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Cryoablation vs radiofrequency ablation for the treatment of renal cell carcinoma: a meta-analysis of case series studies

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OBJECTIVE

- To determine the current status of the literature regarding the clinical efficacy and complication rates of cryoablation vs radiofrequency ablation in the treatment of small renal tumours.

METHODS

- A review of the literature was conducted. There was no language restriction. Studies were obtained from the following sources: MEDLINE, EMBASE and LILACS.
- Inclusion criteria were (i) case series design with more than one case reported, (ii) use of cryoablation or radiofrequency ablation, (iii) patients with renal cell carcinoma and, (iv) outcome reported as clinical efficacy.
- When available, we also quantified the complication rates from each included study.
- Proportional meta-analysis was performed on both outcomes with a random-effects model. The 95% confidential intervals were also calculated.

What's known on the subject? and What does the study add?
The oncological success of partial nephrectomy in the treatment of small renal masses is well established. However, partial nephrectomy has largely supplanted the radical approach. In the last decade, laparoscopy has been adopted as the new surgical approach for the treatment of renal cell carcinoma. Laparoscopy offers the advantage of lower analgesic use, shorter hospital stay, and quicker recovery time. More recently, ablative technologies have been investigated as an alternative to laparoscopic partial nephrectomy. These techniques can often be performed percutaneously in the radiology suite, or laparoscopically without the need for hilar clamping. However, only the cryoablation and radiofrequency ablation modalities have had widespread use with several series reporting short to intermediate results.

This review shows that both cryoablation and radiofrequency ablation are promising therapies in patients with small renal tumours (<4 cm), who are considered poor candidates for more involved surgery.

RESULTS

- Thirty-one case series (20 cryoablation, 11 radiofrequency ablation) met all inclusion criteria.
- The pooled proportion of clinical efficacy was 89% in cryoablation therapy from a total of 457 cases. There was a statistically significant heterogeneity between these studies showing the inconsistency of clinical and methodological aspects.
- The pooled proportion of clinical efficacy was 90% in radiofrequency ablation therapy from a total of 426 cases. There was no statistically significant heterogeneity between these studies.
- There was no statistically significant difference regarding complications rate between cryoablation and radiofrequency ablation.

CONCLUSIONS

- This review shows that both ablation therapies have similar efficacy and complication rates.
- There is urgency for performing clinical trials with long-term data to establish which intervention is most suitable for the treatment of small renal masses.

KEYWORDS

cryoablation, radiofrequency ablation, small renal tumours, meta-analysis of cases series studies

INTRODUCTION

Small renal masses are increasingly being discovered incidentally on imaging for other reasons [1–3]. When surgically excised, about 80% of these masses are revealed to be renal cell carcinoma [4–7]. Traditionally, surgical excision by radical nephrectomy has been the standard treatment for all solid enhancing renal masses. However, since the early 1990s, partial nephrectomy has largely supplanted the radical approach because it has been shown to be equivalent in terms of oncological control while allowing for nephron sparing [8–10]. In the last decade, laparoscopy has been adopted as the new surgical approach for the treatment of renal cell carcinoma. Laparoscopy offers the

advantage of lower analgesic use, shorter hospital stay, and quicker recovery time. These advantages also translate into an overall cost saving in favour of the laparoscopic approach [11]. Despite the appeal of laparoscopic partial nephrectomy, it remains a challenging procedure. The advanced laparoscopic skills required for laparoscopic partial nephrectomy, including intracorporeal suturing, have restricted its use to a few centres with sub-specialized surgeons.

More recently, ablative technologies have been investigated as an alternative to laparoscopic partial nephrectomy. These techniques can often be performed percutaneously in the radiology suite, or laparoscopically without the need for hilar clamping. Other advantages include the fact that ablation is often more nephron sparing than extirpative techniques [12], can be performed as a same-day procedure, and requires less operative time [13]. All of these features should translate into benefits to the patients as well as potential monetary savings to the healthcare system.

Several ablative technologies have been investigated including cryoablation (CA), radiofrequency ablation (RFA), microwave [14], high-intensity focused ultrasound [15,16], laser interstitial thermotherapy [17], microwave thermotherapy and radiosurgery. However, only the first two modalities have had widespread use with several series reporting short to intermediate results. Cryoablation has been used for the treatment of human cancers since the nineteenth century with the use of ice–salt mixtures for the treatment of cervical and breast cancers [18]. In Urology, CA has long been used in the treatment of prostatic diseases: first for benign prostatic hyperplasia in the 1960s [19], and later for prostate cancer [20]. Freezing and thawing causes alteration in various biological processes that ultimately result in cell death.

Radiofrequency ablation is a minimally invasive treatment for localized cancer in which a small needle, attached to a device that delivers radiofrequency energy, is inserted into a tumour to destroy the cancerous tissue either under sedation or under general anaesthesia. The procedure is usually performed percutaneously under CT or ultrasound visualization, and the tumour is destroyed by heating to temperatures exceeding 60 °C [18].

In the last few years, several series of CA and RFA applied to small renal masses have reported short to intermediate results. Unfortunately, no randomized controlled trial comparing the two techniques has been undertaken. Therefore, most clinicians remain confused about the status of the literature regarding which is the superior technology. To clear up the confusion, we propose a meta-analysis of all available studies on CA and RFA. The clinical efficacy and complication rates of CA and RFA in patients with small renal masses will be assessed through a proportional meta-analysis of case-series studies.

METHODS

A review of clinical series with a proportional meta-analysis of renal tumour ablation was performed. There was no language restriction. Studies were obtained from the following sources: US National Library of Medicine (MEDLINE; 1966–2011), Excerpta Medica database (EMBASE; 1980–2011) and Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS; 1982–2011) to identify all case series concerning CA or RFA in renal cell carcinoma.

The databases were searched using a comprehensive search strategy for kidney cancers and CA or RFA, along with MeSH and text words, including an exhaustive list of synonyms (see Appendix 1). The search strategy was adapted for each database to achieve more sensitivity. The bibliographic references in relevant review articles were also examined for eligible studies.

The following inclusion criteria were used: (i) case series studies (number of reported patients in each study greater than one), (ii) use of CA or RFA, (iii) patients with renal tumours regardless of tumour size, and (iv) the studies specified a measure of clinical efficacy based on follow-up imaging. Clinical efficacy was defined as the percentage of tumours treated successfully by the procedure (CA or RFA). Successfully treated tumour was defined as no growth or no evidence of recurrence on CT scan or MRI. The following outcomes were considered as clinical efficacy measurements: cancer-specific survival rate, radiographic success, no evidence of local tumour progression or distant metastases.

We also quantified the complications rates (intraoperative and postoperative) from each included study when they were available. All-causes death was counted as a complication outcome. Case series with incomplete data were excluded from the review.

DATA COLLECTION

Two reviewers independently screened the titles identified by the literature search, extracted the data, and analysed the results. Discrepancies in the results were resolved by discussion.

A standard form was used to extract the following information: authors and year of publication, number of participants, mean age of patients, approach (open, laparoscopic or percutaneous), ablative technique (CA or RFA), number of tumours treated, mean tumour size, duration of patient follow-up and the outcomes of interest. If there was more than one published report of the same group of patients, the articles were analysed to verify whether or not they reported different outcomes. If they presented the same outcomes we extracted the data from the most recent or most complete article. The mean age, mean tumour size and mean follow-up calculated in this study were based on the mean age, tumour size and follow-up from each case series included in this review.

When the article did not present the number of tumours treated we assumed this to be the same as the number of patients enrolled in the study.

Clinical efficacy and complications rates were treated as the dichotomous variable with their respectively 95% CI. Statistical heterogeneity was assessed using the I^2 statistic and significance was assumed when I^2 was >50%. This illustrates the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling error [21,22]. Because of the clear differences among the included studies and several uncontrolled variables, we used a random-effect model [23] to perform a

TABLE 1 Demographics characteristics of patients undergoing renal tumour ablation: comparison of cryoablation and radiofrequency ablation studies

Study	Cryoablation	Radiofrequency ablation
Total case series	20*	11†
No. of patients	457	426
No. of tumours	500	507
Mean tumour size (cm)	2.5 (2.0–4.2)	2.7 (2.0–4.3)
Approach per study		
Percutaneous	6	10
Laparoscopic	13	4
Open	1	0
Mean age (years)	63.8 (44.9–72)	64.0 (39–71.7)
Mean follow-up (months)	17.9 (7–45.7)	18.1 (9.0–30.7)

*Values in parentheses are ranges. *References [32–51]. †References [52–62].*
Seven studies were performed percutaneously. One laparoscopically, and three performed either percutaneously or laparoscopically.

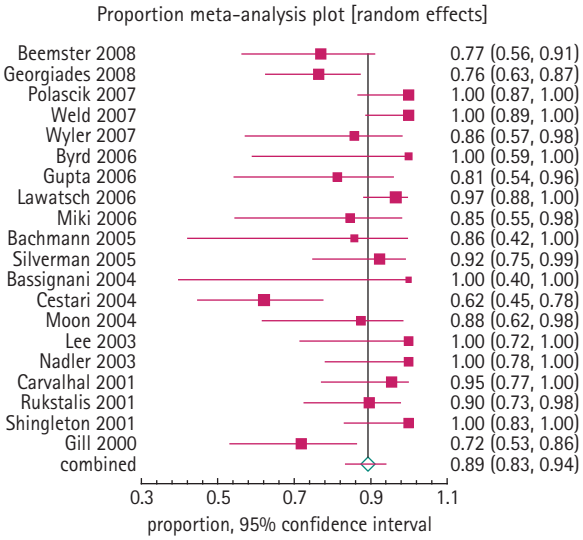


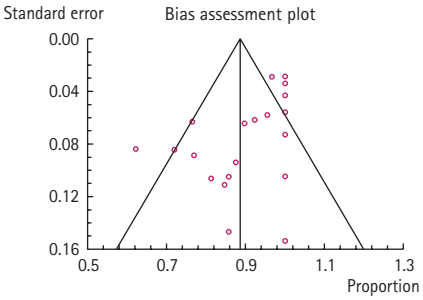
FIG. 1.
Proportional meta-analysis of case series studies regarding clinical efficacy in cryoablation therapy.

proportional meta-analysis. The software used to plot the studies into a meta-analysis was StatsDirect.

Forest plots are presented to summarize the data. Each horizontal line on a forest plot represents a case series included in the meta-analysis. The length of the line corresponds to a 95% CI of the corresponding case series' effect estimate. The effect estimate is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The pooled estimate is marked with an unfilled diamond at the bottom of the forest plot. Confidence intervals of pooled estimates are displayed as a horizontal line through the diamond; this line might be contained within the diamond if the confidence interval is narrow.

Funnel plots were performed using Egger tests to assess the possibility of publications bias as they are useful adjuncts to meta-analyses. Furthermore, when it was possible, we performed an intention-to-treat analysis for dichotomous data of each included studied. The statistically significant difference between both interventions studied was defined if their combined 95% CIs did not overlap. We considered $P < 0.05$ as statistically significant for the calculation of heterogeneity.

FIG. 2. Funnel plot of case series studies regarding clinical efficacy in cryoablation therapy by Egger test.



RESULTS

The search was performed up to January 2011 and identified 1847 titles. After screening by title and then abstract, we obtained full paper copies of 104 studies on RFA and CA that were potentially eligible for inclusion in the review. However, most of these studies were either retrospective, animal studies, reviews, or did not evaluate a relevant clinical outcome. Hence, a total of 31 case series studies (20 CA, 11 RFA) met all inclusion criteria and were included in the meta-analysis.

There were a total of 457 patients with 500 tumours in the CA group compared with 426 patients (507 tumours) in the RFA group. Of the CA case series, 13 were performed laparoscopically, six percutaneously, and one through an open approach. Of the RFA case series, seven studies were performed percutaneously, one laparoscopically, and three were performed either percutaneously or laparoscopically. The mean tumour size in the CA and the RFA series were roughly similar at 2.5 cm (range from 2 to 4.2 cm) and 2.7 cm (range from 2 to 4.3 cm), respectively. The mean follow-up was 17.9 months in the CA group and 18.1 month in the RFA group. The mean age was 63.8 years in CA and 64.0 years in RFA (Table 1).

The pooled proportion of clinical efficacy was 89% (95% CI 0.83–0.94) in CA therapy from 20 studies with a total of 457 cases. There was significance regarding heterogeneity (I^2 value 70.6%) showing the inconsistency of clinical and methodological aspects between the studies included in the meta-analysis ($P < 0.001$) (Fig. 1).

Figure 2 represents an asymmetric funnel plot from the outcome clinical effectiveness

FIG. 3.
Proportional meta-analysis of case series studies regarding clinical efficacy in radiofrequency ablation therapy.

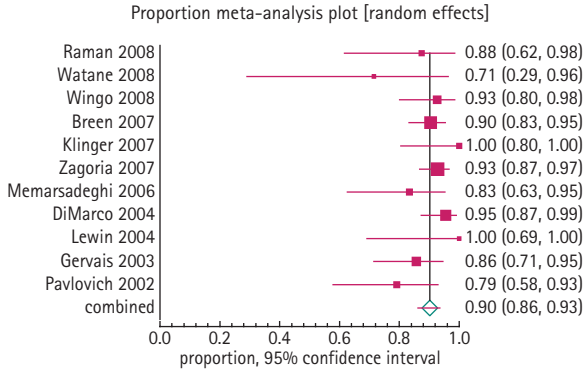
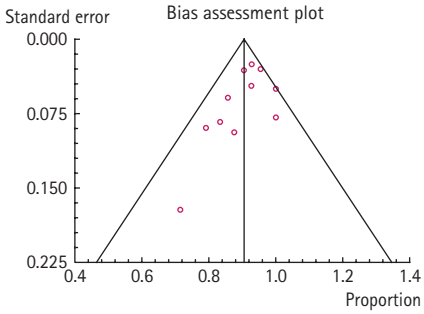


FIG. 4. Funnel plot of case series studies regarding clinical efficacy in radiofrequency ablation therapy by Egger test.



of the CA case series by Egger test that indicates a relationship between treatment effect and study size. This suggests the possibility of publication bias.

The pooled proportion of clinical efficacy was 90% (95% CI 0.86–0.93) in RFA therapy from 11 studies with a total of 426 cases. There was no significance regarding heterogeneity (I^2 value 34.1%) ($P = 0.126$) between the studies included in the meta-analysis (Fig. 3).

Figure 4 presents the results of a funnel plot of case series studies regarding the clinical efficacy outcome in RFA intervention by Egger test. There is a symmetrical inverted funnel shape that arises from a 'well-behaved' data set, in which publication bias is unlikely to occur.

The pooled proportion of complication rate was 19.9% (95% CI 0.13–0.27) in CA therapy from 19 studies with a total of 431 cases. There was significance regarding heterogeneity (I^2 value 73.4%) ($P < 0.001$) (Fig. 5).

The pooled proportion of complication rate was 19.0% (95% CI 0.12–0.27) in RFA therapy from 11 studies with a total of 426 cases. There was significance regarding heterogeneity for this outcome (I^2 value 70.7%) ($P < 0.001$) (Fig. 6).

FIG. 5.
Proportional meta-analysis of case series studies regarding complication rate in cryoablation therapy.

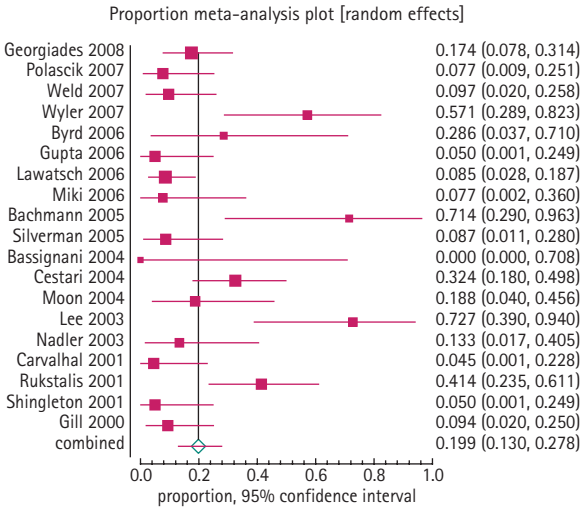
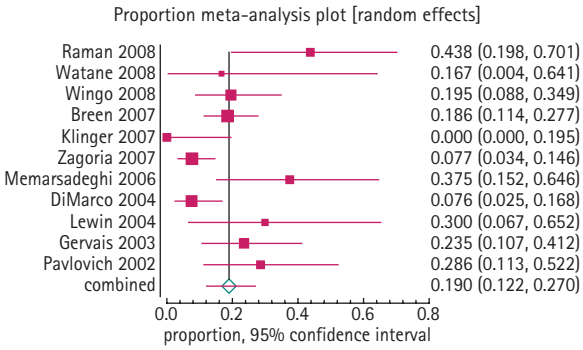


FIG. 6.
Proportional meta-analysis of case series studies regarding complication rate in radiofrequency ablation therapy.



The complications in patients treated with CA included perinephric haematoma, genitofemoral nerve injury, cryoshock, respiratory failure, haematuria, urinary leak, haemorrhage, postoperative ileus, ureteropelvic junction obstruction, pneumonia and all-causes death. Postoperative and preoperative complications in RFA therapy were haematuria, flank numbness, perinephric haematoma, ileus, urinary retention, flank bruising, urinoma, flank pain, pneumonia, haemorrhage, neuropathic pain, hydronephrosis, ureteral stenosis, urinary fistula and all-causes mortality.

There was no significant difference regarding both outcomes (clinical efficacy and complication rates) between CA and RFA therapy as their CIs overlapped (Figs 1, 3, 5 and 6).

DISCUSSION

The oncological success of partial nephrectomy in the treatment of small renal

masses is well established. Several large series have reported 5-year cancer-specific survival rates of 87–90% [24–26]. The rate of local recurrence is presumably (although never directly compared) higher than radical nephrectomy at 4–6% [24–26]. In addition, long-term renal function preservation with partial nephrectomy has been well established at 93% in patients followed for at least 10 years [27]. However, follow-up in this pooled data is relatively short at roughly 18 months. The natural history of untreated small renal masses is not well defined, but one current review reported a growth rate of 0.28 cm/year, with a metastatic rate of 1% at 34 months of follow-up [28]. This would seem to indicate that the reported follow-up for RFA and CA series is too recent to draw any meaningful conclusions about oncological efficacy.

Given the lack of evidence to support these ablative technologies as an alternative to partial nephrectomy, some have advocated reserving their use to the following specific clinical scenarios: (a) patients with co-morbidities that preclude a major surgical intervention, (b) patients with renal insufficiency, (c) patients with solitary kidneys, and (d) patients with recurrent tumours secondary to hereditary disorders such as von Hippel–Lindau disease [29,30]. However, even within these scenarios, it remains unclear which ablative technology offers superior outcomes. This meta-analysis suggests that they may be equivalent over the short term. However, a meta-analysis is only as reliable as the data included within it. None of the case series examined was a properly designed randomized trial. In fact, there were not even any comparative studies. Often in the assessment of emerging therapies and new technologies, controlled studies are lacking. However, it is still desirable to describe the existing data, so that physicians can have the state of current knowledge mapped. For this reason, a proportional meta-analysis was conducted with a comprehensive systematic review of uncontrolled studies (case series).

Our analysis shows that there is significant heterogeneity in CA clinical outcome (I^2 = 70.6%) and complications (I^2 = 73.4%) (Figs 1,5). Reasons for this heterogeneity could be both clinical and methodological. The studies differed considerably in their patient selection, baseline disease severity, techniques (laparoscopically, percutaneously or open), management of outcomes, and duration of follow-up. There were also methodological differences in the handling of withdrawals and losses to follow-up. In addition, the funnel plot for the CA series suggests the possibility that publication bias may have occurred given the asymmetry (Fig. 2).

As for the RFA series, there was far less heterogeneity when it comes to the clinical efficacy outcome (Fig. 3). This suggests that RFA series were far more consistent in patient selection and treatment protocol. In addition, publication bias played less of a significant role as confirmed by the funnel plot and the Egger test (Fig. 4). There was some heterogeneity, however, when it comes to reporting of complications related to RFA (Fig. 6). This would suggest that RFA series, just like CA series, were far less consistent in the way they reported complications. Whereas some studies were very thorough in tracking all major and minor complications, others only reported major urological complications.

The AUA issued a guideline in 2009 regarding the management of stage I renal masses [31]. This was an all encompassing review examining all treatment modalities. Both CA and RFA were examined as part of this meta-analysis, and similar to this review, only observational studies were included. The methodology and statistical approach were also fairly similar. However, the AUA meta-analysis was more stringent about inclusion criteria and definition of success. Different definitions of success were examined in the AUA guideline. Total recurrence-free survival was found to be 87.6% and 85.2% for CA and RFA with a mean follow-up of 26.2 months and 39.3 months, respectively. Only 10 observational studies were included for each modality in the AUA meta-analysis. In addition, local failure was defined as any disease remaining in the treated kidney after the first ablation. Cancer-specific survival was also examined in the AUA review. However, only studies with confirmed renal cell carcinoma were included so this strict definition yielded only six and eight studies for CA and RFA, respectively. In this review, the definition of success was much broader, and included cancer-specific survival, radiographic success, lack of evidence of local tumour progression or distant metastases. Essentially, success was interpreted as per each reporting study's a priori definition of success. This definition lacks the rigour of acceptable reportable cancer outcomes, and adds heterogeneity to the reported outcomes of the meta-analysis. However, given that the stated goal of this review is to gauge the efficacy of only the ablative techniques, and not to make any broader statements about the suitability of these techniques as alternatives to the established extirpative techniques, this definition was deemed suitable. This looser definition of outcomes also allowed for the inclusion of more studies including 20 for CA and 11 for RFA. In the end, regardless of reported outcomes, no significant differences in efficacy were found between the two ablative techniques in both this meta-analysis, and the one reported in the AUA guideline.

This review shows that both CA and RFA are promising therapies in patients with small renal tumours (<4 cm), who are considered poor candidates for more involved surgery. Long-term data on oncological control is lacking. Longer follow-up and more rigorous head-to-head trials are needed to determine the exact role of these ablative therapies in the treatment algorithm of small renal masses. Most studies examining these therapies have been poorly designed case series without proper control. Given the natural history of small renal masses, a properly designed trial would follow these ablated tumours for at least 5 years to determine the true impact of these treatments. In the absence of such data, partial nephrectomy remains the standard of care for small renal masses.

CONFLICT OF INTEREST

Regina El Dib and Anil Kapoor are authors of the forthcoming trial CRYO x RFA for RCC.

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Abbreviations: **CA**, cryoablation; **RFA**, radiofrequency ablation.

APPENDIX 1

Summary of the bibliographic search strategies for type of clinical situation and intervention of interest

Search history

([Kidney Neoplasm] OR [Renal Neoplasms] OR [Renal Neoplasm] OR [Kidney Neoplasms] OR [Cancer of Kidney] OR [Kidney Cancers] OR [Renal Cancer] OR [Renal Cancers] OR [Cancer of the Kidney] OR [Kidney Cancer] OR [Kidney Cancers] OR [Renal masses] OR [Renal cell carcinoma]) AND (Cryosurgeries OR Cryosurgery OR Cryoablation OR Cryoablations OR Cryotherapy OR ablation OR [Radiofrequency ablation] OR [Catheter ablation] OR [Electric Catheter Ablation] OR [Electrical Catheter Ablation] OR [Radiofrequency Catheter Ablation] OR [Transvenous Catheter Ablation] OR [Transvenous Electric Ablation] OR [Transvenous Electrical Ablation] OR [Percutaneous Catheter Ablation] OR [Percutaneous Radiofrequency ablation] OR [Radio frequency] OR Radio-frequency OR [Radiofrequency thermal ablation] OR [Minimally invasive therapy] OR [Tumor ablation] OR [CT-guided percutaneous radiofrequency ablation])