have had previous thoracic radiotherapy.
- Specialist Advisers listed key efficacy outcomes as improvement in disease state, tumour regression, duration of benefit, control of disease, number of procedures needed, better quality of life (measured using standard measures), control of bleeding and reduction in odour from fungating tumours, reduction in pain from painful tumours and cosmesis. Two Specialist Advisers stated that there is uncertainty about the optimal number of sessions, and whether other chemotherapeutic drugs besides bleomycin and cisplatin would be beneficial. One Specialist Adviser stated that there are concerns about meeting patient expectations because it's a palliative treatment.
- Two Specialist Advisers stated that there is a European registry (InspECT) for sharing and recording electrochemotherapy information and a few European studies currently enrolling patients.
- Three Specialist Advisers indicated the need for training for administration of chemotherapeutic drug and delivery of electric pulses and facilities to perform 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 best performed by a surgeon as there will be cases where both electrochemotherapy and surgical excision are required in some patients and can be done at the same time. Alternatively 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 by specialist skin cancer multidisciplinary teams including trained nurse practitioners; chemotherapy facilities and expertise are needed. Three Specialist Advisers stated that the procedure is likely to be performed in at least 10 specialist cancer units with chemotherapy facilities.

- Three Specialist Advisers indicated that provision of electrochemotherapy would have a minor impact on the NHS. Two Specialist Advisers stated that the procedure is promising for a few patients but the speed of diffusion is slow and might increase when it is established well. Only 1 Specialist Adviser stated that the procedure will 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 will 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

- Current trials:
 - NCT01479946 Electrochemotherapy for the treatment of breast cancer that has spread to the skin: location: Sweden; type: randomised Phase II study; estimated enrolment: 120 patients.
- Registry:
 - An online registry for European electrochemotherapy patients was instigated in 2008 and contains data on approximately 80 patients.

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

The following table outlines the studies that are considered potentially relevant to the 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
Belehradec M, Domenge C, Lubinski B et al. (1993) Electrochemotherapy, a new antitumor treatment. First clinical phase I-II trial. Cancer 72(12): 3694–3700	Case Series n=8 Follow-up: 36 days (median)	Instant painless contraction of the muscles were observed. ECT well tolerated. 57% (23/40) nodules had CR within few days.	Larger studies with longer follow-up included in table 2.
Heller R, Jaroszeski MJ, Reintgen DS et al. (1998) Treatment of cutaneous and subcutaneous tumors with electrochemotherapy using intralesional bleomycin. Cancer 83 (1): 148–57	34 patients – 1 patient (SCC, 1 lesion) may be within the scope of this report. Follow-up 12 weeks	Single lesion achieved a PR. Additional safety information: Slight burning of the skin from plate electrodes. Healed in 6–8 weeks – 7/8 patients. Muscle fatigue for 24 hours in treated limbs – ‘a few’ patients. Slight nausea for 24–48 hours post-treatment – 6%.	Potential single patient case study. Origin of SCC is not reported.
Kubota Y, Mir LM, Nakada T et al. (1998) Successful treatment of metastatic skin lesions with electrochemotherapy. Journal of Urology 160(4): 1426.	Case study of patient with multiple cutaneous lesion on the head and neck metastatic to bladder cancer.	Additional safety information: Exudate from head lesions persisted for up to 20 days.	Single patient case study.
Matthiessen LW, Chalmers RL, Sainsbury DC et al (2011) Management of cutaneous metastases using electrochemotherapy. Acta Oncologica 50(5): 621–9	Analysis of registry data from two European centres (UK, Denmark). 51 patients (196 lesions), 24 patients (97 lesions) evaluated after 60 days. Follow-up: 6 months	Additional safety information: 5 patients reported flu-like symptoms 1–2 days post-treatment. 5 patients reported pain 1–2 days post-treatment. 1 patient reported cough. 1 patient reported an allergic skin reaction. 1 patient reported anxiety. Most side effects were seen with a combination	40% of the 51 patients had metastases of melanoma and another 16% had metastases of BCC or SCC of unreported origin. The proportion of these patients in the evaluated group (24 patients) and response data was not reported separately for the non-melanoma patients. No statistical tests are reported and the information provided adds little to what is known from other

		of general anaesthesia and IV bleomycin.	studies. The registry data may be available for evaluation at the post-consultation stage.
Rebersek M, Cufer T, Rudolf Z et al. (2000) Electrochemotherapy with cisplatin of breast cancer tumor nodules in a male patient. Radiology and Oncology.34 (4): 357-361),	Case study of cutaneous metastases of breast cancer in a male patient. Intratumoral chemotherapy (cisplatin) on 3 lesions.	2/3 CR 1/3 PR	Single patient study. No further details in abstract.
Rodriguez-Cuevas S, Barroso-Bravo S, Almanza-Estrada J et al. (2001) Electrochemotherapy in primary and metastatic skin tumours: phase II trial using intralesional bleomycin. Archives of Medical Research 32(4): 273–6	Case series n=15 patients with metastatic skin cancers (4- 2 with breast cancer and 2 with metastatic SCC) Follow-up: 8.6 months (mean)	OR:98% CR: 49% PR:49% No response: 2% Tolerance was adequate, no complications related to ECT.	Larger studies included in table 2.
Skarlatos I, Kyrgias G, Mosa E et al. (2011) Electrochemotherapy in cancer patients: first clinical trial in Greece. In Vivo 25(2): 265–74	52 patients, 15 patients had ECT in combination with radiotherapy (8 patients), brachytherapy (1 patient) or surgery (6 patients). 14 patients within scope of this report. Follow-up 2 months	9/14 CR 4/14 PR 1/14 NR No additional safety information.	Patients with different treatment regimes are not described and responses are not reported separately.
Sersa G, Cemazar M, Rudolf Z et al. (1999) Adenocarcinoma skin metastases treated by electrochemotherapy with cisplatin combined with radiation. Radiology and Oncology.33(4): 291–6	Case study of cutaneous metastases of papillary adenocarcinoma. Follow- up 2 weeks	Intratumoral chemotherapy (cisplatin) was comparable with ECT plus radiotherapy. Both were more effective than radiotherapy alone. ECT + radiotherapy produced a faster tumour response than ECT alone.	Single patient study. No further details in abstract.
Tijink BM, De Bree R, Van Dongen GA et al. (2006) How we do it: Chemo-electroporation in the head and neck for otherwise untreatable patients. Clinical Otolaryngology 31(5): 447–51	7 patients with secondary, recurrent or metastatic tumours of the head and neck or skin. 1 patient within scope. intratumoral bleomycin used.	Additional safety information: 1 patient suffered mild hair loss (normally a side-effect of systemic bleomycin) 1 patient reported slight nausea lasting 2 days post-treatment.	Origin of SCC cancers was not clear. Only a single patient definitely within scope.
Whelan MC, Larkin JO, Collins CG et al. (2006) Effective treatment of an	Case study of breast cancer recurrent in the chest wall following	3 treatment sessions over 7 months required to produce complete	Single patient study with no additional safety outcomes.

extensive recurrent breast cancer which was refractory to multimodal therapy by multiple applications of electrochemotherapy. European Journal of Cancer, Supplement. 4(11): 32–4	chemotherapy and radiotherapy.	response. Follow-up with systemic chemotherapy. Small local recurrence after 30 months also responded to ECT.	
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Appendix B: Related NICE guidance for electrochemotherapy for the treatment of secondary cancers in the skin

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/IPG155publicinfo).
Clinical guidelines	Metastatic malignant disease of unknown primary origin: diagnosis and management of metastatic malignant disease of unknown primary origin. NICE clinical guideline 104 (2010) Note that this is a series of recommendations regarding the organisation of services specifically for patients with cancer of unknown primary origin.
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 one 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 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
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	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 secondary cancers in the skin

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	26/10/12	Issue 10 of 12, Oct 2012	0
Database of Abstracts of Reviews of Effects – DARE (CRD website)	26/10/12	October 2012	0
HTA database (CRD website)	26/10/12	October 2012	0
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	26/10/12	Issue 10 of 12, October 2012	9
MEDLINE (Ovid)	26/10/12	Ovid MEDLINE(R) 1946 to October Week 3 2012	19
MEDLINE In-Process (Ovid)	26/10/12	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 25, 2012	31
EMBASE (Ovid)	26/10/12	1974 to 2012 Week 42	85
CINAHL (NLH Search 2.0 or EBSCOhost)	26/10/12	October 2012	30

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 electropor* 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
- 8 ((skin* or Melanoma* or Cutaneous* or sarcoma* or "non melanoma") adj3 (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
- 21 limit 20 to ed=20120403-20121031