Collaborative Review – Kidney Cancer

Cryoablation for Small Renal Masses: Selection Criteria, Complications, and Functional and Oncologic Results

Homayoun Zargar\textsuperscript{a,*}, Thomas D. Atwell\textsuperscript{b}, Jeffrey A. Cadde\textsuperscript{e}, Jean J. de la Rosette\textsuperscript{d}, Gunther Janetschek\textsuperscript{e}, Jihad H. Kaouk\textsuperscript{a}, Surena F. Matin\textsuperscript{f}, Thomas J. Polascik\textsuperscript{g}, Kamran Zargar-Shoshtari\textsuperscript{h}, R. Houston Thompson\textsuperscript{i}

\textsuperscript{a} Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA; \textsuperscript{b} Department of Radiology, Mayo Clinic, Rochester, MN, USA; \textsuperscript{c} Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX; \textsuperscript{d} Department of Urology, Academic Medical Center, Amsterdam, The Netherlands; \textsuperscript{e} Department of Urology and Andrology, Paracelsus Medical University Salzburg, Salzburg, Austria; \textsuperscript{f} Department of Urology, MD Anderson Cancer Center, Houston, TX, USA; \textsuperscript{g} Division of Urologic Surgery, Department of Surgery, Duke University Medical Center, Durham, NC, USA; \textsuperscript{h} Moffitt Cancer Center, Tampa, FL, USA; \textsuperscript{i} Department of Urology, Mayo Clinic, Rochester, MN, USA

Article info

Article history:
Accepted March 11, 2015

Keywords:
Renal cryoablation
Small renal masses
Cryotherapy
Selection criteria
Complications
Function
Oncology

Abstract

Context: Cryoablation (CA) is a minimally invasive modality with low complication rates, but its use in urology is relatively recent.

Objective: To summarize available evidence for CA for small renal masses (SRMs) and to assess the selection criteria, complications, and functional and oncologic results based on the latest CA literature.

Evidence acquisition: A systematic literature search of the Medline, Embase, and Scopus databases was performed in August 2014 using Medical Subject Headings and free-text protocol. The following search terms were included: kidney cryosurgery, renal cryosurgery, kidney cryoablation, renal cryoablation, kidney cryotherapy, and renal cryotherapy.

Evidence synthesis: Due to the relatively recent mainstream utilization of CA and lack of long-term efficacy data from large prospective or randomized studies, most of the data available on CA are limited to treatment of SRMs in patients who are often older or are poor surgical candidates. The rates of major complications across the CA literature remain relatively low. Studies assessing renal function after CA suggest a degree of functional decline following CA because proper application includes freezing of a tumor margin; however, often this is not clinically significant. Specific oncologic outcomes should be evaluated in patients with biopsy-proven renal cell carcinoma; when SRM series include benign or unbiopsied tumors, the results of these outcomes are skewed. Although earlier series were suggestive of a higher recurrence rate after CA, some studies have challenged this view reporting recurrence rates comparable with extirpative nephron-sparing surgery.

Conclusions: CA represents an alternative approach to treatment for patients diagnosed with renal neoplasm. There is no consensus within the literature on the best patient selection criteria. Due to higher rates of treatment failure, it is often not offered to patients with minimal comorbidities and good life expectancy. In terms of functional outcomes, CA signifies a modality with minimum impact on renal function; however, well-designed studies precisely assessing this factor are lacking. CA is a minimally invasive modality with suitably low rates of complications, particularly if delivered via the percutaneous route.

Patient summary: Cryoablation (CA) represents an alternative approach for treating renal neoplasm. Excellent functional outcomes and low rates of complications make CA an ideal minimally invasive modality. Patient selection criteria and oncologic outcomes require further study.

© 2015 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Cleveland Clinic, Glickman Urology Institute Q 10, 9500 Euclid Avenue, Cleveland, OH 44106, USA. Tel. +1 216 526 6139.
E-mail addresses: homi.zargar@gmail.com, zargarh@ccf.org (H. Zargar).

http://dx.doi.org/10.1016/j.eururo.2015.03.027
0302-2838/© 2015 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Please cite this article in press as: Zargar H, et al. Cryoablation for Small Renal Masses: Selection Criteria, Complications, and Functional and Oncologic Results. Eur Urol (2015), http://dx.doi.org/10.1016/j.eururo.2015.03.027
1. Introduction

The discovery of the anticancer properties of cryoablation (CA) predates the discovery of antibiotics [1]. However, its use in urology, particularly with the shift from surgical to percutaneous application, is considered relatively new. During the process of modern argon-based CA, the rapid cooling (the Joule-Thompson effect) of the probes within the targeted lesion leads to cell necrosis by direct cellular injury and indirectly by changes in the cellular microenvironment [2]. The unique characteristics of CA including real-time image assessment and uniformity of the ablation zone, observed synergy when multiple probes are used simultaneously, potential for outpatient application, and safety with use around cardiac devices such as pacemakers have fostered the uptake of this modality in urology, particularly as an alternative to extirpative therapies to manage small renal masses (SRMs) [3].

Assessment of the American Nationwide Inpatient Sample for the 10-yr period from 1998 to 2008 demonstrated an increase in uptake of all ablative technologies for the treatment of renal masses; however, ablation was the least utilized procedure when compared with partial nephrectomy (PN) and radical nephrectomy (RN) [4]. In a survey of 64 institutions performing ablative procedures for SRMs, Patel et al identified laparoscopic CA as the most commonly performed ablative procedure [5].

The European Association of Urology guidelines explicitly state that, due to lack of high-quality data, no recommendation can be made on CA [3]. The American Urological Association guidelines suggest that ablation in general be offered as an option and not a standard for high-risk patients [6]. This review summarizes the available evidence for CA for SRMs and assesses the selection criteria, complications, and functional and oncologic results based on the latest CA literature.

2. Evidence acquisition

A systematic literature search of the Medline, Embase, and Scopus databases was performed in August 2014 using Medical Subject Headings and free-text protocol. Search was undertaken by applying free-text protocol with the following search terms: kidney cryosurgery, renal cryosurgery, kidney cryoablation, renal cryoablation, kidney cryotherapy, and renal cryotherapy. Only publications written in the English language were assessed. Conference abstracts and single-case reports were not included. Where multiple series from the same institution were identified, the most recent series was assessed when results overlapped.

Additional studies cited in the references of the search papers were further evaluated. Eligibility criteria for study inclusion consisted of percutaneous (PCA) or laparoscopic (LCA) renal CA technique, reporting of patient selection criteria and oncologic, functional, or procedure-related complications, and only high-volume series (minimum of 100 patients) for the review. For meta-analysis studies if assessing the same modalities, the larger more recent article was selected. Articles selected were reviewed and approved by all authors. For long-term (>3 yr) oncologic and functional outcomes, we did not limit our inclusion criteria to the minimum sample size of 100 cases.

3. Evidence synthesis

Figure 1 shows our systematic electronic search method. The search returned a total of 11 noncomparative CA studies [7–17] and 8 comparative studies (including 2 meta-analyses) comparing CA methods (LCA vs PCA) or CA with other modalities [18–25]. Additional articles were included for assessment of long-term oncologic outcomes [26], functional results [27–32], salvage treatment options [33–36], and cost assessment [37–39].

3.1. Patient selection

Due to the relatively recent mainstream utilization of CA and the lack of long-term efficacy data from large prospective or randomized studies, most of the data available on CA are limited to the treatment of SRMs in selected cases. Such patients are often older or because of comorbid conditions they were not ideal surgical candidates. The mean age of the patients in the large Mayo Clinic PCA cohort was 69.7 yr, and the median age of the patients undergoing PCA in the Washington University series was 72.6 yr (Table 1) [10,11]. Given the relatively high rate of recurrence/treatment failure rate in some CA series compared with extirpative techniques [19,24], some clinicians advocate reserving this modality for patients who cannot tolerate the extirpative approach due to age and frailty.

Patients with a history of von Hippel-Lindau or other inheritable familial renal tumors owing to the multifocal recurrent nature of their disease are increasingly at risk of surgically induced renal insufficiency. Studies have shown that CA in this subgroup represents an attractive option as the primary treatment modality or after recurrence following PN [40,41]. Another special indication for CA may include patients with a solitary or transplanted kidney, especially when presenting with recurrent disease [42,43]. The minimally invasive nature of CA, in particular the
Table 1 – Contemporary noncomparative cryoablation series with minimum sample size (n = 100)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of procedures</th>
<th>Patient characteristics</th>
<th>Tumor size, cm</th>
<th>Complications, overall/major, %</th>
<th>Follow up, mo</th>
<th>Function</th>
<th>Treatment failure rate</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laguna et al [17]</td>
<td>148 LCA (144 patients)</td>
<td>Age: 70.5 yr (48.3), CCI: 2.6</td>
<td>2.6”</td>
<td>15.5/3.1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Trivian et al [15]</td>
<td>163 LCA (123 patients)</td>
<td>Age: 66 yr (52.3), CCI: 8.5</td>
<td>2.4”</td>
<td>NR</td>
<td>20</td>
<td>NR</td>
<td>NR</td>
<td>4.3%</td>
</tr>
<tr>
<td>Guazzoni et al [12]</td>
<td>131 LCA (123 patients)</td>
<td>Age: 62.3 yr (51.3), ASA: 2</td>
<td>2.14&quot;</td>
<td>20.3/0.8</td>
<td>NR</td>
<td>41</td>
<td>No change in creatinine</td>
<td>0/52</td>
</tr>
<tr>
<td>Okhunov et al [7]</td>
<td>210 LCA</td>
<td>Age: 64.5 yr (52.3), CCI: 6.5</td>
<td>2.6”</td>
<td>19.5/9.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Duffy et al [16]</td>
<td>116 (107 LCA)</td>
<td>Age: 69.5 yr (48.3), CCI: 6.5</td>
<td>2.76</td>
<td>19.8/1.7</td>
<td>27.4</td>
<td>NR</td>
<td>6%</td>
<td>RFS: 77%</td>
</tr>
<tr>
<td>Blute et al [8]</td>
<td>139 PCAs</td>
<td>Age: 70 yr (48.3), ASA: 6.5</td>
<td>2.4”</td>
<td>12.9/0</td>
<td>24</td>
<td>NR</td>
<td>7%</td>
<td>NR</td>
</tr>
<tr>
<td>Breen et al [9]</td>
<td>171 PCAs</td>
<td>Age: 67 yr (52.3), CCI: 8.5</td>
<td>125/161 ≤ 4</td>
<td>NR/4.6</td>
<td>20</td>
<td>NR</td>
<td>7.6%</td>
<td>NR</td>
</tr>
<tr>
<td>Kim et al [10]</td>
<td>129 PCAs</td>
<td>Age: 72.6 yr (52.3), CCI: 6.5</td>
<td>9/2</td>
<td>30.2</td>
<td>NR</td>
<td>5.2 decline in eGFR, ml/min per 1.73 m², 20% CKD upstage</td>
<td>13%</td>
<td>OS: 85%</td>
</tr>
<tr>
<td>Schmit et al [11]</td>
<td>430 PCAs (389 patients)</td>
<td>Age: 69.7 yr (48.3), CCI: 6.5</td>
<td>3.1</td>
<td>7.8/7.5</td>
<td>27.9</td>
<td>NR</td>
<td>3.5%</td>
<td>NR</td>
</tr>
<tr>
<td>Georgiades et al [13]</td>
<td>134 PCAs</td>
<td>Age: 57 yr (48.3), CCI: 6.5</td>
<td>2.8</td>
<td>NR/6</td>
<td>NR</td>
<td>NR</td>
<td>2/134 (1.5%)</td>
<td>OS: 97.8%</td>
</tr>
</tbody>
</table>
| Johnson et al [14]     | 112 LCA (92 patients) | Age: 59.7 yr (48.3), ACCI: 6.5 | 2.3” | 9.8/1.1 | 97.9 | No change in creatinine | NR | OS: 80.9%

ACCI = age-adjusted Charlson Comorbidity Index; ASA = American Society of Anesthesiologists (score); CA = cryoablation; CCI = Charlson Comorbidity Index; CKD = chronic kidney disease; CSS = cancer-specific survival; DFS = disease-free survival; eGFR = estimated glomerular filtration rate; LCA = laparoscopic cryoablation; NR = not reported; OS = overall survival; PCA = percutaneous cryoablation; PFS = progression-free survival; RFS = recurrence-free survival.

* Median.

Mean.

+ Patients with >5 yr of follow-up; for 44 patients with renal cancer and >5 yr of follow-up.

+ For 104 patients with >6 mo of follow-up.

+ At 3 yr.

+ Major (Common Terminology Criteria for Adverse Events criteria).

+ At 5 yr.

+ For patients with renal cancer.

percutaneous route, and maximal preservation of renal function are cited advantages of this approach. Recurrence after previous needle ablation therapy or PN is another potential indication for CA [44].

In early experience with CA for SRMs, tumor size [10,45], polar location [9], hilar location [10], and degree of tumor complexity played a role in tumor selection for this approach [7], but with increasing experience, all SRMs with a variety of characteristics have been treated using the CA modality [46,47]. With initial experience, LCA was utilized primarily for anteriorly and laterally located tumors, and PCA was the method of choice for posterior tumors [48]. However, experience has demonstrated that although technically challenging, anterior tumors can be successfully treated via the percutaneous route, often with adjunctive displacement maneuvers [49]. Such adjunctive maneuvers may include the infusion of fluid or gas via a small-caliber catheter placed under image guidance, resulting in mechanical displacement of adjacent viscera [50,51]. In addition, repositioning of the patient may cause the adjacent bowel to shift away from the tumor. Larger renal tumors (≥3 cm) may also be treated with CA, taking advantage of the synergy of multiple cryoprobes [46,52].

Proximity of the tumor to the collecting system may represent a relative contraindication to CA due to the risk of urethelial stricture. Ureteral strictures have been documented in the animal model and have been reported following PCA [53,54]. Placement of a ureteral stent with retrograde irrigation of the collecting system, as described for radiofrequency ablation (RFA), may mitigate this risk, although data are lacking [55,56]. Confident identification of the ureter while monitoring the iceball allows the operator to minimize ureteral cryoinjury. Mechanical retraction of the tumor during ablation may also shift the iceball away from the ureter [57].

Extension of the iceball centrally into the kidney during PCA has not been associated with the intrarenal collecting system or vascular injury [58]. With direct puncture of the intrarenal collecting system, CA did not result in urinary fistula in a porcine study [59]. Relative warming of the ablation zone by large central vessels (thermal sink effect) may limit the ability to achieve cytotoxic temperatures at
the central tumor margin, and more aggressive treatment with larger cryoprobes and a greater iceball margin is indicated [60,61].

Data from small single-institution series suggest that PCA is a safe and feasible option in the treatment of oligometastatic renal cell carcinoma (RCC) either as part of a multimodal approach in the setting of metastatic disease or as a relatively cost-effective palliative option [62–64].

In brief, our review of available evidence suggests that CA is usually considered for patients who have contraindications for the extirpative approach including medical comorbidities, previous renal procedures, or purely due to patient choice. It is possible, however, that in the foreseeable future, as expertise develops, longer term data become available, and patient interest increases, CA—particularly PCA—might be used in the general patient population presenting with SRMs.

3.2. Complications

The rate of complications after CA procedures varies among the published series and itself is influenced by the characteristics of the patients and tumors, technique of CA, and the experience of the proceduralist. Classification according to standardized schemes such as the Clavien-Dindo grading system can simplify the comparison of results across studies [65]. Classifying the complications based on the time of occurrence (intraoperative vs postoperative, early vs late) and according to the systems involved (urologic vs nonurologic) can be of further value.

The reported overall rates of complications for renal CA procedures in large single institutional published series (n >100) in the literature range from 7.8% to 20% [7,11,12,16,19]. The stated overall complication rates for CA (7.8–12.9%) [8,11] are lower than the documented rates for LCA (15–20%) [7,12,17,19]. These lower rates of complications could potentially stem from the less invasive nature of PCA compared with LCA; however, case selection, patient comorbidities, and method of anesthesia (general vs regional) all could affect the complications associated with the procedures. Kim et al reported comparable rates of major complications in relatively comparable LCA and PCA cohorts (Table 2) [20]. In contrast, Tsivian et al demonstrated a 10-fold higher rate of major complications (8.3% vs 0.8%; p = 0.01) when comparing LCA (n = 72) with PCA (n = 123) [25]. On multivariable analysis, however, only age and body mass index were predictors of overall complications. However, tumor complexity beyond anterior/posterior and polar locations was not assessed in this analysis.

The rates of major complications, generally defined as Clavien grade ≥3 across the CA literature, remain relatively low (0–9%) for both LCA and PCA (Table 1) [7,8,11]. Caution should be exercised when interpreting these results because outcomes are influenced by patient and tumor selection, along with physician expertise. Since the introduction of standardized validated classification systems for the assessment of renal masses undergoing surgical resection [66,67], many publications have attempted to assess the utility of such tumor complexity scores or their individual components in predicting complications after CA procedures.

Breen et al identified upper pole location as a factor predicting complications in a series of 171 PCAs [9]. Pneumothorax was the most common complication in this series. Tumor complexity scores were not reported by the authors. Okhunov et al reported a major complication rate of 9.5% in their series of 210 patients undergoing LCA [7]. In the subset of 77 patients with available RENAL nephrometry scores, tumor complexity score was a predictor of developing complication after LCA on multivariable analysis. The authors suggested that a RENAL nephrometry score >8 has a high sensitivity and specificity for predicting complications after LCA. Availability of RENAL nephrometry scores in only a small subset of the patients and a limited number of tumors (n = 7) with a high RENAL nephrometry score (9%) in the series limit the applicability of these findings to other settings.

More recently, Lagerveld et al assessed and compared the utilities of the RENAL and PADUA complexity scores in predicting intraoperative complications in 99 LCA procedures [45]. Neither complexity scores were predictors of intraoperative complications on multivariable analysis; however, tumor size was a predictor of intraoperative complications associated with LCA. The authors suggested that tumor diameter >35 mm was a more robust predictor of intraoperative complications associated with the LCA technique. A small number of cases with a high RENAL complexity score (n = 3 [3%]) limits the predictability of this model.

In contrast, earlier endeavors suggested that the RENAL nephrometry score is associated with a higher rate of complications in patients undergoing PCA. Blute et al (Table 1) observed that every unit increase in the RENAL score increased the odds of complications of PCA by 50% [8]. Authors also considered that use of each additional probe increased the odds of complications associated with the procedure, suggesting that size may be the predominant subunit in the RENAL score. Sisul et al also detected the impact of the RENAL score (odds ratio: 1.37) in predicting complications in 154 patients undergoing CA (LCA and PCA) [48]. Proximity to the collecting system was a significant predictor of hemorrhagic complication (5.8% in this series). In contrast, Rosenberg et al reported that driving the iceball into the renal sinus (renal sinus fat was judged as a landmark for the renal calyces and pelvis in this study) during PCA was not associated with hemorrhage or collecting system complications [58].

In assessment of the factors predicting PCA complications in one of the largest published series in the literature [11], Schmit et al compared their proposed composite score combining patient and tumor characteristics with the RENAL nephrometry score. The proposed score suggested a risk prediction score, (MC)2, composed of two tumor-related factors, consisting of maximum tumor diameter and central tumor location, and two patient-related factors, history of myocardial infarction and complicated diabetes. The proposed (MC)2 risk score outperformed the RENAL
<table>
<thead>
<tr>
<th>Study</th>
<th>Modality (n)</th>
<th>Patient characteristics</th>
<th>Tumor size, cm/RENAI score</th>
<th>Complications, overall/major, %</th>
<th>Follow up, mo</th>
<th>Function</th>
<th>Recurrence</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsivian et al [25]</td>
<td>LCA (72) vs PCA (123)</td>
<td>Age: 66 vs 63 yr&lt;sup&gt;*&lt;/sup&gt; Age: 4 vs 5</td>
<td>2 vs 2.2</td>
<td>13.9/8.3 vs 21.0/8</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kim et al [20]</td>
<td>PCA (118) vs LCA (145)</td>
<td>LCA older Comparable CCI</td>
<td>2.7 vs 2.4&lt;sup&gt;<strong>&lt;/sup&gt; /6.5 vs 5.8&lt;sup&gt;</strong>&lt;/sup&gt;</td>
<td>10 vs 0</td>
<td>38.6 vs 71.4&lt;sup&gt;**&lt;/sup&gt;</td>
<td>17% vs 23%</td>
<td>OS* 86.3 vs 79.3&lt;sup&gt;**&lt;/sup&gt; RFS* 86.3% vs 85.5%</td>
<td></td>
</tr>
<tr>
<td>El Dib et al [18]</td>
<td>CA (457) vs RFA (426)</td>
<td>Age: 63.8 vs 64 yr&lt;sup&gt;**&lt;/sup&gt;</td>
<td>2.5 vs 2.7&lt;sup&gt;**&lt;/sup&gt;</td>
<td>19.9 vs 19</td>
<td>17.9 vs 18.1&lt;sup&gt;**&lt;/sup&gt;</td>
<td>CE 89% vs 90%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Atwell et al [21]</td>
<td>PCA (163) vs RFA (222)</td>
<td>Age: 68.2 vs 68.6 yr&lt;sup&gt;**&lt;/sup&gt;</td>
<td>2.3 vs 1.9&lt;sup&gt;**&lt;/sup&gt; Central location</td>
<td>Major 5.1 vs 4.3</td>
<td>1.8 mo vs 3.2 yr&lt;sup&gt;**&lt;/sup&gt;</td>
<td>CE 89% vs 90%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Thanagho et al [22]</td>
<td>LCA/PCA (267) vs RPN (233)</td>
<td>Age: 69.3 vs 57.4 yr&lt;sup&gt;**&lt;/sup&gt;</td>
<td>2.5 vs 2.9&lt;sup&gt;**&lt;/sup&gt; /6.4 vs 7.3</td>
<td>8.6 vs 9.4</td>
<td>39.8 vs 21.9&lt;sup&gt;**&lt;/sup&gt;</td>
<td>GFR decline 6% vs 13%</td>
<td>12.7% vs 0%</td>
<td>DFS&lt;sup&gt;<strong>&lt;/sup&gt; 83.1% vs 100% CS&lt;sup&gt;</strong>&lt;/sup&gt; 96.4% vs 100% OS&lt;sup&gt;**&lt;/sup&gt; 77.1% vs 91.7%</td>
</tr>
<tr>
<td>Guilloteau et al [19]</td>
<td>RPN (210) vs LCA (226)</td>
<td>ASA III/IV (51% vs 80%)</td>
<td>2.4 vs 2.2&lt;sup&gt;**&lt;/sup&gt;</td>
<td>20 vs 12</td>
<td>48 vs 44.5&lt;sup&gt;**&lt;/sup&gt;</td>
<td>New CKD 12.2% vs 16.2%</td>
<td>0% vs 11%</td>
<td>NR</td>
</tr>
<tr>
<td>Klatte et al [24]&lt;sup&gt;a&lt;/sup&gt; (meta-analysis)</td>
<td>LCA vs LPN/RPN</td>
<td>Age: 68.4 vs 61.3 yr&lt;sup&gt;**&lt;/sup&gt;</td>
<td>2.28 vs 2.41&lt;sup&gt;**&lt;/sup&gt;</td>
<td>9.8 vs 21.3</td>
<td>NR</td>
<td>NR</td>
<td>9.4% vs 0.4%</td>
<td>Metastasis 4.4% vs 0.4%</td>
</tr>
<tr>
<td>Thompson et al [23]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CA (187) vs RFA (180) vs PN (1057)</td>
<td>Age: 71.6 vs 70.7 vs 60.1 yr&lt;sup&gt;**&lt;/sup&gt;</td>
<td>2.9 vs 2.1 vs 1.2&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1.9 mo vs 3.6 mo vs 5.2 yr</td>
<td>NR</td>
<td>NR</td>
<td>3% vs 5% vs 36%</td>
<td>Local RFS&lt;sup&gt;<strong>&lt;/sup&gt; 98% vs 98% vs 98% MFS&lt;sup&gt;</strong>&lt;/sup&gt; 100% vs 93% vs 99% OS&lt;sup&gt;**&lt;/sup&gt; 88% vs 82% vs 95%</td>
</tr>
</tbody>
</table>

ACCI = age-adjusted Charlson comorbidity index; ASA = American Society of Anesthesiologists (score); CA = cryoablation; CCI = Charlson Comorbidity Index; CKD = chronic kidney disease; CS = cancer-specific survival; DFS = disease-free survival; GFR = glomerular filtration rate; LCA = laparoscopic cryoablation; LPN = laparoscopic partial nephrectomy; MFS = metastasis-free survival; NR = not reported; OS = overall survival; PCA = percutaneous cryoablation; RPN = robot-assisted partial nephrectomy.

<sup>a</sup> Median.
<sup>b</sup> At 3 yr.
<sup>**</sup> At 5 yr.
<sup>†</sup> Not significant.
<sup>s</sup> CTx.

In predicting complications associated with PCA, given that the RENAL complexity score was developed from surgical resection patients and captures tumor elements essential to surgical resection and subsequent reconstruction, and it does so without any acknowledgment of patient-related factors, it might not be a robust predictor of complications in the setting of PCA owing to selection bias toward patients with more medical comorbidities in the population undergoing PCA. Such comorbidities play a pivotal role in the development of complications around the time of the procedure. Furthermore, considering the mechanics of PCA and the expansion of its application, it is not surprising to observe that size and central tumor location are more commonly associated with complications when compared with other components of the RENAL score.

Researchers have also investigated occurrences of specific complications and complications related to certain patient or tumor characteristics. Of the complications associated with PCA, bleeding is the most common [68], and hemorrhage has been associated with tumor size, central location within the kidney, number of cryoprobes used, and patient age [68].

Another potential complication after renal CA is a venous thromboembolism (VTE) [69]. It has been postulated that changes in patients' coagulation profiles after CA due to release of proinflammatory and procoagulative mediators subsequent to cell death can increase such events by creating a hypercoagulable state. Comparing the rates of VTE events between PCA and PN, Hartman and colleagues did not detect a statistically significant difference in the incidence of a thrombotic event per 100 person-years (4.84% vs 1% for PCA and PN, respectively; p = 0.08) [70]; however, given the absolute difference in the rate of thrombotic events between the two groups and the small sample size of the study, a larger study looking at this specific complication is warranted.
In the early PCA era given the predominant posterior percutaneous approach, a subject’s obesity or anterior tumor location was thought to make the procedure more challenging. However, Schmit et al. did not detect significantly higher major complication rates in obese (9.3%; \( p = 0.23 \)) and morbidly obese (7.7%; \( p = 0.67 \)) patients compared with their nonobese counterparts (5.8%), although the authors concluded that PCA in the obese cohort is technically more challenging [71]. The same group reported a low rate of major complications (3%) in their small series of anteriorly located renal masses (\( n = 38 \) tumors) treated with PCA [49].

With the maturation of data and increase in cumulative CA experience, a number of studies have compared the complication rates of CA with other ablative or extirpative approaches. For CA, a number of studies have compared the percutaneous with the laparoscopic approach with regard to procedure-related complications.

Mues et al. reported equivalent major complication rates, 2% for PCA in 99 tumors compared with 3.1% for LCA for 97 tumors, in a cohort of patients with SRMs (<3 cm) [72]. The tumor sizes were comparable between the groups; however, the tumor complexity was not compared between the groups. In a more recent observation, Kim et al. at Washington University (Table 2) reported similar perioperative complication rates for both procedures (10%) [20].

CA is comparable with other needle-ablative modalities in terms of complications. At first look, in one of the largest published series, PCA was associated with higher rate of major complications (7.8%) compared with percutaneous RFA (2.7%). [47]. However, tumors in the CA cohort were more complex. The same authors reported similar major complications rates (4.3% vs 4.5%) in patients with SRMs undergoing PCA or RFA, respectively. Higher proportions of tumors in the CA group were central (41% vs 7%) [21].

In a pooled analysis of RFA and CA studies, El Dib et al reported overall complication rates of 19.9% for CA and 19% for RFA [18]. The authors acknowledged the significant heterogeneity among the series pooled for the analysis.

Comparing with PN, CA has been shown to have a lower rate of complications. Klatte et al. reported an equivalent complication rate for LCA and open PN (20% vs 17%) in a small propensity matched series of T1a tumors [73]. Compared with laparoscopic partial nephrectomy (LPN), the differences in intraoperative (5.2% vs 1.1%) and postoperative complication rates (11.1% vs 3.3%) for LCA were reported to be statistically insignificant; however, LPN had a higher rate of postdischarge complications (16.3% vs 2.2%; \( p = 0.01 \)) [74]. In a large series of patients with SRMs from the Cleveland Clinic, comparing LCA with robot-assisted partial nephrectomy (RPN), the rate of complications was lower for the LCA group (12% vs 20%; \( p = 0.01 \)). However, the major complications were similar between the two techniques (3% for both) [19]. A recent meta-analysis comparing LCA with minimally invasive PN (LPN/RPN) demonstrated a nearly two-fold higher risk of complications for LPN/RPN, a rate that was similar for both urologic and nonurologic complications [24]. However, most of the studies included in the analysis lacked tumor complexity classifications, which may have biased the results.

### 3.3 Functional outcomes

Preserving renal function while treating cancer, particularly in patients with chronic kidney disease (CKD), is the main advantage of any nephron-sparing approach. Based on principles of achieving lethal temperatures throughout the targeted renal tumor, CA is associated with obligatory damage to a variable amount of adjacent healthy renal tissue to achieve a tumor margin, which may theoretically have some detrimental impact on long-term renal function. A number of studies have compared LCA and PCA with alternative treatments. All such data are collected retrospectively and secondary to selection bias. Often there are differences between patients compared in terms of age, racial status, gender, tumor size, and the nephrometry scores at baseline.

In a study involving 22 PCA patients with preexisting CKD and a mean tumor size of 3.4 cm, there was no difference in the mean estimated glomerular filtration rate (eGFR) prior to treatment compared with the eGFR at 1 mo (41.1 vs 41.4 ml/min per 1.73 m\(^2\)) or at 1 yr (42.1 vs 44.4 ml/min per 1.73 m\(^2\)) in 18 patients [27]. The authors reported that for all 48 patients treated with thermal ablation (including 25 RFAs), at 1-mo follow-up, only three patients had a decrease in GFR >25%, with two patients with stage III CKD progressed to stage IV and one patient with stage IV CKD deteriorated to stage V. At 1 yr, five patients had a decrease in GFR >25% with only one patient with stage III CKD deteriorated to stage IV and two with worsening renal function to stage V. None of these patients required dialysis during the follow-up period. At 1 yr there was no significant correlation between degree of GFR change and tumor size. Similar findings were observed at Duke University where a minimal decline in eGFR was seen in their series of 67 patients undergoing LCA at 2 yr postprocedure [32].

Chapman and colleagues assessed functional outcomes in 17 patients (mean tumor size: 3.5 cm) using an experimental technique of tracer kinetic models and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) [28]. At 1 mo, single-kidney MRI eGFR decreased in 15 of 17 CA-treated kidneys with a mean decrease of 31.7%, and 10 of 14 contralateral kidneys (mean decline: 4.4%). Parenchymal volume decreased in 14 of 17 tumor-bearing kidneys (mean decrease: 9.6%) and increased in 15 contralateral kidneys (mean increase: 3.5%). It is important to note that authors found little correlation between the DCE–MRI calculated GFR (milliliters per minute) and those measured by the modification of diet in renal disease formula (milliliters per minute per 1.72 m\(^2\)).

Using immediate postoperative serum creatinine as a marker for functional outcome, Guazzoni et al did not elicit any changes in renal function after LCA [12]. Beemster et al. assessed eGFR in 73 patients with a mean tumor size of 2.5 cm after laparoscopic or open CA, using the CKD Epidemiology Collaboration formula [29]. At 1-yr follow-up, they reported a significant mean postoperative eGFR
decline of 7 ml/min per 1.73/m² (median baseline GFR: 82 vs 73 at 1 yr). Despite this decline, the observed changes in eGFR had little clinical significance, and only 15% of patients were reclassified as having developed new "moderate" CKD with GFR becoming <60 ml/min per 1.73 m². No patient needed renal replacement. It was shown that eGFR at baseline was the only significant predictor of functional decline developing after surgery, and tumor size did not have an impact in this setting.

In a study of 263 patients undergoing CA (mean tumor size: 2.5 cm; 145 LCAs and 118 PCAs), the measured decline in eGFR was comparable between the two groups [20]. The two arms had a different duration of follow-up, and at the most recent follow-up, the LCA groups had an average decline in eGFR of 3.8 ± 18.5 ml/min per 1.73 m² (at 45.0 ± 35.4 mo) and the PCA groups a decline in eGFR of 6.6 ± 17.1 ml/min per 1.73 m² (at 24.6 ± 20.0 mo). CKD stage progression rates were similar between the LCA and PCA groups (LCA 25%; PCA 28%). Functional outcomes have also been assessed and compared between CA and various nephron-sparing procedures. Mitchell et al reported on the comparative functional outcomes of 62 PNs and 50 percutaneous ablations (21 RFAs and 29 CAs) in patients with a solitary kidney [30]. All PNs were done via the open approach (open partial nephrectomy [OPN]), with larger (median: 3.5 vs 2.5 cm) and more complex (RENAL nephrometry score 9 vs 7) tumors in the PN group. At 3 mo, the authors found no differences in post-treatment GFR (50.3 vs 49.3), decline in GFR (3.3 vs 1.5), or change in CKD stage, regardless of lesion size or nephrometry score. They also reported no significant difference in percentage change in GFR between RFA and CA. A subsequent multi-institutional study comparing the outcomes of CA (n = 98 receiving CA and RFA) and PN (50 OPN and 50 LPN) in patients with a solitary kidney reported no difference in postoperative GFR changes between the ablative and extirpative approaches [31].

Guilloteau et al assessed the functional outcomes between patients undergoing RPN (n = 210) and LCA (n = 226) for SRMs. The baseline eGFR was higher in the RPN arm (mean: 86.3 vs 65.8; CKD ≥3; 12.3% vs 44.4%). The proportional eGFR declines were similar between RPN and LCA at 1 mo (6.5% vs 5.1%) and 6 mo (11.2% vs 8.9%). The authors reported that new-onset CKD occurred more frequently in the LCA group than in the RPN group (18.2% vs 12.2%), and end-stage CKD (eGFR <15 ml/min) occurred more frequently in the LCA group than in the RPN group (4.7% vs 0%) [19]. Given the differences in the baseline GFR and CKD stages between the two groups and lack of comparative data on tumor complexity for the groups, the functional differences appreciated warrant further investigation.

In another study comparing CA (n = 267) with RPN (n = 233), after controlling for tumor characteristics and complexity, the mean proportional decline in eGFR was significantly less in the CA group compared with the RPN cohort (6% vs 13%) [22]. The authors demonstrated that with CA, smaller tumor size and hilar tumor location predicted improved renal functional outcomes.

Overall, studies comparing renal function before and after CA, particularly in a solitary kidney setting [30], suggest a degree of functional decline following CA because proper application includes freezing of a tumor margin. However, in most cases this is not clinically significant. Studies comparing different techniques are characterized by baseline function, tumor size, and complexity differences; however, the proportional decline in the function may be comparable between ablative and extirpative nephron-sparing procedures.

3.4. Survival, recurrence, and oncologic outcomes

Oncologic success in those with proven RCC is ultimately the primary goal of CA therapies. The definition of this success needs standardization, however, as well as proper identification of patients with RCC. With extirpative approaches, oncologic success is defined as a lack of local and systemic disease recurrence in those with proven RCC. For CA procedures, the definitions of treatment success, incomplete treatment, and local recurrence warrant further elaboration. Specific oncologic outcomes such as cancer-specific survival, recurrence-free survival, and metastasis-free survival should be evaluated in patients with biopsy-proven RCC; when SRM series include benign or unbiopsied tumors, the results of these outcomes are highly skewed and likely biased toward showing better outcomes than would be expected.

Standardized terminology within the field of PCA has lent itself to considerable confusion. Specifically, two measures of oncologic outcomes have been proposed by several consensus panels: technical success, meaning the tumor was treated per protocol and covered completely by the ablation zone, and technique efficacy, which can be demonstrated only with clinical follow-up [75,76]. Working from these two definitions, some have defined treatment efficacy as the complete lack of enhancement of the previously enhancing tumor and a decrease in the size of the CA-treated lesion over time [13]. Others defined technical success as an extension of the iceball beyond the tumor margin and postablation images demonstrating lack of contrast enhancement in the area of the original tumor within 6 mo of the initial procedure [8]. Technical success has also been defined by imaging follow-up approximately 2 wk after the procedure [9], with subsequent follow-up imaging at 3 mo when the initial imaging did not provide adequate information about the completeness of treatment.

A more comprehensive and recommended definition for treatment efficacy is technical success and lack of local tumor recurrence [21]. Some have proposed that this definition could be further qualified to include primary efficacy rate, as the proportion of tumors successfully eliminated following the initial procedure or a defined course of treatment, and secondary or assisted efficacy rate, which accounts for tumors that have undergone successful repeated ablation following local tumor persistence/progression [75]. Such a definition allows one to account for successful salvage treatment but at the cost of masking the initial success of the oncologic treatment and limiting the application of the specific ablation outcomes, particularly when comparing them with definitive surgical results.

Please cite this article in press as: Zargar H, et al. Cryoablation for Small Renal Masses: Selection Criteria, Complications, and Functional and Oncologic Results. Eur Urol (2015), http://dx.doi.org/10.1016/j.eururo.2015.03.027
As adapted from the most recent consensus statement from several ablation-related panels and a prior review of recurrence following ablation, technical success may be assessed within 3 mo of ablation by the absence of tumor enhancement and the absence of tumor enlargement [75,36]. Local tumor progression (recurrence) is persistent or recurrent tumor evident because of new nodular enhancement in the ablation zone or enlargement of the ablated tumor 3 mo or later after CA compared with imaging obtained immediately after ablation. Although confusing, such terms are essentially distinguished by the presence of residual recurrent tumor either within or after 3 mo of treatment.

Table 1 demonstrates the oncologic results observed in some of the published CA series. Blute et al reported that patient characteristics rather than tumor characteristics were the predictors of tumor recurrence after CA [8]. At a median follow-up of 24 mo for 139 patients undergoing PCA, the authors observed 10 recurrences. Histology was available for 90 of 139 patients, with 78 of 139 tumors having a histologic diagnosis of RCC. On multivariable analysis of tumor complexity, tumor size and the number of cryoprobes used were not predictive of tumor recurrence; however, skin-to-tumor distance significantly increased the risk of recurrence by 25%. For every centimeter increase in distance, patients were 1.5 times more likely to have a tumor recurrence.

Breen et al reported initial incomplete treatment of 7.6%, which with retreatment CA improved to 2.4% [9]. In this series, 62 of 147 patients had a histologically confirmed diagnosis of RCC. On multivariable analysis, the authors did not identify tumor location (anterior, polar, or central position) as a predictor of treatment failure, although these results were not specific for patients with biopsy-proven RCC. In addition, the follow-up time was short, with a median follow-up of 20 mo for 104 of 147 patients with >6 mo follow-up data.

Researchers from Washington University reported treatment success rate of 87% in their series of 124 patients undergoing PCA with a mean follow-up time of 30.2 mo [10]. From the 17 patients (14%) failing initial treatment, 11 were retreated (1 with RN); 2 of 11 required further PCA. Tumor size ≥3 cm was a predictor of disease recurrence on multivariable analysis. The authors reported cancer-specific survival of 100% and estimated disease-free survival of 89% at 1 yr, 85% at 2 yr, and 85% at 3 yr for the entire series. In this series only 23 of 129 patients had a histologic diagnosis based on tissue biopsy with 13 of 129 having a confirmed diagnosis of RCC. Although it is valid to report overall survival only for the series, evaluation of cancer-specific outcomes in patients with a proven diagnosis of benign disease or without the definitive diagnosis of RCC is problematic.

The treatment failure rate for 430 PCA procedures in 389 patients in the Mayo Clinic series with a mean follow-up of 27.9 mo was 3.5%. It is noteworthy that 63% of the tumors in this series were RCC on biopsy [47]. Interestingly, two publications from the Mayo group showed similar local tumor control rates among those with small (<3 cm) and large (range: 3–8.3 cm) renal masses, suggesting that tumor size is not a risk for tumor recurrence when using appropriate selection criteria [46,21]. Other series have reported a similar rate of treatment failure after PCA [13].

In comparison with PCA, the follow-up times for LCA technique in the CA literature are generally longer, providing us with more robust outcome data. In a series with one of the longest follow-up times for LCA, Aron et al reported the outcomes of 80 patients with a minimum of 5-yr follow-up data [26]. For the subgroup of 55 patients with biopsy-proven RCC at median follow-up of 93 mo, the authors reported a 5-yr overall survival of 84% and a 5-yr cancer-specific survival and recurrence-free survival of 92% and 81%, respectively. The estimated 10-yr rates were 51%, 83%, and 78%, respectively.

Guilloteau et al reported a recurrence rate of 11% in their cohort of 226 LCA patients (181 of 234 masses with biopsy-proven RCC [77%]) with a median follow-up of 44.5 mo [19]. Furthermore, 5.6% of patients developed metastatic disease during the period of follow-up. This relatively high rate of metastasis may be influenced by a history of previous RCC in the LCA group and thus may not be a true reflection of metastatic events in patients with SRMs undergoing LCA. Kim et al reported a recurrence rate of 15.9% (23 of 145), 43% had biopsy-proven RCC, for patients undergoing LCA after a mean follow-up of 71.4 mo. The estimated 5-yr recurrence-free survival (RFS) for the series was 85.5%, but these data were not reported for the subset of LCA patients with proven RCC [20]. Tsvian et al reported a local recurrence rate of 4.3% at the median follow-up of 20 mo for a series of 163 patients undergoing LCA, 118 of 163 with biopsy-proven RCC [15]. Importantly, the authors reported tumor size and endophytic growth pattern as predictors of tumor recurrence after treatment.

Comparative series have reported on oncologic outcomes for different CA techniques and also have compared CA with RFA and PN. Due to biases in patient and tumor selection, heterogeneity in malignancy rates, variations in the definitions of success, and differences in follow-up times limit any objective comparison between provided treatment modalities.

When comparing PCA (189 tumors) with RFA (256 tumors) for renal masses ≤3 cm, Atwell et al reported relatively comparable rates of local recurrence for RFA (3.2%) and PCA (2.8%); however, the patients in the PCA group had larger and more central tumors and were followed up for a shorter time than RFA patients (1.8 vs 3.2 yr) [21]. For the subset of patients with RCC confirmed on histology, estimated local RFS rates at 3 and 5 yr for RFA were 98.1%, and 98.1%, compared with 90.6% and 90.6%, respectively, after PCA. However, it is noteworthy that only small fractions of the cohort had actual long-term follow-up available (12 patients and 1 patient at risk at 5 yr for RFA and CA, respectively).

In a pooled analysis of published CA and RFA series, El Dib et al reported a similar proportion of clinical efficacy for CA (89%; 95% confidence interval [CI], 0.83–0.94) and RFA (90%; 95% CI, 0.86–0.93) [18]. Clinical efficacy was described as the percentage of tumors treated successfully, and successful tumor treatment was defined as no growth or no
evidence of recurrence on imaging. Given the heterogeneity of the studies included in the analysis, the results need to be interpreted with caution.

Comparing LCA and PCA, Kim et al did not identify the method of CA as a predictor of disease recurrence after adjusting for other variables [20].

Guilloteau et al reported a higher recurrence rate for LCA compared with RPN (11% vs 6%); however, the follow-up for the RPN group was considerably shorter (4.8 vs 44.5 mo) [19]. A subsequent report by Tanagho et al, comparing 267 CAs (LCA and PCA) with 233 RPNs, better disease-free survival (100% vs 83.1%) and cancer-specific survival (CSS) (100% vs 96.4%) was observed in the RPN group [22]. In this series, 80 of 153 tumors in the CA group and 185 of 233 of tumors in the RPN group had a histologic diagnosis of RCC. Higher proportions of the RPN tumors were endophytic, and overall tumors in the RPN group were larger and more complex. After adjusting for patient and tumor differences, treatment with CA had a higher probability of local recurrence compared with RPN (hazard ratio:11.4). In contrast to Guilloteau et al, the follow-up times were longer, 39.8 and 21.9 mo (mean) for CA and RPN, respectively; however, the RPN group still had a shorter follow-up.

The rate of local tumor progression in a pooled analysis of published data for LCA in a recent meta-analysis was 9.4% compared with 0.4% for minimally invasive PN, translating to a calculated 9.39-fold increased risk of local tumor progression for patients undergoing LCA [24].

Thompson et al recently compared the oncologic outcomes for cT1a tumors between RFA (n = 180), PCA (n = 187), and PN (n = 1057) [23]. Histologically proven RCC for RFA, PCA, and PN groups was 41% (73 of 180), 58% (108 of 187), and 79% (836 of 1057), respectively. Patients in the CA group were older with a higher rate of comorbidities. On univariable analysis, there was no difference in estimated 3-yr RFS between the three treatment modalities (98% for all three arms). Distant metastasis-free survival (MFS; evaluated only among patients with biopsy evidence of RCC) at 3 yr, however, was better for PN (99%) and CA (100%) compared with RFA (93%). Although encouraging, given the univariable nature of analysis, shorter follow-up time for CA, and small proportion of patients having actual 3-yr follow-up data (48 of 174), longer follow-up and more robust analysis are needed.

Any analysis comparing oncologic outcomes, such as MFS or CSS, of various approaches should include only biopsy-proven (or suspicious for) RCC and account for selection biases as well as tumor complexity as a conceivable source of treatment failure and a potential surrogate for tumor biology that could affect the outcomes. Given the documented possibility of false-negative and false-positive imaging findings, the role of imaging to define success may further evolve with extended patient follow-up.

The role of tumor biopsy in the setting of CA needs further discussion. Accurate data about the histology and grade of the renal mass being treated are imperative, aiding in formulating a postoperative surveillance strategy and for assessing the oncologic outcomes of CA. Although the tissue architecture during the rapid tissue freezing nature of CA is preserved, Truesdale et al reported a superior diagnostic yield and pathologic diagnosis accuracy in preablation biopsy rather than after [77]. Other researchers have reported correct assessment of histology and grade in biopsies following CA [78]. Based on the consensus from the 5th International Symposium on Focal Therapy and Imaging in Prostate and Kidney Cancer, preablation biopsy in every patient treated with CA is recommended [79]. The panel further recommended in cases where the initial biopsy is not diagnostic that immediate postablation biopsies be obtained. The recommendations also encompassed the technique of biopsy, advocating obtaining a minimum of two core biopsies using a ≥18-gauge needle.

3.5. Salvage options

Although no universally accepted criteria for recurrence is defined, persistence of enhancement and tumor growth are highly suggestive of viable tumor that may be confirmed on biopsy. Peripheral enhancement can be seen in 15–20% of patients at 3 mo (largely related to an ongoing inflammatory reaction at the treatment margins); however, this is reduced by 9–12 mo, and only a fraction of these patients may eventually have biopsy-proven recurrences [80,81]. Similarly, MRI may demonstrate insignificant internal tumor enhancement immediately after ablation and lasting up to 6 mo following treatment, likely related to delayed large vessel thrombosis following successful ablation [82]. Short-term surveillance may be one initial option, especially early following CA. These patients can be followed closely, and then salvage therapies considered on a case-by-case basis.

Repeated ablation is the most common salvage nephron-preserving procedure following CA recurrence. Reablation rate in this setting is approximately 1% (0.9–1.3%) [83,84]. There are limited data on the oncologic outcomes or complications of repeated ablation therapies, and only a fraction of reported data concerns post-CA patients. In a report of 63 cases at 2-yr follow-up, local disease progression of 4.2% was reported; however, only 8 of these 63 patients had primary CA [36], and the true rate of local disease progression after salvage CA for failed primary CA is not known. The type of reablation technique depends on tumor factors, and some authors state a preference for repeated LCA for anterior and lateral lesions and PCA for posterior lesions [33].

Not all patients with recurrence are candidates for reablation. PN and RNs have been described in this setting. In an analysis of 337 recurrent CA cases, Long and Park reported a salvage nephrectomy rate of 2.4% [83]. Surgery is complicated by desmoplastic reaction in the perinephric tissue, which has been reported to be more dense after LCA than is observed after failed PCAs or LPN with a higher risk of major complications [34,35].

3.6. Cost

Studies have assessed cost, but their results differ based on some key postulated differences such as period of observation, definition of success and complication rates,
and also whether those with benign biopsies should be treated or followed up.

Chang and colleagues concluded that for healthier younger patients (aged 65 yr with a <2-cm lesion or aged 75 yr with a 3- to 4-cm lesion), immediate surgery (LPN or OPN) represents the optimal nephron-sparing option with the best incremental cost-effectiveness ratio per quality of life-year added [37]. Surveillance with possible delayed PCA was a cost-effective option for older patients or those with increased perioperative mortality risk. Observation represented the best strategy for patients who are poor surgical candidates and who had a life expectancy <3 yr. It is worth noting that laparoscopic ablation was not cost effective in any scenario regardless of age, comorbidities, and tumor size. The cost analysis was based on the assumption that following LPN, 25% of patients will have benign disease and will not require further follow-up, whereas all patients after ablative therapies will require follow-up. They also estimated that recurrent or residual disease will develop in about 20% of patients following ablation and that after two procedures, 8% will still recur.

Bhan and colleagues, using Canadian data and comparing RFA, CA, and observation for the treatment of SRMs, established that active surveillance with no initial biopsy and with subsequent PCA in case of disease progression was more cost effective than immediate CA with or without biopsy and other observation options. They found that in terms of cost effectiveness, all CA techniques were superior to RFA procedures owing to higher rates of retreatment for RFA. They anticipated a 7.7% recurrence rate and assumed successful treatment after reablation [38]. Reporting direct comparative costs of LCA (n = 23) and PCA (n = 16) [39] with PCA performed under regional anesthesia, LCA was significantly more expensive than PCA (3.5 times on average). However, these values need to be adjusted for patient and tumor characteristics to better gauge the cost incurred by each approach. Ideally the cost breakdown should also consider the cost of readmission, ongoing surveillance, and retreatment into the analysis.

### 3.7. Limitations

This review represents a comprehensive literature review of a clinically relevant modality for the treatment of small renal neoplasms. As noted in prior meta-analyses of ablative therapies, the major limitation of this work remains the relatively poor quality of the available data, lack of tissue confirmation, and the scarcity of prospective trials in this field [84]. Almost all studies were retrospective, and the patient selection criteria, definitions of success, and methods of assessment of functional outcomes varied considerably among the studies. The findings highlight the demand for standardization of definitions within the field and the need for well-designed clinical trials assessing the efficacy of CA and comparing it with other available modalities for the treatment of renal neoplasms.

### 4. Conclusions

CA represents an alternative approach for the treatment of patients diagnosed with a renal neoplasm (Table 3). There is no consensus within the literature on best patient selection criteria. Due to the higher rates of treatment failure, it is often not offered to patients with minimal comorbidities and a good life expectancy; however, some experts in the field have challenged this approach. The lack of tissue diagnosis of RCC remains problematic, blurring the ability to assess oncologic outcomes accurately and exposing patients to possible unnecessary treatment of benign tumors. The emergence of robotic nephron-sparing surgery as well as the rising popularity of active surveillance for SRMs has likely had an impact on the utility of CA where these modalities are feasible [85]. From a functional outcome viewpoint, CA signifies a modality with a minimum impact on renal function; however well-designed studies precisely assessing this factor are lacking. CA is a minimally invasive modality with suitably low rates of complications in particular when delivered via the percutaneous route.

**Author contributions:** Homayoun Zargar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Zargar, Atwell, Zargar-Shoshtari, Thompson.

**Acquisition of data:** Zargar-Shoshtari, Zargar.

**Analysis and interpretation of data:** Zargar-Shoshtari.

**Drafting of the manuscript:** Zargar-Shoshtari, Zargar, Atwell.

---

**Table 3 – Summary of selection criteria, complications, functional results, and oncologic results**

<table>
<thead>
<tr>
<th>Selection</th>
<th>Reserved for patients with contraindications for extirpative approach such as medical comorbidities, previous renal procedures, or purely due to patient choice. Further data are needed before CA utility in general patient population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td>The overall rates of complications for renal CA procedures in large published series range from 7.8% to 20% with most complications being minor (Clavien grade &lt;3). Tumor size, location, and medical comorbidities are important factors associated with development of complications.</td>
</tr>
<tr>
<td>Functional results</td>
<td>CA is associated with minimal decline in renal function postoperatively. The studies comparing different nephron-sparing techniques are characterized by baseline function, tumor size, and complexity differences; however, the proportional decline in the function may be comparable for ablative and extirpative nephron-sparing procedures.</td>
</tr>
<tr>
<td>Oncologic results</td>
<td>Any analysis comparing oncologic outcomes, such as metastasis-free survival or cancer-specific survival, should include only biopsy-proven RCC and account for selection biases as well as tumor complexity as a conceivable source of treatment failure and a potential surrogate for tumor biology that could affect the outcomes. Obtaining data about the histology and grade of the renal mass being treated is imperative. Based on the review of the available data, the rate of recurrence-free survival for CA is lower than extirpative surgery, but newer studies suggest that in the intermediate term, outcomes might be comparable. Longer term oncologic follow-up is needed.</td>
</tr>
</tbody>
</table>

CA = cryoablation; RCC = renal cell carcinoma.
Critical revision of the manuscript for important intellectual content: Atwell, Caddeu, de la Rosette, Janetschek, Kaouk, Matin, Polascik, Zargar-Shoshtari, Thompson.

Statistical analysis: None.

Obtaining funding: None.

Supervision: Atwell, Caddeu, de la Rosette, Janetschek, Kaouk, Matin, Polascik, Zargar-Shoshtari, Thompson.

Other (specify): None.

Financial disclosures: Homayoun Zargar certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Jihad Kaouk is a consultant/speaker for Endocare.

Funding/Support and role of the sponsor: None.

References


