

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of cryotherapy for renal cancers

Renal cancer occurs in the lining of the very small tubes in the kidney. Cryotherapy uses cold temperature to destroy cancer cells through the insertion of a freezing probe into the tumour.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making 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 November 2005

Procedure name

- Laparoscopic or percutaneous cryotherapy for renal cancer
- Other terms for cryotherapy include cryosurgery, cryoablation

Specialty societies

- British Association of Urological Surgeons
- Royal College of Radiologists
- Association of British and Irish Cryosurgery
- British Society of Interventional Radiology
- British Society of Gastrointestinal and Abdominal Radiology

Description

Indications:

Renal cancer can occur in one or both of the kidneys. The most common type of renal cancer in adults is renal cell carcinoma (RCC). Most tumours are identified at a relatively late stage. Symptoms and signs may include blood in the urine (haematuria), pain, weight loss and a palpable abdominal mass. Some cases are linked to hereditary syndromes.

Current treatment and alternatives

If operable, the standard treatment for renal cancer has been partial or total nephrectomy. Smaller tumours (less than 4 cm) have better prognosis and some of

these tumours could be treated with nephron-sparing surgery. Nephron-sparing surgery can at times be carried out with minimally invasive techniques, such as laparoscopic partial nephrectomy. Other treatment options for smaller tumours include ablative treatments such as radiofrequency ablation, high-intensity ultrasound, and cryotherapy.

Cryotherapy may be a treatment option for patients who are poor surgical candidates because of tumour stage (making the tumour inoperable) or anaesthetic risk. Cryotherapy may also be a treatment option for patients in whom preservation of renal function is desired in as much as it is possible, for example in patients with a solitary kidney, or with compromised renal function.

What the procedure involves:

Cryotherapy is a method of tumour ablation. It is most commonly performed laparoscopically or percutaneously, under suitable imaging guidance.

Under anaesthesia, a probe is inserted into the tumour. The probe delivers a coolant at subfreezing temperatures, with the tip of the probe acting as the site of freezing. An ice ball is created around the tip of the probe, destroying cells through direct freezing, dehydration and hypoxia. Each freeze cycle is followed by a heat (thaw) cycle to allow removal of the probe. A double freeze-thaw cycle is usually performed to ablate the tumour, with the aim of extending the ice ball approximately 1 cm beyond the tumour margins. Additional freeze/thaw cycles may be repeated if necessary, and more than one freezing probes could be used.

The maximum recommended renal tumour size for cryotherapy is around 4.0 cm (i.e. small stage I tumours). Lesions of such size or smaller can be treated with a single probe, which causes less morbidity than multiple probe use.

Efficacy:

The evidence base for this procedure is based on case-series studies and one non-randomised comparative study. A difficulty in interpreting the evidence is that in some studies tumour diagnosis was only based on imaging, and was not confirmed histologically. Among patients who had histology before the procedure, there was a number of patients who had benign masses. Therefore, the exact proportion of non-malignant tumours that was included in the studies is uncertain. Ascertainment of tumour recurrence status during follow-up was also in some studies based on imaging criteria alone (i.e. without histological confirmation)

Survival and Tumour Recurrence

All studies had relatively short-term follow-up, the longest mean follow-up reported in a case-series of 56 patients undergoing laparoscopic cryotherapy. In this study there was an overall three-year survival rate of 89%.

In a second study comparing laparoscopic cryotherapy with laparoscopic partial nephrectomy, there were 2 recurrences in the cryotherapy group (mean follow-up 24.6 months) compared to 1 in the surgery group (mean follow-up 5.8 months).

Four studies reported no signs of recurrence at a maximum follow-up of 40 months in patients undergoing either laparoscopic or percutaneous cryotherapy.

Specialist Advisors

The Specialist Advisors commented that long-term efficacy has yet to be established because only a small number of patients have been treated with this procedure. It was also noted that the lack of histology makes it difficult to determine whether total ablation of tumours has been achieved.

Safety:

There were few major safety concerns. In one study of 271 patients, complications were reported for both cryotherapy (n=139) and radiofrequency (n=133) for renal cancer. Cryotherapy (performed both laparoscopically and percutaneously) had a complication rate of 14% (19/139), which included 10 instances of probe site pain. In another study comparing laparoscopic cryotherapy (n=78) with laparoscopic partial nephrectomy (n=153) there were 6 complications in the cryotherapy group compared with 49 in the surgery group. Other complications reported in the studies included haematoma, ileus and respiratory difficulty.

Specialist Advisors

The Specialist Advisors listed the main adverse events as bleeding, injury to adjacent structures, urinary leakage and infection.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to cryotherapy for renal cancer. Searches were conducted via the following databases, covering the period from their commencement to November 2005 Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. In March 2006 an updated literature search was undertaken. The updated search did not look at trial registries. (See Appendix C for details of search strategy).

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these 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. In the context of this overview this included studies that had long term follow-up and reported on histological data. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with renal cancer
Intervention/test	Laparoscopic and percutaneous cryotherapy
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 nine studies; seven case series study and one non randomised controlled study.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (Table 2) have been listed in Appendix A.

Existing reviews on this procedure

There were no published reviews identified at the time of the literature search.

Related NICE Guidance:

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

Interventional Procedures:

IPG 091 *Percutaneous radiofrequency ablation of renal cancer*
http://www.nice.org.uk/page.aspx?o=IP_215

Clinical Guidelines:

The Institute has published cancer service guidance on *Improving Outcomes in Urological Cancer*, however this guidance does not include reference to cryotherapy for renal cancer.

Table 2. Summary of key efficacy and safety findings on cryotherapy for renal cancer

Abbreviations used: MRI – magnetic resonance imaging, RFA – radiofrequency ablation, COPD – chronic obstructive pulmonary disease, RCC – renal cell carcinoma			
Study Details	Key efficacy findings	Key safety findings	Comments
<p>Gill et al (2005)¹</p> <p>US</p> <p>Study period: September 1997 – time of writing (not specified)</p> <p>Case-series</p> <p>n=56 patients</p> <p>Indications: Localised small (< 4cm) renal mass as shown on imaging. Patients underwent intraoperative biopsy just prior to cryotherapy.</p> <p>Population: 36 patients RCC 6 patients oncocytoma 14 patients miscellaneous conditions Mean age: 65.2 years (range: 28 – 84 years) Mean tumour size: 2.3cm (range: 1 – 5cm)</p> <p>Technique: Transperitoneal or retroperitoneal laparoscopic cryotherapy with MRI</p> <p>Follow-up: 3 years (all patients)</p> <p>Histological follow-up: Performed at 6 months and again if MRI findings were abnormal</p> <p>Disclosure of interest: Many authors has a financial and or other relationship with Baxter and Pfizer</p>	<p>Outcomes measured: (not all reported on here): technical success, blood loss, warm ischemia time, cryolesion size, operative time, hospital stay, convalescence time, serum creatinine levels, recurrences.</p> <p>Cryolesion size: Cryolesion size decreased with time. At 3 years 17 cryolesions (38%) had disappeared on MRI.</p> <p>Histological follow-up At six months, 39 patients were available to undergo CT guided biopsy. RCC was identified in 2 patients. These patients underwent secondary laparoscopic radical nephrectomy</p> <p>Survival Three year survival rate of 89%</p> <p>Survival rate of 98%in the 51 patients undergoing cryotherapy in the context if a sporadic unilateral renal tumour.</p> <p>1 patient died of metastatic prostate cancer 4 patients died of metastatic disease in the context of bilateral RCC (all 4 patients had undergone previous treatment)</p>	<p>Complications</p> <p>1 patient (2%) Splenic haematoma 1 patient (2%) Heart failure 1 patient (2%) Pleural effusion+ lung atelectasis 1 patient (2%) Herpetic oesophagitis</p>	<p>Since 1997 study group have performed cyroablation on 115 patients.</p> <p>This paper is the most recent and reports outcomes at 3 years (see Appendix A for further publications).</p> <p>Although patients underwent an biopsy prior to cryotherapy it was not part of the selection process.</p> <p>In most cases only one cryoprobe was used and a double-freeze-thaw cycle was applied.</p> <p>All laparoscopic procedures were performed by a one surgeon, all MRI scans were read/re-read and cryolesions were measured by a one radiologist.</p>

Abbreviations used: MRI – magnetic resonance imaging, RFA – radiofrequency ablation, COPD – chronic obstructive pulmonary disease, RCC – renal cell carcinoma

Study Details	Key efficacy findings	Key safety findings	Comments																																																																																	
<p>Desai, Aron and Gill (2005)² US Study period: September 1997 – June 2003 Non randomised controlled study (retrospective)</p> <p>n= 231 patients (consecutive) - 78 patients cryotherapy - 153 patients partial nephrectomy (surgery)</p> <p>Indications: Suspicious peripheral nonhilar renal mass < 3cm as indicated on imaging. Selection of patients for treatment was at the discretion of the surgeon. Patients underwent intraoperative biopsy just prior to cryotherapy.</p> <p>Population: Cryotherapy group: 56% of patients had histological confirmation of RCC, 38% had benign lesions and 6% were inconclusive, Mean age: 65 years (range: 28 – 88) Mean tumour size: 2 cm (range: 0.6-3.0)</p> <p>Surgery group 68% of patients had histological confirmation of RCC, 32% had benign lesions, and there were no patients with inconclusive results. Mean age 60 years (range 17 – 87) Mean tumour size: 2 cm (range 0.7 – 3.0)</p> <p>Technique: laparoscopic cryotherapy with MRI and partial nephrectomy</p> <p>Mean follow-up:</p>	<p>Outcomes measured (not all reported on here): technical success, blood loss, warm ischemia time, operative time, hospital stay, convalescence time, serum creatinine levels, tumour recurrence.</p> <p><i>Cryotherapy</i></p> <p>Technically successful in 78 patients Mean blood loss 100ml Mean rise in serum creatinine 13.7% Cryolesion size: mean reduction of 30% at 3 months and 80% at 3 years. Recurrences 2 (3%) Deaths 3 (1 patient died of noncancer causes, 2 patients died of pre-existing metastatic disease)</p> <p><i>Partial nephrectomy (Surgery)</i></p> <p>Technically successful in 152/153 patients Mean blood loss 211 ml Mean rise un serum creatinine 16.4% Recurrences 1 (0.6%) Deaths 0 patients</p>	<p>Complications:</p> <table border="1" data-bbox="1178 276 1711 507"> <thead> <tr> <th>Intraoperative</th> <th>Cryotherapy</th> <th>Surgery</th> </tr> </thead> <tbody> <tr> <td>Pleural injury</td> <td>1</td> <td>0</td> </tr> <tr> <td>Renal haemorrhage</td> <td>0</td> <td>5</td> </tr> <tr> <td>Ureteral injury</td> <td>0</td> <td>1</td> </tr> <tr> <td>Epigastric artery injury</td> <td>0</td> <td>1</td> </tr> <tr> <td>Tumour capsule breach</td> <td>0</td> <td>1</td> </tr> </tbody> </table> <p>Postoperative and late complications</p> <table border="1" data-bbox="1178 513 1711 1286"> <tbody> <tr> <td>Pneumothorax</td> <td>1</td> <td>0</td> </tr> <tr> <td>Prolonged ileus</td> <td>1</td> <td>2</td> </tr> <tr> <td>Atelectasis</td> <td>1</td> <td>3</td> </tr> <tr> <td>Pleural effusion</td> <td>0</td> <td>1</td> </tr> <tr> <td>Pneumonia</td> <td>1</td> <td>3</td> </tr> <tr> <td>Pulmonary embolism</td> <td>0</td> <td>3</td> </tr> <tr> <td>Haemorrhage</td> <td>0</td> <td>10</td> </tr> <tr> <td>Atrial fibrillation</td> <td>0</td> <td>1</td> </tr> <tr> <td>Gluteal compartment syndrome</td> <td>0</td> <td>1</td> </tr> <tr> <td>Urinoma</td> <td>0</td> <td>1</td> </tr> <tr> <td>Internal jugular vein thrombus</td> <td>0</td> <td>1</td> </tr> <tr> <td>Rhabdomyolysis</td> <td>0</td> <td>1</td> </tr> <tr> <td>Urinary leak</td> <td>0</td> <td>4</td> </tr> <tr> <td>Congestive heart failure</td> <td>0</td> <td>1</td> </tr> <tr> <td>Perirenal haematoma</td> <td>1</td> <td>0</td> </tr> <tr> <td>Wound dehiscence</td> <td>0</td> <td>1</td> </tr> <tr> <td>Hemia</td> <td>0</td> <td>3</td> </tr> <tr> <td>Delayed nephrectomy</td> <td>0</td> <td>1</td> </tr> <tr> <td>Deep vein thrombosis</td> <td>0</td> <td>2</td> </tr> <tr> <td>Perinephric abscess</td> <td>0</td> <td>1</td> </tr> <tr> <td>Open conversions</td> <td>0</td> <td>1</td> </tr> </tbody> </table>	Intraoperative	Cryotherapy	Surgery	Pleural injury	1	0	Renal haemorrhage	0	5	Ureteral injury	0	1	Epigastric artery injury	0	1	Tumour capsule breach	0	1	Pneumothorax	1	0	Prolonged ileus	1	2	Atelectasis	1	3	Pleural effusion	0	1	Pneumonia	1	3	Pulmonary embolism	0	3	Haemorrhage	0	10	Atrial fibrillation	0	1	Gluteal compartment syndrome	0	1	Urinoma	0	1	Internal jugular vein thrombus	0	1	Rhabdomyolysis	0	1	Urinary leak	0	4	Congestive heart failure	0	1	Perirenal haematoma	1	0	Wound dehiscence	0	1	Hemia	0	3	Delayed nephrectomy	0	1	Deep vein thrombosis	0	2	Perinephric abscess	0	1	Open conversions	0	1	<p>Same study group as¹</p> <p>Follow-up is longer for cryotherapy group as study period for partial nephrectomy covers 1999 – 2003.</p> <p>Although patients underwent an biopsy prior to cryotherapy it was not part of the selection process.</p> <p>Those undergoing partial nephrectomy were younger, had larger tumours, were less likely to have a solitary kidney and to have lower baseline creatinine levels compared with those undergoing cryotherapy.</p> <p>In the methods section the authors' state that treatment allocation was based the discretion of the surgeon however in the discussion section it is inferred that patients selected for cryotherapy were more likely to have features rendering them less suitable for surgery.</p> <p>Authors note that the difference in diagnosis of RCC may be because in the surgery group the entire excised tumour specimen was examined in comparison to a limited tissue sample taken from the cryotherapy group.</p>
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Study Details	Key efficacy findings	Key safety findings	Comments
<p>-cryotherapy patients 24.6 months (range 1-60 months) - partial nephrectomy patients 5.8 months (range 1 – 36 years)</p> <p>Histological follow-up: Performed in the cryotherapy group at 6 months postoperatively.</p> <p>Disclosure of interest: none specified</p>			

Abbreviations used: MRI – magnetic resonance imaging, RFA – radiofrequency ablation, COPD – chronic obstructive pulmonary disease, RCC – renal cell carcinoma			
Study Details	Key efficacy findings	Key safety findings	Comments
<p>Lee et al (2003)³ US Case series</p> <p>Study period: October 1997 – January 2001</p> <p>n=20 patients</p> <p>Indications: Renal mass < 4cm as indicated on imaging. Patients with central renal masses were excluded. 18 patients had a preoperative biopsy (in two patients biopsy was not done).</p> <p>Population: Of the 18 patients with histological diagnosis: 11 patients RCC 3 patients benign tubules, 2 patients chronic pyelonephritis, 1 patient oncocyoma, 1 patient fibrosis</p> <p>Mean age: not stated (range: 40 -84 years) Mean tumour size: not stated (range: 1.4cm – 4.5cm)</p> <p>Mean follow-up: 14.2 months Range: 1 - 40 months</p> <p>Technique: laparoscopic cryotherapy using a retroperitoneal approach.</p> <p>Histological follow-up: not done – imaging instead.</p> <p>Disclosure of interest: not specified</p>	<p>Outcomes measured (not all reported): blood loss, operative time, return to normal activity, imaging.</p> <p>Blood loss: 92.5ml</p> <p>Authors note that serum creatinine levels remain stable.</p> <p>Authors note that during the follow-up period there have been no signs of recurrence of the lesions.</p>	<p>Complications:</p> <p>1 patient with a left renal lesion had a pancreatic injury (occurred intraoperatively)</p> <p>5/11 patients with a left-sided tumour had elevated amylase and lipase levels 1-2 days postoperatively.</p> <p>1 patient had an atrial fibrillation</p> <p>Authors report that there were no urinary fistulas or significant haemorrhage.</p>	<p>Lesions were monitored postoperatively by serial imaging (CT/MRI) every 3 to 6 months.</p> <p>A retroperitoneal approach was used for all cases regardless of the position of the tumour – this possibly has an impact on incidence of complications.</p>

Abbreviations used: MRI – magnetic resonance imaging, RFA – radiofrequency ablation, COPD – chronic obstructive pulmonary disease, RCC – renal cell carcinoma			
Study Details	Key efficacy findings	Key safety findings	Comments
<p>Nader et al (2003) ⁴ US</p> <p>Study period: February 1999 – March 2002</p> <p>Case series</p> <p>n=15 patients</p> <p>Indications: Selection criteria: Renal lesions less than 4 cm, solid, solitary, peripheral, exophytic and met radiological criteria for suspected renal malignancies. All patients had intraoperative biopsies taken at the treatment.</p> <p>Population: 10 patients RCC 1 patient oncocytoma 2 patient angiomyolipoma 1 patient scar tissue 1 myxoid degeneration</p> <p>Mean age: 68.5 years (range: 49 – 86 years). Mean tumour size: 2.15 cm (range: 1.2 – 3.2 cm)</p> <p>Mean follow-up: 453 days Range: 147 – 816 days</p> <p>Technique: laparoscopic cryotherapy with either CT/MRI. Approach was transabdominal (n=6) or retroperitoneal (n=9).</p> <p>Histological follow-up: biopsies were performed on patients with RCC at least 3 months after cryotherapy.</p> <p>Disclosure of interest: none specified</p>	<p>Outcomes measured (not all reported here): operative time, blood loss, length of stay, serum creatinine levels</p> <p>Mean blood loss: 67 ml Mean preoperative creatinine was 1.25mg/dl and mean creatinine 1 month was 1.36mg/dl</p> <p>Authors note that all radiographic imaging revealed cryoablative lesions that were either stable or had decreased in size without evidence of enhancement.</p> <p>Tumour recurrence</p> <p>7/10 patients with RCC had follow-up biopsy, 2 patients had a positive result. These 2 patients underwent nephrectomy - with further tests indicating recurrence in 1 patient.</p>	<p>Complications:</p> <p>No intraoperative complications reported</p> <p>Postoperatively:</p> <p>1 patient developed respiratory difficulty requiring intubation for 1 day.</p> <p>1 patient had an 8-day postoperative ileus which resolved with conservative measures.</p>	<p>Not all patients with RCC consented to have a postoperative biopsy.</p> <p>2 patients with positive biopsies. The treatment failure occurred in the patient with the largest tumour treated (3.2cm).</p>

Abbreviations used: MRI – magnetic resonance imaging, RFA – radiofrequency ablation, COPD – chronic obstructive pulmonary disease, RCC – renal cell carcinoma			
Study Details	Key efficacy findings	Key safety findings	Comments
<p>Cestari et al (2004)⁵</p> <p>Case series</p> <p>n= 37 patients</p> <p>Indications: Selection criteria are unclear from abstraction. Patients had preoperative biopsy</p> <p>Population: RCC in 29 patients, oncocytoma in 6 patients and 2 patients had indefinite results.</p> <p>Mean age: 64 years Range: 29 – 89 years. Mean tumour size: 2.5 cm Range: 1cm – 6 cm.</p> <p>Technique: laparoscopic cryotherapy with either CT/MRI. Approach was transperitoneal n=22 or retroperitoneoscopic n=15.</p> <p>Mean follow-up: not stated Range: unclear.</p> <p>Histological follow-up: Performed preoperatively and 6 months postoperatively</p> <p>Selection criteria: Unclear</p> <p>Disclosure of interest: Unclear</p>	<p>Outcomes measured (not all reported here): operative time, histological evaluation, operative time, blood loss, return to normal activities, cryolesion size, follow-up imaging.</p> <p>Technical success in all cases. Mean blood loss:165.3ml</p> <p>Authors note that of the 25 of the 35 patients in whom follow-up biopsy was performed, at a follow-up period of 6 months or more all were found to be recurrence-free.</p>	<p>Complications: Authors note that early and postoperative complications were evaluated. These were not detailed in the abstract.</p>	<p>Only an abstract was available at the time of writing as journal issue could not be located.</p> <p>Postoperative imaging was done at 1,3,6,12,18 and 24 months and then annually.</p> <p>Limited information</p>

Abbreviations used: MRI – magnetic resonance imaging, RFA – radiofrequency ablation, COPD – chronic obstructive pulmonary disease, RCC – renal cell carcinoma			
Study Details	Key efficacy findings	Key safety findings	Comments
<p>Silverman et al (2005)⁶</p> <p>US</p> <p>Case series</p> <p>Study period: October 1997 – January 2001</p> <p>n=23 patients (26 tumours)</p> <p>Indications: Selection criteria - patients with either biopsy proven malignancy or findings on imaging that suggested a malignancy. Patients who were selected based on imaging had a biopsy prior to treatment.</p> <p>Population: 24 RCC 1 transitional cell carcinoma 1 angiomyolipoma Mean age: 66 years (range: 43 -86) Mean tumour size: 2.6 cm (range 1.0-4.6)</p> <p>Mean follow-up: 14 months Range: 4 - 30 months</p> <p>Technique: percutaneous cryotherapy using MRI.</p> <p>Histological follow-up: not done – imaging instead.</p> <p>Disclosure of interest: Supported in part by Galil Medical (manufactures of probe)</p>	<p>Outcomes measured (not all reported here): length of stay, follow-up imaging, serum creatinine levels.</p> <p>Authors note that 24/26 tumours were successfully ablated, with 23 requiring one treatment session.</p> <p>Authors note that there was no change in the serum creatinine level except in one patient.</p>	<p>Complications:</p> <p>1 patient had a haemorrhage requiring a blood transfusion 1 patient had an abscess which was treated successfully with catheter drainage.</p>	<p>This study evaluates percutaneous cryotherapy.</p> <p>Successful ablation was defined as lack of contrast enhancement at follow-up imaging.</p> <p>Authors also indicate that patients had comorbid disease, solitary kidneys or were or advanced age – suggesting unsuitability for surgery.</p> <p>No histological follow-up, imaging was used as a surrogate for successful ablation.</p> <p>Authors note that the three treatment failures occurred early in the study due to the iceballs not covering the entire tumour (practice has since changed).</p>

Abbreviations used: MRI – magnetic resonance imaging, RFA – radiofrequency ablation, COPD – chronic obstructive pulmonary disease, RCC – renal cell carcinoma			
Study Details	Key efficacy findings	Key safety findings	Comments
<p>Gupta et al (2006) /</p> <p>US Case series</p> <p>Study period: June 2003 – June 2004</p> <p>n=20 patients (27 tumours)</p> <p>Indications: Patients has biopsy confirmed tumours or imaging suggestive of a malignancy. Patients with both central and non central tumours were included.</p> <p>Population: Preoperative histopathological results on 12 patients (16 tumours): 7 RCC 5 hereditary tumours 1 metastatic sarcoma 3 non diagnostic pathology Mean age: 66 years (range: 40 -84 years) Mean tumour size: 2.4cm (range: 1.8cm – 4.6cm)</p> <p>Follow-up available on a subset of patients (n=12) In this group mean follow-up: 5.9 months Range: 1.2-10.3 months</p> <p>Technique: Percutaneous cryotherapy.</p> <p>Histological follow-up: not performed, imagining was undertaken instead.</p> <p>Disclosure of interest: one of the authors had a financial or other interest in Endocare, Boston Scientific or Rita Medical.</p>	<p>Outcomes measured: follow-up imaging.</p> <p>Tumour recurrence at follow-up</p> <p>Authors note that in 13/16 tumours follow-up imaging indicated that the mass of the tumour had decreased in size. There have been no signs of recurrence.</p>	<p>Complications:</p> <p>1 patient developed a haematoma near the ablation site and required a blood transfusion.</p>	<p>This study evaluates percutaneous cryotherapy.</p> <p>Successful ablation was defined as lack of contrast enhancement at follow-up imaging.</p> <p>Not all patients had a preoperative biopsy to confirm malignancy.</p> <p>Histological follow-up not performed.</p> <p>Study is really a report on a subset of patients n=12 (16 tumours)</p> <p>Limited outcomes.</p>

Abbreviations used: MRI – magnetic resonance imaging, RFA – radiofrequency ablation, COPD – chronic obstructive pulmonary disease, RCC – renal cell carcinoma																																																						
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<p>Johnson et al (2004)⁸</p> <p>US</p> <p>Case series (4 centres)</p> <p>n=271 patients - 139 cryoablation - 132 RFA</p> <p>Indications: Selection criteria as per each the protocol of each medical centre (not specified in the report). Unclear whether patients had preoperative biopsy.</p> <p>Population: Mean age: not stated. Range: not stated Tumour size: < 5cm</p> <p>Technique: percutaneous (n=181) and laparoscopic (n=90)</p> <p>Histological follow-up: not stated</p> <p>Mean follow-up: not stated Range: not stated</p> <p>Disclosure of interest: not stated</p>	<p>Not aim of the paper</p>	<p>Complications: 30 complications (26 of these attributable to ablative procedure)</p> <p>Major complications:</p> <table border="1"> <thead> <tr> <th></th> <th>Cryotherapy</th> <th>RFA</th> </tr> </thead> <tbody> <tr> <td>Death</td> <td>0 patients</td> <td>1 patient</td> </tr> <tr> <td>Significant haemorrhage</td> <td>1 patient cyroablation (transfusion needed)</td> <td>0 patients</td> </tr> <tr> <td>Ileus</td> <td>0 patients</td> <td>1 patient</td> </tr> <tr> <td>Scarring with UPJ obstruction</td> <td>0 patients</td> <td>1 patient</td> </tr> <tr> <td>Open conversion</td> <td>1 patient</td> <td>0 patients</td> </tr> <tr> <td>Urine leakage</td> <td>0 patient</td> <td>1 patient</td> </tr> <tr> <td colspan="3">Minor complications:</td> </tr> <tr> <td>Probe site pain or paraesthesia</td> <td>10 patients</td> <td>4 patients</td> </tr> <tr> <td>Urinary tract infection</td> <td>2 patients</td> <td>0 patients</td> </tr> <tr> <td>Pneumonia infection</td> <td>1 patient</td> <td>1 patient</td> </tr> <tr> <td>Minor haemorrhage</td> <td>1 patient</td> <td>0 patients</td> </tr> <tr> <td>Elevated serum creatinine</td> <td>1 patient</td> <td>1 patient</td> </tr> <tr> <td>Wound infection</td> <td>1 patient</td> <td>0 patients</td> </tr> <tr> <td>Respiratory difficulty</td> <td>1 patient</td> <td>0 patients</td> </tr> <tr> <td>Pain during procedure</td> <td>0 patients</td> <td>1 patient (procedure terminated)</td> </tr> <tr> <td>Liver burn during procedure</td> <td>0 patients</td> <td>1 patient</td> </tr> </tbody> </table>		Cryotherapy	RFA	Death	0 patients	1 patient	Significant haemorrhage	1 patient cyroablation (transfusion needed)	0 patients	Ileus	0 patients	1 patient	Scarring with UPJ obstruction	0 patients	1 patient	Open conversion	1 patient	0 patients	Urine leakage	0 patient	1 patient	Minor complications:			Probe site pain or paraesthesia	10 patients	4 patients	Urinary tract infection	2 patients	0 patients	Pneumonia infection	1 patient	1 patient	Minor haemorrhage	1 patient	0 patients	Elevated serum creatinine	1 patient	1 patient	Wound infection	1 patient	0 patients	Respiratory difficulty	1 patient	0 patients	Pain during procedure	0 patients	1 patient (procedure terminated)	Liver burn during procedure	0 patients	1 patient	<p>Groups at medical centres throughout the US with reported experience in renal ablation were identified and invited to participate in the study – unclear how many centres refused.</p> <p>Includes both laparoscopic and percutaneous cryotherapy</p> <p>Case experience was divided into 3 groups: initial, immediate and latest.</p> <p>Mean experience at each centre was 68 cases (range 21 – 92)</p> <p>Text and table do not reconcile. Text states 20 complications due to cryotherapy – table lists 19 complications.</p> <p>Death was due to aspiration pneumonia in a patient with a history of COPD.</p> <p>Cryotherapy complications: 4 occurred after laparoscopic ablation 16 occurred after percutaneous ablation</p> <p>Complication rate decreased with experience with 16 (53.3%) complications occurring in the initial period – with all 5 major complications occurring in this time.</p> <p>Minor haematomas were not included in the complication rate.</p>
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Validity and generalisability of the studies

- There are a number of limitations in the studies in terms of how patients were selected and how outcomes were measured such as;
 - Some patients were selected only on the basis of imaging suggestive of malignancy. Pre-procedural biopsy was not undertaken and as such patients with benign lesions may have been treated with cryotherapy.
 - Conversely, in some patients preoperative biopsy was undertaken but the results were made available after treatment and showed that patients with benign lesions were given cryotherapy.
 - Imaging was also used in some of the studies as a surrogate of successful tumour destruction rather than in combination with planned postoperative biopsy.
- The studies also varied in the technique used (percutaneous or laparoscopic), and among laparoscopic procedures, in the approach used (transabdominal and retroperitoneal). There has been suggestion in the literature that percutaneous cryotherapy results in greater injury to adjacent structures than laparoscopic cryotherapy⁹
- Most of the studies included only patients with small renal tumours (less than 4cm) and some studies using a laparoscopic technique excluded those with centrally located tumours. It has been suggested that cryotherapy of centrally located tumours is more difficult¹⁰.
- In two of the studies^{6,8} the authors note that complications and recurrence rates may have been due to the experience of the operator.
- Long-term follow-up is also lacking. The longest reported mean follow-up is 3 years¹ and it is noted by the authors of this report that 5 year data is needed in order to make more definitive statements about recurrence rates.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Mr Gordon Muir, Mr Andrew Doble, Dr David Breen, Dr Tim Fotheringham, Dr Tze Min Wah

- Procedure is best suited to small renal cancers.
- In large renal cell carcinomas it is possible that treatment could trigger cryoshock syndrome causing multi-organ failure
- Long-term cure rate is still unclear due to the paucity of studies critically assessing histological results.
- Confirmation of tumour eradication requires partial nephrectomy after cryotherapy
- Training in cyroablative techniques is important

Issues for consideration by IPAC

The current title does not reflect the different techniques (laparoscopic or percutaneous) used in cryotherapy for renal cancer.

To date it would seem that the procedure has been used for patients who are considered poor candidates for surgery rather than as a primary treatment for renal cancer.

While the majority of published evidence relates to laparoscopic cryotherapy there is a number of small series evaluating percutaneous cryotherapy. Percutaneous cryotherapy is able to be performed under sedation on an outpatient basis and is advocated for posterior tumours or for patients with hereditary renal cancer⁹. Laparoscopic cryotherapy has the advantages of dual views of the lesion and allows mobilisation of the bowel, thereby reducing the risk of bowel injury¹¹.

In the last 12 months there has been a substantial number of abstracts published on cryotherapy for renal cancer. As such it is likely that in the next few years there will be significant increase in the published evidence base on this procedure.

References

- 1 Gill IS, Remer EM, Hasan WA et al. (2005) Renal cryoablation: outcome at 3 years. *Journal of Urology* 173: 1903-1907.
- 2 Desai MM, Aron M, and Gill IS. (2005) Laparoscopic partial nephrectomy versus laparoscopic cryoablation for the small renal tumor. *Urology*. Vol.66(5 SUPPL.) (pp 23-28), 2005. 23-28.
- 3 Lee DI, McGinnis DE, Feld R et al. (2003) Retroperitoneal laparoscopic cryoablation of small renal tumors: intermediate results. *Urology* 61: 83-88.
- 4 Nadler RB, Kim SC, Rubenstein JN et al. (2003) Laparoscopic renal cryosurgery: the Northwestern experience.[see comment]. *Journal of Urology* 170: t-5.
- 5 Cestari A, Guazzoni G, dell'Acqua V et al. (2004) Laparoscopic cryoablation of solid renal masses: intermediate term followup. *Journal of Urology* 172: t-70.
- 6 Silverman SG, Tuncali K, vanSonnenberg E et al. (2005) Renal tumors: MR imaging-guided percutaneous cryotherapy--initial experience in 23 patients. *Radiology* 236: 716-724.
- 7 Gupta A, Allaf ME, Kavoussi LR et al. (2006) Computerized tomography guided percutaneous renal cryoablation with the patient under conscious sedation: initial clinical experience. *Journal of Urology* 175: 447-452.
- 8 Johnson DB, Solomon SB, Su LM et al. (2004) Defining the complications of cryoablation and radio frequency ablation of small renal tumors: a multi-institutional review. *Journal of Urology* 172: 874-877.
- 9 Aron M and Gill IS. (2005) Renal tumor ablation. *Current Opinion in Urology*. Vol. 15(5) (pp 298-305), 2005. 298-305.
- 10 Pavlovich CP, Walther MM, Choyke PL et al. (2002) Percutaneous radio frequency ablation of small renal tumors: initial results.[comment]. *Journal of Urology* 167: 10-15.
- 11 Moinzadeh A, Spaliviero M, and Gill IS. (2005) Cryotherapy of renal masses: Intermediate-term follow-up. *Journal of Endourology*. Vol. 19(6) (pp 654-657), 2005. 654-657.

Appendix A: Additional papers on cryotherapy for renal cancer not included in summary Table 2

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 and does not include abstracts.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non inclusion in Table 2
Bachmann A, Sulser T, Jayet C et al. (2005) Retroperitoneoscopy-assisted cryoablation of renal tumors using multiple 1.5 mm ultrathin cryoprobes: a preliminary report. <i>European Urology</i> 47: 474-479	7 patients Mean MU=13.6 months	No recurrence during follow-up	Small study, lack of histology
Bolte SL, Ankem MK, Moon TD et al. (2006) Magnetic resonance imaging findings after laparoscopic renal cryoablation. <i>Urology</i> 67: 485-489.	33 patients All patients had at least 6 months FU	1 patient developed recurrence	Short-term follow-up, lack of histology
Colon I and Fuchs GJ. (2003) Early experience with laparoscopic cryoablation in patients with small renal tumors and severe comorbidities. <i>Journal of Endourology</i> 17: 415-423	8 patients FU: 5-16 months	No recurrences	Small study and on specific population (those with severe comorbidities)
Hruby G, Reisinger K, Venkatesh R et al. (2006) Comparison of laparoscopic partial nephrectomy and laparoscopic cryoablation for renal hilar tumors. <i>Urology</i> 67: 50-54.	23 patients Mean FU: 11.3 months	Comparative study: no recurrence and no complications	Lack of postoperatively histology, larger comparative study included in Table 1
Moon TD, Lee FT, Jr., Hedican SP et al. (2004) Laparoscopic cryoablation under sonographic guidance for the treatment of small renal tumors. <i>Journal of Endourology</i> 18: 436-440.	17 patients Mean FU=9.6 months	At end of FU there have been no recurrences	Outcomes assessment was based on imaging, small patient numbers and short-term FU
Rodriguez R, Chan DY, Bishoff JT et al. (2000) Renal ablative cryosurgery in selected patients with peripheral renal masses. <i>Urology</i> 55: 25-30.	7 patients Mean FU=14.2 months	No recurrences	Small study, lack of histology
Percutaneous or open cryotherapy studies			
Gore JL, Kim HL, and Schulam P. (2005) Initial experience with laparoscopically assisted percutaneous cryotherapy of renal tumors. <i>Journal of Endourology</i> 19: 480-483.	4 patients FU=8-17 months	One patient had a suspected recurrence and underwent RFA	Small study - percutaneous
Harada J, Dohi M, Mogami T et al. (2001) Initial experience of percutaneous renal cryosurgery under the guidance of a horizontal open MRI system. <i>Radiation Medicine</i> 19: 291-296.	4 patients FU= 6 weeks	No serious complications	Small study - percutaneous
Khorsandi M, Foy RC, Chong W et al. (2002) Preliminary experience with cryoablation of renal lesions smaller than 4 centimeters. <i>Journal of the American Osteopathic Association</i> 102: 277-281.	17 patients Mean FU=30 months	Reduction in the majority of lesion size.	Open cryotherapy

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non inclusion in Table 2
Shingleton WB and Sewell PE, Jr. (2001) Percutaneous renal tumor cryoablation with magnetic resonance imaging guidance.[see comment]. <i>Journal of Urology</i> 165: 773-776.	22 patients Mean FU=9.1 months	No evidence of recurrence during FU	Outcomes assessment was based on imaging, and short-term FU
Uchida M, Imaide Y, Sugimoto K et al. (136) Percutaneous cryosurgery for renal tumours. <i>British Journal of Urology</i> 75: 132-136.	2 patients FU 5, 10 months	Initial experience	Small study - percutaneous
Other publications from the Cleveland Clinic (Gill et al)			
Carvalho EF, Gill IS, Meraney AM et al. (2001) Laparoscopic renal cryoablation: impact on renal function and blood pressure. <i>Urology</i> 58: 357-361.	22 patients Mean FU = 20.6 months	Cryotherapy does not have a negative impact on renal function	Article about safety (renal function and blood pressure).
Chen RN, Novick AC, and Gill IS. (2000) Laparoscopic cryoablation of renal masses. <i>Urologic Clinics of North America</i> 27: 813-820.	35 patients Mean FU=11.2 months	No evidence of local recurrence was found during follow-up	More recent study included in Table 1
Gill IS, Novick AC, Meraney AM et al. (1-11-2000) Laparoscopic renal cryoablation in 32 patients. <i>Urology</i> 56: 748-753.	32 patients Mean FU = 16.2 months	No evidence of local recurrence was found during follow-up	More recent study included in Table 1
Gill IS, Novick AC, Soble JJ et al. (1998) Laparoscopic renal cryoablation: initial clinical series. <i>Urology</i> 52: 543-551.	10 patients Mean FU=5.5 months	No recurrences	More recent study included in Table 1
Remer EM, Weinberg EJ, Oto A et al. (2000) MR imaging of the kidneys after laparoscopic cryoablation. <i>AJR American</i> : 635-640.	21 patients 12 patients had 12 months FU	Cryolesion size decreased following cryotherapy	More recent study included in Table 1

Appendix B: Related published NICE guidance for cryotherapy for renal cancer

Guidance	Recommendation
Interventional Procedures	<p data-bbox="582 421 1273 450">Percutaneous radiofrequency ablation of renal cancer</p> <p data-bbox="497 483 738 512">1 Guidance</p> <p data-bbox="497 546 1353 801">1.1 Limited evidence suggests that percutaneous radiofrequency ablation (RFA) of renal cancer brings about reduction of tumour bulk and that the procedure is adequately safe. However, the evidence of its effect on symptom control and survival is not yet adequate to support the use of this procedure without special arrangements for consent and for audit or research.</p> <p data-bbox="497 853 1329 1061">1.2 Patient selection is important and the procedure should normally be limited to patients who are unsuitable for surgery. The procedure should only be offered after assessment by a specialist multidisciplinary team, which should include a urologist and an interventional radiologist.</p> <p data-bbox="497 1113 1350 1529">1.3 Clinicians wishing to undertake percutaneous radiofrequency ablation of renal cancer should take the following actions.</p> <ul data-bbox="596 1238 1342 1529" style="list-style-type: none"> <li data-bbox="596 1238 1342 1406">• Ensure that patients offered it understand the uncertainty about the procedure's efficacy and provide them with clear written information. Use of the Institute's <i>Information for the Public</i> is recommended. <li data-bbox="596 1458 1307 1529">• Audit and review clinical outcomes of all patients having radiofrequency ablation of renal cancer. <p data-bbox="497 1581 1342 1700">1.4 Controlled research into the long-term clinical outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence.</p> <p data-bbox="497 1751 715 1780">Other comments</p> <p data-bbox="497 1805 1318 1968">The lack of histology and limitations of CT assessment may make it difficult to determine whether total ablation of tumours has been achieved. In addition, little is known about the natural history of small renal tumours and the survival of patients with small tumours.</p>

	The site and size of the tumour seems to be important and results are likely to be better when treating smaller peripheral tumours.
Technology Appraisals	None applicable
Clinical Guidelines	None applicable
Public Health	None applicable

Appendix C: Literature search for cryotherapy for renal cancer

Overview appendix: search history

Databases	Version searched (if applicable)	Date searched
The Cochrane Library	2005 Issue 4	23/11/2005
CRD		23/11/2005
Embase	1980 to 2005 Week 47	23/11/2005
Medline	1966 to November Week 2 2005	22/11/2005
Premedline	November 22, 2005	23/11/2005
CINAHL	1982 to November Week 3 2005	23/11/2005
British Library Inside Conferences (limited to current year only)		23/11/2005
National Research Register	2005 Issue 5	23/11/2005
Controlled Trials Registry		23/11/2005

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

Search strategy used in Medline

1. cryosurgery/
2. cryotherapy/
3. cryoablat\$.tw.
4. cryosurg\$.tw.
5. cryotherap\$.tw.
6. or/1-5
7. carcinoma, renal cell/
8. kidney neoplasms/
9. renal.tw.
10. kidney\$.tw.
11. or/7-10
12. 6 and 11
13. animal/ not human/
14. 12 not 13

