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CIRSE Guidelines on Percutaneous Ablation of Small Renal Cell Carcinoma

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Introduction

Overview of Renal Cell Carcinoma

Renal cell carcinoma (RCC) comprises approximately 3.8% of all new cancers in the western world; the detection rate of RCC has been increasing in the past 10 years by approximately 1.7% per year [1]. This rise is attributed to the increased number of diagnostic cross-sectional scans in which asymptomatic renal tumours are incidentally detected. The median age at diagnosis is 64 years [2].

RCC may be sporadic or congenital. Sporadic RCC has an established link with smoking and obesity. Congenital RCC is linked to specific gene mutations. The autosomal dominant mutation of the von Hippel–Lindau (VHL) gene predisposes to clear cell RCC [3, 4]. Another predisposing mutation is that of the germline MET proto-oncogene (MET). Germline mutations of MET have been detected primarily in patients with hereditary papillary RCC, whereas somatic MET mutations are also detected in 5–13% of patients with sporadic papillary RCC [5, 6].

The most widely accepted histological grading system of RCC is the Fuhrman nuclear grade, which distinguishes 4 different grades (Fuhrman 1 to 4) according to the shape of the nuclei; a simplified division into high (previously 3–4) and low (1–2) grades is now more commonly used [7]. According to the World Health Organization classification, there are three major histological subtypes: clear cell (80–90%), papillary (10–15%) and chromophobe (4–5%) [8]. The classification and grading were both updated in 2013 by the International Society of Urological Pathology (ISUP) Vancouver Classification [9]. The updated RCC histopathology classification is shown in Table 1.

The 5-year survival rate for kidney cancer is 91.8% for localized disease and 12.1% for advanced disease, with the most important prognostic factors being the tumour grade, the local extent and the presence of nodal or distal metastases at presentation [1]. The most common sites of metastasis include the lungs, bone, brain, liver and adrenal glands [4].

The vast majority of small tumours are asymptomatic. Clinical presentation of advanced tumours includes haematuria and flank pain from local infiltration and symptoms from metastatic dissemination (skeletal pain, lymph node enlargement, haemoptysis, convulsions).

Imaging plays a crucial role in the detection and characterization of renal masses. Computed Tomography (CT) before and after the administration of intravenous contrast is usually the first-line scan. A mass is considered to be enhancing if there is an increase of at least 15 Hounsfield Units (HU) after contrast injection [10]. CT also provides staging information including the spread of disease in the

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Table 1 The latest RCC histopathology classification. From Srigley JR et al. [9] (*mod.*)

The Vancouver RCC classification
Clear cell renal cell carcinoma
Multi-locular clear cell renal cell neoplasm of low malignant potential
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Hybrid oncocytic chromophobe tumour
Carcinoma of the collecting ducts of bellini
Renal medullary carcinoma
MiT family translocation renal cell carcinoma
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Clear cell papillary (tubulopapillary) renal cell carcinoma
Hereditary leiomyomatosis-associated renal cell carcinoma
Renal cell carcinoma, unclassified

contralateral kidney, extrarenal tumour extension, venous and lymph node involvement and distal metastases [11]. The specificity of CT is not very high between RCC and other renal masses with similar characteristics such as oncocytomas or fat-free angiomyolipomas [12, 13]. The specificity of Magnetic Resonance Imaging (MRI) is higher for such cases and is indicated if CT is indeterminate [14–16]; MRI is also indicated for patients that are allergic to iodinated contrast medium, for pregnant patients [17] and for patients with severe renal insufficiency where non-contrast sequences such as diffusion-weighted imaging (DWI) or arterial spin labelling (ASL) may be used [18].

RCC treatment strategy varies according to the tumour stage. TNM classification and staging are described in Table 2. The treatment options for Stage I (T1a and T1b) tumours include partial or radical nephrectomy and ablation therapy [19]. Radical nephrectomy is the only treatment option for Stage II and III tumours; for Stage IV tumours, radical nephrectomy is performed only as a cytoreductive measure, which may be combined with metastasectomy, prior to palliative chemotherapy [20]. In such cases, tumour embolization may also be used for relief from haematuria [21, 22].

Management of T1a Renal Tumours

Surgical Approach

Partial nephrectomy (open or laparoscopic) is a minimally invasive nephron-sparing surgical technique. Renal function is a significant prognostic factor for morbidity by cardiovascular events, and hence a nephron-sparing approach is of paramount importance for patients with early-stage RCC [23]. Total nephrectomy dramatically reduces renal function, particularly in patients with bilaterally impaired kidneys due to chronic disease [24]. Total nephrectomy inevitably leads to hyperfiltration and dysfunction of the contralateral kidney in the long term [23]. Given that both partial and radical nephrectomy appear to offer comparable long-term oncological outcomes for T1a tumours [25–28], partial nephrectomy will be the preferred surgical option for treatment of such lesions if resection is technically feasible.

From a technical perspective, partial nephrectomy is more suitable for T1a lesions in the poles of the kidney, whereas partial resection of interpolar lesions may be more technically challenging. In order to classify objectively the anatomical characteristics of the renal masses and to plan surgical resection, specifically described nephrometry scoring systems have been introduced and incorporated into clinical practice. These include the Preoperative Aspects and Dimensions Used for an Anatomical classification system (PADUA), the Radius, Exophytic/endophytic, Nearness, Anterior/posterior, Location (R.E.N.A.L.) nephrometry score and the Centrality index (or C-Index) [29–31]. The characteristics of the three scoring systems are illustrated in Table 3.

Active Surveillance

The rationale behind active surveillance is that the majority of small renal tumours have a slow growth pattern (mean growth rate of 3 mm per year) [32] and may be followed up easily with cross-sectional imaging over time [33]. However, it is reported in the literature that a reasonable number of small renal tumours (approximately 20%) will not follow this slow-growing pattern and will, on the contrary, grow aggressively [34, 35]. Furthermore, data from the National Swedish Kidney Cancer Register were used to assess the metastatic potential of RCCs smaller than 7 cm. These data included 3489 RCCs that were diagnosed between 2005 and 2008 (99% of all RCCs diagnosed nationwide), 2033 of which were smaller than 7 cm. The study revealed that 11% of 3- to 4-cm tumours had either nodal or distant metastases. Surprisingly, 7% of tumours smaller than 4 cm had distant metastases and only tumours smaller than 1 cm had neither lymph node nor distant metastatic deposits [36].

Currently, there is no biomarker available that would identify the behaviour of each small renal tumour, and consensus on whether to proceed with surveillance or treatment is based on the decision of the local Multidisciplinary Meeting, which considers the age and the general status of the patient as well as factors such as patient anxiety about the potential for metastasis.

Table 2 American Joint Committee on Cancer (AJCC), TNM Staging System for Kidney Cancer (7th ed., 2010)

Primary tumour (T)			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour 7 cm or less in greatest dimension, limited to the kidney		
T1a	Tumour 4 cm or less in greatest dimension, limited to the kidney		
T1b	Tumour more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney		
T2	Tumour more than 7 cm in greatest dimension, limited to the kidney		
T2a	Tumour more than 7 cm but not more than 10 cm in greatest dimension, limited to the kidney		
T2b	Tumour more than 10 cm, limited to the kidney		
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia		
T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat but not beyond Gerota's fascia		
T3b	Tumour grossly extends into the vena cava below the diaphragm		
T3c	Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0 or N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Ablation Therapy

Ablation therapy has been developed for the treatment of small renal tumours in an effort to provide a less invasive, nephron-sparing treatment for patients that cannot or do not wish to undergo surgery. McGovern et al. [37] reported in 1998 in *The Journal of Urology* the first case of percutaneous thermal ablation with the use of radiofrequency. It was an 84-year-old patient with a 3.5-cm exophytic mass who refused to undergo open surgery. He was successfully treated with radiofrequency ablation under ultrasound guidance using local anaesthesia and conscious sedation. This milestone case marked the beginning of a very exciting era for the treatment of small renal tumours. A variety of ablation modalities have been reported in recent years, but the most extensively used and studied modalities are radiofrequency ablation (RFA) and cryoablation (CRA).

RFA treatment may lead to 100% ablation in tumours smaller than 3 cm and >90% for sizes between 3 and 5 cm; results are significantly worse (<25%) for tumours that are larger than 5 cm [38]. It has been shown that for every cm of size increase above 3.6 cm the chance of recurrence-free survival decreases significantly ($p < 0.001$) by an estimated factor of 2.19 [39].

With cryoablation, T1b tumours may potentially also be treated as the size of the ablation may be monitored with imaging and volumetric ablation may be more controlled [40–42]. However, it was shown in a previous study that there is trend of subtotal treatment for tumours of size >4 cm [41].

Guidelines on the general management of RCC have been published by other scientific societies [43, 44]. The purpose of this document is to describe the technique, to evaluate the evidence and to conclude by stating the position of CIRSE on the ablation of cT1a RCCs.

Table 3 Summary of the features evaluated for the three nephrometry scores

Scoring system	Evaluated features
PADUA	Radius
	Exophytic/endophytic
	Location
	Renal rim
	Renal sinus
	Collecting system
R.E.N.A.L.	Radius
	Exophytic/endophytic
	Nearness of the tumour to the collecting system
	Anterior posterior
	Location to polar lines
C-index	Measures tumour centrality
	Ratio of the distance between the tumour centre, the kidney centre and the tumour radius
	($\sqrt{x^2} + \sqrt{y^2} = c$; d/2 = r; c/r = C-index)
	C-index <1: part of the tumour is superimposing the centre of the kidney
	C-index = 1: tumour edge at the centre of the kidney

Definitions

TNM classification is a cancer staging notation system that describes the stage of a cancer which originates from a solid tumour with alphanumeric codes; T describes the size of the original (primary) tumour and whether it has invaded nearby tissue, N describes nearby (regional) lymph nodes that are involved and M describes distant metastasis (spread of cancer from one part of the body to another).

Energy-based ablation is the direct application of energy-based (i.e. thermal and non-thermal) therapies to eradicate or substantially destroy focal tumours.

Applicator is the term is used for energy-based ablation and refers to the device used to deliver energy. RFA applicators are "electrodes", microwave applicators are "antennas" and cryoablation applicators are "cryoprobes".

Ancillary procedures are those techniques that are used to separate critical non-target structures from the target ablation zone in order to avoid non-target thermal injury.

Technical success is the term used to describe if the tumour was treated according to protocol and was covered completely by the ablation zone in the immediate post-ablation scan.

Technical efficacy is the term used to describe the success of the ablation after a specified follow-up time (i.e. three months).

Complications of renal mass ablation are classified according to the Clavien–Dindo system from I to V: a grade I complication does not require intervention; a grade II complication requires pharmacologic intervention; a grade III complication requires surgical, radiologic or endoscopic intervention; a grade IV complication is a life-threatening complication requiring intensive care unit management; and a grade V complication is death.

Residual tumour is defined as persistent evidence of enhancement (10–15 HU) within the ablated lesion on the first follow-up imaging (usually at 1 month post treatment).

Tumour recurrence is the new enhancement of the ablated lesion during the follow-up period following a previously documented successful treatment.

Recurrence-free survival (RFS) is the percentage of patients that do not show any local recurrence in the ablation zone.

Metastasis-free survival (MFS) is the percentage of patients without metastatic lesions from the ablated tumour.

Disease-free survival (DFS) is the percentage of patients that are free of local and metastatic disease at the last follow-up.

Cancer-specific survival (CSS) is the percentage of patients who did not die from the progression of the ablated lesion.

Overall survival (OS) is the percentage of patients that died of any cause including the progression of the ablated lesion.

Pre-treatment Imaging

Pre-procedural imaging is of paramount importance for procedure planning. The feasibility of the procedure, the site of access, the number and the pathway of the probes, the risk of adjacent organ injury and the necessity of ancillary procedures need to be defined from pre-procedural imaging [45, 46].

Ultrasound (US) is the least sensitive modality for the detection of T1a RCCs [47]. The use of micro-bubble contrast may increase the diagnostic accuracy of US: however, the relationship with the adjacent organs and the needle pathway cannot be confidently defined in all cases and imaging with contrast-enhanced CT or MRI is necessary [48].

The suggested protocol for the detection of T1a RCCs with CT consists of imaging the kidneys before, in arterial phase, 100 s and 10 min after intravenous contrast [49].

MRI has been shown to be equal to CT for the detection and in some cases superior for the characterization of renal masses [14–16]. However, CT is usually the modality of choice for probe guidance and most operators prefer a pre-

procedural CT scan for planning. MRI of T1a RCCs would usually include axial T1W in phase and out of phase; axial and coronal T2W; DWI using three b-values and ADC maps; and axial and coronal T1W before and after intravenous contrast in corticomedullary, nephrographic and excretory phases [49]. Intravenous gadolinium should not be administered to patients with severe or end-stage chronic kidney disease or with acute kidney disease (estimated glomerular filtration rate less than 30 mL/min/1.73 m^2) due to the risk of nephrogenic systemic fibrosis (NSF) [50, 51]. The option of macrocyclic agents (e.g. gadobutrol) also needs to be considered for these patients.

Indications for Treatment

The main indications and contraindications for percutaneous ablation are summarized in Table 4.

Patient Preparation

Biopsy

Even though current abdominal imaging offers high diagnostic accuracy for large renal masses, the diagnosis of small masses may be challenging. In essence, any enhancing solid lesion is considered an RCC until proven otherwise; 10–20% of those lesions tend to be benign after biopsy. According to the most recent guidelines of the European Association of Urology, percutaneous biopsy of small renal masses is necessary (a) when the mass is characterized as indeterminate from imaging, (b) to select patients that would undergo the pathway of active surveillance and (c) to obtain histology before ablative treatments [43].

There is consensus for biopsy with an 18-gauge needle as a sufficient tissue sample is provided with acceptable morbidity [52]. A coaxial system is preferable to reduce the risk of seeding [43, 52]. Percutaneous biopsies are linked with low morbidity and the most reported complications are subcapsular or perinephric haematoma and haematuria with a very low percentage of clinically significant bleeding (<2%) [53]. The biopsy constitutes part of the diagnostic workup that is usually performed independently from ablation of the tumour [54]. However, there are operators that prefer performing the biopsy that same day of the ablation. This is usually performed through a coaxial needle in order to reduce the number of punctures and offers the opportunity to ablate the biopsy tract.

Clinical Visit and Consent

The interventional radiologist that will perform the ablation procedure needs to visit the patient at an outpatient clinic prior to the date of the procedure. The purpose of the visit is to describe the procedure, the imaging and the ablation modality that is going to be used, explain the risks and the benefits, explain any ancillary procedures that may be required and obtain informed consent from the patient. In addition, during the visit the radiologist needs to assess the general condition of the patient, to investigate comorbidities, to assess whether the procedure may be performed as a day case and to discuss the anaesthesia requirements of the patient. The visit also helps establish a relationship with the patient and the patient's environment [38, 39, 45, 55, 56].

Treatment ideally needs to be performed under general anaesthesia [38, 39, 45, 55, 56]. General anaesthesia (GA) reduces intraoperative patient awareness and recall and offers pain control for prolonged periods of time. It offers a very controlled environment for the operator and allows performing complex cases that may require the insertion of more than one probe. If GA is not available or not possible, then conscious sedation may be used. Bispectral Index (BIS) monitoring is required in such cases, to directly measure the effects of anaesthetics and sedatives on the brain. Both types of anaesthesia may be offered if treatment is performed on a short-stay setting.

Table 4 Indications and contraindications for RCC ablation

Indications for treatment with ablation are the following:
Presence of comorbidities that would increase the risk the surgical intervention (advanced COPD, heart failure)
Single functioning kidney
Impaired renal function (GFR <60 ml/min per 1.73 m^2)
Presence of more than one small renal tumour
Patient's choice not to undergo a surgical procedure
Contraindications are the following:
Uncorrectable coagulopathy
Extensive spinal deformity that would not permit percutaneous access to the lesion (relative contraindication)

Laboratory Evaluation

The clotting function (platelet count, partial thromboplastin time and international normalized ratio) needs to be evaluated prior to the procedure. In the pre-procedural laboratory tests, a full blood count and biochemistry test (urea, creatinine, eGFR and electrolytes) must also be performed [55].

Regarding clotting function, the values of international normalized ratio inferior to 1.5 and platelet count superior to 50,000/μl are required in order to proceed [57]. Antiplatelet or anticoagulation treatment needs to be stopped five days prior to the procedure.

Equipment Specifications

Radiofrequency Ablation

Radiofrequency ablation is the first and most widely studied ablative modality used for the percutaneous image-guided treatment of renal tumours, and the longest follow-up results are available for this modality. RFA technology is based on the interaction between high-frequency (150 kHz–1 MHz) rapidly alternating electric current and biological tissue. The electric current causes vibration of the tissue's water molecules that is then transmitted between adjacent molecules with resulting frictional energy loss. The energy is deposited in the tissues in the form of a rise in temperature that leads to "coagulation" necrosis [58]. The target temperature for RFA is between 55 and 100 °C; at 55 °C, tissue death results within 2 s, whereas at 100 °C evaporation occurs and cellular death is instantaneous. RF ablation is heavily dependent on good electrical and thermal tissue conductivity. If the power is delivered in very short time, desiccation of the tissue around the electrode occurs (charring) and energy transmission is limited. The aim of RFA is to heat tissues to 50°–100 °C for 4–6 min without causing charring or vaporization.

RFA electrodes may be unipolar or multipolar; they may be straight (single or clusters of three) or multi-tined and they can be internally cooled with saline. The electrode acts as the cathode of a closed electrical circuit. The grounding pads that are applied in the patient represent the anode.

Cryoablation

Cryoablation was the first method employed for the ablation of RCCs in an intraoperative setting and is also very widely practised for the percutaneous treatment of renal tumours. CRA causes direct cell injury that is based on two biophysical changes. The first is osmotic dehydration of the cells, which occurs due to the extracellular propagation of freezing and an increase in the solute concentration outside the cell. The second mechanism is the formation of intracellular ice, which occurs when the reduction of the temperature is sufficiently rapid to trap water within the cell and there is not enough time to respond osmotically to this insult [59]. The predominance of one type of injury mechanism over the other depends on the following parameters: the cooling rate, the end temperature, the time held at the minimum temperature and the thawing rate. The end temperature, however, appears as the most predominant parameter of cryoablation. The "lethal temperature" in which the complete destruction of cell or tissue occurs has been shown to be highly dependent upon the cell type; normal renal tissue is expected to be irreversibly damaged at temperatures lower than −25 °C, but renal cancer is more cryo-resistant with a lethal temperature of −40 °C [60]. In addition, cryoablation leads to injury of the microvasculature, due to vessel wall damage from distension and engorgement from the dehydration of the surrounding cells [59].

In the clinical setting of image-guided CRA, the "ice-ball" is visible under all modalities. However, it is important to note that the ice-ball does not correspond to the lethal temperature zone, as the temperature on the ice-ball isotherm is +0.5 °C. According to an experimental study by Georgiades et al. [61] performed in porcine kidney without renal cancer, the distance between the visible isotherm and the non-discernible lethal isotherm was 0.75 ± 0.44 mm. Therefore, it is suggested that the ''ice-ball'' margin must extend at least 6 mm beyond the target lesion. This and other studies [62, 63] confirmed that there is no "heat pump" effect around the blood vessels, within the cryoablated region.

Each applicator is at the minimum 17G and can be individually controlled; the target of the operator is to construct a three-dimensional therapeutic isotherm that covers the target lesion. Treatment is divided into freeze and thaw cycles. Two freeze–thaw cycles of 10–15 min of freezing and 8–10 min of thawing are usually required. The thawing temperature is usually around 42 °C.

Microwave Ablation (MWA)

Microwave ablation is widely used for the percutaneous ablation of other organs (liver, lungs) and most Interventional Radiologists are familiar with this technology. Its inclusion in this Standards of Practice document is due to the increasing use of MWA for the treatment of renal tumours.

Microwave technology uses a high-frequency electromagnetic wave that causes water molecules to rotate. The non-equal distribution of the electric charge on water molecules causes their continuous re-orientation within the

oscillating field; this movement increases their kinetic energy and therefore the temperature of the tissue [64]. The kinetic energy is transformed to thermal energy that is deposited in the cells and causes coagulation necrosis [65]. Microwave frequency for ablation is 915 or 2450 MHz. In comparison to RFA, MWA offers a more extensive ablation area in a shorter time (especially at 2450 MHz) and is not limited by the heat sink effect, desiccation or charring [66]. Ablation is usually performed as a "single-stick" technique, although multiple antennae may be used simultaneously for larger tumours. Perceived disadvantages of MWA are that the shape of the ablation zone is usually ovoid instead of spherical, as would be required for renal masses, and that overheating of the antenna may occur, which can limit power delivery [67]. To overcome these disadvantages, internally cooled, 17G microwave antennas have been created, which are expected to offer larger and more spherical ablation zones [68, 69]. The novel MWA antennas shape the electromagnetic fields by controlling electrical currents on the radiator (field control), prevent unintended heating of tissue by hot microwave cables within the antenna shaft (thermal control) and minimize the elongation of the wavelength on the radiator to maintain effective field control (wavelength control). However, even with the use of the novel antennas there is a relatively higher risk of pelvicalyceal injury with the use of MWA than with the other modalities and the use of this technology in the treatment of renal tumours needs to be limited to the more experienced practitioners.

Procedural Features

There is no consensus on the use of antibiotics prior to the procedure: this relies on the physician's preference. This is not the case for diabetic patients, patients with an ileal loop diversion or when a ureteric stent for pyeloperfusion has been placed; in such cases, prophylactic antibiotics should be used at all times [70]. The suggested protocol is the use of levofloxacin or ciprofloxacin and metronidazole to start 2 days before and continue for 2 weeks after ablation.

Premedication with analgesia and antiemetics prior to the procedure may also be used, according to the operator's preference. A suggested protocol is 100 mg of pethidine injected intramuscularly and 10 mg of metoclopramide injected intravenously, one hour prior to the procedure [71, 72].

Imaging Guidance

The guidance modality relies also on the physician's preference. Nevertheless, there is increasing consensus that kidney ablation procedures need to be guided under CT or MRI [45, 73–75]. The advantage of US is that it provides real-time imaging for needle placement and deployment; however, real-time imaging is also feasible both with CT and MRI. Crucially, with US, the exact anatomical relationship with the surrounding organs (particularly the bowel loops) cannot be easily delineated. Furthermore, post-ablation bleeding cannot always be assessed due to the ablation acoustic shadow [60]. For these reasons, US cannot be recommended as the guidance modality, unless it is performed in selected patients by a very experience operator in both b-mode and contrast-enhanced US (CEUS). CT is available in every radiology department; under CT guidance, reconstruction in three planes is immediate and the distance of the electrode from the surrounding anatomical structures is easily just determined. Furthermore, a quick post-procedure scan will exclude complications such as bowel injury or bleeding. MRI is also available in most radiology departments; however, only specialized centres perform MRI-guided interventions. MRI guidance is more technically demanding, as specific coils, electrodes, patient monitoring equipment and 3D software are required and there is limited space for the operator within the gantry. However, electrode insertion can be monitored in real time and there is no radiation exposure. Another advantage of MRI is that thermography may additionally be employed to measure tissue temperature.

Adjunctive Techniques

The location of the tumour within the kidney also plays an important role in determining the treatment strategy. It is expected that a higher success rate will be obtained for exophytic lesions because the surrounding fat acts as an "insulator" for heat dissipation and increases the effect of ablation treatment.

Renal tumours may be in close proximity to the surrounding organs that need to be protected from the thermal effects of ablation. With the use of fluid and CO_2 dissection, adjacent organs such as the bowel are moved away from the ablation zone [76, 77]. This is achieved by placing a needle with a sheath, under imaging guidance, into the perirenal (retroperitoneal) space between the organ and the tumour. Fluid or CO_2 is then injected from the needle. In the case of RFA, when fluid dissection is performed, it is important to inject non-ionic solutions that act as insulators of the electric current, typically dextrose 5%. A small amount of contrast may be added to the fluid to make it more visible when under CT guidance. Alternatively, CO_2 may be used. The advantages of the use of CO_2 are its low thermal conductivity (less than that of air), the lack of toxicity and the low cost. When CO_2 is injected, it is quickly reabsorbed by blood vessels without the risk of

embolism due to its very high solubility and is then eliminated by respiration. As in the case of fluid injection, a thin needle is inserted in the perinephric area. This is connected to the dedicated CO_2 injection syringe, which has a Luer lock system and a filter to prevent contamination. Up to 1.2 litres may be injected in the abdominal cavity before there is a rise in intra-abdominal pressure. Repeated injections may be required as CO_2 is absorbed rather quickly.

In case of ablation of central lesions or of lesions located in the medial side of the lower pole, there is risk of damage to the ureter and the pelvicalyceal system. In order to reduce the risk of thermal injury, a retrograde ureteric stent may be inserted and connected to perfusion of one litre of cold (2–6 °C) 5% dextrose in the case of RFA, or warm saline in the case of cryoablation [78]. The perfusion pressure should be around 80 cm H_2O. A bladder catheter is also inserted to remove the perfused fluid [79].

Another adjunctive technique is transarterial embolization, which may be performed prior to RFA to reduce heat sink effect and risk of bleeding. The ischaemic effect also enhances the radiofrequency ablation and aids to spare healthy parenchyma but has to be superselective as previously reported [80, 81]. Embolization may also be performed with iodinated oil in order to use the distribution as a marker for CT-guided electrode placement [82].

Medication and Post-Procedure Care

Immediate post-ablation monitoring includes blood pressure, pulse and pulse oximetry every fifteen minutes for the first two hours and every half hour for the following two hours. The patient may be observed until the next morning and painkillers may be administered on demand. If the procedure is a day case, the patient may be discharged after 10–12 h. Prior to discharge, a new CT scan (non-contrast series, an arterial, a nephrographic 100-s phase and a delayed excretory phase) is required to exclude complications such as bleeding or bowel perforation.

Post-Procedural Follow-up Care

Patients may be seen on an outpatient basis four weeks post treatment. During the first visit, the level of pain, the ability to pass urine and the presence of any haematuria and/or fever are assessed, and the skin entry point is examined.

A follow-up contrast CT scan needs to be performed on the day prior to the outpatient visit. The results of the scan need to be discussed with the patient. If there is any suspicion of subtotal treatment, a new "determining" contrast CT scan needs to be performed at 3 months with a view to re-intervention. If treatment is considered definitive on the first scan, follow-up contrast CT scans need to be performed at 1, 3 and 5 years. The treated lesion is expected not to be enhancing after contrast injection, indicating coagulative necrosis. If nodular enhancement of more than 15 HU is noted, this is considered as residual disease or disease progression. The margin between the ablated tissue and the non-ablated renal parenchyma may be replaced gradually by fat that evolves to form a crescent-like band or "halo" that may be identified in the majority of the cases.

In case of deranged renal function (serum creatinine higher than 1.2 mg/dl), pre-hydration or a follow-up scan with CEUS is suggested [83].

The scanning protocol for follow-up CT includes a non-contrast series, an arterial, a nephrographic 100-s phase and a delayed excretory (10 min) phase [84]. The ablated area is expected to appear as non-enhancing [85]. Hyperdense areas may appear within the ablated area in the non-contrast scan, which represent denatured proteins.

In the case of MRI subtraction, late arterial phase imaging may be used. For the follow-up MRI, most centres will obtain a three-plane localizer image and then an axial T2-weighted, an axial T2-weighted fat-sat, axial and coronal dual-echo, axial dynamic 3D gradient-recalled echo before and after gadolinium injection (20-, 70- and 180-s delayed) and 5-min delayed spoiled gradient-recalled echo imaging [74]. The ablated areas in MRI are expected to appear with an increased signal in T1 and with a decreased signal in T2. In addition, diffusion-weighted imaging (DWI) sequences and arterial spin labelling (ASL) may also be obtained [86].

Outcome

Effectiveness

Levels of Evidence

The information provided in this Standard of Practice document is described according to the Levels of Evidence for therapeutic studies, as suggested by the centre for Evidence-Based Medicine [87], illustrated in Table 5.

There is very extensive evidence in the literature from case series and retrospective studies on the technical outcomes, the safety and the effectiveness of the use of RFA and CRA for the treatment of T1a RCCs, with very good outcomes with respect to all three aspects [(38–42, 59, 70–72, 88–94; Level of Evidence 3, [86]; Level of Evidence 2a]. The description of these studies is outside of the scope of this document. The document will focus on the studies with the longest follow-up after percutaneous treatment of sporadic T1a RCCs and on evidence regarding

Table 5 Levels of evidence for therapeutic studies (*mod.*)

Level	Type of evidence
1a	Evidence from systematic review or meta-analysis of randomized controlled trials
1b	Evidence from at least one randomized controlled trial
2a	Systematic reviews (with homogeneity) of retrospective cohort studies
2b	Individual retrospective cohort study or low quality randomized controlled trial
3a	Systematic review (with homogeneity) of case–control studies
3b	Individual case–control study
4	Case series
5	Evidence from a panel of experts

the comparison between percutaneous ablation and surgery for this group of patients.

Long-term Studies

Studies of the largest number of patients with the longest follow-up time are reported in the single-centre retrospective series from Psutka et al. ([88], Level of Evidence 3). The authors excluded known risk factors for recurrence such as a positive RCC, multiple tumours and/or hereditary RCC syndromes, and included only patients with sporadic T1 RCC who were considered as poor surgical candidates and were treated with percutaneous image-guided RFA. In the study, 185 patients were included (143 with T1a and 42 with T1b) with a median tumour size of 3 cm (IQR: 2.1–3.9 cm). Patients were followed up for a median of 6.43 years (interquartile range: 5.3–7.7 years). There were 12 (6.5%) local recurrences after a median time of 2.5 years with a statistically significant difference between T1a and T1b lesions. In a multivariate analysis, tumour stage was the only significant predictor of disease-free survival (DFS), with 96.1% 5-year recurrence-free survival and 91.5% disease-free survival for T1a lesions.

Georgiades et al. ([40], Level of Evidence 2a) reported a prospective, single-centre study of 134 patients with biopsy-proven RCC and tumour size 2.8 ± 1.4 cm who were treated with percutaneous CRA under conscious sedation. In this study, 5-year efficacy was 97.0%, and 5-year recurrence-free survival was 100%. All-cause mortality was three (none tumour related), and 5-year overall survival was 97.8%. The complication rate was 6%.

The abovementioned studies [40, 88] are the series with the longest follow-up in the largest number of patients and offer the strongest evidence for the oncological outcomes of percutaneous RFA and CRA at 5 years post treatment.

As regards long-term data on surgical treatment, and in particular after PN, Lane et al. ([89], Level of Evidence 3) published in 2013 the results of a single-centre retrospective study of 894 T1a RCCs that were excised with either open or laparoscopic PN. The mean follow-up time was 6.6 years for the laparoscopic and 7.8 years for the open group. In terms of oncological outcomes, 5-year recurrence-free survival was 97.8 and 97.1% for laparoscopic and open PN, respectively.

Comparative Studies

Katsanos et al. ([90], Level of Evidence 2a) performed a review and meta-analysis of one RCT and five high-quality cohort studies that compared all types of ablation technology with all types of surgical nephrectomy for the treatment of documented T1 RCCs with at least 1 year of follow-up. The primary outcome measure of this review was disease-free survival (DFS) and no statistically significant difference was identified between the two treatments [pooled hazard ratio (HR) 1.04, 95% confidence interval (CI) 0.48–2.25, $p = 0.92$]. Other measured outcomes were the overall rate of complications, which was significantly lower for thermal ablation than for surgical treatments [7.4 vs 11.1%; pooled relative risk (RR) 0.55, 95% CI 0.31–097, $p = 0.04$], and the need for repeat treatment, which was significantly higher for thermal ablation [7.2 vs 0%; pooled RR: 8.1, 95% CI 1.8–36.3, $p = 0.006$]. However, this meta-analysis included both T1a and T1b tumours, and cases in which the ablation treatment was performed open or laparoscopically as well as percutaneously.

Nevertheless, one of the retrospective studies included in the meta-analysis compared percutaneous RFA to open PN in patients with T1a RCCs. Specifically, Takaki et al. ([91], Level of Evidence 2b) conducted a single-centre retrospective study that was published in 2010, in which they compared the treatment of 115 patients with T1a RCC, 51 of whom received percutaneous RFA, 54 total nephrectomy and 10 partial nephrectomy. The authors included only patients who were followed up for more than 6 months: the mean follow-up period was 34 months for RFA, 41 months for total and 26 months for partial nephrectomy. The 5-year DFS was 98% for RFA and 94.2% for total nephrectomy. For PN, data were only available at 3 years, at which point DFS was 75%, although the difference between the three treatments was

not statistically significant. The percentage decrease of the glomerular filtration rate (GFR) was significantly lower for RFA vs total nephrectomy (7.9 vs 29%) at the end of follow-up but there was no significant difference between RFA and PN.

Furthermore, Thompson et al. ([92], Level of Evidence 3) recently published a retrospective single-centre study of 1424 patients with a T1a tumour, of which 1057 underwent PN, 180 underwent percutaneous RFA and 187 underwent percutaneous cryoablation. Local RFS was similar among the three treatments ($p = 0.49$), whereas metastasis-free survival (MFS) was significantly better after PN ($p = 0.005$) and cryoablation ($p = 0.021$) when compared with RFA. The patients treated with PN were significantly younger and had longer overall survival ($p < 0.001$). The authors stated that recurrence-free survival was similar for PN and percutaneous ablation; metastasis-free survival was superior for PN and cryoablation in comparison to RFA. The conclusion of this large cohort study is that partial nephrectomy and percutaneous ablation for small and localized renal masses are associated with similar rates of local recurrence.

Ablation for Good Surgical Candidates

In all the abovementioned studies, percutaneous ablation treatment appears to show comparable results to PN for patients that are not considered suitable for surgery (mainly patients with American Society of Anesthesiologists (ASA) score >3). In a single-centre retrospective analysis of 11 years of experience, Ma et al. ([93], Level of Evidence 3) reviewed 52 healthy adults with T1a RCC who underwent treatment with percutaneous RFA even though they would have been suitable for surgery (ASA score of 1 or 2). Patients with a hereditary predisposition to RCC or with previous interventions in the same kidney were excluded. The tumours had a mean size of 2.2 cm (SD ± 0.8 cm) and 53.4% of them were exophytic. The patients were followed up for a mean time of 60 months (range 48–90 months), and the authors reported no recurrence after 3 years and recurrence-free survival of 94.2% at both 5 and 10 years. Overall 5- and 10-year survival rates were 95.7 and 91.1%, respectively. The authors concluded that RFA treatment provides durable oncological and functional outcomes for T1a tumour in healthy patients.

Complications

There are complications related to percutaneous image-guided ablation of small renal masses, and these need to be recognized and avoided. The complications of renal mass ablation are classified according to the Clavien–Dindo system from I to V. The main complications are related to bleeding or thermal injury of the surrounding organs. Minor bleeding is inevitable in the majority of procedures to the kidney; however, the coagulation status of the patient needs to be controlled in order to avoid more dramatic occurrences such as retroperitoneal extension of the haematoma. The incidence of haematoma formation is approximately 6%, while massive bleeding that requires transfusion after RFA has been reported in <1% of cases [38–42, 60, 71–73, 88, 93–99]. The acute haematoma usually appears in CT as a hyperdense collection of fluid that decreases in density after a few days. In some cases, transfusion alone is not enough to control the bleeding and embolization is required. Another relatively frequent complication is haematuria with a reported incidence of 0.5–1% [37–41]. Usually, this is self-limiting and resolves after 12–24 h. If haematuria persists, then thermal damage of the pelvicalyceal system needs to be considered. In such cases, a CT scan will reveal thickening of the proximal ureter or the presence of haematoma within the pelvis [100]. Retrograde catheterization and placement of a ureteric stent for irrigation is required. Thermal damage may also occur to the bowel and this may be prevented with the use of fluid or CO_2 dissection as described. In cases of bowel injury, a post-ablation CT scan will demonstrate wall thickening that may evolve to adhesions and perforation [101]. Table 6 illustrates the complications of ablation and describes the including percentage of each complication as reported in the literature and the suggested threshold in clinical practice.

It needs to be taken into account that the complication rate of surgery- and particularly on the novel surgical techniques is significantly higher. In a systematic review of the literature, Froghi et al. [102] compared the results of laparoscopic partial nephrectomy with robotic partial nephrectomy from six studies for a total number of 256 patients. The parameters that were evaluated were operative time, estimated blood loss, warm ischaemia time, length of stay and complications, without significant difference between the two novel surgical methods, concluding that robotic partial nephrectomy does not appear to offer better results than the laparoscopic one. Complications up to 18.5% were reported as related to the robotic PN including extensive blood transfusion, significant lymph leak resulting in diet modification, respiratory distress requiring intubation, pulmonary embolism, ileus and angina, complications up to 20% were reported for the laparoscopic arms of the study including severe bleeding, pseudo aneurysm formation, renal failure, prolonged urine leak requiring urethral stent insertion, pneumonia and haematuria.

Table 6 Complications of ablation, percentage of each complication as reported in the literature and the suggested threshold in clinical practice

Complication	Percentage in the literature (%)	Suggested threshold in clinical practice (%)
Bleeding		
Perirenal haematoma	3–6	<5
Retroperitoneal haematoma	1	<1
Bleeding from arterial source	<1	<1
Haematuria	0.5–1	<1
Injury to or stenosis of the ureter or ureteropelvic junction	1–3	<2
Bowel perforation	1	<1
Infection/abscess	<1	<1
Sensory or motor nerve injury	1–3	<2
Pneumothorax	<2	<1
Needle tract seeding	1	<1
Skin burn	1	<1

Conclusions

According to the European Association of Urology's (EAU) most recent guidelines on the treatment of RCC [43], partial nephrectomy is strongly recommended for patients with T1a tumours (Grade of recommendation A). The European Society of Medical Oncology (ESMO) guidelines [36] state that partial nephrectomy is recommended for the treatment of all T1 tumours only if negative margins are obtained and the risk of morbidity is acceptable, due to the lack of strong evidence for its use (Level of evidence III). Hence, the ESMO's recommendation for PN (Grade of recommendation C) is weaker than that of EAU. Regarding ablation, EAU states that no recommendation can be made on RFA and cryoablation due to the low quality of available data (Grade of recommendation C); ESMO guidelines state that ablation may offer an option in patients with small cortical tumours (<3 cm) and age >70 years, high surgical risk, solitary kidney, compromised renal function, hereditary RCC or multiple bilateral tumours (Grade of recommendation C). The same guidelines consider active surveillance as a valid option for patients >75 years with significant comorbidities and solid tumours <4 cm (Grade of recommendation C). The recommendation of EAU on active surveillance is also weak (Grade C) and the suggestion is that it needs to be offered only to elderly and/or comorbid patients with small renal masses and limited life expectancy, alongside ablation therapy. From all the above, it is clear that there is no strong evidence on any of the existing treatments—not even for partial nephrectomy.

The role of CIRSE is not to undermine confidence in the results of surgery, which is the gold standard for a large number of patients, but to delineate the role of percutaneous treatments. According to the existing evidence, percutaneous ablation represents a valid treatment of T1a RCCs with excellent long-term (>5 years) technical and functional outcomes and a very low complication rate. The procedure is minimally invasive and may be performed under sedation and as a day case (Table 7). Considering that an effective minimally invasive solution is available for patients with T1a RCC, active surveillance has to be reserved only for patients that are not suitable for ablation due to age and comorbidities.

Bhan et al. [103] used a decision-analytic Markov model to compare the costs and the quality-adjusted life expectancy for a 67-year-old patient with a small renal mass undergoing either immediate percutaneous ablation or active surveillance with a subsequent ablation if needed. The authors concluded that the second option appears more

Table 7 Overview of cT1a RCC percutaneous ablation treatment

Overview of cT1a RCC percutaneous ablation treatment
Percutaneous ablation represents an alternative to surgery for the treatment of T1a RCCs
The technical and functional outcomes of the procedure are excellent
The rate of complication is very low
The procedure is minimally invasive and may be performed under sedation and as a day case
The patients that may undergo treatment with percutaneous ablation are those with ASA scores 1–3
>5-year oncological data are available and are also excellent

cost effective than the immediate treatment; however, it needs to be taken into account the factor of the lack of predictability of metastatic disease in those patients managed with active surveillance. As described, the data extracted from the National Swedish Kidney Cancer Register [36] showed that 7% of T1a tumours had distant metastases, with the percentage rising to 11% when dealing with lesions between 3 and 4 cm. There are RCCs that grow slowly and do not metastasize; however, factors such as patient anxiety from knowing that one has a potential malignant tumour, the cost of repeated cross-sectional examinations and the risk of repeated irradiation if CT is used for monitoring need to be taken into account. Considering that the behaviour of renal masses cannot be predicted, all fit patients with a T1a RCC need to be treated and if a minimally invasive option is required or the patient is not willing to undergo surgery, percutaneous ablation is a very effective option.

In addition to the data discussed here, a direct randomized comparison of percutaneous ablation with partial nephrectomy in a large number of patients would be highly desirable in order to elucidate the role of the two treatments for the oncology community and potentially to supply evidence to support a strong (Grade A) recommendation, which is currently not available for either treatment. CIRSE would also consider as robust evidence data obtained from a multi-centre registry with a large number of patients (i.e. >1000) with biopsy-proven sporadic cT1a RCC followed up for a minimum of five years. Until these data are available, the procedure is recommended for patients that are not fit or are not willing to undergo surgical treatment. Active surveillance needs to be reserved only for those patients with cT1a RCC that cannot undergo percutaneous ablation treatment.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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