

# Comparison of cryoablation, radiofrequency ablation and high-intensity focused ultrasound for treating small renal tumours

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## INTRODUCTION

Extirpative surgery for renal tumours adheres to the oncological principle of tumour excision with a wide margin. In 1963 Robson [1] established radical nephrectomy as the standard treatment for renal tumours. Improvements in both the understanding of the biology of RCC and in the surgical treatment of renal masses has significantly increased the focus on nephron-sparing treatment options for small renal masses. For tumours of <4 cm in diameter nephron-sparing surgery is as effective as radical nephrectomy for local tumour recurrence rates [2,3]. Additionally, technological advances and improvements in laparoscopic technique have engendered and perpetuated laparoscopic partial nephrectomy (LPN) as a viable treatment option in the hands of experienced laparoscopists [4,5].

A more recent addition to the urologist's options for managing small renal masses has been ablative technologies; these offer an even more minimally invasive approach to small renal masses, as they can be deployed via a laparoscopic or percutaneous approach. While ablation, rather than extirpation, is clearly a paradigm shift in the management of small renal lesions, careful consideration of these technologies is warranted for two reasons. First, there has been tremendous success with minimally invasive approaches including laparoscopic and partial nephrectomy. Second, with the increased application of advanced imaging methods and the discovery of smaller renal lesions, clinicians are probably treating a different population of renal tumours [6].

For an ablative technology to be considered as a clinically viable alternative for oncological applications, two simple criteria must be met. First, an ablative technology must be able to completely destroy all viable tissue, with no areas of viable tissue left. Second, the surgeon must be able to monitor and precisely target the area to be ablated to assure complete tumour destruction and preservation of surrounding vital structures. Ablative methods that can achieve these two basic requirements while allowing a minimally invasive approach may become the future of surgical management of small renal masses.

Herein, we discuss the currently available data on the efficacy and morbidity rates of the most promising ablative technologies, i.e. cryoablation, radiofrequency ablation (RFA) and high-intensity focused ultrasound (HIFU).

## CRYOABLATION

Cryoprobes can achieve tissue temperatures as low as  $-190^{\circ}\text{C}$  by exploiting the Joule-Thompson effect. Typically, compressed argon gas is allowed to expand through a small orifice, producing temperatures well below those required to ablate normal renal tissue ( $-19.4^{\circ}\text{C}$ ) [7] and cancer cells ( $-40^{\circ}\text{C}$ ) [8]. The histological result of cryoablation is a confluent coagulative necrosis within the cryolesion, with eventual fibrosis and scarring [7].

Renal cryoablation can be accomplished using an open surgical technique, a laparoscopic approach, or via a percutaneous procedure. The ice-ball achieved with cryoablation technology can be readily identified and actively observed with ultrasonography (usually during a laparoscopic or open surgical approach) or with axial MRI or CT (usually during percutaneous procedures). Techniques using a single larger or several smaller cryoprobes (available at  $\geq 1.47$  mm)

may be used depending on the size of the renal mass and the surgeon's preference. Most commonly, a 'double-freeze' cycle (freezing beyond the margins of the tumour, thaw, and second freeze cycle) is used to increase the size of the cryolesion with either active or passive thawing after each cycle. Active thawing with helium gas serves to expedite the procedure and has been shown not to compromise total tissue ablation [9]. With cryoablation, real-time ultrasonographic monitoring of the growing ice-ball allows the surgeon to visualize the ablative process, and ensures that the ice-ball extends beyond the targeted area in every dimension. The edge of the ice-ball is at  $0^{\circ}\text{C}$ , which is inadequate for ablation. Therefore, when possible, the ice-ball is extended  $\approx 10$  mm beyond the margin of the tumour. This 10 mm margin incorporates the 'indeterminate zone' (the outer few millimetres of the ice-ball that are not ablative) and a margin of normal renal parenchyma to optimize oncological control. In the authors' laparoscopic cryoablation experience, the 1.47 mm cryoprobes (IceRods, Oncura, Plymouth Meeting, PA, USA) can be safely removed from the area of ablation after thawing, with no haemostatic measures such as fibrin glue or Floseal (Baxter, Deerfield, IL, USA) application. Typically, gentle momentary pressure with haemostatic material such as Surgicel is adequate for complete haemostasis. When larger cryoablation probes are used, the probe tract can be filled with a haemostatic agent such as fibrin glue or Floseal, with excellent haemostatic results. Table 1 [10–17] summarizes the reported cryoablation series; with a combined total of 326 reported cases and a mean follow-up of 30.8 months, the tumour persistent or recurrent disease rate is 4.6% and the complication rate 10.6%.

## RFA

Contemporary RFA probes are inserted as one needle and deploy up to 10 umbrella-like wire

TABLE 1 Summary of cryoablation series

Reference	Technique	N patients	Median follow-up, months	N (%) persistent/recurrent disease	Morbidity, n (%)
Hasan <i>et al.</i> [10]	Laparoscopic	40	48	2	NA
Rodriguez <i>et al.</i> [11]	3 lap/4 open	7	14.2	0	1 pelvic thrombus 1 CVA
Harmon <i>et al.</i> [12]	39 lap/37 open	76	17	3	6 capsular fractures 2 prolonged ileus 1 CVA
Nadler <i>et al.</i> [13]	Laparoscopic	15	15	1	1 respiratory failure 1 prolonged ileus
Lee <i>et al.</i> [14]	Laparoscopic	20	14.2	1	1 pancreatic injury
Steinberg <i>et al.</i> [15]	Laparoscopic	70	49.3	1	NA
Shingleton <i>et al.</i> [16]	MRI-guided	90	30	7	1 perinephric haematoma 8 minor
Colon <i>et al.</i> [17]	Laparoscopic	8	8	0	0
<b>Overall</b>		<b>326</b>	<b>30.8</b>	<b>15 (4.6)</b>	<b>23 (10.6)</b>

CVA, cerebrovascular accident; NA, not available.

electrodes into the tissue when activated; these probes then achieve temperatures that exceed the required 70 °C for complete tissue ablation. RFA probes deliver a monopolar alternating current of 400–500 kHz in the RF range of the electromagnetic spectrum to the renal tissues [18]. An expanding sphere of coagulative necrosis results from each electrode. Initial reports by several authors have questioned the reliability of the 'killing' zone after RFA, with evidence of viable tumour cells remaining within RFA-treated renal masses [19–21]. However, there is increasing evidence showing that the viable tissue documented by these authors may be a fixation effect of RF energy. More precise viability studies with NADH-diaphorase staining showed that RFA probably results in complete tissue ablation [22,23]. Acutely, RF does not spare the renal urothelium during ablation, but healing of the urothelium over time after RFA has been suggested [24].

As with cryoablation, RFA can be delivered via an open or laparoscopic surgical or percutaneous approach. Contemporary imaging methods allow for precise positioning of the RFA probes. However, the process of RFA itself cannot be actively monitored in real-time imaging without contrast-medium enhancement. While this remains a limitation of current RFA, recent animal studies suggest that contrast-enhanced ultrasonography may alleviate this problem [25].

The adequacy of the ablation is assessed by temperature or impedance data from RF generators. The RF interstitial tumour ablation generator (RITA Medical Systems, Mountain View, CA, USA) is temperature-based. The manufacturer recommends maintaining temperatures of >100 °C for 8 min for thorough tissue ablation. The radiotherapeutics generator delivers RF energy via an impedance-based system. The manufacturer recommends increasing the power gradually to 90 W to achieve an impedance of >200 Ω. Both systems provide equivalent ablative results [26]. With RFA, the procedure may also vary by the number of RF cycles, although two cycles are most typical.

Conventional 'dry' RFA is defined as the probe, or tines from the probe, interacting directly with the tissue. Dry RFA is limited by the high current density at the electrode–tissue interface, which results in high temperatures (>100 °C) with tissue desiccation and vaporization at <1 mm from the electrode. The tissue charring raises local impedance, which can decrease effective ablation further from the probe [27]. 'Wet' RFA was developed to circumvent the problem associated with these high tissue temperatures. Interstitial saline is infused while applying the RF energy. The saline spreads the current density and heat away from the electrode and into the tissue, resulting in more extensive ablation [28]. Alternatively, high temperatures at the electrode–tissue interface can be controlled

by circulating water internally through the electrode in an impedance-controlled system to keep the tip cool (Cool-Tip™, Radionics, Burlington, MA, USA) [29]. Originally, 'low-energy' ablations were accomplished with generators providing 90 W of power. These early generation devices have been replaced as they were ineffective. Presently, newer generators provide 'high-energy' ablation, with power levels up to 200 W. Table 2 [30–39] summarizes reported RFA series; with a combined total of 277 reported cases and a mean follow-up of 10.0 months, the persistent or recurrent disease rate is 7.9% and the complication rate 13.9%.

## HIFU

HIFU ablation results from ultrasound waves which are generated by piezoelectric elements and focused by an acoustic lens or parabolic reflectors [40]. At 0.8–1.6 MHz frequency, tissue penetration is sufficient for focal lengths of 100–160 mm. HIFU energy is absorbed by tissues and results in temperatures within the focal area sufficient for protein denaturation and coagulative necrosis. Tissue cavitation occurs with intensities of 5000–20 000 W/cm<sup>2</sup> and allows for real-time ultrasonographic monitoring. Large tumours can be treated with a narrow focal area by moving the transducer to cover the entire target. However, difficulty with targeting can result from patient respiration,

TABLE 2 Summary of RFA series

Reference	Technique	N patients	Median follow-up, months	N (%) persistent recurrent disease	Morbidity, n (%)
Matsumoto <i>et al.</i> [30]	Laparoscopic	28	13	1	1 PUJ obstruction 2 minor
DiMarco <i>et al.</i> [31]	US/CT guided	66	9	3	1 PUJ obstruction 2 chronic lumbar pain 1 renal infarct 1 major haemorrhage 1 subcapsular haematoma
de Baere <i>et al.</i> [32]	US/CT guided 200 W	5	9	0	
Hwang <i>et al.</i> [33]	9 Laparoscopic 8 US/CT guided 200 W	17	12.7	1	1 PUJ obstruction
Roy-Choudhury <i>et al.</i> [34]	US/CT guided 200 W	8	17.1	1	2 renal infarcts 1 psoas thermal injury
Mayo-Smith <i>et al.</i> [35]	US/CT guided 200 W	32	9	2	2 perinephric haematomas 1 probe site skin met
Su <i>et al.</i> [36]	CT guided 90 W	29	9	2	8 haematomas 1 thermal hepatic injury 1 aspiration/death
McGovern <i>et al.</i> [37]	CT guided	62	9.9	7	NA
Lisson <i>et al.</i> [38]	CT guided	21	12.1	3	NA
Ukimura <i>et al.</i> [39]	US/CT guided 100 W	9	17	2	1 perinephric haematoma
<b>Overall</b>		<b>277</b>	<b>10.0</b>	<b>22 (7.9)</b>	<b>27 (13.9)</b>

interposed ribs, or poorly circumscribed tumours.

Although laparoscopic ultrasound probes capable of delivering HIFU ablative energy have been developed, the main theoretical advantage of tissue ablation with HIFU remains the capacity for a truly minimally invasive approach with transcutaneous, totally extracorporeal, tumour ablation.

Very limited data are currently available on the application of HIFU for ablating renal tumours. Kohrmann *et al.* [40] reported treating a patient with three renal tumours, with curative intent. Two lower pole tumours shrank after treatment but the upper pole tumour was not affected because the ultrasound energy was absorbed by the interposed ribs. One procedure was complicated by a skin burn due to improper coupling.

Marberger *et al.* [41] reported treating 16 patients who had renal tumours; two were treated with curative intent (70 pulses, 6 s duration, 1.8 kW), but follow-up MRI revealed incomplete radiological remission. A

10 × 10 mm area of renal tumour was treated, followed by immediate surgical excision in the remaining 14 patients. Areas of acute tissue necrosis measuring 15–35% of the total targeted area were detected in nine patients. Skin erythema was noted in five patients.

In a phase II clinical trial conducted at the Churchill Hospital, Oxford, UK, four patients with renal tumours were treated with HIFU [41]. Six weeks after HIFU, three of the four patients had surgical excision, with no conclusive evidence of ablation; there were no skin burns.

Wu *et al.* [42] reported treating 13 patients with renal tumours; 10 were treated palliatively for advanced or metastatic disease and three with curative intent for local disease. The authors reported only the results from the palliation, with haematuria resolving in seven of eight patients and tumour-related pain decreasing in nine of 10. With a median follow-up of 14.1 months, the treated tumours decreased by 58% and one disappeared radiographically. One procedure was complicated by a skin burn that healed spontaneously.

## DISCUSSION

Ablative methods for managing small renal masses show great promise as a minimally invasive strategy for treating them. Also, with existing technologies, the degree of technical expertise required to perform ablative procedures is significantly less than that needed for LPN. However, to date, as oncological considerations are paramount, all ablative technologies still require long-term follow-up results before they are considered as a standard of care.

In an effort to contrast these ablative techniques to currently available minimally invasive options, a comparison with LPN is indicated, because LPN is an existing minimally invasive strategy that uses the proven doctrine of tumour extirpation with a margin of normal tissue. Results of major LPN series are summarized in Table 3 [5,43–48]. A direct comparison of key aspects of ablative technologies and LPN is shown in Table 4.

While all the methods discussed are typically considered 'minimally invasive', there are significant differences among the surgical

TABLE 3 Summary of LPN series

Reference	N patients	Median follow-up, months	N positive margins/recurrences	Morbidity, n (%)
Seifman <i>et al.</i> [43]	40	25	1	13 (33)
Allaf <i>et al.</i> [44]	48	37.7	3	NA
Janetschek <i>et al.</i> [45]	25	22.2	0	3 (12)
Harmon <i>et al.</i> [46]	15	8	0	0
Gill <i>et al.</i> [5]	100	18	3	21 (21)
Guillonnet <i>et al.</i> [47]	12	12.2	0	3
Simon <i>et al.</i> [48]	19	8.2	0	4 (21)
<b>Overall</b>	<b>259</b>	<b>21.6</b>	<b>7 (2.7)</b>	<b>44 (21)</b>

TABLE 4 Comparison of ablative techniques with LPN

Characteristic	LPN	Cryoablation	RFA	HIFU
Limited by intrarenal tumour location	No	No	Yes	Yes
Access	Laparoscopic	Laparoscopic or or percutaneous	Laparoscopic or percutaneous	Extracorporeal
Complete tumour resection/ablation	Yes	Yes	Yes	No
Monitoring resection/ablation	Real-time US	Real-time US	Requires CE	Real-time US if cavitation present
Recurrence rate, %	2.7	4.6	7.9	Not proven curative
Morbidity rate, %	20.9	10.6	13.9	Common skin burns

US, ultrasonography; CE, contrast-enhancement.

approaches. Laparoscopic access, while significantly less invasive than an open approach, remains significantly more invasive than percutaneous access. Indeed, laparoscopy may eventually be considered a 'moderately invasive approach' as therapeutic alternatives develop toward a percutaneous, natural orifice, or transcutaneous model. Presently, cryoablation and RFA technologies can be deployed via laparoscopic or percutaneous access routes. HIFU, while still experimental, is the only ablative method that offers the promise of a noninvasive approach to treating renal tumours.

Continuous real-time ultrasonography provides excellent monitoring of tumour resection during LPN and during cryoablation. Monitoring tumour ablation has been a shortcoming for RFA. Simultaneous contrast enhancement, with its associated risks, is necessary for radiologically assessing complete tumour ablation during RFA. Monitoring of HIFU ablation is only reliable if tumour cavitation occurs.

At present, ablative technologies show great promise and are a good clinical alternative for carefully selected patients. The available

recurrence rates of LPN and all ablative techniques are premature, as 5-year data are lacking. However, it is clear that LPN has a lower recurrence rate than the currently existing ablative technologies. Among the latter, cryoablation has the lowest recurrence rate and the least morbidity, and the morbidity rates of all the ablative technologies compare favourably to that of LPN.

## CONCLUSION

Ablative methods such as cryoablation and RFA show great promise for treating small renal masses. While follow-up data are lacking, initial reports show that cryoablation produces recurrence rates approaching, and morbidity rates significantly less, than those of LPN. Also, cryoablation is technically easier to do than LPN. Compared to cryoablation, there are fewer results available for RFA, but RFA may also represent a viable clinical alternative for treating small renal masses. HIFU technology has not been shown to give adequate tumour control and should not be considered a viable clinical alternative. We remain cautiously optimistic about the future

of ablative techniques, with the anticipation of 5- and 10-year follow-up data.

## CONFLICT OF INTEREST

None declared.

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**Abbreviations:** **RF(A)**, radiofrequency (ablation); **HIFU**, high-intensity focused ultrasound; **LPN**, laparoscopic partial nephrectomy.