Mini Review

The Current Status of Renal Cryoablation for Treatment of Small Renal Masses

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Abstract

Recent advances in imaging technology have led to increased detection of Small Renal Masses (SRMs). Nephron-Sparing Surgery (NSS) is considered the gold-standard treatment for most SRMs, but renal cryoablation is recommended in certain comorbid populations. The current literature indicates cryoablation offers similar long-term outcomes and decreased perioperative complication rates compared to NSS despite increased incidences of local disease recurrence. Additional research on long-term measures of treatment success such as Cancer-Specific Survival (CSS) and Metastatic Recurrence-Free Survival (MRFS) is necessary to provide a more accurate assessment of cryoablation effectiveness relative to the alternative treatment options. Future treatment guidelines will likely expand the indications for renal cryoablation as more data emerges regarding its oncologic efficacy, surgeons become more familiar with procedural technique, and technology continues to improve.

ABBREVIATIONS


INTRODUCTION

Over the past two decades, advances in imaging technology have led to an increase in the detection of Small Renal Masses (SRMs), thus allowing urologists to explore less invasive therapies such as Nephron-Sparing Surgery (NSS) and renal ablative treatment [1,2]. Partial nephrectomy is considered the gold-standard treatment for most radiographically enhancing SRMs due to comparable oncologic outcomes, improved preservation of renal function, superior cardiac outcomes, and improved Overall Survival (OS) compared to radical nephrectomy [3-6]. However, renal ablative techniques including cryoablation, Radiofrequency Ablation (RFA), microwave thermotherapy, and chemotherapy have been developed to offer patients additional minimally invasive options due to the limitations and technical challenges posed by NSS.

First described by Uchida et al. in 1995, cryoablation has been the most experimentally and clinically evaluated of the renal ablative techniques [7]. The results of multiple studies have demonstrated favorable outcomes, and renal cryoablation has been found to offer benefits in preserving renal function, shortening hospitalization times, and improving recovery time compared to extirpative treatments [8-11]. In this review, we summarize the current status of the indications, techniques, and outcomes of renal cryoablation.

Indications

NSS is considered the gold standard treatment for most radiographically enhancing small renal masses; however, cryoablation is a recommended treatment option in limited populations, including patients who are elderly, have multiple comorbidities, have a solitary kidney, and/or patients who do not choose active surveillance [12-14]. The maximum tumor size for cryoablation is currently a topic of debate. In the United States, cryoablation is generally only recommended for tumors <4 cm in size, while the European Association of Urology (EAU) guidelines indicate cryoablation is only appropriate for tumors <3 cm in size [14]. A recent retrospective analysis of RFA performed by Psutka et al. showed successful outcomes for tumors 4-7 cm in size (pT1b) [15]. Future treatment guidelines will likely expand the indications for cryoablation as the technology continues to improve, thus allowing for the treatment of larger tumors, and more data emerges regarding its oncologic efficacy [13].
Technique

Cryoablation involves directed application of cold temperatures causing destruction of tissue. Renal cryoablation can be performed laparoscopically or percutaneously under ultrasound, CT, or MRI guidance. The mechanism of tissue injury involves both direct cellular damage during the freezing phase and indirect reperfusion injury during the thawing phase, leading to coagulative necrosis and fibrous scar formation [16]. During rapid freezing, ice crystals form within the intracellular space causing direct damage to the cell membrane and intracellular structures. Extracellular ice crystals formed during more gradual freezing create an osmotic gradient causing a fluid shift that leads to cell membrane rupture and cell death. During the thawing phase, small-vessel thrombosis and microcirculatory failure lead to reperfusion injury [17].

A certain threshold temperature must be reached during activation of the cryoablation probes to ensure tumor destruction. Normal renal parenchyma is destroyed at approximately -19.4°C, while tumor cells generally require lower temperatures due to their more fibrous nature [18]. The minimum preferred target temperature during renal cryoablation is at or below -40°C, with modern cryoablation units typically attaining core treatment temperatures of -130°C to -150°C. The renal vasculature and collecting system tolerate cryoablation without significant long-term adverse effects because high concentrations of collagen and elastin increase tissue resilience to freezing [19]. A double freeze-thaw cycle is employed during renal tumor cryoablation as it has been shown to create a larger area of liquefaction necrosis and improve local tumor control outcomes compared to a single freeze-thaw cycle [20]. Current standard of care is an initial freeze cycle of 8 to 10 minutes followed by a second freeze cycle of 6 to 8 minutes for most tumors. Modern argon-based cryoablation units have the ability to actively thaw tissue through the application of helium gas following ice-ball formation. Active thawing decreases operative times, but passive thawing causes greater tissue destruction due to increased solute effects and recrystallization at temperatures between -20°C and -30°C [21]. Passive thawing should be employed after the first freeze-thaw cycle so temperatures less than -40°C are maintained for a longer period of time, while an active thaw cycle should be used after the second freeze-thaw cycle so potential bleeding can be addressed more quickly. The ablation zone should extend approximately 1 cm beyond the margins of the tumor. Thermosensors may be placed at the tumor margin to ensure adequate treatment temperatures are reached [22].

Laparoscopic Cryoablation: Laparoscopic Cryoablation (LCA) was made possible by the introduction of argon gas-driven treatment systems that use the Joule-Thomson principle (low temperatures are achieved by the rapid expansion of high-pressure, inert gas) in the mid- to late 1990s. These argon gas systems shortened treatment times and allowed for the use of smaller cryoablation probes [23]. LCA can be delivered via an intraperitoneal or retroperitoneal approach depending on the position of the tumor. The procedure involves placement of the patient in the flank position, insufflation of the abdomen, laparoscope insertion, and mobilization of the kidney using a three-port technique. Gerota fascia is opened, and fat overlying the tumor is excised for pathologic analysis. Biopsies of the tumor are then obtained using a 14- or 18-gauge biopsy needle. The number of probes used is determined by probe-specific ablative diameter, and the probes are positioned to ensure cryolesion overlap. Probes are typically arranged in a triangular or quadratic configuration. Probe tips are advanced just beyond the deepest margin of the tumor, and intraoperative ultrasonography is used to confirm adequate depth of placement. Intraoperative ultrasonography also permits real-time monitoring of the freezing process through observation of the propagation of the highly echogenic leading edge of the iceball.

Percutaneous cryoablation: Percutaneous Cryoablation (PCA) is generally preferred over LCA when the position of the tumor allows for a percutaneous approach due to lower associated morbidity. Masses not in direct proximity to bowel and vital organs such as the pancreas, gall bladder, or great vessels are generally amenable to PCA. It can be performed under conscious sedation or general anesthesia. General anesthesia improves targeting accuracy during probe placement by allowing for control of the patient’s respiration; however, conscious sedation eliminates the increased risk associated with general anesthesia and allows the procedure to be performed on an outpatient basis. After administration of anesthesia or sedation, the patient is placed in the prone or flank position, and intravenous contrast may be administered depending on the chosen guidance modality. Imaging is performed to localize the lesion, and a 20-gauge access sheath is inserted near the expected location of the tumor. The access sheath is repositioned if necessary following repeat imaging to confirm localization. An 18-gauge Tru-Cut core biopsy needle is then inserted using the access sheath as a guide, and position is confirmed with repeat imaging before specimens are obtained and sent for section. After specimen collection, the cryoprobes are inserted using the access sheath, and repeat imaging is obtained to confirm positioning. Intraoperative ultrasonography is generally still employed when using CT or MRI guidance during PCA to confirm adequate depth of probe placement and monitor the freezing process. With PCA, additional imaging is required after removal of the cryoprobes to evaluate for potential bleeding.

Follow-Up: Following cryoablation, a contrasted image is always obtained to assess the adequacy of treatment. Lack of enhancement on post-procedure CT scan or MRI is indicative of success [24]. Residual peripheral rim enhancement is a common finding that should be followed but is not necessarily a cause for concern [25-27]. CT with intravenous contrast or MRI with gadolinium contrast should be conducted at 3, 6, 12, 18, and 24 months after treatment [28,29]. Imaging should be repeated annually thereafter, and no data exists that supports the superiority of CT or MRI for follow-up. Cryolesions should decrease in size over time, up to 94% in one year, due to cellular breakdown and phagocytosis [25]. None enhancing infiltrated fat may be noted in the area overlying the cryolesion. Findings indicative of residual or recurrent disease include new rim enhancement on post-procedure CT scan or MRI is indicative of residual or recurrent disease [25].
of treatment success, and the American Urological Association Small Renal Mass (AUA SRM) Guidelines Panel recommends tumor biopsy be performed universally at the time of ablation to establish a diagnosis and allow for the collection of outcomes-based data [30]. Regarding the need for post-procedure biopsies, Weight et al. reported a high correlation of radiographic imaging results with pathologic results following cryoablation, whereas the correlation of radiographic imaging results with pathologic results following RFA was relatively poor [31]. Routine post-procedure biopsies may be indicated after RFA, but there is insufficient evidence to support routine biopsies after renal cryoablation at this time. Biopsies are always indicated regardless of the chosen ablative technique when recurrence or incomplete ablation is suspected.

Outcomes

Cryoablation is generally considered to have lower complication and reintervention rates compared to extirpative treatment. Campbell et al.'s meta-analysis comparing cryoablation, RFA, and extirpative therapy evaluated rates of urologic and nonurologic complications following treatment [30]. Major urologic complications were defined as postoperative hemorrhage requiring transfusion or intervention, urinary leak, abscess, and unanticipated loss of renal function. The incidence of major urologic complications with cryoablation was 4.9% (range 3.3% to 7.4%), which was lower compared to NSS but not significantly different compared to RFA. Postoperative hemorrhage was the most common major urologic complication of cryoablation. Reintervention, defined as any unplanned operation occurring during or after the planned renal surgery, was more common with extirpative treatment than cryoablation and RFA [30].

Ablative therapy is commonly thought to be inferior to extirpative alternatives in controlling and limiting disease recurrence and progression. Recent meta-analyses conducted by Kunkle et al. and Campbell et al. demonstrating a higher relative risk of local recurrence with cryoablation compared to extirpative therapy would seem to support this theory; however, definitive conclusions are difficult to ascertain because the results of most cryoablation studies are limited by relatively small sample sizes, short durations of follow-up, and disparate operative protocols [30,32]. Additionally, an evaluation of long-term markers of success such as Metastatic Recurrence-Free Survival (MRFS) and Cancer-Specific Survival (CSS) rather than more easily defined and measurable end points like margin status would provide a more accurate reflection of treatment effectiveness. Campbell et al. found CSS and MRFS to be relatively high for both ablative and extirpative therapies but did not directly compare CSS and MRFS across treatments due to clinically relevant differences in patient age, tumor size, and follow-up protocols [30]. Future research should focus on long-term markers of success like MRFS and CSS, as confirmation of similar ablative and extirpative long-term treatment effectiveness would enable providers to offer more patients a minimally invasive treatment option with fewer short-term complications.

Recently, studies have emerged comparing renal cryoablation to Robotic-Assisted Partial Nephrectomy (RAPN). Although RAPN is quickly becoming the preferred technique for NSS, appropriately selected patients undergoing cryoablation may have improved perioperative and comparable long-term outcomes despite increased incidences of local disease recurrence with cryoablation. Guillotreau et al. compared RAPN to LCA in a single institution review. They reported outcomes on 226 patients undergoing LCA and 210 patients undergoing RAPN. Patients undergoing RAPN were younger, had higher baseline renal function, longer operative times, greater estimated blood loss, and longer hospital stays. Patients undergoing LCA had smaller tumors and more frequent local recurrence rates (RPN-0%, LCA-11%). Renal function six months after surgery was not significantly different between the two groups [33]. Tanagho et al. compared the outcomes of 267 patients undergoing PCA or LCA and 223 patients undergoing RAPN in another single institution review with a five year follow-up. They found no difference in perioperative complications rates (cryoablation-8.6%, RAPN-9.4%, p=0.75), but cryoablation did show increased preservation of renal function compared to RAPN on multivariate analysis. In patients with pathologically proven Renal Cell Carcinoma (RCC), five year Kaplan-Meier Disease Free Survival (DFS) was 83.1% for cryoablation and 100% for RAPN, and CSS was 96.4% for cryoablation and 100% for RAPN [34]. Unfortunately, similar to the studies assessing renal cryoablation and laparoscopic NSS, most of the studies directly comparing RAPN to cryoablation focus on short-term oncologic outcomes rather than long-term measures of treatment effectiveness and are limited by confounding factors that make meaningful comparisons difficult.

The results of a recent meta-analysis conducted by Klatte et al. examining the perioperative and oncologic outcomes of LCA versus laparoscopic/robotic partial nephrectomy suggest LCA may be a favorable alternative for patients unable to tolerate a partial nephrectomy. LCA was associated with shorter operative times, less blood loss, decreased length of stay, and lower risk of total, urologic, and non-urologic complications compared to partial nephrectomy. Despite these advantages, the authors felt RAPN should be recommended in the majority of cases due to a significantly lower risk of local and metastatic tumor progression. Notably, Klatte et al. does identify a lack of data on the long-term outcomes of RAPN and LCA as a weakness of their meta-analysis [35].

RFA is the most frequently used ablative technique after cryoablation. Comparisons of perioperative complication and reintervention rates show no significant differences between cryoablation and RFA [30,32,36]. The only direct comparison of cryoablation and RFA treatment effectiveness performed by Hegarty et al. found radiographic evidence of disease persistence or recurrence in 1.8% of patients that underwent cryoablation and 11.1% of patients that underwent RFA, but the results of Hegarty et al.’s study are difficult to interpret due to incongruent patient cohorts and treatment approaches [36]. The meta-analyses conducted by Campbell et al. and Kunkle et al. suggest that there are no significant differences in the risk of local tumor recurrence, MRFS, CSS, and OS between cryoablation and RFA, although the data may be conflicting [30,32].

While PCA, when feasible, is preferred over LCA due to lower associated morbidity, the vast majority of renal cryoablation procedures are currently performed laparoscopically. Crouzet et al.’s retrospective comparison of PCA and LCA found a higher
incomplete treatment rate with PCA at a minimum follow-up of 2 years, but no difference in OS, CSS, MRFS, or renal functional outcomes. Additionally, the duration of hospitalization was significantly shorter with the PCA cohort [29]. Several other studies comparing PCA and LCA have confirmed these findings [37-40], but conflicting results have also been published. Finley et al. found no difference in the number of incomplete ablations between PCA and LCA, and Kim et al.’s results showed differences in oncologic outcomes to be dependent on baseline patient and tumor characteristics rather than the cryoablation approach [41,42]. In Kim et al.’s retrospective analysis of 145 patients that underwent LCA and 118 patients that underwent PCA, patient age-adjusted Charlson Comorbidity Index (CCI) was negatively associated with OS, and preoperative eGFR was positively associated with OS. Tumor size, BMI, and tumor depth were all negatively associated with recurrence-free survival. Tumors treated with PCA were typically larger (LCA-2.4 cm, PCA-2.7 cm, p<0.01) while tumors treated with LCA were more often completely endophytic (LCA-19%, PCA-11%, p=0.03). There was no significant difference in age-adjusted CCI between the PCA and LCA groups, however patients in the PCA group had significantly higher BMIs and preoperative eGFRs [42].

CONCLUSION

Cryoablation is an alternative therapy for the treatment of SRMs that is recommended in certain comorbid populations and may be underutilized. Continued research is necessary to better evaluate the effectiveness of renal cryoablation relative to other ablative technologies and extirpative procedures. The literature to date indicates cryoablation is associated with fewer perioperative complications and similar long-term outcomes in appropriately selected patients. Patients undergoing cryoablation may have higher rates of local disease recurrence compared to other ablative therapies that undergo extirpative therapy. Ultimately, renal cryoablation allows urologists without advanced laparoscopic training to provide appropriately selected patients with a minimally invasive nephron-sparing alternative to radical nephrectomy.

REFERENCES

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