National Institute for Health and Clinical Excellence

IP984 Electrochemotherapy for metastases in the skin (of non-skin origin and melanoma).

Consultation Comments table

IPAC date: 13 December 2012

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Registrar, Royal College of Physicians	**1**	The NCRI/RCP/RCR/ACP/JCCO are grateful for the opportunity to respond to the above consultation. We are aware that experts have submitted comments directly regarding significant concerns on this technique being used more generally. As a result, we would recommend that is only used as part of a clinical trial.	Thank you for your comment. The Committee considered your comment and chose not to amend the guidance recommendations. The Committee has recommended normal arrangements in a context of palliative treatment because the evidence presented related to patients unsuitable for first line treatments or with progressive disease despite treatment. 1.1 has been amended to state that 'There is sufficient evidence of efficacy of electrochemotherapy for treating metastases in the skin from tumours of non-skin origin and melanoma to support its use **as a palliative treatment.** There are no major safety concerns. Therefore, **in the**

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				context of palliative treatment the procedure can be used with normal arrangements for clinical governance, consent and audit'. Section 1.4 encourages further data collection.
2	Consultee 2 NHS Professional	**1.2**	Agree with this statement. However, the title is "non skin origin" and therefore these patients may well be discussed in their relevant MDT.	Thank you for your comment. The Committee considered your comment and amended section 1.2 to state that "Patient selection should be carried out by **an appropriate** specialist multidisciplinary team".
3	Consultee 3 NHS Professional	**1**	I entirely agree with these recommendations.	Thank you for your comment.
4	Consultee 4 NHS Professional	**1**	"As part of the local data collection, other options considered as treatment should also be included, as well as follow up consultations after ECT. Part of the assessment of efficacy should not only be whether ECT works,but also whether it is cost effective. It may prove to be as	Thank you for your comments. The Committee considered your comment but chose not to add these points as it felt it is adequate. The focus of IPAC is on efficacy and safety.

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			effective as surgery but cheaper. I would also recommend that once a service is established, pathways to access ECT should be developed within the regional cancer network for each relevant cancer team e.g. H&N, breast, sarcoma, lower GI/anal, gynae. These teams will not automatically be aware of ECT as an option for them as it will correctly be seated within the skin service"	The remit of the IP programme does not include cost effectiveness or pathway development.
5	Consultee 5 NCRN melanoma Clinical Studies Group committee member & surgeon	**1.4**	"What is the InspECT registry? Is it a database owned or under the control of a commercial organisation? Centralised data collection is very desirable but it should not be a mandatory pre-requisite to using the technology"	Thank you for your comments. InspECT registry is an international database. The company IGEA has contractually agreed to do the technical support of the database, without any rights to use the data. The database is governed by the INSPECT network, which has a board for which members are elected by the network members (ie representatives of clinical centers). Agreements are in place so that data belongs to the participating centres and the database and network are controlled by clinicians. Contribution to the registry is recommended

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				but is not mandatory. The Committee amended 1.4 to state that 'Clinicians should submit data on all patients undergoing electrochemotherapy (including details of case selection, methods of follow-up and outcomes) to the InspECT registry, an international register dedicated to electrochemotherapy, and review clinical outcomes locally'.
6	Consultee 6 Chairman of the Inspect network	**1.4**	From the Inspect board and network, we are in agreement with this, and would welcome further UK centers joining the network and database.	Thank you for your comment.
7	Consultee 6 Chairman of the Inspect network	**2.1**	We agree entirely. Patient preference may be added, as a feeling of stigmatisation due to cutaneous metastases may lead to a wish for treatment.	Thank you for your comment.
8	Consultee 2 NHS Professional	**2.1**	Once again, title is "of non skin origin" otherwise agree	Thank you for your comment –please see response to comment 9 for amended version of 2.1.
9	Consultee 3 NHS Professional	**2.1.1**	Alternatives also include regional chemotherapy using isolated limb infusion or perfusion, and carbon dioxide laser. These are more relevant options than curettage, cryotherapy, and radiotherapy, which are	Thank you for your comment. The Committee discussed this comment and decided to amend section 2.1 in order to capture the concepts of limb infusion/perfusion.

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			unsuitable for anything other than very limited low-volume disease. ILI and ILP still have a role for diffuse disease in a limb, especially with lumps>2-3 cm diameter. Such disease is not really amenable to ECT due to the size, and limited amount that can be treated in the 30 minutes available for each iv ECT episode.	'Cutaneous and subcutaneous metastases from non-skin origin and 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 **regional** chemotherapy, curettage, cryotherapy and radiotherapy'.
10	Consultee 7 Chair of Skin Cancer MDT Norfolk and Norwich University Hospiital	**2.1.1**	Also need to add isolated limb infusion, laser ablation and fulguration/cautery as treatments.	Thank you for your comment. The Committee considered your comment and chose not to add the listed treatments to 2.1.1 as this section is a short and simple summary and includes examples of alternative treatments; it is not intended to include all relevant possibilities. See response for comment 9 for amended version of 2.1.1.
11	Consultee 4 NHS Professional	**2.1**	I would add the primary aim of treatment is best palliation with minimum morbidity.	Thank you for your comment. The Committee considered your comment and chose not to amend this sentence in 2.1.1.
12	Consultee 6 Chairman of the Inspect	**2.2**	"We agree. The ESOPE guidelines are well quoted and have proven useful in daily clinical practice.	Thank you for your comments.

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	network		For the overview four recent phase II studies (July 2012) are relevant: (1) Matthiessen LW, Johannesen HH, Hendel HW, Moss T, Kamby C, Gehl J. Electrochemotherapy for large cutaneous recurrence of breast cancer: a phase II clinical trial. Acta Oncol 2012;51:713-21. (2) Campana LG, Valpione S, Falci C, Mocellin S, Basso M, Corti L, et al. The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: a phase-II study. Breast Cancer Research and Treatment 2012;134:1169-78. (3) Campana LG, Valpione S, Mocellin S, Sundararajan R, Granziera E, Sartore L, et al. Electrochemotherapy for disseminated superficial metastases from malignant melanoma. British Journal of Surgery 2012;99:821-30. (4) Curatolo P, Quaglino P, Marenco F, Mancini M, Nardo T, Mortera C, et al. Electrochemotherapy in the Treatment of Kaposi Sarcoma Cutaneous Lesions: A Two-Center Prospective Phase II Trial. Annals of	These studies were identified in our recent update search. The Committee considered adding the first 2 studies to table 2 in 984 overview and the third study to table 2 in 1041 overview. The fourth study (Curtalo 2012) cannot be included in this guidance as Kaposi' sarcoma was considered to be primarily a skin cancer.

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			Surgical Oncology 2012;19:192-8."	
13	Consultee 2 NHS Professional	**2.2**	Agree	Thank you for your comment.
14	Consultee 3 NHS Professional	**2.2**	Agree with this description	Thank you for your comment.
15	Consultee 4 NHS Professional	**2.2.3**	"The ESOPE guidelines have been produced by IGEA the company that makes the cliniporator. I think this should be acknowledged. Firstly the guidlines are specific for their machine. Secondly the acronym ESOPE gives the impression that it is a multidisciplinary, pan european consensus which is not the case. Finally from a copyright perspective one needs to be able to identify the origin of the information. e.g. one can't attribute the results of a specific drug trial to the generic compound, the company drug name is quoted. This point of identification should also apply to the InspECT registry."	Thank you for your comments. The Committee considered your comment and agreed to remove 2.2.3 from the guidance but leave it in the Overview in order to provide an explanation of the abbreviation used in Table 2. Please refer to response to comment number 5.
16	Consultee 6 Chairman of the Inspect network	**2.3**	"Four phase II studies were published at the time of conclusion of this survey (July 2012). These support the conclusions and could be	Thank you for your comment. These studies were identified in our recent

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			included in the overview (1) Matthiessen LW, Johannesen HH, Hendel HW, Moss T, Kamby C, Gehl J. Electrochemotherapy for large cutaneous recurrence of breast cancer: a phase II clinical trial. Acta Oncol 2012;51:713-21. 2) Campana LG, Valpione S, Falci C, Mocellin S, Basso M, Corti L, et al. The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: a phase-II study. Breast Cancer Research and Treatment 2012;134:1169-78. (3) Campana LG, Valpione S, Mocellin S, Sundararajan R, Granziera E, Sartore L, et al. Electrochemotherapy for disseminated superficial metastases from malignant melanoma. British Journal of Surgery 2012;99:821-30. (4) Curatolo P, Quaglino P, Marenco F, Mancini M, Nardo T, Mortera C, et al. Electrochemotherapy in the Treatment of Kaposi Sarcoma Cutaneous Lesions: A Two-Center Prospective Phase II Trial. Annals of Surgical Oncology 2012;19:192-8."	update search. The Committee considered adding the first 2 studies to table 2 in 984 overview and the third study to table 2 in 1041 overview. The fourth study (Curtalo 2012) cannot be included in this guidance as Kaposi' sarcoma was considered to be primarily a skin cancer.

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17	Consultee 2 NHS Professional	**2.3**	Agree	Thank you for your comment.
18	Consultee 3 NHS Professional	**2.3**	The data on efficacy seems reasonable, though is confounded by the routine surgical debulking of larger lesions. I am less sure of the durability of response. I am also uncertain about case-mix; There is a big difference in responsiveness for any modality between patients with <1 cm metastases, and those with >2-3 cm lesions; ILI and ILP seem most suitable for the latter group. There is no data comparing ILI or ILP with ECT in patients with extensive symptomatic locoregional metastases; such data would be useful due to the difference in morbidity and cost	Thank you for your comments. The Committee has recommended normal arrangements in a context of palliative treatment because the evidence presented related to patients unsuitable for first line treatments or with progressive disease despite treatment. The Committee amended 1.1 to state that 'There is sufficient evidence of efficacy of electrochemotherapy for treating metastases in the skin from tumours of non-skin origin and melanoma to support its use as a palliative treatment. There are no major safety concerns. Therefore, in the context of palliative treatment the procedure can be used with normal arrangements for clinical governance, consent and audit'. Section 2.3.3 presents evidence on the relationship between size of tumour and response.

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				Comparative effectiveness and comparative cost-effectiveness of treatment are both outside the remit of the IP Programme.
19	Consultee 4 NHS Professional	**2.3**	Another efficacy outcome could be days in hospital, as the more invasive treatment alternatives frequently require regular or prolonged periods in hospital.	Thank you for your comment. This outcome was not reported in any of the papers.
20	Consultee 6 Chairman of the Inspect network	**2.4**	As the treatment practice has evolved, also patients with larger tumors have been treated, and in a subset of patients post-treatment pain may be present. The Inspect group has recently performed a data analysis (manuscript in preparation) where analysis of 116 patients revealed that the vast majority of patients had low pain scores (0-2 out of maximum 10) after treatment, whereas a subset of patients identifiable by large tumors, pre-treatment pain, and previous irradiation to treatment site would have higher pain scores after treatment. These particular patients at risk for pain may be identified before treatment, and a plan for analgesic treatment may be offered.	Thank you for your comment. Post treatment pain reported in papers is presented in table 2 of the overviews. In section 2.5.2 the Committee has commented on the pain and ulceration that some patients experience following the procedure.

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21	Consultee 2 NHS Professional	**2.4**	Pain is a major factor and patients must be aware of this. Patients who have ECT to are previously treated with radiotherapy seem to suffer the most.	Thank you for your comment. 2.5.2 states that patients may experience pain and ulceration following treatment.
22	Consultee 3 NHS Professional	**2.4**	Agree with this	Thank you for your comment.
23	Consultee 6 Chairman of the Inspect network	**2.5.2**	As mentioned the patients present with quite varied clinical pictures, and some patients with large tumors in previously irradiated areas will be at risk of pain, and ulceration may take time to heal. This is manageable with analgesic plan and nursing follow-up. For an example of this patient category please see (1) Matthiessen LW, Johannesen HH, Hendel HW, Moss T, Kamby C, Gehl J. Electrochemotherapy for large cutaneous recurrence of breast cancer: a phase II clinical trial. Acta Oncol 2012;51:713-21.	Thank you for your comment. Post treatment pain reported in papers is presented in table 2 of the overviews and a Committee comment in section 2.5.2. This paper is included in table 2 of the 984 overview.
24	Consultee 2 NHS Professional	**2.5**	Agree	Thank you for your comment.
25	Consultee 3 NHS Professional	**2.5.1**	I agree that the data is good enough to support the use of ECT for palliation by experienced skin cancer Specialist MDT's routinely dealing with stage 3 and 4	Thank you for your comment.

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			melanoma and other rare metastasising skin cancers such as Merkel cell carcinoma.	
26	Consultee 7 Chair of Skin Cancer MDT Norfolk and Norwich University Hospital	**2.5.1**	Treatment of cutaneous melanoma metastases can be a challenging problem. ECT could be useful in treating cutaneous metastases from melanoma as a palliative treatment. We have treated two patients at Norwich- one had multiple cutaneous melanoma metastases on a lower limb, the other had a large primary melanoma on the sole of the foot. Both had good responses to ECT.	Thank you for your comment.
27	Consultee 4 NHS Professional	**2.5.1**	This appears to suggest that ECT is used as a second or third line for palliation. It may well be appropriate for first treatment as assessed on a patient by patient basis. Palliation is palliation by the best method available. This is why the assessment of treatment option should be made by the Specialist Skin MDT, where collectively clinicians are skilled in providing all treatment options and hence able to suggest the most appropriate one	Thank you for your comments. 2.5.1 states that the Committee noted that this procedure might provide palliation and improved of quality of life for patients with disease unsuitable for, or resistant to, other treatments. This was based on the evidence which related to patients unsuitable for first line treatments or with progressive disease despite treatment. The Committee amended 1.1 to state that 'There is sufficient evidence of efficacy of electrochemotherapy for treating

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				metastases in the skin from tumours of non-skin origin and melanoma to support its use as a palliative treatment. There are no major safety concerns. Therefore, in the context of palliative treatment the procedure can be used with normal arrangements for clinical governance, consent and audit'. About patient selection by specialist MDT, "the Committee considered your comment and amended section 1.2 to state that "Patient selection should be carried out by **an appropriate** specialist multidisciplinary team".
28	Consultee 6 Chairman of the Inspect network	**General**	The database of the Inspect network (International Network for Sharing Practices on Electrochemotherapy) is supported by the company IGEA (Italy), but contracts are in place securing that data belong to the uploading centers, and the database and network are controlled by clinicians.	Thank you for your comment.
29	Consultee 3 NHS Professional	**General**	We have just started providing ECT for palliation of cutaneous metastases	Thank you for your comment.
30	Consultee 8 Clinician	**General**	I am fully in support of the proposed guideline. I would also add that the efficacy of electrochemotherapy has been shown to be	Thank you for your comments.

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			affected, amongst other things, by variation in extracellular drug concentration at the time of electroporation; pulse delivery and the distribution of electric field inside the tumour. Results of trials are only reproducible when confounding factors are controlled. In addition, it appears that study results are particularly favourable when the standard operating procedures (SOP) for ECT are followed (Mali et al, 2012). I would therefore recommend that the guidance makes this clear and that you specify which electrochemotherapy system was used in each pivotal study, since delivery systems have technical differences which can introduce variables that impact on clinical results and patient safety.	The device and use of ESOPE guidelines are indicated in each study in table 2 of each overview. The NICE IP Programme assesses efficacy and safety of new procedures, effectiveness is outside the remit. Mali et al is a systematic review which has not yet been published and therefore cannot be added to the evidence base for this Guidance.
31	Consultee 9 Clinician	**Description**	As to the interventional procedure "Electrochemotherapy for the treatment of malignant melanoma", the following sentence in the description: "Short and intense electric pulses are applied to tumour cells to open up the pores with the aim..." could be misleading. I recommend to write,	Thank you for your comment about the text presented on the NICE web page for the procedure. It does not appear in the Guidance itself. The IP team will use the lay description from the IPCD to update the web page.

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			instead: "Short and intense electric pulses are applied to tumour cells to open up pores in the cell membranes with the aim...	