Renal ablation: current management strategies and controversies

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Abstract: Percutaneous image-guided renal ablation provides minimally invasive and safe treatment to small renal cell carcinomas (RCCs) whilst preserving renal function. In addition, it achieves similar oncologic outcomes as surgery. This article aims to outline an overview of the current types of ablative technology, present the current evidence and discuss controversies on image-guided renal ablation.

Keywords: Radiofrequency ablation (RFA); cryoablation (CRYO); microwave ablation (MWA); irreversible electroporation (IRE); computed tomography (CT); magnetic resonance imaging (MRI); stereotactic ablative radiotherapy (SABR)

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Introduction

Percutaneous image-guided renal ablation provides minimally invasive and safe treatment to small (<4 cm) renal cell carcinoma (RCC) whilst offering preservation of the renal function and there is extensive evidence to support this, particularly in patients who may not be suitable surgical candidates or if they are unwilling to undergo surgery (1-4). In addition, it achieves similar oncologic outcomes as surgery (5,6).

This article aims to outline an overview of the current types of ablative technology, present the current evidence and discuss controversies on image-guided renal ablation.

Current treatment options

Radiofrequency ablation (RFA)

The radiofrequency generator supplies radiofrequency power, using an alternating current, to the tissue through an electrode which causes ionic agitation, generating frictional heating ultimately resulting in thermal coagulation necrosis and cell death once the temperature exceeds 60 ℃ (7,8).

The oncological efficacy is backed up by extensive outcome data from multiple large institutions around the world (9-15). Size (<3 cm) and exophytic tumour location are strong predictors of success. Larger lesions have a reduced success rate with higher rates of subsequent recurrence, as high as 14% in the T1b group (11,16-18). Central tumours are also less effectively treated due to the heat sink effect from surrounding larger central vessels (16-18).

Cryoablation (CRYO)

In CRYO, an ice ball at the end of a cryoprobe is created using the Joule-Thomson effect, where a high-pressurised gas undergoes rapid expansion through a valve resulting in a rapid cooling effect while keeping it insulated so that no heat is exchanged with the environment. This rapid cooling results in ice formation at the end of the cryoprobe (19,20). Cycles of freezing and thawing destroys the cell membranes and organelles due to the mechanical stresses associated with phase change and ice formation (1). Intracellular ice crystal formation causes microvascular injury and ischaemia along with cell membrane injury, and hypotonic cell

disruption leading to cell death (21).

The advantages of CRYO over RFA are the ability to visualize the ice ball on imaging which confirms the ablation zone and the ability of CRYO to overcome heat sink effects particularly centrally within the kidney.

Cohort studies and a meta-analysis comparing RFA and CRYO found similar efficacy and comparable complication rates (14,22-24). A recent large single centre series found no statistical difference in local recurrence, metastases, and death from RCC among partial nephrectomy, RFA, and CRYO cohorts for cT1a patients (15). For tumours >3–4 cm in size CRYO has been shown to have better oncologic outcomes when compared to RFA (11,25,26).

The bleeding complication rate with CRYO is higher than RFA, with on study quoting a bleeding risk of 7.4% for CRYO compared to 1.2% for RFA (24). A newer generation of cryoprobe (Galil Medical, Arden Hills, Minnesota, USA) incorporated a heating element within the distal cryoprobe to allow for subsequent track ablation however despite this, a recent study found this did not decrease the incidence of bleeding complications (27).

Microwave ablation (MWA)

MWA utilises electromagnetic waves through one or multiple antennae, which agitates water molecules causing friction and heat dissipation, resulting in cell destruction by coagulative necrosis (28).

Although there are fewer studies on MWA compared to CRYO, technical success and safety have been proven and the short and intermediate results are comparable to RFA and CRYO, with quoted 3- and 5-year disease-free survival rate of 93% and 88% respectively, although these are from retrospective cohort studies (29-34). A meta-analysis found no difference in local or metastatic recurrence between the treatments for small renal masses, despite the larger median tumour size of 3.13 cm in the microwave group compared to 2.58 cm in the CRYO group (35).

The advantages of MWA include shorter ablation and procedure times compared with the other thermal ablation techniques (36), less effect from the heat-sink effect from the local blood supply compared to RFA and the ability of MWA to achieve larger ablation zones than RFA (28,37,38).

MWA certainly has potential to treat larger (T1b) lesions (39) however the unpredictability of the ablation zone compared to CRYO with the current technology may limit its current widespread adoption until more evidence is available.

Irreversible electroporation (IRE)

IRE is a novel non-thermal ablation method that delivers short high voltage electrical energy between electrodes in order to permeabilise, i.e., cause nanopores in the cell membrane resulting in cell death by apoptosis (40).

Non-cellular tissue, including collagen structures such as vessels contain no lipid bilayer structure and therefore are resistant to damage by the permeability. This ability to preserve vital surrounding structures within the ablation zone is what makes IRE unique, which is particularly effective for cancers adjacent to important structures such as major blood vessels or the ureter (38,40,41). IRE also has the characteristic feature of a sharp demarcation between the ablated zone and the normal surrounding tissue, thereby providing more precise ablation.

The literature in IRE for renal tumours remains limited. Although IRE is supposed to be a non-thermal ablation modality, a secondary rise in temperature has been shown (42) although it is unknown if there is clinically significant thermal damage accompanying the primary non-thermal damage. Knowledge on how to interpret the ablation zone on immediate and follow-up imaging and also what the best modality is required.

Additional considerations in using IRE include the need for general anaesthesia, deep muscle relaxation and electrocardiogram synchronized pulsing of electricity. The application of pulsatile electrical energy, with a high current of approximately 20–50 A and a voltage of up to 3,000 V, poses an issue for anaesthetists due to the risk of cardiac arrhythmias, severe muscle contractions and epileptic seizures (43). Therefore, the contraindications for IRE are atrial fibrillation, epilepsy and cardiac pacemaker.

Although IRE seems feasible and safe, longer follow-up date is required to demonstrate oncological results. There remains an operator learning curve (38), therefore national and/or international multi-centre registries would help collate more data on IRE safety and efficacy in the future and provide more evidence.

Stereotactic ablative radiotherapy (SABR)

Conventional radiotherapy only had a limited role in the treatment of primary RCC, as the doses delivered were too low. With new high-dose SABR technology, new treatment possibilities for RCC with curative intent open up. SABR is currently a treatment option for patients who are at high risk for a general anaesthesia. Data suggests high-dose

radiation has an immune stimulatory effect as the more localised SABR radiation drives the release of antigens by tumours, inducing a tumour-specific T cell response (44). This effect has also been described for other thermal ablative techniques.

Available evidence suggests SABR is safe with low toxicity with the main documented side effects being fatigue, nausea, radiation dermatitis and enteritis.

SABR also has the ability to treat larger T2 lesions with treated tumour sizes up to 7.5 cm in the literature (45,46).

Choice of imaging guidance

Ultrasound, computed tomography (CT), or magnetic resonance (MR) imaging (MRI) can be used to target a lesion during ablation. The modality chosen is largely based on operator preference or expertise, local availability of dedicated equipment such as CT fluoroscopy or open MR systems and capacity to take up scanning time on these machines. Real-time fusion imaging of ultrasound imaging with CT or MRI can also improve the ability to guide and monitor tumour ablation procedures.

The renal tumour ideally must be easily and clearly visualized on the imaging modality chosen. Ultrasound allows for real-time placement of ablation probes and does not require ionizing radiation. The major downside is that ultrasound remains highly operator dependent and may be difficult in certain situations including for large body habitus patients or the presence of adjacent bowel gas obscuring the visualisation of the tumour. Image degradation occurs during ultrasound due to acoustic shadowing from the ice ball for CRYO, and microbubbles in RFA which obscure the target (47).

CT has advantages over ultrasound including being less operator dependent, it has no artefact from bowel gas and gives a clear image of surrounding vital structures. Percutaneous ablation is done using either a conventional CT scanner or a CT scanner with real-time fluoroscopy which can have dose reduction implications (48).

MRI is a less commonly used for percutaneous ablation as due to high cost or lack of free scanning time. It does offer excellent soft tissue resolution and avoids the use of ionizing radiation. Additional features such as fluoroscopic sequences may be used for real-time guidance or MR thermography to assess cytotoxic tissue temperatures non-invasively (47). MRI-guided percutaneous ablation is performed using either a dedicated interventional magnet, a conventional solenoid magnet, or an open magnet. Further considerations include the need for MRI-compatible ablation equipment (47).

Current international guidelines

The current American Urological Association (AUA) guidance suggests that T1a renal masses (<3 cm) should be considered for renal thermal ablation of which RFA and CRYO are recommended although "*priority for partial nephrectomy is recommended for clinical T1a lesions*" (2). The guidelines state that thermal ablation is preferable to a surgical approach, laparoscopic or open, to minimize complications.

The European Society of Medical Oncology (ESMO) guidelines acknowledge the thermal ablative therapies are options in patients with small tumours (≤3 cm), particularly patients who are frail, are a high surgical risk, if they have a solitary kidney, compromised renal function, hereditary RCC or multiple bilateral tumours. Despite this, the ESMO guidance highlights the statement that the "*quality of the available evidence prevents definitive conclusions regarding morbidity and oncological outcomes for RFA and cryoablation*" (49).

The American Society for Clinical Oncology (ASCO) guidelines also recognise the increasing role of ablation stating "*percutaneous thermal ablation should be considered for patients who possess tumours such that complete ablation will be achieved*" although partial nephrectomy is still recommended in patients where the tumour is appropriate for it (50). ASCO also highlights the level of evidence backing up their recommendations as "intermediate-quality" and given as "moderate" strength unlike the AUA who gave the quality of evidence comparing partial nephrectomy and ablation as "low" (2,50). One study cited by ASCO is a large cohort study comparing partial nephrectomy, RFA and CRYO where the 3-year local recurrence-free survival for each treatment was not statistically difference (98% for all groups) (14). As with other studies, there remained selection bias in the nephrectomy group of younger and healthier patients explaining the slightly higher 3-year overall survival (OS) of 95% compared to 82% for RFA and 88% for CRYO (14).

Controversies

Local recurrence rates

The AUA guidelines indicate that a major disadvantage

of percutaneous image-guided renal ablation is the higher quoted local recurrence rate compared to partial and radical nephrectomy (51).

This quoted difference may be exaggerated in certain patient cohorts and not entirely evidence based, but rather due to a lack of long-term disease-free survival data on ablative management of small RCCs (5).

The RFA evidence base is mainly from retrospective cohort studies with small study sample sizes and limited follow-up. Three retrospective studies compared RFA to surgery in patients with T1a tumours and found lower complication rates and comparable oncologic outcomes to partial nephrectomy despite being an older patient cohort with more comorbidities (17,52,53).

The median estimated glomerular filtration rate (eGFR) decrease following RFA was also significantly lower than the nephrectomy group (7.9% *vs.* 29%) consistent with the existing evidence showing ablations with better preservation of renal function (5,17).

A systematic review of RFA and partial nephrectomy suggested a long-term cancer specific survival for RFA, equal to partial nephrectomy together with a low metastasis rate but slightly higher local recurrence rate compared with partial nephrectomy and CRYO (54). A recent meta-analysis found CRYO for T1 renal tumours was associated with poorer oncological outcomes (cancer-specific death, metastases and local-recurrence rates), but this was also accompanied by a lower rate of overall and post-operative complications and superior renal functional preservation (55).

Post-ablation imaging follow-up

CT using a triple-phase protocol (unenhanced, arterial and portal-venous phase studies) or multi-parametric MRI is used to assess the treatment efficacy and locoregional recurrence (56,57).

Each thermal ablative technique results in different rates of temporal resolution of post-ablation follow-up imaging. For RFA the reduction of the zone of ablation at 2 years is 50% compared to CRYO which is 75%. Complete resolution is seen in approximately 33% of patients following CRYO (57-59). The zone of ablation may initially show a degree of enhancement in the first weeks after treatment, which can pose a diagnostic dilemma and it can vary depending on the time interval post-thermal ablation (60,61).

Concomitantly, lack of enhancement does not fully rule out residual or recurrence disease and a previous study found 8% of patients with no enhancement within the zone still had viable disease following biopsy of the non-involuting zone of ablation (62). The literature suggests true residual or recurrent disease can be distinguished from the normal expected marginal enhancement post-ablation by using brisk contrast medium administration (38).

A similar controversy with follow-up imaging also afflicts post-IRE follow-up with little available published guidance. One study found an initial larger hypodense non-enhancing area consistent with the ablation zone at 6 weeks, similar to other thermal ablative techniques, which then involuted by the 6-month CT scan (63). On MRI following IRE, there is a progressive decrease in the treated tumour signal intensity, with a mean follow-up of approximately 6 months (64). More work in this area is required before deciding on the best imaging modality to use for follow-up and how to interpret this.

Biopsies

The rationale behind obtaining a pathological diagnosis prior to ablation is that the differential diagnosis for solid, enhancing renal masses includes RCC as well as benign tumors, non-RCC malignancies and metastatic lesions (2). Ablation leads to tissue necrosis, which will prevent subsequent histological diagnosis.

The AUA, ESMO and ASCO guidelines all recommend a renal biopsy prior to ablation to confirm malignancy, subtype the pathology and guide surveillance after ablation (2,49,50).

Undertaking a biopsy of the zone of ablation remains a debatable issue as it is unclear which site should be biopsied and how many sampling cores should be performed. This may be considered if imaging findings are indeterminate or there is a persistent non-involuting zone of ablation despite lack of imaging enhancement which can be due to residual disease (62). These cases should be a consensus decision by the multidisciplinary tumour board whenever there is suspicion of viable cancer in the zone of ablation post-treatment.

Ablation vs. robotic surgery

Robot-assisted laparoscopic partial nephrectomy (RALPN) is associated with more favourable results than conventional laparoscopic partial nephrectomy in terms of conversion rate to open or radical surgery, warm ischaemia time, renal functional outcomes, and shorter length of hospital stay (65).

Five-year OS, cancer-free survival (CFS), and cancer-specific survival (CSS) were 91.1%, 97.8%, and 97.8%, respectively confirming excellent long-term oncologic outcomes after RALPN in well selected patients (66).

Comparative data with CRYO is mainly from retrospective cohort studies. One study found comparable complication rates, better renal function preservation for CRYO but higher recurrence rates (67). A second study found the local recurrence rate after CRYO was significantly higher than after robotic tumourectomy for T1 renal tumours (68). Taking into account the lower complications profile and shorter length of stay associated with ablation, it is likely that RALPN is also less cost-effective (69).

Treating larger tumours

Retrospective data suggests that T1b tumours can be effectively treated with CRYO, however the quoted complication rate was higher at 8–15% (25,26).

Both MWA and SABR have the potential to treat larger (T1b) lesions (39) however MWA zones may still be unpredictable and SABR requires longer follow-up data to demonstrate clear oncological outcomes.

Patient selection: active surveillance vs. intervention

For patients with a reduced life expectancy, either due to advanced age or severe comorbidities, undertaking even a minimally invasive treatment such as ablation or partial nephrectomy could result in unnecessary psychological and physical stress. In addition, there is data suggesting that some small renal masses may not significantly impact a patient's mortality (70). This highlights the importance of follow-up imaging and/or biopsy to confirm a malignant lesion and published data suggest that the linear growth rate of small renal masses is the most accurate predictor of metastasis (71).

Important considerations for shared decision-making about active surveillance are explicitly defined by the international guidelines (2,49,50) although comparative data on active surveillance is still lacking (5). Anecdotally, patients may request for treatment of their slowly growing cancer after a period of active surveillance highlighting the importance of the discussion and explaining to the patient all the available options. Choosing the most appropriate management strategy requires a conversation between physician and patients to weigh up multiple factors including the evidence based oncological outcome profile for each strategy including local recurrence rate, the renal function outcomes (favouring ablation over even partial nephrectomy), perioperative outcomes, and risk of complications (5). Outcomes are likely to reflect case selection.

Conclusions

Current evidence supports the use of image-guided renal ablation for small, renal tumours with well-established thermal ablative treatments such as RFA and CRYO however the increasing literature showing the safety and efficacy of MWA, IRE and SABR will open up further possibilities of treating larger tumours with MWA and SABR or more central tumours especially with IRE.

Future research should focus on the mechanisms governing systemic immune-modulating effects of ablative therapies with the aim to increase the indications for ablation, both with a curative intent and for palliation. The potential combinations with systemic treatment such as immunotherapy, for treatment intensification or to treat larger lesions or metastatic disease, can help to improve overall patient outcomes.

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Footnote

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