Efficacy of Laparoscopic Renal Cryoablation as an Alternative Treatment for Small Renal Mass in Patients with Poor Operability: Experience from the Korean Single Center

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Abstract

Objective: The aim of this work was to evaluate the efficacy and safety of laparoscopic renal cryoablation (LRC) for the treatment of incidentally found small renal masses in patients with poor operability, from our initial experience in Korea.

Materials and Methods: From June 2005 to April 2009, surgical and oncologic outcomes were evaluated from a database of 45 renal tumors in 39 patients who underwent LRC due to a high American Society of Anesthesiology (ASA) physical status score (i.e., over 3) or old age (i.e., over 70 years old).

Results: Mean (range) age was 63.3 years (range, 43–81), and mean tumor size was 2.5 cm (range 0.7–3.9). Mean of ASA physical status score of whole patients was 2.8 (range, 1–4), and 79.4% (31/39) of patients had an ASA physical status score over 3. Eleven patients (28.2%) were over 70 years old. Among 45 treated lesions, 23 (51.1%) were exophytic tumors, 17 (37.8%) were endophytic tumors, and the other 5 (11.1%) were mesophytic tumors. Mean operating time was 173.7 minutes (range, 110–220), and mean blood loss was 106.3 mL (range, 40–150). None of the patients developed major complications, including adjacent organ injury, collecting system injury, open surgical conversion, or conversion to nephrectomy. Pathologic examination revealed that 60% (27/45) of lesions were renal-cell carcinoma (RCC). During a mean follow-up duration of 23.5 months (range, 6–53), radiologic evidence of tumor recurrence was found in 1 patient (3.7% for RCC). With the exception of this patient, all other patients have remained free of recurrence or metastasis, as determined by a periodic radiologic work-up. Serum creatinine remains stable, with no statistical difference, compared to preoperative levels, in both whole patients and patients with solitary kidney.

Conclusions: In this series, LRC for small renal tumors showed favorable oncologic and surgical outcomes, including maintenance of renal function, without adverse effects in selected patients with poor operability.

Introduction

TREATMENT OPTIONS for small renal masses have expanded over the past decade. Increased use of cross-sectional images during the same period led to “stage migration,” with most masses being diagnosed at an early stage.¹ For these small renal masses, partial nephrectomy has replaced radical nephrectomy as the treatment of choice. However, some patients may be poor candidates or unwilling to accept the risks of surgical resection therapy. Actually, median age at the diagnosis of renal-cell carcinoma (RCC) is approximately 65 years,² and these patients may have accrued

an extensive list of comorbidities that could complicate recovery. As surgical techniques have improved, perioperative morbidity of surgical resection has decreased; however, it remains a relative risk for some elderly patients and for other high-operative-risk populations.^{3,4}

Interest in ablative techniques that destroy tumor tissue, instead of removing it, has grown, mainly due to decreased morbidity and preservation of renal function.^{5–7} Thus, for the patient with advanced age or significant comorbidities who prefer a proactive approach, but are not considered good candidates for conventional surgery, ablation can be an attractive alternative treatment method. Among alternative

ablation modalities, data suggest that cryoablation may result in significantly lower rates of local tumor progression, compared with radiofrequency ablation (RFA) techniques.⁸ In particular, compared to a percutaneous approach, laparoscopic renal cryoablation (LRC) allows the surgeon to position the cryoprobe with greater precision while using intraoperative ultrasonography and to move adjacent organs away from the ablation site, with the ability to monitor and control bleeding during the procedure. However, renal cryoablation is currently in its investigational stage, and data on long-term outcome are lacking. This means that more clinical data for various populations are still needed for validation of this technique. In Korea, LRC was initially conducted, in our institution, from June 2005, mainly for patients with poor operability. In this article, we present the early- to intermediate-term outcome of LRC from our experience. To the best of our knowledge, this is the first report on LRC in Asian lesions.

Materials and Methods

Patients enrolled and data collection

From June 2005 to April 2009, LRC was performed on 45 renal tumors in 39 patients at our institution. Indications for LRC included the presence of a localized, solid, enhancing renal mass smaller than 4 cm in patients with high risk for partial nephrectomy or age of greater than 70 years.⁹ High operative risk in our institution was defined as an American Society of Anesthesiology (ASA) physical status score over 3.¹⁰ Among these inclusion criteria for LRC, absolute indications included bilateral tumors and patients with a solitary kidney or renal insufficiency. Patients with normal contralateral renal function, but poor operability, were defined as an elective indication. All patients underwent a preoperative radiologic evaluation with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), in the case of renal insufficiency, in order to delineate the parameters of the renal lesion, including location, size, depth, and position relative to hilar vessels and the collecting system. All imaging studies were performed within our hospital facility, according to the standard renal protocol, with 3-mm slice cuts.

All RCC patients who underwent LRC in our institution were registered in a specific database that includes all important information pertaining to tumor and patient characteristics, including ASA physical status score, operative time, estimated blood loss, hospital stay, pathology findings, and complication rates, and were followed up under the same strict guidelines. Patients were initially evaluated at 1 and 3 months and, then, every 3 months during the first year. They were evaluated every 6 months during the second year and, then, annually.¹¹ Follow-up evaluations involved a medical history update, physical examination, blood-pressure check, contrast-enhanced CT or MRI, chest radiography, serum electrolytes, and renal function tests. A lack of enhancement on CT or MRI scans, along with stable or decreased tumor size, was considered a sign of successful treatment. Recurrence was defined as increasing tumor size or lack of tumor shrinkage, as shown with image enhancement.¹²

Operative technique

A single surgeon (SHK) performed all LRC procedures. Standardized instruments, with three ports, were used for the

laparoscopic procedure. Tumors anterior to a horizontal line within the coronal plane through the renal hilum were generally approached transperitoneally. Tumors posterior to this line were approached retroperitoneally. The kidney surface was exposed and mobilized within Gerota's fascia, to the extent required for complete visualization of the renal masses under laparoscopy or ultrasonography image. Fat overlying the tumor was retrieved for pathologic examination. Real-time intraoperative ultrasonography (AlokaDynaview II; Americanlab, Miami, FL) was then used, in all cases, to identify the lesion and determine the position of the cryoprobe within the lesion (Fig. 1). In some, but not all, cases with a completely endophytic tumor, complete mobilization of the kidney was necessary to acquire the adequate image from the opposite side of the kidney with intraoperative ultrasound. Before the insertion of the cryoprobes, depending on tumor size before the insertion of a cryoprobe, one or two needle biopsies, with an 18-gauge core, were taken from the tumor under visual and ultrasonographic control. We used two types of cryoprobe, both with a diameter of 1.47 mm. A cryoprobe (Oncura, Plymouth Meeting, PA), which induced a -40°C isothermal lesion measuring 8 mm in diameter, was used from June 2005 to December 2006, and the IceRod™ (Oncura), which induced a -40°C isothermal lesion measuring 14.5 mm in diameter and radiating from the ablation probe, was used from January 2007. Before insertion into the kidney, the proper number and locations of the cryoprobes were carefully calculated, based on the preoperative imaging study and intraoperative ultrasonography. Two temperature probes were then inserted into the middle and peripheral margins of the tumor to ensure that the temperature within the tumor had dropped below 40°C , which is normally required for the effective destruction of malignant renal tissue.¹³ A double-freeze cycle was applied in all cases, with an intervening thawing process. Intraoperative ultrasonography was also used to identify the extension of ice balls during the freezing cycle. Hemostasis was achieved by filling the probe tract with fibrin glue (Baxter, Deerfield, IL) and Surgicel (Johnson & Johnson, Irvine, CA), after the second thaw, to allow for the safe removal of the cryoprobe.

Results

Patient demographics, perioperative characteristics, and outcomes are presented in Table 1. All patients were asymptomatic, and the renal lesion was incidentally found by radiologic evaluation. Mean age was 63.3 years (range, 43–81), and mean tumor size was 2.5 cm (range, 0.7–3.9). Among 39 patients treated with LRC, 11 (28.2%) were over 70 years old, and their mean age was 75 (range, 70–81), with a mean ASA physical status score of 2.2 (range, 1–3). The other 28 patients had an ASA physical status score over 3 (range, 3–4). Mean ASA physical status score of whole patients was 2.8 (range, 1–4), and 79.4% (31/39) of patients had an ASA physical status score over 3. Among the 69% of patients with indications for elective surgery, 2 had ipsilateral multiple lesions. The 45 treated lesions were divided based on tumor location, as originally suggested by Venkatesh et al.¹⁴; 23 (51.1%) were exophytic tumors, defined as lesions that extended more than 60% off the natural surface of the kidney, 17 (37.8%) were endophytic tumors, defined as tumors with less than 40% of the lesion extending off the surface, and the other 5 (11.1%)

FIG. 1. Guidance of intraoperative ultrasonography during installation of the cryoprobe. (A) To determine the direction and depth of the cryoprobe tip, intraoperative ultrasonography was applied after exposure of the renal mass. (B) Ultrasonography finding validated that the tip of the cryoprobe was located exactly within the deep margin of the tumor.

were mesophytic tumors, defined as lesions extending 40–60% off the surface. Among 17 endophytic lesions, 5 tumors were centrally located, which was defined as being completely surrounded by normal parenchyma,¹⁵ with no visual clue regarding the location of the tumor on laparoscopy.

Mean operating time was 173.7 minutes (range, 110–220). Mean time of the first freeze cycle was 7.8 minutes (range, 6–10), and the mean of the second freeze cycle was 7.1 (range, 5–9). Mean blood loss, measured as the amount of blood in the suction device, was 106.3 mL (range, 40–150). Serum hemoglobin, checked 7 days after surgery, showed no statistically significant difference, compared to preoperative levels (13.1 versus 11.8 g/dL; $P = 0.57$). One patient (2.6%), who had a previous subtotal gastrectomy for an early gastric adenocarcinoma, needed a postoperative transfusion due to a low baseline hemoglobin level (8.4 g/dL). Major complications, including open surgical conversion or conversion to nephrectomy, adjacent organ injury, and collecting system injury, did not occur in any patients. Intraoperative precryoablation needle biopsy revealed that 60% (27/45) of the lesions were RCC (Table 1). Mean follow-up duration was 23.5 months (range, 6–53). Twenty lesions (44%) from 17 patients were followed up minimally for 24 months, and the mean follow-up period of the other patients was 13.1 months. Nine lesions from 6 patients were followed up within 12 months, but all of them had, minimally, a 6-month follow-up period.

Radiologic evidence of tumor recurrence, without metastasis, was found in 1 patient (3.7% for RCCs). In a 69 year-old male patient, with a central tumor measuring 2.2 cm, which was confirmed as clear-cell-type RCC, an enhancing portion at the deep peripheral area of the cryoablated site was found during an initial follow-up CT taken 1 month after LRC. Due to this patient's high anesthesiologic risk from a recurrent myocardial attack (ASA physical status score, 4), which required vascular stenting 3 times, and anterior tumor location, which disturbed the deployment of the probes for other minimally invasive ablative techniques, including RFA, he is currently under active surveillance. Follow-up images have shown a slight increase of the enhancing lesion, but no distant

or lymphatic metastasis, for 15 months after initial LRC. With the exception of this patient, all other patients have remained free of recurrence or metastasis, as determined by periodic radiologic work-up. For the patient with a confirmed diagnosis of RCC, although the cryolesion showed a temporary increase in size during the first month after surgery, the mean size decreased gradually on follow-up imaging. Mean sizes of these properly treated lesions were 2.6 ± 0.7 , 2.8 ± 0.4 , 2.5 ± 0.3 , 2.4 ± 0.2 , 2.2 ± 0.2 , 1.3 ± 0.3 , and 1.1 ± 0.4 cm before surgery and at 1, 3, 6, 9, 12, and 24 months, respectively (Fig. 2A, B). Compared to preoperative levels, serum creatinine of the whole patients, which was checked 7 days, 1 month, 6 months, and 12 months after LRC, has remained stable, without statistical difference. A similar pattern was revealed in 5 patients with a solitary kidney (Table 2).

Discussion

RCC incidence rates continue to rise among all races, ages, and tumor-size categories; the most rapid increase has been observed for localized disease and small tumors, due to the widespread use of diagnostic imaging.¹⁶ Incidental renal masses now account for 48–66% of RCC diagnoses,¹⁷ and, consequently, this increasing frequency has also induced a concurrent rise in rates of surgical intervention. Unfortunately, despite earlier diagnosis and treatment, cancer-specific and overall survival have not shown clinically significant improvement.¹⁸ Under these circumstances, questions regarding the best way to treat incidentally found small renal tumors have persisted. While resection that includes nephron-sparing surgery remains the standard of care, due to its durable oncologic outcome, ablative technologies and active surveillance have emerged as an alternative to surgery for selected patients. From a partial nephrectomy series, either open or laparoscopic, 20–30% of tumors are, obviously, benign.¹⁹ Thus, there is also the risk of widening the treatment armamentarium, which could result in overtreatment, for some patients. In this regard, active surveillance is a well-tolerated option for patients who are aged or fragile, and this concept is currently supported by a growing

TABLE 1. PERIOPERATIVE CHARACTERISTICS OF PATIENTS

Number of patients	39
Age over 70 years	11 (28.2%)
ASA physical status score over 3	31 (79.4%)
ASA physical status score 3	30
ASA physical status score 4	1
Mean follow-up (months)	23.5 (6–53)
Mean Age (years)	63.3 (43–81)
Male	28 (69.2%)
Female	11 (30.8%)
Indication of LRC	
Absolute indication	12 (30.8%)
Bilateral tumor	4
Solitary kidney	5
Chronic renal failure	3
Elective indication	27 (69.2%)
Number of tumors treated	45
Retroperitoneal approach	21 (46.7%)
Transperitoneal approach	24 (53.3%)
Mean size of renal mass (cm)	2.5 (0.7–3.9)
Right side	23 (54.2%)
Left side	22 (45.8%)
Tumor position	
Upper	7 (15.6%)
Mid	15 (33.4%)
Lower	23 (51%)
Tumor location	
Exophytic	23 (51.1%)
Mesophytic	5 (11.1%)
Endophytic	17 (37.8%)
Pathologic result	
Renal-cell carcinoma	27 (60%)
Clear-cell type	22
Papillary type 1	3
Chromophobe type	2
Angiomyolipoma	9 (20%)
Fibroadipose tissue	4 (8.8%)
Fibrovascular tissue	2 (4.4%)
Adipose tissue	3 (6.7%)
Operation time (minute)	173.7 (110–220)
Number of cryoprobes	2.9 (1–4)
Estimated blood loss (mL)	106.3 (40–150)
Mean hospital stay (days)	3.8 (3–8)
Complication	
Open surgical conversion	0
Nephrectomy for bleeding	0
Adjacent organ injury	0
Perirenal hematoma	0
Urine leakage	0

ASA, American Society of Anesthesiology; LRC, laparoscopic renal cryoablation.

body of literature. Chawla et al., who conducted a meta-analysis of 10 reports, found that, among 286 lesions with a mean follow-up of 34 months, the annual mean growth rate was 0.28 cm per year, and only 1% of patients experienced distant metastases.²⁰ However, in parallel, it is unquestionable that a significant proportion of incidental tumors can be lethal. In a large, multicenter study, even though tumors were totally asymptomatic, with a mean tumor size of 5.5 cm, pT3–4 tumors accounted for 28.3% of cases and grade 3–4 tumors accounted for 27.6% cases. In all, 14.4% patients died from cancer; in this group, 11.8% of tumors were below 4 cm.²¹ Considering the increasing prevalence of incidental renal

masses, these data suggest that treatment for local lesions will, eventually, be required, even for patients who are initially deemed fit for active surveillance, and surgical management for suspicious renal lesions is likely to play a substantial role in survival improvement.

In situ thermal destruction of renal masses, through the creation of lethally cold temperatures, offers a safer alternative for the treatment of small renal tumors for selected elderly patients with comorbidities, who are not good candidates for a major surgical procedure. In terms of oncologic efficacy, early- to intermediate-term reports in LRC have shown an acceptable tumor recurrence rate^{11,22–27} (Table 3). In two LRC series, with a minimum of a 3-year follow-up, the RCC recurrence rate was 4.5¹¹ and 5.6%.²³ In this series, with a mean follow-up duration of 23.5 months, tumor recurrence after LRC was 3.7% for histologically confirmed RCC lesions. This outcome is comparable with the local recurrence rate of 4.6% from a recent meta-analysis on 496 tumors from 19 studies, with a mean follow-up of 18.3 months.²⁸ The recurrence rate of cryoablation was higher than 2.6% in a partial nephrectomy series from 50 studies of 5037 tumors, with a mean follow-up of 54.0 months, but lower than 11.7% radiofrequency ablation from 18 series for 564 tumors, with a mean follow-up of 16.4 months. Interestingly, metastatic progression showed no statistical differences, regardless of whether lesions were excised or ablated.²⁸

One benefit of ablative therapy for renal tumors would be the potential for the preservation of renal function, because ablation does not require ischemic time. Patients with a solitary kidney, with renal insufficiency, or with comorbidities associated with renal insufficiency may be well served by renal ablation. However, few studies, to date, have examined the effects of kidney ablation on renal function. Gill et al. reported pre- and postoperative serum creatinine levels of 1.2 and 1.4 mg/dL for 56 patients with 3 years of follow-up, respectively.²³ In another series of 14 patients with a solitary kidney, no adverse effect on renal function was noted.²⁹ The present study provides additional evidence of preserved renal function in renal cryoablation. During this series, which featured a minimum of 6 months of follow-up and 5 patients with solitary kidney, serum creatinine was checked routinely

FIG. 2A. Serial changes of the maximal diameter of a cryoablated lesion, histologically proven as renal-cell carcinoma, in radiologic work-up.

FIG. 2B. Serial changes in a right endophytic tumor (white arrow) before and after cryoablation. (A) Preoperative CT image showed a 2.0-cm tumor mass encompassed by a renal parenchyme in the lower pole of the right kidney. (B) Postoperative image at 3 months. (C) Postoperative image at 12 months. (D) In this image, taken 24 months after surgery, the ablated lesion had nearly vanished.

at each follow-up, and mean pre- and postoperative serum creatinine levels were similar from 7 days after surgery, as shown in Table 2. Besides its adverse effects on the functional parenchyme itself, cryoablation can present a potential risk of injury to the collecting system, with a resultant urine leak, particularly for endophytic and central lesions. However, reports on renal cryoablation support the tolerance of the collecting system to the radiographic ice ball formed in the procedure. Targeted renal pelvic cryoablation resulted in no urinary extravasations, from a total of 15 lesions in a swine model.³⁰ In a clinical setting, 6 patients with intraparenchymal tumors, who were treated by percutaneous cryoablation, re-

vealed no clinical evidence of urethral sequelae.³¹ Similar to these observations, radiologic or clinical signs of collecting-system damage were not found in our experience, even with 5 central tumors.

While 38% of the lesions were endophytic located tumor in this series, expanding the indication for cryoablation to all renal tumors, regardless of tumor position, is still under debate. Particularly in the endophytic tumor, because of the proximity to the renal vasculature and collecting system, the cryoablation of an intraparenchymal endophytic tumor can, potentially, be disturbed by natural heat sinks, including the blood and urine. Actually, Wright et al.²⁶ reported on 2 cases

TABLE 2. SERIAL CHANGE OF SERUM CREATININE IN WHOLE PATIENTS AND PATIENTS WITH SOLITARY KIDNEY

Serum creatinine (mg/dL)	Whole patients		Patients with solitary kidney	
	Mean (range)	P-value compared to preoperative level	Mean (range)	P-value compared to preoperative level
Preoperation	1.11 (0.4–3.8)		2.04 (1–3.8)	
Postoperation (POD 7)	1.07 (0.5–3.8)	0.83	2.15 (1.2–3.8)	0.89
Postoperation (POD 30)	1.3 (0.6–4)	0.54	2.2 (1.1–4)	0.89
Postoperation (POD 90)	1.23 (0.7–4.1)	0.57	2.27 (1.1–4.1)	0.84
Postoperation (POD 180)	1.24 (0.5–4.5)	0.61	2.4 (1.3–4.5)	0.76
Postoperation (POD 360)	1.18 (0.5–4.4)	0.76	2.3 (1.2–4.4)	0.82

POD, postoperative day.

TABLE 3. SUMMARY OF THE CURRENT LITERATURE REPORTING ON LAPAROSCOPIC RENAL CRYOABLATION

Authors	Case	Age	Follow-up (months)	Tumor size (cm)	Operative time (min)	Blood loss (mL)	RCC (%)	No. of recurrences (% in RCC)	Major complications
Cestari et al. ²²	37	64	25.2	2.6	194	165	29 (78)	1 (3.5)	No major complications
Gill et al. ²³	56	65.2	36	2.3	180	87	36 (64)	2 (5.6)	1: heart failure
Lawatsch et al. ²⁴	59	62.2	26.8	2.5	203	98	34 (58)	2 (5.9)	4: two open conversions, one nephrectomy and one cardiac infarction
Wyler et al. ²⁵	15	68	21	2.8	167	93	10 (67)	1 (10)	No major complications
Weld et al. ¹¹	31	65.3	45.7	2.1	177	97	22 (71)	1 (4.5)	3: one urine leak, one open conversion, one heart failure
Wright et al. ²⁶	32	67	18	1.9	115	32	18 (56)	2 (11.1)	No major complications
Derweesh et al. ²⁷	34	67	25	2.1	166	129	24 (71)	1 (4.2)	No major complications
Present study	39	63.3	23.5	2.5	174	106	27 (60)	1 (3.7)	No major complications

of treatment failure, both in endophytic tumors (i.e., completely intrarenal lesions), among 35 LRC lesions during an 18-month follow-up. In multivariate analysis, only the endophytic status of a lesion predicted treatment failure in their study. This finding is matched with our result, in which a single case of tumor recurrence was a centrally located endophytic tumor. In contrast, Hruby et al.³² reported the successful treatment of LRC in all 11 patients, with tumors located within 5 mm of the renal vasculature during 11.3 months of follow-up. Considering the technical difficulty of LPN in endophytic and hilar lesions, Nisbet et al. formulated an algorithm that recommended LRC for endophytic and LPN for exophytic and mesophytic lesions, based on published series outcomes.³³

We do not think that our current data are sufficient to justify the use of cryoablation as a first-line option, as the partial nephrectomy remains the gold standard. However, it is noteworthy that our patient criteria for LRC were limited to patients with an ASA physical status score over 3 or age over 70, leaving LRC, rather than surgical resection, as the last surgical treatment option. It is also noteworthy that all procedures were conducted safely, with a negligible complication rate for patients with poor operability. In this regard, LRC, which enables the avoidance of renal ischemia and surgical excision, can be perceived as a safer option in the treatment of small renal tumors. Taken together, these results suggest the potential of renal cryoablation as a minimally invasive treatment method that can compete with nephron-sparing surgery in certain patient categories. Still, the application of cryoablation in renal tumors is in its investigational stage; therefore, there is room for additional advancement in both technical and technologic aspects. However, the lack of sufficient long-term data on the efficacy of the procedure have been the most common reason for not offering this ablation technique for the treatment of renal masses, as shown in a survey of current practice patterns of ablation techniques for 112 academic urologists.³⁴ In addition, while most are acceptable short- to intermediate-term results, there still may be more recurrences that are not yet evident. Therefore, while our data showed an early- to intermediate-term oncologic efficacy for LRC, longer follow-up, with a larger scale series, is still needed before ablative technologies can be established as a valid alternative option for the treatment of renal tumors.

Conclusions

Data from our initial experience in Korea have illustrated that LRC, for small renal tumors, showed favorable oncologic and surgical outcomes without adverse effects in selected patients with poor operability. During early- to intermediate-term follow-up, LRC showed acceptable recurrence rates, with the preservation of renal function. Further studies, with longer term follow-up and larger patient groups, will establish the position of ablative technologies in the treatment of renal tumors.

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Disclosure Statement

No competing financial interests exist.

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