Radiofrequency ablation of renal tumours

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The Evidence Essential of
Radiofrequency ablation of renal tumours

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ASERNIP-S Evidence Essentials

PURPOSE AND SCOPE
The ASERNIP-S Evidence Essentials document is a structured literature review on a given health technology (procedure or device). It may be produced where current published systematic review evidence is available on a procedure nominated for ASERNIP-S assessment.

The Evidence Essentials is designed to inform on the existence and findings of high-level evidence such as systematic reviews and health technology assessments. In this way it reduces duplication of endeavour and provides rapid and timely information to interested end-users, particularly those who have approached ASERNIP-S to investigate the given topic. Evidence Essentials intends to provide a summary of the high-level evidence base, including an appraisal of the quality and appropriateness of the published evidence; a commentary on the appropriateness of the data to the Australian locality (if possible); and a summary of the overall conclusions of the published evidence.

METHODOLOGY
Evidence Essentials presents summary high-level evidence arising from current, English language systematic reviews (published within two years as either a full systematic review/health technology assessment or a peer-reviewed publication). For this purpose, systematic reviews are defined as those studies that meet all the following criteria as defined by Cook et al (1997) (focused clinical question, explicit search strategy, use of explicit, reproducible and uniformly applied criteria for article selection, critical appraisal of the included studies, qualitative or quantitative data synthesis). Evidence Essentials does not encompass any new synthesis of primary data.

Evidence Essentials also provides a comment on any clinical trials in progress, to provide an indication of the current status of research, and also presents available clinical practice guidelines.

Where necessary, recent non-systematic clinical reviews are used to provide background information on the indications and technology. These papers are cited at the end of the document. Evidence Essentials provides a summary on available high-level evidence on a given topic, but does not include direct input from clinical experts as it is anticipated that the included studies have incorporated clinical input as part of their methodology.

INTRODUCTION

DEVICE/PROCEDURE

Radiofrequency ablation of renal tumours.

Radiofrequency ablation (RFA) of renal tumours is a thermal ablative technology which utilises a high-frequency alternating current to produce heat within the target tissues (clinical range 50 – 100°C) causing denaturation of proteins, rupture of cell membranes, and ultimately cell death (Kutikov et al 2009). This technique is usually performed percutaneously with image guidance (El Dib et al 2009), but may be undertaken using the open or laparoscopic approach. The aim of this treatment is to achieve comparable oncological outcomes relative to the gold standard treatment, nephrectomy, while concurrently promoting nephron-sparing technique and reducing complications, and hence, morbidity (Hui et al 2008).
**INDICATION**
Radiofrequency ablation is available for patients with localised renal cell carcinoma (RCC) or small renal masses (SRM’s) with benign or malignant histopathology that are typically smaller than 4cm in diameter. In the elderly, RFA may be considered a viable option to surgery because this population typically suffer greater morbidities as a result of surgery. RFA may also be a recommended option where contraindication to surgical resection exists (i.e., bilateral or multifocal tumours, solitary kidney, renal insufficiency, or comorbidities that increase the risks of surgery), or where surgery is refused (Hui et al 2008).

**ALTERNATIVE TREATMENTS**
The current gold standard treatment is surgical resection (partial or radical nephrectomy). Partial nephrectomy has been shown to have comparable 5, and 10-year survival rates to radical nephrectomy (Hui et al 2008). Less invasive techniques such as laparoscopic partial nephrectomy and thermal ablative technologies have demonstrated both nephron sparing capabilities and reduced morbidity compared with the open approach.

**CURRENT FUNDING STATUS IN AUSTRALIA:**
RFA for the treatment of renal tumours is currently unfunded under the Medicare Benefits Schedule. However, funding for the use of RFA in non-resectable liver carcinoma is currently included under the Australian Medicare Benefits Schedule:

<table>
<thead>
<tr>
<th>MBS item number</th>
<th>Descriptor</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>50950</td>
<td>NONRESECTABLE HEPATOCELLULAR CARCINOMA, destruction of, by percutaneous radiofrequency ablation, including any associated imaging services, not being a service associated with a service to which item 30419 or 50952 applies</td>
<td>Fee: $754.90 Benefit: 75% = $566.20 85% = $686.80</td>
</tr>
<tr>
<td>50952</td>
<td>NONRESECTABLE HEPATOCELLULAR CARCINOMA, destruction of, by open or laparoscopic radiofrequency ablation, where a multi-disciplinary team has assessed that percutaneous radiofrequency ablation cannot be performed or is not practical because of one or more of the following clinical circumstances: - percutaneous access cannot be achieved; - vital organs/tissues are at risk of damage from the percutaneous RFA procedure; or - resection of one part of the liver is possible however there is at least one primary liver tumour in a non-resectable region of the liver which is suitable for radiofrequency ablation, including any associated imaging services, not being a service associated with a service to which item 30419 or 50950 applies</td>
<td>Fee: $754.90 Benefit: 75% = $566.20 85% = $686.80</td>
</tr>
</tbody>
</table>

**NOTES:** MBS Medicare Benefits Schedule

**AVAILABLE HIGH LEVEL EVIDENCE**
A systematic search of the literature was carried out to identify available, current, English-language systematic reviews, health technology assessments, or peer-reviewed publications. The databases searched and terminologies used are included at Appendix A.

**RELEVANT UNIQUE CITATIONS IDENTIFIED**
- Excise, ablate, or observe: the small renal mass dilemma - a meta-analysis and review (Kunkle et al 2008a)
• Cryoablation or radiofrequency ablation of the small renal mass. A meta-analysis (Kunkle et al 2008b)
• Differences in patterns of care: reablation and nephrectomy rates after needle ablative therapy for renal masses stratified by medical specialty (Long et al 2009)
• Other reviews of interest, guidelines and clinical trials are summarised in Appendix B.

EVIDENCE APPRAISAL

The quality of the identified reviews was assessed using the following criteria to appraise the methodology:

<table>
<thead>
<tr>
<th>Domain</th>
<th>Kunkle et al 2008a</th>
<th>Kunkle et al 2008b</th>
<th>Long &amp; Park 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>To perform meta-analysis of published data evaluating nephron sparing surgery,</td>
<td>To perform a comparative meta-analysis evaluating cryoablation and RFA as primary</td>
<td>To study differences in reablation rates, modality utilization, and outcomes after</td>
</tr>
<tr>
<td></td>
<td>cryoablation, RFA, and observation for small renal masses.</td>
<td>treatment for SRMs.</td>
<td>renal tumour cryoablation, and RFA stratified by medical specialty (i.e., urology</td>
</tr>
<tr>
<td></td>
<td>.</td>
<td></td>
<td>and radiology subspecialties).</td>
</tr>
<tr>
<td>Selecting</td>
<td>Sufficient</td>
<td>Sufficient.</td>
<td>Inclusion and exclusion unclear.</td>
</tr>
<tr>
<td>Study flow</td>
<td>Not reported.</td>
<td>Table of included studies.</td>
<td>Listed studies by intervention.</td>
</tr>
<tr>
<td>Validity assessment</td>
<td>Minimal assessment in discussion.</td>
<td>Minimal assessment in discussion.</td>
<td>Limitations of study reported in discussion.</td>
</tr>
<tr>
<td>Data abstraction</td>
<td>Not described.</td>
<td>Not described.</td>
<td>Not described.</td>
</tr>
<tr>
<td>Data synthesis</td>
<td>Data synthesis (meta-analysis). Pooled data, multivariate regression analysis,</td>
<td>Data synthesis (meta-analysis). Pooled data, univariate and multivariate analyses. (P&lt;0.05 defines significance)</td>
<td>Statistical methods not explained. Pooled data, stratification on ablative</td>
</tr>
<tr>
<td></td>
<td>relative risk. (P&lt;0.05 defines significance).</td>
<td></td>
<td>approaches, and comparisons using P&lt;0.05 to define significance.</td>
</tr>
</tbody>
</table>

Not reported, NR; radiofrequency ablation, RFA; small renal masses, SRMs

All reviews were analyses of case series or level IV evidence. Data was typically analysed in terms of numbers of tumours rather than against numbers of patients but this was not always clear. There was considerable heterogeneity between studies. Long-term data was not available.

Kunkle and colleagues published two similar reviews in 2008 (Kunkle 2008 a and b). While all included were listed studies in Kunkel 2008b, this information was not provided in Kunkle 2008a therefore potential data overlap between the two reviews is unknown. Similar outcomes were reported in both studies; however, Kunkle 2008b further reported reablation rates. The two studies failed to control for certain confounding variables including the different approaches to each thermal ablative technique (i.e., open, laparoscopic, or percutaneous). Several patient characteristics were shown to be statistically different between treatment groups at baseline in one or both studies (age, histopathology of tumours, pre-operative biopsy rates.). The mean time at which local tumour progression was assessed after treatment is not clear. A recent
editorial provides further comment on the two studies (Caddedu & Raman 2008).

Due to the apparent overlap between Kunkle (2008a) and (2008b) regarding outcomes for RFA, this Evidence Essential shall report the outcomes of the study with the most comprehensively reported methodology (Kunkle 2008b).

Long & Park (2009) did not provide a clear description of study methodology. However, this study made an attempt to stratify outcomes dependent on procedural approach to RFA and cryoablation. This led to disproportionate numbers between groups. Long et al (2009) reported reablation rates as a primary outcome of the study but did not report the rate of local recurrence. This study reported the rate of salvage nephrectomy between interventions. Data is also stratified according to specialist (urologist or interventional radiologists), and comment is provided on specialist preferences and their experience. Safety outcomes were not reported.

**SUMMARY OF FINDINGS**

Kunkle et al (2008b) assessed oncological outcomes of RFA compared to cryoablation in 47 case series for 1375 renal tumours. Each ablative technique is presented regardless of approach; that is, open, laparoscopic and percutaneous approaches are reported together. Mean follow-up was 15.8 months for RFA compared to 22.5 months for cryoablation (range or confidence intervals not provided). Overall rates for key outcomes are presented. RFA (12.9%; 100/775 lesions) has significantly higher rates of tumour progression than cryoablation (5.2%; 31/600 lesions), \( P<0.0001 \). Reablation rates are also significantly higher following RFA were reported as (8.5%; 66/775) compared with cryoablation (1.3%; 8/600), \( P<0.0001 \). The rates of progression to metastatic disease were similar between RFA (2.5%; 19/775 lesions) and cryoablation (1%; 6/600 lesions), \( P=0.06 \). Univariate and multivariate models analysing local tumour progression and metastatic disease were conducted. Forty-three (91%) of studies reported complete data and were included in the regression analyses. The incidence of local tumour progression correlated significantly with ablation modality in the univariate (\( P=0.001 \)) and multivariate (\( P=0.003 \)) regression analyses. The incidence of malignant pathology was marginally associated with duration of follow-up (\( P=0.076 \)). No other variables were associated with local tumour progression.

Overall, this study shows the incidence of local tumour progression is significantly lower in cryoablation compared with RFA but that no statistical differences were detected in the incidence of progression to metastatic disease. The authors conclude that ablative technologies are viable strategies for small renal masses based on short-term outcomes but that long-term outcomes are lacking.

Long and Park’s (2009) review assessed reablation rates for RFA and cryoablation stratified in terms of the surgical approach (i.e., open, laparoscopic or percutaneous) for 24 studies (\( n = 620 \); this figure was used interchangeably between patient numbers and renal masses). The number of patients for each RFA approach were as follows: open (0), laparoscopic (54/283; 19%), and percutaneous (229/283; 80%); and for cryoablation: open (22/337; 6.5%), laparoscopic (236/337; 76%), and percutaneous (59/337; 18%). Overall reablation rates for RFA were reported as 7.4% vs. 0.9% for cryoablation (\( P<0.05 \)) to achieve 95% success. Reablation rates for the open approach could not be
compared between groups since no patients underwent primary RFA. Reablation rates for the laparoscopic group were reported as RFA (0%) and cryoablation (0%); \( P=\text{ns} \); and for the percutaneous group were reported as RFA (8.8%) vs. cryoablation; (2.5%) \( P<0.05 \). The incidence of salvage nephrectomy was reported as cryoablation (2.4%) vs. RFA (1.1%). Interventional radiologists reported more experience with renal RFA than with cryoablation, whilst urologists were reported to use cryoablation more frequently than RFA. Mean follow-up was 20 months for both RFA (range 7 to 55 months) and cryoablation (range 6 to 25 months).

These authors concluded that that reablation after RFA is more common than cryoablation and that an increased number of RFA reablations is required to achieve 95% cancer-specific success rates. However, they suggest that further research is needed to inform on the comparative effectiveness of each modality. With regard to surgical approach, reablation rates were shown to be significantly higher for the percutaneous approach.

OTHER CONSIDERATIONS

- No long-term outcomes are currently available.
- Safety outcomes for RFA are poorly reported, and may be a reflection of the evidence base.
- The choice of treatment option may depend on the patient and the stage of the disease. Therefore, comparison of results across treatment types may not be a clear representation of treatment outcomes.
- Evidence in relation to other similar ablative technologies (e.g. high intensity focused ultrasound, microwave, etc) is currently lacking.
- Potential improvements of RFA and other similar approaches may include a nephron-sparing technique with likelihood of reduced morbidity.
- All the primary studies included in these reviews were case series conducted in single-centres. The authors of the included reviews suggest that further research including multi-centre trials and studies using higher level evidence is required.

CONCLUSIONS

Two recent reviews were identified which reported on the effectiveness of radiofrequency ablation of renal tumours. The majority of data in the reviews was based on case series evidence and safety was not addressed in detail, which may be a reflection of the available evidence base. Prospective randomised trials are currently underway and higher level evidence is likely to emerge within the next few years. A comprehensive systematic review may be valuable particularly in relation to safety.

Please note that this Evidence Essentials document is not a comprehensive systematic review of the safety and effectiveness of radiofrequency ablation for the treatment of renal tumours, and should not be used for this purpose. This document presents a summary of the current, available high-level evidence and does not include direct input from clinical experts.
REFERENCES

SYSTEMATIC REVIEW EVIDENCE USED TO PRODUCE THIS EVIDENCE ESSENTIALS DOCUMENT

Kunkle DA, Egleston BL, Uzzo RG. Excise, ablate or observe: the small renal mass dilemma – a meta-analysis and review. *Journal of Urology* 2008a Apr; 179(4): 1227 – 1233


FURTHER REFERENCES USED


# APPENDIX A

## DATABASES SEARCHED AND SEARCH TERMS USED

<table>
<thead>
<tr>
<th>Database</th>
<th>Search terms</th>
<th>Date searched</th>
</tr>
</thead>
<tbody>
<tr>
<td>York CRD</td>
<td>(&quot;renal carcinoma&quot; and &quot;renal tumours&quot;) and (&quot;radiofrequency ablation&quot;)</td>
<td>4 August 2009</td>
</tr>
<tr>
<td><a href="http://www.crd.york.ac.uk/crdweb/">http://www.crd.york.ac.uk/crdweb/</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entrez PubMed</td>
<td>(&quot;renal carcinoma&quot; and &quot;renal tumours&quot;) and (&quot;radiofrequency ablation&quot;)</td>
<td>4 August 2009</td>
</tr>
<tr>
<td>The Cochrane Library</td>
<td>(&quot;renal carcinoma&quot; and &quot;renal tumours&quot;) and (&quot;radiofrequency ablation&quot;)</td>
<td>4 August 2009</td>
</tr>
<tr>
<td><a href="http://www.cochrane.org/">http://www.cochrane.org/</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Controlled Trials</td>
<td>(&quot;renal carcinoma&quot; and &quot;renal tumours&quot;) and (&quot;radiofrequency ablation&quot;)</td>
<td>16 July 2009</td>
</tr>
<tr>
<td><a href="http://www.controlled-trials.com/">http://www.controlled-trials.com/</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Trials.gov</td>
<td>(&quot;renal carcinoma&quot; and &quot;renal tumours&quot;) and (&quot;radiofrequency ablation&quot;)</td>
<td>4 August 2009</td>
</tr>
<tr>
<td><a href="http://www.clinicaltrials.gov/">http://www.clinicaltrials.gov/</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australian New Zealand Clinical Trials Registry</td>
<td>(&quot;renal carcinoma&quot; and &quot;renal tumours&quot;) and (&quot;radiofrequency ablation&quot;)</td>
<td>16 July 2009</td>
</tr>
<tr>
<td>Trip database</td>
<td>(&quot;renal carcinoma&quot; and &quot;renal tumours&quot;) and (&quot;radiofrequency ablation&quot;)</td>
<td>16 July 2009</td>
</tr>
<tr>
<td><a href="http://www.tripdatabase.com/index.html">http://www.tripdatabase.com/index.html</a></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTES:** CRD Centre for Reviews and Dissemination
ADDITIONAL INFORMATION

CLINICAL GUIDELINES


CURRENT ONGOING CLINICAL TRIALS IDENTIFIED

Five current clinical trials were identified. These current trials include:

• Magnetic-resonance-guided thermal radiofrequency ablation in treating patients with primary kidney cancer, liver metastases, or other solid tumors
  - NCT00006255
  - John R. Haaga, Ireland Cancer Centre, Cleveland, Ohio, USA
  - Status ongoing; study start date April 2000; estimated study completion date not provided

• Cryoablation versus radiofrequency ablation for small renal masses
  - NCT00922948
  - Anil Kapoor, McMaster University, Hamilton, Canada
  - Study start date September 2009; estimated study completion date October 2010

• Palliative radiofrequency ablation in metastatic renal cell carcinoma patients
  - NCT00891475
  - Illa Tsimafeyeu, Beijing, China
  - Study start date May 2008; estimated study completion date May 2010

• RF ablation of treatment of metastatic lesions in patients undergoing antiangiogenic therapy for stage IV renal cell carcinoma
  - NCT00601120
  - Rupal Bhatt, Beth Israel Deaconess Medical Centre, Boston, Massachusetts, USA
  - Study start date June 2007; estimated primary completion date June 2010

• Comparison between surgery and radiofrequency for treatment of renal tumours
  - NCT00221728
  - Nicholas Grenier, University Hospital, Bordeaux, France
  - Study start date April 2005; estimated study completion date April 2011

OTHER REVIEWS

• Two additional reviews are presented below which were outside the direct scope of this Evidence Essential, but may provide additional information regarding specific aspects of renal tumour ablation. Reasons for study exclusion are provided.

• A recent systematic review was identified which investigated RFA in conjunction with cryoablation (Hui et al 2008). Percutaneous approaches (RFA and cryoaablation) were compared with surgical approaches for renal tumour ablation. PubMed was searched to August 2006 using defined search terms. Inclusion criteria and review methodology were well described. Studies were comprehensively listed, and heterogeneity between studies was summarised using the I² statistic, although a comment on study quality was not provided. Data abstraction and patient characteristics are provided, and data synthesis is explained, with P<0.05 used to define significance.

In total, 46 studies were included. Most case series that comprised the percutaneous group were RFA studies (21/28), while the remainder used cryoaablation. Primary (ablation) and secondary (reablation) effectiveness outcomes were reported. For primary ablation, surgery was more effective than the percutaneous approach (0.94
(95% CI 0.92-0.96) versus 0.87 (95% CI 0.82-0.91), $P<0.05$). However, for secondary ablation, the effectiveness of the surgical approach was similar to the percutaneous approach (0.95 (95% CI 0.93-0.97) versus 0.92 (95% CI 0.90-0.95), $P>0.05$). Fewer patients underwent serious complications following percutaneous ablation than surgical ablation (0.031 (95% CI 0.02-0.045) versus 0.074 (95% CI 0.053-0.097), $P<0.05$). Mean length of follow-up was 13.1 (standard deviation 7.5) months for the percutaneous approach, and 15.9 (standard deviation 8.3) months for the surgical approach.

The overall conclusion was that a percutaneous approach was safer than an open approach, and was equally effective. However, more than one treatment was needed to treat the tumour completely.

- A recent commentary by El Dib et al (2009) was identified which utilised a systematic literature search, but which did not meet other criteria of a systematic review as defined by Cook et al (1997). Therefore this review was excluded from analysis. In summary, statements detailing any defined *a priori* methodology, and comment on study quality and heterogeneity, were not provided. While original data from the primary studies is presented in a simple manner, no attempt was made to synthesise outcomes across studies. Of interest, safety data were reported in terms of major and minor complications but this data was not statistically described or analysed.