The Role of Ablative Therapies in Renal Cancer

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Introduction

With the rising use of cross sectional imaging, the rate of incidentally found renal masses has increased [1, 2]. While the majority of these masses will be T1a (≤4 cm) lesions [3], most will be malignant (approx. 80%) and many will require treatment for cure [4–6].

Currently, the gold standard treatment for T1a renal masses is partial nephrectomy (PN) [5, 7]. However, as urologists continue to look for new techniques to preserve renal function while minimizing the morbidity of surgery, percutaneous focal ablative therapies have evolved and are an option for many patients with T1a renal masses [5, 7]. Ablative techniques have been shown to have low complication rates, low morbidity, comparable short-term oncological outcomes and lower costs [8]. Currently, there are four ablative treatments: radiofrequency ablation (RFA), cryoablation (CRA), microwave ablation (MWA) and irreversible electroporation (IRE).

In this chapter, we will discuss the role of ablative therapies for the treatment of renal masses.

Indications for Ablation Treatment

Urologists can refer to major guidelines, all which discuss ablative techniques in the management of T1a renal tumors. Current guideline recommendations are listed in Table 1. Recommendations range from offering ablative therapies as an option to most patients with T1a renal tumors (ASCO, AUA, NCCN), to only offering ablation to patients who are elderly or have significant comorbidities (EAU).

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Table 1 Major guideline recommendations for the use of ablative therapies in the management of renal tumors

Guideline	Year Published	Recommendation	Strength
ASCO [9]	2017	"Percutaneous thermal ablation should be considered an option for patients who possess tumors such that complete ablation will be achieved. A biopsy should be obtained before or at the time of ablation."	Evidence quality: Intermediate, strength of recommendation: Strong.
AUA [5]	2017	"Physicians should consider thermal ablation (TA) as an alternate approach for the management of cT1a renal masses <3 cm in size. A renal mass biopsy should be performed prior to ablation to provide pathologic diagnosis and guide subsequent surveillance."	Conditional recommendation, evidence level: Grade C.
EAU [7]	2018	"Offer active surveillance, radiofrequency ablation and cryoablation to elderly and/or comorbid patients with small renal masses."	Strength rating: Weak
NCCN [10]	2019	"Thermal ablation (cryosurgery, radiofrequency ablation) is an option for the management of patient with clinical stage T1 renal lesions."	Category of evidence: 2A

ASCO American Society of Clinical Oncology, *AUA* American Urological Association, *EAU* European Association of Urology, *NCCN* National Comprehensive Cancer Network

As mentioned previously, T1a tumors (≤4 cm) are most amenable to treatment [8]. However, there have been reports in the literature of treatment of cT1b tumors in select patients [11, 12]. The size criteria is important not only for oncologic outcomes, but also for bleeding risk as the risk of bleeding increases with tumor size [13]. Most guidelines recommend a renal mass biopsy prior to or at the time of ablation to confirm that the mass is malignant [5, 7, 9]. Finally, location within the kidney is important, as anterior tumors, tumors <5 mm from the collecting system and surrounding structures (colon, larger vessels, "heat sinks") are more difficult/contraindicated to treat [14].

While tumor factors play an important role in determining a patient's eligibility for treatment, there are patient factors to consider. The most important ones are patient's risk for multifocality (i.e. genetic conditions such as von Hippel-Lindau Syndrome), patients where renal preservation is important (i.e. patients with renal dysfunction or solitary kidney) and patients who are not medically fit to undergo a surgical operation (elderly, frail, multiple medical comorbidities) [15, 16]. Patients should not have an uncontrolled coagulopathy, and most clinicians recommend an internal normalized ratio (INR) of <1.5 and platelet count to be greater than 50,000/μL [16].

Technical Considerations for Treatment

All ablative technologies aim to achieve the same final outcome—a negative margin of at least 5–10 mm and to achieve a predictable and continuous lethal cell ablation zone. How each ablation type achieves this is different, and we will briefly review the mechanism of each. Other technical considerations include probe types and number, device settings, patient positioning (patients must tolerate being in the prone position), and the use of local or general anesthesia.

Treatment Types

Radiofrequency Ablation (RFA)

RF energy is part of the electromagnetic (EM) spectrum, specifically, the frequencies between 450 Hz and 1200 kHz. Molecules become heated due to the rapidly alternating current being applied by the electrode, through a process called dielectric hysteresis, causing intense vibration and heat. The RFA electrode itself is not the source of heat. It is the molecules adjacent to the electrode that become heated and transmit heat farther through conductivity [17]. The further the molecules are from the probe, the vibration (energy) and temperature drop exponentially.

When performing RFA, the goal is the slowly heat the entire target area to 50–100 °C (ideally 70–100 °C) for 5–8 minutes in order to cause cell death without charring or vaporization. Charring or vaporization have an insulating effect, thereby limiting energy transmission to tissue and decreasing ablation size. As use of RFA has expanded, improvements to the technology have also occurred. This includes probes that are able to limit tissue charring, and probes that have expandable, multitined/clustered (“Christmas tree vs. umbrella“) electrodes that result increased electrode surface area and ability to treat more complex tumors [16].

Advantages of using RFA are that the technology is widely available, RFA typically only requires one probe and one procedure for treatment, the probe is relatively small (14–17 gauge), the technology is cheaper compared to other types of ablative therapies, it has a hemostatic effect on tissue to minimize bleeding and an acceptable safety profile [16, 18]. Disadvantages to using RFA are the susceptibility to “heat sinks”, size limitation (efficacy of ablation decreases over 4 cm), it requires image guidance and patients can receive skin burns if the grounding pads are not positioned correctly (monopolar systems) [16, 18].

Microwave Ablation

The use of microwave ablation (MWA) to ablate tumors in humans was first described in Japan during the late 1990s [19, 20]. Microwave ablation (MWA) induces heat-based cellular death through a mechanism similar to RFA. It uses EM radiation within the microwave spectrum (3 MHz–3GHz). MWA can heat tissues more rapidly and at higher temperatures than RFA. This has the potential to ablate larger tumors within a shorter treatment time [21]. However, MWA differs from RFA in that the probe (antenna) emits microwave energy that radiates into the tissue surrounding the antenna, causing direct heating [22]. This allows microwaves to be propagated through many types of tissue, even charred or desiccated tissue. Furthermore, multiple microwave probes can be placed in close proximity to each other, allowing for thermal synergy, or they can be widely spaced apart to treat several tumors at once [23]. MWA also offers other advantages over RFA in that no grounding pads are required, thereby eliminating the risk of skin burns and MWA is less susceptible to "heat sinks" than RFA [24].

While MWA has many advantages over RFA, it does have limitations. Microwave energy is more difficult to generate and deliver efficiently and safely to tissue compared to RFA, as the energy must be carried in coaxial cables. Coaxial cables are larger in diameter and more prone to heating than wires used for RFA. This cable and shaft heating can be an obstacle to delivering energy to tissue [25]. Furthermore, this heating effect of the probe can result in proximal tissue thermal damage, creating an unwanted "tail" of ablation and damage to the body wall or other more proximal structures [22]. Many companies have attempted to overcome this limitation by having shaft cooling systems [26]. Furthermore, currently available microwave systems and probes are heterogeneous in their power, frequency, wavelength and probe design. This results in differences in ablation zone characteristics that can make predictability of treatment zones difficult. Finally, many have reported a steeper learning curve with MWA compared to other technologies [21]. This could result in high complication rates and poorer oncologic outcomes for clinicians adopting this technology.

Thermal Ablative Technique that Utilize Cooling

Cryoablation

The origins of cryotherapy began in the 1800s when James Arnott used salt and crushed ice to improve pain and bleeding in tumors [27]. Cryoablation (CRA) of tumors utilizes freezing and thawing cycles, both of which result in cell death through different mechanisms. Cryoablation efficacy can be influenced by cooling rate, treatment time, target temperature, and thawing rate. The temperature will be lowest closest to the cryoprobe and highest at the periphery of the ice ball. Clinicians therefore must ensure that peripheral portion of the ice ball is within the lethal treatment temperature zone to ensure complete cell death [28].

The basic technique for cryoablation utilizes freeze thaw cycles. Tissue cooling should be as rapid as possible and thawing slow and complete. Then this cycle repeated. Most clinician will treat with an initial freeze cycle of 8–10 min, followed by a second cycle of 6–8 min [29]. Different cryoprobes can produce different sizes and/or shapes of ice balls, depending on the treatment area required. Furthermore, multiple probes can be used if needed. A major advantage of cryoablation is the ability to monitor the ablation zone in real time [30]. Cryoablation tends to be less painful than heat-based ablative techniques due to anesthetic effect of cooling [30]. Each cryoprobe acts independently of each other, allowing for multiple probes to be used simultaneously, allowing for ablation zones that conform to the individual tumor shape. Furthermore, CRA invokes an inflammatory response which produces antibodies to the tumor antigen which may result in death of tumor cells outside the treatment zone [31]. Unfortunately, this inflammatory response can also rarely trigger, a systemic inflammatory response, known as cryoshock, resulting in shock, multiorgan failure and disseminated intravascular coagulation [32]. Bleeding complications tend to be more common with cryoablation as the cautery and coagulative effects of heat do not occur. Care must be taken to avoid excessive torque or force on the cryoprobe, as the ice ball may fracture, resulting in bleeding [33]. Finally, as cryoablation systems use argon and helium gas to result in rapid cooling, the cost is higher than other ablative therapies [34].

Non Thermal Ablative Therapies

Irreversible Electroporation

Initially an unwanted byproduct of reversible electroporation, irreversible electroporation (IRE) was eventually investigated as means of tumor treatment in the mid-2000s [35]. IRE is a non-thermal ablative technique that passes an electric current between multiple probes across the ablative zone. This current increases the permeability of the cell membrane, by creating nanopores, resulting in cell death [35, 36]. Connective tissue (blood vessels, collecting system, biliary system) surrounding cells is spared. Since IRE is non-thermal, it has the potential utility of being able to treat central tumors, tumors within close proximity to other structures (ureter, bowel) and tumors near larger vessels (as IRE is not effected by “heat sinks”) [36]. Furthermore, IRE induces cell death through apoptosis without areas of necrosis while preserving extracellular structures allowing for faster tissue regeneration.

While IRE shows promise with its ability to ablate tumors, limitations exist. First, IRE requires ECG synchronization (to avoid arrhythmias), full muscle paralysis (electrical current causes muscle contractions) and the use of multiple probes for successful treatment [37]. Finally, as IRE is the newest technology to be approved, its cost are the highest of all ablative therapies and it lacks longer term efficacy data [38]. Furthermore, for effective treatment, device settings needs to be optimized [39].

Outcomes

Oncological Outcomes

Ablative therapy outcomes are comparable to surgical treatment, however, currently there are no randomized controlled studies comparing the two directly. Long-term oncological outcomes have now been published for CRA and RFA, while long-term data is still lacking for MWA and IRE. As ablative therapies have traditionally treated patients who are older, are medically unfit for surgery or have limited survival, overall survival has been lower [40, 41]. Five to ten year cancer specific survival (CSS) for both CRA and RFA are reported in the literature to be 95–100%, which is similar to

PN [41]. Furthermore, there appears to be no significant difference in metastasis-free survival (MFS) between thermal ablation and PN, however, local recurrence free survival (LRFS) is lower for thermal ablation (98.9% for PN and 93.0% for thermal ablation) [41]. A recent systematic review and meta-analysis by Uhlig et al. compared CRA, RFA and MWA to PN. Select results of the their meta-analysis are summarized in Table 2 [42]. As IRE is the newest treatment modality, oncologic data are still maturing. However, preliminary data appear acceptable [43].

Renal Function and Complication Rates

While PN has been reported to have improved preservation of renal function compared to radical nephrectomy, meta-analyses have reported that ablative therapies have similar, if not improved preservation of renal function compared to PN (Table 2) [41, 42, 44]. Due to the less invasive, non-surgical nature of percutaneous ablative therapies, complication rates tend to be significantly lower than PN (Table 2) [41, 42].

Nuances

Treatment Planning

When considering a patient for ablative treatment, tumor size, imaging characteristics, location and patient factors need to be considered. The acronym, ABLATE, was developed by Schmit et al. to aid in ablation planning [45]. ABLATE stands for:

Table 2 Network Meta-Analysis Outcomes for Ablative Treatments compared to Partial Nephrectomy. (Adapted from Uhlig et al. 2019)

Treatment	All Cause Mortality (IRR)	Cancer Specific Mortality (IRR)	Local Recurrence (IRR)	Preservation of Renal Function (MD)	Complications (OR)
CRA	2.58 (1.92–3.46), $p < 0.001$	2.27 (0.79–6-49), $p = 0.13$	4.13 (2.28–7.47), $p < 0.001$	0.66 (−3.2–4.5), $p = 0.74$	0.67 (0.48–0.92), $p = 0.013$
RFA	2.58 (1.9–3.51), $p < 0.001$	2.03 (0.81–5.08), $p = 0.13$	1.79 (1.16–2.76), $p = 0.009$	6.49 (2.87–10.1), $p < 0.001$	0.89 (0.59–1.33), $p = 0.56$
MWA	3.8 (0.15–93.2), $p = 0.4$	1.27 (0.03–63.8), $p = 0.9$	2.52 (1.09–5.83), $p = 0.03$	−4.4 (−14.08–5.28), $p = 0.37$	0.26 (0.11–0.6), $p < 0.001$

CRA cryoablation, *RFA* radiofrequency ablation, *MWA* microwave ablation, *IRE* irreversible electrophoresis, *IRR* Incidence rate ratio, *MD* Mean difference, *OR* Odds ratio

Axial tumor diameter, bowel proximity, location within kidney, adjacency to the collecting system, touching renal sinus fat, endo- or exophytic [45]. If the tumor is located too close to the body wall, bowel or liver, hydrodissection with 5% dextrose can be used prior to treatment [46]. Furthermore, if the ureter is in close proximity to the treatment zone, some clinicians have found heat injury to be minimized by placing a stent and irrigating the collecting system with cold saline to prevent thermal injury [18, 24].

New Technology

As the minimally invasive treatment approach for small renal masses has gained popularity, other treatments have emerged. Newer treatment technologies include high intensity focal ultrasonography (HIFU) and stereotactic ablative body radiation (SABR). As clinical data is still in its infancy, it remains to be seen whether these treatments will continue to be used.

Conclusion

As long-term oncological data have matured for thermal ablative therapies, it has been shown to be a viable option for the treatment of small renal masses. While local recurrence rates may be higher than surgical treatment, the lower cost, lower complication rate, comparable cancer free survival rate and ability to retreat make ablative therapies a viable treatment option that clinicians should discuss with patients. RFA and CRA have the most data as they are the oldest of the ablative treatments, however, early MWA data has been comparable. IRE is still in the early stages and long term outcomes are lacking. Given the new data available, clinicians should discuss percutaneous ablation as a first line option in the treatment of T1a renal masses with patients.

Key Points

1. Percutaneous ablation of renal masses offers a less invasive treatment option than conventional surgery and can be performed as an outpatient procedure with either local or general anesthetic.
2. The ablation technologies currently available are cryoablation (CRA), radiofrequency ablation (RFA), microwave ablation (MWA) and irreversible electroporation (IRE).
3. For RFA, radiofrequency energy causes molecules to become heated due to the rapidly alternating current being applied by the electrode, through a process called dielectric hysteresis, causing intense vibration and heat.

4. Disadvantages of RFA are the susceptibility to “heat sinks”, size limitation, image guidance is required and patients can receive skin burns.
5. MWA causes cell death using microwave energy in a manner similar to RFA but it is faster and can treat larger areas. MWA differs from RFA in that the probe (antenna) emits microwave energy that radiates into the tissue surrounding the antenna, causing direct heating. This allows microwaves to be propagated through many types of tissue, even charred or desiccated tissue.
6. Disadvantages to MWA are that it requires more energy than RFA, the heating effect of the probe can cause thermal damage to proximal tissue and probes are heterogeneous in their ablation zone characteristics, making treatment zone predictability difficult.
7. Cryoablation (CRA) utilizes freezing and thawing cycles, both of which result in cell death through different mechanisms. Different cryoprobes can produce different sizes and/or shapes of ice balls, depending on the treatment area required.
8. Disadvantages of CRA are that bleeding complications tend to be more common and the cost is higher.
9. Irreversible electroporation is a non-thermal ablative technique that uses electric currents to create nanopores, resulting in cell death. Connective tissue (blood vessels, collecting system, biliary system) surrounding cells is spared, allowing for treatment of tumors in close proximity to vital structures.
10. While currently there are no randomized controlled trials comparing partial nephrectomy (PN) to ablative therapies, cancer specific survival for RFA and CRA are reported in the literature to be 95–100%, roughly similar to PN. Overall survival is lower, however, that may be due to selection bias. Local recurrence rates are higher than surgery. Long term data for MWA and IRE have not yet matured.

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