

# Prospective long-term experience in the treatment of renal tumors with cryotherapy: follow-up with computed tomography scan and contrast-enhanced ultrasound

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**Introduction** The aim of this article was to evaluate the oncological results and safety of cryotherapy for the treatment of renal tumors.

**Material and methods** This study was a prospective review and follow-up of patients who underwent cryotherapy from January 2008 to May 2021. Cryotherapy was offered to patients with bilateral tumors, tumors in solitary kidneys, or comorbid patients. Follow-up consisted of a computed tomography (CT) scan and contrast-enhanced ultrasound (CEUS), with analysis of concordance (kappa index). Overall survival and kidney survival were analyzed (Kaplan-Meier).

**Results** Cryotherapy was performed 71 times in 67 patients. A total of 74.6% of patients were men. The mean age of patients was 69.7 years (standard deviation (SD) 11.3]. Mean follow-up was 52.7 months (SD 36.2). Mean tumor size was 26.2 mm (SD 7.6). 90% were cT1a, 10% cT1b stage. Type of access was open in 1 patient, laparoscopic in 8, percutaneous US-guided in 8 and percutaneous CT-guided in 54 patients. Biopsy was taken in 60 patients (84.5%) and consisted of renal cell carcinoma (22), oncocytoma (9), papillary carcinoma (4), angiomyolipoma (1), sarcoma (1), and non-conclusive (23).

There were 22 complications such as pain in 2 patients, hematoma in 8 and 2 cases of bleeding, all resolved conservatively except for one case of bleeding which required embolization.

Recurrences occurred in 16 cases (22.5%). Management was cryotherapy in 25%, radical nephrectomy in 31.3% and surveillance in 43.8%. Concordance between contrast-enhanced ultrasound and CT was 0.8 (excellent).

Mean glomerular filtration did not change. One patient developed metastasis.

No cancer-specific mortality was found. Overall survival at 12, 24 and 48 months was 98.5%, 96.8% and 76.9% respectively. Kidney survival at 12, 24 and 48 months was 97%, 93.5% and 93.5% respectively.

**Conclusions** Cryotherapy for renal tumors is a safe treatment for comorbid or solitary kidney patients, with rare major complications and good oncological outcome.

**Key Words:** complications ↔ cryotherapy ↔ kidney cancer ↔ results ↔ treatment

## INTRODUCTION

The incidence of renal cell carcinoma has increased in recent decades due to the increased detection

of small renal masses via abdominal imaging. There is an annual trend of 2% increase worldwide [1]. It is believed that 60% of renal cell carcinomas are diagnosed incidentally [2]. In addition, up to 70%

of solid <2 cm incidental masses found in imaging techniques are malignant, and this percentage increases when the size of the mass is greater.

On the other hand, incidental small renal masses have a slow growth rate and a very low rate of progression to metastatic disease during follow-up and a low incidence of metastatic disease at presentation [3].

Traditionally, surgical resection was regarded as a standard procedure for small renal masses, as it provides long-term cancer-specific survival. Current management has evolved to favor nephron-sparing techniques, including partial nephrectomy and radio-frequency ablation and cryotherapy. Partial nephrectomy has proven to have excellent oncological results in the long-term, with a reduced morbidity due to an increase in the development of minimally invasive techniques (laparoscopic and robotic surgery) [1, 2].

However, many of these renal masses are diagnosed in elderly patients or patients with comorbidities. Thus, patients who do not wish to undergo a partial nephrectomy, due to comorbidities or a desire to avoid surgical complications, are often offered ablative techniques [4].

Furthermore, image-guided cryotherapy also has the additional advantage of allowing real-time image evaluation of the ablation site, avoiding complications of non-target treatment [2].

The literature shows the safety and efficacy of cryotherapy in the treatment of clinical stage T1 tumors, similar to surgical partial resection [5]. However, the evidence for the use of cryotherapy for kidney tumors is still scarce, and it is still considered a less used alternative to partial nephrectomy in selected cases with solitary or bilateral kidney tumors, or comorbid patients [6]. Furthermore, most of the evidence is retrospective in nature [2, 7, 8].

On the other hand, contrast-enhanced ultrasound (CEUS) has proven to be an effective method in the follow-up of renal masses treated with cryotherapy. It allows for an easier follow-up, as urologists can perform the examination in their own practice, and also avoids the accumulation of radiation doses to the patient over the years [9].

The objective of our study was to evaluate the results of cryotherapy treatment of renal tumors, in terms of indications, complications and cancer-specific and overall survival, as well as the survival of the renal unit. In addition, a follow-up evaluation was performed by both computed tomography (CT) and CEUS.

## MATERIAL AND METHODS

Starting in January 2008, a prospective study of patients receiving cryotherapy (Endocare TM, Slim-

Line TM, Surgical Systems) for the treatment of renal tumors was carried out in our center, a tertiary care hospital.

Cryotherapy was offered as a treatment option for patients with bilateral tumors or solitary kidney, or for comorbid patients, as indicated by the European Guidelines [6]. Contraindications included tumors larger than 4 cm, hilar location and cystic tumors. The decision to treat a patient was made by the Hospital's Urologic Tumor Committee, which includes urologists, oncologists, pathologists, radiologists, and radiation oncologists. A total of 74.6% of patients were men. The mean age was 69.7 years [standard deviation (SD) 11.3].

The technique and protocol was the same in all patients [2, 8, 10, 11]. The goal of the procedure was coagulative necrosis of the tumor tissue. To do this, cryoprobes are placed in the tumor (the number of cryoprobes depends on the size and morphology of the tumor).

The percutaneous approach is used in tumors located posteriorly and laterally in the kidney. This procedure is performed simultaneously by the interventional radiologist and the urologist.

Laparoscopic access is preferred for tumors located in the anterior pole. In some cases, the use of retroperitoneoscopic or open access may be considered. In this case, the urologist performs the surgery with ultrasound control.

The patient was positioned prone, lateral, or supine, depending on the location of the tumor and the procedure performed. In the case of a surgical approach, the patient underwent general anesthesia. Most cases could be performed percutaneously, CT-guided, or ultrasound-guided. In this case, mild sedation was usually sufficient.

Through a biopsy, a pathological sample was obtained prior to the introduction of the cryoprobes. Cryoprobes were placed 1–2 cm apart and approximately 0.5 cm from the tumor boundary. Adjacent organs were protected by injecting carbon dioxide or saline. Once the cryoprobes were in place, a CT scan or ultrasound confirmed the correct location (dynamic monitoring). After the first phase of freezing, imaging was used again to ensure that the ice ball comprised the entire tumor.

The description of the patient's characteristics and the indications for cryotherapy was made using the mean (SD) or the median (range) for continuous variables and the number and percentage for categorical variables. Tumor characteristics, such as location, stage, and pathology results, as well as factors related to the procedure and complications (Clavien-Dindo classification) [12], were also reported.

Changes in glomerular filtration rate (GFR) were also reported before and after cryotherapy (Student's t-test).

Follow-up was carried out with CEUS and CT at 3 and 12 months after the procedure. Subsequently, semiannual CEUS and CT were performed for the first 3 years. After that time, the follow-up was carried out only with annual CEUS. The Kappa index was performed to evaluate the concordance between CEUS and CT.

Overall and cancer-specific survival, as well as survival of the renal unit during follow-up, were analyzed using Kaplan-Meier curves. For the renal unit survival analysis, deaths were considered censored times. The development of metastases was also assessed during follow-up.

The protocol for this research project was approved by Ethics Committee of the University Hospital and it conforms to the provisions of the Declaration of Helsinki (approval no. 25/05/2021 ACTA 414). Written informed consent was obtained from all subjects.

**Table 1.** Tumor indications, locations and access

Cryotherapy indication N = 67	Location N = 71	Access N = 71
Comorbidity: 46 (64.8%)	Right kidney: 53.5%	Percutaneous, CT-guided: 54 (76.1%)
Solitary kidney: 9 (12.7%)	Posterior valve: 74.6%	
Chronic kidney disease: 3 (4.2%)		Percutaneous, US-guided: 8 (11.3%)
Von Hippel Lindau: 4 (5.6%)	Upper pole: 21.1%	
Bilateral tumor: 4 (5.6%)	Mid pole: 47.9%	Laparoscopic: 8 (11.3%)
Multiple tumors: 3 (4.2%)	Lower pole: 31%	
Elderly patient: 2 (2.8%)		Open: 1 (1.4%)

N – number of patients; CT – computed tomography; US – ultrasound

Most of the indications corresponded to comorbidity. The posterior valve was the most common location, as well as the middle pole. The CT-guided percutaneous technique was the most frequent.

**Table 2.** Complications and management

Complications N = 71		
N = 22 (31%)	Treatment	Clavien-Dindo
Pain: 12 (16.9%)	Conservative	I
Hematoma: 8 (11.3%)	Conservative	I
Active bleeding: 1 (1.4%)	Embolization	IIIa
Active bleeding: 1 (1.4%)	Conservative	I

N – number of patients

Complications were rare, most treated conservatively.

## RESULTS

Cryotherapy was performed in 71 tumors of 67 patients. The mean follow-up was 52.7 months (SD 36.2), with a maximum of 155.76 months.

The mean tumor size was 26.2 mm (SD 7.6). A total of 90% of cases were clinical cT1a stage and 10% were cT1b stage. Table 1 shows the indications, locations and access. Complications and management are shown in Table 2.

Pathological anatomy samples were obtained prior to the procedure by renal puncture in 60 (84.5%) of the tumors. Table 3 shows the results obtained (grade could not be assessed in the majority of cases). Inconclusive biopsies were considered as malignant tumors. The median number of cryoprobes used for each tumor was 2 (1–5).

Radiological recurrences occurred in 16 cases, including one case of oncocytoma (22.5%). Table 4 shows the characteristics of the recurrences, as well as the management.

The Kappa concordance index between CEUS and CT was 0.8 (excellent). The discrepancies were: one case of positive CT and negative CEUS turned out to be tumor in nephrectomy. Two cases of positive

**Table 3.** Pathological anatomy of the lesions

Biopsy	N = 60 (84.5%)	Mean size (SD), mm
Renal cell carcinoma	22 (31%)	24.1 (1.4)
Oncocytoma	9 (12.7%)	28 (1.4)
Papillary carcinoma	4 (5.6%)	22.3 (3.8)
Angiomyolipoma	1 (1.4%)	20
Sarcoma	1 (1.4%)	30
Non-conclusive	23 (32.4%)	26.1 (1.6)

N – number of patients; SD – standard deviation

Most of the lesions corresponded to renal cell carcinoma, but there was a considerable number of inconclusive biopsies.

**Table 4.** Recurrences and management

16 recurrences (22.5%)	Treatment of recurrence	Total treatments
Focal recurrence: 10 (62.5%)	Salvage cryotherapy: 2 (20%)	Salvage cryotherapy: 4 (25%)
	Radical nephrectomy: 2 (20%)	Radical nephrectomy: 5 (31.3%)
	Surveillance: 6 (60%)	
Other recurrence: 6 (37.5%)	Salvage cryotherapy: 2 (33.3%)	
	Radical nephrectomy: 3 (50%)	Surveillance: 7 (43.8%)
	Surveillance: 1 (16.7%)	

There was a recurrence rate of 22.5%, most managed with surveillance. However, some required radical nephrectomy or salvage cryotherapy.

CEUS and negative computed tomography were managed by surveillance.

The mean GFR before and after cryotherapy was 66.9 mL/min and 65.2 mL/min, respectively ( $p = 0.369$ ). One patient developed metastasis during follow-up; the patient is still alive (progression-free survival of 98.2%, excluding benign lesions).

No cancer-specific mortality was found in this series, 17 (23.9% died from other causes). Overall survival at 12, 24, and 48 months was 98.5%, 96.8%, and 76.9%, respectively. The mean overall survival was 111.85 months and the 75<sup>th</sup> percentile was 49.74 months (Figure 1).

Eventually, 5 patients underwent a nephrectomy of the affected kidney. Renal unit survival at 12, 24, and 48 months was 97%, 93.5%, and 93.5%, respectively. The mean survival of the renal unit was 143.29 months (Figure 2).

## DISCUSSION

Partial nephrectomy is still considered the gold standard treatment for small renal masses [6]. However, its management is evolving with the development of microwave ablation, cryoablation and radiofrequency ablation [13].

The clinical use of cryotherapy dates back to the 19<sup>th</sup> century. Around the middle of the century, saline solutions were cooled to treat superficial tumors of the breast and cervix. In the 20<sup>th</sup> century, cryotherapy was used mainly in the field of dermatology. The availability of commercial liquid nitrogen initiated modern cryotherapy and reached clinical importance with modern imaging and miniaturization in the 1990s [8].

The application of cold results in the formation of ice crystals in the extracellular space. The osmotic imbalance produced moves water from the intracellular space to the interstitium, resulting in dehydration and initial cell damage. However, if freezing occurs rapidly, less water leaves the cell, resulting in the formation of intracellular ice crystals, which have a destructive effect on the organelles and the cell membrane. During thawing, more water enters the cells, allowing the production of more crystals. The use of at least two freeze-thaw cycles with slow thaw and quick freeze has been shown to be particularly effective. There is also damage to the endothelium as a result of ice formation, with the consequence of thrombosis and local ischemia. At the periphery of the lesion, apoptosis is a recognized mechanism for tumor therapy. The limits of the tumor must be exceeded at least 5–8 mm beyond the lesion for  $-20^{\circ}\text{C}$  to reach the entire lesion. It must be taken into account that tumor cells have greater resistance to cold

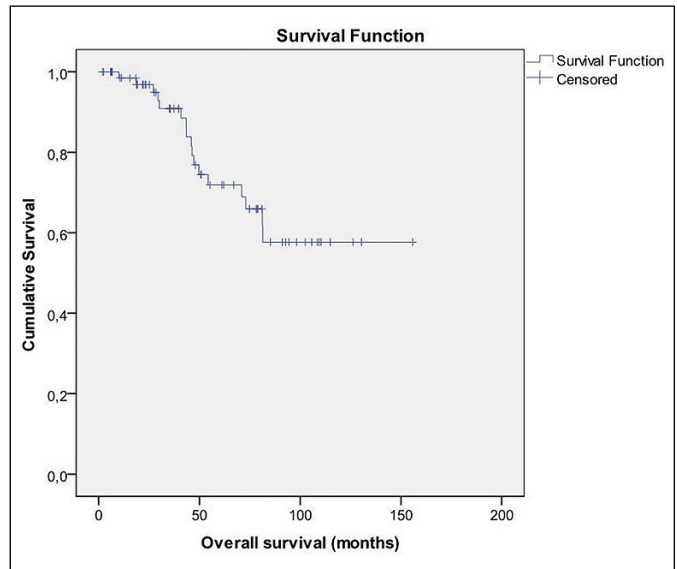


Figure 1. Kaplan-Meier overall survival.

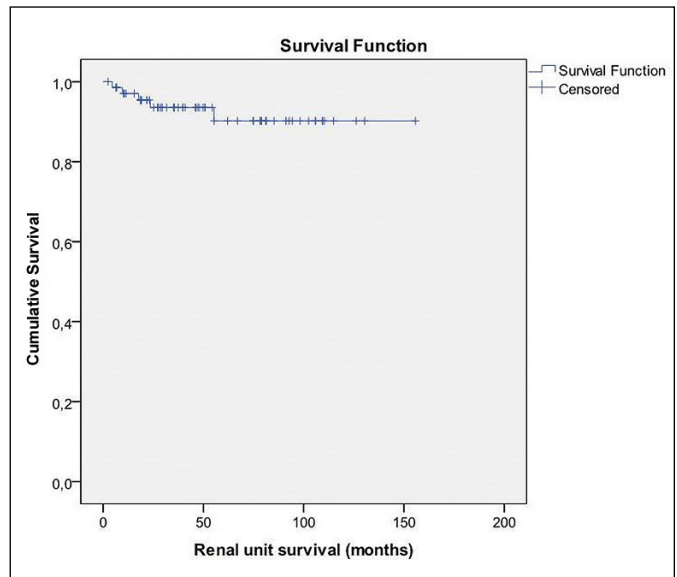


Figure 2. Kaplan-Meier renal unit survival.

compared to healthy cells. In addition, fibroblast and collagen fibers are often resistant to the process [2, 8]. After prostate cancer treatment, the next most common application of cryoablation is in kidney tumors [8].

Initially, cryotherapy was considered only in patients with comorbidities, impaired kidney function or short life expectancy [1, 14].

Kitley et al. [7] reported a retrospective review of the United States national cancer database showing a reduction in overall survival in patients treated with cryotherapy compared to partial nephrectomy at 24, 48 and 96 months. This study included all pa-



tients treated with both modalities in clinical stage T1a. It should be noted that this could be because this procedure is indicated primarily in elderly or comorbid patients. Cancer-specific survival was not analyzed.

Regarding the comparison between cryotherapy and partial nephrectomy, some other studies have been published. A review published in 2018 observed a similar oncological effectiveness of ablative techniques (radiofrequency ablation and cryotherapy) to partial nephrectomy for tumors <3 cm [1]. Sandberg et al., in an observational case-control study adjusted for baseline patient and tumor characteristics, reported a similar estimated 5-year cancer and overall survival with a benefit of more than 1 year in postoperative outcomes in cT1a in older patients [5]. On the other hand, Rai et al. [15] published a systematic review and meta-analysis comparing cryotherapy with robot-assisted partial nephrectomy. Regarding recurrence rates, a statistically significant difference was observed favoring the surgical process (2 included studies). Clavien-Dindo >II and overall complication rates were not statistically different (4 studies included).

Regarding access, percutaneous cryoablation is usually performed for posterior tumors, and laparoscopic cryotherapy is used more frequently for endophytic lesions [16].

There is a lack of long-term efficacy data from large prospective or randomized studies, and most of them are limited to the treatment of renal masses in elderly or poor surgical candidates [17].

The majority of studies are retrospective [10, 18, 19]. A recent study conducted by Cernic et al. [19] retrospectively analyzed 174 renal lesions with an average size of 2.25 cm, treated with cryotherapy (from 2011 to 2020). The median follow-up was 21.92 months, with a maximum of 99.87. They observed a technical success rate of 98.3% and a treatment efficacy rate of 95.3%. The overall complication rate was 29.8%, with no complications above grade II.

However, there are some prospective studies, such as the one by Gobara et al. [20], in which 33 patients were enrolled from 2013 to 2015, followed by a median of 60.1 months. They observed overall and cancer-specific survival rates of 100% and 96.8% at 5 years, without local progression of metastases. In our case, one patient developed metastases during follow-up. Regarding complications, the rate is usually low, from 6% to 10%. Some of the complications reported include urinary fistula, ureteric obstruction, paresthesia, pain, fever, perinephric or urinary tract infection, parenchymal fracture, hematuria, bowel perforation, increased creatine kinase, pulmonary complications, and skin ulceration. The percutane-

ous approach appears to provide less morbidity compared to the laparoscopic, which has been reported to be up to 15%. Bleeding complications increase with increasing tumor size and the complication rate increases with proximity to the collecting system [1, 11, 13, 20]. In our study, complications were mild, with only one grade 3 complication. There were some inconclusive biopsies and some benign lesions. Inconclusive biopsies were considered as malignant tumors in the follow-up. The policy with benign lesions was a less strict monitoring.

The economics are also encouraging, as cryotherapy has increased cost-effectiveness compared with partial nephrectomy, as it reduces hospital stay and overall costs, due to rapid recovery [1]. A systematic review comparing laparoscopic versus percutaneous cryoablation revealed a shorter hospital stay and faster recovery, with similar recurrence-free survival and overall survival, and no significant difference in estimated glomerular filtration rate after the treatment [16]. On the other hand, another systematic review reported higher cost in laparoscopic cryotherapy compared to percutaneous CT-guided cryoablation [21].

Loss of renal function after cryoablation of small renal masses in solitary kidneys has been reported in a retrospective study from the database of the European Registry of Renal Cryoablation. A statistically significant decrease of 3.1 mL / minute / 1.73 m<sup>2</sup> was observed. However, the decrease did not translate into any significant adverse outcome, nor did the patient require dialysis [18]. In our study, there was no statistically significant decrease in GFR. Therefore, cryotherapy should be the preferred treatment in the case of pre-existing chronic kidney disease [13]. Furthermore, the use of cryotherapy seems to be justified in selected cases for palliative indications and oligometastatic patients [8].

On the other hand, the role of active surveillance should be taken into account in small renal masses in very elderly or comorbid patients or with competitive risks of chronic kidney disease. It has been incorporated into existing management algorithms with favorable intermediate monitoring results. However, active surveillance programs are not yet standardised and are at the discretion of the physician [22].

The follow-up programs are similar in the different series. The patient is usually observed overnight and is discharged the next day. The first CT scan is done in the first 1.5–3 months to assess the effectiveness of the treatment. Then, a CT scan is repeated at 6–9 months and then annually. Magnetic resonance imaging has been used in patients allergic to contrast medium. An enhanced lesion may indicate treatment failure, although up to 20% of renal

tumors may enhance in the absence of viable tumor, especially in the post-treatment period. When a residual tumor is seen, it can be monitored, but repeat cryotherapy, radical or partial nephrectomy are viable salvage options [11]. Follow-up must be continued at least 10 years after cryotherapy [13].

Computed tomography is currently the gold standard. However, it requires iodinated contrast, which has shown nephrotoxicity and uses high doses of radiation. In addition, it is advisable to perform it for at least 10 years (although the length of follow-up is not established). Nephrotoxicity is especially problematic in patients with solitary kidney or chronic kidney disease. During follow-up, CEUS represents a safe alternative that has been reported to have a good agreement with respect to the results obtained by computed tomography and magnetic resonance imaging [2, 9]. As most recurrences occur in the first 2–3 years, it may be a good idea to replace CT/MR with CEUS after the first 3–5 years or in patients with poor renal function. In our study, some recurrences were managed by surveillance, due to the slow growth time of the tumors, the close follow-up, and the possibility of early rescue. Regarding the limitations, the limited number of cases and the fact that it is a single-center study

must be taken into account. Regarding the strengths of this study, to our knowledge, this is the largest series with a long-term follow-up and a prospective nature. Likewise, the indications for cryotherapy were homogeneous, according to the current European Urology Guidelines. The use of CEUS should be taken into account during follow-up, which allows good diagnostic results avoiding radiation to patients.

## CONCLUSIONS

Cryotherapy for kidney tumors is a safe treatment option for comorbid or solitary kidney patients, with rare major complications and a good oncological outcome, as well as maintenance of kidney function. Recurrences can be treated with salvage cryotherapy or nephrectomy. Follow-up with CEUS should be considered in these patients, since the concordance with CT is excellent and avoids nephrotoxicity.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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