National Institute for Health and Clinical Excellence

IP838 – Irreversible electroporation for the treatment of liver metastases

Consultation Comments table

IPAC date: 12th July 2012

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Royal College of Physicians	**1**	The NCRI/RCP/RCR/ACP/JCCO are grateful for the opportunity to respond to this consultation. Our experts strongly support the recommendation that the procedure should only be used in research trials.	Thank you for your comment.
2	Consultee 2 NHS Professional	**1**	The technology needs a properly designed randomised trial to compare it with the current gold standard treatment for unresectable liver tumours such as radiofrequency ablation before it is recommended for clinical use. Â We have had serious concerns about this both on the safey and efficacy in either pancreatic or liver patients from our unit, and have written to our new device committee to terminate the clinical use of this until further approval from ethic committee as we have come across some serious adverse results in patients.	Thank you for your comment. Section 1 of guidance recommends that the procedure should only be used in the context of research.
3	Consultee 3 AngioDynamics manufacturer	**1.1**	*1.1 Current evidence on the safety and efficacy of irreversible electroporation for the treatment of liver metastases is limited in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report local and systemic safety outcomes and the effect of the procedure on local* ***tumour***	Thank you for your comment. Section 1.1 of the guidance has been changed.

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			control and survival. Suggest to rephrase to "… tumour control and patient survival."	
4	Consultee 3 AngioDynamics manufacturer	**2.1.1**	*2.1.1 Liver metastases are most commonly caused by colorectal cancer but may also result from other malignancies, such as lung and gastric cancer. Treatment of liver metastases depends on their extent and location. Treatment options include surgical resection, thermal ablation, chemotherapy, different types of arterial embolisation, external beam radiotherapy and selective internal radiation therapy.* ***Irreversible electroporation is a non-thermal cell-destruction technique which may*** *allow more targeted destruction of cancerous cells with less damage to surrounding supporting connective tissue, for example nearby blood vessels and nerves, compared with other types of treatment.* Suggest to rephrase to "….Irreversible electroporation is a non-thermal cell-destruction technique for cell membrane electroporation which may …." to align with IRE's intended use.	Thank you for your comment. The Committee considered this comment and did not wish to change the wording of the guidance.
5	Consultee 3 AngioDynamics manufacturer	**2.2.1**	*2.2.1 The aim of irreversible electroporation* ***is to destroy cancerous cells by subjecting cells to a powerful electrical field using high-voltage direct current.*** *This creates multiple holes in the cell membrane, irreversibly damaging homeostasis mechanisms and leading to cell death.* We suggest rephrasing according to IRE's	Thank you for your comment. Section 2.2.1 of the guidance has been changed.

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			intended use: "… electroporation is to irreversibly open the cell membrane by the application of an intense electric field using high voltage direct current.	
6	Consultee 3 AngioDynamics manufacturer	**2.2.2**	*2.2.2 The procedure is performed with the patient under general anaesthesia. A neuromuscular blocking agent is used to prevent muscle spasms. Bipolar or unipolar electrode needles are introduced percutaneously (or by open surgical or laparoscopic approaches) and guided into place in and adjacent to the target tumour under imaging guidance. A series of very short electrical field pulses are delivered over several minutes to ablate the tumour. The electrodes* ***are then repositioned to extend the zone of electroporation*** *until the entire tumour and an appropriate margin have been ablated.* ***Cardiac synchronisation is used to minimise the risk of arrhythmias.*** *Sections 2.3 and 2.4 describe efficacy and safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the overview, available at www.nice.org.uk/guidance/IP/838/overview* Depending on the lesion size, electrodes may or may not need to be repositioned. Therefore, we suggest to rephrase: "Electrode Probes may be repositioned after each procedure to cover a larger volume of tissue with irreversible electroporation when appropriate." Suggest some rephrasing regarding the cardiac	Thank you for your comment. Section 2.2.2 of the guidance has been changed.

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			synchronization referring to the MOA: "Cardiac synchronisation ensuring pulse delivery in the refractory period of the heart's sinus rhythm is recommended, thereby minimising the risk of arrhythmias."	
7	Consultee 2 NHS Professional	**2.3**	We have seen rapid and extensive progressions of disease within 6 weeks following IRE in patients with both liver and pancreatic cancer .	Thank you for your comment. The guidance recommendation reflects the uncertainty about the safety of the procedure.
8	Consultee 2 NHS Professional	**2.3**	very limited data to show it really benifits patients as outlined in 1.1. showing massive and rappid progression of disease following IRE.	Thank you for your comment. The guidance recommendation reflects the uncertainty about the safety of the procedure.
9	Consultee 3 AngioDynamics manufacturer	**2.3.1**	Recently more data on irreversible electroporation efficacy has been published and we suggest adding these as a reference: 1. In a prospective phase II study in 26 early stage HCC patients with 29 tumors less than 3 cm in diameter, at one month after IRE treatment an overall response of 77% CR, 15% PR, 4% SD, and 4% PD was reported (Lencioni et al, SIR 2012). Clinicaltrials.gov identifier NCT01078415 2. In a case series of 49 patients with 76 unresectable HCC and mCRC liver tumors, 20 patients had CR, 19 had PR, and one had SD as their best response. Average PFS was 11.3 months for all patients (Narayanan et al, SIR 2012). 3. A case series of 44 patients with locally advanced pancreatic cancer have successfully undergone IRE. Twenty-nine patients had pancreatic head primary and 15 with body tumors, with 12 patients undergoing margin accentuation with IRE and 32 undergoing in-situ IRE. In a	Thank you for your comment. Please note that efficacy data that have not been published or accepted for publication following peer review or have been published only as conference abstracts are not are not normally considered adequate to support decisions on efficacy by NICE.

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			comparison of IRE patients to standard therapy a significant improvement was seen in Local progression free survival (14 vs 6 months, P=0.01), Distant progression free survival (15 vs 9 months, p=0.02), and overall survival (20 vs 13 months, p=0.03) (Martin et al, SSO 2012). 4. In a case series of 45 patients undergoing 51 IRE procedures, with 40 (88%) patients having lesions in proximity to major vasculature, bile duct, or other organs, IRE was performed via an open (19.6%), laparoscopic (3.9%), or percutaneous (76.5%) approach. The median number of tumors treated per procedure was 1, with a maximum of three. The most common diagnosis was colorectal metastasis (43.1%), followed by HCC (33.3%). Overall, successful ablation as determined by Kaplan-Meier was maintained in 59.5% at 12 months (Cannon et al, AHBPA 2012) 5. A retrospective review of 29 patients who received IRE treatment to 35 lesions (liver 29, kidney 2, lung 2, and pancreas 2.). All lesions were chosen for IRE ablation due to proximity/involvement of vascular, biliary, or visceral (VBV) structures were ablated under ultrasound guidance, and liver and renal ablations were performed by laparoscopy. Explant histologic assessment of two HCC lesions shows complete tumor destruction (Ali, AHBPA 2012).	
10	Consultee 2 NHS Professional	**2.4**	we have one patient developed fast AF with this leading to very serious adverse result to patient and managment of this patient.	Thank you for your comment.
11	Consultee 3 AngioDynamics	**2.4**	Recently more clinical data on irreversible electroporation has been published confirming the early safety profile in a clinical setting, and we	Thank you for your comment. Please note the IP team will always act on safety data and serious

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	manufacturer		suggest adding that to complete the overview. A brief summary: □ In a case series of 49 patients who underwent percutaneous ablation of unresectable HCC and mCRC liver tumors, reported that IRE was complicated in 6 patients (12%) by pneumothorax (2), pleural effusion (2), and atrial flutter/fibrillation during anesthesia (2). All patients recovered fully from these complications. One patient died within 1 month of the IRE due to disease progression (Narayanan, SIR 2012). □ A phase II prospective, multicenter clinical study to evaluate the efficacy and safety of IRE in 26 patients with early-stage HCC reported major complications included hemothorax due to needle puncture of an intercostal artery and requiring drainage (n =1) and transient hepatic decompensation undergoing spontaneous resolution (n =1) (Lencioni, SIR 2012). □ A case series of seventy-nine IRE procedures on 56 patients, to treat 72 lesions in close proximity (within 1 cm of the treatment zone) to vessels, reported that RPV showed mild narrowing in 2 patients and LPV showed a non-occlusive thrombus in 1 patient after the procedure. All other vessels were found to be patent in the post procedure scans in the follow up period up to 15 months. Overall, narrowing or thrombosis occurred in 3 out of 84 vessels (3.6%; 95% CI 0.7 – 10.1%) (Narayanan, SIR 2012). □ A case series of 29 patients that received IRE treatment to 35 lesions (liver 29, kidney 2, lung 2, and pancreas 2) in the proximity/involvement of vascular, biliary, or visceral (VBV) structures	adverse events, regardless of source. The Lencioni R (2012) conference abstract reported on the use of IRE in early stage hepatocellular carcinoma patients and not patients with liver metastases. The Pech M (2010) study reported on the use of IRE in patients with renal cell carcinoma and not patients with liver metastases. The Committee considered the safety data in the 2 Narayanan G (2012) studies and the Ali NS (2012) conference abstracts but did not wish to include the papers in the overview.

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			reported that no patient experienced ablation-related VBV complications, although one patient suffered transient ascites (Ali, AHBPA 2012). In addition, we would like to suggest referencing the early IRE work of Pech et al in RCC patients: □ A pilot study with IRE to investigate the feasibility and safety of IRE in 6 RCC patients scheduled for curative resection reported a single case of intraoperative supraventricular extrasystole. In the postoperative monitoring phase (< 6 days) and at follow-up examination (after 12 weeks) no ECG-related changes were detected. Also an expected decrease in systolic and diastolic arterial pressure was seen for the perioperative period, and values were restored by 24 h after surgery (Pech, Cardiovasc Intervent Radiol 2011)	
12	Consultee 2 NHS Professional	**general**	Based on our experience, it is unsafe, results in seriously adverse impact to paitents care and it should not be proved by nice for clinical application without proven efficacy and randomised control trials.	Thank you for your comment.
13	Consultee 4 The Royal College of Radiologists	**general**	Thank you very much for the opportunity for the RCR to comment on NICE's provisional recommendations on the safety and efficacy of electroporation for the treatment of liver metastases. The RCR has reviewed this document and feels it is accurate. The RCR has no additional comments.	Thank you for your comment.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."