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Review

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Cryoablation for the management of Small Renal Masses

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Abstract

Renal cell carcinoma is identified most often in the sixth or seventh decade of life, coinciding with the rise in incidental diagnosis of small renal masses as imaging technology has advanced. However, not all patients in this older age group are surgical candidates owing to their comorbidities. Cryoablation is a well-established minimally invasive technique for the treatment of small renal masses. The advent of less invasive ablative treatment has alleviated the surgical dilemma for certain patients who are contraindicated for extirpative procedures. With the appropriate patient selection, cryoablation is safe and effective, resulting in comparable local tumor control, fewer complications, better preservation of renal function, a faster recovery, and a shorter hospital stay. The percutaneous procedure has increased in popularity due to the advantages of reduced pain, shorter hospitalization, the ability to be performed without general anesthesia, and decreased cost relative to surgery.

Keywords: Cryoablation, cryosurgery, focal therapy, small renal tumors, renal cell carcinoma

INTRODUCTION

Renal masses range in clinical significance from benign tumors to malignancies such as renal cell carcinoma (RCC). According to trends from the cancer statistics, it is estimated that in 2022 there will be approximately 79,000 new cases of RCC diagnosed with an estimated 13,920 expected deaths in the US[1].

With the advent of cross-sectional imaging, there has been a stage migration of kidney cancer with increased diagnosis of renal cancer at an earlier stage and coinciding increased 5-year survival rate, 93% for tumors localized to the kidney but 70% for local spread and 12% for distant spread[2]. Thus, there is interest in treating RCC at an early stage before it spreads, but the discovery of small renal masses (SRMs), defined as a contrast-enhancing solid or cystic renal lesion measuring 4 cm, requires a diagnostic and management decision because some SRMs represent benign lesions and others an indolent malignancy with a low risk of metastasis that can be managed with a surveillance strategy[3]. For small renal tumors, surgical extirpation (partial or radical nephrectomy) and active surveillance are frequently considered the best management options. Even if active surveillance is initially used, if the SRM grows at a significant rate, intervention is merited, and not all patients with SRMs are good candidates for surgical resection. For these patients, minimally invasive ablative therapies, particularly thermal ablation (TA) techniques such as cryoablation (CA), radiofrequency ablation (RFA) and microwave ablation (MWA), provide an alternative management strategy.

CA, which has been used for many tissue types for over 30 years, involves cooling targeted tissue while using image guidance to a temperature sufficient to induce cellular death. Rapid cooling within targeted tissue by CA causes coagulative necrosis of cells via direct cellular membrane damage as well as changes in the cellular microenvironment. The use of CA for urologic applications has increased due to the relative benefits of CA, including real-time image monitoring during treatment, decreased anesthetic requirement, and excellent safety profile in patients at increased risk for surgery. This article provides a narrative review of the mechanisms of action and techniques implemented for CA, as well as the selection criteria, complications, renal function outcomes, and oncologic outcomes of CA for the management of SRMs.

METHOD OF EVIDENCE ACQUISITION

A literature search of Medline, Embase, and Scopus databases was conducted in August 2022 using Medical Subject Headings (Mesh) and a free-text approach. In the free-text protocol, the following Mesh terms were used: Small Renal Masses, Renal Cryosurgery/Cryotherapy, Renal Cryoablation and Percutaneous/Laparoscopic Cryoablation/therapy. Only articles in English were considered. Conference abstracts and case reports were excluded. When the findings of multiple series from the same institution overlapped, the most recent series was assessed.

Additionally, references within articles obtained through the initial query were examined further. All writers evaluated and approved the papers that were selected. The reporting of the type of CA method used (percutaneous, laparoscopic, or open), patient selection criteria and reporting of complications with oncologic and functional outcomes were all considered for review.

CRYOABLATION

Cryogenics - mechanism of action

Cooper was the first to document the necrotic impact of CA in 1964[4]; however, its applications in urology and the use of percutaneous probes for treatment are relatively new. CA is characterized by intense and rapid cooling that causes ice ball formation encompassing the target tissue. The temperature nadir of the target tissue and duration of the tissue at the nadir temperature was the initial basis of cryoablative dosimetry[5]. Based on multiple *in-vitro* and *in-vivo* experiments, a temperature nadir of -40 °C has been established as the optimal target temperature to establish cell kill in renal tumors[6]. In addition to temperature nadir, additional factors that modulate the effectiveness of CA in causing cancer cell death include the time of exposure, rate of cooling, rate of thawing, and the number of freeze-thaw cycles[5-7]. CA results in cell death through a variety of mechanisms, including physical damage to the cell membrane

caused by ice formation, cellular stress response ("kill switch" mechanism), necrotic and apoptotic cascades, vasoconstriction leading to stasis during the thawing process, and activation of immune responses[8]. Extracellular ice crystal formation initiates the processes of cell death caused by CA, which results in hyperosmosis and cell dehydration, followed by denaturation. Ice crystal development causes mechanical damage to the cell membrane owing to shearing forces; intracellular ice crystal formation causes permanent cell damage. During thawing, vasoconstriction causes a loss of blood flow, further leading to coagulative necrosis and subsequent inflammation resulting in the release of cytokines that causes apoptosis of the damaged cells[8]. Figure 1 offers a comprehensive depiction of several CA mechanisms of action.

Cryoablation procedure

Imaging

Open CA, laparoscopic CA (LCA), and percutaneous CA (PCA) are all guided by imaging during the procedure to assess cryoprobe placement and ice ball formation; imaging modalities utilized for CA guidance include ultrasonography, a computerized tomography (CT) scan, or magnetic resonance imaging (MRI). The edge of the ice ball can be seen on imaging; however, the edge of the ice ball has a temperature of 0 °C, so the ice ball visualized on imaging must extend beyond the intended treatment zone to ensure the entire treatment zone achieves a sufficiently lethal nadir temperature of approximately -20 °C to -40 °C[9].

Cryoprobes and currently utilized cryogens

The cryoprobes are inserted into the tumor with their tips extending just beyond the tumor margin. The appropriately sized ice ball for the patient's target tissue is accomplished using one or more cryoprobes of the appropriate size for the given lesion. Currently, available commonly used cryoprobes come in diameters ranging from 1.5 mm to 3.8 mm and are selected to form ice balls of spherical or elliptical shapes of various sizes. An access sheath can often be utilized to avoid repetitive skin punctures while allowing for multiple entries of needles for biopsy and cryoprobes[10,11]. The cryoprobe achieves rapid cooling because it contains a Joules-Thompson chamber that allows highly pressurized argon gas to expand, causing the cryoprobe to reach extremely cold temperatures that are then transferred to the target tissue via conduction. Thawing can be accelerated by injecting helium gas into the chamber or using an electrical heating element. The cryoprobes receive gas from the argon and helium tanks via controlled pressure regulators[10].

Precautionary measures

Warming the skin entry points may be necessary to reduce collateral skin injury[12]. To achieve technical success, probes should be inserted parallel to one another with spacing to allow for adequate ice ball overlap so that a uniformly low temperature is reached at the target tissues[9]. In the case of LCA, if post-procedural bleeding is encountered, it can be controlled with argon beam coagulation and hemostatic agents. If neighboring organs such as the bowel are too close to the target renal lesion, routinely used techniques to help create a safer distance include patient repositioning, hydro-dissection, or gas insufflation with CO_2[9,11,12]. An additional technique to help create additional space between the target renal lesion and adjacent organs is to use the cryoprobe itself to provide retraction or torque to the kidney itself[13]. When the renal lesion is close to the proximal ureter, the patient may benefit from the placement of a ureteral stent and pyeloperfusion to protect the ureter from freezing temperatures[14]. For upper pole tumors treated with PCA, there is an increased risk of iatrogenic pneumothorax if the needle path transverses the pleura, this can sometimes be mitigated with patient positioning and an oblique needle trajectory, but sometimes a pneumothorax is unavoidable and a small chest tube can be left in place at the conclusion of the procedure[15].

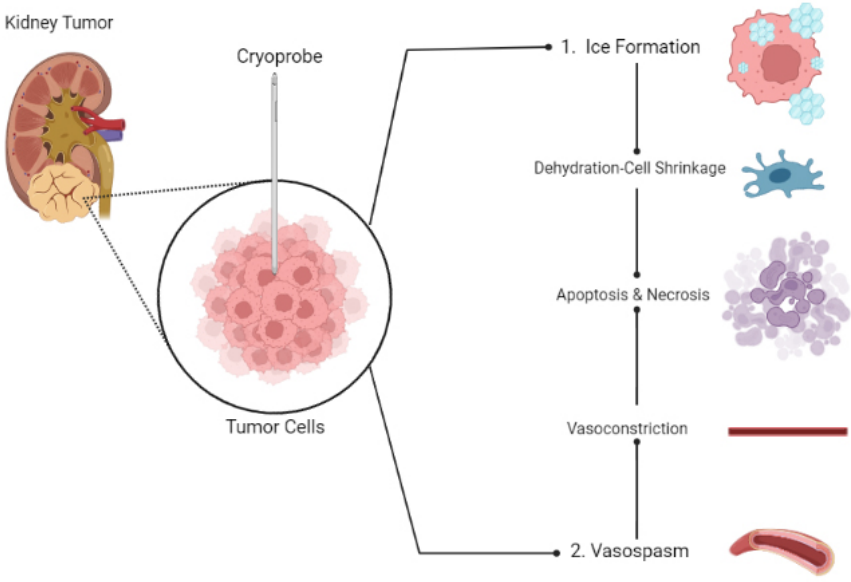

Figure 1. Cryoablation - mechanism of action.

ESTABLISHED INDICATIONS

When determining the management approach for patients diagnosed with SRM, the patient's values/goals, life expectancy, and potential treatment benefits must all be considered and balanced. There is currently no universal agreement on the ideal patient and tumor selection standards for the implementation of CA. The current guidelines for the management of renal cancer from the American Urological Association (AUA) include consideration of CA for RCC tumors < 3 cm, as well as select oligometastatic RCC and recurrent RCC tumors[16]. The National Comprehensive Network (NCCN) guidelines for kidney cancer management include consideration of CA for RCC tumors ≤ 4 cm, as well as select oligometastatic renal tumors and recurrent renal tumors[17]. The European Association of Urology (EAU) recommends consideration of CA for patients with SRM who are frail and/or have comorbidities but recommends against routine use of CA for renal masses > 4 cm, tumors located near the renal hilum or the proximal ureter[18]. The Society of Interventional Radiology (SIR) recommends consideration of CA for patients with clinically localized renal cell cancer with a maximum diameter of ≤ 4 cm (cT1a), and in select patients with clinically localized renal cell cancer with a maximum diameter > 4 cm but ≤ 7 cm (cT1b)[19]. There is limited strength of evidence to compare treatments for SRM, resulting in these differences in recommendations and the need for an individualized approach to patient care.

CONTRAINDICATIONS

The only absolute contraindication to CA is untreatable coagulopathy[20]. Relative contraindications for CA include younger age for patients who are healthy enough to be good candidates for PN, larger tumors such as those > 3 cm, SRM located near the hilum or proximal ureter, intrarenal SRM, small cystic SRM that would be good candidates for active surveillance or patients who have very short life expectancy where expectant management would be preferred[21].

IMPLICATIONS OF TUMOR LOCATION AND APPROACH

Open CA, LCA, and PCA are all viable treatment options for renal masses. PCA is typically used for posterior and lateral tumors, whereas open CA and LCA are preferred for anterior tumors where the

percutaneous placement of cryoprobes is more challenging. CA can be used to treat renal tumors up to three to four centimeters in size. The location of the tumor affects whether additional precautions are required to protect nearby structures. To reduce the risk of collateral tissue damage to vulnerable tissues, such as the colon, a 1-2 cm buffer is advised. Some anterior tumors can be treated percutaneously using patient repositioning and adjuvant displacement techniques. One such technique is hydro-dissection, which involves the injection of fluid through a small-diameter catheter implanted under imaging guidance[12].

When the tumor is more central and closer to larger vessels, these vessels may provide a heat sink effect making it more difficult for the target lesion to reach cytocidal temperatures and require more aggressive treatment with larger or additional cryoprobes and a wider ice ball margin[22]. When tumors are close to the urinary collecting system, there is a small risk of thermal injury to the urinary collecting system that could potentially lead to downstream stricture or urine leak/fistula. To reduce this risk, retrograde pyeloperfusion can be utilized by the instillation of warm saline into the urinary collecting system via a ureteral catheter, thus preserving these crucial structures without significantly impairing the ablation treatment effectiveness[23]. Nevertheless, importantly, ice ball extension into normal kidney tissue has not been linked to intrarenal collecting system injury, and it was previously demonstrated in a porcine model that insertion of the cryoprobe into the renal pelvis with intentional thermal injury did not cause urinary fistula development.

PERIPROCEDURAL ADVANTAGES

The frozen tissue or ice ball can be monitored using ultrasound or CT imaging, facilitating real-time monitoring and assessment of the ablated region[24]. Highly vascular lesions like angiomyolipoma may be effectively ablated with CA because it has a less pronounced heat sink effect that dampens temperature variations and is less likely to injure the urinary collecting system than heat-based methods like RFA[20,25]. In addition, the procedure can often be safely repeated if needed in the future should tumor recurrence occur. Another setting where CA may be advantageous is in obese patients because increased perinephric fat that makes a surgical approach more challenging can actually make CA easier by providing additional space between the SRM and adjacent vulnerable organs[20].

PERIPROCEDURAL DISADVANTAGES

The primary drawback of CA relative to other ablative modalities is lengthier procedure timeframes, although the overall procedural length depends on patient factors including tumor size, tumor location, and perinephric fat, as well as the method of CA (open, LCA, or PCA), the cryoablation system and the imaging system used, and the proceduralist's experience. Additionally, the facility must acquire and store the gases required for cooling, which may raise the financial and logistical expenses associated with conducting CA[20]. Postoperative bleeding from the target site or probe tract might be less likely to occur with RFA due to the coagulation effect of extreme heat[20].

ROLE OF BIOPSY IN CRYOABLATION

Percutaneous renal tumor biopsy (RTB) is contentious in SRM management due to the risk of complications, diagnostic inaccuracy or nondiagnostic sampling, and the limited influence on medical management decisions. The most common complications following RTB include renal hematoma (4.9%), significant pain (1.2%), and gross hematuria (1%)[26]. Needle tract seeding is of theoretic risk of RTB that has been reported in some case series[27,28]. However, an access sheath at the time of RTB and CA can be used to permit many multiple needles to pass through the lesion with only a single pass through the skin, decreasing the theoretic risk of needle tract seeding. Elderly or weak patients who will be handled conservatively regardless of RTB findings and young or healthy individuals who would be reluctant to accept the potential

uncertainties and are not planned for treatment with CA do not require RTB[16]. However, for patients who are going to undergo CA, there is more consensus that RTB should be performed in order to help guide follow-up, and percutaneous RTB can be performed at the time of CA prior to the ablation of the lesion. In terms of RTB type, core needle biopsy (CNB) is preferred due to better diagnostic yield compared to fine needle aspiration (FNA); a recent systematic review found CNB to have sensitivity and specificity of 99.1% and 99.7%, whereas FNA had sensitivity and specificity of 93.2% and 89.8%[29]. The reason RTB is important for patients undergoing CA is that the histology and grade of the treated renal mass are crucial for defining a postoperative surveillance plan following CA, as well as for assessing CA oncologic outcomes[30]. Indeed, benign masses account for 15-20% of SRMs[31,32], and these lesions may not need further follow-up after an ablative procedure[31]. Thus, the Focal Therapy Society (FTS) recommends pre-ablation biopsy in all patients undergoing CA, and if the initial biopsy prior to ablation was nondiagnostic, the panel advised a post-ablation biopsy[33]; however, the diagnostic accuracy of RTB may be decreased following ablation[34].

COMPLICATIONS

The rate of complications with CA is relatively low, ranging from 7.8% to 20%, and most of the complications are minor[35-38]. Generally, flank pain or paresthesia is reported as the most common complication of PCA, with reported rates ranging from 4.3% to 8.3%, although several authors discount the accounting of self-limited flank pain as a complication[39,40]. Post-ablation syndrome is characterized by fever and flu-like symptoms following CA and occurs in a minority of patients, but a much larger proportion of patients will experience some post-ablation flu-like symptoms, which are typically self-limited[41]. Other rare but potential complications include UTI, hematuria, hemorrhage, perinephric hematoma, nerve injury, pneumothorax, and damage to the urinary collecting system, which can rarely lead to urinoma or ureteral stricture[23,39,42-44]. In addition to the potential procedure-related complications, we must also consider device-related complications, which might differ depending on the ablation approach used. In a review of the Food and Drug Administration's Manufacturer and User Facility Device Experience (MAUDE) database, the authors found CA had a small number of device-related complications, including a small number of cases that had to be aborted due to instrument/system malfunction and hemorrhage requiring an additional procedure[45]. Although some studies have attempted to compare complication rates between CA and PN or between various techniques for TA, there have not been any head-to-head randomized comparisons, so all such comparisons are inherently influenced by selection bias. Patients selected to undergo TA generally have more comorbidities and risk factors, which can only partially be controlled for by attempts at patient matching. Table 1 offers a comprehensive review of complications associated with CA.

Complications by tumor complexity scores

Various reports have tried to evaluate the utility of scoring systems to quantify the risk of complication based on tumor complexity related to CA. Previously developed scoring systems for tumor complexity were based on PN experiences and included the RENAL nephrometry score (Radius, Exophytic/endophytic, Nearness to collecting system/sinus, Anterior/posterior, and Location relative to the polar line) and PADUA score (Preoperative Aspects and Dimensions Used for Anatomical classification of renal tumors). In studies of CA, the RENAL score was found to have some correlation with the incidence of complication[38,50,56,57], but the PADUA score was not predictive of the incidence of complication[57]. An ablation-specific renal tumor scoring system, the (MC)2 score (Maximum tumor diameter, Central tumor location, prior Myocardial infarction, and Complicated diabetes mellitus), was initially proposed in 2014[51] because the factors that impact risks associated with treating a renal tumor from a surgical approach are not necessarily the same factors that impact the risks associated with treating a renal tumor with ablation, especially from a percutaneous approach. The (MC)2 score has been externally validated[58] and has been shown to outperform the RENAL nephrometry score in predicting the risk of complications following PCA[51]. An additional factor that increases the risk of complication for PCA, which is different from PN, is

Table 1. Complication outcomes - cryoablation

Variables	Breen *et al.*[46]	Tsivian *et al.*[47]	Kim *et al.*[48]	Laguna *et al.*[49]	Blute *et al.*[50]	El Dib *et al.*[43]	Schmit *et al.*[51]	Guazzoni *et al.*[35]	Guillotreau *et al.*[37]	Klatte *et al.*[52]	Lucignani *et al.*[53]	Cobelli *et al.*[54]	Nielsen *et al.*[55]
Overall complication rate (%)	NR	13.9/21.1	3/3	15.5	12.9	19.9/19	NR	20.3	20/12	9.5/18	36.2/24	9.8/6.2	16.6%
Minor complication rate (%)	NR	5.6/20.3	2.75/1.6	15.2	12.9	NR	NR	17.8	17/8	NR	34.5/18.6	9/6.2	2.5%
Major complication rate (%)	4.9	8.3/0.8	0.6/0.8	20	NR	NR	7.5%	NR	6/8	NR	1.7/5.4	NR	3.2%
Common complication	Pneumothorax (Major)	Flank pain/paresthesia	Pulmonary embolism (LCA) Perinephric hematoma (PCA)	Ileus > UTI > flank haematoma	Perinephric hematoma	Perinephric hematoma	Hemorrhage	Fever > hematoma	NR	hemorrhage	Hemorrhage	Hemorrhage effusion	hemorrhage
Procedure	PCA	LCA/PCA	LCA/PCA	LCA	PCA	CA/RFA	PCA	LCA	RPN/LCA	LCA/L(R)PN	CA/MWA	CA/MWA	LCA

LCA: Laparoscopic cryoablation; LPN: laparoscopic partial nephrectomy; MWA: microwave ablation; NR: not reported; PCA: percutaneous cryoablation; RFA: radiofrequency ablation; RPN: robotic partial nephrectomy.

that superior pole tumors have been demonstrated to have a higher risk of pneumothorax[46]. More recently, the ABLATE score has been proposed as a scoring system to use to help predict the risk of complications and recurrence following percutaneous ablation treatment of renal lesions, and in addition to taking into account the diameter and location of the tumor, this scoring system also takes into account proximity of other organs, the angle of the tumor on the kidney, whether the lesion is recurrent, and whether there are adjacent renal cysts[59]. The differences in what factors affect the risk of complication following PCA compared to PN demonstrate the need to take an individualized approach to patient care to determine the management option that would best suit the individual patient based on their differential risks from each treatment approach. These differences also highlight the problem with attempts at controlling for tumor complexity when making retrospective comparisons between different techniques for treating renal masses.

Complications - assessment

In the literature on the treatment of SRM, there is considerable variation in the reported rates of complications, their classification systems, and the scores used to predict them. This high degree of variability is most likely attributable to differences in baseline patient characteristics, the expertise of the provider, and surveillance after the procedure. Nonetheless, the total incidence of CA complications appears to be quite low, with the great majority minor in nature as

compared to radical approaches[60,61]. The factors most predictive of complications after CA appear to be tumor size and tumor location, with centrally located tumors and upper pole tumors at the highest risk for complications[46,51,58]. Complications were associated with higher RENAL scores, and the (MC)2 score, which includes myocardial infarction and diabetic patients, was found to be the best predictor of complications after CA, with tumor size and location appearing to be the best tumor characteristics predicting complications.

RENAL FUNCTIONAL OUTCOMES

The necessity to reduce renal function loss in order to minimize secondary morbidity and mortality drives the pursuit of nephron-sparing therapies for SRMs, including PN, CA, and other ablative technologies. Although these techniques are nephron-sparing because they are intended to avoid loss of the entire affected kidney, there is, by necessity, some healthy renal tissue that is sacrificed in order to have a margin around the renal mass to prevent the residual tumor from being left behind. CA is no exception to this principle, as in any ablative modality, the healthy renal tissue needs to be treated around the SRM to ensure complete tumor ablation. Because there is expected to be some cryoinjury to the renal tissue adjacent to the SRM, this can cause a small but measurable decrease in renal function following the procedure.

LCA *vs.* PCA

LCA had no immediate postoperative changes, with a small decline in serum creatinine level two years following the treatment as a measure of renal functional outcome[35,47]. Studies comparing estimated glomerular filtration rate (eGFR) between patients undergoing laparoscopic or open CA found that measured eGFR reduction was comparable in the two groups, with baseline eGFR being the only reliable indicator of functional impairment occurring after CA; tumor size had no bearing in this situation with rates of CKD stage progression were equal in the PCA and LCA cohorts[48,62]. Wehrenberg-Klee *et al.* found no statistically significant change between mean baseline eGFR values before the start of treatment and the values at one month (41.1 *vs.* 41.4 mL/min per 1.73 m^2) and one year (42.1 *vs.* 44.4 mL/min per 1.73 m^2) in 22 CKD patients who received PCA[63]. Only one patient with stage III CKD had advanced to stage IV after one year, while two patients had decreased renal function to stage V. GFR dropped by more than 25% in five cases. During the follow-up period, none of these people required dialysis. Sriprasad *et al.* investigated renal function loss following cryoablation of an SRM in solitary kidneys in 102 individuals[64]. Data on renal function, including eGFR and CKD classification, were collected both before and three months after the operation. The preoperative mean eGFR was 55.0 mL/min/1.73 m2 (SD = 18.1), while the postoperative mean eGFR noted was 51.8 mL/min/1.73 m^2 (SD = 18.8). The difference was statistically significant (P = 0.004) at -3.1 mL/min/1.73 m^2 (95%CI: -5.2 to -1.0) units. The difference in CKD stages before and after LCA, on the other hand, was not statistically significant.

CA *vs.* PN

In a study by Mitchell *et al.*[65], neither the post-treatment eGFR (50.3 *vs.* 49.1) nor changes in the CKD stage were different between PN and ablation procedures in individuals with a single kidney at three months. The same study observed no significant difference between CA and RFA in terms of the percentage change in eGFR. In a multi-institutional comparison of PN and CA, Mues *et al.*[66]. found no differences in postoperative eGFR alterations between the two methods.

In a meta-analysis study, Uhlig *et al.*[67]. examined renal function between CA and PN in 6,618 patients. Comparing PN with CA, there was no statistically significant difference in renal function (P = 0.921). After controlling for tumor characteristics and complexity, the mean proportional fall in eGFR was higher in the Robotic PN (RPN) as compared to the CA group (13% *vs.* 6%). The study revealed that the smaller tumor size is predictive of better renal functional outcomes in patients with CA[48].

The functional results of Robotic PN (RPN) (n = 210) and LCA (n = 226) in patients with a SRM were studied and the RPN arm had a higher baseline eGFR (mean: 86.3 *vs.* 65.8; CKD ≥ 3: 12.3% *vs.* 44.4%). One-month and six months proportionate eGFR decreases were comparable between RPN and LCA. New-onset CKD has a lower prevalence in the RPN group compared to the LCA group (12.2% *vs.* 18.2%), while end-stage CKD (eGFR 15 mL/min) showed a higher prevalence in the LCA group contrary to the RPN group (4.7% *vs.* 0%). In view of the disparities in CKD stages and baseline GFR between the two groups, as well as the absence of comparative analysis on tumor complexity between the groups, the observed functional differences merit additional investigation[37].

Cryoablation had a significantly better renal functional outcome as compared to PN with a mean difference of eGFR (MD: -4.5; 95%CI: -7.02 to -2.36; $P < 0.001$) and the PN had a creatinine rise of 0.15 (95%CI: 0.04 to 0.26; $P = 0.006$) in T1 renal tumor cases, proving the protected renal functional outcomes of cryoablation in small renal masses[60]. This finding was confirmed in a recent meta-analysis, where patients undergoing ablation were found to have a smaller decrease in eGFR compared to PN patients (MD: -7.42; 95%CI: -13.15 to -1.70; $P = 0.01$)[61].

CA *vs.* other ablation technologies

Uhlig *et al.*[67]. compared the renal function of CA and RFA in a meta-analysis and showed that CA performed less well than RFA in terms of deterioration in renal function, as measured by the mean difference in eGFR [5.82 (0.55-11.1); $P = 0.03$] and there was no statistically significant decline in renal function with the mean eGFR change between CA and MWA, which was consistent with findings from other studies. Cobelli *et al.*[54]. examined the outcomes of renal function following either CA or MWA percutaneous ablation and found no difference in renal function decrease (GFR) by creatinine levels recorded before and after the treatment.

Functional outcome - assessment

These reviews have attempted to compare the effect on renal function of different nephron-sparing techniques, but there have not been any head-to-head randomized comparisons that included CA, so all studies comparing CA to other treatment modalities are inherently limited by selection bias as well as heterogeneity in data collection and reporting. Although such studies should attempt to control for baseline patient characteristics and tumor complexity, there is such a large difference between patients selected to undergo PN (typically used as the method of comparison) and patients selected to undergo CA that a significant degree of residual confounders will always remain. With the available data, cryoablation was found to have better renal functional outcomes. Patients who have imperative indications for surgery and cannot risk more invasive approaches could benefit from ablation therapies.

ONCOLOGICAL OUTCOMES

The primary objective of CA therapy for SRM is successful oncologic treatment in patients with confirmed RCC. Several consensus panels have proposed standardized terminology for oncologic outcomes following ablation therapy. "*Technical success*" may be determined within three months post-ablation by imaging showing the absence of tumor enhancement and the absence of tumor expansion, and "*local tumor progression*" (recurrence) is recurrent imaging evidence of new nodular enhancement in the ablation zone or enlargement of the ablated tumor after at least one imaging study has documented adequate ablation of the targeted SRM[68].

Investigations of the risk factors correlating to local recurrence rate following CA have found that increased SRM size and endophytic growth are the factors most predictive of local tumor recurrence[69,70], which parallels the finding that SRM size and central tumor location are the factors most predictive of procedural complication[46,51,58].

PCA

Schmit *et al.*[71] reported a 3.5% treatment failure rate, with 63% of tumors being RCC with a mean follow-up of 27.9 months. Breen *et al.*[46] reported a 7.6% primary treatment failure rate, which was reduced to 2.4% after PCA retreatment. Stacul *et al.*[72] reported 97.8% of treatment success rates in 338 SRM patients who underwent cryoablation, 47% of whom had histologically confirmed RCC with a mean tumor size of 2.53 cm and were followed up for 5 years. Recurrence-free survival rates were 90.5% at 3 years and 82.4% at 5 years in a subset of 159 patients with biopsy-proven RCC. Overall survival (OS) rates were 96.0% at 3 years and 91.0% at 5 years, with no patient developing the metastatic disease in this subset. Although there were studies reporting oncological outcomes following PCA in small renal masses, most of them assessed cancer-specific outcomes in all individuals either with a validated diagnosis of benign illness or without a clear RCC diagnosis which is challenging to be included in this review[73,74].

LCA

Aron *et al.*[75] studied the five-year OS of 80 patients with biopsy-proven RCC and reported it to be 84% at a median follow-up of 93 months, as well as cancer-specific survival and recurrence-free survival of 92% and 81%, respectively. Guilloteau *et al.*[37] found an 11% recurrence rate in 181 out of 234 masses [77% biopsy-proven RCC] with a median follow-up of 44.5 months. Tsivian *et al.*[69] reported a 4.3% local recurrence rate at a median follow-up of 20 months for a group of 163 patients receiving LCA, 118 of whom had "biopsy-proven RCC". Importantly, the authors identified t tumor size and endophytic growth pattern as indicators of post-treatment tumor recurrence.

Metastasis-free survival (MFS) rates and local recurrence-free survival (LRFS) were studied in 220 patients with biopsy-proven RCC at three-year and five-year outcomes, with an estimated 97.7% and 97.2% at three years and 94.4% and 93.9% at 5 years. At three and five years, the estimated OS for all 433 patients was 91.7% (95%CI: 87.5%; 94.5%) and 78.8% (95%CI: 71.1%; 84.6%), respectively[76]. This is significantly lesser than the reported LRFS rate for partial nephrectomy, but no significant difference was noted in cancer-specific survival and LRFS rates, which were comparable with recent studies by Thompson *et al.*[77] and Georgiades and Rodriguez[78].

Nielsen *et al.*[79] investigated the five- and ten-year survival results in individuals with biopsy-proven RCC after cryoablation. The study comprised 179 individuals (116 males and 63 women) with an average age of 64 years and a mean tumor size of 27mm. The predicted Disease-free survival rate (DFS) after five years was 79%. The 5- and 10-year OS rates were 82% and 61%, respectively. The same study reported a 5-year and 10-year disease-free survival rate of 90.4% and 80%, and OS rate of 83.2% and 64.4%, respectively, in a multi-institutional trial of patients who underwent LCA that was comparable to the recurrence and metastasis-free survival following extirpative surgery for RCC[55,79,80].

CA *vs.* other ablative techniques

Oncologic results with various CA procedures have been documented in comparative series, as well as comparisons of CA with PN and RFA. Owing to inherent biases in patient and tumor selection, variations in rates of malignancies, disparities in the success criteria, and differences in follow-up timeframes, any objective comparative analysis of provided treatment methods is limited.

Atwell *et al.*[74] noted a relatively comparable overall local recurrence rate (3.2% *vs.* 2.8%) between RFA and PCA for renal masses ≤ 3 cm; however, patients in the PCA group had larger and more central tumors with a lesser time follow-up interval compared to the RFA patients (1.8 *vs.* 3.2 years). El Dib *et al.*[43] showed a comparable percentage of clinical effectiveness for RFA (90%; 95%CI: 0.86-0.93) and CA (89%; 95%CI: 0.83-0.94) in a pooled study of published RFA and CA series.

After controlling for other factors, Kim *et al.*[48] found that LCA was not a predictor of disease recurrence compared to PCA. Studies have compared the LRFS, OS, DFS and CSS rates between RPN and CA (LCA and PCA), respectively. RPN was shown to have better results compared to CA, but the baseline patients' characteristics and tumor variables such as size and location were not matched. RPN patients had a much shorter follow-up period compared to the CA group[37,81].

In a recent meta-analysis, the probability of local tumor progression of published data for LCA was 9.4% in comparison to 0.4% for the minimally-invasive PN, leading to a projected 9.39-fold greater risk of local tumor advancement in patients receiving LCA[52]. Recently, Thompson *et al.*[77] examined the oncological results of cT1a tumors treated with RFA, PN, and PCA. RCC was histologically verified in 41% of the RFA, 58% of PCA and 79% of PN groups, respectively. The projected 3-year RFS were similar among all groups, with CA group patients being older and having more comorbidities. The MFS in biopsy-confirmed patients at three years was higher for CA (100%) and PN (99%) than RFA (93%).

In a study by Martin *et al.* [82] SRMs treated using CA or MWA were compared for local (4.07 *vs.* 2.53; P = 0.46), metastatic recurrence (0.8% *vs.* 0%; P = 0.12), primary effectiveness (93.75 *vs.* 91.27; P = 0.40), and CSS (98.27% *vs.* 96.8%; P = 0.47) which were found to have similar results. The same result was confirmed by Cobelli *et al.*[54], where disease recurrence in patients treated with image-guided percutaneous ablation with either MWA or CA was studied and found disease recurrence in 3/47 and 1/30 treated nodules, respectively, without any statistical significance (98%; P = 0.06). Recurrences are found at 6, 12, and 18 months after CA, as well as 12 months after MWA.

CA *vs.* PN

In a meta-analysis by Deng *et al.*[60] compared with PN, cryoablation for cT1 renal masses was found to have poorer oncological outcomes. The OS (HR: 0.52; 95%CI: 0.41 to 0.65; P < 0.001), CSS (HR: 0.43; 95%CI: 0.21 to 0.91; P = 0.03) and RFS (HR: 0.35; 95%CI: 0.25 to 0.50; P < 0.001) rates of PN were significantly lower compared to the CA group. When evaluating oncological outcomes, the inclusion of elderly patients with a high comorbidity index profile in the cryoablation group should not be overlooked. This meta-analysis included studies comparing outcomes in T1b tumors, where CA's therapeutic application is still being debated. In a meta-analysis conducted by Uhilig *et al.*[67] comparing partial nephrectomy versus ablative techniques for SRMs, all-cause mortality was higher for CA (IRR = 2.58; 95%CI: 1.92-3.46; P < 0.001), whereas differences in the cancer-specific mortality were not statistically significant, and CA had a higher local recurrence rate (IRR = 2.76; 95%CI: 1.5-5.08; P < 0.001). The majority of studies were actually retrospective, patients' baseline characteristics such as age, tumor complexity, and location, comorbidities were not similar, and these findings are not to be taken as conclusive. Whereas in a recent meta-analysis by Chan *et al.*[61] in T1a patients, AT was found to have a worse OS rate (HR 1.64; 95%CI: 1.39-1.95) and patients are significantly older than PN (MD: 5.70; 95%CI: 3.83-7.58). LRFS with a median five-year follow-up (HR: 1.54; 95%CI: 0.88-2.71), CSS (HR_{RE}: 0.68; 95%CI: 0.43-1.08; P = 0.10), MFS (HR: 1.01; 95%CI: 0.35-2.94; P = 0.98) were similar with PN patients.

Oncological outcomes - assessment

Analysis of oncologic outcomes comparing nephron-sparing techniques is limited in reliability and utility due to biases in patient and tumor selection, disparities in success criteria, differences in follow-up timeframes, and variability in malignancy rates since many studies report outcomes that are not limited to patients with positive tissue diagnosis. Additionally, although many studies discuss the local tumor recurrence rate, patients who undergo CA for treatment of SRM often undergo repeat treatment with CA, so the local tumor recurrence rate is likely of less clinical relevance than metastasis-free survival and cancer-specific survival. Similarly, in a long-term follow-up study of patients who underwent PCA, the majority of patients who did have local tumor recurrence after initial technical success underwent repeat PCA[72].

CA AND ITS IMPLICATIONS ON T1B RENAL MASSES

As discussed in complications and oncologic outcomes, both the rate of complications and the rate of recurrence are higher with increased maximum tumor diameter[51,58,69,70]. This explains why the guidelines from the AUA, NCCN, and EUA do not currently recommend the use of ablation techniques for the treatment of renal cancer for cT1b renal masses[16,17]. The SIR guidelines do discuss the consideration of CA for the treatment of cT1b tumors, but they also suggest the need for continued investigation and improved evidence to make stronger recommendations regarding the use of ablation techniques for cT1b tumors[19]. There have been several studies reporting outcomes on patients with cT1b renal tumors treated with CA, but no randomized trials have been performed to compare CA to PN or other ablative techniques, so any comparisons made with retrospective studies that attempt to control for patient factors and tumor factors will have limited reliability and utility. Nonetheless, in a recent systematic review of reports on ablation techniques for the treatment of cT1b renal tumors treated with CA, the reported outcomes show that CA appears to be a safe and effective treatment strategy[83]. Further long-term and higher-quality evidence will be necessary to truly assess the efficacy of CA in treatment of larger renal masses, but this appears to be a reasonable treatment strategy for select patients with cT1b renal tumors in the hands of experienced providers. Table 2 shows the comprehensive review of CA and its implications on T1b renal masses.

POST-TREATMENT MONITORING

Post-procedure follow-up imaging is used for assessment of technical success following ablation procedures since there is no surgical margin for pathology to assess for complete treatment of the tumor margins. When there is residual tumor evident at initial follow-up imaging 1-3 months following CA, this is considered a "*Residual Unablated Tumor*"[66], and the rate of patients with residual unablated tumor is used to assess the "*primary technical efficacy*" of treatment[83]. When patients have residual unablated tumors, they most often undergo another ablation procedure, and the rate of patients with residual unablated tumors after including those who underwent a second ablation procedure is used to assess "*secondary technical efficacy*"[83]. The terms "*local tumor progression*" and "*local tumor recurrence*" are used when there is a tumor focus on the margin of the ablation zone after initial follow-up imaging shows the technical success of complete tumor ablation[68,83]. Reports on patients who underwent ablative procedures must be interpreted with caution when cancer-specific outcomes including the rate of technical efficacy and rate of local tumor recurrence are discussed because accurate analysis of cancer-specific outcomes requires that patients have undergone a biopsy to prove they had malignancy, but many reports will include all patients treated instead of limiting to patients with positive biopsy[90].

There appears to be a survival benefit to follow-up surveillance after treatment of renal cancer[91,92], but there is not a universally agreed upon follow-up surveillance strategy for patients who underwent treatment for renal cancer. Post-treatment monitoring should include history and physical, as well as imaging of the abdomen and chest to assess for recurrence and metastasis, but the interval of follow-up and imaging, as

Table 2. Percutaneous CA outcomes of stage T1b RCC

Study	Atwell *et al.*[84]	Andrews *et al.*[85]	Hasegawa *et al.*[86]	Hebbadj *et al.*[87]	Gunn *et al.*[88]	Grange *et al.*[89]
Tumor diameter mean (cm)	4.8	4.8	4.6	4.8	4.7	4.6
Sample size (Patients)	46	48	3	27	37	23
Biopsy (RCC)	Yes	No (Imaging)	Yes	Yes	Yes	Yes
Follow-up (months)	24 (Mean)	NR	24.9 (Median)	20 (Mean)	26.4 (Mean)	13.9 (Mean)
Technical efficacy	98%	NR	96%	88%	87%	86.3%
Secondary Technical efficacy	NR	NR	100%	NR	91%	100%
Local recurrence	1/36 (2.8%)	3/48 (6%)	2/21 (9%)	3/26 (12%)	8/34 (23.5%)	2/23 (9%)
Metastatic disease	2/36 (6%)	2/35 (6%)	2/21 (9%)	NR	NR	1/23 (4%)
Major complications	8%	NR	9%	11%	13%	NR
Follow-Up Months (Mean/Median)	24 (Mean)	NR	24.9 (Median)	20 (Mean)	26.4 (Mean)	13.9 (Mean)

NR: Not reported; RCC: renal cell carcinoma.

well as modality of imaging, should be individualized based on the patient's risk of recurrence or metastasis. The AUA, NCCN, and EAU all recommend that the intensity of post-treatment follow-up and monitoring be individualized based on the patient's risk of recurrence[16-18]. This highlights the importance of obtaining RTB prior to CA or at the time of CA to help determine the follow-up strategy. Although there is consensus among guidelines that patients should have follow-up monitoring with imaging for at least 5 years following treatment of RCC, there is less consensus on whether follow-up monitoring should be performed beyond 5 years. However, in a multinational and interdisciplinary Delphi consensus project, practitioners reached a consensus that 10 years follow-up is preferred following focal therapy for RCC including CA. The Delphi consensus initiative issued its follow-up proposal: the first scan be performed three months after therapy; in the second year, the biannual imaging is performed; from the third year forward, annual imaging is required. The first choice should be a 3-phase CT, and the second choice would be MRI using a multiparametric technique[93].

Patients who have undergone an ablation procedure can still usually undergo salvage surgical extirpation with PN or RN for residual unablated tumors or local recurrent tumors, but salvage surgery following ablation is more challenging[94]. Since many patients who undergo ablation were poor candidates for surgery in the first place, it is not surprising that the majority of patients who have local tumor recurrence following PCA undergo repeat PCA, similar to patients who have residual unablated tumors[72].

A LOOK TO THE FUTURE - POSSIBILITY OF COMBINATION THERAPIES AND ADJUNCTS TO CRYOABLATION

Efforts have continued to develop techniques and technology that enhance the safety and effectiveness of cryoablation. These efforts have included research focusing on optimizing parameters of cryoablation, including temperature nadir, cryoprobe size and placement, ice ball margin, freeze-thaw cycle parameters, and freeze-thaw cycle repetition. In addition to efforts to optimize cryoablation techniques and technology, there has been recent interest in combining the use of cryotherapy with other treatments such as systemic chemotherapy, systemic immunotherapy and transarterial embolization.

Sorafenib

Baust *et al.*[95] studied the *in vitro* response of RCC to CA alone compared to combination therapy with Sorafenib and CA. Pre-treatment with 10.61 μM sorafenib increased the reported minimum critical/lethal temperature using a single or double freeze technique from -25 °C to -20 °C and from -20 °C to -15 °C,

respectively. After combinatorial treatment, this increased the overall ablation volume from the ice ball and tumor susceptibility to freezing by 32%. These *in vitro* findings imply that combination therapy may be a viable therapeutic adjunct when using CA to treat RCC.

Liu *et al.*[96] studied the efficacy of sorafenib alone compared to the therapy of sorafenib + PCA in 156 patients with advanced RCC who were not candidates for surgery. Objective response rate (ORR) and disease control rate (DCR) were considerably higher in the combination therapy group, and progression-free survival (PFS) and overall survival (OS) was also significantly longer in the combination group (both $P < 0.05$). Immune function-related markers significantly improved after therapy in the CA + sorafenib group ($P < 0.05$), while there was no significant change between before and after treatment in the sorafenib-only group ($P > 0.05$).

Sunitinib

Cheng-Yuan Gu *et al.*[97] compared the efficacy of sunitinib alone to combination therapy with sunitinib and PCA in 178 patients with metastatic RCC. The combination therapy group who were treated with PCA and sunitinib group had a superior PFS of 13.8 months *vs.* 7.2 months ($P < 0.005$) as well as a superior OS of 31.7 months compared to 19.8 months ($P < 0.001$). These findings suggest that chemotherapy plus CA may be better than chemotherapy alone for select patients with metastatic RCC, but additional larger studies will be needed to fully define the role of CA in this setting.

Tremelimumab

Campbell *et al.*[98] conducted a pilot study to compare the efficacy of Tremelimumab (an anti-CTLA-4 agent) alone to combination therapy with Tremelimumab and CA in patients with metastatic RCC. This pilot study was relatively small, with only 29 total patients, but they did not find a difference in treatment discontinuation, PFS, or OS, but they did find that combination therapy with CA and tremelimumab appeared to promote a greater immune cell response in patients with clear cell RCC.

Allogenic NK cell immunotherapy

Lin *et al.*[99] studied CA alone compared to CA combined with allogenic NK cell immunotherapy in patients with advanced RCC. The patients who underwent combination therapy with CA and allogenic NK cell immunotherapy had a smaller post-ablation tumor size and a higher Karnofsky performance status, but they did not have a sufficient sample size and follow-up to determine whether there was an effect on PFS or OS.

Transarterial embolization

Pre-ablation transarterial embolization (TAE) of a renal tumor prior to CA has been reported in several small series as a successful method for treatment for large tumors and central tumors[100,101]. Donato *et al.*[102] recently reported a series where TAE was employed prior to PCA for patients with cT1b or central cT1a tumors. In this series, the authors reported that 19 patients underwent TAE prior to PCA, with one patient having major complications and three patients with minor complications, all patients achieving technical success, and one patient had local tumor recurrence at a median follow-up of 26 months. TAE followed by PCA may be a useful strategy for surgery would present an unacceptably high risk but who have large renal tumors or central renal tumors that would have a decreased chance of successful treatment with PCA alone; however, more research will be needed to determine if this strategy is safer and/or more effective than PCA alone for these patients.

Nanoparticles

There has been increasing interest in the use of nanoparticles for the treatment of cancer, and there are future potential applications of various types of nanoparticles to make cryoablation more effective[8]. Depending on the nanomaterial used, nanomaterials have the potential for use in the setting of cryotherapy for enhanced image guidance, enhancing target tissue death from cryoablation, minimizing systemic drug toxicity, and/or minimizing cryoinjury to adjacent healthy tissue[8]. These technologies are still in the early phases of development but represent exciting areas of potential further advancement of the safety and efficacy of cryoablation techniques.

Conclusion

CA is a safe and effective alternative treatment for select patients with SRMs, as well as in select cases of recurrence after primary treatment and select patients with metastatic RCC. Previously CA was considered primarily for patients with increased age and comorbidities that put them at increased risk for PN. However, given increasing evidence of safety and efficacy as well as increased availability of PCA, younger and healthier patients may also benefit from CA after receiving full risk and benefits counseling. The key benefits of CA include shorter hospital stays, lower morbidity, and minimal changes in postoperative renal function. Patients should be counseled on the potential risks associated with CA, including the potential need for repeat CA if there is incomplete ablation or local recurrence. Patients should be actively monitored for recurrence using serial imaging based on their risk of recurrence owing to tumor characteristics and pathology.

There have been significant advances in accessible data regarding safety, and outcomes following CA for SRM, especially in long-term follow-up; however, further research is still needed to fully define the utility of cryoablation in SRM management because there is little reliability in making the comparison between treatment methods based on the current level of evidence. It can be anticipated that the safety and efficacy of CA will continue to improve with continued developments in imaging, utilized instruments, related technologies, and combined treatment methods. Thus, in addition to further study on current outcomes following CA, there is a need for continued re-assessment of CA outcomes as the technologies and techniques used continue to improve.

DECLARATIONS

Authors' contributions

Substantial contribution to conception or design of the work, acquisition, drafting and interpretation of data for the work: Deivasigamani S
Substantial contribution to the drafting and interpretation of data for the work: Adams ES
Substantial contribution to the drafting and interpretation of data for the work: Seguier D
Substantial contribution to the drafting and interpretation of data for the work: Kotamarti S
Revising the work critically for important intellectual content and final approval of the version to be published: Polascik TJ

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022;72:7-33. DOI PubMed
2. Saad AM, Gad MM, Al-Husseini MJ, Ruhban IA, Sonbol MB, Ho TH. Trends in renal-cell carcinoma incidence and mortality in the United States in the last 2 decades: a SEER-based study. *Clin Genitourin Cancer* 2019;17:46-57.e5. DOI PubMed PMC
3. Conti A, Santoni M, Sotte V, et al. Small renal masses in the era of personalized medicine: Tumor heterogeneity, growth kinetics, and risk of metastasis. *Urol Oncol* 2015;33:303-9. DOI PubMed
4. Cooper IS. Cryobiology as viewed by the surgeon. *Cryobiology* 1964;1:44-51. DOI PubMed
5. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. *Cryobiology* 1998;37:171-86. DOI PubMed
6. Kaouk JH, Aron M, Rewcastle JC, Gill IS. Cryotherapy: clinical end points and their experimental foundations. *Urology* 2006;68:38-44. DOI PubMed
7. Baust JG, Gage AA, Bjerklund Johansen TE, Baust JM. Mechanisms of cryoablation: clinical consequences on malignant tumors. *Cryobiology* 2014;68:1-11. DOI PubMed PMC
8. Kwak K, Yu B, Lewandowski RJ, Kim DH. Recent progress in cryoablation cancer therapy and nanoparticles mediated cryoablation. *Theranostics* 2022;12:2175-204. DOI PubMed PMC
9. Breda A, Lam JS, Riggs S, et al. In vivo efficacy of laparoscopic assisted percutaneous renal cryotherapy: evidence based guidelines for the practicing urologist. *J Urol* 2008;179:333-7. DOI PubMed
10. Mues AC, Landman J. Image-guided percutaneous ablation of renal tumors: outcomes, technique, and application in urologic practice. *Curr Urol Rep* 2010;11:8-14. DOI PubMed
11. Rioja J, Tzortzis V, Mamoulakis C, Laguna MP. [Cryotherapy for renal tumors: current status and contemporary developments]. *Actas Urol Esp* 2010;34:309-17. PubMed
12. Buy X, Lang H, Garnon J, Sauleau E, Roy C, Gangi A. Percutaneous renal cryoablation: prospective experience treating 120 consecutive tumors. *AJR Am J Roentgenol* 2013;201:1353-61. DOI PubMed
13. Tsoumakidou G, Buy X, Garnon J, Enescu J, Gangi A. Percutaneous thermal ablation: how to protect the surrounding organs. *Tech Vasc Interv Radiol* 2011;14:170-6. DOI PubMed
14. Hinshaw JL, Lubner MG, Ziemlewicz TJ, Lee FT Jr, Brace CL. Percutaneous tumor ablation tools: microwave, radiofrequency, or cryoablation - what should you use and why? *Radiographics* 2014;34:1344-62. DOI PubMed PMC
15. Seager M, Kumar S, Lim E, Munneke G, Bandula S, Walkden M. Renal cryoablation - a practical guide for interventional radiologists. *Br J Radiol* 2021;94:20200854. DOI PubMed PMC
16. Campbell SC, Clark PE, Chang SS, Karam JA, Souter L, Uzzo RG. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: part I. *J Urol* 2021;206:199-208. DOI
17. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2022;20:71-90. DOI
18. Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European association of urology guidelines on renal cell carcinoma: the 2022 update. *Eur Urol* 2022;82:399-410. DOI
19. Morris CS, Baerlocher MO, Dariushnia SR, et al. Society of interventional radiology position statement on the role of percutaneous ablation in renal cell carcinoma: endorsed by the canadian association for interventional radiology and the society of interventional oncology. *J Vasc Interv Radiol* 2020;31:189-194.e3. DOI PubMed
20. Janzen N, Zisman A, Pantuck AJ, Perry K, Schulam P, Belldegrun AS. Minimally invasive ablative approaches in the treatment of renal cell carcinoma. *Curr Urol Rep* 2002;3:13-20. DOI PubMed
21. Cantwell CP, Wah TM, Gervais DA, et al. Protecting the ureter during radiofrequency ablation of renal cell cancer: a pilot study of retrograde pyeloperfusion with cooled dextrose 5% in water. *J Vasc Interv Radiol* 2008;19:1034-40. DOI PubMed
22. Rodríguez-Faba O, Palou J, Rosales A, et al. Prospective study of ultrasound-guided percutaneous renal cryotherapy: case selection as an optimization factor for a technique. *Actas Urol Esp* 2015;39:8-12. DOI PubMed
23. Marion JT, Schmitz JJ, Schmit GD, et al. Safety and efficacy of retrograde pyeloperfusion for ureteral protection during renal tumor

cryoablation. *J Vasc Interv Radiol* 2020;31:1249-55. DOI PubMed

24. Welch BT, Callstrom MR, Morris JM, et al. Feasibility and oncologic control after percutaneous image guided ablation of metastatic renal cell carcinoma. *J Urol* 2014;192:357-63. DOI PubMed
25. Zargar H, Atwell TD, Cadeddu JA, et al. Cryoablation for small renal masses: selection criteria, complications, and functional and oncologic results. *Eur Urol* 2016;69:116-28. DOI PubMed
26. Campbell SC, Uzzo RG, Karam JA, Chang SS, Clark PE, Souter L. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: part II. *J Urol* 2021;206:209-18. DOI PubMed
27. Andersen MF, Norus TP. Tumor seeding with renal cell carcinoma after renal biopsy. *Urol Case Rep* 2016;9:43-4. DOI PubMed PMC
28. Macklin PS, Sullivan ME, Tapping CR, et al. Tumour seeding in the tract of percutaneous renal tumour biopsy: a report on seven cases from a UK tertiary referral centre. *Eur Urol* 2019;75:861-7. DOI
29. Marconi L, Dabestani S, Lam TB, et al. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. *Eur Urol* 2016;69:660-73. DOI
30. Campbell S, Uzzo RG, Allaf ME, et al. Renal mass and localized renal cancer: AUA guideline. *J Urol* 2017;198:520-9. DOI
31. Allen BC, Remer EM. Percutaneous cryoablation of renal tumors: patient selection, technique, and postprocedural imaging. *Radiographics* 2010;30:887-900. DOI PubMed
32. Ramanathan R, Leveillee RJ. Ablative therapies for renal tumors. *Ther Adv Urol* 2010;2:51-68. DOI PubMed PMC
33. Tsivian M, Rampersaud EN Jr, del Pilar Laguna Pes M, et al. Small renal mass biopsy - how, what and when: report from an international consensus panel. *BJU Int* 2014;113:854-63. DOI PubMed
34. Truesdale MD, Mues AC, Sartori S, et al. Comparison of two core biopsy techniques before and after laparoscopic cryoablation of small renal cortical neoplasms. *JSLS* 2011;15:509-16. DOI PubMed PMC
35. Guazzoni G, Cestari A, Buffi N, et al. Oncologic results of laparoscopic renal cryoablation for clinical T1a tumors: 8 years of experience in a single institution. *Urology* 2010;76:624-9. DOI
36. Duffey B, Nguyen V, Lund E, Koopmeiners JS, Hulbert J, Anderson JK. Intermediate-term outcomes after renal cryoablation: results of a multi-institutional study. *J Endourol* 2012;26:15-20. DOI PubMed
37. Guillotreau J, Haber GP, Autorino R, et al. Robotic partial nephrectomy versus laparoscopic cryoablation for the small renal mass. *Eur Urol* 2012;61:899-904. DOI PubMed
38. Okhunov Z, Shapiro EY, Moreira DM, et al. R.E.N.A.L. nephrometry score accurately predicts complications following laparoscopic renal cryoablation. *J Urol* 2012;188:1796-800. DOI
39. Sidana A, Aggarwal P, Feng Z, Georgiades CS, Trock BJ, Rodriguez R. Complications of renal cryoablation: a single center experience. *J Urol* 2010;184:42-7. DOI PubMed
40. Autorino R, Kaouk JH. Cryoablation for small renal tumors: current status and future perspectives. *Urol Oncol* 2012;30:S20-7. DOI PubMed
41. Zhong J, Bambrook J, Bhambra B, et al. Incidence of post-ablation syndrome following image-guided percutaneous cryoablation of renal cell carcinoma: a prospective study. *Cardiovasc Intervent Radiol* 2018;41:270-6. DOI PubMed PMC
42. Rivoire M, De Cian F, Meeus P, Gignoux B, Fréring B, Kaemmerlen P. Cryosurgery as a means to improve surgical treatment of patients with multiple unresectable liver metastases. *Anticancer Res* 2000;20:3785-90. PubMed
43. Dib R, Touma NJ, Kapoor A. Cryoablation vs radiofrequency ablation for the treatment of renal cell carcinoma: a meta-analysis of case series studies. *BJU Int* 2012;110:510-6. DOI PubMed
44. Silverman SG, Israel GM, Trinh QD. Incompletely characterized incidental renal masses: emerging data support conservative management. *Radiology* 2015;275:28-42. DOI PubMed
45. Kotamarti S, Michael Z, Silver D, et al. Device-related complications during renal cryoablation: insights from the manufacturer and user facility device experience (MAUDE) database. *Urol Oncol* 2022;40:199.e9-199.e14. DOI PubMed
46. Breen DJ, Bryant TJ, Abbas A, et al. Percutaneous cryoablation of renal tumours: outcomes from 171 tumours in 147 patients. *BJU Int* 2013;112:758-65. DOI PubMed
47. Tsivian M, Caso J, Kimura M, Polascik TJ. Renal function outcomes after laparoscopic renal cryoablation. *J Endourol* 2011;25:1287-91. DOI PubMed
48. Kim EH, Tanagho YS, Saad NE, Bhayani SB, Figenshau RS. Comparison of laparoscopic and percutaneous cryoablation for treatment of renal masses. *Urology* 2014;83:1081-7. DOI PubMed
49. Laguna MP, Beemster P, Kumar V, et al. Perioperative morbidity of laparoscopic cryoablation of small renal masses with ultrathin probes: a European multicentre experience. *Eur Urol* 2009;56:355-61. DOI
50. Blute ML Jr, Okhunov Z, Moreira DM, et al. Image-guided percutaneous renal cryoablation: preoperative risk factors for recurrence and complications. *BJU Int* 2013;111:E181-5. DOI
51. Schmit GD, Schenck LA, Thompson RH, et al. Predicting renal cryoablation complications: new risk score based on tumor size and location and patient history. *Radiology* 2014;272:903-10. DOI PubMed
52. Klatte T, Shariat SF, Remzi M. Systematic review and meta-analysis of perioperative and oncologic outcomes of laparoscopic cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal tumors. *J Urol* 2014;191:1209-17. DOI PubMed
53. Lucignani G, Rizzo M, Ierardi AM, et al. Percutaneous microwave ablation is comparable to cryoablation for the treatment of T1a

renal masses: results from a cross-sectional study. *Clin Genitourin Cancer* 2022;20:e506-11. DOI PubMed

54. De Cobelli F, Papa M, Panzeri M, et al. Percutaneous microwave ablation versus cryoablation in the treatment of T1a renal tumors. *Cardiovasc Intervent Radiol* 2020;43:76-83. DOI PubMed
55. Nielsen TK, Lagerveld BW, Keeley F, et al. Oncological outcomes and complication rates after laparoscopic-assisted cryoablation: a European registry for renal cryoablation (EuRECA) multi-institutional study. *BJU Int* 2017;119:390-5. DOI PubMed
56. Sisul DM, Liss MA, Palazzi KL, et al. RENAL nephrometry score is associated with complications after renal cryoablation: a multicenter analysis. *Urology* 2013;81:775-80. DOI PubMed
57. Lagerveld BW, Brenninkmeijer M, van der Zee JA, van Haarst EP. Can RENAL and PADUA nephrometry indices predict complications of laparoscopic cryoablation for clinical stage T1 renal tumors? *J Endourol* 2014;28:464-71. DOI PubMed
58. McCafferty BJ, Huang JJ, El Khudari H, et al. External validation of the renal ablation-specific (MC)2 risk scoring system in predicting complications from percutaneous renal cryoablation. *Cardiovasc Intervent Radiol* 2021;44:1763-8. DOI PubMed
59. Papa M, Suardi N, Losa A, et al. ABLATE: a score to predict complications and recurrence rate in percutaneous treatments of renal lesions. *Med Oncol* 2020;37:26. DOI PubMed
60. Deng W, Chen L, Wang Y, et al. Cryoablation versus partial nephrectomy for clinical stage t1 renal masses: a systematic review and meta-analysis. *J Cancer* 2019;10:1226-36. DOI PubMed PMC
61. Chan VW, Abul A, Osman FH, et al. Ablative therapies versus partial nephrectomy for small renal masses - a systematic review and meta-analysis. *Int J Surg* 2022;97:106194. DOI
62. Beemster PW, Barwari K, Mamoulakis C, Wijkstra H, de la Rosette JJ, Laguna MP. Laparoscopic renal cryoablation using ultrathin 17-gauge cryoprobes: mid-term oncological and functional results. *BJU Int* 2011;108:577-82. DOI PubMed
63. Wehrenberg-Klee E, Clark TW, Malkowicz SB, et al. Impact on renal function of percutaneous thermal ablation of renal masses in patients with preexisting chronic kidney disease. *J Vasc Interv Radiol* 2012;23:41-5. DOI PubMed
64. Sriprasad S, Aldiwani M, Pandian S, et al. Renal function loss after cryoablation of small renal masses in solitary kidneys: european registry for renal cryoablation multi-institutional study. *J Endourol* 2020;34:233-9. DOI PubMed
65. Mitchell CR, Atwell TD, Weisbrod AJ, et al. Renal function outcomes in patients treated with partial nephrectomy versus percutaneous ablation for renal tumors in a solitary kidney. *J Urol* 2011;186:1786-90. DOI PubMed
66. Mues AC, Korets R, Graversen JA, et al. Clinical, pathologic, and functional outcomes after nephron-sparing surgery in patients with a solitary kidney: a multicenter experience. *J Endourol* 2012;26:1361-6. DOI PubMed PMC
67. Uhlig J, Strauss A, Rücker G, et al. Partial nephrectomy versus ablative techniques for small renal masses: a systematic review and network meta-analysis. *Eur Radiol* 2019;29:1293-307. DOI PubMed
68. Ahmed M, Solbiati L, Brace CL, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria - a 10-year update. *Radiology* 2014;273:241-60. DOI
69. Tsivian M, Lyne JC, Mayes JM, Mouraviev V, Kimura M, Polascik TJ. Tumor size and endophytic growth pattern affect recurrence rates after laparoscopic renal cryoablation. *Urology* 2010;75:307-10. DOI PubMed
70. Maxwell AWP, Baird GL, Iannuccilli JD, Mayo-Smith WW, Dupuy DE. Renal cell carcinoma: comparison of RENAL nephrometry and PADUA scores with maximum tumor diameter for prediction of local recurrence after thermal ablation. *Radiology* 2017;283:590-7. DOI PubMed
71. Schmit GD, Thompson RH, Kurup AN, et al. Usefulness of R.E.N.A.L. nephrometry scoring system for predicting outcomes and complications of percutaneous ablation of 751 renal tumors. *J Urol* 2013;189:30-5. DOI
72. Stacul F, Sachs C, Giudici F, et al. Cryoablation of renal tumors: long-term follow-up from a multicenter experience. *Abdom Radiol* 2021;46:4476-88. DOI PubMed PMC
73. Schmit GD, Atwell TD, Callstrom MR, et al. Percutaneous cryoablation of renal masses [greater than or equal to] 3cm: efficacy and safety in treatment of 108 patients. *J Endourol* 2010;24:1255-62. DOI
74. Atwell TD, Schmit GD, Boorjian SA, et al. Percutaneous ablation of renal masses measuring 3.0 cm and smaller: comparative local control and complications after radiofrequency ablation and cryoablation. *AJR Am J Roentgenol* 2013;200:461-6. DOI PubMed
75. Aron M, Kamoi K, Remer E, Berger A, Desai M, Gill I. Laparoscopic renal cryoablation: 8-year, single surgeon outcomes. *J Urol* 2010;183:889-95. DOI PubMed
76. Breen DJ, King AJ, Patel N, Lockyer R, Hayes M. Image-guided cryoablation for sporadic renal cell carcinoma: three- and 5-year outcomes in 220 patients with biopsy-proven renal cell carcinoma. *Radiology* 2018;289:554-61. DOI PubMed
77. Thompson RH, Atwell T, Schmit G, et al. Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. *Eur Urol* 2015;67:252-9. DOI
78. Georgiades C, Rodriguez R, Azene E, et al. Determination of the nonlethal margin inside the visible "ice-ball" during percutaneous cryoablation of renal tissue. *Cardiovasc Intervent Radiol* 2013;36:783-90. DOI PubMed
79. Nielsen TK, Vedel PF, Borgbjerg J, Andersen G, Borre M. Renal cryoablation: five- and 10-year survival outcomes in patients with biopsy-proven renal cell carcinoma. *Scand J Urol* 2020;54:408-12. DOI PubMed
80. Ismail M, Nielsen TK, Lagerveld B, et al. Renal cryoablation: multidisciplinary, collaborative and perspective approach. *Cryobiology* 2018;83:90-4. DOI PubMed
81. Tanagho YS, Bhayani SB, Kim EH, Figenshau RS. Renal cryoablation versus robot-assisted partial nephrectomy: Washington University long-term experience. *J Endourol* 2013;27:1477-86. DOI PubMed
82. Martin J, Athreya S. Meta-analysis of cryoablation versus microwave ablation for small renal masses: is there a difference in

outcome? *Diagn Interv Radiol* 2013;19:501-7. DOI PubMed

83. Cazalas G, Jambon E, Coussy A, et al. Local recurrence and other oncologic outcomes after percutaneous image-guided tumor ablations on stageT1b renal cell carcinoma: a systematic review and network meta-analysis. *Int J Hyperthermia* 2021;38:1295-303. DOI PubMed
84. Atwell TD, Vlaminck JJ, Boorjian SA, et al. Percutaneous cryoablation of stage T1b renal cell carcinoma: technique considerations, safety, and local tumor control. *J Vasc Interv Radiol* 2015;26:792-9. DOI
85. Andrews JR, Atwell T, Schmit G, et al. Oncologic outcomes following partial nephrectomy and percutaneous ablation for cT1 renal masses. *Eur Urol* 2019;76:244-51. DOI
86. Hasegawa T, Yamanaka T, Gobara H, et al. Radiofrequency ablation versus cryoablation for T1b renal cell carcinoma: a multi-center study. *Jpn J Radiol* 2018;36:551-8. DOI PubMed
87. Hebbadj S, Cazzato RL, Garnon J, et al. Safety Considerations and local tumor control following percutaneous image-guided cryoablation of T1b renal tumors. *Cardiovasc Intervent Radiol* 2018;41:449-58. DOI PubMed
88. Gunn AJ, Joe WB, Salei A, et al. Percutaneous cryoablation of stage T1b renal cell carcinoma: safety, technical results, and clinical outcomes. *Cardiovasc Intervent Radiol* 2019;42:970-8. DOI PubMed PMC
89. Grange R, Tradi F, Izaaryene J, et al. Computed tomography-guided percutaneous cryoablation of T1b renal tumors: safety, functional and oncological outcomes. *Int J Hyperthermia* 2019;36:1065-71. DOI PubMed
90. Babaian KN, Okhunov Z, Juncal S, et al. Clinical outcomes of patients with nondiagnostic biopsy during cryoablation of small renal masses. *Urology* 2015;85:605-9. DOI PubMed
91. Scoll BJ, Wong YN, Egleston BL, Kunkle DA, Saad IR, Uzzo RG. Age, tumor size and relative survival of patients with localized renal cell carcinoma: a surveillance, epidemiology and end results analysis. *J Urol* 2009;181:506-11. DOI PubMed PMC
92. Powles T, Albiges L, Staehler M, et al. Updated european association of urology guidelines: recommendations for the treatment of first-line metastatic clear cell renal cancer. *Eur Urol* 2018;73:311-5. DOI PubMed
93. Zondervan PJ, Wagstaff PG, Desai MM, et al. Follow-up after focal therapy in renal masses: an international multidisciplinary Delphi consensus project. *World J Urol* 2016;34:1657-65. DOI PubMed PMC
94. Jiménez JA, Zhang Z, Zhao J, et al. Surgical salvage of thermal ablation failures for renal cell carcinoma. *J Urol* 2016;195:594-600. DOI PubMed
95. Baust JM, Santucci KL, Snyder K, et al. In Vitro Investigation of renal cell carcinoma response to combination sorafenib and cryoablation treatment. clinical oncology and research 2022. Available from: https://www.sciencerepository.org/in-vitro-investigation-of_COR-2022-1-101 [Last accessed on 28 Mar 2023].
96. Liu C, Cao F, Xing W, et al. Efficacy of cryoablation combined with sorafenib for the treatment of advanced renal cell carcinoma. *Int J Hyperthermia* 2019;36:220-8. DOI PubMed
97. Gu CY, Wang JJ, Zhang HL, Shi GH, Ye DW. Survival in metastatic renal cell carcinoma patients treated with sunitinib with or without cryoablation. *Front Oncol* 2021;11:762547. DOI
98. Campbell MT, Matin SF, Tam AL, et al. Pilot study of Tremelimumab with and without cryoablation in patients with metastatic renal cell carcinoma. *Nat Commun* 2021;12:6375. DOI PubMed PMC
99. Lin M, Xu K, Liang S, et al. Prospective study of percutaneous cryoablation combined with allogenic NK cell immunotherapy for advanced renal cell cancer. *Immunol Lett* 2017;184:98-104. DOI PubMed
100. Harmon TS, Matteo J, Meyer TE, Kee-Sampson J. Pre-cryoablation embolization of renal tumors: decreasing probes and saving loads. *Cureus* 2018;10:e3676. DOI PubMed PMC
101. Matteo J, Loper T, Hood P, Soule E, Kee-Sampson J, Martin JT. Embolization-induced renal tumor shrinkage followed by definitive cryoablation. *Cureus* 2018;10:e3251. DOI PubMed PMC
102. Donato F, Ahrar K, Karam J, Matin S, Abdelsalam ME, Sabir S. Combined transarterial embolization and percutaneous image-guided ablation for the treatment of T1B and central renal tumors in patients with high surgical risk. *AJIR* 2022;6:11. DOI