# Cryotherapy and radiofrequency ablation for renal cell carcinoma

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**Thermal ablation is being increasingly used for the treatment of clinical stage T1a renal cell carcinoma. However, it is not uncommon to hear mixed messages regarding this issue. Hence, it is necessary for every urologist to understand the basics of thermal ablation and its clinical outcome based on the latest literature to help guide their patients through treatment options. Patient selection criteria are also analysed. Among thermal ablation techniques, cryotherapy and radiofrequency are the most commonly performed ablative procedures. The superiority of one technique over the other is difficult to demonstrate in the absence of a randomised controlled trial. Local recurrence seems more likely after radiofrequency ablation than after cryotherapy, with the latter achieving better local control. When compared to partial nephrectomy, higher local recurrence rates are described with the thermal ablation techniques. However, the small difference at five year follow-up and the better tolerability profile of thermal ablation procedures in elderly and/or comorbid patients explain the rationale for their use in selected cases. Follow-up is mandatory in these patients to diagnose recurrence or persistence of the disease, to monitor renal function and to detect complications. Of note, redo-techniques and surgical approach, though challenging, remain possible salvage procedures after primary failure.**

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## Introduction

The growing use of abdominal imaging over the past three decades contributed to the increased incidence of renal cell carcinoma (RCC) and to a significant downward shift in tumour stage and size observed in numerous clinical series.[1] At present, small renal masses account for nearly one-half of all newly diagnosed renal masses and about 80% of these masses are RCC.[2] The current standard of care for clinical stage T1 RCC is surgical, preferably with partial nephrectomy because of the reported excellent oncologic outcome.[3] However, subsets of patients are elderly and/or at high surgical risk and, as an option, thermal ablation and active surveillance represent acceptable management strategies that could be offered after discussion with the patient.[3] Among thermal ablation techniques, cryotherapy and radiofrequency (RF) are the most commonly performed ablative procedures.[4] Early experience with these minimal invasive modalities was suggestive of lower rates of complications compared to extirpative surgery.[5,6] However, they were also associated with lower cancer control rates, leaving many urologists unsure as to what to tell their patients with clinical stage T1 RCC.

Recent advances in the technology of these two techniques responsible for producing rapid tissue ablation have served to improve their accuracy and predictability.[7] In addition, our understanding of cryotherapy and RF ablation equipment, mechanism of action and their interactions with tissue have also improved. These refinements were critical to avoid some complications and to improve patient oncologic outcomes, and were marked by their widespread use and excellent results in the management of clinical stage T1 RCC. Recently, Thompson et al. observed similar recurrence free survival rates between partial nephrec-

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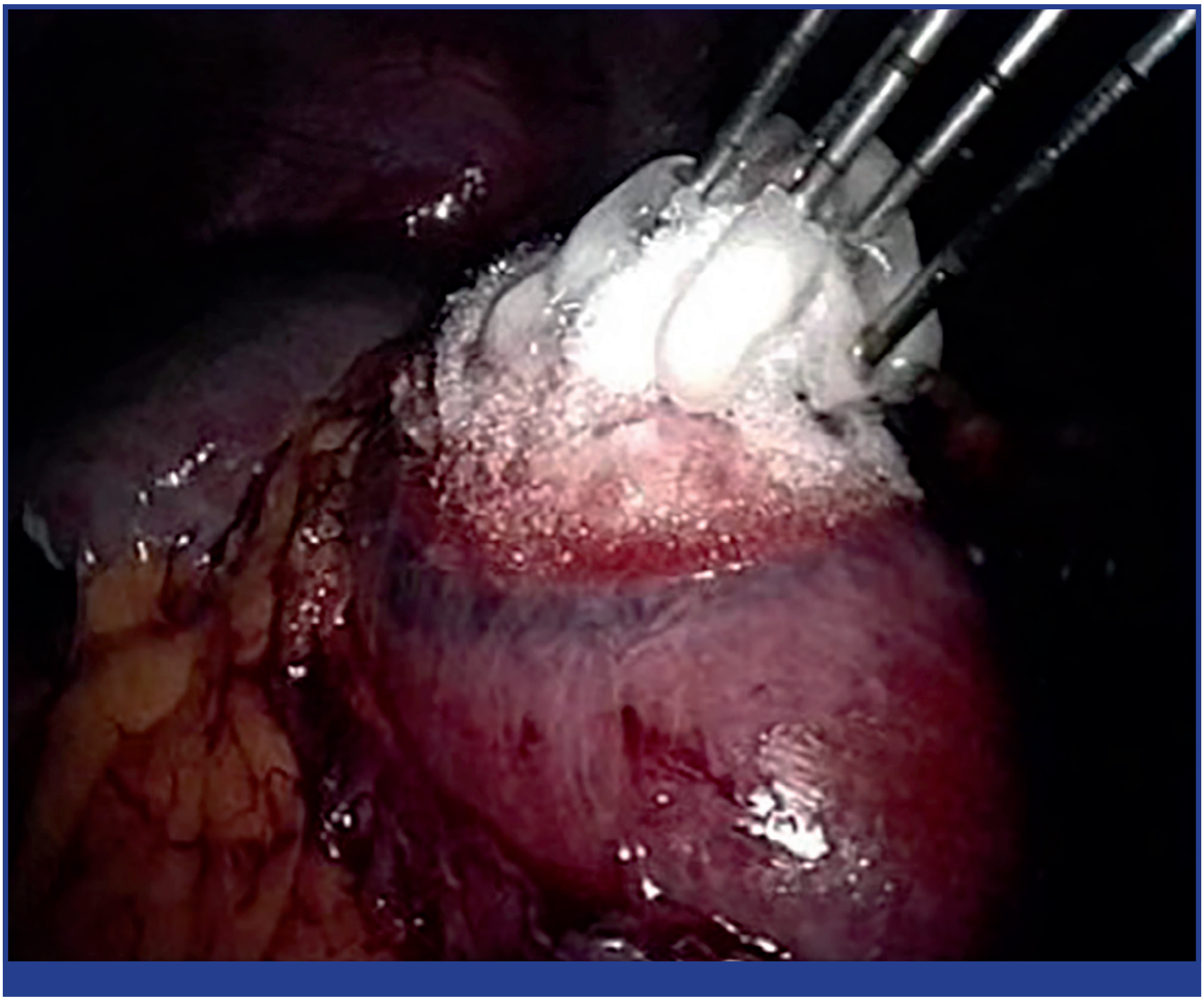

**Figure 1.** Laparoscopic view of the treated kidney showing the ice ball created by five cryoprobes inserted into the tumour.

tomy and percutaneous ablation in a large cohort of patients with sporadic cT1 RCC of the Mayo Clinic Renal Tumor Registry.[8] Hence, the aim of this review based on the latest literature is to understand the basics of thermal ablation, patient selection criteria and the functional and oncologic results as well as the complication rates of these techniques in order to help urologists guide their patients through treatment options. The role of percutaneous renal biopsy will also be analysed.

## Basic principles of thermal ablation

The primary purpose of thermal ablation is to completely eradicate all viable malignant cells within the target tumour. To do so, a thermal ablation procedure involves completion of three basic steps: accurate localisation of the tumour to be ablated, correct application of an optimal temperature able to cause irreversible cell injury and subsequent cell death, and reliable intraoperative monitoring. The lesion is identified and characterised preoperatively on imaging. In the vast majority of cases a contrast enhanced CT scan is required to plan the treatment preoperatively.

## Cryotherapy

The mechanism of action of cryotherapy is based on the established Joule-Thomson effect to create unique freeze and thaw cycles.[9] Rapidly cooling tissue (−20° to −40°C), slow thawing, and repetition of the freeze–thaw cycle (usually two cycles) are necessary to cause irreversible cell injury. When temperatures decrease rapidly to an appropriate level, water

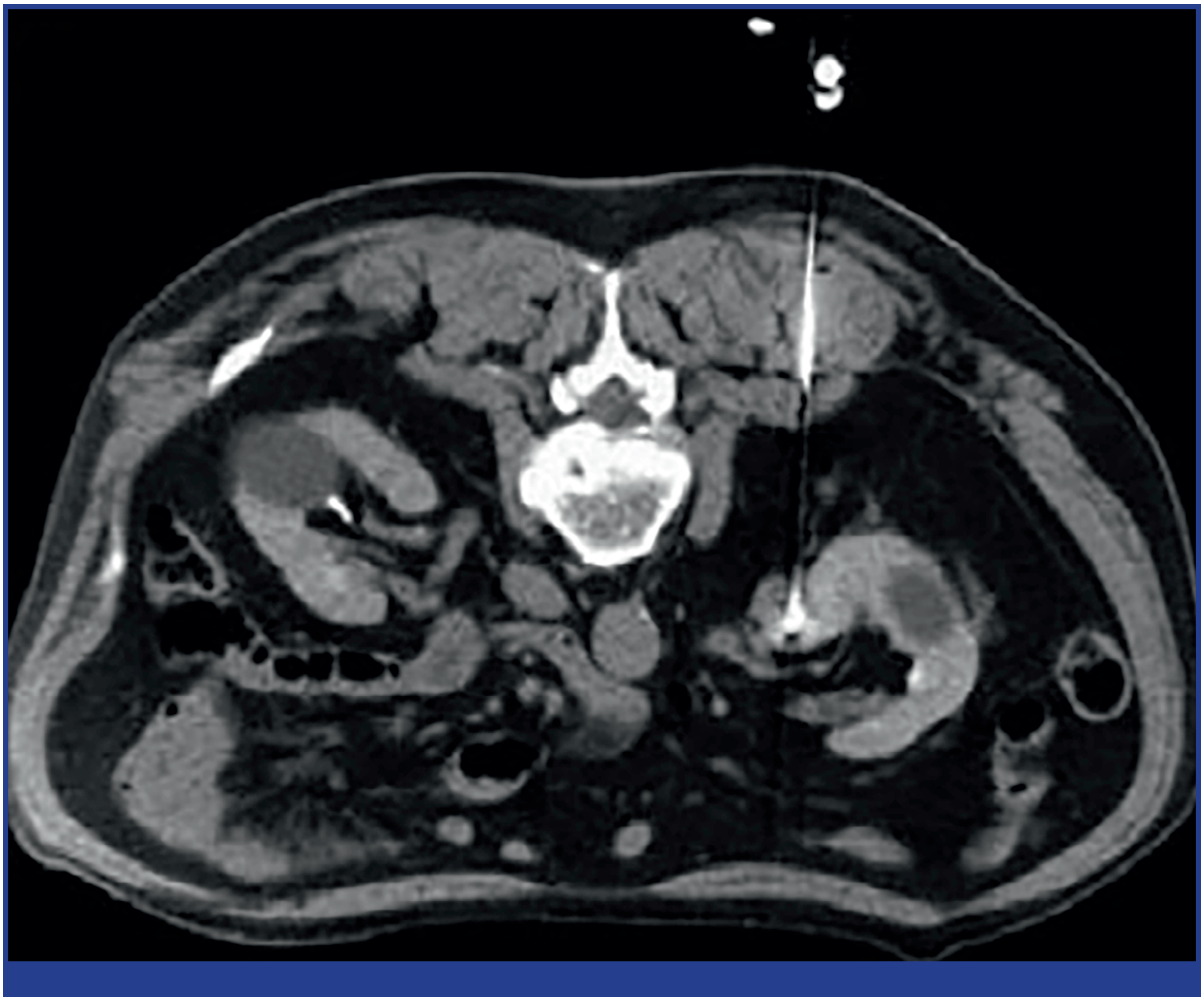

**Figure 2.** The radiofrequency probe is placed percutaneously under CT scan guidance at the margin of the renal tumour.

in the extracellular and intracellular compartments will freeze. The ice crystal formation will disrupt the cellular membrane. During the thawing cycle, the microcirculatory system will be damaged. This physical process of destruction is immediate but the thermal ablation zone then undergoes a series of steps related to vascular damage, and cytokine release resulting in fibrosis and collagen deposition. The specific access route for placing the probes varies among the different case series. Placement could be made via open, laparoscopic or percutaneous approach with image guidance.[11] In a study comparing laparoscopic versus percutaneous cryotherapy, there was no significant difference in the overall survival, cancer specific survival, recurrence free survival as well as complication rates.[12] However, a significant shorter average length of hospital stay was noted with the percutaneous group (2.1 days) compared to the laparoscopic group (3.5 days). For the open and laparoscopic approach, the lesion to be ablated is characterised and measured via ultrasound to determine the number of probes needed *(Figure 1)*. Of note, the size of the ablation zone correlates to probe diameter, that is why two or more probes are inserted in proximity to achieve adequate complete coverage of the tumour.[13] The percutaneous approach uses smaller probes and thus the number needed to be inserted is higher. The insertion is usually monitored using ultrasound, spiral or fluoroscopic CT, or more recently MRI.[14] In case of tumours located adjacent to large blood vessels or organs, temperature probes are needed to assess in real time mode safety as well as efficacy. The uses of a template and/or specific cryotherapy probe configurations are useful in some cases to achieve adequate thermal ablative margin.

## Radiofrequency ablation

RF ablation for clinical stage T1 RCC is usually performed percutaneously *(Figure 2)*.[15] There are several commercially available devices and a variety of electrodes and generators with different feedback and control systems.[16] These devices, either mono- or bipolar, consist of a high-frequency, rapidly alternating electric current generator, two electrodes, and cables.[17] RF ablation is based on the interaction between the delivered current and the biological tissue that acts as the resistive element. The rapidly alternating current causes vibration movement of water contained in the tissue. The frictional agitation at the ionic level leads to heat generation, known as the Joule effect. When the temperature reaches above 45°C, coagulative necrosis and irreversible cell damage occurs. Coagulative necrosis is, generally, achieved with electromagnetic energy sources in the range of 375–500 kHz. The main drawback of RF ablation is that it depends on the thermal conductivity of the adjacent tissues. In order to limit decrease in energy transmission, tissue desiccation and vaporisation should be avoided by gradual tissue energy deposition or by the use of internally cooled electrodes. The heat sink phenomenon due to the presence of adjacent blood vessels is another well-established limitation of the effectiveness of the ablation process. It is noteworthy to mention that there are no differences in the results among the different devices. However, results depend on the operator's experience and the size of the tumour to be ablated. A 1 cm 'ablation margin' is necessary around the treated lesion to cover microscopic tumour extension. The shape of the electrode could help to achieve adequate coverage of the area to be treated. The umbrella shape electrodes and the ability of new electrodes to inject or to infuse saline solution resulted in a larger and more reproducible ablation zone in contemporary series.

## Patient selection

The indications for cryotherapy or RF ablation in RCC have not been definitively established. Elderly and/or comorbid patients considered unfit for surgery with incident cortical small renal masses (≤ 3 cm) and limited life expectancy (≤ 5 years) are preferably advocated ablation.[3] Patients with a genetic predisposition to develop multiple tumours, or with a high risk of complete renal function loss after PN (solitary kidney, renal insufficiency, multiple tumours, and local recurrence) are also offered this type of treatment. Ablation techniques are also indicated for palliation of intractable tumour-related haematuria and/or pain even for benign small renal masses and for the management of symptomatic distant metastases from a primary kidney tumour. Some patients are also treated based on their preference for a minimally invasive approach despite receiving information about the limitations of such an approach. In contrast, the treatment should be avoided in patients with irreversible coagulopathy, sepsis, extensive metastatic disease, or a poor life expectancy (< 1 year). Pacemaker presence is a relative contraindication for RFA. Large tumours or those located at the hilum or near the proximal ureter are not recommended for ablation.[18] Injury to surrounding thermal energy sensitive structures such as the bowel, the duodenum or the pancreas could be avoided using the hydrodissection technique. Central tumours are preferably treated with cryotherapy and are reported to have higher success rates and less risk of injury to the collecting system. Some researchers used the pyeloperfusion technique with RFA for central tumours to avoid injuring the collecting system.[18] For upper pole tumours, a lateral decubitus position on the treating side decreases the risk of pneumothorax. A pre-treatment percutaneous renal core biopsy should always be performed, as imaging does not accurately differentiate benign from malignant disease except in patients with known Von-Hippel Lindau syndrome, hereditary RCCs, and with previous RCC where treatment could be given without the histologic evidence of the disease.[19] An 18-G coaxial biopsy technique is performed usually before the ablation, under local anaesthesia, using ultrasound or CT guidance, but performing the biopsy in the same session with the ablation is more cost-effective. It may be associated with less bleeding and seeding complications due to the ablation of the lesion and the tract after the biopsy. However, in recent years, no cases of seeding of renal tumours have been reported with the coaxial technique that allows multiple biopsies to be sampled. However, the number and location of core biopsies have not been defined. The ideal biopsy strategy with the highest diagnostic yield consists of obtaining, by an experienced operator, two non-fragmented cores with a length of > 1 cm at the periphery of the tumour to avoid necrotic areas.[20]

In case of a complex cystic lesion, combined fine needle aspiration and core biopsies are recommended.[21] Despite this, assessment of Fuhrman grade is inaccurate in 25-50% of cases.[22] The procedure is safe and well-tolerated. Bleeding and pain are self-limited in the majority of cases.[23]

## Oncologic results

In the management of cT1a RCC, both cryotherapy and RFA have demonstrated favourable outcomes with valid local control of the disease. Most studies with intermediate- and long-term oncologic follow-up after RFA have shown RFS rates of > 90%. Psutka et al. reported 96% RFS rates in 143 patients undergoing RFA at a median follow-up of six years.[24] Similarly, Tracy et al. found 93% 5-year RFS rates in 208 patients treated by RFA at a median follow-up of 27 months.[25] CSS and OS rates comparable with those achieved after partial nephrectomy were also described.[26] In the treatment of cT1a RCC, cryotherapy is also highly effective, and investigators have reported promising oncologic outcomes. Johnson et al. examined 92 patients followed for a median of eight years after cryotherapy: in patients with biopsy-proven RCC, RFS and CSS rates were 91% and 98.5%, respectively.[27] Similarly, Aron et al. reported a 92% CSS rate at five years after cryotherapy.[28] Attempts in comparing RFA and cryotherapy have been made, though these are commonly biased by differences in R.E.N.A.L. scores and patient characteristics. However, local recurrence seems more likely after RFA than after cryotherapy, with the latter achieving better local control. The highest level of evidence comes from a meta-analysis of 99 studies, where local recurrences after cryotherapy were significantly lower compared to RFA (4.6% versus 11.7%). Progression to clinical metastasis was also significantly lower with cryotherapy compared to RFA (1.2% versus 2.3%).[29] Moreover, Weight et al. analysed 109 and 192 renal lesions treated respectively by RFA and cryotherapy. All these patients were offered a protocol based biopsy at six months after the treatment. The authors demonstrated significantly higher positive biopsy rates in the RFA compared to the cryotherapy group (35.2% versus 6.2%). Of note, only half of patients with positive biopsy in the RFA group had a documented contrast enhanced lesion on control CT scan.[30] Indeed, the poor correlation between imaging contrast enhancement and biopsy-proven viable neoplastic tissue (as well as the timing of the biopsy) makes oncologic follow-up troublesome after ablative treatment of RCC, as well as comparison across techniques. Finally, no randomised controlled trials compared ablative techniques, RFA or CA, with PN. Match pair analysis and retrospective studies suggest a higher local recurrence rate for ablation compared with PN. A retrospective population-based study of 8,818 incident cases of RCC in the Surveillance, Epidemiology and End Results cancer registry treated with either partial nephrectomy (7,704) or ablation (1,114) demonstrated a two-fold increase in cancer specific mortality in the ablation group. However, the difference was small at five years of follow-up (98.3% with NSS and 96.6% with ablation).

## Morbidity and functional complications

Renal ablative procedures, though minimally invasive, are not devoid of complications. These may be a consequence of the access to the tumour (percutaneous versus laparoscopic) or of the ablation itself. Overall, complications rates range from 7.8-20%, although they depend on patient characteristics, tumour size and position, operator experience and the type of ablative energy source.[18] Although a laparoscopic approach may seem more invasive, investigators found similar complications rates when comparing this to a percutaneous approach in cryotherapy series.[31] Length of hospital stay is generally longer with the laparoscopic access, although patient selection and tumour localisation maybe a major bias when comparing laparoscopic to percutaneous procedures.[32] When examining percutaneous procedures, probe placement is similar between cryotherapy and RFA and access related complications can range from bowel to vessel injury. In cryotherapy, as larger masses can be treated, requiring more probes, bleeding can be more significant and occurs in 3-5% of patients. Atwell et al. reported an increased risk of bleeding with increased number of probes placed and increased tumour size during percutaneous cryotherapy ($p<0.05$). Complications related instead to the ablation technique may vary across series: while bleeding and haematuria are more frequent with cryotherapy, nerve and urothelial injury are more commonly seen after RFA.[33] Globally however, there does not seem to be

## Key messages for clinical practice

1. Cryotherapy and RFA are promising techniques for the management of small renal masses.
2. They have minimal morbidity and yield favourable oncologic outcomes.
3. Careful selection of patients for each technique is fundamental.

any significant difference in complication rate across the two techniques: El Dib et al., in a pooled analysis, reported 19.9% of complications after cryotherapy and 19% after RFA, though comparing highly heterogeneous studies.[34] In a large series analysing 627 patients undergoing cryotherapy and RFA, Schmit et al. found similar complications rates when treating small renal masses, notably 4.3 versus 4.5% for cryotherapy and RFA, respectively.[35] Regarding renal function, the decline varies between 6-25% and is comparable for ablative and extirpative nephron sparing procedures.[36]

## Radiologic evaluation following treatment

The purpose of the follow-up is to diagnose recurrence or persistence of the disease, to monitor renal function and to detect complications. Experts in the domain recommend a contrast-enhanced abdominal CT scan, a chest X-ray and liver and kidney function tests at six weeks, six months, twelve months, and then yearly. Incomplete ablation or persistence of a residual disease is defined as any enhancement within the tumour ablation zone on CT on the initial 6-week imaging, while recurrence is defined as any enhancement or increase in size of the tumour ablation zone, after an initial non-enhancing six weeks CT. These patients are given the option of a repeat salvage ablation or extirpative surgery or even, in some cases, the possibility to undergo active surveillance. It is important to mention that most local recurrences can be treated with repeat ablation but only a subset of patients need salvage surgery. Of note, the surgical approach is very challenging in the salvage setting due to the extensive fibrotic reaction induced by the previous treatment, especially after cryotherapy.[37]

## Conclusion

Cryotherapy and RFA are promising technologies that have proven to exhibit a positive balance between oncologic benefits and surgical harms. However, in the lack of long-term data, implementation of these new modalities should be offered in carefully controlled settings. Further refinements in technique and close co-operation between urologist and radiologist are paramount to the successful treatment of these small renal lesions. Randomised prospective controlled, multi-institutional trials will ultimately lead to better understanding of the full potential of these energy-based procedures.

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