Actas Urológicas Españolas

www.elsevier.es/actasuro

Review–Kidney cancer

Cryotherapy for renal tumors: Current status and contemporary developments

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ARTICLE INFORMATION

Article history:
Received on 15 December, 2009
Accepted on 23 December, 2009

Keywords:
Cryotherapy
Renal tumor
Laparoscopy

ABSTRACT

The proportion of renal tumors found incidentally has dramatically increased in the past decade. More than half were diagnosed in patients over 70 years of age, a population with a high rate of associated comorbidity. Nephron-sparing minimally invasive surgical procedures are aimed at treating patients with small renal tumors and multiple comorbidities. Cryotherapy stands out among all other ablative procedures because of its better mid-term oncological outcome.

A non-systematic review of the literature on cryotherapy as a treatment for renal tumors was made, analyzing its indications, actual and future application techniques, results, and complications

Crioterapia de tumores renales: estado actual y desarrollos contemporáneos

Palabras clave:
Crioterapia
Tumorrenal
Laparoscopia

RESUMEN

La proporción de tumores renales incidentales ha incrementado drásticamente en la ultima década, siendo diagnosticados en más de la mitad de los casos en pacientes mayores de 70 años, población con una alta comorbilidad asociada. Las técnicas ablativas mínimamente invasivas conservadoras de parénquima están destinadas a tratar a pacientes con tumores renales pequeños y múltiple comorbilidad. La crioterapia destaca sobre otras técnicas ablativas por sus mejores resultados oncológicos a medio plazo.

Realizamos una revisión no sistemática de la literatura médica analizando la crioterapia como tratamiento de los tumores renales, analizando sus indicaciones, las técnicas de aplicación actuales y las perspectivas de futuro, los resultados y las complicaciones.

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Introduction

Due to the growing use of imaging techniques over the past decade, there has been an increase in the incidence of small renal masses discovered incidentally. Between 1982 and 1997, the proportion of renal tumors diagnosed incidentally increased from 13 to 66%[1]. More than half the patients diagnosed with renal masses were older than 70 years. A higher rate of comorbidities is expected in this patient population[2]. Nephron-sparing surgery was initially developed for patients with solitary kidney or with an impaired renal function. However, the rates of recurrence and long-term survival are similar to those after radical surgery, for which reason nephron-sparing surgery is a therapeutic option for tumors smaller than 4 cm, even in the presence of a normal contralateral kidney[3,4].

Nephron-sparing minimally invasive ablative procedures are aimed at treating patients with small renal tumors and multiple comorbidities. In contrast to surgery, which removes tissue, ablative techniques destroy it; the advantages are lower morbidity, shorter hospital stay, and better preservation of the renal function. Of all ablative techniques, cryotherapy is the most extensively studied and most clinically tested.

Indications and contraindications

The optimal case for cryotherapy is a peripheral, contrast-enhancing, circumscribed lesion smaller than 4 cm. Generally, all patients with a small renal tumor are candidates for cryotherapy. Besides cases of tumors with certain characteristics, some populations such as elderly patients with comorbidities—especially hypertension, diabetes, kidney stones, renal insufficiency, stroke, and congestive heart failure—can benefit from renal cryotherapy. Other indications include unique situations such as lesions smaller than 4 cm in solitary or transplanted kidneys, accompanied by hereditary diseases such as Von Hippel-Lindau syndrome, tuberous sclerosis, and hereditary papillary renal cell carcinoma[5]. Relative contraindications to cryotherapy include young patients, tumors larger than 4 cm, and renal sinus, intrarenal, and cystic tumors (table 1). The only absolute contraindication is intractable or irreversible coagulation disorder[6].

Table 1 – Indications for cryotherapy

Peripheral mass smaller than 4 cm
Central mass, if visible with ultrasound
Elderly patient with comorbidities
Patient's desire
Congenital syndromes
Solitary kidney

Mechanism of tissue ablation by cryotherapy

The mechanisms of tissue damage resulting from freezing are not completely understood; currently, they are described as acute and late[7]. The damage is caused by the formation of ice in the tissue. Initially, at low freezing rates of around –5°C/min, ice forms in the extracellular space because the cell membrane's lipid bilayer inhibits the development of crystals. The formation of extracellular ice increases the osmotic concentration and causes intracellular water to move to the extracellular space. This eventually causes changes in the intracellular solution and the pH, and protein denaturation. Later, the formation of extracellular crystals may cause the cell membrane to rupture and lead to the formation of intracellular ice[8,9]. However, when the freezing rate reaches –20°C/min, ice is formed simultaneously in the intra- and extracellular spaces, a transmembrane gradient develops, and the intracellular ice ruptures the cell membrane, causing irreversible cell damage[10]. Chosy et al found that in order to achieve necrosis of the renal tissue, a temperature of –19.4°C is necessary[11]. That study was confirmed by Campbell et al, who observed complete necrosis within the borders of the ice ball, which correlates with a temperature of –19.4°C[12].

Tissue damage occurs in the hours and days after cryotherapy, and is the result of indirect injury to the microvasculature of the target tissue[13]. During the acute phase, endothelial cells are injured by the mechanisms mentioned. In time, the integrity of the microvasculature is progressively lost, causing fluid extravasation in the injured capillaries and the extension of the thrombosis in the vascular bed. This combination of events leads to reduced tissue perfusion and delayed cell death[14]. This is probably the most important mechanism of cell death occurring in cryotherapy. *In vitro* studies have shown that cryotherapy-induced apoptosis plays an important role in cell death[15].

Cell destruction is achieved with both processes: freezing and thawing. Renal cryotherapy techniques have evolved by using data from the treatment of liver tumors, in which the first double freeze cycle method was used. Compared to the single freeze cycle, the double cycle produces a much longer area of necrosis in laboratory animals. It is not clear whether the thaw cycle provides any advantages over the rapid thaw cycle in the clinical context, but in general, a double freeze and thaw cycle is preferred[16,17].

Cryotherapy equipment

The first generation of cryotherapy machines was tested in 1960 with probes that used liquid nitrogen. The first application was on the prostate. The second generation of cryosurgery was developed in the 1990s, and used 3-mm probes and liquid nitrogen. The third generation of cryotechnology is being developed since 2000. The technology currently used is based on the release of argon and helium gases through 1.5-mm fine probes (second- and third-generation probes are used indistinctly in various centers). Technological advances have led to the development of probes of various diameters and lengths with the purpose of producing a cryolesion in accordance with the treatment plan.

Cryoablation is done using argon gas systems based on the Joule-Thomson principle. According to that principle, helium gas is used for active thawing[18]. There are currently three versions of third-generation 17-gauge probes that produce ice balls of different shapes and sizes. The elliptical cryoprobe (IceRod®) creates a 32–56-mm elliptical ice ball in *ex vivo* studies. The bulb-shaped cryoprobe (IceBulb®) creates a 32–60-mm ice ball in the shape of a bulb. Finally, the standard cryoprobe (IceSeed®) is the 17-gauge standard probe that creates an 18–27-mm ice ball[19].

Technique

Open, laparoscopic, and percutaneous cryotherapy techniques for renal cryoablation have been described. Each has advantages and disadvantages; the minimally-invasive procedure concept applies to laparoscopic or percutaneous procedures.

The transperitoneal laparoscopic approach is indicated for lesions on the anterior aspect of the kidney; the retroperitoneal approach is more indicated for cases in which the lesion is on the dorsal aspect of the kidney. So far, the percutaneous approach is indicated only for tumors on the dorsal side of the kidney; this is due to problems of involvement of neighboring organs, even when distancing maneuvers are used.

Laparoscopic cryoablation

A transperitoneal or retroperitoneal classic approach is usually employed. The protocol must be followed step by step. The steps include mobilization of the kidney, ultrasound visualization of the lesion, incision in the perinephric fat, and visualization of the mass and placement of the probes using direct visualization. Before placing the probes, a needle biopsy of the tumor must be taken for histological analysis, if this hasn't been done already. The exact size configuration of the tumor must be measured before surgery. The number and type of probes depend on the exact size of the lesion.

The probe design, size, and number depend on the anatomical characteristics of the renal mass. The correct placement of the cryoprobes must be verified with intraoperative ultrasound. Thermosensors may be placed in the center or in the periphery of the lesion, or in the healthy parenchyma to monitor the target temperatures (fig. 1).

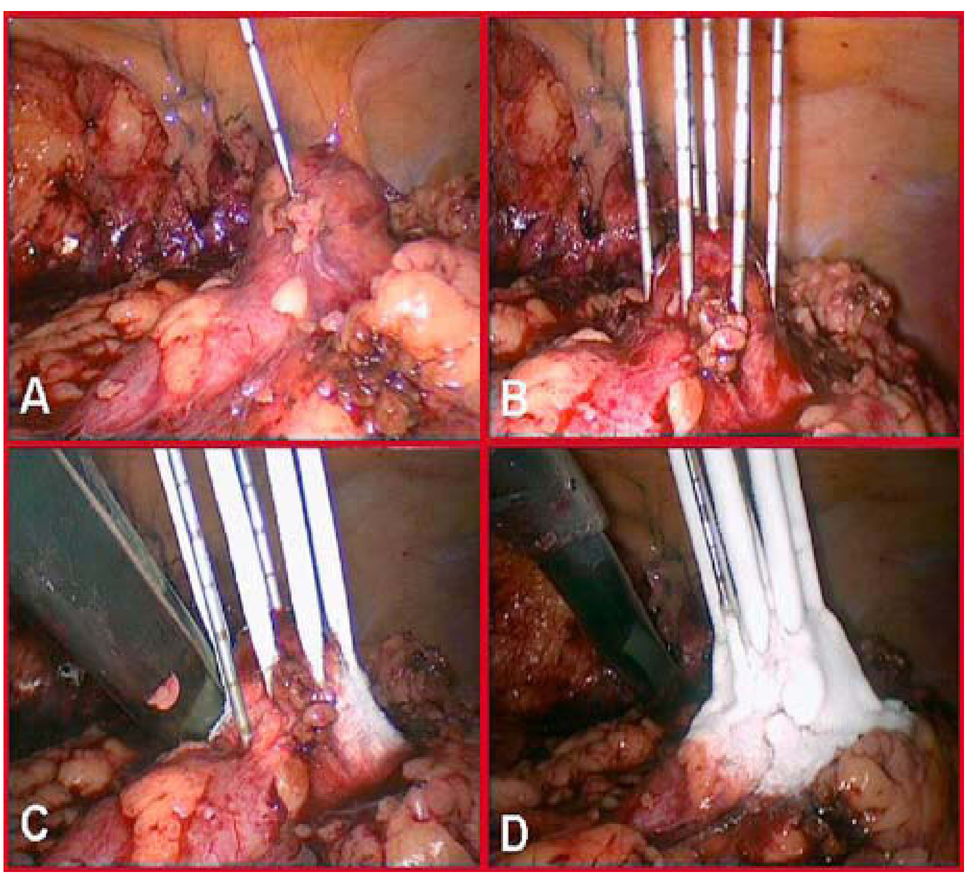

Figure 1 – Laparoscopic cryotherapy technique. A) Visualization of the mass and needle biopsy. B) Placement of cryoprobes and thermosensor. C) Monitorization of the cryoablation with laparoscopic ultrasound (note the two thermosensors: one is central and the other peripheral, like probes without ice). D) Visualization of the ice ball that includes the entire tumor plus a wide safety margin.

It is usually recommended to cover the tumor with an ice ball with a 10-mm excess margin. Cryotherapy begins with a freeze cycle in the target tissue at 20 to –40°C. The cryolesion becomes visible as an ice ball, and it is sonographically hypoechoic. The current trend is to wait to cover the tumor with the cryolesion seen by the ultrasound, and freeze for about 2–3 min longer. If the sonographic image is not clear, it is recommended that a temperature of 0°C be reached in all thermosensors (fig. 2). At the end of the freeze and thaw cycle, a surgeon carefully withdraws the probes. In time, the probes loosen by themselves; premature manipulation before adequate warming could cause bleeding in the probe path[20].

Single-port access cryotherapy

One development in the laparoscopic cryotherapy technique is the single port access. This approach allows the complete cryotherapy procedure to be done through the umbilicus, which means abdominal surgery without scars and the resulting decrease in wound morbidity. Goel and Kaouk[21] recently reported an initial experience of this procedure in six patients. They used a multichannel single port designed especially for curved laparoscopic instruments. Using the Hasson open technique, the multichannel port was positioned at the tip of the 12th rib during the retroperitoneal approach; for the transperitoneal approach, a 1.5-cm semicircular incision was made in the internal edge of the umbilicus. After exposing the tumor, an intraoperative biopsy was taken, and a 3.8-mm cryoprobe was inserted with ultrasound guidance. Two cryoprobes were used in one patient with a tumor larger than 1 cm. All the procedures were completed satisfactorily. There were no intraoperative complications. The only postoperative complication was congestive heart failure in one patient.

Natural orifice endoscopic surgery

Natural orifice translumenal endoscopic surgery (NOTES) is an emerging technology that may reduce morbidity and offer a non-scar surgery, which would help to reduce the invasiveness of standard laparoscopic and robotic techniques currently accepted[22]. NOTES represents the next step in minimally invasive surgery. It is done through natural orifices, with potentially better recovery and fewer complications like hernias[23]. Transgastric and

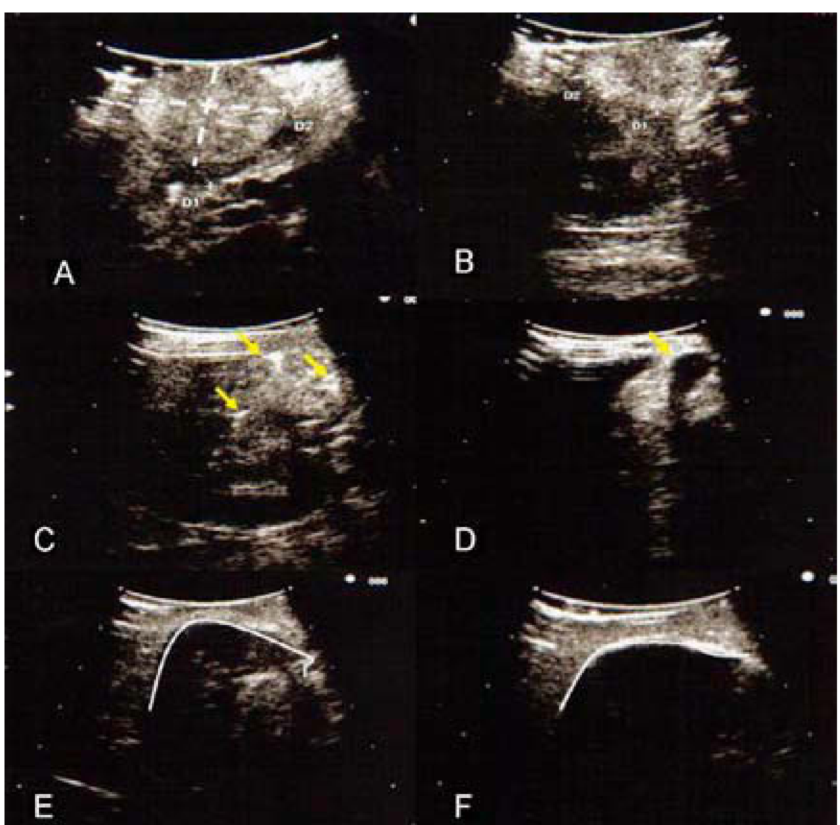

Figure 2 – Laparoscopic ultrasound. A and B) Visualization and measurement of the tridimensional diameters of the tumor. C) Placement of cryoprobes (yellow arrow). D) Beginning of cryotherapy and monitorization of the formation of the ice balls. E) Visualization of the formation of a single ice ball. F) Ice ball covering a safety margin around the tumor.

transvaginal approaches have been used successfully to access the peritoneal cavity[24]. However, to date, this procedure has been done only in animal models. Croutzet et al reported their experience with NOTES-guided renal cryoablation. The procedure was performed successfully with a transgastric or transvaginal approach for each kidney, respectively. They reported that all the procedures were successful, with no intraoperative complications. No additional laparoscopic ports or open conversion were necessary. The visualization of the kidney and the ice-ball was adequate for all cases; the mean operative time was 83 min[25].

Image-guided percutaneous cryotherapy

In addition to being less invasive, the percutaneous approach has the advantages of shorter hospitalization, excellent monitorization of the ice ball (with magnetic resonance [MRI] or computed tomography [CT]), less requirement of sedatives, and more cost-effectiveness than the laparoscopic approach[26]. It can be done guided with ultrasound, CT, or MRI. The advantages of ultrasound are real-time visualization and the absence of ionizing radiation. However, the sonographic image is highly dependent on the technician, and can be compromised in several instances, such as in obese patients, in the presence of abundant abdominal fat, and when the tumor is near an intestinal loop[27]. CT is not technician-dependent and is reasonably affordable. Its large vision field is excellent to cover critical organs and structures that must be avoided. CT is much less sensitive to human habits than ultrasound, and is not affected by intestinal gas. If CT is chosen as the guiding method, the target lesion should be visible in the non-contrast phase. Percutaneous ablation can be done with conventional CT or with real-time fluoroscopic CT[28]. MRI is the least utilized imaging technique in percutaneous cryoablation because the cryotherapy equipment needs to be especially adjusted for MRI habilitation. However, it provides exceptional tridimensional vision fields without ionizing radiation[29]. MRI-guided percutaneous cryotherapy can be performed using interventional magnetic equipment or a conventional equipment with wide gantry. The ice ball can is visualized as a low-intensity area in sequence T1[30].

Currently, most percutaneous procedures with probes are performed with endotracheal intubation and standard assisted ventilation, so the kidney moves during ventilation. This movement can be countered by the anesthetist holding the patient's breath during specific phases of the scanning, and when the probes are being inserted. Holding the patient's breath repeatedly is complicated and lengthens the procedure; if it is not perfectly synchronized, it can yield inadequate images that will have to be repeated, thus requiring more radiation exposure, incorrect probe placement, or failed biopsy. A possible alternative to assisted ventilation is high frequency oscillatory ventilation (HFOV). HFOV provides low tidal volume with high mean airway pressure and high frequency (180–600 breaths/min)[31]. This high frequency and low tidal volume eliminate to a large extent the movement of the diaphragm, so the kidney stays in a stable position. Beck et al recently published their experience with HFOV. They found that this modality can reduce the time necessary to perform the cryoablation, possibly due to the elimination of the kidney movement during the procedure, which facilitates planning and access to the renal mass. Additionally, patients tolerated HFOV without incidents, and surgeons found the procedure easier to perform[32].

Follow-up

Cryolesions require close monitoring to ensure that the tumor has shrunk. The renal mass does not disappear entirely for months or years because it may be replaced with fibrosis; however, it should progressively shrink. A 4-cm angiomyolipoma took more than 2 years to resolve, but its size decreased progressively[33]. There are no algorithms to monitor post-procedure follow-up, but patients are thought to need a close monitoring (every 3 months) for 12–18 months, followed by long-term monitoring until a complete reduction is achieved; if the lesion is stable, annual follow-up is required in order to ensure that there is no relapse potential in the margin[34]. Gadolinium-enhanced MRI is an effective way to follow-up after treatment. However, contrast CT is the method most commonly used[35].

Contrast enhancement in a lesion 30 days after treatment can be an ominous sign. The size of the lesion and a nodular enhancement are important criteria to diagnose tumor relapse with CT or MRI. A rim enhancement plus a growing size is more dangerous than rim enhancement alone[36] (fig. 3).

The role of biopsy during follow-up is being questioned due to its low sensitivity and inability to provide a definitive diagnosis[37]. Our results show that rim enhancement during the first few months after cryoablation is relatively common and does not justify systematic biopsies; firstly, because, according to our results, this enhancement disappears spontaneously, and secondly, because it is very difficult to obtain a biopsy from this thin rim[38]. In a recent study conducted at the Cleveland Clinic[39], the authors demonstrated that a biopsy did not add any substantial information to the CT or the MRI (contrast enhancement) in the first six months, and should be avoided.

Contrast ultrasound is an alternative for assessing the kidney after cryoablation. Contrast-enhanced ultrasonography combines microbubble contrast with contrast pulse sequence imaging. This technology allows real-time control of perfusion in the treated zone[40].

Results

Medium- and long-term results of several approaches to renal cryotherapy have been published in the past few years. (tables 2 and 3)[4-41]. Furthermore, results of the two most recent meta-analyses have shown that local recurrence (treatment failure) ranges between 4.6[55] and 5.2%[56], and progression between 1 and 1.2%[55,56].

Figure 3 – Follow-up of one patient after cryotherapy for renal tumor. A) Computed tomography at 3 months post-treatment; rim enhancement is observed, which had disappeared by the B) 6-month follow-up.

Table 5 – Open laparoscopic cryoablation: outcome and follow-up

	Approach	Tumor	Size, cm	Probe, mm	T, min	Follow-up, months	Rec./pers.
Cestari, 2004[41]	lap	37	2.6	3.2	194	20.5	2.7%
Ankem, 2005[42]	lap	22	2.6	2.4–5	188	10.4	0
Gill, 2005[43]	lap	60	2.3	4.8	180	>36	5.3%
Lawatsch, 2006[44]	lap	81	2.5	5	190	25.2	2.3%
Davol, 2006[45]	lap/open	48	2.6	3–5	–	36	4%
Schwartz,2006[46]	lap/open	85	2.6	8–5	–	10	3.6%
Hegarty, 2006[47]	lap	164	2.56	4.8	–	>36	1.8%
Desai, 2006[48]	lap	89	2.05	4.8	188	24.6	3%
Weld, 2007[49]	lap	36	2.1	5–3.4	177	>36	3%
Bandi, 2007[50]	lap	68	2.7	–	247	22	0.8%

Complications

The goal of cryotherapy for renal carcinoma is to reduce the morbidity associated with the treatment of *in situ* tumors by obviating the need to remove them; however, there are potential complications.

There are often minor renal tears in the cryoablated area which are easily treated by applying direct pressure with a hemostatic agent for 10 minutes, followed by observation for 10–15 minutes (with a decrease in the insufflation pressure)[57]. Renal parenchyma fracture and subsequent hemorrhage can be avoided by placing the cryotherapy probes perpendicular to the kidney, maintaining this position throughout the procedure, and removing the probes carefully (especially if they are large) after thawing the renal tissue surrounding the cryoprobe[58]. To avoid inadvertent contact and a resulting injury, the adjacent organs must be protected from cryolesion. Several iatrogenic lesions have been published, including pancreatic lesions, stenosis of the pyeloureteral juncture, and total intestinal obstruction[59,60]. When the ice ball or the cryolesion involve the collecting system, the outcome is not clear. Studies with animals with intentional cryoinjury in the collecting system have revealed minimal scarring in the lamina propria and the smooth muscle, and regrowth of the surrounding urothelium[61]. The relationship between the ice ball and the collecting system has been described in series with human patients with open surgery and in animal models; no urinary leak was found[62]. The results of a multicenter retrospective study of radiofrequency and cryotherapy in 139 cases showed that the rates of major and minor complications attributable to cryotherapy range between 1.8 and 9.2%, respectively. The five major complications were adynamic ileus, hemorrhage, conversion to open surgery, scarring obstructing the pyeloureteral junction, and urine leak. The most common complication, and a minor one, was pain or paresthesia in

Table 3 – Percutaneous cryoablation: outcomes and follow-up

	Control	Tumor	Size, cm	Probe, mm	T, min	Follow-up, months	Rec./ pers.
Shingleton, 2001[51]	MRI	22	3.2	2–3	97	9.1	5%
Silverman, 2005[52]	MRI	26	2.6	2.4	–	–	4%
Gupta, 2006[53]	CT	27	2.5	2.4	–	5.9	6%
Atwell, 2007[54]	CT	115	3.3	2.4	–	13.3	3%
Bandi, 2007[50]	–	20	2.2	–	148	12	10%

the area where the probes were inserted[63]. More recently, the results were published of a multicenter prospective study of cryotherapy (third-generation probes) using the Clavien system for the classification of complications; this study showed complications or negative outcomes in 15.5 and 17%, respectively. Most complications were Clavien grade 1 or 2. Cardiac conditions, female gender, and tumor size were independent prognostic factors for the development of complications[64].

Gill et al published a study with a 3-year follow-up in which the patients' creatinine rose from 1.2 to 1.4 mg/dL. Ten patients with solitary kidney had a mean creatinine of 2.2 and 2.6 mg/dL before and after surgery, respectively. Three patients with baseline renal failure had creatinine levels of 3.0 and 2.7 mg/dL before and after surgery, respectively. Mean blood pressure did not change significantly: systolic pressures before and after were 135.6 and 131.2 mmHg, respectively, and diastolic pressures were 78 and 72.7 mmHg, respectively[65].

Conclusion

Renal cryotherapy has been amply researched; the results at 5 years show that it is a safe and effective procedure. The main indication in the kidney is peripheral lesions smaller than 4 cm in patients who can benefit from nephron-sparing surgery. Future advances in renal cryotherapy will include improving approaches (single port, NOTES), improving the cryotechnology, and the administration of cryopotentiators with the purpose of maximizing cell death.

Conflict of interest

The authors state that they have no conflicts of interest.

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