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Ablative Therapies for the Treatment of Small Renal Masses: a Review of Different Modalities and Outcomes

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Abstract The widespread utilization of abdominal imaging has led to an increase in incidentally detected small renal masses. Although partial nephrectomy is still considered the gold standard treatment for these masses, there are risks associated with surgical excision, potentially limiting treatment for older patients with multiple comorbidities. A variety of ablative techniques have developed over the past several decades, altering the management of small renal masses. It is likely that improvements in technology will only broaden the applications of ablative therapy. This article provides an update on the various ablative techniques and outcomes.

Keywords Small renal mass · Ablation

Introduction

Widespread use of abdominal imaging has increased the incidence of renal cell carcinoma (RCC) [1, 2]. Concurrently, the historic aggressive management of these masses has been replaced by minimally invasive and nephron-sparing surgery. This is especially true for small renal masses (SRMs) less than or equal to 4 cm in maximum axial diameter. At least 20 % of SRMs are pathologically benign and increased detection of these masses has not led to a decrease in RCC mortality [3, 4]. This complicates treatment strategies, particularly for patients with decreased life expectancy who may not tolerate extirpative management. Evaluation of these patients warrants a careful weighing of the risks and benefits of surgery and consideration of alternative therapies. The 2009 AUA Guidelines regarding SRMs recommend ablative techniques for older patients or those with multiple comorbidities [3]. In the face of an aging population and increased detection of SRMs, the improvements in techniques and technologies surrounding ablative therapy has made the treatment modality all the more relevant.

Applications and Considerations

Though a variety of ablative techniques are currently available, the goal of each is the same: to deliver a lethal amount of energy to cancer cells in a given treatment zone while minimizing the destruction of surrounding healthy tissue. This can be achieved via open, laparoscopic, or more commonly, a percutaneous route allowing for a versatile application of the technology regardless of the location of the renal tumor. Multiple factors should be considered prior to choosing the route and technology used, including tumor size, endophytic/exophytic properties, and proximity to critical structures (e.g., bowel, renal sinus, collecting system, ureter, vascular structures) For example, thermal ablation near the collecting system or major vascular structures might lead to a "heat sink," preventing adequate temperatures for ablation due to loss of thermal energy [5]. Prior research has evaluated algorithms to systematically measure these variables [6].

Percutaneous ablation minimizes blood loss and postoperative pain in the management of SRMs and can be performed as an outpatient. Conscious sedation can often be used, decreasing the risk of general anesthesia and hospitalization time [7]. Additionally, ablative techniques can limit normal parenchymal damage and therefore play a vital role

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in the management of patients at risk for end-stage renal disease, including those with solitary kidneys, bilateral renal tumors, and hereditary syndromes predisposing to multiple renal masses [8, 9]. As ablative technologies develop and evolve, their role in RCC management will continue to broaden [10]. Though multiple ablative techniques are continually evaluated, outcomes among techniques are comparable, and deciding on which modality to use should be based on tumor properties and operator experience [11]. Herein, we discuss the most studied ablation technologies of cryoablation (CA) and radiofrequency ablation (RFA), and newer technologies including microwave ablation (MWA) and irreversible electroporation (IRE) (Table 1).

Ablative Techniques

Cryoablation

CA refers to the use of extreme cold temperatures for destruction of tissue. Since its introduction in the 1980s, the technology has evolved into an argon gas-based system, which achieves freezing through the Joule-Thomson principle [12]. Tissue destruction occurs in an area around the cryoprobe, which creates an expanding ice ball. Immediately adjacent to the probe, rapid freezing leads to intracellular ice crystal formation causing mechanical trauma to cell membranes and subsequent apoptosis. Farther away from the probe, extracellular ice crystal formation dehydrates cells through an increasing osmotic gradient, and during thawing, leads to cellular edema and death. These effects also occur in the endothelium causing thromboembolism and vascular necrosis, accentuating tissue damage. This process can be actively monitored via ultrasound. Although CA leads to tissue destruction at −19.4 °C, some animal models suggest that lower temperatures are required for cancerous tissues due to increased fibrosis. This ultimately led to a clinical target goal below −40 °C [13].

As the ablation zone is not a uniform temperature with respect to distance from the cryoprobe, expansion of the ice ball should include a margin around the renal mass. Intrarenal measurements of temperature during CA show a temperature of 0 °C at the leading edge of the ice ball, with temperatures consistently less than −20 °C within 3 mm from the leading edge. Thus, for adequate ablation, the planned treatment zone should reach 5–10 mm beyond the targeted region, though as shown by Ge et al., a 1.5-mm margin of a well-centered ice ball correlated with a successful ablation [14].

Currently, it is recommended to perform a double freeze-thaw cycle to amplify the destructive effects of CA. There is some concern that a rapid, forced (active) thaw using helium gas, despite being faster, may decrease the interval of exposure to subfreezing temperatures and be deleterious to tumor destruction. Thus, a passive thaw, using body heat for warming, is recommended for the first cycle while an active thaw may be appropriate during the second cycle. Though the duration of treatment to achieve irreversible tissue damage is not clear, freezing tissue between 5–10 min seems to adequately cause cell death [15]. Durable and similar outcomes have been seen with both laparoscopic and percutaneous approaches [16].

Radiofrequency Ablation

Radiofrequency ablation (RFA) utilizes energy created by a high frequency alternating electrical current to heat tissue and cause cellular death. An electrical probe, or series of probes, is used to deliver a high frequency current (460–500 kHz), inducing the vibration of intracellular ions and generating heat through molecular friction in an expanding sphere. This can be achieved through two types of systems: a temperature-based system, which drives the current to reach a particular temperature, or an impedance-based system, which continues ablation until a pre-determined impedance (i.e., resistance) level is reached [17].

Current systems utilize single- or multi-tined probes, which may allow for increased tissue volume ablation or more accurate monitoring of temperature and successful ablation. Each electrode is insulated except at the tip, which allows for selective positioning in the tissue for ablation. Additionally, some

Table 1 Comparison of oncologic outcomes and complications among modalities

Modality	Oncologic outcomes (%)		Complications (%)			
	5-year LRFS	5-year CSS	Clavien I/II	Clavien III/IV	Blood transfusion	Urinary tract injury
RFA [3, 28••, 29, 49–51, 54–56]	87–95	98–100	2.0–6.7	1.3–9.7	1.6–3.5	1.7–4.8
Cryo [6, 30••, 31••, 49, 50, 52, 53, 57, 58]	86–87	95–99	1.9–15	0.7–16.7	1.3–25	0.4–0.8
MWA [37, 38•, 39, 61]	68–92[a]	–	1.9–20	7.1–20	2	1.5–20
IRE [22•, 41]	15[b]	–	35	–	–	–

[a] Longest follow-up at 3 years

[b] Longest follow-up at 1 year

systems are designed to have a constant infusion of irrigation around the probe, referred to as "wet" RFA. This reduces impedance by limiting tissue charring, allowing for a wider ablation zone [18].

Tissue death is dependent on energy delivered through the probe, maximum temperature, and total ablation time. Although temperatures above 60 °C cause protein denaturation and cell death, most modern temperature-based systems heat to a target temperature of 105 °C to ensure homogenous tissue death. This corresponds to a resistance of 200–500 ohms in impedance-based systems. However, if the energy applied is too high, charring of the tissue can occur increasing impedance and leading to a non-uniform distribution of energy or incomplete heating [17]. It should be noted that unlike CA, which can be monitored during the procedure radiographically, RFA can be monitored with heat and impedance feedback only. Furthermore, the ablation zone may be affected by a heat sink effect: if the renal mass is close to large vessels or the collecting system, thermal energy may dissipate through the cooler flowing blood/urine [17].

Microwave Ablation

Microwave ablation (MWA) induces cellular death in a similar manner to RFA by generating heat through rapid water ion oscillation. Energy is delivered through microwaves via probes at a frequency between 900 MHz and 2.5 GHz. The most common frequencies used are 915 MHz or 2.45 GHz due to the Federal Communications Commission permissions. Unlike RFA, this propagation is independent of the tissue conductivity and a zone of ablation forms regardless of tissue impedance. In this manner, MWA is able to achieve higher temperatures faster than RFA and is not as susceptible to charring or heat sink effects [19].

Early MWA systems had less success due to bulky coaxial cables and inefficient antennas. Newer systems have more efficient cables and antennas utilizing gas or liquid to minimize power loss [19]. Currently, most systems are composed of a generator, a power distribution system, a cooling system, and antennas.

Irreversible Electroporation

Unlike the other modalities, irreversible electroporation (IRE) is a non-thermal method of tissue ablation. Longstanding literature has recognized the ability of electrical currents to induce reversible poration in cellular membranes [20]. By modulating the energy used, a more powerful current and a larger number of pulses leads to irreversible poration and eventual cell death [21]. In a typical IRE procedure, 2–4 monopolar probes are inserted in the target tissue and an electric field is generated across cells. Based on theoretical models, currently practiced IRE protocols involve spacing electrodes 10–20 mm apart and applying 70 pulses between each probe pair. Polarity of pulses is reversed and repeated in some series to give a total of 140 pulses administered [22•]. The amount of energy applied should achieve a goal current of 30–40 amperes to signify adequate cell death [23]. Ablation of larger tumors can be achieved by increasing the number of surrounding probes.

There is appropriate concern regarding severe muscle contraction and the induction of cardiac arrhythmias due to the applied energy pulses. Therefore, IRE is performed under general anesthesia with paralysis. Patients are electrocardiographically monitored, and it is recommended to apply defibrillation pads pre-procedure in case of a significant arrhythmia. However, there is no literature to our knowledge describing a significant intraoperative arrhythmia due to electroporation.

Outcomes

Defining Success

The goal of renal tumor ablation is curative despite the lack of standardized protocols for each modality and variations in the definition of ablative oncologic success. Immediately after the procedure, technical success is determined based on radiographic evidence of an ablation zone entirely encapsulating the desired lesion, although this may not translate to oncologic success. Post-ablation, cross sectional imaging is the accepted measure of treatment efficacy [24]. Per the AUA Guidelines, a CT or MRI with intravenous contrast should be obtained within 3–6 months after ablation and annually thereafter up to 5 years [25]. In general, loss of contrast enhancement, development of a halo/rim of fibrotic tissue, or decrease in size by 50 % in the target area is considered evidence of complete tissue destruction and enlarging or enhancing lesions are evidence of local tumor recurrence or progression [26]. However, some evidence suggests temporary enhancement may still be seen after CA in some successfully treated patients. In one cohort, Nielsen et al. found that 31 % of patients had enhancement on follow-up imaging after CA. On subsequent imaging, 45 % of these enhancing lesions resolved spontaneously, suggesting that imaging alone may not be the most accurate test to evaluate oncologic success [27]. The role of post-ablation biopsy is still controversial as interpretation of the results is challenging. Further work must be done to better characterize treatment success for ablative therapies.

Oncologic Outcomes of CA and RFA

The body of literature evaluating ablative therapies has rapidly increased allowing for a more accurate assessment of oncologic success. The meta-analysis supporting the 2009 AUA Guidelines suggested that both CA and RFA have poorer local

recurrence-free survival (LRFS) compared to laparoscopic and open partial nephrectomy despite a similar cancer-specific (CSS) and overall survival (OS) [3]. These conclusions, however, were reached in the setting of smaller tumors with short follow-up. More contemporary literature has improved our understanding of the oncologic outcomes of thermal ablation.

The AUA meta-analysis demonstrated LRFS of 91 and 87 % at a mean of 19–23 months for CA and RFA, respectively. More recently, Psutka et al. demonstrated LRFS of 95 % for cT1a tumors after RFA with a median follow-up of 6.5 years [28••]. Similar success was supported in a separate series by Olweny and colleagues with a minimum of 5 years of follow-up [29]. The long-term CA literature, comparatively, has shown 5-year LRFS of 86–87 % [16, 30••].

The AUA meta-analysis further concluded that thermal ablation and surgical extirpation have comparable CSS and OS rates. However, the thermal ablation mean follow-up time was 17–19 months, a significant shortcoming. Psutka and colleagues demonstrated CSS of 100 % at median follow-up of 6.5 years in 143 cT1a renal masses, but an OS of 74 % owing to the comorbidities of this population [28••]. Similarly, Kim et al. showed 5-year CSS of 99 % in 263 cT1a masses undergoing CA, with OS rates of 79 and 86 % for the laparoscopic and percutaneous routes, respectively [28••]. In an even longer follow-up period, Caputo et al. showed a 10-year CSS of 93 % and OS of 54 % in 131 tumors after CA, with median follow-up of 92 months [30••].

Additionally, recent comparisons of ablation to surgical excision of SRMs show similar long-term outcomes. In an evaluation of 1424 patients with T1a disease undergoing either PN, RFA, or CA, Thompson et al. demonstrated no significant LRFS difference between the three groups at 5 years, though metastatic free survival seemed to be better in the partial nephrectomy (99 %) and cryoablation (100 %) groups [31••]. The group assessed a likely selection bias in evaluated studies for patients undergoing partial nephrectomy as well as a small number of metastases ($n = 4$) in patients undergoing RFA and caution interpretation of these results as truly significant. Though these retrospective studies suggest good oncologic outcomes at long-term follow-up, prospective studies are necessary to better elucidate the oncologic success of CA and RFA.

It is likely that the therapeutic efficacy of thermal ablation will improve with better patient and tumor selection, allowing for a further application of the technology. For example, Gahan et al. used a modified R.E.N.A.L. nephrometry score, where the R variable was modified to stratify tumors less than 4 cm. They found significant differences in ablation success and recurrence-free survival between low, medium, and high complexity tumors [32, 33]. Similarly, Best et al. demonstrated 5-year overall disease free survival of 95 % in tumors <3.0 cm compared to 79 % in tumors larger than 3.0 cm [34]. The outcomes of ablative therapies, however, are likely not solely influenced by size. For example, Lay et al. found improved ablation success in papillary RCC types compared to clear cell types, likely due to differing vascularity of the tumor types [35]. Given that many patients do not have a biopsy prior to their ablation, they also assessed CT enhancement, noting that tumors with enhancement greater than 60 Hounsfield units experienced a higher risk of incomplete ablation compared to less-enhancing tumors [36].

Oncologic Outcomes of Ablative Therapies—MWA and IRE

Oncologic outcomes for MWA and IRE are limited by small, retrospective studies without long-term results. MWA has shown mixed early results, with more recent encouraging findings given improvements in the technology. An early study evaluating MWA by Castle et al. found a disappointing 38 % tumor recurrence rate at 18 months follow-up, for renal masses. However, they studied comparatively larger (mean 3.65 cm) and more complex tumors with 50 % abutting the renal sinus [37]. This small series, additionally, used older technology that likely further limited technical success. Using a more advanced system, Moreland et al. found no progression in 55 tumors (mean diameter of 2.7 cm) at a mean follow-up of 8 months [38•]. Additionally, with longer follow-up, Yu et al. showed favorable outcomes in 46 patients who underwent MWA for RCC with a 7.7 % local progression rate at 3 years [39]. These results show promise for the application of MWA in treating SRMs.

IRE has been shown to be safe in animal models and has been examined more recently in humans [40, 41]. A phase 1 study evaluating IRE followed by immediate resection showed safety of IRE in human subjects without any complications, though oncologic effectiveness was not well evaluated as all ablated tumors were resected on average 15 min after electroporation [42]. The largest single series evaluation of oncologic efficacy, performed by Trimmer et al., evaluated 20 patients with a mean tumor diameter of 2.2 cm. Two patients (10 %) failed initial ablation, and one patient developed a local recurrence at 1 year that was subsequently treated with robotic partial nephrectomy [22•]. Both MWA and IRE are still under active investigation for routine use in SRM ablation.

Renal Function Outcomes

Maintaining renal function after treatment for SRM is independently associated with increased post-procedural renal volume [43]. Ablative techniques minimize normal renal parenchyma loss and improve long-term renal function compared to mass excision. A retrospective review of patients with SRMs treated by partial nephrectomy, cryoablation, or

radiofrequency ablation revealed a comparatively decreased renal parenchymal volume loss with thermal ablation versus extirpation [9]. A corresponding and significant decrease in mean glomerular filtration rate (GFR) was also noted (−8.2 versus −13.7 %, respectively) [9]. Ji et al. further found improved GFR for laparoscopic CA compared to partial nephrectomy with 5-year follow-up [44]. Similar studies suggest that thermal ablation preserves renal function in patients with pre-existing chronic kidney disease (CKD) and complex tumors [32]. Wehrenberg-Klee et al. evaluated 48 patients with a mean GFR of 39.8 mL/min and found no significant change in renal function 1 year after renal mass ablation [45].

Salvage

Limited data is available regarding surgical management of local recurrences after ablation. Karam et al. described the outcomes of 14 patients undergoing salvage surgery. In total, 11 patients underwent partial nephrectomy and three underwent radical nephrectomy. One patient had a positive microscopic margin and four patients (29 %) had Clavien grade III complications [46]. Similarly, Jimenez et al. published their results of 27 patients requiring salvage nephrectomy ($n = 12$) or partial nephrectomy ($n = 15$). Complications occurred in 17 patients (63 %) with six (22 %) being Clavien grade III or greater [47]. Both studies noted significant peri-tumor fibrosis making dissection difficult. Though a desmoplastic reaction has been elsewhere reported after treatment, it is unclear if laparoscopic versus percutaneous ablation impact ease of dissection. Regardless, it should be understood that partial nephrectomy is feasible after failed thermal ablation in select patients, and significant complications can occur regardless of approach. These cases should be referred to high-volume centers.

Complications

Percutaneous ablation minimizes complications compared to excisional therapy. Typically, ablation complications are due to uncontrolled or expansive energy distribution outside of the target zone, and occur more frequently in complex renal masses [48]. The 2009 AUA meta-analysis regarding SRM management reported no significant difference for major urologic complications between CA (4.9 %) and RFA (6 %). More recent evaluations have better elucidated the complications of ablation.

The majority of complications associated with ablation are minor, one of the most common being pain or paresthesia at the insertion site. Significant pain or nerve injury lasting after the procedure can be seen in up to 4 % of patients [49, 50]. This is usually temporary and resolves with time and oral pain medication. Additionally, small perinephric hematomas can occur in up to 14 % of patients after ablation but are rarely symptomatic [2, 51].

The most common major complication after CA is hemorrhage, often from a combination of renal capsule fracture during rapid thawing and a local coagulopathy due to platelet dysfunction [50, 52]. The literature regarding hemorrhage in CA has shown transfusion rates of up to 8 % and need for angiography with possible ablation in 3 % of patients in the series described by Atwell et al. [50, 53]. In contrast, the coagulative effect of heat ablation seem to protect against hemorrhage after RFA as major bleeding rates are less than 4 % in most series [50, 54].

For RFA, the most common major complication is urothelial injury leading to urinary leak or possible stricture, and has been reported in up to 4.8 % of cases [51, 54]. This is more likely to occur in tumors near the collecting system or ureter [55, 56]. CA, in comparison, has a relatively low risk of collecting system injury with reports of urine leak in only 1–2 % of cases [57, 58].

Uncommon complications, but equally concerning, include pleural injury and pneumothorax, which may occur when placing ablation probes or during laparoscopy. The incidence of pleural injury is around 2 %, though most are asymptomatic and rarely require a chest tube [50, 56, 59, 60]. Infection and bowel injury are increasingly rare with an incidence of approximately 1 % in contemporary series [16, 50, 51]. Such complications can be minimized by appropriate pre-procedural imaging and patient selection.

Given the novelty of MWA and IRE, literature on complication rates is limited. Due to the heating properties of MWA, we expect a similar complication profile to RFA. Prior reports have demonstrated a low risk of hemorrhage, with increased risk of collecting system injury leading to urinoma, ureteropelvic junction obstruction, or urinary fistula [37, 38•, 39, 61]. With fewer reports on IRE and the athermal technology, complications are not well understood. Trimmer et al. described only minor complications in 35 % of patients, including urinary retention (likely due to anesthesia), increased pain post-procedurally, and asymptomatic retroperitoneal hematoma [22•]. The theoretical benefits regarding the safety of IRE has been shown in animal models, but more research is required to exemplify this in humans.

Conclusions

In light of the increasing incidence of small renal masses and an aging population, a variety of ablative therapies have developed for the treatment of SRMs. The techniques have durable results over the past decade though larger, prospective studies may better elucidate oncologic outcomes. Furthermore, compared to extirpative therapy, ablation comes with a decrease risk in complications. As the technology

evolves, it is likely that the application for ablation will expand to include a variety of populations.

Compliance with Ethical Standards

Conflict of Interest Nicholas Kavoussi, Noah Canvasser, and Jeffrey Caddedu each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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