Cryoablation of Small Renal Tumors

Steve Konrad Williams a, Jean J.M.C.H. de la Rosette b, Jaime Landman c, Francis Xavier Keeley Jr. a,*

a Bristol Urological Institute, Bristol, UK
b Academic Medical Center, Amsterdam, The Netherlands
c Columbia University Medical Center, New York, NY, USA

1. Introduction

The American Cancer Society estimates 38,890 new cases and 12,840 deaths from cancer of the kidney in 2006. Renal cell carcinoma (RCC) represents almost 85% of all newly diagnosed malignancies of the kidney, occurring at a rate of 4.4 to 11.1/100,000 person years. Recent data from the United States Surveillance, Epidemiology and End Results program demonstrate a steady increase in the rate of renal cell carcinoma between 1975 and 1995 [1].

Historically, a large percentage of new renal cancer cases were diagnosed with metastases. Widespread application of imaging modalities, has
led to a dramatic increase in the incidental detection of renal tumors [2–5]. The incidentally detected renal cell cancers tend to be smaller in size, and these tumors have an improved prognosis. This increase in the diagnosis of tumors smaller than 3 cm over the past 20 years may be partially attributable to early detection through widespread use of non-invasive techniques, though this alone cannot explain the upward trend [5]. The increases are most notable among persons aged 65 to 84 years and were generally least pronounced among individuals older than 85 years.

Historically, most patients have been treated with radical nephrectomy [6]; however, in the management of small tumors in the last decade, there has been a trend away from radical nephrectomy toward nephron-sparing surgery.

Nephron-sparing surgery, initially developed for patients with solitary kidneys or compromised renal function, is emerging as a viable treatment option for renal tumors smaller than 4 cm, even in the non-imperative setting, and is considered the treatment of choice by some authorities. Three factors have been associated with this phenomenon. Firstly, it was demonstrated that patients undergoing radical nephrectomy suffer a greater degree of renal compromise than patients undergoing partial nephrectomy [7]. Preservation of nephrons has been suggested to be protective against hyperfiltration injury with resultant superior long-term global renal function. Secondly, several large studies with long-term follow up of conservative treatment of renal tumors <4.5 cm demonstrated no increase in the risk of recurrence [8,9]. These tumors have a reportedly slow growth rate (0.35 cm/year) and low metastatic potential, with up to 22% of these tumors being benign on final pathology. Thirdly, a contralateral renal tumor may develop metachronously in those that are not curable, even with early detection and removal.

Several minimally invasive nephron-sparing procedures are being advocated for select patients with a small renal tumor, promising comparable oncologic control while decreasing operative morbidity. Laparoscopic surgery includes extirpative (laparoscopic partial nephrectomy) and a variety of ablative procedures. Laparoscopic partial nephrectomy is a technically challenging procedure that requires considerable laparoscopic dexterity and time-sensitive intracorporeal suturing [10]. Ablative techniques include a variety of treatment methods, where the tissue is destroyed in situ rather than by surgical extirpation. These technologies include cryosurgery, radiofrequency ablation, microwave thermotherapy, interstitial laser, and interstitial photon radiation. The objective behind these approaches, besides oncological efficacy and sparing renal function, is to decrease pain, morbidity, and hospital stay [10].

2. Natural history of small renal tumors

Renal cell carcinoma represents a single entity with a variety of histological appearances. The most common subtypes of RCC include conventional (clear cell), papillary and chromophobe. RCC is most commonly discovered in the seventh decade of life [11], and therefore many patients are older and have significant co-morbid disease with an increased risk of perioperative mortality and morbidity. Although morbidity from nephrectomy, whether open or laparoscopic, has decreased with improved techniques, it is still significant and reported in 11% to 40% of cases [12,13].

In selected patients, particularly the elderly, or in the presence of significant co-morbidities, expectant management may be a reasonable option [7,8]. In retrospective studies, Bosniak et al suggested that tumors less than 3.5 cm in diameter rarely metastasize and have a slow growth rate, suggesting a role for active surveillance with possible delayed intervention in these patients [3]. Metastases were not reported for tumors of this size at nephrectomy. Furthermore, Bosniak et al described the growth rate of renal tumors as a mean of up to 0.36 cm per year change in diameter on serial imaging. Most tumors showed little or no change in diameter with a small proportion accounting for most of the growth. They hypothesized that these same fast growing tumors are those that are not curable, even with early detection and removal.

In contrast, Oda et al retrospectively reviewed the records of 16 patients with a mean tumor size of 2 cm whose lesions were found incidentally and who did not undergo immediate surgical treatment for solid renal tumors that were later proven to be RCC [14]. They found that the median growth rate of primary lesions was 0.54 cm (range 0.10 to 1.35 cm/year, significantly higher than those reported by Bosniak et al). This may be due to the difference in clinicopathologic features of the patients involved in the two studies. While the study by Bosniak et al included oncocytoma and unknown renal tumors, Oda et al included patients with histologically-proven RCC. Oda et al concluded that candidates for watchful waiting should be selected very carefully, as the clinical behavior of renal tumors cannot be predicted. The implication of this is that the standard practice of immediate partial or radical nephrectomy in the elderly would need to be reviewed.
Given the natural history of these small renal tumors in the context of strategies aimed at tumor surveillance, patient selection for active surveillance with possible delayed intervention should be based on a combination of patient co-morbidity as well as tumor size. The heterogeneity of growth of renal tumors dictates that long-term radiographic follow-up is mandatory.

3. Renal tumor ablation

Ablation of renal tumors has emerged as a viable alternative to resection for local control when partial or complete nephrectomy is undesirable [15]. An important aspect in the management of these tumors is the eradication of neoplastic tissue with preservation of as much of the adjacent normal tissue as possible.

There are several clinical scenarios where ablation may be preferable to resection. In patients likely to have multiple renal tumors in their lifetime, such as those with von Hippel-Lindau disease, a minimally invasive approach is essential in balancing management of the underlying disease, maintaining quality of life and preserving kidney function. As stated earlier, the majority of small renal tumors are slow growing tumors, and a less invasive procedure may be preferable in elderly patients or those with multiple co-morbidities, as they present a significant operative risk.

The two ablation modalities that are currently clinically viable are cryotherapy and radiofrequency ablation (RFA). These two ablation modalities remain early in their development. The mechanisms of tissue destruction associated with these techniques are very different and the best method for ablation of renal tumors remains unknown. High-intensity focused ultrasound, microwave thermotherapy and laser interstitial thermal therapy have only been tried in animal models or small pilot studies, thus making any assessment of their value premature. These ablative modalities remain experimental and should not be used clinically without approved investigational protocols.

4. Renal cryoablation overview

The principle of cryoablation for renal tumors is derived in part from previous experience with cryotherapy for hepatic lesions. The clinical setting of RCC is markedly different, however, as the vast majority of patients have resectable, curable disease and the renal parenchyma is different in its nature and vascular supply. In using ablation in the management of these patients, careful patient selection is warranted, especially until long-term follow-up is available. With the introduction of newer and more sophisticated cryosurgical equipment, there has been increasing interest in the wider clinical application of these techniques, particularly in the management of renal tumors. The development of sensitive and sophisticated imaging modalities, such as intraoperative laparoscopic ultrasound (IOLUS) for intraoperative monitoring, as well as magnetic resonance imaging (MRI) and computerized tomography (CT) for postoperative surveillance, has also been important to the renewed interest in renal cryotherapy.

Various clinically-relevant cryogens are available. The boiling point of each of these cryogens determines the nadir temperature that the specific cryoprobe can produce. Liquid argon and liquid nitrogen, the two most commonly used cryogens, have boiling points of \(-186\, ^\circ\text{C}\) and \(-196\, ^\circ\text{C}\) respectively. In addition to the type of cryogen, the physical and thermal characteristics of a cryolesion also depend on the size and area of contact of the cryoprobe, and the rapidity of freezing. Early clinical experience with renal cryoablation incorporated the insertion of a single 3 to 5 mm cryoablation probe. Recently 17 gauge (1.47 mm) cryoprobes have been introduced that incorporate a modified heat exchange mechanism [16]. Larger cryoprobes typically result in larger ice balls because of increased circulation of the cryogen. Smaller cryoprobes minimize the risk of significant bleeding and allow the surgeon to shape the ice ball if one dimension of the ablation does not seem adequate.

To achieve the goal of reliable cancer cell ablation, cryosurgery should be carried out for small renal tumors (i.e., less than 3 cm). This tumor should ideally be located away from the major renal blood vessels, which can interfere with the cooling process; however, cryoablation can be carried out for a tumor abutting the collecting system, which appears to heal well following freezing. For a larger (>4 cm) tumor, a significantly larger ice ball is necessary, requiring the use of more cryoprobes, which increases not only the technical complexity of the procedure but also the potential for inadequate cryoablation, leaving residual viable cancer cells. Previous ipsilateral renal surgery is a relative contraindication for renal cryosurgery.

4.1. Renal cryoablation: Experimental studies

Freezing and thawing tissue results in complete tissue necrosis within well-defined parameters.
Experimental studies have helped characterize the process of cryoablation and have provided important guidelines for clinical renal cryotherapy. Investigations in animal models have demonstrated that renal cryoablation produces predictable and reproducible tissue destruction [17]. On the tissue level, cryoablation causes tissue necrosis by the deposition of intracellular and extracellular ice, an event that leads to the disruption of the cell membrane, organelles, proteins and local microvasculature. In addition, there is an increase in intracellular osmolarity that adds further injury. Eventually, these changes lead to coagulation necrosis followed by fibrosis and scarring. In swine, it has been demonstrated that complete renal tissue ablation occurred at temperatures of $-19.4 \, ^\circ C$ [18]. For cancer cells, however, lower temperatures may be required and a temperature of $-40 \, ^\circ C$ has been recommended to ensure cancer cell death.

Baust et al. found that a temperature of $-40 \, ^\circ C$ is found 5–6 mm inside the edge of the forming ice ball [19]. This suggests that extension of the ice ball 1 cm beyond the tumor edge would ensure adequate tumor ablation. Damage to the vasculature within the ice ball causes hyperpermeability of the microvasculature, resulting in thrombosis, vascular occlusion, regional tissue ischemia, and edema leading to delayed cell death [20]. In vitro studies have shown that induced apoptosis may also play a role [21]. It is important to note that cryotherapy injures not only individual cells at the time of therapy (direct damage) but also the tissue as a whole by impairing the microvasculature (indirect damage). The indirect damage is noted over the ensuing days and months.

Two types of cell thaw have been described: a passive or active thaw. Cell thaw and a second freeze cycle enhances further tissue destruction; the thaw may be carried out in an active fashion with helium gas or entirely passively, i.e., a slow thaw. Wooley et al. [22] compared lesion size as well as volumes of confluent necrosis resulting from combinations of single and double freeze-thaw cycles with active and passive thaws. This study found no difference between use of an active and passive thaw. Most investigators, however, recommend a slow thaw, arguing that this allows faster recrystallization to occur, enhancing direct cell damage [15,23,24]. The cryobiology literature defines a slow thaw as approximately 20 $\, ^\circ C$/min and a fast thaw as approximately 200 $\, ^\circ C$/min [25]. Slow thawing of the frozen tissue is thought to be a prime destructive factor and is done by allowing the tissues to thaw with no assistance from heating. The longer the duration of the thaw, the greater the damage to cells because of the solute effects, ice crystal restructuring (recrystallization), prolonged oxidative stress and growth of ice crystals [23]. The mode of ice crystal growth is greatest at $-15$ to $-40 \, ^\circ C$ and especially $-20$ to $-25 \, ^\circ C$.

Cellular survival depends not only on the freezing and thawing rates but also, most importantly, upon the lowest temperature reached and the hold time at subzero temperatures [23]. Experimental models show that over 90% of renal cell carcinoma cells survived temperatures above $-10 \, ^\circ C$, but only 15% survived temperatures of $-20 \, ^\circ C$ [24]. Other studies, using a single-freeze cycle and monitoring tissue with thermosensors have shown complete cell death at temperatures below $-19.4 \, ^\circ C$. The dual-freeze technique, however, increases physical damage to tumor cells, and a passive thaw may help to maximize tumor destruction.

Although the temperature at the tip of the cryoprobe (core temperature) is $-145 \, ^\circ C$ to $-190 \, ^\circ C$, depending upon the cryogen used, there is an incremental increase in temperature as one proceeds radially outwards, with the temperature at the visible edge of the ice ball being $0 \, ^\circ C$. Campbell et al. [26] confirmed that the critical lethal temperature of $-19.4 \, ^\circ C$ was uniformly achieved at a distance of 3.1 mm inside the visible margin of the ice ball (Fig. 1). This requires the ice ball to extend at least 3.1 mm

![Fig. 1 – Cryo-probe temperature diagram demonstrating isotherms.](image-url)
beyond the visible margin of the tumor to achieve uniform destruction of all viable tumor cells.

Weld et al. [16] recently characterized the size and shape of the ablated area as well as the surrounding intermediate zone associated with single and multiple rod configurations in a porcine model. They found that the average distance of complete tissue ablation beyond the tip of the rod was 4 mm and that the intermediate zone around the tip of the rod was consistently thinner compared to the width measured on cryolesion cross-sections (1.5 vs. 3 mm). As anticipated, there was complete tissue destruction centrally with viable renal cells found only in the intermediate zone. To ensure adequate treatment in clinical use, it is therefore recommended that the ice ball be extended 1 cm beyond the tumor margin [16,27]. This may be confirmed by direct laparoscopic observation superficially and with intraoperative ultrasound guidance for deeper components of the target lesion.

The histologic sequelae of renal cryoablation show characteristic features of necrosis. At 1 hour, gross examination demonstrates a well-defined area of dark red, interstitial hemorrhage with an abrupt line of demarcation. On light microscopy, generalized vascular congestion is evident with only subtle signs of early coagulation necrosis. Electron microscopy shows marked ultrastructural evidence of irreversible cell death, with chromatid condensation, loss of nuclear membranes and thrombi in almost all glomerular capillaries [28]. At 24 hours, on light microscopy, a well-defined central area of complete coagulative necrosis with a surrounding area of partial necrosis is seen [17]. The area of complete necrosis is characterized by loss of cell borders, nuclear pyknosis, absence of cytoplasmic organelles, and ghost renal tubules. The zone of partial necrosis contains some viable cells, thus representing an area of sublethal injury. On electron microscopy, tubular cells appear as proteinaceous aggregates, completely devoid of membranes. Glomeruli are degenerated, and glomerular spaces are filled with necrotic cellular debris [28]. At 1 month, microscopic examination reveals chronic inflammation, fibrotic glomeruli and tubules, hemosiderin deposition, and necrosis with no evidence of viable renal parenchyma. Fibrosis, scarring and collagen deposition of the mature infarct zone ensue, resulting in the telltale contracted scar typical of the chronic, long-term renal cryolesion [28].

4.2. Renal cryoablation: Clinical experience

Renal cryotherapy can be performed open, laparoscopically or percutaneously. It appears that the three approaches offer similar results as long as the tumor can be successfully localized and the probe inserted safely. The preferred approach may ultimately depend on the location of the tumor and user comfort level with the different imaging modalities.

In 1996, Delworth and colleagues [29] reported the earliest series of renal cryoablations in human subjects with solitary kidneys. These early series were performed via an open approach, and renal parenchymal preservation around the tumors as well as good renal function was noted.

In 1998 Gill et al. [30] performed cryoablation using the laparoscopic technique in an initial series of 10 cases. The laparoscopic approach has the advantage of limiting the perioperative morbidity associated with a flank incision while permitting the dual control of direct laparoscopic visualization and ultrasonographic monitoring to ensure the creation of an adequate ice ball. The anatomic location of the tumor on the kidney determines the laparoscopic approach: posterior tumors are preferably approached retroperitoneoscopically and anterior and anterolateral tumors transperitoneally.

Gill recently reported on 56 patients each with a 3-year follow-up [31]. They noted that the cryolesions decreased in size by 75% and completely disappeared in 8%, while needle biopsy confirmed locally persistent/recurrent tumor in 5.6%. Renal function was not compromised and surgical complications were minimal. Three-year cancer specific survival in 51 patients undergoing cryotherapy for a unilateral, sporadic tumor was 98%.

Schwartz et al. [32] recently reported on 85 consecutive patients with an average age of 67 years and a mean tumor size of 2.6 cm. Seventy cases were treated laparoscopically, of which seven were converted to the open approach. These conversions were early in the authors experience and were due to failure of progression because of inadequate exposure or tumor inaccessibility. A minimum of 3-month follow-up was available on at least 55 patients. One patient had a suspicious lesion on CT and MRI at the cryosite 12 months after the procedure was performed. A subsequent needle biopsy of the lesion revealed RCC, and a radical nephrectomy was performed. Post cryoablation mean creatinine levels were identical to pre-surgery levels. The authors concluded that laparoscopic cryoablation was safe with minimal morbidity.

Percutaneous cryoablation is also an option for treatment of selected small renal tumors. MRI, CT fluoroscopy and real time ultrasound have all been used to facilitate needle placement and to monitor progression and development of the cryolesion.
Uchida first described percutaneous cryotherapy in 1996 in two patients with metastatic RCC [33]. Although both patients had metastatic disease at presentation and died within 10 months of treatment, the authors noted shrinkage in size of the lesion and symptomatic improvement. Recently, Shingleton [34] reported on 55 patients undergoing MRI-guided percutaneous cryoablation of renal tumors less than 4 cm in size. With a mean follow-up of 18 months, 51 showed complete regression; however, 7 (14%) required more than one treatment session owing to incomplete initial tumor ablation. Two patients had local residual disease, and four died of non-renal disease. No complications were reported intraoperatively, with one patient requiring a transfusion postoperatively.

Several recent series [35–37] have subsequently confirmed that percutaneous cryoablation is a reasonable and safe option for the management of small renal tumors. The image guidance necessary for the percutaneous approach is a limitation for most urologists, however, as the approach commonly requires use of CT fluoroscopy or, rarely, an open MRI scanner. The procedures can be done by urologists in collaboration with interventional radiologists in the execution of these modalities for treating small renal tumors. Since the entire probe is cooled, care must be taken to avoid cryo-injury to sensory nerves at the body surface.

### 4.3. Renal cryoablation: Laparoscopic technique

The essential technical steps during laparoscopic renal cryoablation include complete mobilization of the kidney within Gerota’s fascia, excision of the perirenal fat overlying the tumor for histopathologic evaluation, in situ ultrasound imaging of the tumor and the remainder of the kidney, needle biopsy of the tumor, puncture cryoablation, and confirmation of hemostasis.

During laparoscopic renal cryoablation, intraoperative laparoscopic ultrasound (IOLUS) is a reliable and vital imaging technique [38]. Onik initially characterized the ultrasound appearances of the developing cryolesion in an animal model [39]. The IOLUS utilizes a flexible, steerable, color Doppler ultrasound probe. On IOLUS the renal tumors are mildly hyperechoic or have a mixed echogenicity, and the hyperechoic renal sinus fat is clearly visualized. By placing the IOLUS probe on the surface of the kidney opposite the tumor, precise advancement of the tip of the cryoprobe up to the deep margin of the tumor and adequate visualization of the leading edge of the ice ball as it obliterates the tumor margins can be achieved. The advancing front of the ice ball is seen as a hyperechoic rim with post-acoustic shadowing. The leading edge of the ice ball can be visualized on laparoscopic ultrasound to confirm that it advances approximately 1 cm beyond the margins of the tumor. This margin is immediately apparent laparoscopically as well (Figs. 2–4). This is important, as animal models have shown that the target temperature occurs within a few millimeters of the edge of the ice ball as seen on ultrasound; the actual zone of complete ablation (lethal ice) is a few millimeters smaller than the ice ball [22]. Several studies have corroborated this finding and have suggested that the ice ball tends to over represent the actual area of ablation.

**Fig. 2** – Placement of cryoablation needles into 2.8 cm right anterior renal tumor.

**Fig. 3** – Ice ball forming. Note laparoscopic ultrasound probe positioned posterolaterally to monitor depth of ice ball and thermocouples to monitor temperature in the center and at the edge of tumor.
Laparoscopy, though more invasive than the transcutaneous approach, provides better image of the ice ball and permits the kidney to be manipulated once it has been exposed, thereby protecting adjacent organs and ensuring adequate tumor ablation. Anterior tumors (Fig. 5) are typically located adjacent to bowel, while lower pole tumors may lie adjacent to the ureteropelvic junction.

4.4. Renal cryoablation: Percutaneous technique

Percutaneous cryoablation (PRC) offers the least invasive method of performing renal cryoablation. PRC may be performed on an outpatient basis, with the patient under minimal conscious sedation [37]. Ultrasound, open gantry MRI and CT scanning are the currently available modalities for image guidance for PRC. Ultrasound guidance was described in the first clinical application of PRC by Uchida et al. [33]. Ultrasound provides the advantage of ready availability and low cost, the capacity for real-time guidance of needle placement with non-axial and oblique imaging, and the absence of ionizing radiation. Ultrasound, however, is operator dependent, offers less precise visualization of the ice ball edge, and provides limited resolution in obese patients [36]. Open gantry MRI consists of 2 vertical cylinder-shaped magnets with a bore. The surgeon steps between the vertical magnets on either side of the bore to approach and treat the patient. This allows a direct hands-on approach with instruments introduced percutaneously. MRI yields 3-dimensional pictures that are of greater clarity and definition, crisp resolution of the ice ball, dynamic imaging that may be reconstructed in multiple planes, lack of ionizing radiation and the capacity to provide clinically useful follow-up images [34]. Open gantry MRI systems, however, are presently expensive and not widely available.

Reiser et al. [40] first indicated that CT may be a useful continuous monitoring technique for PRC. CT guidance is currently the method of choice for intra-procedural monitoring of PRC because it provides clear visualization of the ice ball and distinguishes it well from neighboring structures, such as bowel. Overall, the advantages of CT are that it is readily available, offers excellent visualization of the ice ball and critical neighboring structures, and provides real-time guidance in the CT fluoroscopy mode. A major disadvantage, however, is the consequent high radiation dose to which patients and cryosurgeons are exposed during real-time fluoroscopy [41]. Radiation protection measures must, therefore, be taken for these individuals; this is not a concern with MRI or ultrasound. Additional challenges may arise in cases where oblique angles may be difficult to achieve or when intraparenchymal lesions are not visible on non-contrast images. Finally, the gantry may interfere with optimal probe placement. However, this obstacle has been partially overcome by the use of newer right-angle probes.

4.5. Renal cryoablation: Complications

Complications following laparoscopic renal cryoablation include bleeding and injury to adjacent organs. Several reports have noted that the integrity of some structures is not compromised by exposure to cryogenic temperatures. The renal collecting system recovers well after cryosurgery even when
exposed to very low temperatures, unless it is physically punctured with a probe [42]. Inadvertent contact of the active cryoprobe or ice ball with surrounding viscera, however, may cause significant complications. Complete bowel obstruction, ileus, ureteropelvic junction obstruction and pancreatic injury have all been described [9,15,26].

Post-operative hemorrhage is less common with cryoablation as compared to laparoscopic partial nephrectomy (see Table 1). Carvalhal et al. [45] reviewed 22 patients who were followed after cryoablation for a mean of 20.6 months. No significant differences were noted in their pre-operative and postoperative serum creatinine levels or systolic and diastolic blood pressure values. A multi-institutional review showed that, following cryoablation, major and minor complications were 1.4 and 12.2% respectively [46].

4.6. Renal cryoablation: Follow-up

There is no consensus algorithm for monitoring patients radiographically in follow-up after renal cryoablation. The radiologic hallmark of successful renal cryoablation is lack of enhancement on contrast-enhanced CT or MRI. Lesions typically do not disappear for many months or even years but should progressively decrease in size. Weld et al. [47] recently reported their 3-year experience with laparoscopic renal cryoablation. The authors reported that the ablation zones initially increased in size by 52% on postoperative day 1 and then steadily decreased to the original tumor size by 6 months after surgery. The ablation zone was noted to shrink on average by 71% relative to the original tumor size at the three year follow-up period. We recommend a follow-up protocol of CT or MRI scans at three months and one year.

It is important to note that adherence to the recommended radiologic follow-up protocol may be mixed. Davol et al. [48] recently reported long-term results on a series of 48 patients followed after renal cryoablation. They found that once the treated renal tumor appeared resolved radiologically both patients and physicians became less attentive to the recommended follow-up protocol. Radiologic appearance of a renal lesion treated with cryoablation is complex, however, and as long as 12 to 24 months is required for disease persistence to be determined. Failure of a lesion to decrease in size, or any enhancement, mandates further intervention, which may include renal biopsy, repeat cryoaulation, partial nephrectomy or radical nephrectomy.

Several studies with intermediate follow-up have demonstrated safe and effective treatment of small renal tumors, as documented by radiographic follow-up and/or post-treatment needle biopsy [49,50]. It is important to realize, however, that salvage or repeat procedures may be required in up to 12.5% of patients [48]. Therefore, individual patients must provide full informed consent regarding the potential for additional procedures and monitoring relative to other extirpative procedures such as laparoscopic partial nephrectomy. A limitation of radiographic follow-up is the risk of false negative imaging results. Also, negative renal biopsy results may not be completely reassuring. Tumor cytology is often indeterminate, even in the hands of an experienced cytologist. Nevertheless, it represents a viable attempt to obtain histopathologic data in a minimally invasive manner in patients who are otherwise doing well from a clinical and radiological standpoint. Ethically, it may be difficult to justify a more thorough laparoscopic or open renal biopsy in patients with decreasing tumor sizes on follow-up scanning. This underscores the need for meticulous long-term (at least 10 year) radiological monitoring following renal cryoablation.

5. Other minimally invasive modalities

Laparoscopic partial nephrectomy (LPN) may be performed either transperitoneally or retroperitoneally. Despite advanced laparoscopic techniques, LPN poses several challenges, LPN has a steep learning curve and a high complication rate (up to 50%), with conversion to open surgery in up to a third of cases [51], possible renal injury caused by warm ischemia [52,53], urine extravasation due to late necrosis of the coagulated surface [53] and delayed bleeding [54]. LPN offers a more definitive oncological

### Table 1 – Comparison of perioperative morbidity in various series of renal cryosurgery

<table>
<thead>
<tr>
<th>References</th>
<th>Mean age (yr)</th>
<th>No of pts.</th>
<th>Mean tumor size (cm)</th>
<th>Mean operative time (h)</th>
<th>Blood loss (ml)</th>
<th>Hospital stay</th>
<th>Complication rate</th>
<th>Conversion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moon et al, 2004 [43]</td>
<td>61</td>
<td>16</td>
<td>2.6</td>
<td>3.1</td>
<td>40</td>
<td>1.9</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Schwartz et al, 2006 [32]</td>
<td>67</td>
<td>70</td>
<td>2.6</td>
<td>N/A</td>
<td>58</td>
<td>3</td>
<td>4%</td>
<td>10%</td>
</tr>
<tr>
<td>Cestari et al, 2004 [44]</td>
<td>64</td>
<td>34</td>
<td>2.5</td>
<td>1.9</td>
<td>165.3</td>
<td>3.8</td>
<td>20%</td>
<td>0</td>
</tr>
<tr>
<td>Gill et al, 2005 [31]</td>
<td>65.2</td>
<td>56</td>
<td>2.3</td>
<td>3</td>
<td>65.2</td>
<td>1.7</td>
<td>4%</td>
<td>0</td>
</tr>
</tbody>
</table>
outcome than cryoablation, albeit with a slightly higher major complication rate, longer hospital stay, and greater blood loss (Table 2). These results are highly dependent on the surgeon’s experience – laparoscopic partial nephrectomy is among the most challenging surgical procedures.

Radiofrequency ablation (RFA) works by converting RF waves into heat, resulting in thermal damage to parenchymal tissue [53,60]. When the temperature of tumor cells increases to >70°C there is direct cytological destruction [53]. Zlotta and colleagues first described RFA for renal tumors [59]. Several problems associated with RFA exist, including intraprocedural radiofrequency interference of the ultrasound images, even with shielding the US probe, irregularly shaped lesions of variable size that make it challenging to ensure consistent ablation of tumors without injuring sizable portions of normal parenchyma or surrounding structures. The most significant concern regarding RFA is the finding of ‘skip lesions’ of viable tissue in some RFA studies [61–63]. Although RFA has low short-term morbidity, the data from these studies (see Table 3) suggests that RFA at this time remains unproven until consistent and reproducible long-term oncological efficacy is demonstrated.

Newer energy sources for tumor ablation include high intensity focused ultrasound, laser, and microwave coagulators. Theoretic and experimental evidence suggests that the primary mechanism of tissue destruction by high intensity focused ultrasound (HIFU) is thermo-necrosis. HIFU generates beams of the required frequency region of a few MHz by resonant electrical excitation of the thin plates of a piezoceramic. Intersitial laser ablation is another emerging thermoablative minimally invasive modality that has been investigated as a treatment option for a variety of neoplasms, including the brain and breast [69,70]. Intersitial laser ablation utilizes optical fibres to deliver a high-energy laser to the target lesion. MR imaging is used both for the placement of the laser in the tumor and for monitoring progress of the thermocoagulation. Though interstitial laser ablation is an emerging technique, evidence of viable cells within treatment zone of benign parenchyma of an animal model mandates further refinement of the technique before further application in humans [70]. Microwave thermotherapy utilizes microwaves in the 300–3000 MHz range of the electromagnetic spectrum [71]. These waves interact with tissue and produce heat. The depth of tissue penetration is inversely related to the frequency and the water content of the targeted tissue. The initial report of microwave therapy in renal tissue was made by Hradec [72] in 1969. There have, however, been very few reports on its effectiveness since then. Kigure et al. [73] reported on its application on a tumor model in rabbit kidneys and found no difference in the survival between rabbits treated with laparoscopic microwave therapy and those undergoing open nephrectomy. These reports are encouraging, but further investigation is required to confirm the clinical utility of this modality.

6. The role of needle biopsy

Needle biopsy is essential in the diagnosis of renal tumors and should no longer be a source of
continuing controversy. At our institution, needle biopsy is performed under laparoscopic guidance immediately before the ablation procedure. Biopsy results are used primarily to guide the intensity of follow-up [74]. A substantial number of biopsies are read as non-diagnostic by the pathologist on final histologic analysis. We treat these cases as RCC unless proven otherwise and maintain the same follow-up regimen as in patients with biopsy proven malignancies.

The argument has been made that a biopsy may theoretically cause seeding or implantation; trigger significant bleeding, particularly as a result of neovascularization; and prove indeterminate [75]. Clinical parameters, especially with modern imaging techniques, it is argued, are accurate enough in the vast majority of cases to make a definitive diagnosis.

Despite these limitations, we believe that needle biopsy represents the standard of care, given that only histology can provide a definitive diagnosis. In the largest series to date, Gill et al. [31] reported that intraoperative precryoablation needle biopsy confirmed renal cell carcinoma in 36 of 56 patients (64%), oncocytoma in 6 (11%) and benign tissue in 12 (21%). For renal tumors less than 3 cm in diameter, one would expect this proportion of biopsies to show renal cell carcinoma, given that 68% of small renal tumors in modern laparoscopic partial nephrectomy series [10] are found to contain RCC. One must assume, therefore, that not every small renal tumor is malignant. Biopsy results are very useful in guiding follow-up, given that conventional clear cell RCC has a significantly worse prognosis than other histologic subtypes; however, frozen section evaluation of intraoperative needle biopsy samples is not generally considered a necessary prerequisite to proceeding to renal cryoablation.

7. Conclusion

In conclusion, initial experience with laparoscopic renal cryoablation suggests that it is a safe and feasible technique, with minimal patient morbidity and excellent short-term efficacy. Laparoscopic renal cryoablation has definite advantages compared to partial nephrectomy in that there is less blood loss, it does not involve hilar clamping and warm ischemia, does not involve technically difficult reconstructive technique, does not result in urine leaks, and decreases the need for ureteral stenting. It also offers advantages compared to partial nephrectomy in that it is easier to treat less exophytic tumors because of ultrasonic monitoring of the ice ball. Partial nephrectomy has advantages in that its margin status is known and follow-up biopsy is unnecessary.

Although cryodestruction of a renal tumor can be performed in a well-monitored and reproducible fashion, longer follow-up is needed before the true efficacy of this procedure can be determined. Meticulous follow-up with serial radiographic imaging of the cryoablated site is imperative, and any evidence of either enlargement or absence of reduction in the size of the cryoablated tumor should be investigated with a needle biopsy or laparoscopic or open exploration. Preliminary experimental data into renal RFA have identified viable tumor cells within a treated lesion, casting doubts regarding the efficacy of the procedure. Based on the available data, RFA at this time cannot be recommended as a first line treatment modality.

References

CME questions

Please visit www.eu-acme.org/europeanurology to answer these CME questions on-line. The CME credits will then be attributed automatically.

1. Small renal masses (<3 cm)
   A. Are benign in up to 14% of cases.
   B. Grow at a rate of 0.35 cm/yr.
   C. Incidence is increasing, especially in patients younger than 50 yr of age.
   D. Radical nephrectomy is associated with less renal compromise than partial nephrectomy.

2. Indications for ablation as opposed to resection of renal masses include:
   A. von Hippel-Lindau disease.
   B. Young age.
   C. Presence of metastatic disease.
   D. Large size.

3. Cryoablation
   A. Has a nadir temperature determined by the freezing point of the gas used.
   B. Commonly causes urinary leakage when the collecting system is treated.
   C. Has been associated with “skip lesions” on histologic examination.
   D. Produces a lesion that is affected by the size of probe and rapidity of freezing.
4. Tissue death in cryoablation is caused by the following mechanism(s):
   A. Formation of intracellular ice that causes disruption of cell membranes and organelles.
   B. Decreased cellular osmolarity leading to edema.
   C. Inpermeability of the microvasculature resulting in thrombosis leading to immediate cell death.
   D. DNA damage, especially for cells in S phase of the cell cycle.

5. Which of the following statements is true regarding lethal temperatures in renal cryoablation?
   A. A temperature of \(-19.4\,^\circ C\) leads to reliable tissue ablation in kidney tumors.
   B. In vitro, 90% of kidney cancer cells survive \(-20\,^\circ C\) but only 15% survive \(-40\,^\circ C\)
   C. A single freeze with active thaw maximizes tumour destruction.
   D. The nadir temperature and hold time at subzero temperatures affect cellular survival.

6. Renal cryoablation long-term results
   A. Are better for the percutaneous than laparoscopic or open approaches.
   B. Show that the tumour completely disappears in only 45% of cases.
   C. Demonstrate a 98% cancer-specific survival at 3 yr of follow-up.
   D. Rely on needle biopsies as the gold standard for outcome.