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A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Focal Ablation 3: Focal Tumour Ablation for Renal Cell Carcinoma

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Evidence Summary

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

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INTRODUCTION

In 2015, it was estimated that 6200 Canadians would receive a diagnosis of kidney cancer, and 1800 Canadians would die from the disease [1]. The most frequent type of kidney cancer is renal cell carcinoma (RCC). The overall incidence is growing by 2% per year, and most identified are small renal masses [2].

Traditional treatment for localized, nonmetastatic RCC is surgery (partial or radical nephrectomy). With the goal of providing a less invasive treatment option, focal ablation treatments such as radiofrequency ablation (RFA), microwave ablation (MWA) and cryoablation therapy (CAT) have been introduced more recently for small (usually <4 cm), localized RCC. Among the potential advantages of these ablative techniques are reduced morbidity, shorter hospitalization, faster recovery, preservation of renal function, lower costs, and the possibility to treat patients who are older or at high risk for surgery [3]. However, these technologies are not universally used, and there is variation of practice in Ontario.

In order to inform decision making, the Working Group of the Interventional Oncology Steering Committee developed this evidentiary base. Based on the objective of this evidence summary, the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

The objective of this evidence review was to determine the effectiveness of focal tumour ablation, including radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation therapy (CAT) for the treatment of patients with localized renal cell carcinoma (RCC).

Three research questions were used to develop the evidence base that could be used to meet this objective:

- What is the effectiveness of focal ablation for the treatment of patients with RCC?
- What are the toxicities associated with focal ablation for RCC?
- What patient populations are most likely to benefit from focal ablation for RCC?

TARGET POPULATION

Patients with localized, non-metastatic RCC.

INTENDED PURPOSE

To provide a systematic literature review that will be one of the six components of the Recommendation Report being developed by the Interventional Oncology Steering Committee. The additional components to their report are demand forecasting, costing analysis, jurisdictional review, system capacity, and current state.

INTENDED USERS

Interventional radiologists, radiation oncologists, urological surgeons, medical oncologists, and healthcare professionals caring for patients with RCC.

METHODS

This evidence review was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing guidelines and systematic reviews: If one or more existing systematic reviews of reasonable quality were identified that addressed the research questions, then those systematic reviews would form the core of the evidence review.
2. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

Search for Systematic Reviews

Systematic reviews published as stand-alone systematic reviews, or as part of practice guidelines, were considered eligible for inclusion.

The electronic databases MEDLINE, EMBASE, and the Cochrane Library were searched from 2008 to May 29, 2015 for guidelines and systematic reviews. In addition, the authors' files were searched, and an Environmental Scan was conducted searching the web sites of some of the major guidelines producers worldwide (i.e., European Society of Medical Oncology [ESMO] [http://www.esmo.org/Guidelines], National Guideline Clearinghouse [http://www.guideline.gov/], National Institute for Health and Care Excellence [NICE] [https://www.evidence.nhs.uk/], the European Association of Urology [http://uroweb.org/], the American Urological Association [https://www.auanet.org/], and Kidney Cancer Canada [http://www.kidneycancercanada.ca/]). The search terms and the search strategies are reported in Appendix 3A.

Search for Primary Literature

The search of the primary literature was aimed to cover areas that were left incomplete by the eligible systematic reviews.

Literature Search Strategy

The electronic databases MEDLINE, EMBASE, and the Cochrane Library (Cochrane CENTRAL) were searched from 2013 to May 13, 2016 for primary studies of MWA. The search terms and the search strategies are reported in Appendix 3B.

Study Selection, Data Extraction and Analysis

The methodologist (FB) reviewed the titles and abstracts of retrieved citations to identify potentially relevant articles that were then retrieved for full-text review. The methodologist reviewed the full text of the systematic reviews and of the primary studies selected at the title and abstract level. The selection criteria applied are reported in Appendix 2.

Identified systematic reviews were further evaluated based on their clinical content and the similarity of the questions they addressed to the questions and objectives of this systematic review. Systematic reviews that were found to be directly relevant, and therefore potential foundations for this evidence review, were assessed using "a measurement tool to assess the methodological quality of systematic reviews" (AMSTAR) tool [4]. The results of the assessments were used to determine whether an existing systematic review could be used as evidentiary base. Any identified reviews that did not meet the criteria above, or that were otherwise not incorporated as part of the evidence base, are reported in the reference list but not described or discussed any further.

For primary studies, it was planned to use the Cochrane Risk of Bias Tool [5] to evaluate the quality of included randomized controlled trials (RCTs), and the Cochrane Risk Of Bias In Nonrandomized Studies of Interventions tool (ROBINS-I) for nonrandomized trials [6].

The data from the included systematic reviews and included primary studies, as well as their quality assessments were summarized in tables. All extracted data and information was audited by an independent auditor. The results of the highest quality systematic reviews and those most relevant to the questions asked by the Panel are reported in detail in the Results section. The initial plan was to pool in a meta-analysis the RCTs if they were sufficiently clinically homogeneous, and to follow a narrative approach if the RCTs were heterogeneous.

RESULTS

Search for Existing Systematic Reviews

The study flow chart in Appendix 3A reports the details of the search and selection process for systematic reviews. The methodologist (FB) reviewed the titles and the abstracts against the selection criteria, first of guidelines and then of systematic reviews. Twenty-one guidance and 50 systematic review documents were considered potentially relevant after title and abstract review. The full text of these documents was retrieved and reviewed by the methodologist (FB) and by two other members of the Working Group (AK and MOB), who selected one guideline [7] and 15 systematic reviews. Eight of the systematic reviews, reported in nine publications, included comparative along with non-comparative studies [8-16]; the other seven included only non-comparative trials [17-23] and they are not discussed any further. The general characteristics of the included systematic reviews of comparative

studies are presented in Table 1. A list of the systematic reviews that were excluded, with the reasons for exclusion, is reported in Appendix 4.

Table 1. Focal ablation: summary table of included systematic reviews of thermal ablation – RCC.

Author, date, funding source,	Search cut-off date	Review objectives/ Design	Study Number and design included	Population	Intervention/ comparison(s)	Outcomes
Systematic reviews that were part of guidelines						
Ljungberg, 2015 [7] **Funding:** European Association of Urology	31 Oct 2013	Guideline on general management of RCC	18 comparative studies	Pts >18 yrs old with primary RCC clinical stage T1aN0M0.	Multiple interventions	OS Measures of disease control; perioperative complications, recovery and QOL; renal function, long term outcomes on cardiovascular disease and related events.
Stand-alone systematic reviews*						
Pierorazio, 2016 [8] **Funding** U.S. Government	Oct 14 2014	[A]To compare the effectiveness and safety of the available management strategies on health outcomes To compare the benefits and harms of the available management strategies in different pts subgroups **Design:** SR of summary data	30 observational studies; 2 prospective and 28 retrospective.	Pts with localized renal cancer	Thermal ablation versus radical nephrectomy Thermal ablation versus partial nephrectomy CA vs. partial nephrectomy (open or laparoscopic) Thermal ablation vs. active surveillance RFA vs. radical nephrectomy RFA vs. partial nephrectomy	**Oncological outcomes:** OS MFS RFS **Renal function outcomes:** changes in serum creatinine, GFR, incidence of chronic kidney disease **QOL** **Perioperative outcomes** blood loss, blood transfusion rate, conversion to open surgery, and LoS **AE**

Author, date, funding source,	Search cut-off date	Review objectives/ Design	Study Number and design included	Population	Intervention/ comparison(s)	Outcomes
Tang, 2014 [9] **Funding:** National Natural Science Foundation of China and the National Major Scientific and Technological Special Project for Significant New Drugs Development (China)	Oct 1, 2013	To evaluate the safety and efficacy of two strategies for the management of SRTs **Design:** SR of summary data with meta-analysis	9 comparative studies: 2 prospective and 7 retrospective	Pts with SRTs	LRCA vs. LPN	**Surgical and oncological outcomes:** Renal function **Perioperative outcomes:** Operative time Blood loss AE
Klatte, 2014, [10] **Funding**: nr	Sept 4, 2013	To compare safety and oncologic outcomes of 2 different strategies **Design:** SR of summary data with meta-analysis	13 comparative, retrospective, non-RCTs,	Pts with SRTs	LRCA vs. LPN/ robot-assisted LPN	**Oncologic outcomes:** Local tumour progression **Perioperative outcomes:** Operative time, blood loss, LoS, AE
Katsanos, 2014 [11] **Funding**: nr	Aug 2013	To compare surgical techniques with thermal ablation **Design:** SR of summary data with meta-analysis	6 comparative studies (1 RCT and 5 retrospective cohort) studies	Pts with T1 stage renal tumours	Thermal ablation vs. surgical nephrectomy	**Oncologic outcomes:** OS, PFS, renal function **Perioperative outcomes** Operative time, blood loss, length of stay, AE
Kapoor, 2013 [12] **Funding**: *nr*	Jan 2011	To evaluate the safety and effectiveness of CA **Design:** SR of summary data	23 studies: 18 case series and 5 retrospective comparative studies with sample size ≥30	Pts with SRTs	CA vs. RFA, and LPN	**Technical success** **AE** (definitions were very variable)
MacLennan, 2012a [13] MacLennan, 2012b [14] **Funding**: UCAN Cancer Charity and MacMillan Cancer Charity	Jan 2012	To review literature reporting on QOL and perioperative outcomes of surgical management of localized renal cancer **Design:** SR of summary data with meta-analysis	3 studies out of 39 included were on thermal ablation: one was a prospective comparative non-RCT. One was a matched-pair study. One study (matched-comparison) compared laparoscopic CA with open PN	Pts with localized RCC	LRCA vs. PN, RN, laparoscopic or open or robotic compared with any intervention or no intervention	**Oncologic outcomes** OS rate at 5 and 10 years, CSS, local recurrence, metastasis, positive surgical margins. **Perioperative outcomes:** analgesic requirement, length of hospital stay, time to normal activity level, surgical morbidity and complications, ischemia time, renal function, blood loss, operative time, need for blood transfusion,

Author, date, funding source,	Search cut-off date	Review objectives/ Design	Study Number and design included	Population	Intervention/ comparison(s)	Outcomes
						and perioperative mortality. **QOL**
Barwari, 2011 [15] **Funding**: *nr*	Dec 2010	To assess the best combination of ablation technique In situations where thermal ablation is considered suitable **Design:** SR of summary data	7 observational comparative studies for complication rates of CA and 1 study for RFA 6 case series: 3 on RFA and 3 on CA. Studies had a min follow-up of 36 months and >70 cases.	Pts with SRTs	Percutaneous vs. laparoscopic and CA vs. RFA	**Operative outcomes** LoS, costs, salvage surgery after recurrence AE
El Dib, 2009 [16] **Funding:** nr	Sept 2008	To examine the state of knowledge of RFA in the treatment of renal tumours **Design:** SR of summary data	6 retrospective comparative studies and 1 cross sectional study; 4 case series; 3 retrospective non-comparative studies	Pts with T1a renal disease	RFA vs. PN or RN RFA vs. CA	**Operative outcomes** CSS, radiographic success, tumour recurrence, local tumour progression or distant metastases, need for repeat ablation, renal function, AE

*These systematic reviews included comparative and noncomparative studies.
[A] This report had also other focus on diagnosis, and the questions reported here were Key questions 3a and 3b of the report.

AE = adverse events; CA = cryoablation; CSS = cancer-specific survival; GFR = glomerular filtration rate; LRCA = laparoscopic renal cryoablation; LoS = length of stay; LPN = laparoscopic partial nephrectomy; MFS = metastasis-free survival; *nr* = not reported; OS = overall survival; PFS = progression-free survival; PN = partial nephrectomy; Pts = patients; QOL = quality of life; RCC = renal cell carcinoma; RCTs = randomized controlled trials; RFA = radiofrequency ablation; RFS = recurrence-free survival; RN = radical nephrectomy; SR = systematic review; SRTs = small renal tumours; UCAN = Urological Cancer Charity, UK; vs = versus; yrs = years.

Members of the Working Group evaluated the systematic reviews for their clinical content, and the methodologist further assessed those considered clinically relevant (9 of 10 publications) [7-16] using the AMSTAR tool [24]. Table 2 shows the results of the AMSTAR assessment.

Table 2. AMSTAR assessment of included systematic reviews of renal cell carcinoma

Study	An *a priori* design provided	Duplicate study selection and data extraction	Comprehensive literature search performed	Status of publication used as an inclusion criterion	List of studies (included and excluded) provided	Characteristics of included studies provided	Quality of included studies assessed and documented	Quality of included studies used appropriately in formulating conclusions	Methods used to combine the findings of studies appropriate	Likelihood of publication bias assessed	Conflict of interest included
Ljungberg, 2015 [7]	Y	Y	Y	Y	Y	N	N	N	Y	N	Y
Pierorazio, 2016 [8]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Tang, 2014 [9]	Y	Y	Y	Y	N[a]	Y	Y	N	Y	N	Y
Klatte, 2014, [10]	Y	Y	Y	N	N[a]	N	Y	Y	Y	Y	N
Katsanos, 2014 [11]	Y	Y	Y	N	N[a]	Y	Y	Y	Y	Y	Y
Kapoor, 2013 [12]	Y	Y	Y	N	N[a]	Y	N	N	Y	N	Y
MacLennan, 2012a, 2012b [13] [14]	Y	Y	Y	N	N[a]	Y	Y	Y	Y	N	Y
Barwari, 2011 [15]	Y	N	N	N	N[a]	Y	N	N	Y	N	Y
El Dib, 2009 [16]	Y	N	Y	N	N[a]	Y	N	N	Y	N	Y

[a] only included studies are listed

The methodologist (FB) identified eight relevant comparisons, which are illustrated in Table 3 along with the studies that explored them:

Table 3. Comparisons that were considered in the included systematic reviews*

Study	1. CA vs. PN	2. LCA vs. LPN	3. RFA vs. PN[A]	4. RFA vs. RN	5. TA vs. PN	6. TA vs. RN	7. MWA vs. PN or RN	8. TA vs. surveillance
Ljungberg, 2015 [7]	✓	*nr*	✓	*nr*	*nr*	*nr*	✓[a]	*nr*
Pierorazio, 2016 [8]	✓	✓	✓	✓	✓	✓	*nr*	✓
Tang, 2014 [9]	*nr*	✓	*nr*	*nr*	✓	*nr*	*nr*	*nr*
Klatte, 2014, [10]	*nr*	✓	*nr*	*nr*	✓	*nr*	*nr*	*nr*
Katsanos, 2014 [11]	✓	*nr*	*nr*	*nr*	✓	*nr*	✓	*nr*
Kapoor, 2013 [12]	*nr*	✓	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
MacLennan, 2012a [13] MacLennan, 2012b [14]	✓	✓	*nr*	*nr*	*nr*	✓[a]	*nr*	*nr*
Barwari, 2011 [15]	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*	*nr*
El Dib, 2009 [16]	*nr*	*nr*	✓	✓	*nr*	*nr*	*nr*	*nr*

* Comparisons of different approaches of CA or RFA (i.e., laparoscopic versus percutaneous) have not been reported in this table because this was not of interest to this report.
[a] The authors searched for studies on microwave ablation, but did not find any.

CA = cryoablation; LCA = laparoscopic cryoablation; LPN = laparoscopic partial nephrectomy; MWA = microwave ablation; PN = partial nephrectomy; *nr* = not reported; RFA = radiofrequency ablation; RN = radical nephrectomy; TA = thermal ablation.

The systematic review by Pierorazio et al. [8] scored the best among others when assessed with the AMSTAR. In addition, this review covered the largest number of comparisons identified, including evidence regarding RFA and cryoablation. This report, however, did not include data about MWA because the authors considered this procedure still an experimental intervention (personal communication, Phillip Pierorazio, August 27, 2015, 9:26 am).

The members of the Working Group considered the Pierorazio et al. review [8] as having adequately addressed the research questions with respect to RFA and cryoablation, so no further literature search was necessary for those topics. The full Pierorazio et al. report [8] can be found at:

https://effectivehealthcare.ahrq.gov/ehc/products/601/2185/renal-cancer-report-160224.pdf, and the detailed results directly relevant to this evidence summary can be found starting on page 44 of the original report.

Systematic Review of Primary Literature on Microwave Ablation

For primary studies related to MWA, the Working Group members used the evidence identified by two previous systematic reviews [7,11]. The data for these are current up to 2013, which was the end date for the last literature search of these reviews. The Working Group conducted a new search for more recent studies since that date.

Literature Search Results

Two studies were included after full-text selection: an earlier RCT identified by one of the included systematic reviews [25], and a retrospective observational study [26], identified by our search. The study flow chart in Appendix 3B presents the results of study selection in detail. Table 4 presents the characteristics, and Table 5 presents the summary results of the included studies.

Table 4. General characteristics of the studies selected for inclusion.

Author, year, (ref), Country, Funding	Design, Data collection Follow-up	Population	Intervention(s)	Control(s)	Outcomes
RCT					
Guan, 2012 [25] **China** **Funding:** *nr*	RCT **Data collection:** Started in December 2004 **Follow-up:** (median, range) MWA: 32, 24 to 54 mos PN: 36, 25 to 66 mos	N = 102 pts with a solitary small renal tumour pT1 stage RCC	MWA*: open: n = 28 laparoscopic: n = 20	PN: open: n = 19 laparoscopic: n = 35	RFS CSS AE Renal function
Observational studies					
Yu, 2015 [26] **China** **Funding:** government funding	Retrospective chart review **Data collection:** Apr 2006 to Oct 201 2 **Follow-up (median, range):** MWA: 25.8 (3.7 to 75.2) mos LRN: 26.1 (3.0 to 73.6) mos	N = 426 pts with RCC ≤4 cm diameter	Perc MWA (n= 98 [23%], 105 lesions)	LRN (n= 328 [77%], 331 lesions)	OS CSS MFS Recurrence Renal function AE

*Patients (n=2) who were found to have an incomplete ablation at one-month follow-up were reablated.
AE = adverse events; CSS = cancer-specific survival; mos = months; LRN = laparoscopic radical nephrectomy; MFS = metastasis-free survival; MWA = microwave ablation; OS = overall survival; Perc = percutaneous; PN – partial nephrectomy; pts = patients; RCC = renal cell carcinoma; ref = reference number; RFS = recurrence-free survival.

Table 5. Summary results of primary studies of microwave ablation

Author, year, (ref)	Intervention and comparison	Survival	Renal function*	AE, LoS	Recurrence	Authors conclusions
RCTs						
Guan, 2012 [25]	MWA[A] vs. PN	**RFS rate** at 3 yrs: For all pts: 91.3%; 95% CI, 74.7 to 97.2 vs. 96.0%; 95% CI, 83.8 to 99.1, p=0.5414 For pts with pathologically confirmed RCC: 90.4%; 95% CI, 65.3 to 97.6 vs. 96.6%; 95% CI, 78.0 to 99.6, p=0.4650 **CSS:** 100% vs. 100%	Decline in eGFR: A) from pre- to postoperative: 5.5% vs. 19.4%, p=0.0092 B) at median 36 mos: 6.7% vs. 7.9%, p=1.0000	**Complication rate:** 12.5% vs. 33.3%, p = 0.0187 **Estimated blood loss (mean ± SD, range):** 138±69.4, 0 to 200 vs. 465.9±577.1, 50 to 3000, p=0.0002 **LoS median, (range):** 15ds, (13ds to 26ds) vs. 19ds , (10ds to 47ds), p=0.7566	*nr*	MWA has equivalent or better (in the short term) efficacy compared with PN for pts with SRTs. Longer follow-up required.
Observational studies						
Yu, 2015 [26]	MWA[B] vs. LRN	**OS rate:** At 1 yr: 98.3% vs. 99.7% (p values *nr*) At 3 yrs: 93.3% vs.98.6% (p values *nr*) At 5 yrs: 82.6% vs. 98.6%, p=0.0004 **CSS rate** at 5 yrs: 97% vs. 98%, p=0.38	Pts treated with MWA showed less renal function damage than LRN p<0.0001	**Major complication rates:** 1.7% vs. 1.5%, p=0.75 **Estimated blood loss:** 7.5mL (range 5.0 to 20.0) vs. 30.0mL (range 10 to 1000), p<0.0001 **LoS (mean ± SD, range):** 5.2ds ± 2.9ds (range 2ds to 18ds) vs. 11.5 ds ± 5.1 ds (range 2 ds to 43 ds), p<0.0001	At 32 mos: 1 local progression vs. 0	MWA and laparoscopic RN provide comparable results in patients with small RCC.

*Determined by estimated glomerular filtration rate (eGFR)
[A]MWA was open in 41.7% of sessions and retroperitoneal in 58.3%.
[B]Patients in the MWA group were significantly older (p<0.0001) and had more comorbidities p<0.0001) that patients in the surgical arm.

AE = adverse events; CI = confidence interval; CSS = cancer-specific survival; ds = days; eGFR = estimated glomerular filtration rate; LoS = length of stay; LRN = laparoscopic radical nephrectomy; mos = months; MWA = microwave ablation; nr = not reported; OS = overall survival; PN = partial nephrectomy; pts = patients; RCC = renal cell carcinoma; ref = reference number; RFS = recurrence-free survival; RN = radical nephrectomy; SD = standard deviation; SRTs = small renal tumours; vs. = versus; yrs = years

Study Design and Quality

Pierorazio et al. [8] included 30 observational studies of RFA, cryoablation, or both; these studies compared thermal ablation with radical nephrectomy, partial nephrectomy, or active surveillance. Two of these studies were prospective and the remainder retrospective. The authors judged the strength of evidence to be generally low to moderate.

The RCT by Guan et al. [25] compared MWA with partial nephrectomy. Its risk of bias appeared to be high [5]. This study suffered from lack of allocation concealment, lack of blinding of both participants and outcome assessors, and the follow-up time in the two groups were different (Appendix 4A).

The observational study by Yu et al. [26] was a retrospective comparative chart review that compared MWA with laparoscopic radical nephrectomy. The risk of bias for this study appeared critical [6] (Appendix 4B).

Outcomes

In the next paragraphs, we present the summary results. For more detailed data on radiofrequency ablation and cryoablation, refer to the full Pierorazio et al. report available at: https://effectivehealthcare.ahrq.gov/ehc/products/601/2185/renal-cancer-report-160224.pdf. The data on MWA are presented in Tables 4 and 5 above. We did not perform a meta-analysis of these two studies because the studies were clinically heterogeneous.

Question 1: What is the effectiveness of focal ablation for the treatment of patients with RCC?

Radiofrequency ablation and cryoablation (i.e., thermal ablation) [8]

Survival outcomes

- Thermal ablation demonstrated similar cancer-specific survival (CSS) and metastasis-free survival compared with radical nephrectomy and partial nephrectomy. A meta-analysis of four studies based on the Surveillance, Epidemiology, and End Results (SEER) database comparing radical nephrectomy with thermal ablation showed no difference in CSS (effect size, 1.18; 95% confidence interval [CI], 0.94 to 1.42).
- At 12 to 35 months' follow-up, overall survival (OS) rates at five years ranged from 75% to 99% for partial nephrectomy, 71% to 81% for radical nephrectomy, 83% to 95% for thermal ablation, and 69% to 94% for active surveillance.
- Local recurrence-free survival was worse for thermal ablation than for radical or partial nephrectomy. The interquartile ratio ranged from 84.7% to 94.7% for thermal ablation and from 97% to 100% for partial nephrectomy across studies. A meta-analysis of local recurrence rates for partial nephrectomy versus thermal ablation among five studies with follow-up of 48±12 months showed risk ratio (RR): 0.37, (95% CI, 0.15 to 0.89) in favour of partial nephrectomy.
- However, local recurrence-free survival was equivalent for thermal ablation and for partial nephrectomy when multiple ablative treatments were considered. A meta-analysis of local recurrence-free survival for partial nephrectomy compared with secondary efficacy of thermal ablation (three studies) showed no difference (RR, 1.21; 95% CI, 0.58 to 2.50).
- No evidence was found on quality of life for thermal ablation.

Renal function outcomes

- Renal function decreased postoperatively with all management strategies and improved within one to six months.
- When radical nephrectomy was compared with thermal ablation in a pooled analysis of four studies, the mean difference in glomerular filtration rate (GFR) change favoured thermal ablation (i.e., decreased by a larger amount in the radical nephrectomy than in the thermal ablation group)(weighted mean difference [WMD], 11.5 mL/min/1.73 m^2; 95% CI, 7.8 to 15.2; I^2 0.0%). The pooled risks of chronic kidney disease stage ≥III (three studies) failed to show a statistically significant difference (RR, 3.3; 95% CI, 0.9 to 12.7; I^2=69%).
- When partial nephrectomy was compared with thermal ablation in a pooled analysis of 16 studies, the mean change in creatinine decreased more in the partial nephrectomy group than in the thermal ablation group (WMD, 0.07 mg/dL; 95% CI, 0.00 to 0.15; I^2=9.3%), and the mean change in estimated GFR decreased by a larger amount in the partial nephrectomy group (WMD, 1.30 mL/min/1.73m^2; 95% CI, 0.00 to 2.59; I^2=62.1%). The pooled risks of chronic kidney disease stage ≥III (nine studies) failed to show a statistically significant difference (RR, 0.9; 95% CI, 0.6 to 1.3; I^2=61.6%).

Microwave ablation [25,26]

- Relapse-free survival and CSS were similar for MWA compared with partial nephrectomy at three years' follow-up in the Guan et al. study [25]. In the study by Yu et al. [26], at five-year follow-up, OS was statistically significantly worse for patients in the MWA arm, (p=0.0004), while CSS was not statistically significantly different (Table 5).

Question 2. What are the toxicities associated with focal ablation for RCC?

Radiofrequency ablation and cryoablation (i.e., thermal ablation) [8]

- All interventions (i.e., radical nephrectomy, partial nephrectomy, thermal ablation) were similar with respect to post-operative harms. The rate of end-stage renal disease was low with all management strategies (range, 0.4% to 2.8%).
- In a pooled comparison of perioperative outcomes of radical nephrectomy compared with thermal ablation (two studies), no statistically significant differences were detected for need of blood transfusion (RR, 1.08; 95% CI, 0.63 to 1.87; I^2=0.0%), and for incidence of acute kidney injury (RR, 1.57; 95% CI, 0.88 to 2.80; I^2=0.0%). Conversely, in a pooled comparison of 11 studies reporting on perioperative outcomes and harms of partial nephrectomy and thermal ablation, the RR was 1.62 (95% CI, 1.07 to 2.46; I^2=0.0%) for need of blood transfusion in favour of thermal ablation. For other outcomes (incidence of stage 3 chronic kidney disease, incidence of acute kidney injury, and incidence of minor and major Clavien complications), no statistically significant differences were detected.
- Thermal ablation had higher rates of bleeding compared with radical nephrectomy (one study, 0% versus 16.0%). Compared with partial nephrectomy, thermal ablation had similar rates of harms (15 studies) with the exception of urologic complications (one study showing 5.9% versus 25%).

Microwave ablation [25,26]

- Patients in the MWA group experienced statistically significantly fewer complications [25] than patients assigned to partial nephrectomy (Table 5).
- Major complications were not statistically significantly different [26] between patients assigned to MWA and those assigned to laparoscopic radical nephrectomy (Table 5).

- Patients in the MWA group experienced significantly less blood loss than patients who received partial [25] or radical [26] nephrectomy (Table 5).

Question 3. What patient populations are most likely to benefit from focal ablation for RCC?

Radiofrequency ablation and cryoablation (i.e., thermal ablation) [8]

- CSS rate at five years' follow-up was 95% with all management strategies for T1a tumours (i.e., radical nephrectomy, partial nephrectomy, thermal ablation).
- Thermal ablation provides the best perioperative and harm profile for patients with a localized renal tumour who have high competing health risks compared with partial nephrectomy.

Microwave ablation [25,26]

The studies by Yu et al. [26] and Guan et al. [25] showed that MWA may have similar outcomes as partial or radical nephrectomy in patients with small renal tumours.

Ongoing, Unpublished, or Incomplete Studies

No conference abstracts of interim analyses were identified by our searches. We searched the registry clinicaltrials.gov for ongoing trials combining the key terms: "renal cell carcinoma", "microwave ablation", "thermal ablation", "cryoablation", and "radiofrequency ablation". The results of our search are reported in Table 6.

Table 6. Ongoing trials as of June 20, 2016

Interventions	Official title	Study design	Status	Protocol ID	Completion Date	Last updated
CA	Study to Evaluate the Efficacy of Percutaneous Cryoablation for Renal Tumours < 4cm in Patients Who Are Not Candidates for Partial Nephrectomy (CRYOREIN)	Single arm	Recruiting	NCT01471002	Dec 2015	Sept 2015
CA	Percutaneous Renal Tumor Cryoablation Followed by Biopsy	Single arm – open label	Ongoing but not recruiting participants	NCT01012427	Nov 2015	Sept 2014
LMWA vs. L surgery	Comparison of Zero Ischemia Laparoscopic Microwave Ablation-Assisted Enucleation and Conventional Laparoscopic Nephron-Sparing Surgery in the Treatment of T1a Renal Cell Carcinoma	RCT – open label	Ongoing, but not recruiting participants	NCT02326558	Dec 2019	Jul 2015
RFA vs. SBRT to RFA	A Phase II Randomized Trial Comparing Stereotactic Body Radiation Therapy to Radiofrequency Ablation for the Treatment of Localized Renal Cell Carcinoma (RCC)	RCT – open label, parallel assignment	Recruiting	NCT02138578	Feb 2019	May 2015
RFA vs. CA vs. PN	CONSERVE: a Feasibility Study for a Multicentre Randomised Controlled Trial to Compare Surgery (Partial Nephrectomy) With Needle Ablation Techniques (Radiofrequency Ablation/Cryotherapy) for the Treatment of People With Small Renal Masses (4cm)	RCT open label – feasibility study	Unknown	NCT01608165	Jun 2014	Jun 2013
CA	Post Marketing Surveillance for ICE-SENSE™3 a Cryotherapy Treatment of Renal Cell Carcinoma (ICE-SECRET)	Single arm post marketing	Recruiting	NCT02399124	Jan 2017	Mar 2015
RFA	A Phase II Study of Magnetic Resonance Guided and Monitored Interstitial Thermal Radiofrequency Ablation of Primary Renal Cell Carcinoma, Hepatic Metastasis, and Other Sites of Solid Organ Tumor and Metastases	Phase II single arm	Completed	NCT00006255	Mar 2005	Jun 2010
RFA	A Phase II Study to Evaluate Radiofrequency Ablation of Renal Cancer	Phase II single arm	Completed	NCT00019955	*nr*	Apr 2015
RFA	Thermal Ablation With a Loosely Wound Helical Coil for Radiofrequency Treatment of Large Renal and Hepatic Tumors in Patients Undergoing Partial or Total Nephrectomy or Heptectomy	Non-RCT parallel assignment	Recruiting	NCT01720706	Dec 2015	May 2015
MWA	Zero Ischemia Laparoscopic Radio Frequency/Microwave Ablation Assisted Enucleation of Renal Cell Carcinoma With T1 Stage	RCT open label –	Recruiting	NCT02734329	Sept 2020	May 2016
SBRT MWA	PII SBRT + Microwave Ablation in Renal Cell Carcinoma	SBRT: Phase 1 MWA: Phase 2 single arm	Not yet open for participant recruitment	NCT02782715	Jan 2019	May 2016
LMWA	Comparison of Microwave Ablation-Assisted Enucleation and Conventional Laparoscopic Nephron-Sparing Surgery in the Treatment of T1a Renal Cell Carcinoma	Randomized parallel assignment, open label	Ongoing, but not recruiting participants	NCT02326558	Dec 2019	Jul 2015
Tremelimumab CA	Pilot Study of Presurgical Tremelimumab With or Without Cryoablation in Patients With Metastatic Renal Cell Carcinoma (RCC)	Randomized parallel assignment, open label	Recruiting	NCT02626130	Mar 2021	Mar 2016
CA	Post Marketing Surveillance for ICE-SENSE™3 a Cryotherapy Treatment of Renal Cell Carcinoma (ICE-SECRET)	Single group assignment (safety)	Recruiting	NCT02399124	Jan 2017	Jan 2016
RFA PN	Zero Ischemia Laparoscopic Radio Frequency Ablation Assisted Enucleation of Renal Cell Carcinoma With T1a Stage: Clinical Outcomes of a Randomised Controlled Trial	Randomized	Recruiting	NCT01838720	Oct 2014	Aug 2014

CA = cryoablation; L = laparoscopic; MWA = microwave ablation; *nr* = not reported; PN = partial nephrectomy; RCT = randomized controlled trial; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy

DISCUSSION

The quality of the evidence on thermal ablation interventions is generally at high risk of bias. Existing studies are mostly non-randomized, their follow-ups are often short, and their sample sizes, except for studies that used the SEER database, are usually small. No studies compared quality of life outcomes of patients undergoing thermal ablation and surgery.

However, the existing evidence consistently shows that thermal ablation is generally associated with similar or worse OS compared with partial nephrectomy, while CSS and metastasis-free survival were similar for thermal ablation and partial or radical nephrectomy. Local recurrence-free survival was worse with thermal ablation, but when multiple ablative treatments were taken into account, no difference among procedures was detected. These results could be explained because multiple interventions are sometimes required to completely ablate tumours, and older, less fit patients are generally selected for less-invasive procedures.

Thermal ablation is similar to partial and radical nephrectomy with respect to post-operative harms. However, thermal ablation was found to have a more favourable profile for perioperative outcomes such as blood loss. Length of hospital stay was also shorter with thermal ablation compared with radical nephrectomy.

Included studies generally focussed on patients with small, localized renal tumours; therefore, the results of this review can be generalized to patients with these characteristics.

INTERNAL REVIEW

The evidence summary was reviewed by the Director of the PEBC. The Working Group is responsible for ensuring the necessary changes are made.

The Director of the PEBC reviewed the document on June 23, 2016 and made some minor editorial comments that were incorporated in the final version of the document.

Approval by the Interventional Oncology Steering Committee

After internal review, the report is presented to the Interventional Oncology Steering Committee. The Interventional Oncology Steering Committee reviewed the document and discussed at a meeting held in Toronto on August 5, 2016, and formally approved the document.

ACKNOWLEDGEMENTS

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Appendix 1
Search strategies

A) Search for systematic reviews and guidelines

Database: Ovid MEDLINE(R) Daily Update <May 22, 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

---

1 (kidney or renal).tw.
2 (cancer or carcinoma or neoplasm or tum?r or malignancy or adenocarcinoma).ti,ab.
3 ("RCC" or "renal mass:" or "hypernephroma:" or "garwitz tumo?r" or nephroid).ti,ab. (15280)
4 kidney neoplasms.mp. or exp Kidney Neoplasms/
5 1 and 2
6 3 or 4
7 5 or 6
8 ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
9 (RFTA or RFA or RFT or RFCA).mp.
10 (thermotherapy or CAablation or CAsurgery).mp. or CAsurgery/ or exp Hyperthermia, Induced/
11 exp microwaves/ or coagulation therapy.mp. or exp Electrocoagulation/
12 8 or 9 or 10 or 11
13 7 and 12
14 (systematic adj (review: or overview:)).mp.
15 (meta-analy: or metaanaly:).mp.
16 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
17 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
18 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
19 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
20 or/14-19
21 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
22 (stud: adj1 select:).ab.
23 (21 or 22) and review.pt.
24 20 or 23
25 (guideline or practice guideline).pt.
26 exp consensus development conference/
27 consensus/
28 (guideline: or recommend: or consensus or standards).ti.
29 25 or 26 or 27 or 28
30 24 or 29
31 13 and 30

32 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
33 31 not 32
34 animal/ not human/
35 33 not 34
36 limit 35 to english language
37 limit 36 to yr="2008 -Current"

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Database: Embase <1996 to 2015 Week 21>
Search Strategy:
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1 (kidney or renal).tw. and (cancer or carcinoma or neoplasm or tumo?r or malignancy or adenocarcinoma).ti,ab.
2 ("RCC" or "renal mass:" or "hypernephroma:" or "garwitz tumo?r" or nephroid).ti,ab.
3 kidney neoplasms.mp. or exp kidney tumor/
4 1 or 2 or 3
5 ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
6 (RFTA or RFA or RFT or RFCA).mp.
7 (thermotherapy or CAablation or CAsurgery).mp.
8 CAsurgery/
9 microwave.mp. or microwave radiation/ or coagulation therapy.mp. or microwave therapy/ or electrocoagulation/
10 5 or 6 or 7 or 8 or 9
11 (systematic adj (review: or overview:)).mp.
12 (meta-analy: or metaanaly:).mp.
13 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
14 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
15 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
16 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
17 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
18 (stud: adj1 select:).ab.
19 (17 or 18) and review.pt.
20 or/11-16
21 19 or 20
22 consensus development conference/
23 practice guideline/
24 *consensus development/ or *consensus/
25 *standard/
26 (guideline: or recommend: or consensus or standards).kw.
27 (guideline: or recommend: or consensus or standards).ti.
28 or/22-27
29 21 or 28
30 4 and 10 and 29
31 (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
32 30 not 31
33 animal/ not human/
34 32 not 33
35 limit 34 to english language
****

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>
Search Strategy:
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1 (kidney or renal).tw. and (cancer or carcinoma or neoplasm or tum?r or malignancy or adenocarcinoma).ti,ab.
2 ("RCC" or "renal mass:" or "garwitz tumo?r" or carcinoma).ti,ab.
3 kidney neoplasms.mp. [mp=ti, ot, ab, tx, kw, ct]
4 ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp.
5 (RFTA or RFA or RFT of RFCA).mp.
6 (thermotherapy or CAablation or CAsurgery).mp.
7 microwave ablation.mp.
8 coagulation therapy.mp.
9 4 or 5 or 6 or 7 or 8
10 1 or 2 or 3
11 9 and 10

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B) Search for Primary studies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2016>
Search Strategy: May 16, 2016
---
1 (kidney or renal).tw. and (cancer or carcinoma or neoplasm or tum?r or malignancy or adenocarcinoma).ti,ab.
2 ("RCC" or "renal mass:" or "garwitz tumo?r" or carcinoma).ti,ab.
3 kidney neoplasms.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 1 or 2 or 3
5 microwave ablation.mp.
6 coagulation therapy.mp.
7 5 or 6
8 4 and 7
9 limit 8 to english language

****

Database: Ovid MEDLINE(R) without Revisions <1996 to May Week 1 2016>, Ovid MEDLINE(R) Daily Update <May 13, 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 13, 2016>
Search Strategy:
---
1 (kidney or renal).tw.
2 (cancer or carcinoma or neoplasm or tum?r or malignancy or adenocarcinoma).ti,ab.
3 ("RCC" or "renal mass:" or "hypernephroma:" or "garwitz tumo?r" or nephroid).ti,ab.
4 kidney neoplasms.mp. or exp kidney neoplasms/
5 1 and 2
6 3 or 4
7 5 or 6
8 exp microwaves/ or coagulation therapy.mp. or exp electrocoagulation/
9 7 and 8
10 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
11 9 not 10 (156)
12 animal/ not (exp human/ or humans/)
13 11 not 12
14 limit 13 to english language
****

Database: Embase <1996 to 2016 Week 19> May 16, 2016
Search Strategy:
---
1 (kidney or renal).tw. and (cancer or carcinoma or neoplasm or tumo?r or malignancy or adenocarcinoma).ti,ab.
2 ("RCC" or "renal mass:" or "hypernephroma:" or "garwitz tumo?r" or nephroid).ti,ab.
3 kidney neoplasms.mp. or exp kidney tumor/
4 1 or 2 or 3
5 microwave.mp. or microwave radiation/ or coagulation therapy.mp. or microwave therapy/ or electrocoagulation/
6 4 and 5
7 animal/ not human/
8 6 not 7
9 (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
10 8 not 9
11 limit 10 to english language

****

Appendix 2

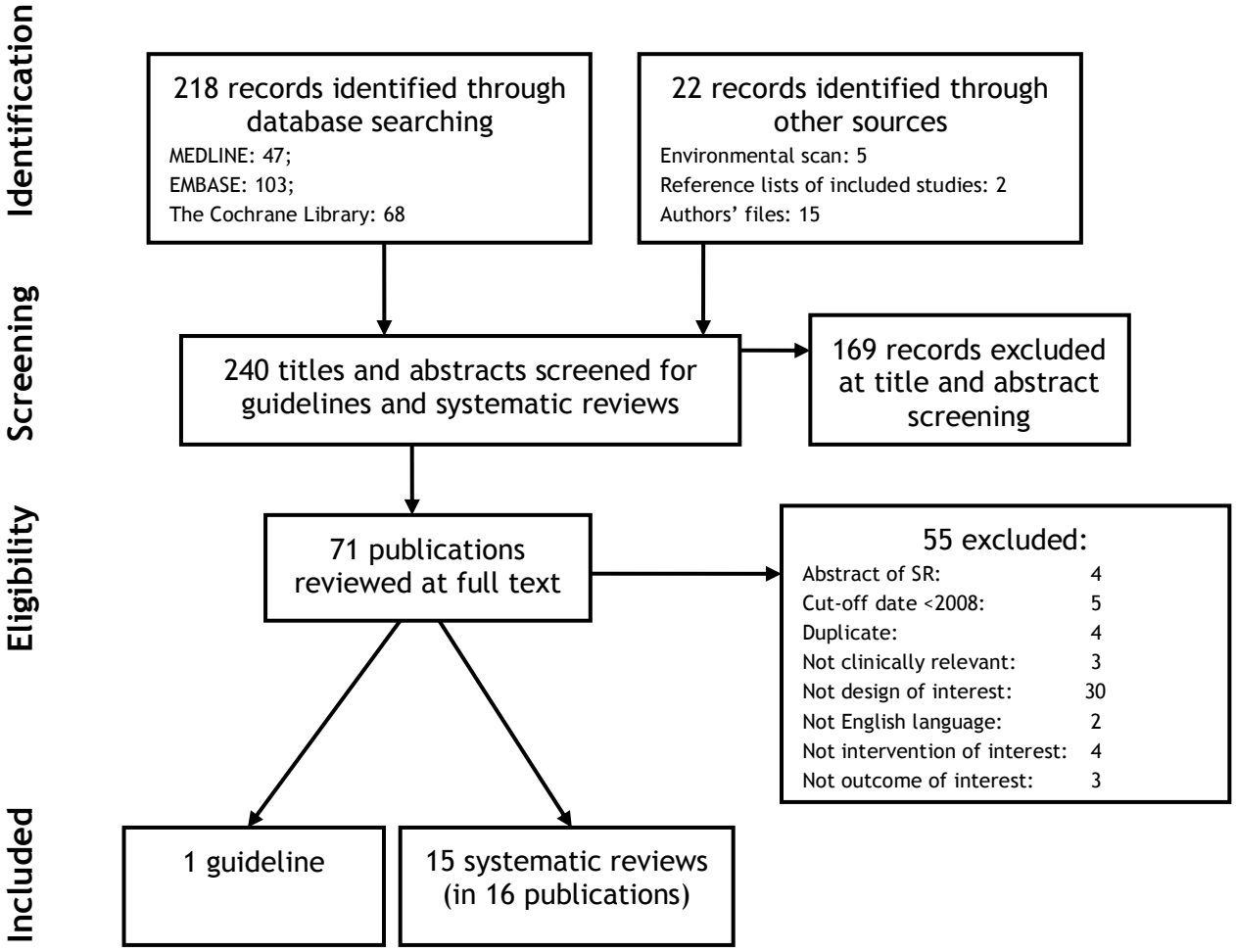
Selection criteria

Systematic reviews
Included
• Systematic reviews including studies with a population of patients with renal cell carcinoma. • Systematic reviews with a research question looking at focal ablation. • If focal ablation is only used as a comparison, but the review focus is on another strategy, and the discussion of these treatment modalities is tangential, the review will be excluded. • Systematic reviews with search strategy dated 2008 or later. • Systematic reviews that include RCTs, or RCTs and non-randomized comparative studies for efficacy questions.
Excluded
• Studies that are not systematic reviews (i.e., reviews that do not have a specific question and did not state inclusion/exclusion criteria) • Systematic reviews in language other than English • Systematic reviews of a population of patients with metastases. • Systematic reviews with a question only tangential to focal ablation (i.e., reviews that do not have a major focus on focal ablation) • Systematic reviews with search cut off prior to 2008 • Systematic reviews that do not report enough data (i.e., protocols, abstracts of systematic reviews) • Systematic reviews that do not include a non-focal ablation arm • Systematic reviews of high intensity focused ultrasound (HIFU) • Systematic reviews of laser interstitial thermal therapy (LITT)
Primary studies
Included
Studies will be included if published in 2013 or later • Population: Studies of patients with renal cell carcinoma and sample size ≥30
• Intervention: microwave ablation • Comparison: any other intervention or best supportive care
• Outcomes: efficacy (OS, PFS, DFS, etc.), safety, and quality of life
• Design: RCT, comparative prospective and retrospective studies published from the latest cut-off date in the included systematic reviews onwards (2013). Ljunberg and Katsanos both searched up to 2013.
Excluded
• Articles not in English • Publications that do not provide enough data or not outcomes of interest (e.g., cost) • Abstracts of interim analysis • Abstracts of non-comparative studies
Note: the search for RCTs covered areas that were not discussed by systematic reviews. For example in terms of time periods, adverse events, or topics that the existing systematic reviews did not discuss. Therefore, the criteria for inclusion and exclusion for primary literature were specified after these evidence gaps are known.

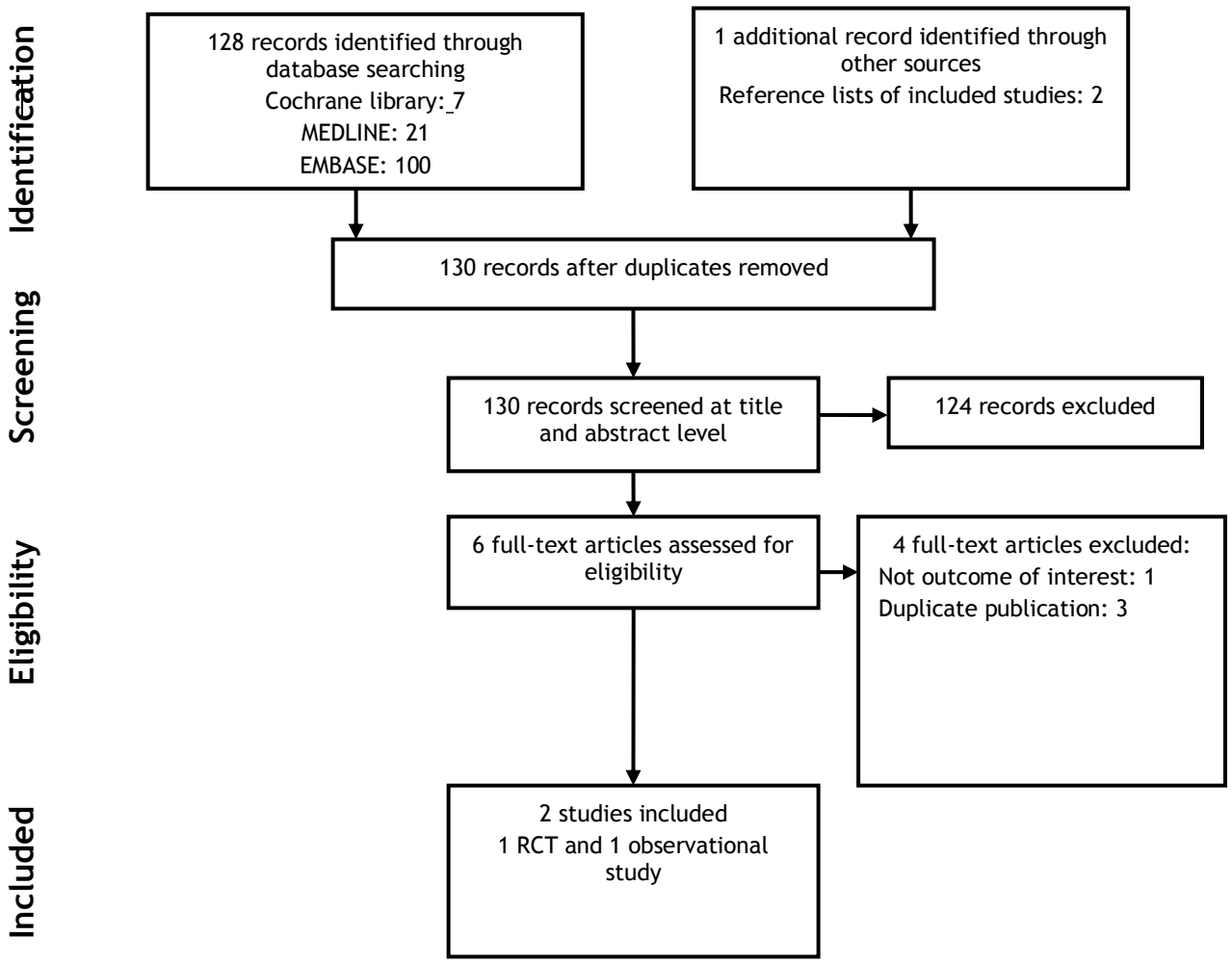
Abbreviations: DFS = disease-free survival; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial

Appendix 3

A) Focal Tumour Ablation of Renal Cancer. Review of systematic reviews: Study Flow Chart



B) Focal Tumour Ablation of Renal Cancer. Review of Primary Studies of Microwave Ablation: Study Flow Chart



Appendix 4

Systematic reviews excluded with reasons for exclusion

Abstracts of systematic reviews

1. Siva S, Corcoran N, Foroudi F. A systematic review of stereotactic ablative body radiotherapy for primary renal cell carcinoma. Asia Pac J Clin Oncol. 2012;8:33-4.
2. Mailli L, Katsanos KN, Krokidis M, Karunanithy N, McGrath A, Sabharwal T, et al. Systematic review and meta-analysis of thermal ablation versus nephrectomy for small renal tumors. Cardiovasc Intervent Radiol. 2013;36:S325.
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4. Modabber M, Athreya S. Thermal vs impedence-based ablation of renal tumours: Does it matter? Review of literature. J Vasc Interv Radiol. 2012;23 (6):853.e23.

Search cut-off date prior to 2008

1. Long L, Park S. Differences in patterns of care: reablation and nephrectomy rates after needle ablative therapy for renal masses stratified by medical specialty. J Endourol. 2009;23(3):421-6.
2. Kunkle DA, Egleston BL, Uzzo RG. Excise, ablate or observe: the small renal mass dilemma--a meta-analysis and review. J Urol. 2008;179(4):1227-33; discussion 33-4.
3. Hui GC, Tuncali K, Tatli S, Morrison PR, Silverman SG. Comparison of percutaneous and surgical approaches to renal tumor ablation: meta-analysis of effectiveness and complication rates. J Vasc Interv Radiol. 2008;19(9):1311-20.
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Duplicates

1. Klatte T, Grubmuller B, Waldert M, Weibl P, Remzi M. Laparoscopic cryoablation versus partial nephrectomy for the treatment of small renal masses: systematic review and cumulative analysis of observational studies. Eur Urol. 2011;60(3):435-43.
2. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, et al. Guideline for Management of the Clinical T1 Renal Mass. J Urol. 2009;182(4 SUPPL.):1271-9.
3. Dissemination CfRa. Systematic review and meta-analysis of perioperative and oncological outcomes of laparoscopic cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal tumors (Provisional abstract). Database of Abstracts of Reviews of Effects. 2015(2). Abstract and Commentary for: Klatte T, Shariat SF, Remzi M. Systematic review and meta-analysis of perioperative and oncological outcomes of laparoscopic cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal tumors. J Urol. 2014;191(5):1209-1217.
4. Dissemination CfRa. Systematic review and meta-analysis of thermal ablation versus surgical nephrectomy for small renal tumours (Provisional abstract). Database of Abstracts of Reviews of Effects. 2015(2). Abstract and Commentary for: Katsanos K, Mailli L, Krokidis M, McGrath A, Sabharwal T, Adam A. Systematic review and meta-analysis of thermal ablation versus surgical nephrectomy for small renal tumours.

Cardiovasc Intervent Radiol. 2014;37(2):427-437.
5. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, et al. EAU guidelines on renal cell carcinoma: the 2010 update. Eur Urol. 2010;58(3):398-406.

Not clinically relevant

1. Van Poppel H, Becker F, Cadeddu JA, Gill IS, Janetschek G, Jewett MA, et al. Treatment of localised renal cell carcinoma. Eur Urol. 2011;60(4):662-72.
2. El Dib R, Nascimento Junior P, Kapoor A. An alternative approach to deal with the absence of clinical trials: a proportional meta-analysis of case series studies. Acta Cir Bras. 2013;28(12):870-6.
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Not design of interest

1. Salas N, Ramanathan R, Dummett S, Leveillee RJ. Results of radiofrequency kidney tumor ablation: renal function preservation and oncologic efficacy. World J Urol. 2010;28(5):583-91.
2. Remzi M, Javadli E, Ozsoy M. Management of small renal masses: a review. World J Urol. 2010;28(3):275-81.
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Appendix 5

A. Risk of bias of Guan, et al. [25] study as measured with the Cochrane Risk of Bias tool for randomized trials [5]

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk.	Patients were prospectively randomized by a computer-generated program (page 316).
Allocation concealment (selection bias)	High risk.	No information about the allocation.
Blinding of participants and personnel (performance bias)	High risk.	No information about blinding.
Blinding of outcome assessment (detection bias) (Mortality)	High risk.	No information about blinding.
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes [>6 weeks])	High risk.	Attrition bias is likely because the two groups have different median (range) follow-up: MWA: 32 (24 to 54), and PN 36 (25 to 66).
Selective reporting (reporting bias)	Low risk.	No other outcomes were reported than those planned.

B. Risk of bias of Yu, et al. [26] study as measured with the Cochrane Risk of Bias tool for nonrandomized trials [6]
Confounding areas expected in this body of literature at the protocol stage: The patients in the microwave arm of the trial had a worse prognosis than patients assigned to laparoscopic radical nephrectomy.
Additional confounding relevant to this particular study: Treatment modalities
Preliminary consideration of co-interventions: other treatments

Bias domain	Judgement	Support for judgement
Bias due to confounding	Critical	The authors did not use appropriate analysis for adjusting for all the important confounding areas and time-varying confounding.
Bias in selection of participants in the study	Critical	The selection of participants into the study was based on participant characteristics observed after the start of intervention, and adjustment techniques were not used to correct for the presence of selection biases.
Bias of classification of interventions	Serious	Patients in the MWA group might have received the intervention more than once.

Appendix 6
Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy (PEBC Conflict of Interest [COI] Policy), the evidence summary authors, the Interventional Oncology Steering Committee members, and internal reviewers were asked to disclose potential conflicts of interest. The conflict of interest statements of the working group are summarized in Table 1 below.

The COI declared did not disqualify any individuals from performing their designated role in the development of this evidence summary, in accordance with the PEBC COI Policy.

Table 1. Conflict of Interest Disclosures: Members of the Working Group

Members	Role	Conflict of Interest
John Kachura	Chair	Past President of CIRA (Canadian Interventional Radiology Association). The following parties contribute financially to CIRA: Abbott Vascular, Angiodynamics, Bard, Boston Scientific, Cook Medical, Cardis Endovascular, Covidier, GE Healthcare, Gore, InterV Medical, Medtronic and Philips
		Co-applicant for patent regarding an invention for thermal therapy
		Investigator in a sponsored research agreement between University Health Network and Bard regarding thermal therapy invention.
Mark Baerlocher	Member	Temporary consultant to Cook In to help with documents related to PICC lines
Ania Kielar	Member	GE CHAR grant for MRI post RFA investigation
Fulvia Baldassarre	Member	None declared