NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous cryotherapy for renal cancer

Treating kidney tumours by freezing (cryotherapy) through a cut in the skin

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), with the aim of destroying 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

- Percutaneous 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

Cryotherapy for renal cancer (performed percutaneously or laparoscopically) aims to treat lesions with less morbidity than surgical resection.

Percutaneous cryotherapy for renal cancer is carried out with the patient under local anaesthesia and sedation or general anaesthesia. A biopsy of the tumour may be carried out. With suitable imaging guidance, a probe is inserted percutaneously into the tumour to deliver a coolant at subfreezing temperatures, creating an ice ball around the probe's tip, to destroy cells. 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), aiming to extend the ice ball approximately 1 cm beyond tumour margins. More than 1 probe can be used.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous cryotherapy for renal cancer. Searches were conducted of the following databases, covering the period from their commencement to 30 March 2011: 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	Percutaneous cryotherapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 2140 patients (1055 treated with percutaneous cryoablation) from 1 systematic review[1], 7 non-randomised comparative studies[2,3,4,5,6,7,8], 2 case series[9,10]and 2 case report[11,12].

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 percutaneous cryotherapy for renal cancer

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation

<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 percutaneously in 23% of cases, and surgically in 77% (12% open and 65% laparoscopic). [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 either univariate or multivariate analyses. No significant differences were observed with regard to the incidence of metastases, although p value bordered conventional significance levels.</td>
<td>No safety outcomes were reported.</td>
<td>Study population issues:
• An important problem is that 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 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</td>
</tr>
</table>

performed percutaneously and the other 6% laparoscopically.] **Mean follow-up: 18.7 months** Conflict of interest/source of funding: none declared			certain small renal masses must be considered when analysing the treatment efficacy of ablative technologies.

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation

Study details

Strom KH (2011)[2]

Non-randomised comparative study

USA
Recruitment period: 1998–2010
Study population: patients with small renal masses

n = **145 (61 percutaneous cryotherapy vs 84 laparoscopic cryotherapy)**

Mean age: percutaneous cryotherapy: 68.6 years; laparoscopic cryotherapy: 65.7 years

Sex: percutaneous cryotherapy: 69.7% male; laparoscopic cryotherapy: 58.3% male

Mean tumour size: percutaneous cryotherapy: 2.7cm; laparoscopic cryotherapy:2.5cm

Patient selection criteria: patients with minimum 12-month follow-up.

Technique: percutaneous cryotherapy under local anaesthesia and sedation (general anaesthesia used where necessary) vs laparoscopic cryoablation.

Mean follow-up: **31 months (percutaneous cryotherapy) vs 42.3 months (laparoscopic cryotherapy) p = 0.008**

Conflict of interest/source of funding: none

Key efficacy findings

Number of patients analysed: **145 (61percutaneous cryotherapy vs 84 laparoscopic cryotherapy)**

	Perc cryo	Lap cryo	p value
Recurrence	16.4% (10/61)	5.9% (5/84)	0.042
Disease-free survival	93.7%	91.7%	0.654
Overall survival	88.9%	89.3%	0.939
Number of patients with evidence of disease at last follow-up	4	7	NR

Of patients with recurrence:

	Perc cryo	Lap cryo	p value
Biopsy confirmed RCC before cryotherapy	80% (8/10)	80% (4/5)	1.000
Upper pole tumours	60% (6/10)	100% (5/5)	0.231
Tumours > 4cm and ≤ 6cm	20% (2/10)	0	0.524
Recurrences treated with nephron-sparing surgery	70% (7/10)	40% (2/5)	0.329
Radical surgery	30% (3/10)	60% (3/5)	0.329

Key safety findings

Complications

	Perc cryo	Lap cryo	p v lue
Total number	9	13	1.000
Patients with more than 1 complication	13.1% (8/61)	11.9% (10/84)	1.000
Clavien I	6.6% (4/61)	8.3% (7/84)	0.761
Clavien II	6.6% (4/61)	7.1% (6/84)	1.000
Clavien IIIa	1.6% (1/61)	0	0.421
Bronchospasm	1.6%	1.1%	0.736
Cellulitis	0	1.1%	0.387
Perinephric hematoma	6.6%	3.5%	0.234
Hypotension	1.6%	0	0.251
Ileus	0	2.4%	0.219
Pleural effusion	0	1.1%	0.387
Pneumothorax	1.6%	0	0.251
Transfusion	3.2%	3.6%	0.775
Urinary retention	0	1.1%	0.387
Urinary tract infection	0	1.1%	0.387

Comments

Follow-up issues:
- All patients had a minimum 12-month follow-up.

Study design issues:
- Multicentre study
- Retrospective study
- Patients with anterior lesions offered laparoscopic cryotherapy and patients with posterior lesions offered percutaneous cryotherapy.

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Pirasteh A (2011)[3]
Non-randomised comparative study
USA
Recruitment period: 2006–9
Study population: patients with suspected renal cell carcinoma technically amenable to CT-guidance access
n = 111 (70 percutaneous cryotherapy vs 41 percutaneous RFA)
Mean age: 70 years
Sex: not reported
Mean diameter of mass: 2.2 cm (range: 0.8 to 4.8 cm)
Patient selection criteria: not stipulated in paper

Technique: both under CT-guidance (not further described)

Follow-up: 12 months

Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 111 (70 percutaneous cryotherapy vs 41 percutaneous RFA)
Preoperative biopsy results: clear cell RCC in 67% (74/111), papillary type RCC in 16% (18/111), oncocytoma in 8% (9/111), angiomyolipoma in 4% (4/111), and biopsy was not obtained in 5% (6/111) tumours

Recurrence
<table>
<tr><th></th><th>Percutaneous cryotherapy (n = 70)</th><th>Percutaneous RFA (n = 41)</th></tr>
<tr><td>Suspicious* enhancement on follow-up CT or MRI</td><td>4</td><td>4</td></tr>
<tr><td>Recurrence confirmed on histologic biopsy**</td><td>0</td><td>0</td></tr>
<tr><td>Estimating imaging recurrence at 10 months***</td><td>11%</td><td>7%</td></tr>
</table>
* nodular, thick or central enhancement
**1 of the 8 who had biopsy for suspicious enhancement had inconclusive results, but it was not clear in the study which group this patient was in.
***estimated by Kaplan-Meier method
Log rank test indicated that there was no significant difference between rates of imaging recurrence between the 2 groups at 12 months (p = 0.6044).</td>
<td>Complications
There was one minor complication in each group:
- skin thermal injury after cryoablation
- perinephretic haemorrhage after percutaneous RFA.</td>
<td>Follow-up issues:
• Any ablation bed with suspicious enhancement or signal characteristics on follow-up imaging (CT or MRI) underwent core biopsy).

Study design issues:
• 2 institutions.
• Retrospective.
• Selection for type of ablation was reported not to be based on institution or operator but criteria not described.

Study population issues:
• No significant difference in age, gender, size or number of lesions treated.</td>
</tr>
</table>

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation

Study details

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) (20 percutaneous cryotherapy vs 59 laparoscopic cryotherapy vs 15 percutaneous RFA)**

Mean age: 66 years
Sex (ratio of men to women): 4:1 vs 1.32:1 vs 2.8:1
Mean diameter of mass: 2.2 cm in both percutaneous cryotherapy and RFA, 2.6 cm in laparoscopic cryotherapy

Patient selection criteria: not stipulated in paper

Technique: percutaneous and laparoscopic cryoablation under general anaesthesia; postoperative analgesia (RFA not described)

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

Conflict of interest/source of funding: not reported

Key efficacy findings

Number of patients analysed: **93 (20 percutaneous cryotherapy vs 59 laparoscopic cryotherapy vs 15 RFA)**

Technical success

Persistently enhancing lesions at early follow-up suggesting incomplete ablation: 10% (2/20) of patients who had percutaneous cryoablation and 3.6% (2/56) with laparoscopic cryoablation (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.

Percutaneous cryotherapy used significantly fewer probes per lesion (mean 1.1 vs 1.5, p = 0.04) and had a shorter mean anaesthesia time (mean 148 vs 247 minutes; p < 0.001) compared with laparoscopic cryotherapy.

Recurrence

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

Survival

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

Patient-reported outcomes

In a telephone survey, the following was reported:

	Perc cryo	Lap cryo	Perc RFA
Return to nonstrenuous activity (days)	3.1[a]	8.1	2.9[b]
Return to strenuous activity (days)	16.2	22.1	10.5[b]
Return to complete	13.5[a]	27.5	18.0

Key safety findings

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)

Percutaneous cryoablation

Event	# of patients
Urine leak	1
Haematoma detected intraoperatively	1
Significant postoperative prolonged neuropraxia	2

Laparoscopic cryoablation

Event	# of patients
Intraoperative	
Significant bleeding managed with haemostatic agents and observation	1
Bowel injury repaired laparoscopically	1
Postoperative	
Atrial fibrillation	1
Narcotic overdose necessitating longer hospitalisation	1
Respiratory failure	1
Symptomatic perirenal haematoma	1
Symptomatic haematoma treated with nephrectomy at another institution	1

Percutaneous RFA

Event	# of patients
Haematoma identified intraoperatively	1
Large retroperitoneal haematoma	1

Comments

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 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:

recovery (days)				
Return to work (days)	6.2	17.5	4.0 [b]	
Mean patient satisfaction (0 – 5 scale)	4.8	4.9	4.8	
Would recommend to others (%)	95	100	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

requiring blood transfusion	
Significant postoperative prolonged neuropraxia	2

- Some patients included in Hinshaw 2008[3] but recruitment period differed slightly.
- 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: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation

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

Non-randomised comparative study
USA
Recruitment period: 2003–7 (percutaneous), 2001–7 (laparoscopic)
Study population: patients with solid renal masses
n = 90 patients (30 percutaneous vs 60 laparoscopic cryotherapy)
Mean age: 67 vs 67.4 years
Sex: 70% vs 52% male
Mean tumour size: 2.1 cm vs 2.5 cm

Exclusion criteria: previous laparoscopic or percutaneous cryoablation

Technique: percutaneous or laparoscopic cryoablation with argon-based system (CryoCare, Endocare Inc.) under general anaesthesia

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])

Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 90 patients (30 percutaneous vs 60 laparoscopic cryotherapy)

Treatment success
<table>
<tr><th></th><th>Percutaneous</th><th>Laparoscopic</th><th>p value</th></tr>
<tr><td>Technical success*</td><td>100% (30/30)</td><td>98.3% (59/60)</td><td>NS</td></tr>
<tr><td>Residual disease** within 6 months on follow-up imaging [a]</td><td>10% (3/30)</td><td>6.7% (4/60)</td><td>0.68</td></tr>
<tr><td>Primary effectiveness***</td><td>90% (27/30) [b]</td><td>93.3% (56/60) [c]</td><td>0.68</td></tr>
<tr><td>Secondary effectiveness***</td><td>100% (30/30) [b]</td><td>100% (58/58) [c]</td><td>1.0</td></tr>
</table>
* whether tumour was treated according to protocol and covered completely.
** Residual disease defined as nodular enhancement within or directly adjacent to the renal tumour and zone of ablation. All were considered for reablation.
*** Effectiveness refers to complete ablation of macroscopic tumour
[a] Three patients in the percutaneous group had second cryoablation and then had no further evidence of local tumour progression; in laparoscopic group, 1 died from unrelated causes before retreatment, 2 had successful retreatment with percutaneous cryoablation and 1 continued with imaging because the findings were thought to be indeterminate.
[b] Three patients with residual disease were excluded but included in secondary effectiveness as they were successfully retreated.
[c] Four patients with residual disease not included in primary effectiveness; 2 not included in denominator for secondary effectiveness because they had not had retreatment.

Recurrence (defined as nodular enhancement within or directly adjacent to the renal tumour and zone of ablation) (after more than 6 months)
One patient treated with laparoscopic cryoablation had a local</td>
<td>Complications
Complications considered major occurred only in those with 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
- 1 patient had postoperative atrial fibrillation.

Four patients treated with percutaneous and 1 with laparoscopic cryoablation had minor procedural complications including:
- Symptomatic perinephric haematoma
- Asymptomatic and self-limited urine leak identified at imaging
- Self-limited flank paraesthesia and neuralgia
- Intercostal neurapraxia
(Not clear which of these occurred in 2 patients; no transfusions or reoperations required for any of these complications and no more details provided.)

Death unrelated to renal disease
6 patients treated with laparoscopic cryoablation died from other causes at least 30 days after the procedure (from myocardial infarction, lung cancer, hepatic adenocarcinoma, oesophageal carcinoma, pancreatic cancer and squamous cell cancer [location of squamous cell cancer not reported]).</td>
<td>Follow-up issues:
• MRI or CT every 3 months.
• One patient with percutaneous approach did not show up for follow-up so was excluded.
• Some confusion about loss to follow-up for laparoscopic approach. Some patients lost to follow-up may not be included in the patients included here though it is not clear how many (study says all attended first follow-up but then that the similarity in length of follow-up between approaches despite laparoscopic being performed longer is because more patients in the laparoscopic group were lost to follow-up).
Study design issues:
• Retrospective data taken from database.
• Percutaneous cryoablation offered since 2003, initially only in posterior or posterolateral tumours and if puncture path was free of overlying bowel but later in anterior and inferior masses.
• AI cases and follow-up imaging were re-evaluated by one author.
Study population issues:
• Some patients included in Bandi 2008[2] (recruitment period differed slightly).</td>
</tr>
</table>

	recurrence 14 months after the procedure which was treated with open partial nephrectomy. Ten months later, the patient developed another recurrence which was treated with percutaneous cryoablation and was being treated with immunotherapy for locally advanced cancer at the time of writing. ***Disease-specific survival*** 100% in both groups but there were deaths from other causes (see complications) ***Hospital stay*** **Percutaneous (mean ± SD)** | **Laparoscopic (mean ± SD)** | **p value** Hospital stay(days) | 1.1 ± 0.3 | 2.4 ± 2.1 | < 0.0001		• Patients treated with laparoscopic cryoablation had significantly larger tumour size. **Other design issues**: • The study does not report if preoperative biopsy was performed.

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Malcolm JB (2009)[6]

Non-randomised comparative study
USA
Recruitment period: 2003–7
Study population: patients with small renal masses with at least 12 months follow-up
n = 66 (46 percutaneous vs 20 laparoscopic) (72 tumours: 20 vs 52)
Mean age: 66.5 years
Sex: 56% male
Mean tumour size: 2.33 cm
Medical comorbidities: 76% (50/66) hypertension, 24% (16/66) CKD, 36% {24/66) hyperlipidemia, 29% (19/66) diabetes mellitus, 36% (24/66) tobacco use and 32% (21/66) heart disease

Exclusion criteria: incomplete records, follow-up less than 12 months

Technique: percutaneous cryoablation with Perc 17 or Perc 24 (Endocare, Irvine, CA) with intravenous sedation (general anaesthesia used, if necessary); laparoscopic cryoablation using argon-based cryoablation system (Endocare, Irvine, CA) (use of anaesthesia not reported for laparoscopic procedure)

Maximum follow-up: 63 months

Conflict of interest/source of funding: two authors have a research grant from Endocare, one author is consultant and</td>
<td>Number of patients analysed: 66 (46 percutaneous vs 20 laparoscopic) (72 tumours: 20 vs 52)
Preoperative biopsy results: RCC in 57% (41/72), benign/nondiagnostic in 34.7% (25/72) and biopsy was not obtained in 8.3% (6/72) tumours.

Treatment success

<table>
<tr><th></th><th>Percutaneous</th><th>Laparoscopic</th><th>p value</th></tr>
<tr><td>Treatment failures</td><td>25% (5/20) [a]</td><td>3.8% (2/52) [b]</td><td>0.015</td></tr>
</table>
[a] Four of the five patients who failed percutaneous treatment received retreatment resulting in no recurrent enhancement during 6 to 36 months of secondary follow-up. One patient who also had secondary percutaneous cryotherapy had ad small focus of enhancement within the cryolesion at 3-month follow-up and denied further treatment (and radiographic appearance has been stable over a 12-month follow-up).
[b] In one patient, failure was detected at 3-month follow-up. The patient declined retreatment and there were no demonstrable changes on follow-up imaging.
[b] In the other patient with failure, there was a small focus of enhancement near the cryolesion so the patient was treated with open partial nephrectomy (2 years after laparoscopic cryoablation) and had negative imaging over the following 18 months.
Survival rates
Overall cancer specific and cancer-free survival was 100% and 97%, respectively, at mean 30-month follow-up.

Local or metastatic progression
There was no significant local or metastatic progression.</td>
<td>Complications
These only occurred in patients treated 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 with bowel rest
- 1 required a 5-day hospital stay for prolonged ileus.</td>
<td>Follow-up issues:
• CT imaging and physical examination (and any appropriate laboratory studies) at 1, 3, 6, 12, 18 and 24 months.

Study design issues:
• Retrospective review of records.
• Cryoablation was offered initially for patients who were felt to have high-risk for significant complications from extirpative surgery but this was extended to any patient with a small renal mass and no evidence of metastatic disease.
• Laparoscopic approach was used for anterior and percutaneous for posterior tumours.

Study population issues:
• Medical comorbidities were high but not separated by approach.</td>
</tr>
</table>

speaks for Sanofi-Aventis.

Hospital stay

	Percutaneous	Laparoscopic	p value
Mean hospital stay (days)	1	4	0.004

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation

Study details

Finley DS (2008)[7]

Non-randomised comparative study

USA

Recruitment period: 2003–7

Study population: patients with small renal masses

n = **37 (43 masses) (18 percutaneous vs 19 laparoscopic)**

Mean age: 61.3 vs not explicitly stated
Sex: not reported
Mean tumour size: 2.7 vs 3.0 cm

Patient selection criteria: not reported

Technique: percutaneous and laparoscopic cryoablation with argon-based cryoablation system (CryoCare) (percutaneous under general anaesthesia but not reported for laparoscopic; laparoscopic performed retroperitoneal in 4 and transperitoneal in 15)

Maximum follow-up: **14.8 and 34.7 months**

Conflict of interest/source of funding: one author is said to have a 'financial interest and/or other relationship' with Endocare, METI Inc., Astellas, Storz Endoscopy, Simbioniz, Intuitive Surgical and Ethicon Endo-Surgery; another with Applied Urology, Cook Urological, EndoCare, Greenwald Inc., Microvasive, Orthopedic Systems Inc., Astellas, Boston Scientific and Karl Storz Endoscopy.

Key efficacy findings

Number of patients analysed: **37 (43 masses) (18 percutaneous vs 19 laparoscopic)**

Biopsy results: RCC in 67.4% (29/43), oncocytoma in 11.6% (5/43), metastatic disease in 2.3% (1/43) and non-diagnostic in 18.6% (8/43).

Evidence of persistent enhancement (mean follow-up 11.4 [perc] vs 13.4 [lap] months)

There were 2 cases of persistent enhancement on follow-up imaging over the follow-up period, one in each group. One in a patient with a metastatic osteosarcoma and the other was a clear-cell RCC.

Procedural characteristics

	Percutaneous (mean, range)	**Laparoscopic (mean, range)**	**p value**
Operative time (hours)	2.5 (1.5–3.5)	4.2 (2.5–6.0)	< 0.05
No. of morphine equivalents (mg)	5.1	17.8	< 0.05
Hospital stay (days)	1.3 (1–4)	3.1 (1–6)	< 0.05

Key safety findings

Complications

Haemorrhage requiring transfusion occurred in:

- 11.1% (2/18) of patients treated with the percutaneous procedure
- 27.8% (5/20) of patients treated with laparoscopic procedure (19 patients had treatment of 24 lesions in 20 sessions; 1 occurred during first case due to injury of branch of renal vein unrelated to cryoprobes).

(Haemorrhage occurred only with the use of multiple probes; not related to tumour size.)

Other complications:

	Percutaneous	**Laparoscopic**
Deep vein thrombosis	5.6% (1/18)	5% (1/20)*
Internal jugular thrombus	0% (0/18)	5% (1/20)
Small bowel injury	0% (0/18)	5% (1/20)
Loss of kidney	5.6% (1/18)	0% (0/20)

* The table says that this occurred in 1 patient in each group but the text says that it is only in 1 patient in the percutaneous group (not clear which is correct).

No other details of these complications were given in the study (i.e. time of occurrence, how they were treated, or subsequent sequelae). No complications required conversion to open surgery. There were no acute or delayed embolisations for renal bleeding or deaths.

Comments

Follow-up issues:

- CT with and without IV contrast (or MRI) every 6 months for 2 years and then yearly (even if benign).

Study design issues:

- Retrospective from database.

Study population issues:

- In a subsequent publication, authors reported that patients in the percutaneous group were significantly younger. When looking at just those treated with a single probe, age was no longer significantly different (authors suggest higher rate of haemorrhage in the laparoscopic group is not necessarily related to age of the patient).

Other issues:

The study does not report if preoperative biopsy was performed.

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Permpongkosol S (2006)[8]

Non-randomised comparative study
USA
Recruitment period: 2000–4
Study population: patients with non-diagnostic (indeterminate, non-specific) biopsy pathological findings who underwent renal tumour ablation
n = 20 (7 percutaneous cryotherapy vs 13 RFA)
Mean age: 66.3 years
Sex: 80% male

Patient selection criteria: severe medical comorbidities, previous abdominal surgery complicating operative management, or hereditary conditions predisposing to multiple tumour recurrence (ie. von Hippel-Lindau disease), patients with decreased renal function (such as with solitary kidney)

Technique: CT guided percutaneous cryoablation or RFA (use of anaesthesia not reported)

Maximum follow-up: 56.2 months

Conflict of interest/source of funding: one author has a financial interest and/or other relationship with Image Guide, In Touch Health and Perc Sys.</td>
<td>Number of patients analysed: 19 (7 percutaneous cryotherapy vs 13 RFA)
Primary effectiveness and recurrence
Primary effectiveness was defined as the percentage of tumours successfully eradicated after the initial procedure.
Recurrence was defined as evidence of enhancement and/or increase in tumour size after successful ablation.
<table>
<tr><th></th><th>Indeterminate pathology (n = 20)</th><th>Known pathology (n = 88)</th></tr>
<tr><td>Primary effectiveness</td><td>90%</td><td>89.7%</td></tr>
<tr><td>Recurrence</td><td>35.0%</td><td>5.88%</td></tr>
</table>
(Of those diagnosed, 72.2% [57/88] were RCC, 6.8% [6/88] were oncocytoma, 4.6% [4/88] angiomyolipoma, and 1.1% [1/88] metastatic alveolar sarcoma; 10.2% were unequivocal benign pathological findings.)
Details of recurrence
80% (16/20) had no contrast enhancement at first follow-up and radiographic follow-up showed continued stability in 17 patients.
In the other 3 patients:
- 1 RFA-treated patient had a questionable small area on CT 6 months after the procedure but after observation for 17.5 months, there was no further evidence of residual viable tumour
- 1 cryoablation-treated patient had residual enhancing tumour on first follow-up imaging at 1 month and so had laparoscopic partial nephrectomy which confirmed histology of clear cell RCC
- 1 RFA-treated patient had recurrence detected at 30 months which was originally considered successful (technical success with complete ablation). The patient had laparoscopic radical nephrectomy and histopathological findings confirmed clear cell RCC.

In all 9 patients (10 tumours) with benign pathological findings</td>
<td>Complications
No serious complications and no patients required blood transfusion.
<table>
<tr><th>Event</th><th>No. of patients</th></tr>
<tr><td>Hypertensive episode after the procedure requiring longer period of observation in recovery room</td><td>1</td></tr>
<tr><td>Small renal haematomas requiring no treatment</td><td>3</td></tr>
</table>
(It was not reported if these patients had cryotherapy or RFA.)
No patients died from metastatic disease but 3 died from heart disease, stroke and pancreatic cancer, respectively (CT scans at 30.9, 16.4 and 6.39 weeks of follow-up, respectively, were negative for enhancing renal masses)</td>
<td>Follow-up issues:
• CT or MRI and serum creatinine at least at 1 to 3 months and then every 6 months.

Study design issues:
• 79 patients (with 88 suspicious renal masses) had biopsy; 20 non-diagnostic renal tumours had ablation.
• RFA ablation from 2000–3 and cryoablation from 2003 onwards.
• Not all outcomes were separated by type of ablation.

Study population issues:
• Characteristics were not separated by type of ablation.
• Medical comorbidities in 17 patients included chronic renal insufficiency, insulin-dependent diabetes mellitus, chronic obstructive pulmonary disease, and primary malignancy. One patient had von Hippel-Lindau disease.</td>
</tr>
</table>

	on biopsy, renal ablation treatment was successful after a single treatment session. At mean follow-up of 24 months, no enhancing lesions were identified after ablation. Radiographic follow-up revealed stable ablation in 8 patients at the last visit. One recurrent tumour was identified by MRI at 23 months in a patient who had previously undergone left nephrectomy. He had a successful RFA for this residual tissue and the first MRI confirmed no enhancement.		

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation

Study details	Key efficacy findings	Key safety findings	Comments
Schmit (2010)[9] **Case series** USA Recruitment period: 2003–9 Study population: patients with solid renal tumours ≥ 3cm n = **108 (110 tumours)** Mean age: 73 years Sex: 69.4% (75/108) male Mean tumour size: 4.1 cm (49 were ≥ 4.0 cm) Patient selection criteria/indications for a percutaneous procedure: contraindications to surgery because of significant medical comorbidity, previous surgical intervention in one or both kidneys and patient preference. Technique: percutaneous cryoablation using Perc-24 cryoablation system (Endocare, Inc.) under general anaesthesia and combined CT and ultrasound guidance Mean follow-up: **15 months (mean)** Conflict of interest/source of funding: none	Number of patients analysed: **108 (110 tumours)** **Biopsy results** (obtained for 83% [91/110] of tumours) **Biopsy results** / **% (no.)** RCC: 66% (60/91) Oncocytoma: 12% (11/91) Oncocytic neoplasm: 8% (7/91) Thyroid cancer metastasis: 1% (1/91) Non-diagnostic: 13% (12/91) **Technical success** (defined as extension of ice ball beyond tumour margin on contrast-enhanced CT or MRI performed with 3 months of the procedure): 97% (107/110) All 3 treatment failures resulted from incomplete tumour ablation along the deepest margin of the centrally located renal mass. One of these patients was subsequently treated with laparoscopic radical nephrectomy, another patient elected to be treated elsewhere and was lost to follow-up and the third patient was not retreated due to significant co-morbidities. The third patient died at 1 year due to unrelated causes. **Local tumour recurrence** (defined as a new hyperenhancing or enlarging tissue nodule in or around the ablation zone on contrast to CT or MRI performed 3 months or later following the procedure): none of the 82 patients who had follow-up CT or MRI at 3 months or later reported recurrence. Average length of hospital stay: 1.8 days	**Complications** Severe adverse events: 9 events in 6 patients. including: • Significant bleeding after removal of cryoprobes (4 patients). 3 required arterial embolisation for active bleeding and 2 received blood transfusion (2 units each). • Periprocedural myocardial infarction: 3 patients. • Acute on chronic renal failure: 1 patient. • Pulmonary embolism diagnosed on CT angiogram at 8 days: 1 patient. Minor events: • Post ablation gross haematuria and or urinary obstruction: 8% (8/108). Five of the patients required bladder irrigation via an indwelling Foley catheter and 3 patients also needed cystoscopic clot evacuation and temporary externalised ureteral stent placement. • Corneal abrasion due to tape used on eyes during general anaesthesia: 1 patient. No uretral or bowel injuries reported.	**Follow-up issues**: • Loss to follow-up at 3 months or later CT or MRI follow-up: 24.1% (26/108). **Study design issues**: • Retrospective. • One or two core biopsies were obtained from each tumour. Percutaneous cryoablation was performed regardless of result. • Average of 3 cryoprobes used in each procedure. **Study population issues**: • Additional procedures: preablation selective arterial embolisation was performed in 9% (10/110) of tumours, hydrodisplacement of the bowel in 19% (21/108) of patients and retrograde pyeloperfusion in 10% (11/108) of patients.

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation

Study details	Key efficacy findings	Key safety findings	Comments
Atwell TD (2010)[10] **Case series** **(some patients included in Kunkle review from earlier publication)** USA Recruitment period: 2003–7 Study population: patients with solid renal mass confirmed on CT or MRI n = **91 (93 tumours)** Mean age: 73 years Sex: 67% (61/91) male Mean tumour size: 3.4 cm (27 were > 4.0 cm) Patient selection criteria: decision to proceed based on clinical appropriateness and technical feasibility. Technique: percutaneous cryoablation using Perc-24 cryoablation system (Endocare, Inc.) under general anaesthesia and combined CT and ultrasound guidance Mean follow-up: **26 months (mean)** Conflict of interest/source of funding: not reported	Number of patients analysed: **91 (93 tumours)** **Biopsy results (obtained for 78.5% [73/93] of tumours)** **Biopsy results** — **% (no.)** RCC — 60% (44/73) Oncocytoma — 19% (14/73) Oncocytic tumour — 8% (6/73) Suspicious — 3% (2/73) Non-diagnostic — 10% (7/73) **Technical success** 96% (89/93) (Defined as extension of ice ball beyond tumour margin and post-ablation imagines showing no contrast enhancement in tumour parenchyma.) Of the 4 procedures considered technical failures, 3 occurred in central tumours. **Residual tumours** Four residual tumours in 4 patients seen within 3-month follow-up. Three of these patients died (2 of unknown causes and 1 of an unrelated co-morbidity). The remaining patient had subsequent laparoscopic nephrectomy and was disease-free 13 months after surgery. **Local progression (defined as new enhancement in the ablated tumour or increase in ablated tumour size beyond 3 months after the procedure)** 1 patient had a tumour recurrence 14 months after the procedure. This patient was re-treated with percutaneous cryotherapy and patient was disease-free 5 months after the procedure. **Death** 14 patients died during follow-up including 2 patients due to metastatic RCC at cryoablation. The	**Complications** **Event** — **No. of patients** Major complications — 9% (8/92) Retroperitoneal haemorrhage requiring angiography — 3 Obstructive haematuria requiring stent placement — 1 Pulmonary oedema — 1 Pulmonary embolus — 1 Delayed urosepsis 1 week after ablation — 1 RCC metastasis (confirmed by biopsy) in the cryoprobe tract 12 months after treatment. — 1 (No additional detailed about time of occurrence or subsequent sequelae of these events were reported.)	**Follow-up issues**: • 3-month follow-up available: 93.3% (83/89) of successful cryoablation procedures. **Study design issues**: • Single centre study. • Retrospective. • A biopsy was performed at time of ablation but the tumour was treated as the tissue was being processed. • Complications were only recorded if they were considered severe adverse events (grade 3 in the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0). • CT or MRI at 3, 6 and 12 months and then yearly. **Study population issues**: • 2 patients presented with gross haematuria, 2 with metastastic RCC and all remaining patients 96% (87/91) were asymptomatic. • Proportion of tumours in the right and left kidney were similar (47% or 52% and 44% or 48% respectively). • 44% (41/93) tumours extended to the renal sinus fat.

	remaining 9 patients died of unrelated causes (no further details provided). Mean length of hospital stay: 1 day		

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation		
Study details	**Key efficacy and safety findings**	**Comments**
Romero FR (2007)[11] **Multiple case report of safety** USA Study population: patients with pleural effusion after percutaneous cryoablation of the kidney n = **2** Conflict of interest/source of funding: not reported	Case 1: 60-year old woman with history of hypertension, transient ischaemic attack, asthma and Cushing syndrome who originally had laparoscopic cryoablation for a left renal tumour was treated with percutaneous cryoablation for 2 right renal tumours which developed subsequently. Several hours after the procedure the patient experience nausea and vomiting and a CT scan snowed **perirenal haematoma with a right-side pleural effusion with no evidence of pneumothorax** and she was admitted into intensive care. After chest pain, breath and fatigue, sanguineous fluid was removed from her chest with a tube and a chest X-ray showed resolution of the pleural effusion. Case 2: 87-year old woman with history of chronic obstructive pulmonary disease, hypertension, congestive heart failure and atrial fibrillation (on anticoagulant therapy, recent pacemaker implant and exploratory laparotomy for peritonitis) was treated with percutaneous cryoablation to treat a mass in the left kidney (anticoagulation was halted during the procedure). On postoperative day 3, she developed shortness of breath and left-sided chest pain which was shown on CT to be caused by a **large left-sided pleural effusion**. This was drained with a chest tube. Anticoagulation was stopped and she received a blood transfusion. 20 days later, she was readmitted and **died of a pulmonary embolism in the right main pulmonary artery**.	

Abbreviations used: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SD, standard deviation		
Study details	**Key efficacy and safety findings**	**Comments**
Schmit GD (2010)[12] **Case reports** USA Study population: patients prior renal surgery, who have chosen ablation over surgery, or with contraindications to surgery because of significant morbidities, n = **2** Technique: percutaneous cryotherapy with CT- guidance and under general anaesthesia Conflict of interest/source of funding: none	Case 1: 82-year old woman with 8.3 cm maximal diameter mass in posterior right kidney who was deemed unsuitable for surgery because of severe comorbidities (severe chronic obstructive pulmonary disease, ischaemic cardiomyopathy, and chronic renal insufficiency). Eight cryoprobes were used to ablate the mass. A biopsy was taken at the time of ablation. An **ice ball crack** was identified on the 2 minute refreeze images during the second cryoablation cycle. Following active thawing and removal of the cryoprobes, a CT scan showed development of a large perinephric hematoma originating at the location of the ice ball crack. A new large bladder haematoma was also observed. Angiography indicated active bleeding from the right arterial branch which was not pre-embolised. This branch was then successfully embolised with coils. A right uretral stent and a Foley catheter were inserted. The patient's hospital stay was complicated including transfusion of 9 units of blood, acute renal failure requiring temporary haemodialysis and prolonged intubation. The patient recovered and was discharged 21 days after the procedure. The patient died 4 months after the procedure due to ischaemic cardiomyopathy and chronic obstructive pulmonary disease. Case 2: 80-year old man with a 4.4cm mass in the medial upper pole of the left kidney was discovered incidentally on CT angiogram. Percutaneous cryoablation was chosen because of the patient's significant cardiac comorbidity. Four cryoprobes were used to ablate the mass. An **ice ball crack** was identified on the 2 minute refreeze images during cryoablation. Following active thawing and removal of the cryoprobes, a CT scan showed complete ablation of the tumour and active bleeding from the upper pole of the left kidney. Despite a moderate sized perinephric hematoma, the patient remained stable and no blood transfusion was required. The patient was discharged form hospital the following morning and had no recurrence or metastatic disease 1 year after the procedure.	

Efficacy

Completeness of ablation/recurrence/disease progression

A systematic review reported that repeat ablations were required in significantly fewer patients treated with cryotherapy than RFA (1% [8/600] vs 9% [66/775], $p < 0.0001$)[1]. The review reported that significantly fewer 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], $p < 0.0001$). Fewer patients treated with cryotherapy had progression to metastatic disease but this was not significant (1% [6/600] vs 3% [19/775], $p = 0.06$)[1].

A non-randomised study of 145 patients (61 percutaneous cryotherapy vs 84 laparoscopic cryotherapy) reported significantly higher recurrence in the percutaneous group in comparison to the laparoscopic group (16% [10/61] vs 6% [5/84], $p = 0.042$). In this study the mean follow-up was significantly shorter in the percutaneous group in comparison to the laparoscopic group (31 months vs 42 months, $p = 0.008$)[2].

A non-randomised study of 111 patients (70 percutaneous cryotherapy vs 41 percutaneous radiofrequency ablation) reported 11% recurrence in the cryotherapy group compared to 7% in the radiofrequency ablation group ($p = 0.6044$) at 10-month follow-up[3].

A non-randomised comparative study of 93 patients comparing patients treated with percutaneous cryoablation, laparoscopic cryoablation, and percutaneous RFA reported that 10% (2/20) of patients who had percutaneous cryoablation and 3% (2/56) of patients treated with laparoscopic cryotherapy 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 22, 12 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 non-randomised comparative study of 90 patients reported primary effectiveness (complete ablation of macroscopic tumour after the initial procedure) in 90% (27/30) of patients treated with percutaneous cryotherapy and 93% (56/60) of patients treated with laparoscopic cryotherapy ($p = 0.68$). The 3 with residual disease in the percutaneous group required a second ablation and 2 of those with residual disease in the laparoscopic group then had percutaneous cryoablation (all were successful), 1 died from unrelated causes before retreatment and 1 continued with imaging because of indeterminate findings.

Consequently, secondary effectiveness rates were 100% (30/30) and 100% (58/58), respectively[5].

The same study reported only 1 recurrence in a patient treated with laparoscopic cryoablation 14 months after the procedure[5].

In a non-randomised comparative study of 66 patients there were significantly more treatment failures among the tumours treated with percutaneous cryotherapy than the tumours treated with laparoscopic cryotherapy (25% [5/20] vs 4% [2/52], p = 0.015). All patients with failures in the percutaneous group were re-treated and 4 had no recurrent enhancement in the 6 to 36 months follow-up but 1 had a small focus of enhancement at 3-month follow-up (the patient denied retreatment but had stable radiographic appearance over 12-month follow-up). Of the 2 with laparoscopic cryotherapy, 1 denied retreatment (with no further changes on follow-up imaging) but another was treated with open partial nephrectomy 2 years after initial treatment[6].

The same study reported no significant local or metastatic progression[6].

A non-randomised comparative study of 37 patients comparing 18 patients treated with percutaneous cryotherapy with 19 treated with laparoscopic cryotherapy reported 2 cases of persistent enhancement on follow-up imaging (1 in each group) over a mean follow-up of 11.4 and 13.4 months, respectively[7].

The same study reported 1 case of persistent enhancement on follow-up imaging in each group of patients (percutaneous and laparoscopic) during a mean follow-up of 11.4 and 13.4 months, respectively. One was a metastatic osteosarcoma and the other was a clear-cell RCC[7].

A non-randomised comparative study which included 20 patients with nondiagnostic results from percutaneous cryotherapy or RFA reported that one patient treated with cryotherapy had enhancing tumour on the first follow-up imaging after 1 month so had laparoscopic partial nephrectomy confirming RCC; 2 patients treated with RFA had recurrence after 23 and 30 months (one had laparoscopic radical nephrectomy confirming RCC and another had another RFA)[8].

A case series of 108 patients reported technical success (defined as extension of ice ball beyond tumour margin on contrast-enhanced CT or MRI performed with 3 months of the procedure) in 97% (107/110) of tumours. The same study reported no tumour recurrence in the 82 patients who had follow-up CT or MRI at 3 months or later[9].

A case series of 91 patients reported technical success (defined as extension of ice ball beyond tumour margin and post-ablation imagines showing no contrast enhancement in tumour parenchyma) in 97% (89/93) of tumours. The same study reported 4 residual tumours within 3 months follow-up. Three of these patients died (2 of unknown causes and 1 from an unrelated co-morbidity) and

the remaining patients had subsequent laparoscopic nephrectomy and was disease free 13 months later[10].

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 nonstrenuous activity within 3, 8 and 3 days when treated with percutaneous cryoablation, laparoscopic 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 16, 22 and 11 days in patients of the three groups, respectively, but only the difference between percutaneous RFA and laparoscopic cryotherapy was significant ($p < 0.05$). 'Complete recovery' occurred within 14, 28 and 18 days in patients of the three groups, respectively ('complete recovery' in the percutaneous cryotherapy group was significantly less than the laparoscopic procedure; $p < 0.05$). Return to work was reported within 6, 18 and 4 days, respectively for the three groups, with only the difference between the percutaneous RFA and laparoscopic cryotherapy groups being significant ($p < 0.05$). Patient satisfaction and the rates of whether or not the patients would recommend the procedure to others were not significantly different between the groups[4].

Survival

The non-randomised study of 145 patients reported similar disease free survival (94% vs 92%) and overall survival (89% vs 89%) in the percutaneous and laparoscopic groups respectively. Follow-up was significantly shorter in the percutaneous group in comparison to the laparoscopic group (31 months vs 42 months, $p=0.008$)[2].

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 comparative study of 90 patients reported 100% disease-specific survival in patients treated with both percutaneous and laparoscopic cryotherapy at mean 14.5 and 14.6 months, respectively[5].

The non-randomised comparative study of 66 patients reported 100% cancer-free survival at mean 30 month follow-up[6].

Safety

Overall comparison of complications

The non-randomised study of 145 patients reported 9 patients with any complication in the percutaneous group and 13 patients in the laparoscopic group (p=1.000)[2].

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].

The non-randomised comparative study of 90 patients reported major complications only in those treated with laparoscopic cryotherapy (severe respiratory distress in 1, intraoperative bowel injury in 1, and postoperative atrial fibrillation in 1)[5].

The non-randomised comparative study of 66 patients reported that complications only occurred in those treated with laparoscopic cryotherapy (2 required blood transfusions and 2 had prolonged ileus requiring further hospital stay)[6].

The case series of 91 patients reported major complications in 9% (8/92) of procedures[10].

Specific complications

The non-randomised study of 145 patients reported 1 patient with pneumothroax in the percutaneous group and 1 patient with urinary retention in the laparoscopic group (p=1.000). Two patients in the percutaneous group and 3 patients in the laparoscopic group required a transfusion [2].

The non-randomised study of 111 patients reported 1 patient with skin thermal injury in the cryoablation group and 1 patient with perinephretic haemorrhage after radiofrequency ablation[3].

The non-randomised comparative study of 93 patients reported that complications occurring in those treated with percutaneous cryotherapy included urine leak in 1 patient, intraoperative haematoma in 1 patient and significant postoperative prolonged neuropraxia in 2 patients[4].

The non-randomised comparative study of 90 patients reported that four patients treated with percutaneous cryotherapy had minor procedural complications including symptomatic perinephric haematoma, asymptomatic and self-limited urine leak identified at imaging, self-limited flank paraesthesia and neuralgia, intercostals neuropraxia[5].

The non-randomised comparative study of 37 patients reported that haemorrhage requiring transfusion occurred in 11% (2/18) patients treated with percutaneous cryotherapy and 28% (5/20) of patients treated with laparoscopic cryotherapy). Deep vein thrombosis occurred in 1 patient treated with each

procedure and loss of kidney (no other details provided) occurred in 1 patient treated with percutaneous cryotherapy[7].

The non-randomised comparative study of 20 patients reported 1 patient had a hypertensive episode after the procedure requiring longer observation and 3 had small renal haematomas which did not require further treatment (it was not reported if these patients were treated with cryotherapy or RFA)[8].

The case series of 108 patients reported significant bleeding after removal of cryoprobes in 4 patients, 3 of whom required arterial embolisation and 2 received blood transfusions (2 units each). This study also reported periprocedural myocardial infarction in 3 patients, acute renal failure in 1 patient and pulmonary embolism at day 8 in 1 patient[9].

The case series of 91 patients reported retroperitoneal haemorrhage requiring angiography in 3 patients, obstructive haematuria requiring stent placement in 1 patient, pulmonary oedema in 1 patient, pulmonary embolus in 1 patient, delayed urosepsis at 1 week in 1 patient and RCC metastasis confirmed by biopsy at 12 months in 1 patient[10].

A case report reported that 1 patient with a history of hypertension, transient ischaemic attack, asthma and Cushing syndrome had perirenal haematoma with a right-side pleural effusion with no evidence of pneumothorax a few hours after the procedure. After being admitted into intensive care and the fluid removed from her chest, a chest X-ray showed resolution of the pleural effusion[11].

The case report also reported a second patient with multiple comorbidities (including atrial fibrillation which she was being treated with anticoagulant therapy and had a recent pacemaker implant) had evidence of a large left-sided pleural effusion 3 days after the procedure. This was drained with a chest tube, her anticoagulation was stopped and she received a blood transfusion. She was readmitted 20 days later but died of a pulmonary embolism in the right main pulmonary artery[11].

Two case reports reported ice ball cracks during cryoablation. The first case led to development of a large perinephric hematoma and a new large bladder haematoma. This patient required arterial embolisation to stop the active bleeding, a right ureteral stent and foley catheter, blood transfusion of 9 units and temporary haemodialysis for acute renal failure during their 21-day hospital stay. This patient died 4 months after discharge from ischaemic cardiomyopathy and chronic obstructive pulmonary disease. The ice ball crack in the second patient led to active bleeding in the upper pole of the left kidney and a moderate sized perinephric hematoma. No further treatment was required and the patient had no recurrence or metastatic disease at 1-year follow-up[12].

Validity and generalisability of the studies

- The study in table 2 with longest mean follow-up is Malcolm (2010)[4] with mean 30 months of follow-up (with a maximum 63 months).
- The majority of the comparative evidence for percutaneous cryotherapy is with laparoscopic cryotherapy rather than nephrectomy or RFA.
- Smaller probes are now available for this procedure but they do not yet appear to have been reported in the published evidence.
- 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, two case series (n = 43) included in table 2 were of percutaneous cryotherapy and one case series (n = 271) had patients with both approaches.

Existing assessments of this procedure

The European Association of Urologists have published guidelines on the management of renal cancer. They 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 retreatments 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 comorbidity who are unfit for surgery should be considered for an ablative approach, e.g. 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). For more information, see 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. Two considered it a minor variation of an existing procedure, unlikely to alter the procedure's safety and efficacy.
- One noted that the percutaneous approach has a shorter history than the laparoscopic approach but it is a faster growing approach because it is less invasive than laparoscopic surgery.
- 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 (but is less in the percutaneous version) but pancreatic, bowel or ureteric injury have also occurred but are rare.

- Additional theoretical adverse events include pneumothorax and thermal skin injury.
- Key efficacy outcomes include is usually success rate of cryoablation based on radiological criteria, retreatment rates, recurrence, disease-specific and overall survival.
- 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, experience with imaging techniques, 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 Disability Discrimination Act. There are 3 patients included in this overview with this condition (1 study in table 26, and 2 in appendix A).

References

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

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.

3. Pirasteh A, Snyder L, Boncher N et al. (2011) Cryoablation vs. radiofrequency ablation for small renal masses. Academic Radiology 18: 97–100.

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

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11. Romero FR, Muntener M, Sulman A et al. (2007) Hemothorax after percutaneous cryoablation of the kidney. European Urology 51: 841–3.

12. Schmit GD, Atwell TD, Callstrom MR et al. (2010) Ice ball fractures during percutaneous renal cryoablation: risk factors and potential implications. Journal of Vascular and Interventional Radiology 21: 1309–12.

Appendix A: Additional papers on percutaneous 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
Abraham JB, Gamboa AJ, Finley DS et al. (2009) The UCI Seldinger technique for percutaneous renal cryoablation: protecting the tract and achieving hemostasis. Journal of Endourology 23:43–9.	Case series n = 12 Follow-up = 11 months	2 patients required blood transfusions because of a drop in haemoglobin. No evidence of persistent disease in follow-up.	Larger studies 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.
Atwell TD, Farrell MA, Callstrom MR et al. (2007) Percutaneous cryoablation of large renal masses: technical feasibility and short-term outcome. AJR American: 1195–200.	Case series n = 40 Follow-up = 9 months	Technical success in 95% (38/40). No local tumour recurrence or progression.	Larger studies in table 2. [and patients included in study in table 2[7]]
Atwell TD, Farrell MA, Callstrom MR et al. (2007) Percutaneous cryoablation of 40 solid renal tumors with US guidance and CT monitoring: initial experience. Radiology 243:276–83.	Case series n = 40 Follow-up = 8 months	8% (3/40) complication rate: 2% (1/40) with large perinephric haemorrhage with hypotension requiring multiple transfusions and hospitalisation for investigation (patient later had myocardial infarction and transient acute renal failure), 1 had large perinephric haemorrhage requiring treatment but not transfusion and 1 (with pre-existing hypertension) had hypertensive crisis and developed pulmonary oedema requiring oxygen supplementation but discharged after 3 days in good condition). No local recurrences.	Larger studies in table 2. [and patients included in study in table 2[7]]
Bachmann A, Sulser T, Jayet C et al. (2005) Retroperitoneoscopy-assisted cryoablation of renal tumors using multiple 1.5 mm ultrathin	Case series n = 7 Follow-up = 13.6 months	All patients had technical success without need for conversion. No evidence of residual tumour or recurrence at	Larger studies in table 2.

cryoprobes: a preliminary report. European Urology 47:474–9.		follow-up.	
Bandi G, Wen CC, Hedican SP et al. (2007) Cryoablation of small renal masses: assessment of the outcome at one institution. BJU International 100:798–801.	Non-randomised comparative study n = 20 (percutaneous) vs 58 (laparoscopic) Follow-up = 19 months	Overall, cancer-specific and recurrence-free survival rates at last follow-up: 88.5%, 100%, and 98.7%. 4 required repeat treatment because of persistent disease and 1 had progression to locally advanced disease.	Patients included in Bandi 2008[1].
Beck SM, Finley DS, Box GN et al. (2008) High-frequency oscillatory ventilatory support during CT-guided percutaneous cryotherapy of renal masses. Journal of Endourology 22:923–6.	Case series n = 7 Follow-up = ?	Study about ventilator support during procedure. No complications related to procedure or anaesthesia.	Larger studies in table 2.
Blaschko SD, Deane LA, Borin JF et al. (2007) Percutaneous cryoablation of an upper pole renal mass: use of contralateral single lung ventilation to avoid pleural and pulmonary puncture. Urology 69:384.e1–3.	Case report n = 1 Follow-up = 4 months	Description of procedure in an obese patient. Atelectasis in left lung on CT after procedure which resolved with reposition of endotracheal tube. Bladder neck stricture treated with balloon dilation. No enhancement of mass on follow-up.	Larger studies in table 2.
Bodily KD, Atwell TD, Mandrekar JN et al. (2010) Hydrodisplacement in the percutaneous cryoablation of 50 renal tumors. AJR American: 779–83.	Case series n = 50 Follow-up = ?	1 patient with haemorrhage resulting from injury to intercostal artery branch. 2 failures occurring early in experience	Larger studies in table 2
Caviezel A, Terraz S, Schmidlin F et al. (2008) Percutaneous cryoablation of small kidney tumours under magnetic resonance imaging guidance: medium-term follow-up. Scandinavian Journal of Urology & Nephrology 42:412–6.	Case series n = 7 Follow-up = 28 months	No radiographic evidence of disease recurrence or new tumour development during follow-up	Larger studies in table 2.
Derweesh IH, Malcolm JB, Diblasio CJ et al. (2008) Single centre comparison of	Non-randomised comparative study n = 26 (percutaneous) vs 26 (laparoscopic)	Residual enhancement in 1.5% vs 2.9%. Complications in 26.9% vs 14.7%.	Later publication from same centre included in table 2[4].

laparoscopic cryoablation and CT-guided percutaneous cryoablation for renal tumours. Journal of Endurology 22:2461–7.	Follow-up = 25 months	Atelectasis developed in 34.6% vs 70.6% (p = 0.005).	
Georgiades CS, Hong K, Bizzell C et al. (2008) Safety and efficacy of CT-guided percutaneous cryoablation for renal cell carcinoma. Journal of Vascular & Interventional Radiology 19:1302–10.	Case series n = 46 (51 lesions) Follow-up = 28 weeks	Technical success in 100% with 20% requiring some form of thermal protection on an adjacent organ. Significant complications in 18%, mostly intercostal or genitofemoral nerve injury, but also bleeding requiring transfusion, cryoshock and haematuria (all recovered fully).	Larger studies in table 2.
Gore JL, Kim HL, and Schulam P. (2005) Initial experience with laparoscopically assisted percutaneous cryotherapy of renal tumors. Journal of Endourology 19: 480–83.	Case series n = 4 Follow-up = 8–17 months	One patient had a suspected recurrence and underwent RFA	Larger studies in table 2.
Gupta A, Allaf ME, Kavoussi LR et al. (2006) Computerized tomography guided percutaneous renal cryoablation with the patient under conscious sedation: initial clinical experience. Journal of Urology 175:447–52.	Case series n = 27 Follow-up = 5.9 months	1 perinephretic haematoma requiring blood transfusion. Of the 16 tumours with data, 15 had no signs of enhancement on follow-up.	Larger studies in table 2. (in table 2 of original overview)
Haber GP, Crouzet S, Remer EM et al. (2010) Stereotactic percutaneous cryoablation for renal tumors: initial clinical experience. Journal of Urology 183:884–8.	Case series n = 10 (13 tumours) Follow-up = 6 months?	All were successfully cryoablated. No intraoperative complications. 1 died of heart failure at 2 months No residual cancer at 6-months Chronic kidney disease upgraded by 1 stage in one patient.	Larger studies in table 2.
Harada J, Dohi M, Mogami T et al. (2001) Initial experience of percutaneous renal cryosurgery under the guidance of a horizontal open MRI system. Radiation Medicine 19: 291–6.	Case series n = 4 Follow-up = 6 weeks	No serious complications	Larger studies in table 2.

Hruby GW, Fine JK, and Landman J. (2006) Ultrasound-guided percutaneous ablation of a renal mass in a renal allograft. Urology 68:891–6.	Case report n = 1 Follow-up = 9 months	No residual tumour on follow-up.	Larger studies in table 2.
Hui GC, Tuncali K, Tatli S et al. (2008) Comparison of percutaneous and surgical approaches to renal tumour ablation: metaanalysis of effectiveness and complication rates. Journal of Vascular Interventional Radiology 19:1311–20.	Systematic review	46 studies included. Primary effectiveness was significantly lower in the percutaneous group (87 vs 94%, $p < 0.05$) but secondary effectiveness was not significantly different. Major complication rate was significantly lower in the percutaneous group (3 vs 7%, $p < 0.05$)	Study compared percutaneous with surgical (including laparoscopic) ablation. Outcomes were not separated by type of ablation (ie. laparoscopic with open or cryotherapy with RFA).
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 = ?	Outcomes were related to the safety of the procedure. Major: significant haemorrhage requiring transfusion (n = 1), conversion to open surgery (n=1) Minor: probe site pain or paraesthesia (n = 10), urinary tract infection (n = 2), and pneumonia infection, minor haemorrhage, elevated serum creatinine, wound infection and respiratory difficulty in 1 patient each.	Larger studies in table 2. (in table 2 of original overview)
Khorsandi M, Foy RC, Chong W et al. (2002) Preliminary experience with cryoablation of renal lesions smaller than 4 centimeters. Journal of the American Osteopathic Association 102: 277–81.	Case series n = 17 Mean follow-up = 30 months	Reduction in the majority of lesion size.	Larger studies in table 2.
Kodama Y, Abo D, Sakuhara Y et al. (2005) MR-guided percutaneous cryoablation for bilateral multiple renal cell carcinomas. Radiation Medicine 23:303–7.	Case report n = 1 Follow-up = 9 months	Description of patient with von Hippel-Lindau disease with five RCCs in the kidneys treated with the procedure. Some tumours showed slight regrowth at 9 month follow-up.	Larger studies in table 2.
Littrup PJ, Ahmed A, Aoun HD et al. (2007) CT-guided percutaneous cryotherapy of renal masses. Journal of Vascular & Interventional Radiology	Case series n = 48 (49 procedures) Mean follow-up = 1.6 years	11.1% (4/48) failures determined on imaging in follow-up but one determined to be inflammatory tissue (one of these patients had von Hippel-Lindau	Larger studies in table 2.

18:383–92.		syndrome) Major complication in 6% (3/49; infection, urinary obstruction and stricture) and minor complications in 22% (11/49; 7 small perinephric haematoma and 4 transient haematuria).	
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, 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].
Miki K, Shimomura T, Yamada H et al. (2006) Percutaneous cryoablation of renal cell carcinoma guided by horizontal open magnetic resonance imaging. International Journal of Urology 13:880–4.	Case series n = 13 Mean follow-up = 35 months (maximum 42 months)	Mild retroperitoneal haematoma occurred in one patient but this subsided spontaneously. There was no enhancement in masses in 11 of 13 cases on 3 month CT scan and neither of these 11 had recurrent disease at last follow-up. The 2 with enhancement had partial nephrectomy which confirmed presence of tumour (one developed multiple lung and ipsilateral adrenal metastases 13 months after surgical resection).	Larger studies in table 2.
Malcolm JB, Gold R, and Derweesh IH. (2007) Pilot experience with transhepatic percutaneous renal cryoablation. Journal of Endourology 21:721–5.	Case series n = 3 Follow-up = 6 months?	No conversion to open procedure. 1 patient had treatment failure with 5-cm mass showing enhancement on 3-month follow-up. 1 had perirenal haematoma requiring blood transfusion.	Larger studies in table 2.
McClung C, Wright A, Pierce K et al. (2007) Case report: percutaneous	Case report n = 1	Description of use of lateral decubitus position to help probe placement. Uneventful	Larger studies in table 2.

cryoablation of a small renal lesion necessitating modified lateral decubitus position. Journal of Endourology 21:1339–40.		postprocedural course.	
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.	n = 180 (99 perc vs 81 lap) 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). Local recurrence in 2 treated with lap cryo (on 12- and 18-month CT scan), but none treated with perc cryo have had local recurrence. No cancer specific deaths.	No significantly new information to table 2 (and despite larger study, has shorter follow-up than studies in table 2)
Permpongkosol S, Link RE, Kavoussi LR et al. (2006) Percutaneous computerized tomography guided cryoablation for localized renal cell carcinoma: factors influencing success. Journal of Urology 176:1963–8.	Case series n = 21 (23 tumours with 25 sessions) Follow-up = 12.3 months	2 recurrences (tumour location and size were major determinants of achieving tumour eradication)	Larger 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 one institution. Treatment of renal tumours has increased as has minimally invasive techniques.	More recent study from first author in table 2[6].
Permpongkosol S, Sulman A, Solomon SB et al. (2006) Percutaneous computerized tomography guided renal cryoablation using local anesthesia: pain assessment. Journal of Urology 176:915–8.	Case series n = 25 (26 sessions) Follow-up = ?	Successful completion in 84.62% (22/26) sessions without sedation (4 required intravenous supplementation).	Larger studies in table 2.
Porter CA, Woodrum DA, Callstrom MR et al. (2010) MRI after technically successful renal cryoablation: early contrast enhancement as a common finding. AJR American:790–3.	Case series n = 23 Follow-up = ?	7 of 8 lesions which were enhanced on MR images within 6-36 hours had no enhancement at the 6-month of follow-up.	Larger studies in table 2.

Schmidt GD, Atwell TD, Leibovich BC et al. (2010) Percutaneous cryoablation of anterior renal masses: technique, efficacy, and safety. AJR American (6) 1418–22.	Case series n = 35 (38 tumours) mean FU = 18 months	All had technical success. 1 adverse event in one patient: pulmonary embolism diagnosed on CT angiography the day after ablation. No local recurrence in 29 with follow-up 3 months or longer.:	larger and comparative studies in table 2. Anterior tumours are covered in Atwell study.
Shingleton WB and Sewell PE, Jr. (2001) Percutaneous renal tumor cryoablation with magnetic resonance imaging guidance. Journal of Urology 165: 773–6.	Case series n = 22 Mean follow-up = 9.1 months	No evidence of recurrence during FU	Larger 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.	n = 162 (101 perc, 52 lap, 9 open) FU = not reported	Flank pain in 11 treated with perc procedure. Cardiovascular complication more common in open procedure and lowest in perc. Perinephretic haematoma reported commonly.	Study on safety only (no new information).
Silverman SG, Tuncali K, vanSonnenberg E et al. (2005) Renal tumors: MR imaging-guided percutaneous cryotherapy--initial experience in 23 patients. Radiology 236: 716–24.	Case series n = 23 (26 tumours) Follow-up = 14 months	24/26 tumours were successfully ablated with 23 requiring one session. 1 patient had haemorrhage requiring blood transfusion 1 had an abscess successfully treated with catheter drainage	Larger studies in table 2. (in table 2 of original overview)
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.	n = 195 (123 perc vs 72 lap) 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.
Tuncali K, Morrison PR, Tatli S et al. (2006) MRI-guided percutaneous cryoablation of renal tumors: use of external manual displacement of adjacent bowel loops. European Journal of Radiology 59:198–202.	Case series n = 14 Follow-up = 10 months	12 of the 15 had follow-up that showed no tumour recurrence	Larger studies in table 2.

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.	Non-randomised comparative study n = 101 (33 laparoscopic cryoablation vs 3 percutaneous cryoablation vs 36 LPN vs 29 RFA) Median follow-up = 24 (cryoablation) vs 42.5 vs 14 months	Local recurrence in 16.7% (6/36) with cryoablation and 44.8% (13/29) with RFA. Pleural injury occurred in 1 patient, anuria in 2 and urine leak, haemothorax, atelactasis in one patient each (in the cryoablation group).	Outcomes related to pain control which was not an outcome of particular interest to the Committee.
Uchida M, Imaide Y, Sugimoto K et al. (136) Percutaneous cryosurgery for renal tumours. British Journal of Urology 75: 132–6.	Case series n = 2 Follow-up = 5 and 10 months	Describes initial experience	Larger studies in table 2.
Vricella GJ, Haaga JR, Adler BL et al. (2011) Percutaneous cryoablation of renal masses: impact of patient selection and treatment parameters on outcomes. Urology 77: 649–54.	n = 52 (54 masses) mean FU = 21 months	Recurrence-free, overall and disease-specific survival was: 96.2%, 98.1% and 100%, respectively. Complication rate was significantly higher when more cryoprobes were used ($p < 0.005$).	Study on safety only and it mainly covers issues on the consideration of patient selection.
Wagner AA, Solomon SB, and Kavoussi LR. (2005) Imaging following cryoablation of a renal lesion. Nature Clinical Practice Urology 2:52–7.	Case report n = 1 Follow-up = ?	Description of procedure followed by PET-CT imaging.	Larger studies in table 2.
Warlick CA, Lima GC, Allaf ME et al. (2006) Clinical sequelae of radiographic iceball involvement of collecting system during computed tomography-guided percutaneous renal tumor cryoablation. Urology 67:918–22.	Case series n = 6 Follow-up = 167.7 days	No evidence of urine leak, fistula formation, ureteral narrowing or stricture formation.	Larger studies in table 2.
Weisbrod AJ, Atwell TD, Frank I et al. (2010) Percutaneous cryoablation of masses in a solitary kidney. AJR American:1620–5.	Case series n = 31 (35 procedures) Follow-up – 14 months	60% (15/25) of patients with ≥3 months follow-up had decrease in renal function (67% [10/15] of these had history of previous renal ablation or partial nephrectomy involving the same solitary kidney) Complications: retroperitoneal haematoma controlled with coil embolisation (1) , urosepsis treated with IV antibiotics (1), temporary ureteral stent requiring because of symptomatic clot (2)	Larger studies in table 2.

		Local tumour control rate was 92%	
Woodrum DA, Atwell TD, Farrell MA et al. (2010) Role of intraarterial embolization before cryoablation of large renal tumors: a pilot study. Journal of Vascular & Interventional Radiology 21:930–6.	Case series n = 11 Follow-up = 15 months	Postprocedural images only available in 10. 40% (4/10) had selective intraarterial tumour embolisation before cryoablation. 1 became hypotensive after the procedure and CT showed perinephrenic haematoma Complete resolution of haematoma and no local recurrence in all follow-up patients.	Larger studies in table 2.
Wyler SF, Sulser T, Ruszat R et al. (2007) Intermediate-term results of retroperitoneoscopy-assisted cryotherapy for small renal tumours using multiple ultrathin cryoprobes. European Urology 51:971–9.	Case series n = 14 Follow-up = 21 months	1 intraoperative complication (bleeding requiring intracorporeal stitch). During follow-up, 2 patients died from unrelated disease and 12 patients had no evidence of local recurrence	Larger studies in table 2.

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

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	30/03/2011	Issue 3 of 12, Mar 2011
Database of Abstracts of Reviews of Effects – DARE (CRD website)	30/03/2011	n/a
HTA database (CRD website)	30/03/2011	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	30/03/2011	Issue 1 of 4, Jan 2011
MEDLINE (Ovid)	30/03/2011	1948 to March Week 3 2011
MEDLINE In-Process (Ovid)	30/03/2011	March 29, 2011
EMBASE (Ovid)	30/03/2011	1980 to 2011 Week 12
CINAHL (NLH Search 2.0/EBSCOhost)	30/03/2011	n/a
BLIC (Dialog DataStar)	30/03/2011	n/a

Trial sources searched on 30/03/2011

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

Websites searched on 30/03/2011
National Institute for Health and Clinical Excellence (NICE)
Food and Drug Administration (FDA) - MAUDE database
French Health Authority (FHA)
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