

# Surgical cryoablation as an option for small renal masses in patients who are not ideal partial nephrectomy candidates: intermediate-term outcomes

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## Abstract

**Objective:** There has been increasing interest in surveillance and ablative techniques for small renal masses (SRM), given the increasing number being diagnosed at smaller sizes. Of the currently available ablative techniques, radiofrequency ablation and cryoablation have been the popular ones. We describe our intermediate-term outcomes with using cryoablation for SRM in patients who were not ideal candidates for partial nephrectomy.

**Materials and methods:** Nineteen patients treated with cryoablation were included. Patients with renal lesions <4 cm were considered for cryoablation, and all patients were treated between 2002 and 2007. Access was either laparoscopic (transperitoneal) or via open surgical techniques. From 2002 to 2004, the CryoCare System (Endocare, Inc., Irvine, CA) was used, with probe sizes ranging from 3 to 5 mm. Before 2004, the SeedNet system (Galil Medical, Arden Hills, MN) was used, with 17-gauge (1.47 mm) IceRod cryoneedles. Recurrence-free survival (RFS) and overall survival (OS) were calculated using Kaplan Meier methodology.

**Results:** The mean age was 56.7 years. The mean tumour size was 2.6 cm (range 1.2–4.0 cm). There were no intraoperative or postoperative complications in the 19 patients. One patient has been lost to follow-up; mean follow up was 41.6 months (range 7–84 months) in the cohort. Recurrence, defined as either increase in size of lesion or enhancement on follow-up imaging, was seen in 4 patients. There was 1 non-cancer specific death, and 1 cancer specific death.

**Conclusions:** The 4-year RFS rate and OS rate were 83.6% and 94.1%, respectively, in patients with SRM who were unsuitable for partial nephrectomy.

étaient considérés, et tous les patients ont été traités entre 2002 et 2007. L'abord se faisait par laparoscopie (transpéritonéale) ou par chirurgie ouverte. De 2002 à 2004, on a eu recours au système CryoCare (Endocare, Inc., Irvine, Calif.), avec des sondes de 3 à 5 mm. Avant 2004, on utilisait le système SeedNet<sup>MC</sup> (Galil Medical, Arden Hills, Minn.), avec des cryo-aiguilles IceRod de calibre 17 (1,47 mm). Les taux de survie sans récurrence (SSR) et de survie globale (SG) ont été calculés par la méthode de Kaplan Meier.

**Résultats :** L'âge moyen était de 56,7 ans; la taille moyenne des tumeurs était de 2,6 cm (de 1,2 à 4,0 cm). Aucun des 19 patients n'a présenté de complication intra ou postopératoire. Un patient a été perdu de vue lors du suivi. La durée moyenne du suivi était de 41,6 mois (7 à 84 mois). Quatre patients ont présenté une récurrence, définie comme une augmentation de la taille de la lésion ou une lésion plus visible lors des épreuves d'imagerie de suivi. Un patient est décédé de causes non liées au cancer, et un autre, des suites du cancer.

**Conclusions :** Les taux de SSR et de SG après 4 ans étaient de 83,6 % et de 94,1 %, respectivement, chez des patients avec petites masses rénales à qui une néphrectomie partielle ne convenait pas.

## Introduction

Between 1996 to 2005, the incidence of renal cell carcinoma (RCC) in Canada has been rising (especially in young women), possibly due to the rising prevalence of obesity and improved detection. The most recent Canadian cancer statistics show that for 2009 there will be an expected 4600 cases, with an expected 1600 deaths.<sup>1</sup>

There has been increasing interest in surveillance and ablative techniques for small renal masses, given the increasing number being diagnosed at smaller sizes.<sup>2</sup> Furthermore, histopathology results show that 20% to 27.9% of clinical T1 renal masses are benign in large partial nephrectomy series.<sup>3,4</sup> Of the currently available ablative techniques, interest is on radiofrequency ablation and cryoablation. Both of these ablative techniques can be performed percutaneously or via surgical techniques (either open or laparoscopic). With the main alternative to ablative techniques being either radical nephrectomy or partial nephrectomy, the perceived benefits of ablative techniques include lower postoperative morbidity and improved renal preservation.

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## Résumé

**Objectif :** Le diagnostic étant de plus en plus précoce, on note un intérêt croissant pour les techniques de surveillance et d'ablation des petites masses rénales. Parmi les techniques actuelles, l'ablation par radiofréquence et la cryoablation sont les plus utilisées. Nous présentons ici nos résultats à moyen terme avec la cryoablation de petites masses rénales chez des patients à qui la néphrectomie partielle ne convenait pas.

**Matériel et méthodologie :** Dix-neuf patients traités par cryoablation ont été inclus. Les patients présentant des lésions rénales de < 4 cm

The main disadvantage to ablative techniques is the lack of histopathological confirmation of complete ablation, with patients requiring careful follow-up. There have been few reports describing the intermediate-term efficacy of laparoscopic cryoablation for renal masses. We describe our medium-term outcomes using cryoablation for small renal masses in patients who were not ideal candidates for partial nephrectomy.

## Methods

Since 2002, renal cryoablation has been offered at the University of Western Ontario for patients who were not ideal surgical candidates with renal lesions <4 cm. Between 2002 and 2007, 19 patients were treated with cryoablation. Indications for cryoablation were medical comorbidities in 9 patients (American Society of Anesthesiologists [ASA] 3) and surgical considerations in the other 10 (including solitary kidneys, previous renal surgery and anatomical considerations related to partial nephrectomy). Access was either laparoscopic (11 patients) or via open surgical techniques (8 patients).

Most patients underwent a biopsy prior to starting cryoablation for diagnostic purposes, unless prior imaging had indicated a definitive diagnosis (e.g., if the prior imaging was consistent with angiomyolipoma, then biopsy was not undertaken). Trucut biopsy was performed after mobilization of the kidney, and prior to cryoablation.

Before 2004, the CryoCare system (Endocare, Inc., Irvine, CA) (which is argon based) was used, with probe sizes ranging from 3 mm to 5 mm. Subsequent to 2004, the SeedNet system (Galil Medical, Arden Hills, MN) was used, with 1.47 mm IceRods. Cryoablation was performed either by open or laparoscopic access. In all cases, real-time ultrasound guidance was used to localize the tumour and to monitor the progression of iceball formation, which is very visible as a hyperechoic edge. A double freeze-thaw cycle was used.

Patients were followed-up using serial imaging, usually with computed tomography (CT) scanning or ultrasound. For patients with renal insufficiency, magnetic resonance imaging was used in place of CT scanning. Lack of enhancement and stability or reduction in size of the lesion on follow-up imaging was considered a successful cryoablation.<sup>5</sup>

Statistical analysis was performed using StataC 10.1 (StatCorp, College Station, TX), and survival was calculated using Kaplan Meier techniques. A paired students t-test was used to test for any significant differences between preoperative and postoperative serum creatinine levels.

## Results

The mean age was 56.7 years (range 27-78), and there were 6 females and 13 males. The mean tumour size was 2.6 cm (range 1.2-4.0). In total, 21 renal masses were ablated in 19 patients (Table 1).

Eight patients underwent open cryoablation, with the remaining 11 patients had transperitoneal laparoscopic cryoablation. None of the laparoscopic group required conversion to an open procedure. Seven tumours were located at the lower pole, 7 were interpolar and 5 tumours were located at the upper pole. There were no intraoperative complications. The mean hospital stay was 4.8 days for the open surgical group, and 2.6 days for the laparoscopic group. No patient required a blood transfusion and there was no statistically significant difference between preoperative and postoperative serum creatinine levels (89 vs. 98;  $p = 0.29$ ). Biopsy was performed intra-operatively in 14 patients prior to cryoablation. The biopsy showed RCC in 9 cases (64%), benign histology in 4 cases, and was non-diagnostic in 1 case.

At the mean follow-up of 41.6 months, 1 patient was lost to follow-up.

Recurrence, defined as either an increase in size of the lesion or enhancement on follow-up imaging, was seen in 4 patients. Recurrences occurred at 28 months, 37 months, 54 months and 55 months, respectively; the mean time to recurrence was 43.5 months. The 4-year recurrence-free survival rate was 83.6%. One patient with local recurrence eventually developed metastatic disease and died, and there was 1 non-cancer related death. The 4-year overall survival rate was 94.1%. No patient developed renal failure during follow-up.

## Discussion

Cryoablation dates back to the Egyptian and Ancient Greek civilizations. Modern cryoablation began in 1961, when

**Table 1. Preoperative characteristics**

No. of patients	19
Mean age $\pm$ (SD)	56.7 $\pm$ (16.0) yrs
Mean ASA	2.4
No. of patients with 2 masses ablated	2
Mean tumour diameter $\pm$ (SD)	2.6 $\pm$ (0.7) cm
Distribution of tumours	
Lower pole	37%
Interpolar	37%
Upper pole	26%
No. of patients with solitary kidneys	3

SD = standard deviation; ASA = American Society of Anesthesiologists score.

neurosurgeon Irving Cooper and his colleagues performed a stereotactic thalamectomy using liquid nitrogen. In 1995, Uchida and colleagues described the use of percutaneous renal cryoablation on 2 patients with advanced RCC.<sup>6</sup> Porcine work in 1998 established a lethal temperature of  $-19.4^{\circ}\text{C}$  in the kidney.<sup>7</sup> The mechanism of action of renal cryoablation is believed to be a combination of cell rupture, necrosis (both primary and secondary) and freezing induced apoptosis in cells with intact membranes. Recent work using the human renal cell cancer line 786-O has shown that freezing to below  $-20^{\circ}\text{C}$  causes complete cell death within all cells,<sup>8</sup> unlike work in prostate cancer cells which has shown that some cells survive at  $-80^{\circ}\text{C}$ .<sup>9</sup>

Our cohort had good outcomes following renal cryoablation, with a 4-year overall survival of 94.1%, and a 4-year recurrence-free survival rate of 83.6% at a median follow-up of 41.6 months. This outcome is comparable to published recurrence-free survival results, which ranged from 93.3% to 95.8%.<sup>10,11</sup> The major limitation with the published literature is the short follow-up, with most studies ranging from 6 to 24 months; there are limited published series with mean follow-up exceeding 3 years (Table 2).<sup>12-14</sup> A recent meta-analysis found the mean weighted follow-up of the published cryoablation literature to be 18.3 months.<sup>2</sup>

This present study demonstrated the low morbidity of renal cryoablation, especially compared to the published complication rates of partial nephrectomy.<sup>15</sup> However, we noted that other published complications of renal cryoablation include bleeding requiring transfusion, bowel injury and renal fracture. Despite the absence of complications within our series, it is difficult to draw conclusions due to the low number of patients in our report, which is one of the limitations of our study. A recently published European multicentre study found that Clavien grade  $\geq 3$  complications occurred in only 4% of cases.<sup>16</sup>

Newer developments in minimally invasive urology, such as laparo-endoscopic single-site surgery (LESS)<sup>17,18</sup> or natural orifice transluminal endoscopic surgery (NOTES),<sup>18</sup> continue to miniaturize instruments and are suited to procedures, such as renal cryotherapy. Further refinements in instrumentation or careful patient selection are required prior to the adoption of these technologies. Nevertheless, with evidence mounting for the need to preserve as much renal parenchyma as possible, ablative technologies which require no clamping of the renal hilum will continue to play a role in the urological armamentarium; therefore, the development of newer technologies, such as LESS, should be encouraged within a controlled and regulated environment.

Surprisingly, our 2 recurrences occurred late, both after 4 years of follow-up. In the published literature, most recurrences occur early, typically within the first 2 years. These 2 late recurrences serve to underscore one of the current controversies in renal cryotherapy – the optimal follow-up

**Table 2. Published series with mean follow up exceeding 3 years**

Authors	Year	Patients (n)	Follow-up (mos)	Recurrences (%)	Overall survival
Davol <sup>12</sup>	2006	48	64	5 (12.5%)	89.6%
Weld <sup>13</sup>	2007	31	45.7	1 (3.2%)	N/R
Gill <sup>14</sup>	2005	56	36	2 (3.6%)	89%

schedule for these patients.

The ideal schedule is yet to be determined. Some groups have advocated using repeat biopsy with serial imaging; others have used serial imaging alone.<sup>5</sup> The problems with renal biopsy are well-known. These problems preclude its routine use in clinical practice, in that a negative biopsy does not exclude cancer, and also because of the difficulty for pathologists to distinguish between chromophobic RCC and oncocytoma. Furthermore, in the context of a positive biopsy with no growth on serial imaging, some would argue that such patients could be effectively managed with active surveillance; currently a randomized clinical trial is underway to study the outcomes of surveillance for small renal masses. We would recommend long-term imaging follow-up, exceeding 5 years at the minimum, based on our pattern of recurrences.

Limitations of this study include its retrospective nature, the lack of clearly defined inclusion criteria, and the lack of repeat biopsies on patients after cryoablation to confirm the absence of viable tumour. However, a negative biopsy does not exclude cancer, and so we kept our patients on a follow-up schedule which was imaging-based. Furthermore, current thinking on the small renal mass has changed from 2002,<sup>19</sup> such that some patients may be candidates for active surveillance.

Percutaneous renal cryoablation has been increasingly reported in the last 5 years, with comparable efficacy rates to laparoscopic cryoablation,<sup>20,21</sup> although more than one treatment session may be needed. The morbidity and costs may be lower with the percutaneous approach,<sup>21,22</sup> and in some institutions percutaneous renal cryoablation has become the preferred treatment modality for the asymptomatic small renal mass.<sup>10</sup> In most institutions, however, the techniques of laparoscopic and percutaneous cryoablation are complementary, with the percutaneous approach being used for posteriorly located tumours and the laparoscopic approach being used for the remainder.<sup>23</sup> Percutaneous cryoablation was not available in the early part of the study period at our institution; however, it is now part of our armamentarium. Novel ideas, such as using injected air or saline to displace vital structures (such as bowel), have been used to expand the use of percutaneous renal cryotherapy.<sup>24</sup>

## Conclusion

Further prospective studies with longer follow up are needed to determine the exact role of cryoablation to treat small renal masses; however, preliminary data are encouraging. The 4-year recurrence-free survival rate was 83.6% and the 4-year overall survival rate was 94.1%. Long-term follow-up is required in these patients, as demonstrated by the mean time to recurrence of 43.5 months.

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