NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of laparoscopic cryotherapy for renal cancer

Treating kidney tumours by keyhole surgery and freezing (cryotherapy)

Renal cancer occurs in the lining of the very small tubes in the kidney. Cryotherapy involves applying freezing temperatures to the tumour by inserting a surgical instrument (cryoprobe) through several small incisions in the abdomen ('keyhole' surgery), with the aid of an internal telescope and camera system (laparoscope). The aim is to destroy cancer cells.

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 December 2010.

Procedure name

- Laparoscopic cryotherapy for renal cancer

Specialty societies

- British Association of Urological Surgeons
- British Society of Interventional Radiology.

Description

Indications and current treatment

The most common type of renal cancer in adults is renal cell carcinoma. Symptoms and signs may include pain and haematuria. Some tumours are

identified asymptomatically, through imaging. Establishing diagnosis and assessing the prognosis of some renal tumours may be difficult.

Treatment options include laparoscopic (or open) partial or total nephrectomy, and ablation techniques including radiofrequency ablation (RFA).

What the procedure involves

Laparoscopic cryotherapy for renal cancer is carried out with the patient under general anaesthesia. A transperitoneal or retroperitoneal approach can be used. A biopsy of the tumour may be carried out. Under laparoscopic visualisation, a probe is inserted into the tumour to deliver a coolant at subfreezing temperatures, creating an ice ball around the probe's tip, which destroys the surrounding tissue. Each freeze cycle is followed by a heat (thaw) cycle, allowing removal of the probe. Two freeze–thaw cycles are usually performed to ablate the tumour (additional cycles may also be performed if necessary), with the aim of extending the ice ball approximately 1 cm beyond tumour margins. More than 1 probe can be used.

The maximum renal tumour size for which cryotherapy is recommended is approximately 4 cm (small, stage I tumours).

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to laparoscopic cryotherapy for renal cancer. Searches were conducted of the following databases, covering the period from their commencement to 2 June 2010: 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 a 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 renal cancer.
Intervention/test	Laparoscopic 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 approximately 2007 patients from 1 systematic review, 7 non-randomised comparative studies and 2 case reports.

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.

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

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Kunkle DA (2008)[1]

Meta-analysis (prospective and retrospective non-randomised comparative studies and case series)

USA

Search date: October 2007

Study population: patients with clinically localised, sporadic (non-hereditary) renal tumours

n = 1375 renal tumours (600 cryoablation vs 775 RFA) from 47 studies

Mean age (weighted by sample size): 67.2 years
Sex: not reported
Median tumour size: 2.6 cm

Study selection: meta-analysis was limited to series that analysed clinically localised (not further defined), sporadic renal tumours. Series that included only patients with hereditary or metastatic RCC were excluded.

Technique: cryoablation was performed surgically in 77% cases (12% open and 65% laparoscopic), and percutaneously in 23%. [Of RFA procedures, 94% were</td>
<td>Number of tumours analysed: 1375 (600 cryoablation vs 775 RFA)
Pre-ablation biopsy was available for 82% (494/600) of patients treated by cryoablation and 62% (482/775) of patients treated by RFA (p < 0.0001). Overall, 53.9% were confirmed RCC, 12.7% were confirmed benign, and 33.5% had unknown or indeterminate pathology.

The cryoablation procedures were predominantly surgical and RFA procedures were predominantly percutaneous (see ‘Technique’ under Study details column).

<table>
<tr><th></th><th>Cryoablation</th><th>RFA</th><th>p value</th></tr>
<tr><td>Repeat ablations</td><td>1.3% (8/600)</td><td>8.5% (66/775)</td><td>< 0.0001</td></tr>
<tr><td>Local tumour progression*</td><td>5.2% (31/600)</td><td>12.9% (100/775)</td><td>< 0.0001</td></tr>
<tr><td>Progression to metastatic disease</td><td>1.0% (6/600)</td><td>2.5% (19/775)</td><td>0.06</td></tr>
</table>
* defined as radiographic or pathological evidence of residual disease after initial treatment, at any follow-up time

91% (43/47) of studies were included in regression analysis:
Higher incidence of local tumour progression was found to be significantly associated with RFA treatment on univariate analysis (p = 0.001) and on multivariate regression analysis (p = 0.003).

Malignant pathology, unknown pathology, patient age, and tumour size were not associated with local recurrence in</td>
<td>No safety outcomes were reported.</td>
<td>Study population issues:
• An important problem is that preoperatively there were statistically significantly more lesions of both RCC and unknown or indeterminate pathology in the RFA group (90% vs 72% and 40% vs 25%).
• A second important problem with interpreting the comparative efficacy of the 2 procedures compared in this study is that the approach was usually surgical in the cryotherapy group, and percutaneous in the RFA group.
•
• No statistically significant differences were observed between</td>
</tr>
</table>

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

Study details	Key efficacy findings	Key safety findings	Comments
performed percutaneously and the other 6% laparoscopically.] **Mean follow-up: 18.7 months** Conflict of interest/source of funding: none declared	either univariate or multivariate analyses. No significant differences were observed with regard to the incidence of metastases, although p value bordered conventional significance levels.		the groups with regard to age, tumour size, or duration of follow-up. **Other issues:** • The authors note that the natural history of small renal tumours shows some variability (growth rates of 0.09 – 0.86 cm per year). The indolent nature of certain small renal masses must be considered when analysing the treatment efficacy of ablative technologies.

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Weight CJ (2008)[2]

Non-randomised comparative study
USA (Cleveland Clinic, Cleveland, OH)
Recruitment period: 2002–6
Study population: patients with small renal lesions
n = 264 (176 laparoscopic cryotherapy vs 88 percutaneous RFA); 301 lesions (192 vs 109)
Median age: 68 years
Sex: 68% vs 72% male
Mean tumour size: 2.5 vs 2.4 cm

Patient selection criteria: not reported

Technique: laparoscopic cryoablation under general anaesthesia vs percutaneous RFA with local anaesthetic and mild sedation

Follow-up: 6 months?

Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 264 (176 laparoscopic cryotherapy vs 88 percutaneous RFA); 301 lesions (192 vs 109)
Pretreatment biopsy was available for 100% (192/192) vs 90.8% (99/109) lesions: 55.2% (106/192) vs 55.6% (55/99) were malignant, 24.5% (47/192) vs 8.2% (9/109) were benign, and 20.3% (39/192) vs 35.4% (35/99) were indeterminate.

Radiographic success (at 6 months; defined as no evidence of central or nodular enhancement)
Available in 72.4% (139/192) vs 67.0% (73/109) of lesions
<table>
<tr><th>Laparoscopic cryotherapy</th><th>Percutaneous RFA</th><th>p value</th></tr>
<tr><td>90% (125/139)</td><td>84.9% (62/73)</td><td>0.6183</td></tr>
</table>
2 in each group had suspicion of cancer so had immediate radical nephrectomy without biopsy (RCC revealed in all 4).

Pathological success (at 6 months; defined as lack of malignant/atypical cells)
Available in 44.5% (134/301) of lesions (50.5% [97/192] vs 33.9% [37/109], p = 0.0054).
Reasons biopsy not completed include anticoagulation (n = 3 vs 25), loss to follow-up (n = 23 vs 9), solitary/remnant/chronic renal insufficiency (n = 38 vs 44), recurrence/metastatic disease (n = 11 vs 12), benign pretreatment biopsy (n = 41 vs 21) and death before 6 months (in 2 treated with RFA; cause of death not reported)
<table>
<tr><th>Laparoscopic cryotherapy</th><th>Percutaneous RFA</th><th>p value</th></tr>
</table>
</td>
<td>Not reported in study.</td>
<td>Follow-up issues:
Imaging at 3, 6, and 12 months and then annually.
At 6 months, loss to follow-up in significantly more patients treated with cryoablation (23 vs 9; p < 0.03; reasons not reported).
Study design issues:
Retrospective.
Purpose of study to test hypothesis that post-ablation kidney biopsy would confirm treatment success.
Biopsy taken with percutaneous kidney biopsy of ablation site.
Study population issues:
Tumours in RFA group were significantly more likely to be centrally located and have an indeterminate pretreatment biopsy</td>
</tr>
</table>

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

Study details	Key efficacy findings	Key safety findings	Comments
	93.8% (91/97)[a] | 64.9% (24/37)[b] | p < 0.0001 [a] 2 percutaneous RFA, 1 repeat cryoablation, 1 laparoscopic radical nephrectomy (showing RCC clear cell variant grade 3) (the other 2 not reported in the study); pretreatment biopsy in these patients was malignant in 1, favoured malignant in 2, and benign in 3. [b] 8 had retreatment (6 showing no further evidence and 2 having persistent thin rim of enhancement so are being followed up); 2 had serial imaging showing stable central enhancing lesions (other 3 not reported in the study); pretreatment biopsy in these patients was malignant in 8, favoured malignant in 4 and benign in 1. ***Combined radiographic and pathological success*** Laparoscopic cryotherapy | Percutaneous RFA | p value 88.6% (86/97) | 80.6% (29/36) | 0.2248		result. • Of patients not available for biopsy at 6 months, the cryotherapy group had significantly less because of solitary/remnant/chronic renal insufficiency and more because of a benign pretreatment biopsy.

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

Study details

Turna B (2009)[3]

Non-randomised comparative study

USA (Cleveland Clinic, Cleveland, Ohio)

Recruitment period: 1997–2006 (RFA from 2003)

Study population: patients with tumours in a solitary kidney

n = **101 (36 cryoablation vs 36 LPN vs 29 RFA)**

Mean age: 64.1 vs 60.3 vs 60.7 years
Sex: 64% vs 58% vs 62% male
Tumour size: 2.5 vs 3.7 vs 2.6 cm

Patient selection criteria: localised tumours less than 4 cm in select patients with tumours in a solitary kidney and with significant comorbidities.

Technique: cryoablation (33 laparoscopic, 3 percutaneous) and LPN using general anaesthetic; RFA (using sedoanalgesia on an outpatient basis).

Maximum follow-up: **84 vs 81 vs 44 months**

Conflict of interest/source of funding: 1 author was reported to have a financial interest and/or other relationship with Intuitive Surgical.

Key efficacy findings

Number of patients analysed: **101 (36 cryoablation vs 36 LPN vs 29 RFA)**

Biopsy results on final histopathology

Biopsy results	Cryoablation*	LPN	RFA
RCC	73.3% (22/30)	63.9% (23/36)	82.8% (24/29)
Benign	26.7% (8/30)	36.1% (13/36)	17.2% (5/29)
Positive surgical margins	n/a	5.6% (2/36)**	n/a

* preoperative data not available for 6 patients treated with cryoablation
** 1 underwent nephrectomy

Recurrence (at median 24 vs 42.5 vs 14 months)

	Cryoablation	LPN	RFA
Local recurrence (persistent enhancement or growth on radiography or positive biopsy)	16.7% (6/36)*	0	44.8% (13/29) **
Distant	8.3% (3/36)	0	13.8% (4/29)

(% calculated by analyst)
*1 had repeat cryotherapy, 1 RFA and 1 OPN and 3 are being observed with radiography; 3 had metastatic disease 3, 6, and 12 months after treatment, respectively
**2 of 13 had no abnormalities on radiography but biopsy at 6 months showed RCC (subsequent treatment not reported in these 2); 7 underwent RFA, 2 cryotherapy (1 with additional

Key safety findings

Complications

	Cryoablation	LPN	RFA
Intraoperative adverse events	2.8% (1/36)	13.9% (5/36)	0
Postoperative complications*	13.8% (5/36)	58.3% (21/36)	6.7% (2/29)
- non-urological	3	9	1
- urological	2	12	1

*% calculated by analyst

Cryoablation

Event	# of patients
Pleural injury (intraoperative)	1
Postoperative	
Anuria	2
Urine leak, haemothorax, atelactasis	1 each

LPN

Event	# of patients
Intraoperative	
Ureteral injury	1
Haemorrhage*	2
Open conversion	2
Postoperative	
Urine leak	

Comments

Follow-up issues:

- MRI every 3 months and then every year
- 6-month postoperative biopsy was not done in 10 with cryoablation and 13 with RFA

Study design issues:

- Of 1019 patients treated with nephron sparing surgery at centre, patients were included in study from prospective database if treatment in only 1 kidney. A significantly larger proportion of patients were treated for 1 kidney only with RFA more patients
- Choice of surgery at discretion of surgeon (RFA used if patient at risk with general anaesthesia).

Study population

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

Study details

Key efficacy findings

sunitinib), 1 radiotherapy to brain and liver ablation, and 1 was observed with radiography; 4 had metastatic disease 6, 20, 23 and 28 months after treatment

Death (at median 24, 42.5, and 14 months)

	Cryoablation	**LPN**	**RFA**
From RCC	8.3% (3/36)	0% (0/36)	10.3% (3/29)
Other cause	2.8% (1/36)	8.3% (3/36)	3.4% (1/29)

2-year survival

	Cryoablation	**LPN**	**RFA**
Cancer specific	88.5 (95% CI 82.2–94.8)	100*	83.9 (95% CI 73.5–94.4)
Overall	88.5 (95% CI 82.2–94.8)	91.2 (95% CI 82.4–98.6)	83.9 (95% CI 73.5–94.4)
Disease free	69.6 (95% CI 61.0–78.3)	100*	33.2 (95% CI 22.3–44.0)

*confidence intervals not reported

Key safety findings

Postoperative haemorrhage	3
Acute renal failure	3
Atrial fibrillation	3
Pneumonia	2
Pulmonary embolus, deep vein thrombosis, sepsis, peritonitis, congestive heart failure, wound infection, epididymitis	1 patient each

*1 underwent nephrectomy

RFA (postoperative only)

Event	# of patients
Haemorrhage	1
Blood transfusion	1

Renal function

Estimated glomerular filtration rate*	**Cryoablation**	**LPN**	**RFA**
Increased	11.1% (4/36)	5.6% (2/36)	13.8% (4/29)
Unchanged	13.9% (5/36)	8.3% (3/36)	17.2% (5/29)
Decreased	75% (27/36)	86.1% (31/36)	68.9% (20/29)

*included 2 patients on permanent dialysis; 20% decrease was considered significant; p = 0.5805

Number on haemodialysis	**Cryoablation**	**LPN**	**RFA**
Temporary	0	3	0
Permanent	0	2	0

(p = 0.0613 between LPN and cryoablation or RFA)

Comments

issues:

- Patients with LPN were of significantly greater tumour size and RFA were posterior or lateral position tumours.
- Unless in the case of patients with a solitary kidney, or with bilateral tumours, renal function outcomes may be indicators of procedural safety, in patients with unilateral tumours and adequate renal function in the opposite kidney.

Other design issues:

- The study does not report if preoperative biopsy was performed.

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Bandi G (2008)[4]

Non-randomised comparative study
(some patients included in Kunkle review from earlier publication)
USA
Recruitment period: 2000–6
Study population: patients with small renal masses
n = 93 (103 small renal masses) (59 laparoscopic cryotherapy vs 20 percutaneous cryotherapy vs 15 percutaneous RFA)
Mean age: 66 years
Sex (ratio of men to women): 1.32:1 vs 4:1 vs 2.8:1
Mean diameter of mass: 2.6 cm in laparoscopic cryotherapy, 2.2 cm in both percutaneous cryotherapy and RFA
Patient selection criteria: not stipulated in paper
Technique: laparoscopic and percutaneous cryoablation under general anaesthesia; postoperative analgesia (RFA not described)

Follow-up: 22 months (laparoscopic cryotherapy) vs 12 months (percutaneous cryotherapy) vs 15 months (percutaneous RFA)

Conflict of interest/source of funding: not</td>
<td>Number of patients analysed: 93 (59 laparoscopic cryotherapy vs 20 percutaneous cryotherapy vs 15 RFA)
Technical success
Persistently enhancing lesions at early follow-up suggesting incomplete ablation: 3.6% (2/56) of patients who had laparoscopic cryoablation and 10% (2/20) with percutaneous cryoablation and (percentages calculated by analyst). Patients with persistent enhancement were treated with percutaneous ablation (n = 3; type of ablation not specified) or radical nephrectomy (n = 1) with no recurrences at the last follow-up.
Laparoscopic cryotherapy used significantly more probes per lesion (mean 1.5 vs 1.1, p = 0.04) and had a longer mean anaesthesia time (mean 247 vs 148 minutes; p < 0.001) compared with percutaneous cryotherapy.

Recurrence
At mean follow-up of 22 (laparoscopic cryotherapy), 12 (percutaneous cryotherapy) and 15 months (percutaneous RFA) only 1 patient with laparoscopic ablation had evidence of local recurrence at the site of ablation.

Survival
7 treated with laparoscopic cryotherapy and 2 patients treated with percutaneous cryotherapy died of unrelated causes during follow-up.

Patient-reported outcomes
In a telephone survey, the following was reported:
<table>
<tr><th></th><th>Laparoscopic cryoth</th><th>Percutaneous cryother</th><th>Percutaneous</th></tr>
</table>
</td>
<td>Complications
There was no difference in intraoperative (p = 0.25) or preoperative complications (p = 0.56) between groups. (Time of occurrence and details of how complications and/or subsequent sequelae were treated are given where reported in the study)

Laparoscopic cryoablation
<table>
<tr><th>Event</th><th># of patients</th></tr>
<tr><td>Intraoperative</td><td></td></tr>
<tr><td>Significant bleeding managed with haemostatic agents and observation</td><td>1</td></tr>
<tr><td>Bowel injury repaired laparoscopically</td><td>1</td></tr>
<tr><td>Postoperative</td><td></td></tr>
<tr><td>Atrial fibrillation</td><td>1</td></tr>
<tr><td>Narcotic overdose necessitating longer hospitalisation</td><td>1</td></tr>
<tr><td>Respiratory failure</td><td>1</td></tr>
<tr><td>Symptomatic perirenal haematoma</td><td>1</td></tr>
<tr><td>Symptomatic haematoma treated with nephrectomy at another institution</td><td>1</td></tr>
</table>
Percutaneous cryoablation
<table>
<tr><th>Event</th><th># of patients</th></tr>
<tr><td>Urine leak</td><td>1</td></tr>
<tr><td>Haematoma detected intraoperatively</td><td>1</td></tr>
<tr><td>Significant postoperative prolonged neurapraxia</td><td>2</td></tr>
</table>
</td>
<td>Follow-up issues:
• At time of survey, 9 had died of unrelated causes (2 percutaneous, 7 laparoscopic cryotherapy) and 11 were not contactable.
Study design issues:
• 2 institutions.
• Retrospective for convalescence data.
• Telephone survey for patient satisfaction data (at mean 15 vs 28 vs 20 months after procedure); 79% response rate.
• Selection for percutaneous or laparoscopic ablation based on preoperative imaging showing amenable position (for example, whether it is posterolateral). Selection between ablation types not clear from the study.
• Methods used to recruit patients not</td>
</tr>
</table>

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

Study details	Key efficacy findings	Key safety findings	Comments

reported

	erapy	apy	RFA
Return to nonstrenuous activity (days)	8.1	3.1[a]	2.9[b]
Return to strenuous activity (days)	22.1	16.2	10.5[b]
Return to complete recovery (days)	27.5	13.5[a]	18.0
Return to work (days)	17.5	6.2	4.0[b]
Mean patient satisfaction (0–5 scale)	4.9	4.8	4.8
Would recommend to others (%)	100	95	100

[a] $p < 0.05$ pair-wise comparison between laparoscopic cryoablation and percutaneous cryoablation

[b] $p < 0.05$ pair-wise comparison between laparoscopic cryoablation and percutaneous radiofrequency ablation

Percutaneous RFA

Event	# of patients
Haematoma identified intraoperatively	1
Large retroperitoneal haematoma requiring blood transfusion	1
Significant postoperative prolonged neurapraxia	2

described.

- Few details provided about the questions asked in the telephone survey, such as whether family members were used as a proxy.

Study population issues:

- No significant difference in age, mean BMI, median ASA scores between groups.
- Mean diameter of mass was significantly larger in laparoscopic group ($p = 0.027$ for difference with percutaneous cryotherapy and $p = 0.05$ with percutaneous RFA).

Other design issues:

- The study reports no difference in preoperative biopsy rates between groups but does not report results of the biopsy.

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Lin YC (2008)[5]

Non-randomised comparative study
USA (Cleveland Clinic, Cleveland, Ohio)
Recruitment period: 1998–2006
Study population: patients renal tumours and concomitant major abdominal aortic or vena caval pathology
n = 66 (29 laparoscopic cryoablation vs 20 LRN vs 17 LPN)
Median age: 70
Sex: 91% male
Concomitant pathology: abdominal aortic disease (n = 54), vena caval disease (n = 9) or both (n = 3)
Median tumour size: 3.3 cm

Patient selection criteria: not reported

Technique: laparoscopic renal surgery (laparoscopic cryotherapy, LPN or LRN)

Maximum follow-up: 98.5 months

Conflict of interest/source of funding: 1 author has a financial and/or other relationship with Pfizer</td>
<td>Number of patients analysed: 66 (29 cryoablation vs 20 radical nephrectomy vs 17 partial nephrectomy)

Results of histopathology
RCC was confirmed in 72.7% (48/66) of patients

Survival (median 48.5 months)
<table><tr><td>Overall survival</td><td>92.1%</td></tr><tr><td>Cancer specific survival</td><td>96.1%</td></tr><tr><td>In patients with benign tumours</td><td>100%</td></tr></table>(absolute figures not reported)
Hospital stay
<table><tr><th></th><th>Cryoablation</th><th>LPN</th><th>LRN</th></tr><tr><td>Median hours of hospital stay</td><td>42.5</td><td>74.5</td><td>78.0</td></tr></table>Estimated blood loss
<table><tr><th></th><th>Cryoablation</th><th>LPN</th><th>LRN</th></tr><tr><td>Median blood loss (cc)</td><td>100</td><td>150</td><td>200</td></tr></table>There was a statistically significant difference in the log of estimated blood loss using the transperitoneal approach, between laparoscopic cryoablation and LPN (p = 0.0092), between cryotherapy and LRN (p < 0.0001) and between LRP and LPN (p = 0.011) (estimated blood loss for patients treated with transperitoneal approach not reported).</td>
<td>Complications
<table><tr><th></th><th>Cryotherapy</th><th>LPN</th><th>LRN</th></tr><tr><td>Intraoperative complications requiring conversion to open surgery*</td><td>1</td><td>1</td><td>1</td></tr><tr><td>Postoperative complications managed conservatively** *</td><td>3</td><td>3</td><td>3</td></tr></table>* these included splenic haemorrhage, mesenteric artery haemorrhage and inability to progress due to retroperitoneal scarring (not clear which patients had respective complications). Also, there appears to be an error in the study as the text describes 3 intraoperative complications resulting in open conversion, however, the table only reports 2 complications in patients treated by LPN and LRN. Since the table reports that 1 in each group had conversion to open surgery, it was assumed this additional patient with intraoperative complication was in laparoscopic cryotherapy group).
** ileus in 3, surgical site haematoma in 2, scrotal haematoma, myocardial infarction, deep vein thrombosis, and pneumonia in 1 each (not clear which patients had respective complications); the patient with pneumonia died of pulmonary sepsis</td>
<td>Follow-up issues:
• Not reported.

Study design issues:
• Retrospective.
• Of 1826 laparoscopic renal procedures performed for tumour.
• All patients had computerised spiral tomography before surgery.

Study population issues:
• 27 patients had prior vascular interventions (median 5.5 years prior): 10 AAA repair, 3 open aortic transection, 2 endovascular aortic stent insertion, 10 vena caval filter placement, 2 both open AAA repair and vena caval placement.
• 87.8% (58/66) were on anticoagulant therapy which was</td>
</tr>
</table>

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

Study details	Key efficacy findings	Key safety findings	Comments
			stopped for 7 days before and 7 days after surgery. **Other issues**: • This paper demonstrates that laparoscopic total or partial nephrectomy, or laparoscopic cryoablation are feasible treatment options for patients suffering from renal tumours and concomitant major vascular pathology (such as abdominal aortic aneurysm or inferior vena cava filters for prevention of thromboembolism). The authors argue that these major vascular conditions affect 'surgical anatomy'. About half of all patients were treated by cryotherapy. • The study does not report if preoperative biopsy was performed.

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

Study details	Key efficacy findings	Key safety findings	Comments
Ko YH (2008)[6] **Matched cohort** Korea Recruitment period: 2004–7 Study population: patients with pathologically confirmed RCC with tumour size less than 4 cm n = **40 (20 laparoscopic cryoablation vs 20 OPN)** Mean age: 56.3 vs 57.3 years Sex: 70% vs 75% male Mean tumour size: 2.4 vs 2.2 cm Patient selection criteria: confirmed RCC, tumour less than 4 cm the indication was solitary kidney in 5 vs 2 patients, bilateral tumour in 1 vs 0, renal insufficiency in 2 vs 3 and elective in 12 vs 15. Technique: laparoscopic cryotherapy with general anaesthesia with cryoprobes (IceRod, Oncura, Plymouth Meeting, PA) Mean follow-up: **27.3 vs 28.7 months** Conflict of interest/source of funding: not reported	Number of patients analysed: **40 (20 laparoscopic cryoablation vs 20 OPN)** ***Local recurrence or metastases*** All patients remained disease-free with no evidence of local recurrence or metastases in the follow-up period. ***Hospital stay*** **Laparoscopic cryoablation** | **LPN** Days of hospital stay | 4.21 ± 1.5 | 8.2 ±1.14* * p = 0.004	***Complications*** **Laparoscopic cryoablation** | **OPN** Blood transfusions | 10% (2/20)* | 40% (8/20)** Perirenal haematoma | 0 | 0.5% (1/20) Urine leakage | 0 | 0.5% (1/20) Subcutaneous emphysema successfully treated conservatively | 10% (2/20) | 0 Neuropathic pain requiring prolonged pain management for 6 weeks | 0 | 0.5% (1/20) *1 had preoperatively pernicious anaemia from a previous gastrectomy for stomach cancer and the other had subcutaneous haematoma because of bleeding at trocar site ** p = 0.03	**Follow-up issues**: • At 1 month and then every 3 months in 1st year, every 6 months in the 2nd and then annually. **Study design issues**: • 35 patients treated with laparoscopic cryotherapy but only the 20 with confirmed RCC and tumours less than 4 cm were included. • Matched patients were selected from a database of 72 patients who had OPN during the same period based on preoperative characteristics.

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

Study details

O'Malley RL (2006)[7]

Matched cohort

USA (NY)

Recruitment period: 2003–5 (2002–5 for LPN)

Study population: elderly patients with renal mass and known comorbidities.

n = **30 (15 laparoscopic cryotherapy vs 15 LPN)**

Mean age: 76.1 vs 75.7 years
Sex: 57% vs 79% male

Patient selection criteria: not reported

Technique: laparoscopic cryotherapy and LPN

Mean follow-up: **9.8 vs 11.9 months**

Conflict of interest/source of funding: none declared.

Key efficacy findings

Number of patients analysed: **30 (15 laparoscopic cryotherapy vs 15 LPN)**

Recurrences
There were no recurrences detected in either group during the follow-up period.

Hospital stay

	Laparoscopic cryoablation	**LPN**
Operative duration (minutes)	152.2	248.4*
Days of hospital stay	3.3	4.4**

* $p < 0.001$
** $p = 0.412$

Key safety findings

Complications

	Laparoscopic cryoablation	**LPN**
Major		
Pneumonia	1	0
Myocardial infarction	1	0
Myocardial infarction and deep vein thrombosis	0	1*
Minor		
Gout	1	0
Hyponatraemia with confusion	1	0
Transfusion thought to be from a self-contained perirenal haematoma	0	1
Conversion of LPN to laparoscopic radical nephrectomy	0	1

*this patient required conversion to open surgery

Comments

Follow-up issues:

- At 3, 5, 12 and 18 months.

Study design issues:

- Retrospective from patients' charts.
- Matched patients were selected from a pre-existing database of 104 patients who had LPN based on patient age and tumour size.

Other design issues:

- The study does not report if preoperative biopsy was performed.

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Nguyen CT (2008)[8]

Non-randomised comparative study
USA (Cleveland Clinic)
Recruitment period: 1997–2006
Study population: patients with ipsilateral recurrence after cryoablation or RFA
n = 36 (14 cryoablation vs 22 RFA)(16 vs 26 recurrences)
Mean age: 70 vs 68 years
Sex: 73% male
Size of tumour: 2.9 vs 3 cm
Patient selection criteria:
Indications for surgical salvage: persistent enhancement of ablated tumour on radiographic imaging (4), recurrent enhancement of imaging (2), radiographic increase in size of ablated tumour (2), needle biopsy diagnosis of recurrent cancer (3), development of renal vein thrombus (2) or development of retroperitoneal lymphadenopathy (1).

Technique: cryoablation performed laparoscopic in all but 1 (done surgically); percutaneous RFA.

Follow-up: not reported

Conflict of interest/source of funding: 1 author has a financial and/or other</td>
<td>Number of patients analysed: 36 (14 cryoablation vs 22 RFA)(16 vs 26 recurrences)
Recurrence rates at the centre were 7.4% (13/175) after cryoablation and 25% (26/104) after RFA. (this study includes 3 cases of recurrence after cryoablation in patients treated elsewhere)
<table>
<tr><th>Salvage treatment</th><th>Post- laparoscopic cryoablation (n = 26)</th><th>Post- RFA (n = 16)</th></tr>
<tr><td>RFA</td><td>6</td><td>16</td></tr>
<tr><td>Cryoablation</td><td>3</td><td>1</td></tr>
<tr><td>ORN</td><td>1[a]</td><td>2</td></tr>
<tr><td>LRN</td><td>3[b]</td><td>1[c]</td></tr>
<tr><td>OPN</td><td>3[d]</td><td>1[e]</td></tr>
<tr><td>Immunotherapy</td><td>0</td><td>1[f]</td></tr>
<tr><td>Observation</td><td>0</td><td>1[g]</td></tr>
</table>
[a] converted from attempted OPN
[b] 1 patient had residual tumour so adherent that a 1 cm section of adjacent liver was excised with specimen
[c] patient had exhibited residual tumour within ablated site and had developed renal vein thrombosis at follow-up
[d] only 1 completed, 1 aborted because of excessive fibrosis and scar tissue from previous cryoablation and 1 converted to radical because of excessive perinephric scarring
[e] patient had existing ureteropelvic junction obstruction of contralateral kidney and mild compromise of renal function on the same side
[f] because of multifocal recurrent disease with vascular involvement in solitary kidney and distant metastatic disease in lungs and pancreas
[g] with significant comorbidities including atrial fibrillation on anticoagulation, severe coronary atherosclerotic disease and</td>
<td>Complications
Intraoperative complications occurred more frequently in post-cryoablation surgical procedures than RFA.
<table>
<tr><th></th><th>Post - laparoscopic cryoablation</th><th>Post-RFA</th></tr>
<tr><td>Intraoperative (major)</td><td></td><td></td></tr>
<tr><td>Renal artery injury</td><td>1</td><td>0</td></tr>
<tr><td>Intraoperative (minor)*</td><td></td><td></td></tr>
<tr><td>Diaphragmatic injury</td><td>1</td><td>0</td></tr>
<tr><td>Pleurotomy requiring chest tube</td><td>1</td><td>0</td></tr>
<tr><td>Peritoneotomy</td><td>3</td><td>0</td></tr>
<tr><td>Postoperative</td><td></td><td></td></tr>
<tr><td>Urine leak**</td><td>1</td><td>0</td></tr>
<tr><td>Anephric state requiring haemodialysis***</td><td>1</td><td>0</td></tr>
</table>
*all occurred in patients with OPN
**occurred in patient treated with OPN
***in a patient with removal of a solitary kidney prompted by hostile surgical findings
(no more details of complications provided in study)</td>
<td>Follow-up issues:
1 in cryotherapy group and 3 in RFA group were lost to follow-up.
Study design issues:
Retrospective review of records of those treated for recurrence at Cleveland Clinic.
Purpose to examine potential use of ablation as a ‘salvage’ (i.e. recurrent) treatment, and also whether initial management with ablation makes ‘salvage surgery’ (to manage local recurrence) more difficult because of fibrosis.
Recurrence in the ablated tumour bed and at other sites in the kidney was considered recurrence.</td>
</tr>
</table>

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
relationship with Endocare, another with Hansen and another with Pfizer, Novartis and Sanofi-Aventis.	prostate cancer with in situ RCC recurrence ***Final pathological data (only available in 9 patients who had salvage surgery)*** clear cell RCC in 5, papillary RCC in 1, mucinous tubular-spindle cell carcinoma in 1, cystic chromophil RCC in 1, and no viable cancer in 1 All but 1 with a positive renal vascular margin had negative margins. (mean tumour size was 3.56 cm and histological necrosis was present in 70% of cases)		

Abbreviations used: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radial nephrectomy; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation

Study details	Key efficacy findings	Key safety findings	Comments
Lane BR (2005)[9] **Case report of safety** USA (Cleveland Clinic) n = **1** Technique: laparoscopic cryoablation Conflict of interest/source of funding: not reported	A 67-year-old man with a solitary left kidney with a history of right nephrectomy 35 years prior to treatment, long-standing hypertension and chronic renal insufficiency was treated with laparoscopic cryoablation of 2 enhancing left renal masses. Postoperatively, there was a complication of **large blood clot in renal collecting system causing acute obstruction and anuria**. This was treated successfully with a temporary ureteral stent. There was no enhancement of the renal tumour and no additional lesions on MRI at 3 months follow-up.		
Chen VH (2008)[10] **Case report of safety** USA n = **1** Technique: laparoscopic cryoablation Conflict of interest/source of funding: 1 author is a research consultatnt to Galil Medical	63-year-old morbidly obese man with coronary artery disease with a history of right radial nephrectomy 5 years prior, and radical retropubic prostatectomy and ventral hernia repair 5 weeks prior. Patient had laparoscopic cryoablation of enhancing tumour deep in posterior aspect of left kidney which was biopsy-confirmed to be clear cell RCC. Approximately 3 months after the procedure, the patient presented with left flank pain and fever. MRI showed **an obstructed kidney and retrograde ureteropyelography showed a partial urothelial slough in the renal pelvis**. The patient was treated with ureteroscopic slough removal (shown to be necrotic tissue without malignancy) and a temporary stent placement. The patient was then clinical asymptomatic.		
Instances of **haemorrhage requiring transfusion** reported in additional studies Non-randomised comparative studies: - Finley DS (2008)[11], n = 37 (18 percutaneous vs 19 laparoscopic cryotherapy) - Malcolm JB (2009)[12], n = 66 (46 percutaneous vs 20 laparoscopic cryotherapy) Case series: - Bourne AE (2009)[13], n = 123 - Ham BK (2010)[14], n = 37	Some instances of **haemorrhage requiring transfusion** reported in additional studies: Finley DS (2008): 26.3% (5/19 of patients treated with laparoscopic cryotherapy and 11.1% (2/18) treated with percutaneous cryotherapy Malcolm JB (2009): 10% (2/20) treated with laparoscopic cryotherapy (none treated with percutaneous cryotherapy) Bourne AE (2009): 2.4% (3/123) Ham BK (2010): 10.8% (4/37) - 1 of 4 tumours greater than 4 cm and 3 of 10 with tumours between 3 and 4 cm		

Efficacy

Completeness of ablation/recurrence/disease progression

A systematic review reported that repeat ablations were required in significantly fewer patients treated with cryotherapy than radiofrequency ablation (RFA) (1% [8/600] vs 8% [66/775], $p < 0.0001$)[1]. The review reported that significantly less patients treated with cryotherapy had local tumour progression (defined as radiographic or pathological evidence of residual disease after initial treatment, regardless of time to recurrence) than those treated with RFA over a mean follow-up of 18.7 months (5% [31/600] vs 12% [100/775], $p < 0.0001$). Less patients treated with cryotherapy had progression to metastatic disease but this was not significant (1.0% [6/600] vs 2.5% [19/775], $p = 0.06$)[1].

In a non-randomised comparative study of 264 patients with 6-month radiographic results in 72% (139/192) of lesions treated with laparoscopic cryotherapy and 67% (73/109) of lesions treated with percutaneous RFA, radiographic success (no evidence of central or nodular enhancement) was reported in 90% (125/139) and 85% (62/73) of lesions ($p = 0.6183$)[2].

In the same study, biopsy was undertaken in 45% (134/301) of lesions at 6 months (51% [97/192] vs 34% [37/109], $p = 0.0054$) revealing no malignancy or atypical cells in 94% (91/97) and 65% (24/37) of lesions, respectively ($p < 0.0001$)[2].

A non-randomised comparative study of 101 patients treated with cryoablation (n = 36), laparoscopic partial nephrectomy (LPN) (n = 36) or percutaneous RFA (n = 29) reported local recurrence on radiography and/or biopsy in 17% (6/36) treated with cryoablation (most laparoscopic except 1 surgical), none treated with LPN, and 45% (13/29) treated with RFA at median 24, 43 and 14 months follow-up, respectively[3].

A non-randomised comparative study of 93 patients comparing patients treated with laparoscopic cryoablation, percutaneous cryoablation, and percutaneous RFA reported that 4% (2/56) of patients treated with laparoscopic cryotherapy and 10% (2/20) of patients who had percutaneous cryoablation had persistently enhancing lesions at early follow-up, suggesting incomplete ablation which required further treatment (3 percutaneous cryotherapy or 1 radical nephrectomy). These patients had no recurrences at the last follow-up[4].

The same study reported that over mean follow-up periods of 12, 22 and 15 months, respectively, there was only 1 patient with a local recurrence at the laparoscopic cryoablation site, which was subsequently treated with laparoscopic cryoablation[4].

A matched cohort of 20 patients treated with laparoscopic cryoablation comparing 20 treated with open partial nephrectomy, reported that all patients

remained disease-free with no evidence of local recurrence or metastases during a mean follow-up of 27 and 29 months, respectively[6].

A matched cohort of 15 patients treated with laparoscopic cryotherapy compared with 15 treated with laparoscopic partial nephrectomy reported no recurrences over a mean follow-up of 10 and 12 months, respectively[7].

A study which retrospectively analysed records of patients with ipsilateral recurrence after cryoablation or RFA reported recurrence rates of 7% (13/175) after cryoablation and 25% (26/104) after RFA at the centre[8].

Patient-reported outcomes/quality of life

The non-randomised comparative study of 93 patients reported results from a telephone survey with a 79% response rate. Patients returned to non-strenuous activity within 8, 3 and 3 days when treated with laparoscopic cryoablation, percutaneous cryoablation, and percutaneous RFA, respectively (this was significantly shorter for percutaneous procedures compared to laparoscopic cryotherapy; $p < 0.05$ for both). Return to strenuous activity occurred within 22, 16 and 10 days, but only the difference between percutaneous RFA and laparoscopic cryotherapy was significant ($p < 0.05$). Complete recovery occurred within 28, 14 and 18 days in these groups (percutaneous cryotherapy was significantly less than the laparoscopic procedure; $p < 0.05$). Return to work occurred within 18, 6 and 4 days but only the difference between percutaneous RFA and laparoscopic cryotherapy was significant ($p < 0.05$). Patient satisfaction and the rates of whether the patients would recommend the procedure to others were not significantly different between the groups[4].

Survival

The non-randomised study of 101 patients reported cancer-specific survival to be 89% (95% confidence interval [CI] 82–95), 100%, and 84% (95% CI 74–94) in the 30, 36 and 29 patients treated with cryoablation, LPN and RFA, respectively at 2 years[3].

The non-randomised comparative study of 93 patients reported no disease related deaths in either those treated with laparoscopic cryotherapy or percutaneous cryotherapy over 22 months and 12 months follow-up, respectively[4].

The non-randomised study of 66 patients reported cancer-specific survival in patients treated by any treatment to be 96.1% in a median follow-up of 48.5 months (absolute figures not reported) [5].

Safety

Overall comparison of complications

The non-randomised study of 101 patients reported intraoperative complications occurred in 3% (1/36) of patients treated with cryotherapy and 14% (5/36) treated with LPN and postoperative complications occurred in 14% (5/36) treated with cryotherapy, 58% (21/36) treated with LPN and 7% (2/29) treated with RFA[3].

The non-randomised comparative study of 93 patients reported no difference in intraoperative ($p = 0.25$) and postoperative ($p = 0.56$) complications between those treated with percutaneous cryotherapy, laparoscopic cryotherapy and percutaneous RFA[4].

Specific complications

The non-randomised study of 101 patients reported that the intraoperative complication which occurred in the cryotherapy group was pleural injury in 1 patient. Postoperative complications in this group included anuria in 2 patients and urine leak, haemothorax, and atelectasis in 1 patient each (no more details provided)[3].

The non-randomised comparative study of 93 patients that intraoperative complications occurring in those treated with laparoscopic cryotherapy included significant bleeding managed with haemostatic agents and then observation 1 patient and bowel injury repaired laparoscopically in another patient. Postoperative complications in patients treated with laparoscopic cryotherapy included atrial fibrillation and respiratory failure in 1 patient each, and symptomatic perirenal haematoma in 2 patients (1 required treatment with nephrectomy at another institution)[4].

A non-randomised controlled study of 66 patients comparing 29 patients treated with laparoscopic cryoablation, 20 (laparoscopic radial nephrectomy) LRN and 17 LPN reported that 1 patient in each group had intraoperative complications requiring conversion to open surgery for reasons including splenic haemorrhage, mesenteric artery haemorrhage and the inability to progress due to retroperitoneal scarring (not clear in which treatment group each event occurred in)[5].

The same study reported postoperative complications in 3 patients in each treatment group (ileus in 3, surgical site haematoma in 2, scrotal haematoma, myocardial infarction, deep vein thrombosis and pneumonia causing death in 1 each; again, it is not clear in which treatment group each of these events occurred)[5].

The matched cohort of 40 patients reported that there were significantly more blood transfusions required in patients treated with open partial nephrectomy (40% [8/20]) than those treated with laparoscopic cryoablation (10% [2/20];

p = 0.03). The same study reported 10% (2/20) of patients treated with laparoscopic cryotherapy had subcutaneous emphysema, which was successfully treated conservatively[6].

The matched cohort of 30 patients reported major complications in 2 patients treated with laparoscopic cryoablation (pneumonia and myocardial infarction) and 1 patient treated with LPN (myocardial infarction and deep vein thrombosis requiring conversion to open surgery)[7].

The same study reported that gout and hyponatraemia with confusion occurred each in 1 patient among those treated with laparoscopic cryoablation.

A case reported that 1 patient with a history of right nephrectomy 35 years earlier, long-standing hypertension and chronic renal insufficiency was treated with laparoscopic cryoablation of 2 enhancing left renal masses. Postoperatively, a large blood clot developed in the renal collecting system causing acute obstruction and anuria which was successfully treated with a temporary ureteral stent[9].

Another case report of a patient with a history of coronary artery disease and a right radical nephrectomy 5 years prior who was treated with laparoscopic cryotherapy in the left kidney presented with left flank pain and fever caused by a kidney obstructed with a partial urothelial slough 3 months after the procedure. The patient was successfully treated with ureteroscopic slough removal (shown to be necrotic tissue without malignancy) and a temporary stent placement resulting in a resolution of the symptoms[10].

Haemorrhage requiring transfusion occurred in 28% (5/20) of patients treated with laparoscopic cryotherapy compared with 11% (2/18) treated with percutaneous cryotherapy in a non-randomised study of 37 patients; in 10% (2/20) of patients treated with laparoscopic cryotherapy in a non-randomised study of 66 patients (20 treated with laparoscopic cryotherapy); and in 2% (3/123) and 11% (4/37) in 2 case series of 123 and 37 patients, respectively[11,12,13,14] .

Validity and generalisability of the studies

- There are a number of publications from 1 centre for different time periods, some of which overlap. Therefore, it is possible that there is some duplicate reporting of patients.
- The original overview which informed the initial guidance was on cryotherapy for renal cancer and included evidence on both laparoscopic and percutaneous approaches. In the original overview, there was 1 non-randomised comparative study with laparoscopic partial nephrectomy (n = 231) and 5 case series (n = 187) on patients treated with laparoscopic cryotherapy were included in table 2 and 1 case series (n = 271) had patients with both approaches (maximum 40 month follow-up).

- Conversion to open surgery was only reported in 1 patient in the comparative studies in table 2[5], but has been reported more frequently in case series which are included in appendix A, 2 of which were included in the original overview (2 in Cestari et al [2007], 1 in Johnson et al [2004], 4 in Laguna et al [2009], and 2 in Lawatch et al [2006]).
- Smaller probes are now available for this procedure but they do not yet appear to have been reported in the published evidence.
- Most studies are retrospective.

Existing assessments of this procedure

The European Association of Urologists has published guidelines on the management of renal cancer. It made the following conclusions and recommendations about therapeutic approaches as an alternative to surgery.

Conclusions:

- Radiofrequency and cryoablation are the only minimally invasive approaches for the treatment of small renal tumours with medium follow-up data.
- Although the oncological efficacy is not yet known, currently available data strongly suggest that cryoablation, when performed laparoscopically, results in fewer re-treatments and improved local tumour control compared with RFA.
- For both RFA and cryoablation, recurrence rates are higher than with nephron-sparing surgery.

Recommendations:

- Patients with small tumours and/or significant co-morbidity who are unfit for surgery should be considered for an ablative approach for example, cryotherapy and radiofrequency ablation.
- Pre-treatment biopsy has to be carried out as standard.
- Other image-guided percutaneous and minimally invasive techniques, such as microwave ablation, laser ablation and high-intensity focused ultrasound ablation, are still experimental in character. The experience obtained with radiofrequency ablation and cryoablation should be considered when using these related techniques.

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 of renal cancer. NICE interventional procedures guidance 353 (2010). Available from www.nice.org.uk/Guidance/IPG353
- Laparoscopic partial nephrectomy. NICE interventional procedures guidance 151 (2006). Available from www.nice.org.uk/Guidance/IPG151
- Laparoscopic nephrectomy (including nephroureterectomy). NICE interventional procedures guidance 136 (2005) For more information, see www.nice.org.uk/Guidance/IPG136
- Laparoscopic live donor simple nephrectomy. NICE interventional procedures guidance 57 (2004). Available from www.nice.org.uk/Guidance/IPG57

Technology appraisals

- Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal 169 (2009). Available from www.nice.org.uk/guidance/TA169
- Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal 178 (2009). Available from www.nice.org.uk/guidance/TA178

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.

Mr Neil Barber, David Cranston (British Association of Urological Surgeons), Dr David Breen (British Society of Interventional Radiology), Dr Tze Wah (Royal College of Radiologists)

- Two Specialist Advisers considered cryotherapy for renal cancer established practice and no longer new. One considered it a minor variation of an existing procedure, unlikely to alter the procedure's safety and efficacy. One considered it both established practice but of uncertain efficacy and accuracy.

- The comparator would be partial nephrectomy (open, laparoscopic or robotic), radical nephrectomy, or other ablative techniques (such as RFA; percutaneous microwave ablation has also now been described).
- The most common complication is bleeding though pancreatic, bowel, ureteric (including pelviureteric junction) injury have also occurred but are rare.
- Additional theoretical adverse events include the inherent risks of laparoscopic surgery (such as neurapraxia, port site hernia, CO_2 embolus, trocar injury), deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident.
- Key efficacy outcomes include success rate of cryoablation based on radiological criteria, retreatment rates, recurrence, disease-specific and overall survival. Another Specialist Adviser considered complete devascularisation of the tumour on computerised tomography or magnetic resonance imagnig as a surrogate marker of tumour ablation.
- There is some concern about intra-tumoural cell viability despite negative radiology.
- The success rate is higher for the laparoscopic versus the percutaneous approach.
- Training in a dedicated cryotherapy course and mentoring is advisable.
- Patient selection within a multidisciplinary team is important.

Patient Commentators' opinions

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

Issues for consideration by IPAC

- The evidence highlighted that the rare genetic condition von Hippel-Lindau disease is associated with renal cell carcinoma and there was some evidence of this condition in patients treated with this procedure. However, the impact of this information on any guidance produced to the Committee is minimal since

(as highlighted in the scope) all individuals with renal cell carcinoma are covered by the equalities legislation. There was no evidence on the use of this procedure in patients with this condition.

References

1. Kunkle DA, Uzzo RG. (2008) Cryoablation or radiofrequency ablation of the small renal mass. Cancer 113: 2671–80.

2. Weight CJ, Kaouk JH, Hegarty NJ et al. (2008) Correlation of radiographic imaging and histopathology following cryoablation and radio frequency ablation for renal tumors. Journal of Urology 179: 1277–81.

3. Turna B, Kaouk JH, Frota R et al. (2009) Minimally invasive nephron sparing management for renal tumors in solitary kidneys. Journal of Urology 182: 2150–7.

4. Bandi G, Hedican S, Moon T et al. (2008) Comparison of postoperative pain, convalescence, and patient satisfaction between laparoscopic and percutaneous ablation of small renal masses. Journal of Endourology 22: 963–7.

5. Lin YC, Haber GP, Turna B et al. (2008) Laparoscopic renal oncological surgery in the presence of abdominal aortic and vena caval pathology: 8-year experience. Journal of Urology 179: 455–60.

6. Ko YH, Park HS, Moon DG et al. (2008) A matched-cohort comparison of laparoscopic renal cryoablation using ultra-thin cryoprobes with open partial nephrectomy for the treatment of small renal cell carcinoma. Cancer Research and Treatment 40: 184–9.

7. O'Malley RL, Berger AD, Kanofsky JA et al. (2007) A matched-cohort comparison of laparoscopic cryoablation and laparoscopic partial nephrectomy for treating renal masses. BJU International 99: 395–8.

8. Nguyen CT, Lane BR, Kaouk JH et al. (2008) Surgical salvage of renal cell carcinoma recurrence after thermal ablative therapy. Journal of Urology 180: 104–9.

9. Lane BR, Moinzadeh A, and Kaouk JH. (2005) Acute obstructive renal failure after laparoscopic cryoablation of multiple renal tumors in a solitary kidney. Urology 65: 593.

10. Chen VH, Mayes JM, Mouraviev V et al. (2008) Urothelial sloughing with obstruction after laparoscopic cryoablation of small renal carcinoma in solitary kidney. Urology 72: 716–2.

11. Finley DS, Beck S, Box G et al. (2008) Percutaneous and laparoscopic cryoablation of small renal masses. The Journal of Urology 180: 492–8.

12. Malcolm JB, Berry TT, Williams MB et al. (2009) Single centre experience with percutaneous and laparoscopic cryoablation of small renal masses. Journal of Endourology 23: 907–11.

13. Bourne AE, Kramer BA, Steiner HL et al. (2009) Renal insufficiency is not a contraindication for cryoablation of small renal masses. Journal of Endourology 23: 1195–8.

14. Ham BK, Kang SG, Choi H et al. (2010) The impact of renal tumor size on the efficacy of laparoscopic renal cryoablation. Korean Journal of Urology 51: 171–7.

Appendix A: Additional papers on laparoscopic cryotherapy for renal cancer

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
Allaf ME, Varkarakis IM, Bhayani SB et al. (2005) Pain control requirements for percutaneous ablation of renal tumors: cryoablation versus radiofrequency ablation--initial observations. Radiology 237: 366–70.	Case series n = 10 (cryoablation) vs 14 (percutaneous RFA)	Cryoablation was associated with slightly lower doses of fentanyl and midazolam. No difference in analgesic requirements	Outcomes related to pain control which was not an outcome of particular interest to the Committee.
Anderson SM and Brown JA. (2010) Laparoscopic cryoablation of renal tumors: Assessment of learning curve and outcomes in a low volume practice. Current Urology 4: 81–4.	Case series n = 5 FU = 19 months	All completed successfully. No recurrence or metastases. Complications: 1 patient had conversion because of severe perinephric fibrosis and small renal capsular tear, 1 small peri-ureteral vein laceration and left arm phlebitis.	Comparative studies in table 2.
Aron M, Kamoi K, Remer E et al. (2010) Laparoscopic renal cryoablation: 8-year, single surgeon outcomes. Journal of Urology 183: 889–95.	Case series n = 340 Follow-up = minimum 5 years	5 had local recurrence 6 died of cancer 5-year overall, disease specific and disease-free survival rates were 84%, 92% and 81% (10-year rates were 51%, 82% and 78%) at median follow-up of 93 months in those with biopsy proven RCC	Comparative studies 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. European Urology 47: 474–9.	Case series n = 7 Mean follow-up = 13.6 months	No recurrence during follow-up	Comparative studies in table 2.
Badger WJ, de Araujo HA, Kuehn DM et al. (2009) Laparoscopic renal tumor cryoablation: appropriate application of real-time ultrasonographic monitoring. Journal of Endourology 23: 427–30.	Case series n = 27 Follow-up = 22 months	No recurrences and 3% (1/27) metastatic lesion at follow-up.	Comparative studies in table 2.
Bandi G, Wen CC, Hedican SP et al. (2007) Cryoablation of small renal masses: assessment of the	Non-randomised comparative study n = 20 (percutaneous) vs 58 (laparoscopic)	Overall, cancer-specific and recurrence-free survival rates at last follow-up: 88.5%, 100%,	Patients included in Bandi 2008[1].

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
outcome at one institution. BJU International 100: 798–801.	Follow-up = 19 months	and 98.7%. 4 required repeat treatment because of persistent disease and 1 had progression to locally advanced disease.	
Beemster PW, Wijkstra H, de la Rosette JJ et al. (2010) Quality of life and perceived pain after laparoscopic-assisted renal cryoablation. Journal of Endourology 24: 713–9.	Case series n = 57 Follow-up = 3 months?	General health perceptions were the only scores lower than the general population at baseline. Time of assessment and complications did not affect quality of life but age and comorbidity did.	Comparative studies in table 2.
Beemster P, Phoa S, Wijkstra H et al. (2008) Follow-up of renal masses after cryosurgery using computed tomography; enhancement patterns and cryolesion size. BJU International 101: 1237–42.	Case series n = 47 (but 26 with at least 6 month follow-up included in study) Follow-up = 17.2 months	Residual tumour on first scan in 1 lesion. Of the other 25 cryolesions, 20% had rim enhancement after treatment (1 showed focal enhancement) but this disappeared within 6 months.	Comparative studies in table 2.
Bolte SL, Ankem MK, Moon TD et al. (2006) Magnetic resonance imaging findings after laparoscopic renal cryoablation. Urology 67: 485–9.	Case series n = 33 Follow-up = at least 6 months and up to 48 months in 18 patients	Of the 18 patients, 7 had peripheral rim enhancement within 3 months (4 resolved) and 1 patient had rim enhancement at 7 months. 1 patient had nodular enhancement at 10 months	Comparative studies in table 2.
Bourne AE, Kramer BA, Steiner HL et al. (2009) Renal insufficiency is not a contraindication for cryoablation of small renal masses. Journal of Endourology 23: 1195–8.	Case series n = 123 Follow-up = ?	LRC has minimal impact on renal function as measured with serum creatinine levels. Complications included 1 postoperative stroke, 1 intraoperative pleurotomy necessitating chest tube placement and 3 blood transfusions for intraoperative haemorrhage. In those with renal insufficiency, there was 1 wound infection.	Comparative studies in table 2.
Cestari A, Guazzoni G, Buffi NM et al. (2007) Laparoscopic Cryoablation of small renal masses: technique and results after 6-Year	Case series n = 86 Follow-up = ? (37 had at least 36 months)	Reduction in size noted in all with no positive biopsies at 6 months; complete disappearance of lesion obtained in all 37 with 36 months	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
experience. European Urology, Supplements 6: 646–52.		follow-up. Intraoperative complications in 6% (5/86) (2 open surgical conversions and 3 fractures of cryoablated tissue) and postoperative complications in 23% (20/86) (including ureteropelvic junction obstruction requiring open pyeloplasty 4 died of metastases during follow-up and 2 of unrelated comorbities	
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.	Case series n = 37 Follow-up = ?	All had technical success. 25 of those with follow-up available at 6 months were recurrence-free.	Comparative studies in table 2. (in table 2 of original overview)
Chalasani V, Martinez CH, Lim D et al. (2010) Surgical cryoablation as an option for small renal masses in patients who are not ideal partial nephrectomy candidates: intermediate-term outcomes. Canadian Urological Association Journal 4: 399–402.	Case series n = 19 (11 lap and 8 open) FU = 41.6 months	4-year recurrence-free survival: 83.6% 4-year overall survival: 94.1% (4 recurrences, 1 death from cancer and 1 non-cancer death)	Larger studies in table 2.
Colon I and Fuchs GJ. (2003) Early experience with laparoscopic cryoablation in patients with small renal tumors and severe comorbidities. Journal of Endourology 17: 415–23	Case series n = 8 Follow-up = 5-16 months	No recurrences	Comparative studies in table 2.
Derweesh IH, Malcolm JB, Diblasio CJ et al. (2008) Single centre comparison of laparoscopic cryoablation and CT-guided percutaneous cryoablation for renal tumours. Journal of Endurology 22: 2461–7.	Non-randomised comparative study n = 26 (percutaneous) vs 26 (laparoscopic) Follow-up = 25 months	Residual enhancement in 1.5% vs 2.9%. Complications in 26.9% vs 14.7%. Atelectasis developed in 34.6% vs 70.6% (p = 0.005).	Later publication from same centre included in table 2[4].

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 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.) 23–8.	Non-randomised comparative study n = 231 (78 cryotherapy vs 153 partial nephrectomy) Follow-up = 24.6 months vs 5.8 months		Some patients likely included in Turna 2008[3].
Finley DS, Beck S, Box G et al. (2008) Percutaneous and laparoscopic cryoablation of small renal masses. The Journal of Urology 180:492–8.	Non-randomised comparative study n = 37 (43 masses) (18 percutaneous vs 19 laparoscopic) Maximum follow-up: 14.8 and 34.7 months	There were 2 cases of persistent enhancement on follow-up imaging over the follow-up period, 1 in each group. 1 in a patient with a metastatic osteosarcoma and the other was a clear-cell RCC. Haemorrhage requiring transfusion occurred in: 11.1% (2/18) in percutaneous group and 27.8% (5/20) of patients in laparoscopic group. Deep vein thrombosis, internal jugular thrombus and small bowel injury occurred in 1 patient each (laparoscopic group).	Comparisons with RFA and nephrectomy which were considered more relevant comparators included in table 2.
Gill IS, Remer EM, Hasan WA et al. (2005) Renal cryoablation: outcome at 3 years. Journal of Urology 173: 1903–7.	Case series n = 56 Follow-up = 3 years (in all patients)	3-year survival rate: 89% 39 available for follow-up at 6 months detecting RCC in 2 who had laparoscopic radical nephrectomy 1 died of metastatic prostate cancer and 4 died of metastatic disease in the context of bilateral RCC	Comparative studies in table 2. (in table 2 of original overview)
Goel RK and Kaouk JH. (2008) Single port access renal cryoablation (SPARC): a new approach. European Urology 53:1204–9.	Case series n = 6 Follow-up = ?	Description of new approach. No intraoperative complications; 1 had prolonged hospital stay from pre-existing respiratory condition. No conversion to open surgery and no residual tumour enhancement.	Comparative studies in table 2.
Guazzoni G, Cestari A, Buffi N et al. (2010) Oncologic results of laparoscopic renal cryoablation for clinical	Case series n = 123 (131 masses)	Cancer-specific survival: 100% Overall survival: 93.2%. None with follow-up > 5 years had radiographic	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
T1a tumors: 8 years of experience in a single institution. Urology 76: 624–9.	mean FU = 46 months	recurrence.	
Ham BK, Kang SG, Choi H et al. (2010) The impact of renal tumor size on the efficacy of laparoscopic renal cryoablation. Korean Journal of Urology 51:171–7.	Case series n = 37 (split into 4 groups based on size) Follow-up = 31.6 months	1 of 4 patients with tumours greater than 4 cm and 3 of the 10 with tumours between 3 and 4 cm required postoperative transfusions. Only 2 of the 4 patients with tumours greater than 4 cm had recurrence during follow-up.	Comparative studies in table 2.
Hegarty NJ, Gill IS, Desai MM et al. (2006) Probe-ablative nephron-sparing surgery: cryoablation versus radiofrequency ablation. Urology 68 (1:Suppl) Suppl-13.	Comparative case series n = 164 laparoscopic cryotherapy vs 83 percutaneous RFA Follow-up = 3 vs 1 year	Tumour recurrence in 1.8% (3/164) with cryoablation and 11.1% (9/83) with RFA. Cancer-specific survival was 98% at median follow-up of 3 years vs 100% at median 1-year.	Later publications from same centre included in table 2[2,3].
Hinshaw JL, Shadid AM, Nakada SY et al. (2008) Comparison of percutaneous and laparoscopic cryoablation for the treatment of solid renal masses. Vascular and Interventional Radiology191: 1159–68.	Non-randomised comparative study n = 90 patients (30 percutaneous vs 60 laparoscopic cryotherapy) Mean follow-up: 14.5 vs 14.6 months (at least 12 months follow-up in 47% of patients in each group [14/30 vs 8/60])	Technical success in 100% (30/30 vs 98.3% (59/60) Residual disease within 6 months in 10% (3/30) and 6.7% (4/60). Major complications only in laparoscopic cryoablation: 1 patient had severe respiratory distress requiring 15-day hospital stay, 1 patient with a history of multiple previous surgeries had intraoperative bowel injury related to trocar placement and 1 patient had postoperative atrial fibrillation.	Comparisons with RFA and nephrectomy which were considered more relevant comparators included in table 2.
Hruby G, Reisiger K, Venkatesh R et al. (2006) Comparison of laparoscopic partial nephrectomy and laparoscopic cryoablation for renal hilar tumors. Urology 67: 50–4.	Comparative case series n = 23 patients (hilar tumours) (11 laparoscopic cryotherapy vs 12 LPN) Follow-up = 11.3 months	No recurrence and no complications	Larger comparative studies in table 2.
Hui GC, Tuncali K, Tatli S et al. (2008) Comparison of percutaneous and surgical approaches to	Systematic review	46 studies included. Primary effectiveness was significantly lower in the percutaneous group (87 vs 94%, $p < 0.05$)	Outcomes not separated by type of ablation (ie. cryotherapy with RFA).

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
renal tumour ablation: metaanalysis of effectiveness and complication rates. Journal of Vascular Interventional Radiology 19:1311–20.		but secondary effectiveness was not significantly different. Major complication rate was significantly lower in the percutaneous group (3 vs 7%, $p < 0.05$)	
Jang TL, Wang R, Kim SC et al. (2005) Histopathology of human renal tumors after laparoscopic renal cryosurgery. Journal of Urology 173: 720–4.	Case series n = 3 Follow-up = ?	2 had positive post-cryosurgery biopsies and 1 with a metachronous lesion decided to have radial nephrectomy.	Comparative studies in table 2.
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: 874–7	Comparative case series n = 271 (181 laparoscopic cryoablation VS 90 percutaneous cryoablation vs 132 RFA) Follow-up = ?	Cryotherapy major complications: 1 significant haemorrhage requiring transfusion, 1 conversion to open surgery. RFA major complications: 1 death, 1 ileus, 1 scarring with obstruction, 1 urine leakage	Events reported in table 2. (in table 2 of original overview)
Ko YH, Choi H, Kang SG et al. (2010) Efficacy of laparoscopic renal cryoablation as an alternative treatment for small renal mass in patients with poor operability: experience from the Korean single center. Journal of Laparoendoscopic & Advanced Surgical Techniques 20: 339–45.	Case series n = 39 (45 tumours) Follow-up = 23.5 months	None had major complications. Tumour recurrence found in 1 patient in follow-up but none other had recurrence or metastasis.	Comparative studies in table 2.
Laguna MP, Beemster P, Kumar P et al. (2009) Perioperative morbidity of laparoscopic cryoablation of small renal masses with ultrathin probes: a European multicentre experience. European Urology 56: 355–61.	Case series n = 144 (148 procedures) Follow-up = ?	Study about perioperative outcomes 4 conversions to open surgery from tumour crack and bleeding 28 complications in 23 cases - 15.5 % (23/148)	Comparative studies in table 2.
Lawatsch EJ, Langenstroer P, Byrd GF et al. (2006) Intermediate results of laparoscopic cryoablation in 59 patients at the Medical College of Wisconsin. Journal of Urology	Case series n = 59 (81 tumours with 65 cryoablations) Follow-up = 26.8 months	Conversion to open surgery in 2. Nephrectomy for bleeding in 1. 2 recurrences requiring salvage nephrectomy with no current evidence of disease.	Comparative studies in table 2. (in table 2 of original overview)

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
175: 1225–9.			
Lee DI, McGinnis DE, Feld R et al. (2003) Retroperitoneal laparoscopic cryoablation of small renal tumors: intermediate results. Urology 61: 83–8.	Case series n = 20 Follow-up = 14.2 months	No signs of recurrence in follow-up. 1 had pancreatic injury 1 had atrial fibrillation 5 of 11 with left-sided tumour had elevated amylase and lipase for 1 to 2 days postoperatively	Comparative studies in table 2. (in table 2 of original overview)
Lehman DS, Hruby GW, Phillips CK et al. (2008) Laparoscopic renal cryoablation: efficacy and complications for larger renal masses. Journal of Endourology 22:1123–7.	Case series n = 44 (51 masses; group 1 was 30 tumours in 23 patients with tumour less than 3.0 cm and group 2 was 21 tumours in 21 patients with tumour greater than 3.0 cm) Follow-up = 9 months (group 1) and 11 months (group 2)	No complications in group 1 but 62% (13/21) complications in group 2 with 2 mortalities. There were no recurrences in group 1 and there was 1 recurrence in group 2.	Comparative studies in table 2.
Lin YC, Turna B, Frota R et al (2008) Laparoscopic partial nephrectomy versus laparoscopic cryoablation for multiple ipsilateral renal tumors. European Urology 53: 1210–6.	Non-randomised comparative study n = 27 (13 with 31 tumours had laparoscopic cryoablation vs 14 with 28 tumours with LPN) Follow-up = ?	Patients in LPN group had significantly fewer tumours, larger dominant tumour size. Patients treated with laparoscopic cryoablation had significantly less blood loss and shorter hospital stay. Complication rates were similar.	Larger studies in table 2.
Long L and Park S. (2009) Differences in patterns of care: reablation and nephrectomy rates after needle ablative therapy for renal masses stratified by medical specialty. Journal of Endourology 23: 421–6.	Systematic review	Majority of RFA and cryotherapy are performed by urologists. Tumour ablation rates were significantly higher for RFA than cryoablation *7.4 vs 0.9%, p = 0.009)	Kunkle review[1] in table 2 includes more recent studies and was considered to be better quality (for example, it describes methods of meta-analysis).
Malcolm JB, Berry TT, Williams MB et al. (2009) Single centre experience with percutaneous and laparoscopic cryoablation of small renal masses. Journal of Endourology 23:907–11.	Non-randomised comparative study n = 66 (46 percutaneous vs 20 laparoscopic) (72 tumours: 20 vs 52) Maximum follow-up: 63 months	Significantly more treatment failures in percutaneous group (25% [5/20] vs 3.8% [2/52], p = 0.015). Complications occurred only with laparoscopic cryotherapy: 2 required blood transfusions for bleeding, 1 had a 9-day hospital stay for prolonged ileus versus a partial small bowel obstruction that resolved	Comparisons with RFA and nephrectomy which were considered more relevant comparators included in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
		with bowel rest and 1 required a 5-day hospital stay for prolonged ileus.	
Malcolm JB, Logan JE, Given RW et al. (2009) Renal functional outcomes after cryoablation of small renal masses. Journal of Endourology 24:479–82.	Non-randomised comparative study n = 62 (19 percutaneous vs 43 laparoscopic) Mean follow-up = 30 months	Study reported renal function outcomes which were mostly not separated by approach.	Outcomes primarily not separated by approach. Patients from this study are reported in Malcolm 2009 in table 2[4].
Moon TD, Lee FT, Jr., Hedican SP et al. (2004) Laparoscopic cryoablation under sonographic guidance for the treatment of small renal tumors. Journal of Endourology 18: 436–40.	Case series n = 17 Follow-up = 9.6 months	No recurrences.	Comparative studies in table 2.
Mues AC, Okhunov Z, Haramis G et al. (2010 Comparison of percutaneous and laparoscopic renal cryoablation for small (< 3.0 cm) renal masses. Journal of Endourology 24: 1097–100.	Non-randomised comparative study n = 180 (81 lap vs 99 perc) median FU = 11 months	No significant difference in major complications. 3.1% (3/81) with lap and 9.1% (9/99) with perc had treatment failure (one treated with perc required open radical nephrectomy)	More relevant comparators in table 2
Nadler RB, Kim SC, Rubenstein JN et al. (2003) Laparoscopic renal cryosurgery: the Northwestern experience. Journal of Urology 170: t-5.	Case series n = 15 Follow-up = 453 days	70% (7/10) with RCC had follow-up biopsy and 2 had positive result undergoing nephrectomy and further tests indicated recurrence in 1. 1 postoperative respiratory difficulty requiring intubation for a day. 1 had 8-day postoperative ileus resolving with conservative management.	Comparative studies in table 2. (in table 2 of original overview)
Nisbet AA, Rieder JM, Tran VQ et al. (2009) Decision tree for laparoscopic partial nephrectomy versus laparoscopic renal cryoablation for small renal masses. Journal of Endourology 23:431–7.	Comparative case series n = 73 (51 LPN vs 22 laparoscopic cryotherapy) Follow-up = ?	Purpose of study to present an alternative decision algorithm between laparoscopic cryoablation and LPN and compare it to published series. Total complication rate of 30.7% (17/73).	Difficult to determine outcomes for each procedure (appear to be presented together only).

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Pareek G, Yates J, Hedican S et al. (2008) Laparoscopic renal surgery in the octogenarian. BJU International 101: 867–70.	Comparative case series n = 26 patients ≥ 80 years old (laparoscopic-assisted cryotherapy in 7, hand-assisted LPN in 10, hand-assisted LRN in 10, hand-assisted laparoscopic nephroureterectomy in 4, laparoscopic RFA in 1, laparoscopic unroofing of a renal cyst in 1) Follow-up = 40 months	2 major and 5 minor complications. 19 of 22 patients evaluable had no evidence of disease at the last follow-up. 3 patients died of unrelated causes.	Larger studies in table 2.
Park SH, Kang SH, Ko YH et al. (2010) Cryoablation for endophytic renal cell carcinoma: intermediate-term oncologic efficacy and safety. Korean Journal of Urology 51: 518–24.	Case series n = 39 (45 tumours) FU = 32.6 months	No major complications. Only one recurrence (radiological evidence) in a patient with RCC	Comparative studies in table 2.
Permpongkosol S, Bagga HS, Romero FR et al. (2006) Trends in the operative management of renal tumors over a 14-year period. BJU International 98: 751–5.	Comparative case series n = 111 (percutaneous) vs 883 (laparoscopic) vs 664 (open)	Purpose of study to look at trends in operative management at 1 institution. Treatment of renal tumours has increased as has minimally invasive techniques.	More recent study from first author in table 2[6].
Polascik TJ, Nosnik I, Mayes JM et al. (2007) Short Term Clinical Outcome after Laparoscopic Cryoablation of the Renal Tumor < or = 3.5 cm. Technology in Cancer Research & Treatment 6: 621–4.	Case series n = 26 Follow-up = 20.9 months	1 required blood transfusion and 1developed transient ileus. No evidence of recurrence or progression and overall survival of 100%.	Comparative studies in table 2.
Powell T, Whelan C, and Schwartz BF. (2005) Laparoscopic renal cryotherapy: biology, techniques and outcomes. Minerva Urologica e Nefrologica 57:109–18.	Case series n = 25 Follow-up = 16.2 months	3 cases were converted to open surgery. 2 complications included transfusion and hydronephrosis (both managed conservatively) No recurrences despite rigorous surveillance protocol.	Comparative studies in table 2.
Rodriguez R, Chan DY, Bishoff JT et al. (2000) Renal ablative cryosurgery in selected patients with peripheral renal masses. Urology	Case series n = 7 Follow-up = 14.2 months	No recurrences	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
55: 25-30.			
Schwartz BF, Rewcastle JC, Powell T et al. (2006) Cryoablation of small peripheral renal masses: a retrospective analysis. Urology 68: Suppl-8.	Case series n = 85 (70 were laparoscopic and 11 open) Follow-up = 10 months	7 laparoscopic procedures were converted to open procedure and 2 of these considered a technical failure Abnormal postoperative enhancement in 2 patients at 3 and 12 months.	Comparative studies in table 2.
Sidana A, Aggarwal P, Feng Z et al. (2010) Complications of renal cryoablation: a single center experience. Journal of Urology 184: 42–7.	Non-randomised comparative study n = 162 (52 lap, 101 perc, 9 open) FU = not reported	Cardiovascular complication more common in open procedure and lowest in perc. Perinephretic haematoma reported commonly.	more relevant comparators in table 2.
Stein AJ, Mayes JM, Mouraviev V et al. (2008) Persistent contrast enhancement several months after laparoscopic cryoablation of the small renal mass may not indicate recurrent tumor. Journal of Endourology 22: 2433–9.	Case series n = 30 (32 cases) Follow-up = ?	15.6% (5/32)ablation sites showed enhancement at 3 months and 3 of these persisted by 6 months but only 1 by 9 months. This later patient had partial nephrectomy showing no recurrence.	Comparative studies in table 2.
Strom KH, Derweesh I, Stroup SP et al. (2011) Second prize: recurrence rates after percutaneous and laparoscopic renal cryoablation of small renal masses: does the approach make a difference? Journal of Endourology 25: 371–5.	Non-randomised comparative study n = 145 (84 lap vs 61 perc) mean FU = 31 months	Disease-free and overall survival: 93.7% and 88.9% for perc and 91.7% and 89.3% for lap.	more relevant comparators in table 2.
Tsivian M, Chen VH, Kim CY et al. (2010) Complications of laparoscopic and percutaneous renal cryoablation in a single tertiary referral center. European Urology 58: 142–7.	Non-randomised comparative study n = 195 (72 lap vs 123 perc) FU = not reported	No significant difference in complication rates (13.9% for lap vs 21.1% for perc, p = 0.253). Mild complications occurred more commonly with perc than lap (20.3% vs 5.6%, p = 0.001) but severe events were more common with lap (0.8% vs 8.3%, p = 0.011).	more relevant comparators in table 2.
Tsivian M, Lyne JC, Mayes JM et al. (2010) Tumor size and	Case series n = 163	4.3% (7/163) local recurrences over a median of 20 months	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
endophytic growth pattern affect recurrence rates after laparoscopic renal cryoablation. Urology 75: 307–10.	Follow-up = at least 6 months (median 20 months)	with median 15 month time to recurrence.	
Weld KJ, Figenshau RS, Venkatesh R et al. (2007) Laparoscopic cryoablation for small renal masses: three-year follow-up. Urology 69: 448–51.	Case series n = 81 Follow-up = minimum 3 years	Renal tumour 3-year cancer-specific survival rate was 100% and none developed metastatic disease. 1 had return of abnormal enhancement within the cryolesion during follow-up. 1 had haemorrhage and urinary leak treated conservatively.	Comparative studies in table 2.
White WM, Goel RK, Kaouk JH. (2009) Single-port laparoscopic retroperitoneal surgery: initial operative experience and comparative outcomes. Urology 73: 1279–82.	Matched cohort n = 8 (5 laparoscopic cryotherapy vs 1 LPN vs single-port cyst decortications vs 1 laparoscopic metastectomy) Follow-up = ?	No intra or postoperative complications. No significant difference between single-port and standard retroperitoneal cryotherapy cohorts in age, BMI, blood loss or hospital stay.	Larger studies in table 2.
Wink MH, Laguna MP, Lagerveld BW et al. (2007) Contrast-enhanced ultrasonography in the follow-up of cryoablation of renal tumours: a feasibility study. BJU International 99: 1371–5.	Case series n = 7 Follow-up = ?	Study about contrast-enhanced ultrasonography after the procedure. 5 lesions showed no enhancement and 1 investigated after 18 months was not recognised. In 1 patient who had no enhancement at 1 month, had minimal contrast signals at 7 months.	Comparative studies in table 2.
Wright AD, Turk TM, Nagar MS et al. (2007) Endophytic lesions: a predictor of failure in laparoscopic renal cryoablation. Journal of Endourology 21: 1493–6.	Case series n = 32 (35 lesions) Follow-up = 18 months	6% (2/35) treatment failures. Endophytic status was shown to be a significant predictor of failure ($p < 0.05$)	Comparative studies in table 2.
Yoost TR, Clarke HS, and Savage SJ. (2010) Laparoscopic cryoablation of renal masses: which lesions fail? Urology 75: 311–4.	Case series n = 45 (47 lesions) Follow-up = 13 months	17% (8/47) had treatment failure and 87.5% (7/8) of these had broad-based contact with the renal sinus.	Comparative studies in table 2.

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

Guidance	Recommendations
Interventional procedures	**Cryotherapy for renal cancers. NICE interventional procedures guidance 207 (2007) [*Current guidance*]** 1.1 Current evidence suggests that cryotherapy for renal cancer ablates tumour tissue and that its safety is adequate. However, the evidence about its effect on long-term local control and survival is not yet adequate to support the use of this procedure without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake cryotherapy for renal cancer should ensure that patients understand the uncertainties about its effect on quality of life and long-term survival, and provide them with clear written information. Use of the Institute's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG207publicinfo). 1.3 The procedure should only be offered after assessment by a specialist multidisciplinary team, which should include a urologist, an oncologist and an interventional radiologist. 1.4 Controlled studies into the long-term clinical outcomes will be useful. Clinicians are encouraged to collect long-term data and should enter all patients with renal cancer treated with cryotherapy into the British Association of Urological Surgeons Cancer Registry (www.baus.org.uk). The Institute may review the procedure upon publication of further evidence. **Percutaneous radiofrequency ablation of renal cancer. NICE interventional procedures guidance 353 (2010).** 1.1 Current evidence on the safety and efficacy of percutaneous radiofrequency ablation (RFA) for renal cancer in the short and medium term appears adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit, and provided that patients are followed up in the long term. 1.2 Patient selection for percutaneous RFA for renal cancer should be carried out by a urological cancer multidisciplinary team. 1.3 NICE encourages data collection to provide information about the outcomes of this procedure in the long term. Further research should compare the long-term outcomes of RFA with those of other treatments for renal cancer.

	Laparoscopic partial nephrectomy. NICE interventional procedures guidance 151 (2006). 1.1 Current evidence on laparoscopic partial nephrectomy suggests that it is safe and efficacious when undertaken by surgeons with special expertise in this technique. Surgeons undertaking laparoscopic partial nephrectomy should have specific training and regular experience in laparoscopic renal surgery. 1.2 Clinicians wishing to undertake this procedure should ensure that patients fully understand the risks, including that of serious haemorrhage. In addition, use of the Institute's Information for the public is recommended (available from www.nice.org.uk/IPG151publicinfo). 1.3 Clinicians should audit and review their results. The British Association of Urological Surgeons runs a cancer registry, and clinicians are encouraged to enter all patients undergoing laparoscopic partial nephrectomy onto this database (www.baus.org.uk/Display.aspx?item=319). **Laparoscopic live donor simple nephrectomy. NICE interventional procedures guidance 57 (2004).** 1.1 Current evidence on the safety and efficacy of laparoscopic live donor simple nephrectomy appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. **Laparoscopic nephrectomy (including nephroureterectomy). NICE interventional procedures guidance 136 (2005)** 1.1 Current evidence on the safety and efficacy of laparoscopic nephrectomy (including nephroureterectomy) 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 Patient selection is important when this procedure is being considered for the treatment of malignant disease. Long-term follow-up data are lacking, and clinicians are encouraged to collect data on rates of recurrence in patients with malignant disease.

Technology appraisals	**Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal 169 (2009).** 1.1 Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 1.2 When using ECOG performance status score, clinicians should be mindful of the need to secure equality of access to treatments for people with disabilities. Clinicians should bear in mind that people with disabilities may have difficulties with activities of daily living that are unrelated to the prognosis of renal cell carcinoma. In such cases clinicians should make appropriate judgements of performance status taking these considerations into account. 1.3 People who are currently being treated with sunitinib for advanced and/or metastatic renal cell carcinoma but who do not meet the criteria in 1.1 should have the option to continue their therapy until they and their clinicians consider it appropriate to stop. **Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal 178 (2009).** 1.1 Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma. 1.2 Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic renal cell carcinoma. 1.3 People who are currently being treated with bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for advanced and/or metastatic renal cell carcinoma should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

Appendix C: Literature search for laparoscopic cryotherapy for renal cancer

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	03/06/2010	June 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	03/06/2010	n/a
HTA database (CRD website)	03/06/2010	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	03/06/2010	June 2010
MEDLINE (Ovid)	03/06/2010	1950 to May Week 3 2010
MEDLINE In-Process (Ovid)	03/06/2010	June 2 2010
EMBASE (Ovid)	03/06/2010	1980 to 2010 Week 21
CINAHL (NLH Search 2.0/EBSCOhost)	03/06/2010	n/a
BLIC (Dialog DataStar)	03/06/2010	n/a

Trial sources searched on 03/06/2010

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on 03/06/2010:

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

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

1	exp Cryotherapy/
2	exp Cryosurgery/
3	(cryo* or crymo*).tw.

4	(cold adj3 therap*).tw.
5	(freez* adj3 (therap* or surg*)).tw.
6	1 or 2 or 3 or 4 or 5
7	Laparoscopy/
8	Laparoscopes/
9	exp Laparotomy/
10	exp Surgical Procedures, Minimally Invasive/
11	laparo*.tw.
12	telescop*.tw.
13	percutan*.tw.
14	endoscop*.tw.
15	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	Kidney Neoplasms/
17	carcinoma, renal cell/
18	kidney*.tw.
19	renal*.tw.
20	18 or 19
21	(neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan*).tw.
22	20 and 21
23	16 or 17 or 22
24	6 and 15 and 23
25	Animals/ not Humans/
26	24 not 25