NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of irreversible electroporation for treating primary lung cancer and metastases in the lung

Treating cancer in the lungs using pulses of electricity

Cancer that starts in the lungs is called primary lung cancer. When cancer has spread from other parts of the body to the lung the tumours are called lung metastases. Irreversible electroporation is a process that uses electrical pulses to kill cancer cells. They are applied directly to the tumour through special needles. The main difference between this procedure and thermal techniques for destroying tumours is that it does not produce extreme heat or cold.

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 May 2012 and updated in September 2012.

Procedure name

- Irreversible electroporation for treating primary lung cancer and metastases in the lung.

Specialist societies

- British Society of Interventional Radiology
- British Thoracic Society
- The Association for Cancer Surgery
- The Royal College of Radiologists.

Description

Indications and current treatment

Lung cancer is one of the most common cancers in the UK. The symptoms often do not appear until the disease is at an advanced stage, and the prognosis is generally poor. There are 2 main types of primary lung cancer: small-cell lung cancer and non-small-cell lung cancer. The lung is also a common site for metastases from other primary cancers such as breast or colon cancer.

The choice of treatment for primary lung cancer and for metastases in the lung is influenced primarily by the type of tumour and stage of the disease. Treatments include surgical resection (open or thoracoscopic), chemotherapy, radiotherapy, photodynamic therapy or thermal ablation, or a combination of these. If the tumour protrudes into the major airways, interventional bronchoscopic treatments including diathermy, laser therapy, cryotherapy, brachytherapy or photodynamic therapy may be used.

The aim of irreversible electroporation (IRE) is to destroy cancerous cells by subjecting them to a series of short electrical pulses using high-voltage direct current. This creates multiple holes in the cell membrane, irreversibly damaging the cell's homeostasis mechanisms and leading to cell death. IRE is a non-thermal cell-destruction technique which is claimed to allow targeted destruction of cancerous cells with less damage to supporting connective tissue (such as nearby blood vessels and nerves) than with some other types of treatment.

What the procedure involves

The procedure is performed with the patient under general anaesthesia. Use of a neuromuscular blocking agent is essential to prevent uncontrolled severe muscle contractions caused by the electric current. Bipolar or unipolar electrode needles are introduced percutaneously (or by open surgical or laparoscopic approaches) and guided into place in and adjacent to the tumour using imaging guidance.

The distance between the electrodes is confirmed by imaging to ensure that the electrodes are correctly placed parallel to one another and that sufficient current flow would be generated to ensure IRE.

Each ablation cycle consists of pulses of high-voltage direct current delivered in groups (of about 10) with a brief time for recharging between groups (a cycle is usually completed in less than 2 minutes). Electrodes may be repositioned under imaging guidance to extend the zone of electroporation until the entire tumour and an appropriate margin have been ablated. The number of ablations is determined by the volume of the target tumour. When the ablation procedure is completed, further imaging may be carried out to confirm satisfactory ablation. Total procedure time has been reported to range from 2.5 to 4.5 hours.

Cardiac synchronisation is used to time delivery of the electrical pulse within the refractory period of the heart cycle, minimising the risk of arrhythmias. Precautions should be taken for patients with implantable electrical devices. Ablation of lesions in the vicinity of implanted electronic devices or implanted devices with metal parts should be avoided. It is important to ensure that interventions (such as a defibrillator) and people trained to treat cardiac arrhythmias are available.

Outcome measures

The Response Evaluation Criteria in Solid Tumors (RECIST) are used for assessing tumour response after X-ray, CT and magnetic resonance imaging. There are four categories:

- Complete response: disappearance of all target lesions.
- Partial response: 30% decrease in the sum of the longest diameters of target lesions.
- Progressive disease: 20% increase in the sum of the longest diameters of target lesions.
- Stable disease: small changes that do not meet the above criteria.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to irreversible electroporation for treating primary lung cancer and metastases in the lung. Searches were conducted of the following databases, covering the period from their commencement to 27 September 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, editorial, or 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 primary lung cancer or metastases in the lung.
Intervention/test	Irreversible electroporation.
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 106 patients from 3 case series[1-2;] and 1 case report[3].

One study that was considered to be relevant to the procedure but was not included in the main extraction table (table 2) has been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on irreversible electroporation for treating primary lung cancer and metastases in the lung

Abbreviations used: CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors.

Study details	Key efficacy findings	Key safety findings	Comments
Thomson KR (2011)[1] **Case series** Australia Recruitment period: 2008–9 Study population: Patients with 1 or more tumours of the target organs (liver, lung and kidney). n=**38 patients; 69 separate tumours** Age: not reported Sex: not reported Patient selection criteria: Indications: Patients with 1 or more tumours of the target organs (liver, lung and kidney) in whom conventional therapy was not possible or had been unsuccessful. Contraindications included cardiac failure, recent liver embolisation and imminent liver failure from tumour load. Technique: Nanoknife device was used (AngioDynamics, USA). IRE was performed with the patients under general anaesthesia with muscle paralysis and using CT and/or ultrasound image guidance. Adequate cardiac synchronisation	Number of patients analysed: **1 patient with non-small-cell lung carcinoma (1 tumour) and 3 patients with lung metastasis from colorectal carcinoma (5 tumours).** **Response rate** IRE produced ground-glass opacity, which interfered with tumour margin visibility on CT. None of the patients treated had a satisfactory tumour response and all had progressive disease when assessed by modified RECIST at 3 months. Biopsy in 1 patient (no further details provided) showed coagulative necrosis of a portion of the tumour but viable tumour at the margin of the treated lesion.	**Key safety findings related to use of IRE (including safety findings specifically identified in patients treated for tumours in the lung)** **Complication** / **Number reported** Mortality at 30 days: None reported Transient ventricular arrhythmia (with inadequate ECG synchronisation)[a, b]: 4 patients (no treatment needed) Transient supraventricular tachycardia (with adequate ECG synchronisation)[b]: 1 patient (resolved without treatment) Atrial fibrillation (with adequate ECG synchronisation)[b]: 1 patient (needed cardioversion) Pneumothorax: Occurred in half (2/4) of the lung ablation procedures where the lesions were centrally located; no specific treatment required and resolved spontaneously Collapse of the right upper lobe during the prone portion of the procedure: 1 patient with advanced lung cancer (Karnofsky score of 40; patient observed for 40 hours while the lobe re-expanded spontaneously; lost to imaging and biochemical follow-up	It is likely some reporting has been duplicated because the study centre and some of the authors are the same for references 1 and 2. **Follow-up issues**: • One patient with advanced lung cancer was lost to follow-up. **Study design issues**: • This study was designed to report outcomes in the first treatment of people with IRE. • Response was assessed using CT scan 1 month and 3 months after the procedure. • No formal statistical tests were performed for data on outcome (whether there was complete response, stable disease or progressive disease). **Study population issues**: • Study recruited and reported patients with different tumours. Only 4/38 patients (6/69 tumours) were treated for tumours in the lung. Consequently, some of the safety findings highlighted may not relate to treatment of patients with tumours in the lung. **Other issues**: • Reporting of the total number of patients who received IRE for tumours in the lung was

Abbreviations used: CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors.

Study details	Key efficacy findings	Key safety findings	Comments
was achieved with AccuSync model 72. This was used after 4 patients reported cardiac arrhythmias with AccuSync model 42 R-wave trigger device. Follow-up: **3 months** Conflict of interest/source of funding: One author or his department received funding/sponsorship from AngioDynamics (Queensbury, New York). None of the other authors have identified a conflict of interest.		<table><tr><td></td><td>after discharge from hospital)</td></tr><tr><td>Transient increase in serum creatinine level</td><td>1 patient with lung tumours and 4 patients with kidney tumours (levels returned to baseline by 1 month)</td></tr><tr><td>Brief flushing/allergic reaction after the procedure</td><td>1 patient (appeared to be related to anaesthesia)</td></tr></table> [a] Cardiac arrhythmia led to 2 procedures being aborted before the planned number of ablations was completed (blood pressure dropped but all symptoms resolved on stopping treatment). In addition, 1 of these 4 patients developed bigeminy after resolution of ventricular tachycardia, which resolved within 24 hours without treatment. Percentages were not calculated because the actual number of patients who had IRE without adequate ECG synchronisation was not reported. [b] Timing unclear; most likely during the procedure. .	inconsistent between figures presented in table 3 of the paper and the text. The table shows that 4 patients received 6 IRE procedures for treatment of lung tumours. The text states: 'IRE was performed in the lung in three patients.' In addition, it is noted in the text that 1 patient who had IRE to the lung was lost to follow-up after discharge from the hospital, yet all 4 patients treated for lung tumours had an outcome reported at 3 months in table 3 of the paper. • Karnofsky score is a subjective score between 0 and 100, used by a physician to describe a patient's ability to function and perform common tasks.

Abbreviations used: CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ball C (2010)[2]
Case series
Australia
Recruitment period: not reported
Study population: Patients with either primary or metastatic cancer, some in more than 1 site.
n=21 patients; 28 tumours
(17 liver, 8 kidney, 3 lung)
Mean age: 59 years (range 42–81)
Sex: not reported

Patient selection criteria: not reported

Technique: Nanoknife device was used (AngioDynamics, USA). IRE was performed with the patients under general anaesthesia with muscle paralysis and using CT and/or ultrasound image guidance. All patients had intra-arterial blood pressure monitoring to detect arrhythmias. An ECG synchronisation device (AccuSync Model 72) was used from early on in the study (though not from the start of the trial phase) with variable success with synchronisation. The lung procedures involved a variety of patient positions depending on the site of the tumours.</td>
<td>Not reported.</td>
<td>Key safety findings potentially related to use of IRE for tumours in the lung
<table>
<tr><th>Complication</th><th>Procedures % (n/n)</th></tr>
<tr><td>Ventricular bigeminy on induction of anaesthesia and intermittently throughout IRE procedure</td><td>3.6 (1/28)</td></tr>
<tr><td>Brief runs of ventricular tachycardia[a]</td><td>25.0 (7/28) (including 66.7 [2/3] of patients with lung tumours)</td></tr>
<tr><td>Pneumothorax[b]</td><td>66.7 (2/3) of patients with lung tumours</td></tr>
<tr><td>Transient increase in systolic blood pressure of ‘approximately 20–30 mmHg’ after the treatment cycles[c]</td><td>100 (all patients)</td></tr>
<tr><td>Postoperative pain</td><td>46.4 (13/28)</td></tr>
<tr><td>Acid–base disturbances with associated hyperkalaemia[d]</td><td>14.3 (4/28)</td></tr>
</table>
[a] Arterial blood pressure was ‘markedly decreased’ in 4 of the 7 procedures. Two out of 3 patients with lung tumours experienced these arrhythmias. The authors noted the lack of sufficient numbers to enable determination of the relationship between the distance of the electrodes from the heart, the output of the IRE machine, and the occurrence of arrhythmias, but noted that they seemed to occur more frequently when the electrodes were in close proximity to the heart. The patient who experienced the most significant cardiac rhythm disturbances underwent IRE for a very large liver lesion directly beneath the diaphragm and near to the</td>
<td>It is likely some reporting has been duplicated because the study centre and some of the authors are the same for references 1 and 2.

Follow-up issues:
• Patients were only followed up for 24 to 48 hours.

Study design issues:
• The CT scanning room was not initially designed for procedures needing anaesthesia and presented challenges of remote anaesthesia practice.
• Formal method to assess postoperative pain not reported.
• Study only reported safety findings but no reports on efficacy of IRE.

Study population issues:
• Study recruited and reported patients with different tumours, not specific to tumours in the lung. Consequently, the safety findings highlighted may not relate to patients with lung tumours.</td>
</tr>
</table>

Abbreviations used: CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Follow-up: **24 to 48 hours** Conflict of interest/source of funding: One author received funding/sponsorship from AngioDynamics and a family member has a personal pecuniary interest. None of the other authors have identified a conflict of interest.		inferior cardiac border. Blood pressure and heart rhythm returned to normal immediately after completion of treatment with no evidence of ischaemia on the ECG. [b] Caused by insertion of the electrodes. One patient needed insertion of intercostal catheters to drain a pleural effusion as well as the pneumothorax. No treatment was needed for the other patient. [c] This increase was not modified by opioids, was not sustained beyond a few minutes, and did not need treatment. [d] None of these patients had disturbances that were significant enough to limit the duration of the procedure. **Other complications** In inadequately paralysed patients, the discharge of the electrodes produced contractions of the entire upper body with each pulse, similar to those seen in a grand mal seizure (actual numbers not reported). When patients were adequately paralysed, some muscular contractions were still visible, mainly confined to the treatment area but sometimes including the diaphragm. These contractions were probably caused by direct muscle stimulation.	

Abbreviations used: CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors.

Study details	Key efficacy findings	Key safety findings	Comments
Usman M (2012)[3] Case reports USA Recruitment period: unclear Study population: Patients with lung neoplasm n=2 Age: 33-year-old and 70-year-old Sex: 50% female Patient selection criteria: unresectable malignancies in the lung. Technique: IRE (Angiodynamics) delivered with patient under general anaesthesia (n=1). Follow-up: case 1: 2.5 years; case 2: 1 year. Conflict of interest/source of funding: One of the authors was on the medical advisory board for a company that had no affiliation with the current research. Authors declared no other potential conflicts of interest or sources of funding.	Number of patients analysed: 2 **Case 1** The hilar mass showed an increase in size, displayed uniform enhancement on a contrast CT study and increased metabolic activity was seen on PET imaging (6 months after the procedure). The patient was still alive 2.5 years after the procedure. **Case 2** An increase of the right suprahilar mass with contrast enhancement suggesting tumour growth was reported 2 months after the procedure.	**Case 2** Moderate parenchymal haemorrhage was observed at the time of the procedure (no further details). There was a suggestion that the tumour had invaded the trachea (at 9-month follow-up). The cancer progressed and the patient had died within 1 year.	**Other issues:** Authors stated that these cases illustrate a failure of IRE within the lungs. The exact reason for failure is uncertain. One potential reason is that lung tissue causes significant impedance of current flow, related to the low density of lung tissue. The presence of air in the lung could further result in decreased energy deposition within the tumour because of the potential of a bypass circuit around the tumour.

Abbreviations used: CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Hays D (2011)[4]
Conference abstract only
Case series
USA
Recruitment period: 2009–10
Study population: Patients were treated for lesions in the liver (33 lesions), lung (12 lesions), pelvis (3 lesions), lymph nodes (1 lesion) and pancreas (1 lesion). Average lesion size was 1.97 cm in the liver, 1.3 cm in the lung, 3.0 cm in the pelvis, 1.6 cm in the lymph nodes and 3.3 cm in the pancreas.
n=45 patients; 67 lesions (50 IRE procedures)
Mean age: 62.5 years (range 42–84)
Sex: 44.4% (20/45) male

Patient selection criteria: exclusion criteria included atrial fibrillation and lesion size >5 cm.

Technique: IRE was performed with the patients under general anaesthesia using cardiac synchronisation.

Follow-up: not reported
Conflict of interest/source of funding: not reported</td>
<td>Efficacy findings from conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview.</td>
<td>Complications
Overall complication rate: 24%.
Procedural or immediate post-procedural complications include:
<table>
<tr><th></th><th>Number reported</th></tr>
<tr><td>Pneumothorax[a]</td><td>14% (7/50) of procedures</td></tr>
<tr><td>Transient intraprocedural hypertension</td><td>1 patient</td></tr>
<tr><td>Transient urinary retention</td><td>1 patient</td></tr>
<tr><td>Perianal fissure (no details provided)</td><td>1 patient</td></tr>
</table>
[a] 85.7% (6/7) were treated with small-calibre thoracostomy tubes. Most commonly occurred in patients treated for lung lesions and lesions high within the liver (no details provided for 1).

One patient returned 4 days after the procedure with tachycardia, which resolved spontaneously.

Hospital readmission
Readmission rate within 30 days after discharge=2.0%.</td>
<td>Follow-up issues:
• Patients were not followed up in the long term.

Study design issues:
• Information was only available from a conference abstract, which gave limited details of study design.
• This is a retrospective study to evaluate the technical feasibility and clinical safety of IRE.

Study population issues:
• Study recruited and reported patients with different tumours. The underlying tumour treated was not described for all safety events.</td>
</tr>
</table>

Efficacy

Tumour response

A case series of 38 patients with a variety of tumours reported no satisfactory tumour response in any of the 4 patients treated for lung tumours, and all 4 patients had progressive disease when assessed by the modified RECIST at 3 months[1].

A case report of 2 patients with primary and metastatic lung tumours reported progression of disease (at 2 months after the procedure in 1 patient and at 6 months in the other patient)[3].

Safety

Cardiac arrhythmia

Transient ventricular arrhythmia was reported in 4 patients with inadequate ECG synchronisation in the case series of 38 patients (timing unclear; most likely during the procedure)[1]. No cardioversion or other treatment was needed. One of the 4 patients developed bigeminy after ventricular tachycardia resolved. The bigeminy resolved within 24 hours without treatment. One patient with adequate ECG synchronisation reported transient supraventricular tachycardia, which resolved without treatment. One patient who had adequate ECG synchronisation developed atrial fibrillation, which needed cardioversion after the IRE procedure.

Transient ventricular tachycardia was reported in 2 out of 3 procedures in patients with lung tumours in a case series of 21 patients with primary or metastatic cancer (liver, kidney or lung)[2]. In the same case series, arterial blood pressure was 'markedly decreased' (not defined) in 4 out of a total of 7 procedures where transient ventricular tachycardia occurred (not stated whether this occurred in the patients with lung tumours). Blood pressure and heart rhythm returned to normal immediately after treatment with no evidence of ischaemia on the ECG.

Tachycardia was reported in 1 patient 4 days after the procedure in a case series of 45 patients[4]. This resolved spontaneously.

Pneumothorax

Pneumothorax in patients with centrally located lung lesions was reported in half (2/4) of the lung tumour ablation procedures in the case series of 38 patients[1]. No specific treatment was needed and the pneumothoraces resolved spontaneously.

Pneumothorax was reported in two thirds (2/3) of the lung ablation procedures in the case series of 21 patients[2]. These occurred because of insertion of the electrodes. One patient needed insertion of intercostal catheters to drain a

pleural effusion as well as the pneumothorax. No treatment was needed for the other patient.

Pneumothorax was reported in 14% (7/50) of procedures in the case series of 45 patients; 86% (6/7) were treated with small-calibre thoracostomy tubes[4]. The pneumothoraces occurred most commonly in patients treated for lung lesions and lesions high within the liver.

Brachial plexus injury

Significant but transient neurapraxia was reported in 17% of patients (2/12 procedures) in the case series of 21 patients[2]. All patients were positioned supine with their arms extended above their heads during the procedure.

Muscle spasms

Contractions of the entire upper body with each pulse of the electrodes, similar to those seen in a grand mal seizure, were reported in inadequately paralysed patients (absolute numbers not reported) in the case series of 21 patients[2]. When patients were adequately paralysed, some muscular contractions were still visible. These were mainly confined to the treatment area, but sometimes including the diaphragm. The authors noted that these contractions were probably caused by direct muscle stimulation.

Parenchymal haemorrhage

The case report of 2 patients reported moderate parenchymal haemorrhage at the time of the procedure in 1 patient.

Other complications

Transient increase in serum creatinine level was reported in 1 patient with lung tumours and 4 patients with kidney tumours in the case series of 38 patients[1]. All levels returned to baseline by 1 month.

Collapse of the right upper lobe during the prone portion of the procedure was reported in 1 patient with advanced lung cancer in the case series of 38 patients)[1]. The patient was observed for 40 hours while the lobe re-expanded spontaneously.

Validity and generalisability of the studies

- Only 2 case series[1-2] and 1 case report[3] were identified that had been published as full peer-reviewed articles. Only the case report of 2 patients was restricted to patients with tumours in the lung. There is likely to be some

patient overlap between the 2 case series, which share some of the same authors.

- One conference abstract has been included in accordance with the Interventional Procedures Programme methods guide, which states that data on safety may be considered by the Committee regardless of their source and publication status[4]. It is difficult to assess the quality of this study and the validity of the assessment measures used.
- Most studies included patients with either primary or secondary cancer, some in multiple sites (liver, lung or kidney); however, outcomes were not usually reported separately so it was not possible to identify safety and efficacy findings specifically for lung cancer.
- There were no long-term or comparative data.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Percutaneous radiofrequency ablation for primary or secondary lung cancers. NICE interventional procedures guidance 372 (2006). Available from www.nice.org.uk/guidance/IPG372
- Cryotherapy for malignant endobronchial obstruction. NICE interventional procedures guidance 142 (2005). Available from www.nice.org.uk/guidance/IPG142
- Photodynamic therapy for localised inoperable endobronchial cancer. NICE interventional procedures guidance 137 (2005). Available from www.nice.org.uk/guidance/IPG137
- Photodynamic therapy for advanced bronchial carcinoma. NICE interventional procedures guidance 87 (2004). Available from www.nice.org.uk/guidance/IPG87

Clinical guidelines

- Lung cancer: the diagnosis and treatment of lung cancer. NICE clinical guideline 121 (2011). Available from www.nice.org.uk/guidance/CG121

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.

Dr Antony Goode (British Society of Interventional Radiology); Dr Andrew Medford (British Thoracic Society); Mr James McGuigan (The Association for Cancer Surgery); Dr David J Breen and Professor Edward Leen (The Royal College of Radiologists).

- One Specialist Adviser has performed this procedure at least once and 4 have never performed it.
- Three Specialist Advisers consider the procedure to be definitely novel and of uncertain safety and efficacy; 1 considers it to be the first in a new class of procedure; 1 considers it to be a minor variation on an existing procedure.
- The comparators are surgical lobectomy or pneumonectomy, radiofrequency ablation, cryoablation, microwave ablation, stereotactic radiotherapy and external-beam radiotherapy.
- Theoretical adverse events include arrhythmias (including atrial fibrillation), sepsis, tumour seeding, residual necrotic tissue, changes such as fibrosis and bronchiolitis (although these changes are not likely to be a major problem as they are a result of replacing malignant tissue with healthier tissue), muscle contractions, hypertension, pneumothorax, cavitation, bronchopleural fistula, bleeding, pain and electrolyte disturbances.
- Anecdotal adverse events include arrhythmias, sepsis, lobar collapse, muscle contractions, hypertension, pneumothorax, cavitation, bleeding, pain and electrolyte disturbances.
- Adverse events reported in the literature include arrhythmias (supraventricular tachycardia, atrial fibrillation and brief ventricular tachycardia), sepsis, non-target organ damage, lobar collapse, pneumothorax, haemorrhage, hypertension, muscle contractions (if induced paralysis is suboptimal), postoperative pain and hyperkalaemia.
- Key efficacy outcomes include patient survival, tumour response on follow-up imaging, local tumour control, time to disease progression, improvement in health-related quality of life and reduction in tumour-related symptoms.
- Two Specialist Advisers acknowledged that there are very little data available on the use of IRE in humans and that the limited published studies reported recurrent tumour, treatment failures and progressive disease following IRE of lung tumours. One Specialist Adviser stated that data on longer-term tumour control, time to progression and overall survival are not available. One

Specialist Adviser noted concerns with the duration of response and adequacy of treatment of all malignant tissue as with similar modalities. One Specialist Adviser is concerned with subtotal treatment.

- One Specialist Adviser stated that significant prior experience in lung tumour ablation, best previously achieved with radiofrequency ablation or microwave ablation, before moving on to careful CT-guided IRE, is needed. The procedure requires CT expertise and full and careful general anaesthesia with muscle relaxation to control involuntary muscle contraction. Two Specialist Advisers noted that interventional radiological expertise and training are needed for this procedure.
- The Specialist Advisers noted that facilities for general anaesthesia, imaging and monitoring (oximetry, ECG, temperature, capnography, blood pressure, biochemistry and arterial blood gases) and sufficient technical equipment (electrodes and pulse-generating devices) are needed. One Specialist Adviser stated that the ready availability of a thoracic surgical team in case of pneumothorax or damage to major vessels leading to haemorrhage into the airway is also needed.
- One Specialist Adviser thought that the procedure would have a major impact on the NHS but believed that NICE should not approve IRE in the lung at present until more strictly run research and development protocols have been reported. The procedure has only slow diffusion at present and it needs to be limited to centres with significant experience in radiofrequency ablation, microwave ablation and cryoablation for the moment and within the confines of a strict research protocol.
- Two Specialist Advisers thought that the procedure would have a moderate impact on the NHS. One of them stated that, as is the case for radiofrequency ablation, only a subset of patients with lung cancer or lung metastases are likely to be eligible for treatment with IRE and it is likely that if this treatment were to become widespread, it would be replacing treatments such as radiofrequency ablation and lobectomy, rather than being used in a new cohort of patients for whom no locoregional treatment was previously feasible. The other Specialist Advisers stated that IRE would not play a major part in most lung cancer patients' therapy because patients tend to have a survival of less than a year and many will have early spread of cancer to lymph nodes and other organs, which would usually preclude the use of this technique. It is likely to be used in a small number of specialist centres where there are specialists in all aspects of lung cancer treatment and not to be used except in those patients fully discussed at a multidisciplinary meeting.
- Two Specialist Advisers thought that the procedure would have a minor impact on the NHS. One Specialist Adviser noted that the diffusion of IRE is likely to be slow because of lack of efficacy data in patients with lung cancer, the need for high technical expertise in a very small number of centres and the length of the procedure (3–4 hours per patient). However, the position might change if the evidence became more substantial. There are likely to be many patients with lung metastases and inoperable lung cancer. In addition to the lack of efficacy data, other current issues are tolerability, and the likely costs of the

technique (for example, equipment, general anaesthesia, team and overnight stay).

Patient Commentators' opinions

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

Issues for consideration by IPAC

- Future trials:
  - NCT01442324 Pilot study of irreversible electroporation (IRE) to treat metastatic liver cancer and cholangiocarcinoma: location: Italy; type: single-arm pilot clinical trial; estimated enrolment: 5 patients; estimated primary completion date: September 2012.
  - Two studies managed by the manufacturer of the IRE device are in progress:
  - 1. NCT01078415 Pilot study of irreversible electroporation (IRE) to treat early-stage primary liver cancer (HCC): locations: France, Germany, Italy and Spain; type: single-arm pilot clinical trial; estimated enrolment: 25 patients; estimated primary completion date: October 2011 (A first abstract on the primary endpoint of RECIST criteria has been accepted and will be presented at Society of Interventional Radiology (SIR) meeting in March 2012); estimated study completion date: October 2013.
  - 2. NCT01369420 NanoKnife low energy direct current (LEDC) system in subjects with locally advanced unresectable pancreatic cancer: location: Italy; type: single-arm pilot clinical trial; estimated enrolment: 10 patients; primary endpoint data are expected to become available in April 2012.
  - In addition, several projects are being run by investigators on IRE in cancer of the lung, prostate, liver and pancreas.

- Registry:
  - The soft tissue ablation registry (STAR), USA collects data on patients treated by irreversible electroporation for liver, pancreas, lung, prostate and kidney tumours, as well as other soft tissue tumours.

References

1. Thomson KR, Cheung W, Ellis SJ et al. (2011) Investigation of the safety of irreversible electroporation in humans. Journal of Vascular and Interventional Radiology 22: 611–21

2. Ball C, Thomson KR, Kavnoudias H (2010) Irreversible electroporation: a new challenge in 'out of operating theater' anesthesia. Anesthesia & Analgesia 110: 1305–9

3. Usman M, Moore W, Talati R (2012) Irreversible electroporation of lung neoplasm: A case series. Medical Science Monitor 18(6): CS43-7

4. Hays D, Robbins KV, Goodwin WJ et al. (2011) Single center, multiuser experience and safety of 50 irreversible electroporation (IRE) ablations. Journal of Vascular and Interventional Radiology 22 (3 Suppl.): S80–1 (Abstract)

Appendix A: Additional papers on irreversible electroporation for treating primary lung cancer and metastases in the lung

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
Thomson KR, Cheung W, Ellis S et al. (2009) Irreversible electroporation with the NanoKnife in humans [abstract]. Cardiovascular and Interventional Radiology 32 (Suppl. 2): 407.	Case series n=18 procedures (12 liver tumours, 3 lung tumours, 3 renal tumours; 4 patients received more than 1 procedure) Follow-up: 30 days	IRE appears to have high safety profile and a low incidence of after-effects. ECG synchronisation appears to be necessary to avoid arrhythmia.	• Likely to be an interim report of Thomson KR (2011)[1] with potential overlap of patients. • Conference abstract only. • Follow-up CT at 30 days not yet completed in all patients at time of abstract submission.

Appendix B: Related NICE guidance for irreversible electroporation for treating primary lung cancer and metastases in the lung

Guidance	Recommendations
Interventional procedures	**Percutaneous radiofrequency ablation for primary or secondary lung cancers. NICE interventional procedures guidance 372 (2010).** 1.1 Current evidence on the efficacy of percutaneous radiofrequency ablation (RFA) for primary or secondary lung cancers is adequate in terms of tumour control. There is a small incidence of complications, specifically pneumothorax, which may have serious implications for these patients with already compromised respiratory reserve. This procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Patient selection for percutaneous RFA for primary or secondary lung cancers should be carried out by a multidisciplinary team, which will usually include a thoracic surgeon, an oncologist and a radiologist. 1.3 This procedure should only be carried out by radiologists who regularly undertake image-guided interventional procedures. 1.4 NICE encourages further research into this procedure. Research studies should include a clear description of case mix and lesion size, and report long-term survival. **Photodynamic therapy for advanced bronchial carcinoma. NICE interventional procedures guidance 87 (2004).** 1.1 Current evidence on the safety and efficacy of photodynamic therapy for advanced bronchial carcinoma appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 These recommendations apply only to the use of this technique to treat advanced bronchial carcinoma. The Institute will consider photodynamic therapy for early bronchial carcinoma separately. **Photodynamic therapy for localised inoperable endobronchial cancer. NICE interventional procedures guidance 137 (2005).** 1.1 Current evidence on the safety and efficacy of photodynamic therapy for localised inoperable

	endobronchial cancer appears adequate to support the use of this procedure provided that the normal arrangements are in place for audit and clinical governance. 1.2 This procedure is a treatment option for patients with localised endobronchial cancer that is unsuitable for surgical resection. Clinicians should ensure that patients understand the aim of the treatment, especially when its purpose is palliation. Patients should also be informed of the alternative treatment options available. Clinicians should provide them with clear written information and, in addition, use of the Institute's information for the public is recommended. 1.3 Further research and audit will be useful in clarifying the indications and benefits of this procedure. **Cryotherapy for malignant endobronchial obstruction. NICE interventional procedures guidance 142 (2005).** 1.1 Current evidence on the safety and efficacy of cryotherapy for malignant endobronchial obstruction appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Clinicians should ensure that patients fully understand that this is one of a variety of treatment options available. In addition, use of the Institute's information for the public is recommended.
Clinical guidelines	**Lung cancer: diagnosis and treatment. NICE clinical guideline 121 (2011)** Irreversible electroporation is not currently included in the guideline as a treatment option.

Appendix C: Literature search for irreversible electroporation for treating primary lung cancer and metastases in the lung

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	27/09/2012	September 2012
Database of Abstracts of Reviews of Effects – DARE (CRD website)	27/09/2012	September 2012
HTA database (CRD website)	27/09/2012	September 2012
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	27/09/2012	September 2012
MEDLINE (Ovid)	27/09/2012	1946 to September Week 2 2012
MEDLINE In-Process (Ovid)	27/09/2012	September 25, 2012
EMBASE (Ovid)	27/09/2012	1974 to 2012 Week 38
CINAHL (NLH Search 2.0 or EBSCOhost)	27/09/2012	N/A
JournalTOCS	27/09/2012	N/A

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

# ▲	Searches
1	exp Lung Neoplasms/
2	((lung* or pulmon* or thora*) adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta*)).tw.
3	1 or 2
4	Electroporation/
5	Electric Stimulation/
6	Nanoknife.tw.
7	exp Nanotechnology/
8	(irrevers* adj3 (electropor* or electro-por* or electropermeab* or electro-permeab*)).tw.
9	(electric* adj3 (field* or stimul* or pulse* or cell? or membrane* or pore?)).tw.

10	Electric Stimulation Therapy/
11	IRE.tw.
12	LEDC.tw.
13	Electrochemotherapy/
14	electrochemo*.tw.
15	Ablation Techniques/
16	(bipolar adj3 (pulse? or electrod* or mode?)).tw.
17	((tissue* or tumor* or tumour*) adj3 ablat*).tw.
18	or/4-17
19	**3 and 18**