NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of electrochemotherapy for melanoma metastases in the skin

Treating melanoma metastases in the skin 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 melanoma metastases in the skin

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 from melanoma 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 chemotherapy, curettage, cryotherapy and radiotherapy.

What the procedure involves

Electrochemotherapy is a local treatment that 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 intratumourally. 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 is intended to make 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) provide 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): over 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 size.
- progressive disease (PD): over 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 melanoma metastases in the skin. 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 melanoma metastases in the skin
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 160 patients from 2 randomised controlled trials [1, 2], 3 non-randomised comparative studies [3, 4, 5] and 3 case series [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 melanoma metastases in the skin

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

Study details

Byrne CM (2005)[1]

Randomised controlled trial
Australia

Recruitment period: not reported

Study population: patients with cutaneous and subcutaneous metastatic MM, stage 3 or 4

n = **19 patients (46 lesions)**
ECT (17 lesions) vs IT bleomycin (19 lesions)

Age: 75 years (mean)

Sex: 57% (11/19) male

Patient selection criteria: at least 2 MM metastatic lesions, over 18 years old, and life expectancy of over 6 months

Technique: 2— 4 lesions per patient included in the study. Local anaesthetic. IT bleomycin 1 U/ml lesion volume. Lesions less than 0.5 ml were injected with 0.5 U 2 to 20 minutes later. EPT was applied to a depth greater than the tumour depth. Genetronics Medpulser electroporator, 560-1500 V was used. Lesions could be retreated at the clinician's discretion for PR or SD response at 4, 8 or 12 weeks. Lesions treated with bleomycin alone could be crossed over to ECT for PD response at 4, 8 or 12 weeks. Additional 'non-study'

Key efficacy findings

Number of patients analysed: **15 (36 lesions)**

Size: 3 × 3 to 50 × 50 mm

Lesion response rate (at 12 weeks)

Treatment	PR % (n)	CR % (n)
ECT	12 (2/17)	47 (8/17)
Bleomycin	16 (3/19)	11 (2/19)

Lesion response rate (at end of follow-up)

Treatment	PD % (n)	NR % (n)	PR % (n)	CR % (n)
ECT	5 (1/18)	18 (3/18)	5 (1/18)	72 (13/18)
Bleomycin	53[¥] (10/19)	15* (3/19)	5 (1/19)	26* (5/19)

*1 lesion with NR was retreated and had a CR.
[¥]1 lesion with PD crossed over to ECT and had a CR; response included in both rows.

Lesion control (at 12 weeks)
3 patients with CR in ECT-treated lesions had these excised for histological examination: 2 patients had fibrosis, multi-nuclear giant cells and no evidence of malignancy; 1 patient had a 'single small focus of residual melanoma present'.

Key safety findings

Complication	% (n)
Death within 12 weeks 1 due to advanced melanoma at 2 months 1 due to unrelated upper gastrointestinal haemorrhage at <1 month	8 (2/19)
Unpleasant 'electric shock' sensation, muscle spasms and pain during pulses.	Numbers not reported.
Inflammatory response leading to superficial necrosis and an eschar. Completely healed by 16 weeks.	'Invariably' in ECT treated lesions

Comments

Follow-up issues

- Patients followed up at 2, 4, 8, 12, 18 and 24 weeks.
- 21% (4/19) of patients (10/46 lesions) did not complete 12 week follow-up; 2 patients died, 1 hospitalised for palliative care of disseminated melanoma, 1 patient had excision of all lesions at week 4.
- Long term outcomes determined from clinical records.
- Follow-up is reported as 'average' 21 months in paper

Design issues

- Lesions were randomised so that each patient had at least 1 lesion in each treatment arm.
- Table data appears to show 2 lesions (same patient) retreated for NR (ECT) and DP (bleomycin only), but only 1 lesion is described as retreated in the text.
- Authors report an ITT analysis in the discussion and further results of 'non-study lesions'.

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>lesions treated at the investigator’s discretion.

Follow-up: 21 months (average)

Conflict of interest/source of funding : Study funded by Genetronics Inc (Medpulser manufacturer)</td>
<td>Lesion OR rate by analysis method (at end of follow-up)
<table>
<tr><th>Treatment</th><th>Per protocol % (n)</th><th>ITT % (n)</th></tr>
<tr><td>ECT</td><td>78 (14/18)</td><td>64 (14/22)</td></tr>
<tr><td>Bleomycin</td><td>32 (6/19)</td><td>29 (6/21)</td></tr>
<tr><td>p value</td><td>0.002</td><td>0.02</td></tr>
</table>
Survival
26% (5/19) patients were alive at an ‘average’ follow-up of 36.5 months.
Average survival period in 74% (14/19) of patients who died was 14 months.
50% of patients required subsequent procedures to treat metastatic disease.</td>
<td></td>
<td>Study population issues
• 1 lesion initially treated with bleomycin only then crossed over to ECT is included in both groups for the end-of-study response rates.

Other issues
• Adverse events reported vaguely – precise frequency or intensity not reported.</td>
</tr>
</table>

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

Study details

Gaudy C (2006)[2]

Randomised controlled trial
France

Recruitment period: not reported

Study population: patients with metastatic MM.

n = **12 patients (54 tumours)**

ECT (30 tumours) vs IT bleomycin (24 tumours)

Age: mean 62 years

Sex: 75% (9/12) male

Patient selection criteria: age >18 years, ≥2 MM metastatic tumours, disease stage 3 (unresectable, recurrent) or 4 (with no response to chemotherapy).No local therapy within 12 weeks. Exclusions: MM on digits, bleomycin allergy, pacemaker/severe arrhythmia. 4 patients had in-transit MM only.

Technique: 2—12 tumours treated per patient. Tumours, randomised to treatment arm. Local anaesthetic. IT bleomycin at 1 mg/cm^3 tumour volume (≤40 mg per patient). Electric pulses delivered after 10 mins using Genetronics Medpulser with needle electrodes.

Follow-up: **24 weeks**

Source of funding: not reported

Key efficacy findings

Number of patients analysed: **12 ; varies between analyses**

Tumour response rate at 12 weeks

Treatment	Per protocol 7 patients (28 tumours)		ITT 12 patients (54 tumours)	
	CR % (n)	**OR % (n)**	**CR % (n)**	**OR % (n)**
ECT	64 (11/17)	82 (14/17)	37* (11/30)	46 (14/30)
Bleomycin	18 (2/11)	54 (6/11)	8 (2/24)	25 (6/24)
p value	0.017	0.12	0.016	0.10

***** Note incorrect percentage reported in paper.

Recurrence

None of the treated tumours in 9 patients (38 tumours) with CR at ≥1 month: 74% (17/23) and 13% (2/15) showed evidence of clinical recurrence at 12 and 24 weeks follow-up.

Time to response

Tumour response occurred 24—48 hours following bleomycin-only and after 2—3 weeks following ECT.

Time to complete healing

Complete healing was obtained in a median time of 2 weeks. 1 patient required 8 months for 3 tumours treated by ECT.

Key safety findings

Complication	% (n)
Death due to disease progression (weeks 1-28) 2 of these patients were not evaluated due to death or new chemotherapy treatment before first evaluation)'	50 (6/12)
Discomfort during ECT	100
Local pain	75 (9/12)
Muscle spasm with myoclonia secondary to electric pulses	25 (3/12)
Erythema/oedema	17 (2/12)
Necrosis	42 (5/12)

Comments

Follow-up issues

- Follow-up at weeks 2, 4, 8, 12, 18 and 24.
- At 12 weeks 5 patients were lost to follow-up: 2 died from disease progression, 1 started new systemic chemotherapy before evaluation, 2 lost to follow-up.
- Four patients remained in the study at week 24.

Design issues

- Tumours were randomised rather than patients. Each patient had at least 1 tumour in each treatment arm.
- All tumour assessments were made by a single clinician.

Population issues

- No eligibility restrictions were placed on performance status or life expectancy.
- In contrast to some other studies, no wash out period was stipulated; 8 of 12 patients were receiving systemic chemotherapy at inclusion.
- 4 patients had in transit melanoma metastases and were free of other therapy.

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

Study details	Key efficacy findings	Key safety findings	Comments
Marty M (2006)[3] **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: 32 MM (190 tumours), 29 non-melanoma (100 tumours) Of 41: 20 MM (98 tumours), 21 non-melanoma (73 tumours) **ECT with IT bleomycin (41 tumours) vs ECT with IV bleomycin (86 tumours) vs ECT with IT cisplatin (44 tumours)** Age: 66 years (median) Sex: 33%(20/61) male Patient selection criteria: life expectancy >3 months, 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 Cliniporator (IGEA, Italy) with surface (superficial tumours) or	Number of patients analysed: **41 patients (171 tumours), including 20 patients with MM (98 tumours**) **Tumour response (at ≥60 days), absolute numbers not reported** **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 response (at end of follow-up), absolute numbers not reported** **Tumour type** / **PD %** / **NR %** / **PR %** / **CR %** / **OR %** All / 4.7 / 10.5 / 11.1 / 73.7 / 84.8 **Tumour response according to drug delivery (at 150 days), absolute numbers not reported** **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 There was no significant difference in response rates between the 3 methods (p=0.09).	**Complications (n=61; 290 tumours)** Muscle contractions were assessed by the clinician and classified as either 'no' or 'low' in 78% of patients (n=48). Contractions ceased immediately when treatment was stopped. Hexagonal electrodes produced the least strong muscle contractions and surface electrodes the greatest. Five serious adverse events were reported but not associated with ECT (3 patients died from pulmonary metastases or disease progression, hypoxia and thoracic pain in another patient that spontaneously disappeared in 1 hour).	**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 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. • 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 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

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

Study details	Key efficacy findings	Key safety findings	Comments
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	**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 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.		patient) and 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 MM are 52.4% (32/61) of the whole study population. **Other issues** • Objective rate (OR) is not defined in the paper, although all other response criteria are. • The 29 (99 tumours) non-melanoma patients are outside the scope of this report. • Results are often reported as percentages only.

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

Study details

Campana LG (2009)[4]

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)**

34 in transit MM (373tumours), 18 patients with other cancer types: 11 breast cancer (174 tumours), 5 sarcoma (29 tumours), 1 SCC (31 tumours), 1 HNC (1 tumour).

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. ECT was given with the Cliniporator (IGEA) and type II or type III needle electrodes. Patients with NR or PR at 4 weeks after 1

Key efficacy findings

Number of patients analysed: **52 (266 tumours) including 34 patients with in transit MM (171 tumours)**
20 stage III, 14 stage IV

Per-patient response
50% (17/34) of MM patients had a CR at 4 weeks.

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)

Response after 2nd treatment for PR (14 patients, 158 tumours; evaluation time point uncertain)

	PR % (n)	CR % (n)
Patients	21 (3/14)	79 (11/14)
Tumours	17 (27/158)	83 (131/158)

Tumour response according to drug delivery (evaluation time point uncertain)

Route	NR % (n)	PR % (n)	CR % (n)
IT bleomycin	8 (2/24)	34 (8/24)	58 (14/24)
IV+IT bleomycin	0	59 (13/22)	41 (9/22)
IV bleomycin	0	50 (3/6)	50 (3/6)

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

Key safety findings

Adverse events in entire study

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)
GradeI-II rush, desquamation or pigmentation at 4 weeks	12% (6/52)
Postoperative pain managed with minor analgesics	88% (46/52)

Comments

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); 171/373 MM 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

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>ECT session were re-treated.

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 relations, pain control, acceptance of retreatment and overall satisfaction).

Follow-up: 9 months (median)

Conflict of interest/source of funding: not reported.</td>
<td>(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.

100% (2/2) of patients with NR (both melanoma) were retreated with ECT and achieved CR. Each had ‘local relapse’ after 7 months and 17 months respectively in a single large tumour.

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><th></th><th>Overall QOL score (range)</th><th>p value</th></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 quality of life. P values vs pre-treatment scores; 34/36 (94%) reported an improvement following ECT in 1 or more of the 6 parameters in the questionnaire.

9/22 (41%) patients with painful pre-treatment tumours reported better pain control after ECT; 34/36 (94%) of patients were amenable to further ECT.</td>
<td>
<table>
<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>
</td>
<td>using a non-validated 8 item questionnaire (bleeding, ulceration, aesthetics, activities of daily living, social 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.
• 18 patients with non-melanoma cancers are outside the scope of this report.</td>
</tr>
</table>

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>
Heller R (1998)[5]
Non-randomised comparative study
USA
Recruitment period: 1995–1996
Study population: Patients with cutaneous/subcutaneous metastatic cancer
n = 34 patients (169 lesions)
12 MM (96 lesions), 22 non-melanoma (73 lesions)
IT bleomycin ECT (143 lesions) vs IT bleomycin alone (20 lesions) vs pulses alone (6 lesions)
Age: 59.6 years (mean)
Sex: 85% (29/34) male

Patient selection criteria: patients with basal cell carcinoma, advanced MM, squamous cell carcinoma or Kaposi’s sarcoma. No restriction was made on the basis of performance status or life expectancy.

Technique: IT bleomycin administered at a concentration of 5000 IU/ml dependent on tumour volume (500 IU <100 mm^3 up to 4000 IU > 5000mm^3). Electric pulses delivered 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) (MM only)
Conflict of interest/source of funding: research grant from Genetronics, Inc. Heller is scientific advisor for Genetronics Inc and received stock options.
</td>
<td>
Number of patients analysed: 12 patients with MM (96 tumours)

ECT lesion response rates (at 12 weeks)
<table>
<tr><th></th><th>No. lesions</th><th>NR % (n)</th><th>PR % (n)</th><th>CR % (n)</th></tr>
<tr><td>ECT</td><td>84</td><td>1.2 (1/84)</td><td>9.5 (8/84)</td><td>89.3 (75/84)</td></tr>
<tr><td>EPT</td><td>3</td><td>100</td><td>0</td><td>0</td></tr>
<tr><td>Bleomycin</td><td>9</td><td>100</td><td>0</td><td>0</td></tr>
</table>
Time to response and healing
Treated tumours showed signs of response within the first 24–48 hours. Complete wound healing by secondary intention took an average of 6–10 weeks.

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 bleomycin only or pulses only showed no significant histologic changes

Recurrence (at 20 months)
89% (75/84) of nodules with a CR at 12 weeks did not report any recurrence during the 20-month mean follow-up.
</td>
<td>
<table>
<tr><th>Finding</th><th>Frequency</th></tr>
<tr><td>Muscle contractions, subsided after pulsing</td><td>100%</td></tr>
<tr><td>Discomfort during pulse. Greater intensity was towards extremities, with plate electrodes and with large gap between plate electrodes.</td><td>‘Majority’ of patients</td></tr>
<tr><td>Slight burning of skin from plate electrodes. Healed within 6–8 weeks.</td><td>7/8 patients treated with plate electrodes.</td></tr>
<tr><td>Muscle fatigue in treated limbs lasting 24 hours</td><td>A ‘few’ cases</td></tr>
<tr><td>Slight nausea for 24–48 hours</td><td>6% (2/34)</td></tr>
</table>
</td>
<td>
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 not described. Intrapatient comparisons are not performed.
• The choice of needle or plate electrodes was not described.
• The distribution of biopsies between lesion types not described.

Other issues
• 22 non-melanoma patients (73 lesions) are outside 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)[6].
</td>
</tr>
</table>

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

Study details	Key efficacy findings	Key safety findings	Comments
Mir LM (1998)[6] **Case series** France (3 centres), Slovenia, United States Recruitment period: not reported Study population: patients with cutaneous and subcutaneous tumours including metastatic MM n = **50 patients (291 tumours)** 20 MM (142 tumours), 30 other cancer types (149 tumours) Age: 55.8 years (mean) Sex: Not reported Patient selection criteria: patients with MM had received previous surgery, chemotherapy or radiotherapy. Technique: European centres: IV or IT bleomycin was administered at either 18 U/m2 or 27 U/m2. Pulse delivery using PS 15 Jouan electropulsator and plate electrodes. US centre: IV bleomycin at 10 U/m^2 infused at a rate of 1.5 U/min or IT at 0.25–1.0 U/tumour. Pulses delivered using Genetronics BTX T820 generator and plate or needle electrodes. Follow-up: **not reported** Conflict of interest/source of funding: Some funding provided from Genetronics Inc.	Number of patients analysed: **20 patients (142 tumours)** MM mean diameter 8.1 mm. **Response rate (at ≥30 days)** | | NR % (n) | PR % (n) | CR % (n) | OR % (n) | |---|---|---|---|---| | Per tumour | 7.7 (11/142) | 39.4 (56/142) | 52.8 (75/142) | 92.2 (131/142) | | Per patient* | | 35 (7/20) | 30 (6/20) | | * Further numbers not reported. **Recurrence** The 53% (75/142) of tumours with a CR within 1 to 2 weeks after ECT did not report any recurrence. **Controls**: 15 additional lesions were treated with bleomycin alone; resulted in 100% PD. 8% (11 tumours) tumours with NR included 2 tumours that that could not be entirely treated and 5 tumours in 2 patients receiving IV bleomycin in poorly perfused areas.	**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 outcomes defined at least 30 days post treatment. Actual time point of assessment is unclear. **Study design issues** • Prospective multicentre study. • The data is 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 and response rate. **Other issues** • 30 patients (149 tumours) with basal cell carcinoma, adenocarcinoma and head and neck squamous cell carcinoma 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)[5].

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Quaglino P (2008)[7]

Case series
Italy
Recruitment period: 2005–2007
Study population: patients with stage III cutaneous/subcutaneous MM metastases.
n = 14 patients (233 lesions)
Age: 61 years (median)
Sex: 57% (8/14) male

Patient selection criteria: As per ESOPE, histologically confirmed MM with unresectable persistent cutaneous/subcutaneous metastases; age ≥18 years, Karnofsky performance status >70%, life expectancy >3 months, with no treatment in preceding 3 weeks. All patients had stage III disease and relapsed following previous treatments.

Technique: As per ESOPE guidelines using IT bleomycin and Cliniporator (IGEA) plate or needle electrodes. Patients had general anaesthetic. All lesions were treated; 4-7 lesions >5 mm diameter per patient selected as index lesions. 1 index lesion on each patient selected for histological confirmation.

Follow-up: 21 months (median)

Conflict of interest/source of funding: Supported by a grant from “Associazione AMICI DI JEAN”</td>
<td>Number of patients analysed: 14 (233 lesions)

Lesion response rates – overall (A+B)
<table>
<tr><th>NR % (n)</th><th>PR % (n)</th><th>CR % (n)</th><th>OR % (n)</th></tr>
<tr><td>8 (17/233)</td><td>34 (80/233)</td><td>58 (136/233)</td><td>93 (216/233)</td></tr>
</table>
NB this included 14 patients (160 lesions) treated at first session (A); 7 patients treated for 73 new lesions in a second session (B).

Repeated treatments
3 patients had a second treatment for 29 lesions (25 PR, 4 NR) and 5 of these lesions received a third treatment – time point not reported. 15 of 29 were index lesions (11 PR, 4 NR) resulting in 9 CRs, 4 PRs and 2 NRs.

Lesion response by size (at 8 weeks)
<table>
<tr><th>Tumour size</th><th>OR % (n)</th><th>CR % (n)</th></tr>
<tr><td>≤1 cm^2</td><td>98 (181/184)</td><td>68 (125/184)</td></tr>
<tr><td>>1 cm^2</td><td>73 (36/49)</td><td>22 (11/49)</td></tr>
<tr><td>p value</td><td><0.001</td><td><0.001</td></tr>
</table>
Response duration
Local lesion control rate at 2 years was 74.5%. Median duration of time to treatment failure: 18.3 months.

Recurrence
No CR lesions relapsed during a median follow-up of 21 months whereas 67.5% (54/80) PR lesions showed a >25% increase in size.</td>
<td>Local erythema and oedema occurred in 21% (3/14) of patients and resolved in ‘a few days’.

Electrode marks and superficial erosions occurred in all patients, followed by scars healing within 1 month. No further details reported.</td>
<td>Follow-up issues
• Patients were followed-up at 2, 4, 8 and 12 weeks, then every 2 months. Response was evaluated 8 weeks post treatment.

Design issues
• Local lesion control defined as time between lesion response achievement and relapse (CR lesions), >25% increase in size (PR lesions) or last follow-up date.
• Time to treatment failure defined as time from first treatment to disease recurrence requiring new treatment, discontinuation of therapy, death (any cause) or date of last follow-up.

Other issues
• The time point for session B and repeated treatments are not given. Evaluations are assumed to be 8 weeks following each treatment session.</td>
</tr>
</table>

Abbreviations used: CR, complete response; ECT, electrochemotherapy; EPT, electroporation therapy; ESOPE, European Standard Operating Procedures for Electrochemotherapy; IT, intratumoural; ITT, intention to treat; IV, intravenous; MM, malignant melanoma; NR, no response; OR, objective response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; U, units.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Kis E (2011)[8]

Case series
Hungary
Recruitment period: 2007–2009
Study population: patients with cutaneous and subcutaneous unresectable MM metastases.

n = 9 patient (158 tumours)
Age: 74 years (median)
Sex: 22% (2/9) male

Patient selection criteria: As ESOPE guidelines; disease progression despite standard treatments, life expectancy >3 months, treatment-free interval of ≥2 weeks, Karnofsky performance status >70%.

Technique: ECT with IV bleomycin as per ESOPE guidelines under general sedation. Electric pulses delivered using a Cliniporator (IGEA) and needle electrodes.

Follow-up: 195 days (median)

Conflict of interest/source of funding: no conflict of interest stated. TAMOP 4.2.2-08/1 grant</td>
<td>Number of patients analysed: 9 (158 tumours)
Tumour diameter : mean 1.47 cm

Lesion response (at ≥60 days)
<table>
<tr><th>PD % (n)</th><th>NR % (n)</th><th>PR % (n)</th><th>CR % (n)</th><th>OR % (n)</th></tr>
<tr><td>8 (13/158)</td><td>30 (47/158)</td><td>39 (61/158)</td><td>23 (37/158)</td><td>62 (98/158)</td></tr>
</table>
The degree of pain decreased in previously painful tumours.</td>
<td>Erythema and slight oedema around the treated lesions were reported 1 day post treatment. Numbers not reported.

Muscle contractions during pulse delivery were reported to result in muscle soreness 1 day post treatment. Numbers not reported.

Marks of needle electrodes were visible on the skin for approximately 1 month. Further details not reported.

Central or complete necrosis of the treated tumours were visible for a ‘couple’ of weeks. Further details not reported.</td>
<td>Follow-up issues
Patients monitored in hospital for 1 day. Followed-up at 2 and 4 weeks, then monthly up to 6 months, then every two months.
Tumour response was assessed at least 60 days after treatment.
Study design issues
Prospective study
Pain assessment is not described.
Study population issues
1 patient had metastases on trunk, 8 patients had 142 metastases on limbs, 78% patients had metastases larger than 0.5 cm2. 8 patients had treatment in previously irradiated areas.</td>
</tr>
</table>

Efficacy

Tumour response (clinical observation)

A randomised controlled trial compared intratumoural electrochemotherapy with intratumoural chemotherapy alone in 19 patients with melanoma metastases[1]. In lesions treated with electrochemotherapy it reported complete response in 72% (13/18) of tumours, partial response in 6% (1/18), no response in 17% (3/18) and progressive disease in 6% (1/18) at end of follow-up ('average' of 21 months). Per protocol analysis reported that objective response in the electrochemotherapy group was significantly greater than in the chemotherapy alone group (78% versus 32%, p=0.005). On an intention-to-treat basis, objective response for electrochemotherapy was significantly greater than for chemotherapy alone (64% versus 29%, p=0.02)[1].

Another randomised controlled trial with the same comparison as above in 12 patients (54 tumours) reported an intention-to-treat complete response in 37% (11/30) of tumours treated with electrochemotherapy and 8% (2/24) treated with chemotherapy alone (p=0.016) at 12-week follow-up[2].

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, a 66% complete response and an 81% objective response were reported in 20 patients with 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)[3].

A non-randomised comparative study of 52 patients (608 tumours) including 34 patients with malignant melanoma (171 tumours) reported a complete response of 50% (17/34) in melanoma patients at 4 weeks follow-up [4].

Tumour response by tumour size

The non-randomised comparative study of 61 patients including 20 patients with melanoma metastases evaluated for tumour response reported no significant relationship between tumour size and response (p=0.59). However, tumours greater than 0.5 cm^3 responded better to systemic rather than intratumoural chemotherapy (objective response 94% versus 75%, p=0.047). Absolute numbers not reported[3].

The non-randomised study of 52 patients, including 34 with melanoma, reported a significant inverse correlation between maximum tumour diameter and

complete response: 66% for diameters less than 1.5 cm, 36% for diameters between 1.6 cm and 3 cm and 28% for diameters greater than 3 cm (p=0.0035)[4].

Recurrence

The randomised controlled trial comparing intratumoural electrochemotherapy with intratumoural chemotherapy alone in 12 patients reported no recurrence at 12 and 24 weeks follow-up in tumours that obtained a complete response at 1 month; 74% (17/23) versus 13% (2/15) respectively [2].

The non-randomised comparative study of 52 patients including 34 patients with malignant melanoma reported that 9% (3/34) of patients with melanoma developed recurrence in the areas treated with electrochemotherapy. One patient developed recurrence at 7 months following an initial complete response. Two patients with an initial non-response were retreated and achieved complete responses, but then had recurrences at 7 and 17 months[4].

Duration of response

A case series of 14 patients with 233 malignant melanoma metastases reported that local tumour control was 75% 2 years after treatment. The median time to treatment failure was 18 months [7].

Survival

In the trial of 19 patients, 26% (5/19) of patients were alive at an ‘average’ follow-up of 37 months. The average survival period in the 74% (14/19) of patients who died was 14 months[1].

Quality of life

The study of 52 patients including 34 patients with malignant melanoma 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). This was 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 before and after treatment (bleeding, ulceration, aesthetics, activities of daily living, social relations and pain control)[4].

Safety

Muscle spasms

Muscle spasms during electric pulse delivery, which stopped immediately when treatment stopped, were reported in all 15 patients in the randomised controlled trial comparing electrochemotherapy with intratumoural chemotherapy alone[1]. They were also reported in the non-randomised comparative study of 34 patients

and in the case series of 50 patients (100% of cases) [5,6]. Muscle spasms with myoclonia secondary to electric pulses were reported in 25% (3/12) of patients treated by electrochemotherapy in the randomised controlled trial of 12 patients [2]. Muscle contractions classified by the treating clinician as of 'low' or 'no' level, which stopped after treatment stopped, were reported in 78% (48/61) patients in the non-randomised comparative study of 61 patients[3]. In this study, the surface electrodes produced greater effects than hexagonal-centred electrodes [3].

Skin changes

Slight burning of the skin was noted in 7 out of 8 patients treated with electrochemotherapy using plate electrodes in the non-randomised comparative study of 34 patients [5]. The burns healed within 6–8 weeks[5].

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 study[4].

Erythema or slight oedema, which resolved in 24 hours, was reported in all patients in the case series of 50 patients [6]. The case series of 14 patients reported that 2% (3/14) of patients had erythema and oedema at treated areas which resolved in a 'few' days[7]. This event was also reported in 17% (2/12) of patients treated with electrochemotherapy in the randomised controlled trial of 12 patients (further details not reported)[2].

An inflammatory reaction leading to superficial necrosis and an eschar occurred in all tumours treated with electrochemotherapy in the randomised controlled trial of 19 patients[1]. Tumour necrosis was also reported in 42% (5/12) of patients treated with either intratumoural electrochemotherapy or intratumoural chemotherapy alone in the other randomised controlled trial[2].

An inflammatory reaction in treated tumours was reported in all patients in the non-randomised comparative study of 52 patients[4]. This resolved at the end of follow-up (mean 9 months) in 88% (46/52) of patients[4].

Nausea

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 non-randomised comparative study of 34 patients (no further details reported)[5]. Nausea and vomiting was also reported in 4% (2/52) of patients in the non-randomised comparative study of 52 patients (no further details reported)[4].

Electrode marks

Visible marks of needle electrodes after electrochemotherapy were reported in the case series of 9 patients with metastatic melanoma[8]. The marks were visible for 1 month (number of patients affected not reported)[8]. Electrode marks and superficial erosions occurred in all patients after electrochemotherapy in the case series of 14 patients. The marks healed within 1 month[7]. Transient marks 'often' visible were also reported in a case series of 50 patients (no further details reported)[6].

Muscle fatigue

Muscle fatigue in treated limbs after electrochemotherapy, lasting for 24 hours, was reported by a 'few' patients in the study of 34 patients (no further details reported)[5].

Lipothymia (postoperative syncope)

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

Validity and generalisability of the studies

- The technical delivery of electrochemotherapy varies. Most of the included studies use bleomycin as the cytotoxic drug and many studies apply ESOPE methods or make small deviations from ESOPE. Studies published before 2006 pre-date ESOPE. There are several different electrical current generators used in the studies. The studies that use the ESOPE standardised method use the Cliniporator device (IGEA, Italy). The number of electrochemotherapy treatments given to patients varies and is not consistently reported across studies. In 1 study patients had up to 5 electrochemotherapy treatments[4].
- In no studies are participants or clinicians who assess outcomes blinded to interventions.
- The studies do not consistently report precisely how many patients (or tumours) need more than 1 electrochemotherapy session until a satisfactory tumour response is achieved, although repeat treatments are sometimes given.
- The length of follow-up in the studies very seldom extends beyond the point of assessment of tumour response, typically 12–24 weeks. The studies are not designed to examine survival in patients with metastatic melanoma, and electrochemotherapy is a treatment to improve quality of life rather than improve survival.
- There is high general consistency in the criteria used to define tumour response, which are largely based on a definition set by the World Health

Organization or that of 'Response evaluation criteria in solid tumors'. Most studies assess tumour response 8–12 weeks after electrochemotherapy.

- Outcomes tend to be reported by number of tumours rather than number of patients although this may be because of the generally small sample size in the studies. Some studies provide results separately for additional tumours that appeared at new sites during follow-up. In the randomised studies[1,2] and other comparative studies there is a degree of non-independence arising from allocation of tumours, rather than patients, to different treatment strategies.
- The quality of life data is reported in only 1 study [4] and relates to a series of patients in which approximately half of patients had non-melanoma cutaneous or subcutaneous malignancies.
- No studies were in the UK. All studies were in Europe except for 1 Australian study and 1 in the USA.
- Adverse events are described variably across the studies.

Existing assessments of this procedure

A Horizon Scanning Report update conducted for Australia and New Zealand in 2008 addresses electrochemotherapy for the treatment of local malignant tumours. It is based mainly on studies involving patients with melanoma and has a high degree of overlap with the studies included in this overview. 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.

Cancer service guidance

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

Public health guidance

- Skin cancer: prevention using public information, sun protection resources and changes to the environment. NICE public health guidance 32 (2011). Available from www.nice.org.uk/guidance/PH32

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 the 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 stated that the title of the overview should reflect the role of electrochemotherapy in disseminated malignant melanoma.
- Two Specialist Advisers considered the procedure as an established treatment in the UK, with fewer than 10% or 10–50% of relevant clinicians performing it. The other 3 Specialist Advisers considered it to be definitely novel and performed by only 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 sarcoma.
- One Specialist Adviser indicated that the results after electrochemotherapy are variable and patient selection is critical. Two Specialist Advisers had experience in selecting patients for this procedure regularly.
- One Adviser stated that repeated treatments may also be needed and 1 stated that the number of optimal treatments is unknown.
- One Specialist Adviser has undertaken bibliographic and clinical research in electrochemotherapy 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. 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 and 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.

- Specialist Advisers listed key efficacy outcomes as improvement in disease state, control of disease, tumour regression, duration of benefit, 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 are some unknowns about 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 as it is 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 electroporation 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 is 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 sent xxx questionnaires to xxx trusts for distribution to patients who had the procedure (or their carers). NICE received xxx completed questionnaires.

Section to be inserted where Patient Commentary was not gathered

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

Section to be inserted where Patient Commentators raised no new issues

The Patient Commentators' views on the procedure were consistent with the published evidence and the opinions of the Specialist Advisers.

Section to be inserted where Patient Commentators raised new issues

The Patient Commentators raised the following issues about the safety/efficacy of the procedure which did not feature in the published evidence or the opinions of Specialist Advisers, and which the Committee considered to be particularly relevant:

- [insert additional efficacy and safety issues raised by Patient commentators and highlighted by IPAC, add extra rows as necessary].
- [Last item in list].

Issues for consideration by IPAC

- A suggestion for the title of this overview is 'electrochemotherapy for the treatment of cutaneous or subcutaneous metastases of malignant melanoma'.
- Future trials:
  - NCT00918593 Palliative Treatment of Ulcerated Cutaneous Metastases: Trial Between Electrochemotherapy and Radiotherapy. Phase II randomised efficacy study (any histology). Target recruitment: 98 patients. Status: withdrawn.
  - NCT00006035 Bleomycin With or Without Electroporation Therapy in Treating Patients With Stage III or Stage IV Melanoma. Phase I. Target

recruitment: 20 patients (10 per treatment arm). Start date: June 2000. Status: Active, not recruiting.

- The InspECT database is a registry of electrochemotherapy procedures collated by centres in Denmark, Germany, UK and Italy and is supported by supported by IGEA (Carpi, Italy), manufacturer of the Cliniporator electrical pulse generator. To date a publication from the InspECT database (Matthiessen and co-workers 2011, see appendix A, row 1) is available but does not disaggregate efficacy outcomes for patients with malignant melanoma from patients with metastases of other histologies.
- Electrochemotherapy appears to be of potential value for patients with cutaneous or subcutaneous metastases of malignant melanoma that may be painful, unsightly and damaging to body image and quality of life. No published studies in this overview have aimed to measure any effect on survival arising from electrochemotherapy; the setting of care is palliative. Electrochemotherapy may be an additional treatment option for this group of patients if no other treatment is available, considering that isolated limb perfusion/infusion are more invasive procedures and cannot be used to treat metastatic tumours on the trunk.
- A large (n=85) retrospective analysis was published after the literature search cut-off date and should be considered for inclusion at the next available stage in IP guidance development. The study is by Campana et al (2012)[10].
- The ESOPE standardised method for delivery of electrochemotherapy appears to base the technique on the Cliniporator (IGEA) electric pulse delivery system. Some studies in this overview used different systems to provide the electric pulses for electrochemotherapy.

References

1. Byrne CM, Thompson JF, Johnston H et al. (2005) Treatment of metastatic melanoma using electroporation therapy with bleomycin (electrochemotherapy). Melanoma Research 15 (1): 45-51
2. Gaudy C, Richard MA, Folchetti G et al. (2006) Randomized controlled study of electrochemotherapy in the local treatment of skin metastases of melanoma. Journal of Cutaneous Medicine & Surgery 10 (3): 115-121
3. Marty M, Sersa G, Garbay JR et al. (2006) Electrochemotherapy - An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. European Journal of Cancer, Supplement.4 (11) (pp 3-13), 2006.Date of Publication: November 2006. (11): 3-13
4. Campana LG, Mocellin S, Basso M et al. (2009) Bleomycin-based electrochemotherapy: clinical outcome from a single institution's experience with 52 patients. Annals of Surgical Oncology 16 (1): 191-199
5. Heller R, Jaroszeski MJ, Reintgen DS et al. (1-7-1998) Treatment of cutaneous and subcutaneous tumors with electrochemotherapy using intralesional bleomycin. Cancer 83 (1): 148-157
6. Mir LM, Glass LF, Sersa G et al. (1998) Effective treatment of cutaneous and subcutaneous malignant tumours by electrochemotherapy. British Journal of Cancer 77 (12): 2336-2342
7. Quaglino P, Mortera C, Osella-Abate S et al. (2008) Electrochemotherapy with intravenous bleomycin in the local treatment of skin melanoma metastases. Annals of Surgical Oncology 15 (8): 2215-2222
8. Kis E, Olah J, Ocsai H et al. (2011) Electrochemotherapy of cutaneous metastases of melanoma--a case series study and systematic review of the evidence. [Review]. Dermatologic Surgery 37 (6): 816-824
9. Australia and New Zealand Horizon Scanning Network. (2008) Electrochemotherapy for the treatment of local malignant tumours. Horizon scanning technology prioritising summary update.
10. Campana LG, Valpione S, Mocellin S et al. (2012) Electrochemotherapy for disseminated superficial metastases from malignant melanoma. Br.J.Surg. 99 (6): 821-830

Appendix A: Additional papers on electrochemotherapy for the treatment of malignant melanoma

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
Campana LG, Pasquali S, Basso M et al. (2010) Electrochemotherapy: Clinical outcome and predictive factors from a single institution experience on 50 melanoma patients. Annals of Surgical Oncology. Conference: 63rd Annual Cancer Symposium of the Society of Surgical Oncology St. Louis, MO United States. Conference Start: 20100303 Conference End: 20100307.Conference Publication: (var.pagings).17 (pp S106), 2010.Date of (var.pagings): S106-	Type: Case series n=50 Indication: MM Intervention: ECT Follow-up: mean 16 months	Efficacy: OR 66% CR 47% Safety: 12% of patients experienced local recurrence	Conference abstract
Campana LG, Valpione S, Chiarion-Sileni V et al. (2011) Health-related quality of life outcomes in advanced melanoma patients after palliative treatment with bleomycin-Based Electrochemotherapy. European Journal of Cancer.Conference: 2011 European Multidisciplinary Cancer Congress Stockholm Sweden.Conference Start: 20110923 Conference End: 20110927.Conference Publication: (var.pagings).47 (pp S656), 2011.Date of Publication: September 2011. (var.pagings): S656-	Type: Case series n=51 Indication: MM Intervention: ECT Follow-up: 6 months	Efficacy: demonstrates improvement in global health score from ECT Safety: no abstracted data	Conference abstract
Cavalcanti A, Souadka A, Mateus C et al. (2010) Clinical experience with eletrochemotherapy (ECT) in the skin melanoma metastases. European Journal of Surgical Oncology.Conference: 15th Congress of the European Society of Surgical Oncology Bordeaux France.Conference Start: 20100915 Conference End: 20100917.Conference Publication: (var.pagings).36 (9) (pp 909), 2010.Date of Publi (var.pagings): 909-	Type: Case series n=12 Indication: MM Intervention: ECT Follow-up: not reported	Efficacy: OR 83% CR 50% Safety: no abstracted data	Conference abstract

Article	Number of patients / follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Farricha V, Vasques H, Carvalhal S et al. (2010) Electrochemotherapy: A technique for multiple approaches in the treatment of locally advanced melanoma. Melanoma Research.Conference: 6th Congress of the European Association of Dermatologic Oncology Athens Greece.Conference Start: 20100616 Conference End: 20100619.Conference Publication: (var.pagings).20 (pp e53-e54), 2010.Date of Publication: June 20 (var.pagings): e53-e54	Type: Case series n=129 sessions Indication: MM Intervention: ECT Follow-up: not reported	Efficacy: OR 97% CR 88% Safety: no abstracted data	Conference abstract
Farricha V, Vasques H, Carvalhal S et al. (2010) Electrochemotherapy: two years of experience in a cancer centre. Melanoma Research: June 2010 - Volume 20 - Issue - p e53 doi: 10.1097/01.cmr.0000382854.52630.d6	Type: Case series n=113 Indication: cutaneous metastases Intervention: ECT Follow-up: not reported	Efficacy: OR 97% CR 88% Safety: no abstracted data	Conference abstract
Gehl J and Geertsen PF. (2000) Efficient palliation of haemorrhaging malignant melanoma skin metastases by electrochemotherapy. Melanoma Research 10 (6): 585-589	Type: Case report n=1 Indication: MM Intervention: ECT Follow-up: not reported	Efficacy: treatment immediately resolved bleeding tumours Safety: no abstracted data	Case report
Gehl J, Matthiessen LW, Humphreys A et al. (2010) Management of cutaneous metastases by electrochemotherapy. Journal of Clinical Oncology.Conference: 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States.Conference Start: 20100604 Conference End: 20100608.Conference Publication: (var.pagings).28 (15 SUPPL.1) , 2010 (var.pagings):	Type: Case series n=47 Indication: cutaneous metastases Intervention: ECT Follow-up: 60 days	Efficacy: OR 80% CR 64% Safety: treatment was well tolerated	Conference abstract
Giraud P, Bachaud JM, Teissie J et al. (1-12-1996) Effects of electrochemotherapy on cutaneous metastases of human malignant melanoma. International Journal of Radiation Oncology, Biology, Physics 36 (5): 1285-	No data	No data	No data

Article	Number of patients / follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Glass LF, Pepine ML, Fenske NA et al. (1996) bleomycin-mediated electrochemotherapy of metastatic melanoma. Archives of Dermatology 132 (11): 1353-1357	Type: Case series n=5 Indication: MM Intervention: ECT Follow-up: not reported	Efficacy: CR 78% PR 17% Safety: no abstracted data	n=5
Guida M, Porcelli G, Ruggieri E et al. (2009) Electrochemoterapy (ECT) for the treatment of superficial tumor localizations. Journal of Clinical Oncology.Conference: 2009 Annual Meeting of the American Society of Clinical Oncology, ASCO Orlando, FL United States.Conference Start: 20090529 Conference End: 20090602.Conference Publication: (var.pagings).27 (15 SUPPL.1) (pp e1 (var.pagings): e13526-	Type: Case series n=26 Indication: cutaneous metastases Intervention: ECT Follow-up: 1–2 months	Efficacy: CR 70% PR 10% Safety: no abstracted data	Conference abstract
Heller R. (1995) Treatment of cutaneous nodules using electrochemotherapy. [Review] [32 refs]. Journal of the Florida Medical Association 82 (2): 147-150	Type: Case series n=6 Indication: cutaneous metastases Intervention: ECT Follow-up: not reported	Efficacy: All patients responded to ECT	Larger studies included in table 2
Heller R, Jaroszeski MJ, Glass LF et al. (1-3-1996) Phase I/II trial for the treatment of cutaneous and subcutaneous tumors using electrochemotherapy. Cancer 77 (5): 964-971	Type: Case series n=6 Indication: Intervention: ECT Follow-up: not reported	Efficacy: OR 2/3 patients with MM Safety: no abstracted data	Larger studies included in table 2
Kaehler KC, Egberts F, Hauschild A. (2010) Electrochemotherapy in symptomatic melanoma skin metastases: intraindividual comparison with conventional surgery. Dermatologic Surgery 36 (7): 1200-1202	No data	No data	No data

Article	Number of patients / follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Kis E, Szegesdi I, Ocsai H et al. (2010) Electrochemotherapy of melanoma cutaneous metastases. [Hungarian] OT - Melanoma-borattetek elektrokemoterapiaja. Orvosi Hetilap.151 (3) (pp 96-101), 2010.Date of Publication: 01 Jan 2010. (3): 96-101	Type: Case series n=7 Indication: MM Intervention: ECT Follow-up: median 218 days	Efficacy: CR 25% PR 43% NR 26% PD 6% Safety: no abstracted data	Conference abstract
Kubota Y, Tomita Y, Tsukigi M et al. (2005) A case of perineal malignant melanoma successfully treated with electrochemotherapy. Melanoma Research 15 (2): 133-134	Type: Case report n=1 Indication: perineal MM Intervention: ECT Follow-up: not reported	No data	No data
Kyrgias G, Mosa E, Filopoulos E et al. (2010) Electrochemotherapy (ECT) as a new anticancer therapeutic modality: The Hellenic Group of ECT (HeGECT) experience. Melanoma Research.Conference: 6th Congress of the European Association of Dermatologic Oncology Athens Greece.Conference Start: 20100616 Conference End: 20100619.Conference Publication: (var.pagings).20 (pp e42-e43), 2010.Date of Publication: June 20 (var.pagings): e42-e43	Type: Case report n=44 Indication: cutaneous metastases Intervention: ECT Follow-up: not reported	No data	Conference abstract
Larkin JO, Collins CG, Aarons S et al. (2007) Electrochemotherapy: Aspects of preclinical development and early clinical experience. Annals of Surgery.245 (3) (pp 469-479), 2007.Date of Publication: March 2007. (3): 469-479	Type: Case series n=111 Indication: cutaneous metastases Intervention: ECT Follow-up: not reported	Efficacy: CR 60% PR 22% NR 18% Safety: no abstracted data	Tumours of any histologic type

Article	Number of patients / follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Matthiessen LW, Chalmers RL, Sainsbury DC et al. (2011) Management of cutaneous metastases using electrochemotherapy. Acta Oncologica 50 (5): 621-629	Type: Case series n=52 Indication: cutaneous metastases Intervention: ECT Follow-up: not reported	Efficacy: CR 68% PR 18% Safety: no abstracted data	Data for patients with MM are aggregated with other histologies
Miklavcic D, Snoj M, Zupanic A et al. (2010) Towards treatment planning and treatment of deep-seated solid tumors by electrochemotherapy. Biomedical Engineering Online 9 10-	Type: Case report n=1 Indication: MM Intervention: ECT Follow-up: 2 months	Efficacy: A partial response was obtained in the deep seated tumour Safety: no abstracted data	n=1
Mir LM, Gehl J, Sersa G et al. (2006) Standard operating procedures of the electrochemotherapy: Instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the CliniporatorTM by means of invasive or non-invasive electrodes. European Journal of Cancer, Supplement.4 (11) (pp 14-25), 2006.Date of Publication: November 2006. (11): 14-25	None	Not an empirical study. Provides ESOPE framework to standardise ECT.	Not an empirical study.
Muir T, Matthiessen LW, Humphreys A et al. (2010) Electrochemotherapy control of cutaneous metastatic disease. European Journal of Surgical Oncology.Conference: 15th Congress of the European Society of Surgical Oncology Bordeaux France.Conference Start: 20100915 Conference End: 20100917.Conference Publication: (var.pagings).36 (9) (pp 800-801), 2010.Date of P (var.pagings): 800-801	Type: Case series n=52 Indication: cutaneous metastases Intervention: ECT Follow-up: 60 days	Efficacy: OR 78% CR 64% PR 14% NR 12% PD 6% Not evaluable 4% Safety: no abstracted data	Conference abstract
Orr RM. (2000) Technology evaluation: electroporation therapy, Genetronics Inc. [Review] [41 refs]. Current Opinion in Molecular Therapeutics 2 (2): 205-210	Review	No data	Paper unavailable from British Library

Article	Number of patients / follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Peycheva E and Daskalov I. (1999) Electrochemotherapy of skin tumours. Journal of B.U.ON.4 (2) (pp 185-188), 1999.Date of Publication: 1999. (2): 185-188	Type: Case series n=24 Indication: cutaneous metastases Intervention: ECT Follow-up: not reported	Efficacy: CR 3/4 patients Safety: no abstracted data	4 patients had MM
Plesnicar A, Sersa G, Vodovnik l. et al. (1994) Electric treatment of human melanoma skin lesions with low level direct electric current: An assessment of clinical experience following a preliminary study in five patients. European Journal of Surgery, Acta Chirurgica, Supplement (574): 45-49	Type: Case series n=5 Indication: MM Intervention: ECT Follow-up: not reported	Efficacy: 4/5 patients had partial response. Safety: no abstracted data	Larger studies included in table 2
Quaglino P, Mortera C, Marenco F et al. (2009) Electrochemotherapy with intravenous bleomycin in the treatment of cutaneous and subcutaneous metastases: Results of a prospective single centre trial. European Journal of Cancer, Supplement.Conference: Joint ECCO 15 - 34th ESMO Multidisciplinary Congress Berlin Germany.Conference Start: 20090920 Conference End: 20090924.Conference Publication: (var.pagings).7 (2-3) (pp 586), 2009.Date of Publication (var.pagings): 586-	Type: Case series n=36 Indication: cutaneous metastases Intervention: ECT Follow-up: median 24 months	Efficacy: OR 88% CR 40% Safety: after 24 months follow-up there were no relapses in tumours with CR	Conference abstract
Quan K. (1994) Analysis of the clinical effectiveness of 144 cases of soft tissue and superficial malignant tumours treated with electrochemical therapy. European Journal of Surgery, Acta Chirurgica, Supplement (574): 37-40	Type: Case series n=144 Indication: cutaneous metastases Intervention: electroporation Follow-up: 4 years	Efficacy: OR CR 58% PR 29% NR 10% PD 5% Safety: 4 year survival rate 73%	Intervention isn't within scope: standard chemotherapy with electroporation

Article	Number of patients / follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Rodriguez-Cuevas S, Barroso-Bravo S, Almanza-Estrada J et al. (2001) Electrochemotherapy in primary and metastatic skin tumors: phase II trial using intralesional bleomycin. Archives of Medical Research 32 (4): 273-276	Type: Case series n=15 Indication: cutaneous metastases Intervention: ECT Follow-up: 8.6 months	Efficacy: OR 98% CR 49% PR 49% NR 2% Safety: no abstracted data	Larger studies included in table 2
Rols M-P, Bachaud J-M, Giraud P et al. (2000) Electrochemotherapy of cutaneous metastases in malignant melanoma. Melanoma Research.10 (5) (pp 468-474), 2000.Date of Publication: 2000. (5): 468-474	Type: Case series n=4 Indication: MM Intervention: ECT Follow-up: not reported	Efficacy: OR 90% CR 9% Safety: no abstracted data	Larger studies included in table 2
Rudolf Z, Stabuc B, Cemazar M et al. (1995) Electrochemotherapy with bleomycin. The first clinical experience in malignant melanoma patients. Radiology and Oncology.29 (3) (pp 229-235), 1995.Date of Publication: 1995. (3): 229-235	Type: Case series n=2 Indication: MM Intervention: ECT Follow-up: not reported	Efficacy: OR 92% CR 92% Safety: no abstracted data	Larger studies included in table 2
Ruggeri R, Bono A, Crippa F et al. (2010) Electrochemotherapy with intravenous bleomycin in the local treatment of cutaneous and subcutaneous melanoma metastases. Pigment Cell and Melanoma Research.Conference: Melanoma 2010 Congress Sydney, NSW Australia.Conference Start: 20101104 Conference End: 20101107.Conference Publication: (var.pagings).23 (6) (pp 908), 2010.Date of Publication: December 2010. (var.pagings): 908-	Type: Case series n=51 Indication: MM Intervention: ECT Follow-up: 2 years	Efficacy: CR 45% Safety: local control 83% at 2 years follow-up	Conference abstract

Article	Number of patients / follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Sainsbury D, Stevens D, Humphreys A et al. (2009) Electrochemotherapy treatment of metastatic cutaneous cancer. European Journal of Cancer, Supplement.Conference: Joint ECCO 15 - 34th ESMO Multidisciplinary Congress Berlin Germany.Conference Start: 20090920 Conference End: 20090924.Conference Publication: (var.pagings).7 (2-3) (pp 589), 2009.Date of Publicatio (var.pagings): 589-	Type: Case series n=18 Indication: cutaneous metastases Intervention: ECT Follow-up: not reported	Efficacy: no abstracted data Safety: No systemic complications occurred. Three patients presented with localised skin infection following treatment, a skin rash and severe pain after a second scalp treatment in 1 patient each.	Conference abstract
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	Type: Case series n=4 Indication: cutaneous metastases Intervention: ECT Follow-up: 7 months	Efficacy: CR 63% Safety: high toleration with minimal scarring and depigmentation of skin	Larger studies included in table 2
Sersa G, Stabuc B, Cemazar M et al. (2000) Electrochemotherapy with cisplatin: the systemic antitumour effectiveness of cisplatin can be potentiated locally by the application of electric pulses in the treatment of malignant melanoma skin metastases. Melanoma Research 10 (4): 381-385	Type: Case series n=9 Indication: MM Intervention: ECT Follow-up: 21 weeks	Efficacy: OR 48% CR Safety: median time to progression was 21 weeks in ECT treated tumours.	Larger studies included in table 2
Sersa G, Stabuc B, Cemazar M et al. (2000) Electrochemotherapy with cisplatin: clinical experience in malignant melanoma patients. Clinical Cancer Research 6 (3): 863-867	Type: Case series n=10 Indication: MM Intervention: ECT Follow-up: 124 weeks	Efficacy: OR 87% CR 80% Safety: 77% local control rate at 124 weeks follow-up	Only a minority of patients received ECT

Article	Number of patients / follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Sersa G, Snoj M, Cemazar M. (2011) Electrochemotherapy as an approach to enhance the efficacy of chemotherapeutics. In Vivo.Conference: 4th International Congress of Molecular Medicine Istanbul Turkey.Conference Start: 20110627 Conference End: 20110630.Conference Publication: (var.pagings).25 (3) (pp 502), 2011.Date of Publication: May-June 2011. (var.pagings): 502-June	Review	No data	Conference abstract
Sersa G, Cemazar M, Snoj M. (2011) Electrochemotherapy of solid tumors--preclinical and clinical experience. Conference Proceedings: Annual International-31	Review	No data	Conference abstract
Snoj M, Rudolf Z, Cemazar M et al. (2005) Successful sphincter-saving treatment of anorectal malignant melanoma with electrochemotherapy, local excision and adjuvant brachytherapy. Anti-Cancer Drugs 16 (3): 345-348	Type: Case report n=1 Indication: anorectal MM Intervention: ECT Follow-up: 14 months	Efficacy: patient is recurrence free at 14 months and continent. Safety: no abstracted data	n=1
Snoj M, Rudolf Z, Paulin-Kosir SM et al. (2006) Long lasting complete response in melanoma treated by electrochemotherapy. European Journal of Cancer, Supplement.4 (11) (pp 26-28), 2006.Date of Publication: November 2006. (11): 26-28	Type: Case series n=1 Indication: MM Intervention: ECT Follow-up: 8 years	Efficacy: CR = 1 patient Safety: no abstracted data	n=1
Snoj M, Cemazar M, Slekovec KB et al. (2007) Effective treatment of multiple unresectable skin melanoma metastases by electrochemotherapy. Croatian Medical Journal 48 (3): 391-395	Type: Case series n=1 Indication: MM Intervention: ECT Follow-up: not reported	Efficacy: good local control achieved Safety: no abstracted data	n=1

Article	Number of patients / follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Snoj M, Cemazar M, Srnovrsnik T et al. (2009) Limb sparing treatment of bleeding melanoma recurrence by electrochemotherapy. [Review] [30 refs]. Tumori 95 (3): 398-402	Type: Case series n=1 Indication: MM with bleeding tumours Intervention: ECT Follow-up: not reported	Efficacy: bleeding stopped immediately on ECT application Safety: no abstracted data	n=1
Testori A. (2010) Electrochemotherapy with bleomycin: A local treatment with possible systemic implication. Pigment Cell and Melanoma Research.Conference: Melanoma 2010 Congress Sydney, NSW Australia.Conference Start: 20101104 Conference End: 20101107.Conference Publication: (var.pagings).23 (6) (pp 882), 2010.Date of Publication: December 2010. (var.pagings): 882-	Type: Case series n=105 Indication: cutaneous metastases Intervention: ECT Follow-up: not reported	Efficacy: OR 90% CR 72% Safety: no abstracted data	Conference abstract
Testori A, Verrecchia F, Ferrucci P. (2011) Electrochemotherapy with bleomycin: A local treatment with possible systemic implication. Annals of Surgical Oncology.Conference: 64th Annual Cancer Symposium of the Society of Surgical Oncology San Antonio, TX United States.Conference Start: 20110302 Conference End: 20110305.Conference Publication: (var.pagings).18 (pp S42), 2011.Date of (var.pagings): S42-	Duplicates above publication	Duplicates above publication	Duplicates above publication
Xin Y-L. (1994) Advances in the treatment of malignant tumours by electrochemical therapy (ECT). European Journal of Surgery, Acta Chirurgica, Supplement (574): 31-35	Type: Case series n=4,081 Indication: malignant tumours Intervention: electroporation Follow-up: 5 years	5-year survival rate 47%	Intervention is electroporation alone

Appendix B: Related NICE guidance for electrochemotherapy

Guidance	Recommendations
Cancer service guidance	**Improving outcomes for people with skin tumours including melanoma. Cancer service guidance CSGSTIM (2006). Available from www.nice.org.uk/guidance/CSGSTIM** • 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 infrastructure for well-conducted research to take place in order to contribute to the skin cancer evidence base in epidemiology, treatment and management.
Public health guidance	**Skin cancer: prevention using public information, sun protection resources and changes to the environment. Public health guidance 32 (2011). Available from www.nice.org.uk/guidance/PH32** The recommendations focus on preventing the first occurrence (primary prevention) of skin cancer attributable to overexposure to natural and artificial ultraviolet (UV). There are no relevant recommendations for electrochemotherapy in this published guidance.

Appendix C: Literature search for electrochemotherapy for the treatment of malignant melanoma

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	3/4/2012	March 2012	5
Database of Abstracts of Reviews of Effects – DARE (CRD website)	3/4/2012	March 2012	1
HTA database (CRD website)	3/4/2012	March 2012	1
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	3/4/2012	March 2012	9
MEDLINE (Ovid)	3/4/2012	1946 to March Week 3 2012	339
MEDLINE In-Process (Ovid)	3/4/2012	April 02, 2012	21
EMBASE (Ovid)	3/4/2012	1980 to 2012 Week 13	636
CINAHL (NLH Search 2.0 or EBSCOhost)	3/4/2012	N/A	26
BLIC (Dialog DataStar)	3/4/2012	N/A	0

Trial sources searched on 02.04.2012

- Current Controlled Trials metaRegister of Controlled Trials – mRCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched on 02.04.2012

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

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

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
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