National Institute for Health and Care Excellence

IPG 447 (IP1017) Electrochemotherapy for primary basal cell carcinoma and primary squamous cell carcinoma

Consultation Comments table

IPAC date: 14th November 2013

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Chair, Therapy and Guidelines Sub-Committee British Association of Dermatologists	**1**	The British Association of Dermatologists would like to thank NICE for the opportunity to comment on this revised guidance, but retains its previous position on this interventional procedure, where it does not support the use of electrochemotherapy for the treatment of primary basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). There is neither data on the proof of principle nor medium-term response and efficacy to support its use within the scope of this consultation. We question the need for unproven technology as a putative curative treatment option for both these conditions when standard treatments are well accepted and widely practised. The non-randomised and non-comparative data presented do not give confidence that the use of electrochemotherapy for the treatment of primary BCC and SCC is equivalent in efficacy to conventional surgery, Mohs surgery (which isn't mentioned in section 2.2), or radiotherapy. The data strongly suggests that efficacy is at least 10% worse at around 12 months. The amount of data for SCC is inadequate in terms of numbers, and that this particular skin cancer should probably not be treated with electrochemotherapy at all. Only until data from properly-conducted randomised trials are available can patients be given accurate information about the outcomes for this procedure. If it is to be used for inoperable or incurable disease, comparative data with other palliative treatments such as radiotherapy, vismodegib (BCC) and cetuximab (SCC) would be needed. Other than in the setting of a properly conducted clinical trial, or perhaps in exceptional cases where surgery and radiotherapy are contraindicated, the BAD has grave concerns with a NICE-badged approval of this technology.	Thank you for your comment. The Committee considered your comments carefully. They were informed that this technique may be useful in patients with inaccessible or otherwise difficult to treat cancers and therefore chose to recommend special arrangements with data collection by an established register rather than 'research only'. Sections 1.1, 1.3 and 6.1 are designed to address concerns about the technique being used more generally. The following text has been added to 1.1 to further clarify: "because the cure rates for established treatments in accessible sites are very high".

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2	Consultee 2 NIHR Melanoma representative Chair TVCn skin cancer NHS professional	**1 & 2**	Surgical excision is straightforward, cheap, convenient and has published success rates of 95%. There is not an area of cancer where survival or outcomes are questionable. This technique should not be permitted without a randomised controlled trial comparing it to established therapies including side effects, patient experience and costs has been carried out. It willbe heavily promoted bu industry if permitted without this evidence	Thank you for your comment. The focus of IPAC is on efficacy and safety of a procedure and comparing technologies and/or cost effectiveness is not within the remit of the IP programme. The Committee were informed that this technique may be useful specifically in patients with inaccessible or otherwise difficult to treat cancers and therefore chose to recommend special arrangements with data collection by an established register rather than 'research only'. Sections 1.1, 1.3 and 6.1 are designed to address concerns about the technique being used more generally. The following text has been added to 1.1 to further clarify: "because the cure rates for established treatments in accessible sites are very high".

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3	Consultee 2 NIHR Melanoma representative Chair TVCn skin cancer NHS professional	**4**	These figures are completely unacceptable. BCC are 97 % excised with a 4 mm margin. Recent paper in JApras of SCC including all comers shows 92% excision rate. NICE cannot contemplate allowing a treatment that does not match up	Thank you for your comment. The Committee were informed that this technique may be useful specifically in patients with inaccessible or otherwise difficult to treat cancers and therefore chose to recommend special arrangements with data collection by an established register. Sections 1.1, 1.3 and 6.1 are designed to address concerns about the technique being used more generally. The following text has been added to 1.1 to further clarify: “because the cure rates for established treatments in accessible sites are very high”. **Text in the final sentence of section 4.1 has been amended to present only the response rate at 12 months; “**The complete response rate was 83% at 12 months.

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4	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**4.1-4.3**	These figures are dramatically inferior to conventional surgery or radiotherapy which would expect recurrence rates of <5% at 5 years, let alone 12 months and 6 months respectively. How can 100% response be claimed if 14% recur at 2 months? This is unacceptable if the treatment really is with 'curative intent' (section 1)	Thank you for your comment. The Committee were informed that this technique may be useful specifically in patients with inaccessible or otherwise difficult to treat cancers and therefore chose to recommend special arrangements with data collection by an established register. Sections 1.1, 1.3 and 6.1 are designed to address concerns about the technique being used more generally. The following text has been added to 1.1 to further clarify: "because the cure rates for established treatments in accessible sites are very high". **Text in the final sentence of section 4.1 has been amended to present only the response rate at 12 months; "**The complete response rate was 83% at 12 months.
5	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**6.1**	This is a key issue. Our experts consider that there is insufficient evidence for NICE to recommend the use of ECT with curative intent outside the context of well designed, randomised trials. Until such data are available, we believe that NICE should recommend that it is reserved for treatment of patients in whom conventional therapy is not appropriate ie with palliative rather than curative intent	Thank you for your comment. The Committee were informed that this technique may be useful specifically in patients with inaccessible or otherwise difficult to treat cancers and therefore chose to recommend special arrangements with data collection by an established register. Sections 1.1, 1.3 and 6.1 are designed to address concerns about the technique being used more generally. The following text has been added to 1.1 to further clarify: "because the cure rates for established treatments in accessible sites are very high".

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6	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**1.3**	Given the lack of data, outside the context of a clinical trial, the recommendation should be that ECT is offered by SSMDTs only when other surgical or radiation treatments are considered to be inappropriate by either clinician or patient	Thank you for your comment. The Committee were informed that this technique may be useful specifically in patients with inaccessible or otherwise difficult to treat cancers and therefore chose to recommend special arrangements with data collection by an established register. Sections 1.1, 1.3 and 6.1 are designed to address concerns about the technique being used more generally. The following text has been added to 1.1 to further clarify: “because the cure rates for established treatments in accessible sites are very high”.
7	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**1.4**	This would benefit from further information and detail being included: What training is agreed to be required? Who should provide this? How many cases are deemed to be required for the training phase of ECT delivery?	Thank you for your comment. Recommendations about the number of cases required to achieve competency in a procedure are beyond the remit of the IP Programme.

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8	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**1.5**	This is a pharma-sponsored database which raises considerable concerns regarding probity. We believe there should be an independent UK database. Alternatively, is there is a precedent for NICE recommending pharma-sponsored databases upon which to model this approach. If so, does the inSPECT database fulfil any pre-specified requirements? Whilst the contract states that the data is owned by the contributing centre, what happens if the company (with the license for the distribution of the equipment), goes into liquidation (not an uncommon occurrence for medical device companies)? A better way might be to maintain a local audit and report annually to the SMDT and/or local chemotherapy committee.	Thank you for your comment. 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). Contracts are in place so that data belongs to the participating centres and the database and network are controlled by clinicians. During the development of guidance the following responses were received from organisations who had been asked to consider giving their support for the register. BAD; technology not mainstream or available to most clinicians therefore not appropriate to support the Inspect database. RCR “is willing to support the use of the INSPECT register as the main data collection tool for this new technology”. IPAC thought that the objections raised by the consultee are not sustainable.

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9	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**2**	There are important omissions here. This must include mention of palliative treatment and mention of when not to recommend ECT - adverse pathological features such as perineural spread, Lymphovascular invasion etc	Thank you for your comment. Section 2 is intended to be a short simple summary of the indication and current treatments. It includes examples of alternative treatments; it is not intended to include all relevant possibilities. Section 1.3 states that patient selection should be done by MDTs. The Committee were informed that this technique may be useful specifically in patients with inaccessible or otherwise difficult to treat cancers and therefore chose to recommend special arrangements with data collection by an established register. Sections 1.1, 1.3 and 6.1 are designed to address concerns about the technique being used more generally. The following text has been added to 1.1 to further clarify: “because the cure rates for established treatments in accessible sites are very high”.
10	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**2.2**	There is no mention of targeted therapy here, particularly vismodegib, which is likely to supersede ECT for palliation of inoperable tumours. Current treatments should include topical treatments such as imiquimod cream, efudix ointment(for superficial BCC)	Thank you for your comment. **See response to comment 9**

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11	Consultee 2 NIHR Melanoma representative Chair TVCn skin cancer NHS professional	**3**	re SCc there is no pathology indicating tumour depth, differentiation which are key prognostic indicators. This determicnes follow up regime (see national guidance and recent AJCC advice). there is no confirmation of complete excision. The patient will need a biopsy first as opposed to a clinical disgnosis (with dermoscopy is highly accurate) and a one off excision (BCC 95% successful.	Thank you for your comment. Section 3 is intended to be a short simple summary of the procedure.
12	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**4.1**	The reference to '100% initially' should be removed - % at 12 months is the relevant figure. It should be emphasised that this is significantly inferior to conventional treatments.	Thank you for your comment. Comparative effectiveness is outside the remit of the IP Programme. **IPAC amended 4.3 as follows** *A non-randomised comparative study of 113 patients (85 basal cell carcinoma [BCC] and 28 squamous cell carcinoma [SCC]) compared 2 different electric pulse sequences for electrochemotherapy of stage I (T1N0M0) BCC and SCC tumours. The complete response rate was 83% at 12 months.*

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13	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**4.2**	94% at 12 weeks is inferior to conventional treatment and the study did not provide longer term follow up data which is a more appropriate comparator for treatment of BCC and SCC.	Thank you for your comment. The Committee were informed that this technique may be useful specifically in patients with inaccessible or otherwise difficult to treat cancers and therefore chose to recommend special arrangements with data collection by an established register. Sections 1.1, 1.3 and 6.1 are designed to address concerns about the technique being used more generally. The following text has been added to 1.1 to further clarify: "because the cure rates for established treatments in accessible sites are very high". **Text in the final sentence of section 4.1 has been amended to present only the response rate at 12 months; "**The complete response rate was 83% at 12 months.
14	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**4.3**	The reference to 100% initial response should be removed. This is meaningless in the context of treatment for BCC and SCC, especially when it is not adequately defined and there was 14% recurrence within 6 months. Unless, of course, these were all tumours not amenable to treatment by conventional therapy and the therapeutic intent was palliative rather than curative. The latter applies to 4.1. and 4.2 also - and should be made clear when reporting these studies.	Thank you for your comment. Comparative effectiveness is outside the remit of the IP Programme. **IPAC amended 4.3 as follows** *The study of 113 patients (85 BCC and 28 SCC tumours) reported that 14% (16/113) of tumours recurred between 2 and 6 months after treatment (no further details reported).*

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15	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**4.4-4.6 - (and 4.1-4.3)**	These end points are considered inappropriate and it is the view of our experts that they should not be included in a NICE document as 'evidence'. If these data are to be included as evidence, then the entire section should be preceded by a statement emphasising that there are few long term clinical data (ie beyond 12 months) on efficacy, recurrence etc and that there are no randomised data comparing to surgery, radiation or other standard therapies (in addition to the rather non-specific comments on quality and quantity of data already made in 1.1)	Thank you for your comment. Comparative effectiveness is outside the remit of the IP Programme. The Committee were informed that this technique may be useful specifically in patients with inaccessible or otherwise difficult to treat cancers and therefore chose to recommend special arrangements with data collection by an established register. It is not customary for NICE IP guidance to comment on absence of evidence in the efficacy section – Sections 1.1, 1.3 and 6.1 are designed to address concerns about the technique being used more generally. The following text has been added to 1.1 to further clarify: "because the cure rates for established treatments in accessible sites are very high". **Text in the final sentence of section 4.1 has been amended to present only the response rate at 12 months; "**The complete response rate was 83% at 12 months". Paragraph 4.4 presents data for ECT use in an inaccessible area.
16	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**4.6**	This is only relevant in context of palliation, which is not otherwise mentioned in this document.	Thank you for your comment. IPAC routinely seeks advice from Specialist advisors on both efficacy and safety of the procedure. The additional outcomes listed in 4.6 are quotes from Specialist Advisers and there are no reports of these outcomes in the literature.

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17	Consultee 2 NIHR Melanoma representative Chair TVCn skin cancer NHS professional	**5**	A not insignificant complication profile	Thank you for your comment.
18	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**5.5**	Please supply a definition of leukonecrosis?	Thank you for your comment. Definition of leukonecrosis is not available from the authors. Therefore IPAC agreed to delete section 5.5 from the guidance.
19	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**5.6**	Our experts were uncertain of the intended meaning here. They assumed epiphora and damage to the lacrimal duct system, since the lacrimal gland in not found in the medial canthus.	Thank you for your comment. Section 5.6 has been amended to make this clear: Increased tear production in the ispilateral eye was reported in 2 patients who received treatment for tumours in the medial canthus in the case series of 6 patients. This caused no visual impairment and resolved within 2 months. No further details were reported.
20	Consultee 3 representing the joint organisation view of the NCRI/RCP/RCR/ACP/JCCO.	**5.9**	The risk of pulmonary fibrosis should be clarified. This is a major side effect for treatment of tumours for which other therapies currently exist.	Thank you for your comment. Specialist Advisers considered pulmonary fibrosis to be a recognized risk with Bleomycin treatment but there were no reports of the complication in the literature. This section has been amended to clarify that pulmonary fibrosis was considered to be due to bleomycin.

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21	Consultee 2 NIHR Melanoma representative Chair TVCn skin cancer NHS professional	**6**	In 12 years of consultant practice as part of a skin and head and neck MDT, I can think of no patients in whom this treatment is indicated.	Thank you for your comment.