Abdominal Radiology

Published online: 25 February 2016

Abdom Radiol (2016) 41:754–766
DOI: 10.1007/s00261-016-0682-2

Percutaneous image-guided cryoablation of small renal masses

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Abstract

Renal cell carcinoma is a common malignancy with increasing incidence due to the incidental detection of non-symptomatic small renal masses on imaging. Management of these small tumors has evolved toward minimally invasive nephron-sparing techniques which include partial nephrectomy and image-guided ablation. Cryoablation and radiofrequency ablation are the most utilized ablation modalities with the former more suited for larger and central renal masses due to intra-procedural visualization of the ablation zone and reduced pelvicalyceal injury. In this article, we review the epidemiology and natural history of renal cell carcinoma, the role of biopsy, and the management options available—surgery, image-guided ablation, and active surveillance—with a focus on cryoablation. The clinical outcomes of the longer term maturing cryoablation data are discussed with reference to partial nephrectomy and radiofrequency ablation. Image-guided ablation has often been the management choice in patients deemed unfit for surgery; however, growing evidence from published series demonstrates image-guided ablation as a sound alternative treatment with equivalent oncological outcomes and minimal patient impact.

Key words: Cryoablation—Ablation—Renal—RCC—Percutaneous

Renal cell carcinoma (RCC) is a common malignancy with increasing incidence. 338,000 new cases of kidney cancer were diagnosed worldwide in 2012 with 144,000 deaths [1]. The highest rates are in Northern America, Europe, Australia, and New Zealand. Kidney cancer is the fifth most common cancer in Europe excluding gender-specific cancers. 84,400 new cases were identified in the European Union (EU-27) in 2012, accounting for 3.2% of all malignancies [2]. This is an increase from 59,900 cases in 2004 (EU-25) [3]. There is roughly a 2:1 male-to-female ratio with a European incidence of 17.4 and 8.1 per 100,000, respectively, in 2012 [2].

The incidence of RCC has been increasing globally—with a 226% increase between 1975 and 2008 according to the SEER database [4]. The 5-year survival in this cohort has increased from 50.9% during 1975–1979 to 74.9% in 2007. A large proportion of this increase has been attributed to the detection of incidental renal masses on imaging, with 67% of renal masses discovered incidentally in a European cohort [5, 6]. This is also reflected in a stage migration pattern—with an increase in stage 1 RCC from 43% to 57%, over a 12-year period (1993–2004), and a decrease in all other stages [7]. Additionally, there was a reduction in mean size of stage 1 tumors from 4.1 cm in 1993 to 3.6 cm in 2003. Histological grade as assessed by Fuhrman classification is significantly lower in incidentally discovered masses than symptomatic counterparts, although this does not appear to be size matched [8, 9]. Despite this increase in early-stage small-volume disease, mortality rates have slowly risen since the 1970s. Cancer Research UK data show an increase in mortality rate from 2.9 to 4.5 per 100,000 in 1972 and 2012, respectively, but with a plateau in mortality rate more recently [10]. This rise is mirrored in the US, although the rise has been slower, with a recent downward trend in mortality rate which may reflect increased treatment of small-volume disease [4].

Two additional factors have to be considered for the increase in RCC incidence—age and obesity. The highest incidence of RCC are in those aged 75 and older [11]. The UK mortality rate in the 80 and older group has increased from 15 (1971–1973) to 48.4 (2010–2012) per 100,000 [10]. This is coupled with decreasing mortality from cardiovascular and cerebrovascular disease in the developed world. Obesity has been identified as an independent risk factor for developing RCC with the risk increasing 24% for men and 34% for women for every 5 kg/m^2 rise in BMI [12]. However, tumors that develop

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in obese patients are less aggressive, lower stage at presentation, and have a reduced cancer-specific mortality [13, 14]. Age and obesity, are therefore, becoming increasingly important factors in an aging and overweight society where interventions have increasing risks.

The transition toward incidental detection on imaging has led to 70% of kidney cancer cases in 2008 presenting as small renal mass (SRM), which is defined as less than 4 cm in longest dimension and classified as a T1a lesion [15, 16]. Of these masses, 20–30% are benign and 10–20% are of higher oncological risk. In a study of 2770 excised solid renal tumors, the rate of RCC increased with size of the lesion. They identified that the RCC rate was 70% for less than 2 cm tumors, 78% between 2 and 2.9 cm, 80.1% between 3 and 3.9 cm, and 92.2% for those greater than 4 cm [17]. Additionally, the rate of RCCs being high grade increased with larger tumor size. Size and histological grade are therefore linked but smaller masses can still harbor the risk of high-grade tumors. A factor to consider is the high proportion of grade heterogeneity within SRMs with many high-graded tumors (Fuhrman grade 3–4) containing lower grade components (Fuhrman grade 1–2) [18]. Grade discordance increases with tumor size and higher grade tumors. This has an implication with biopsy assessment when considering active surveillance due to the risk of under sampling.

Role of biopsy

Accurate diagnosis of SRMs prior to management has been a contentious issue in the past. There are no specific radiological features that can separate indolent benign lesions from low- and high-grade RCCs [19, 20]. These benign lesions include fat-poor angiomyolipoma and oncocytoma as well as rare renal tumors such as metanephric adenoma, leiomyoma, and juxtaglomerular cell tumor. There have been recent advances in differentiating oncocytoma from RCC on multi-phase CT although this is rarely utilized in clinical practice with many equivocal SRMs [21, 22]. There has been historical concern with percutaneous renal mass biopsy in the ability to distinguish oncocytoma from RCC [23]. A key concern was regarding hybrid oncocytoma/RCC tumors as seen in a study by Schmidbauer et al. [24]. They identified 2 cases of hybrid tumors out of 13 cases (15.4%) with a preoperative diagnosis of oncocytoma on renal biopsy. However, a recent series has suggested that hybrid tumors are rare with only 3% of 147 excised oncocytomas or angiomyolipomas contained coexistent malignant tissue with no high-grade components [25]. Hybrid tumors are shown to have good oncological outcomes with little or no evidence of disease progression [25, 26]. This has led to a shift from a previous surgical management for oncocytomas to a conservative approach.

Renal mass biopsy technique has improved with technical failure around 5% and indeterminate or inaccurate pathological findings decreasing from 10% to 4% [27]. False-negative rates are often due to inaccurate placement of the needle tip in a SRM or sampling of usually central, necrotic areas [28]. Early difficulties in differentiating oncocytoma and chromophobe subtype RCC on core biopsy specimens are being resolved with modern immunohistochemical and molecular advances and interpretation, especially with assessment by experienced uropathologists [29]. These advances have increased specificity of biopsy and reduced technical failure leading to a reuptake in renal mass biopsy prior to management. The role of renal biopsy has made a significant clinical impact on the management of SRMs with unnecessary nephrectomy being avoided [30]. In the author's institution, we largely perform a core needle biopsy in advance of definitive management.

Surgical management

The historical standard of treatment for RCC is radical nephrectomy (RN). The short-term morbidity associated with open radical nephrectomy, which include increased blood loss and transfusion, longer hospitalization, and later ambulation, have been reduced through the use of laparoscopic radical nephrectomy techniques [31]. Outcomes are similar with no difference in cancer-specific survival on long-term follow-up between the two groups [32]. The major morbidity associated with radical nephrectomy is renal dysfunction. In a randomized European trial assessing renal function after nephron-sparing surgery (NSS) vs. radical nephrectomy for sub-5 cm masses (EORTC 20904), the RN arm patients had moderate renal dysfunction of 85.7% (estimated glomerular filtration rate (eGFR) <60 mL/min/m^2), severe renal dysfunction 10.0% (eGFR <30), and end-stage renal disease of 1.5% (eGFR <15) [33]. Renal dysfunction is an independent risk factor of death, cardiovascular events, and hospitalization [34]. This risk increases with worsening renal dysfunction. The associated renal dysfunction with RN has led to an evolution of nephron-sparing techniques which include NSS and ablation. This becomes even more relevant as 26% of patients with SRMs have chronic renal dysfunction at the outset [35].

The main surgical nephron-sparing technique is partial nephrectomy (PN), which has been shown to be as effective as RN with similar oncological outcomes at 10 years [36, 37]. In a randomized trial of PN and RN for sub-5 cm RCCs, PN was associated with a higher complication rate which includes severe hemorrhage, reoperation, and urinary fistulas [38]. Despite this, the trade-off is renal preservation and the international consensus is that PN should be the standard of care for SRMs with the European Association of Urology (EAU) guidance stating that PN should be offered for all T1a tumors and for technically feasible T1b tumors [39]. Interestingly, the

randomized EORTC 20904 trial showed that renal function for the NSS arm was 64.7% moderate dysfunction, 6.3% severe dysfunction, and 1.6% end-stage renal disease [33]. The only perceivable beneficial impact of NSS vs. RN was with slightly reduced moderate renal dysfunction and there was no improved survival in this study population.

The advent of laparoscopic techniques has helped minimize the invasive approach of NSS for SRMs. The 10-year oncological outcomes of laparoscopic PN are similar to open PN with choice of operative technique (transperitoneal or retroperitoneal) dependent on surgeon preference and experience, as well as tumor location (anterior vs. posterior) [40, 41]. Laparoscopy remains a highly skilled technique which requires adequate hemorrhage control and judicious use of renal hilar clamping to reduce warm ischemic injury times. Preservation of renal function is multifactorial after PN and includes amount of parenchyma preserved, baseline function and warm ischemia injury times [42]. Warm ischemic injury of >25 min has been shown to be a predictor of short- and long-term renal compromise even adjusting for other factors. One technique employed is the use of cold ischemia with ice slush, which can be tolerated up to 2 h by the kidney with good nephron recovery [43]. Meticulous intracorporeal suturing and reconstruction of the renal parenchyma has been evolving to reduce ischemic time and decrease the complication rate [41]. Clampless techniques have also evolved where the renal artery is dissected up to the initial branches feeding the lesion with emerging vessels in the resection bed selectively coagulated during the procedure. This technique has seen the maximal nephron-sparing benefit in those patients with the poorest baseline renal function but with no long-term significant difference in those with normal baseline function [44, 45]. Robot-assisted partial nephrectomy aids accessibility during endosurgery and helps reduce the complexity of the surgery. Long-term oncological outcomes are still awaited and the main perceived benefits are reported as improved accessibility and reduction in warm ischemic time [46, 47].

Active surveillance

It is worth considering the role of active surveillance in the management of SRMs. The EAU guidelines reserve the use of active surveillance and limit it to those patients who are elderly and/or comorbid patients with limited life expectancy given the low evidence base [39]. A 2006 meta-analysis study of SRMs undergoing active surveillance revealed a mean growth rate of 0.28 cm/year and that initial tumor size and grade had no impact on growth rate [48]. There appears to be no difference in average growth between biopsy-proven RCC or benign tumors. Additionally, biopsy-proven RCC may not grow and up to 10% of these lesions may decrease in size which suggests that some RCCs may regress [49]. The risk to metastatic disease in the 2006 meta-analysis was 1% but this has been found to be as high as 6% for 3.1–4.0 cm lesions with risk related to larger tumor size and higher grade [48, 50].

Patients undergoing active surveillance will have serial imaging with ultrasound, CT, or MRI at 6–12 month intervals. The most readily definable marker of change on imaging is tumor growth but this is subject to inter-observer measurement error. Measurement error is particularly important as small linear measurements can impact significantly on volumetric growth. Additionally, we have seen that growth is a poor differentiator for benign vs. malignant disease, which is especially important if there is no biopsy-proven disease [48]. A renal biopsy is recommended prior to enrolment into surveillance and EAU recommends delayed intervention in those that show clinical progression [39]. The guidance of enrolment into active surveillance is not clear and is at clinical discretion and patient choice. Active surveillance appears to be preferentially utilized in elderly and comorbid patients but other factors such as racial and socioeconomic disparities have led to a health care inequality, although outcomes remain similar [51, 52]. In a pooled analysis of SRMs undergoing active surveillance, up to 45.4% of patients underwent delayed intervention with patient preference (57.2%) being the largest factor compared to improved medical condition (7.1%), and tumor growth (35.7%) [53]. At this point, it is worth mentioning the role of image-guided ablation (IGA) especially if extirpative surgery is not suitable or due to patient choice of intervention over active surveillance. The EAU guidance advises either ablation or active surveillance in patients with T1a lesions who are elderly and/or comorbid [39]. IGA can be offered as the primary intervention in such patients who often have slow-growing or relatively indolent disease.

Nephrometry scoring

There are no specific radiological characteristics that help determine tumor grade or benignity of SRMs. However, attempts have been made to provide scoring systems to risk stratify treatment options [54]. The R.E.N.A.L. nephrometry scoring system is one such tool and provides a standardized way of quantitating renal masses [55]. Five variables are assessed which include: radius, exophytic/endophytic properties, proximity to collecting system, anterior/posterior location, and location relative to polarity. The scoring system helps objectify treatment decision-making for SRMs with lower scores tending toward minimally invasive techniques [56]. The usefulness of the scoring system also appears to apply to IGA techniques and is able to predict treatment efficacy and complications [57]. Scoring has been further adapted to form a modified R.E.N.A.L nephrometry score and the ABLATE renal ablation

planning algorithm for IGA to help anticipate and mitigate potential complications [58, 59].

Role of IGA in the treatment of RCC

Image-guided ablation (IGA) is a useful tool in the management paradox of SRMs—i.e., the risk of leaving potentially aggressive disease vs. over treating potentially indolent disease with surgery and its consequent morbidity vs. watchful waiting. It is clear that patient preference is the major factor in those undergoing delayed intervention [53]. IGA provides a nephron-sparing treatment modality that reduces the morbidity associated with surgical resection but shows increasing evidence of good oncological outcomes [60]. It must be noted from the outset that there are no randomized trials assessing the efficacy of IGA against partial nephrectomy for T1a lesions. This forms a selection bias in most early IGA case series demonstrating data for those that are elderly and/or comorbid, and therefore, unsuitable for surgery.

There are several ablation techniques that are available for the treatment of renal tumors. The main focus of this review is in the role of cryoablation (CRA) in the treatment of RCC with occasional reference to radiofrequency ablation (RFA), as both these techniques are well established in the role of renal tumor ablation [28]. Before discussing CRA, we will briefly address the other ablation techniques and their utility in the treatment of renal masses.

Radiofrequency ablation (RFA) generates high-frequency alternating current (approximately 500 kHz) via an electrode placed in the targeted tumor [61]. This agitates ions within millimeters of the probe tip creating an intense frictional heat that conducts outwards causing coagulative necrosis in the adjacent tissues. This process is regulated to ensure optimal temperature control to ensure tumor cell death but not to char tissue which inhibits conduction [62]. RFA is the most widely used IGA treatment modality for RCC.

Microwave ablation (MWA) is also a heat-based thermal ablation technique that agitates water molecules in an oscillating electromagnetic field adjacent to the probe tip. Inefficiency of polar water molecule oscillation leads to heating resulting in coagulative necrosis and cell death. MWA has a theoretical advantage of a more predictable thermal profile over RFA and intermediate term results of MWA in the treatment of SRMs have demonstrated comparable cancer-specific survival and complication rate to laparoscopic radical nephrectomy [63].

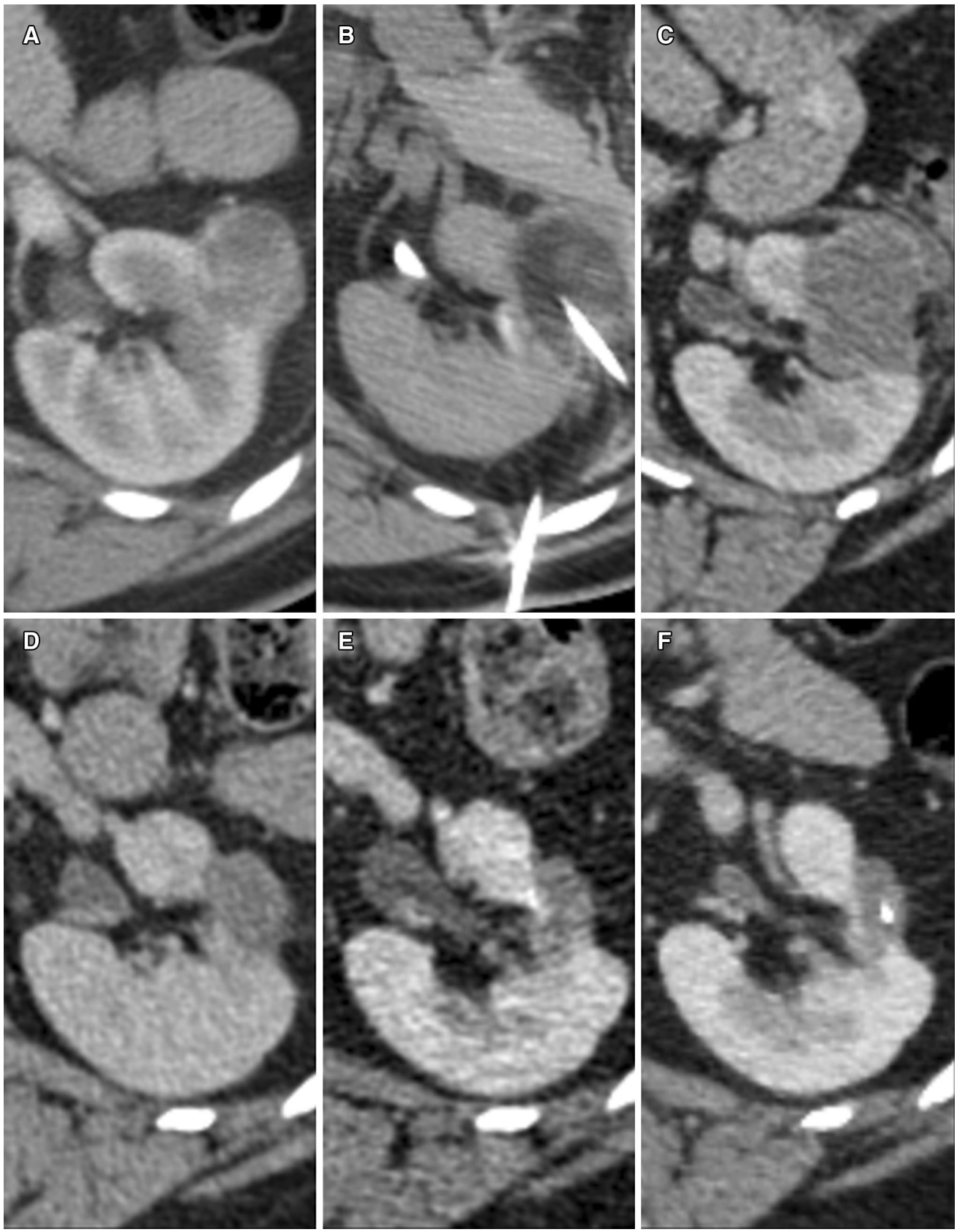
Irreversible electroporation (IRE) is a non-thermal ablation modality in which there is irreversible cell membrane permeabilization from the application of rapid electrical pulses leading to cell necrosis. IRE is still in its infancy and current use is limited to research with the majority of in vivo treatments involving liver and pancreatic lesions [64]. High intensity focused ultrasound (HIFU) uses the principles of converting mechanical energy from focused ultrasound into heat leading to cavitation and coagulative necrosis. Results from small trials have been disappointing with technique limited by variable thermal profile in the target tissue as well as the targeting limitations of extracorporeal techniques which are sub-optimal compared to laparoscopic approach [65].

Fig. 1. **A** 30-mm exophytic left anterior interpolar RCC. **B** ► Intra-procedural CT demonstrating an iceball around a cryoprobe. Note the bowel has been displaced by hydrodissection. **C** 2 weeks post-CRA demonstrating typical post-ablation appearance with complete devascularisation of the tumor. A crescent of high attenuation is seen at the anterior aspect which demonstrates a typical marginal rind seen with cryoablation. **D** 1 year post-CRA showing an 18-mm involuted devascularised ablation zone. **E** 3 years post-CRA demonstrating involuted scar tissue with no enhancing nodule. **F** 5 years post-CRA the ablation zone remains involuted with a central fleck of calcification.

Cryoablation

CRA is a cold-based thermal ablation technique which has been recognized as a treatment modality for decades, but has experienced a recent clinical resurgence due to the advent of newer 'third generation' 17-gage cryoprobes suitable for percutaneous treatment [66]. The target tissue undergoes a phase change from liquid to solid during the freezing cycle, which is achieved through the closed-system circulation of a cryogen into the probe leading to the formation of a therapeutic 'iceball' around the tip. Centrally within this 'iceball,' there is rapid intra- and extracellular ice formation, while peripherally there is extracellular ice formation. Intracellular ice formation leads to damage of the cell membrane and intracellular proteins, while extracellular ice formation produces an osmotic gradient that leads to a fatal fluid shift out of cells. Additionally, microvascular injury secondary to freezing is thought to be synergistic with these effects [28, 67, 68]. The rate of cooling, the nadir tissue temperature, the duration of freezing, and thawing rate are all elements that lead to cellular injury and the process of tissue destruction is ensured by a double freeze-thaw cycle [69]. The cell lethal isotherm lies at −30 to 40°C and this is fully lethal to the target tissue during a double freeze-thaw cycle [70].

One of the key benefits of CRA is the intra-operative visualization of the 'iceball' (see Fig. 1B), which acts as good imaging surrogate for the ultimate ablation zone as seen in Fig. 1C. The visualization of frozen tissue in solid organs is seen as approximately 50 Hounsfield units less than that of unfrozen tissue on CT scan. The thin peripheral ice front (freeze margin) is not tissue-lethal with temperatures of around 0°C. However, this can act as proxy marker for the cell lethal zone and the visualized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F

iceball should, in practice extend beyond the margin of the tumor by at least 5–6 mm [69, 71]. Visualization of the iceball is also possible with ultrasound and MRI. On ultrasound, the ice front is seen as a hyperechoic line and often casts acoustic shadowing which obscures visualization of the deep margin. On MRI, signal voids are seen on all sequences giving good delineation of the iceball. However, CT remains the most practical and utilized imaging modality both intra-procedural and during follow-up (Fig. 1).

A disadvantage of thinner cryoprobes is a smaller ablation zone. To incorporate large tumors, multiple probes have to be sited with careful planning of in situ probe position. Different probe designs enable spherical, ellipsoid, or cylindrical ablation zones. Pre-procedural planning with a selection of various probes enables a larger ablation zone to form, with the probes working synergistically. There are a number of software packages to help plan more robust and predictable ablation zones [66]. Each cryoprobe can be regulated independently to precisely shape the ablation zone, which may prove useful for complex lesions or near critical structures and this makes CRA particularly suited for renal masses [72]. As a general guide, cryoprobes are placed in 'clock-face' configuration (as demonstrated in Fig. 2A) no greater than 1 cm from the tumor edge and the distance between adjacent cryoprobes should be less than 2 cm to prevent intra-tumoral clefts of sub-optimal thermal zones [73].

CRA has shown to be less injurious to the pelvicalyceal system through collagen-sparing effects, as shown in porcine models and clinical experience [74, 75]. Blood vessels are also a critical structure that should be considered—with larger vessels providing a local 'cold sink' effect analogous to the 'heat-sink' effect seen with hyperthermic ablative modalities. CRA is less prone than RFA to perfusion-mediated thermodilution effects, however, to mitigate these effects, spacing between cryoprobes should be reduced near large vessels [73].

Imaging guidance

The two main methods of CRA delivery are imaging-based percutaneous technique and laparoscopy. A 2008 comparative meta-analysis by Hui et al. evaluated percutaneous and surgical approaches to renal tumor ablation by looking at tumor effectiveness and complication rates [76]. They identified that the primary efficacy rate was 87% for the percutaneous group vs. 94% for the surgical group with a similar secondary ablation efficacy rate of 92%. The major complication rate was significantly lower in the percutaneous group at 3% against 7% for surgical. It should be noted that techniques have evolved since early IGA techniques and with experience an improvement in outcomes and reduced complications are seen. Results may be partially influenced by preferential selection of surgical candidates. Two recent single-center studies have shown similar outcomes and complication rates between percutaneous and laparoscopic CRA with outcomes influenced by patient and tumor characteristics [77, 78]. Percutaneous CRA also benefits from reduced operative and anesthetic time, reduced analgesic requirements, reduced transfusion requirement, and shorter length of stay [79]. These benefits with equal oncological outcomes make percutaneous ablation a suitable treatment modality for primary treatment and secondary salvage treatment for residual or recurrent disease.

Fig. 2. **A** Coronal reformat of a 57-mm left renal mass demonstrating the 'clock-face' arrangement of 7 cryoprobes. **B** Gas insufflation tracking around a stented ureter (*solid arrow*) creating some separation from the central right renal mass. An attempt at contrast-tinted hydrodissection is also seen. **C** Close proximity (approximately 1 cm) of a large exophytic left lower pole renal mass to the descending colon anterolaterally (*horizontal arrow*) and a loop of small intestine anteriorly. **D** Displacement of descending colon (*vertical arrow*) by contrast-tinted 5% dextrose solution instilled into the left anterior pararenal space increasing the space by several centimeters. ▶

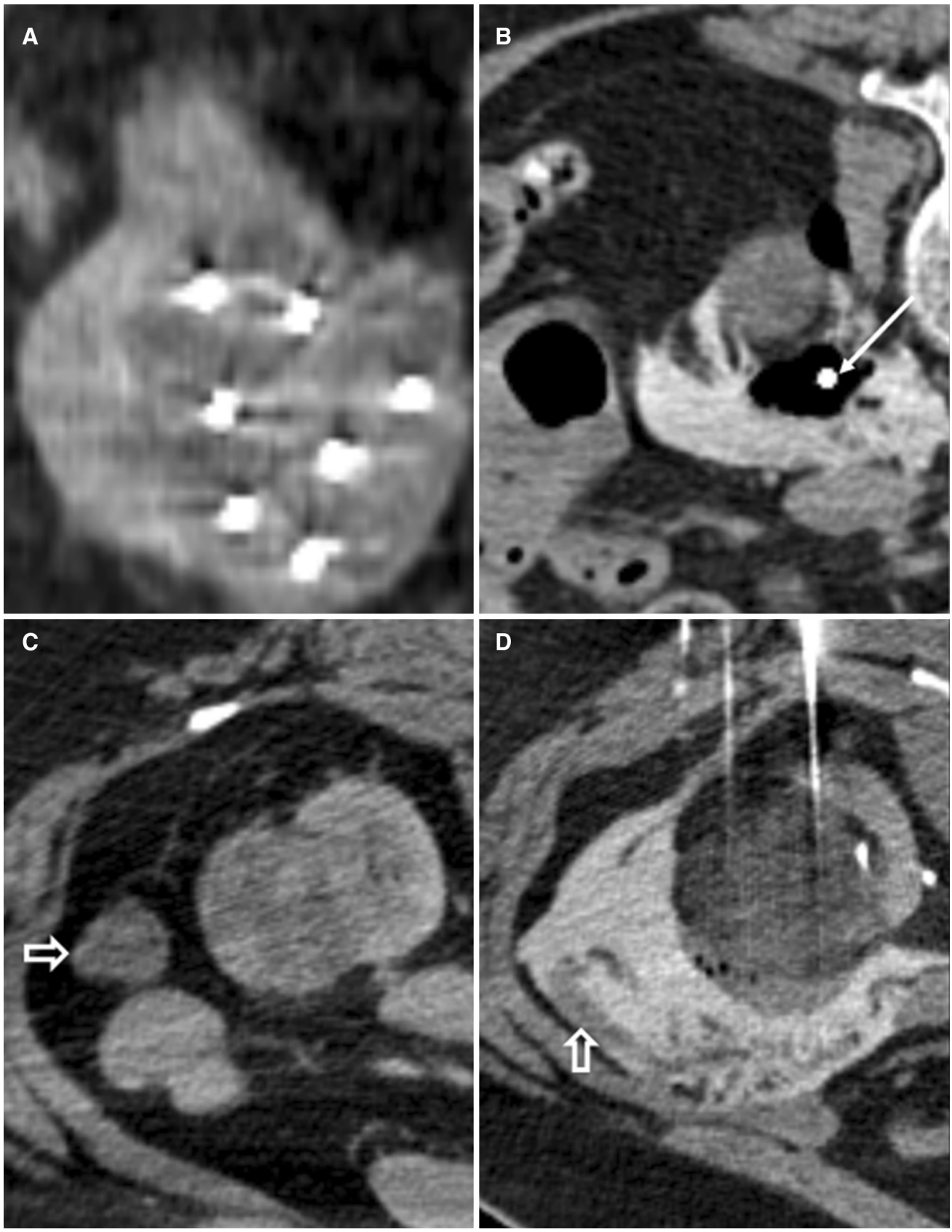
Procedural considerations

There are several benefits to performing percutaneous ablation under general anesthesia. The patient can be optimally positioned in a prone-oblique position which allows better access and visualization of the kidney through widening of the intercostal spaces. Additionally, respiratory suspension is reproducible enabling better probe placement. Ablation is painful and analgesic requirements are reduced with general anesthetic. It must be noted that CRA benefits from lower analgesic requirements than RFA due to the cooling analgesic effect on nerves [80].

Adjunctive maneuvers

Critical structures such as bowel (usually colon) and the renal pelvis are susceptible to injury with ablation. Prior to the advent of protective techniques, a major contraindication to IGA was proximity of the tumor to these structures. Simple maneuvers can assist in the displacing of bowel from the tumor such as patient positioning. In our local practice, the use of disposable enema the morning of the procedure helps reduce gas distension of the colon [28].

Hydrodissection is a technique which is commonly used to displace bowel away from the renal mass, using contrast-tinted fluid. This is usually achieved by percutaneous instillation via an 18–21G co-axial needle into the anterior pararenal space by imaging guidance. 5% dextrose in water is preferred for RFA as it is less ionic but this is not an issue with CRA and 0.9% saline can be used. The fluid is approximately 2% contrast-tinted to enable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adequate visualization on CT, which is demonstrated in Figs. 2B–D. Aliquots of 50–100 mL are used but larger volumes may be required depending on the degree of displacement required and if there is any fluid spillage into the paracolic gutters or subhepatic space [81].

Gas insufflation is achieved by introducing sterilized carbon dioxide or air to displace bowel or other critical structures (Fig. 2B). Disadvantages of this technique are obscuration of view on ultrasound or MRI and larger quantities of gas required due to gaseous diffusion. Balloon interposition utilizes angioplasty or oesophageal dilation balloons to displace bowel away but can be poorly predictable. It is a second-line technique after other techniques fail. A major disadvantage is slippage of balloon and several balloons may be required. Torquing uses the ablation probes as a lever to displace the kidney. This can be used in addition to other techniques but caution is required to ensure that the probes are not deformed and there is no renal hilar or soft tissue injury—although no cases have been reported [82].

Pyeloperfusion with ureteral stenting is a method to prevent urothelial injury. This works on the principle of thermodilution within the renal pelvis by applying cold fluid (5% Dextrose in water) for RFA or MWA and warmed fluid for CRA [83]. CRA has the additional collagen-sparing benefit and is less injurious to the renal pelvis [74, 75].

Clinical outcomes

An increasing number of published case series demonstrate percutaneous CRA as an effective modality for the treatment of SRMs with longer follow-ups now filtering through on these larger case series. The outcomes and complication rates from these series can be seen in Table 1 which is limited to series with greater than 100 CRA [77, 84–91]. Smaller case series were excluded due to shorter follow-up and due to a relative inexperience in performing CRA. Breen et al. demonstrated the relevance of experience in 153 consecutive treatments that subtotal treatment significantly decreased in consecutive tertiles from 8/51 to 3/51 and subsequently 1/51 treatments [88].

Primary local control is defined as an imaging absence of residual unablated disease, disease recurrence, or metastatic disease. This ranges from 85.4% to 98.5% (Table 1), although this figure improves to 92.7–99.3% with repeat ablation. Thompson et al. retrospectively compared the outcomes following PN, percutaneous RFA, and CRA. They identified a local recurrence-free survival rate at 3 years for T1a tumors of 98% in each group with no significant difference in the biopsy-proven RCC subset. Metastases-free survival at 3 years were similar in PN (99%) and CRA (100%) and significantly different to the RFA subset (93%). It must be noted that PN patients were younger (60.1 year (PN), 70.7 year (RFA), and 71.6 year (CRA)) and were significantly less comorbid compared to the ablation group. When comparing PN and CRA for T1b tumors, there was again no statistical difference for local recurrence-free survival or metastases-free survival, although numbers are small ($n = 48$) for the CRA group [90]. With increasing longer term data and experience with CRA, oncological out-

Table 1. Outcomes of percutaneous cryoablation of small renal tumors limited to studies with greater than 100 procedures

Study	Total number of renal lesions ablated (patients)	Biopsy-proven RCC	Mean tumor size (cm)	Mean age (years)	Mean Follow-up (months)	Primary local control	Complications[a]	
							Significant	Minor
Rodriguez et al. [84]	117 (113)	81	2.7	68[b]	15.4[b]	79/81 (97.5%) RA 80/81 (98.7%)	8/117 (7%)[c]	39/117 (33.3%)[c]
Buy et al. [85]	120 (90)	71	2.6	69	28	113/120 (94%)	9/122 (7.4%)[d]	NR
Blute et al. [86]	139	79	2.4	70	24[b]	129/139 (92.8%)	3/139 (2.2%)	15/139 (10.7%)
Kim et al. [87]	129 (124)	13	2.7	72.6	30	112/129 (86.8%) RA 120/129 (93%)	3/124 (2.4%)	8/124 (6.5%)
Breen et al. [88]	171 (147)	97	3.3	67	20.5	157/170 (92.4%) RA 166/170 (97.6%)	7/153 (4.6%)	9/153 (5.9%)
Georgiades et al. [89]	265 (246)	134	2.8	NR	NR	132/134 (98.5%) RA 133/134 (99.3%)	15/265 (6%)[e]	NR
Thompson et al. [90]	187[f]	108	2.9	71.6	21[b]	171/174 (98.3%)	NR	NR
	53[g]	36	5.0	74.9	21[b]	45/48 (93.8%)	NR	NR
Zargar et al. [77]	137	82	2.2[b]	67.2	37.8[b]	117/137 (85.4%) RA 127/137 (92.7%)	1/137 (0.7%)	9/137 (6.6%)
Okhunov et al. [91]	236 (235)[h]	93	2.4	68.2	26.7	218/236 (92.4%)	7/236 (3.0%)	18/236 (7.6%)

NR not recorded, *RA* repeat ablation

[a] Clavien–Dindo classification of surgical complications: significant = Grade II or greater. Minor = Grade I

[b] Median

[c] Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v.3.0): Significant = Grade 2 or greater. Minor = Grade 1

[d] 2 Deaths post-cryoablation were due to Mendelson syndrome and myocardial infarction. No local renal complication in these 2 patients

[e] Common terminology criteria for adverse events version 4.0 (CTCAE v.4.0): Grade 2 or greater

[f] T1a tumors

[g] T1b tumors

[h] Combined local anesthesia with conscious sedation and general anesthetic sub-cohorts

Table 2. Overall complications in reported series (>100 procedures) according to Clavien–Dindo classification system (Grade II–V)

Clavien–Dindo classification system[a,b]	Complications (management)	Total (n = 1293)[c]
Grade II		24 (1.9%)
	Perinephric hematoma (blood transfusion)	13
	Intestinal injury (conservative)	7
	Urinary tract infection	2
	Cerebral ischemia (supportive care)	2
Grade IIIa		18 (1.4%)
	Pelvicalyceal/ureteric injury or stricture (ureteric stent/nephrostomy)	6
	Pneumothorax (chest drain)	5
	Pleural effusion (chest drain)	2
	Bladder outlet obstruction (bladder irrigation)	2
	Post-procedural hemorrhage (embolization)	1
	Retroperitoneal abscess and duodenoureteral fistula (percutaneous drain and nephrostomy)	1
	Perirenal abscess (percutaneous drain)	1
Grade IIIb		1 (0.1%)
	Hematuria (ureteric stent)	1
Grade IV		8 (0.6%)
	Myocardial infarction (coronary stent)	3
	Arrhythmias (spontaneous recovery)	2
	Subcapsular hematoma (surgical decompression)	1
	Pulmonary embolism	1
	Cryoshock	1
Grade V		2 (0.2%)
	Mendelson syndrome	1
	Myocardial infarction	1

[a] Rodriguez et al. classified complications according to CTCAE v. 3.0 criteria [84]. This has been reclassified into Clavien–Dindo classification for purposes of review
[b] Georgiades et al. classified complications according to CTCAE v 4.0 criteria [89]. This has been reclassified into Clavien–Dindo classification for purposes of review
[c] Pooled data from 8 published case series [77, 84–89, 91]

comes are equipoise with standard PN for small renal masses.

The longer term data for PN and RFA for treatment of T1a RCC is well established with a 97.2% 5-year overall survival for both groups in an observational single-institution study with no statistical difference in cancer-specific survival and overall disease-free survival [92]. Chang et al. identified no statistical difference in 5-year clinical and oncological outcomes in both groups that were propensity-score matched [93]. The 5-year outcomes for CRA will be expectantly published in the coming years with maturation of the larger center databases but intermediate term data has been promising.

The reported time to local recurrence varies in the literature and this may be due to poor discrimination of primary subtotal treatment from local recurrence and that diligent treatment and assessment plays a role here. Recurrence occurs late in the post-ablation course as demonstrated by the 3 cases of local recurrence in the Thompson et al. study with recurrence times of 2.3–4.7 years [90]. Recurrence is often slow-growing, presenting as an enhancing nodule at the margin of the involuting ablation zone and is often not appreciated on imaging during the first 6 months. As such, we have adapted our local imaging follow-up with contrast-enhanced CT or MRI at 1 month post-treatment to assess for subtotal treatment and if satisfactory, follow-up imaging at 1, 3, and 5 years to exclude local recurrence as demonstrated in Fig. 1. If any concerns arise during the initial post-ablation study then an interim study can be performed at 3–6 months.

Complications

Complications in IGA techniques are mainly published using the Clavien–Dindo Complication Classification, which is a reliable classification system used for surgical procedures [94]. We have described significant complications as grade II and above. The majority of minor complications (grade I) include perinephric hematomas and pneumothoraces that require only conservative management. An underreported complication of ablation is injury to nerves within the abdominal wall which include intercostal, ilioinguinal, and genitofemoral nerves which can lead to chronic pain.

The significant complication rate is 0.7–7.4% (Table 1) and the vast majority of these are grade II. Table 2 demonstrates the described significant complications among the published series stratified according to Clavien–Dindo classification [77, 84–89, 91]. The pooled significant complication rate (>grade II) is 4.1% (53/1293 procedures) with the majority representing grade II complications. The most common reported significant complications include perinephric hematoma requiring blood transfusion, pelvicalyceal injury requiring stenting or nephrostomy, pneumothorax or pleural effusion requiring

drainage, and intestinal injury that is managed conservatively. Life-threatening complications are uncommon (0.6%) and only 2 deaths have been reported among the studies—Mendelson syndrome and massive myocardial infarction [85]. In both cases, the patients had pre-existing comorbidities, which precluded surgery and neither case had local renal complications. Cryoshock is a cytokine-mediated response to CRA resulting in coagulopathy, shock, acute respiratory distress syndrome, and multiorgan failure [95]. Cryoshock is uncommon in the treatment of renal masses with only 1 case reported and is more commonly seen in the treatment of hepatic lesions.

Tumor characteristics are related to the risk of complications. Maximal tumor diameter and central tumor location are associated with an increase in major renal CRA complication [96]. In the same study, prior myocardial infarction and complicated diabetes mellitus was also related to an increase in complication rates. It has also been identified that upper pole lesions are more likely to have increased incidence of pneumothorax, whereas anterior or posterior location does not appear to have any significant difference in complication rate [88]. Only 5% of procedures in which there has been pleural transgression results in chest drain placement as identified by Georgiades et al. [89].

Direct comparison of complication rates between percutaneous RFA and CRA are difficult due to differing complexity of tumors treated. Schmit et al. identified a complication rate of 7.9% vs 2.9% (CRA vs RFA) but they attributed this to more complex and larger tumors treated by CRA with high RENAL nephrometry score [57]. When ablated masses are limited to less than 3.0 cm, there is no significant difference between RFA and CRA in complication rate and treatment success, although a higher likelihood of treatment failure is seen in RFA-treated central tumors due to 'heat-sink' effect [97]. Percutaneous RFA is therefore particularly suited to small peripheral exophytic lesions that can be treated by 'single-stick' ablation, whereas CRA should be utilized for larger complex tumors, especially if centrally located. IGA complication rates for SRMs are similar to those seen with PN. A 2012 UK audit, identified a complication rate of 4.9% (Clavien–Dindo >grade III) for those undergoing PN for T1a tumors with an overall complication rate of 17.4% [98]. A comparable pooled complication rate for CRA from the published series in Table 2 is 2.2% (Clavien–Dindo >grade III) with some series including small T1b masses within their data.

Patient groups particularly suited for cryoablation

The benefits of CRA have already been shown in several specific patient groups—elderly, obese, solitary kidney, heritable RCC syndromes, and local recurrence post-surgery. Outcomes of percutaneous renal CRA in elderly population (>80 years) has a technical success of 98.4% in 61 (33 biopsy-proven RCC) patients with no recurrence recorded and an 8.6% major complication rate [99]. Obese patients are often poor surgical candidates due to extensive comorbidities and technical surgical challenges. Percutaneous renal CRA may be an alternative option with complication rates and short-term outcomes in obese and morbidly obese patient similar to those in non-obese patients [100]. The major technical challenge for percutaneous ablation is increased skin-to-tumor depth which has shown to have a higher likelihood of treatment failure [86]. Patients with a solitary kidney require meticulous care to ensure minimal loss of renal function. Treatment of 38 tumors in 31 patients with a solitary kidney demonstrated a 92% local tumor control and caused minimal loss in renal function at follow-up with no patient requiring dialysis [101]. The nephron-sparing benefit is also suited for patients with pre-existing renal disease or patients with inheritable renal cancer syndromes such as von Hippel–Lindau disease. Additionally, percutaneous CRA is suited as a salvage therapy in patients with previous ipsilateral PN with acceptable oncologic outcomes, preservation of renal function, and relative preservation of renal function [102].

Conclusions

The increased use of cross-sectional imaging has identified an increasing number of SRMs leading to stage migration shift of kidney cancer toward smaller tumors. Kidney cancer remains an important cause of mortality and had previously provided a management conundrum of whether benign or low-grade tumors were being over treated. Pre-procedural biopsies have become more confident in characterizing SRMs, and many of those still carry a significant malignant potential. Urological guidelines still hold PN or RN as the gold standard, but IGA is now demonstrating equivalent oncological outcomes with minimal patient impact. This is emphasized by case series in what has been a comparatively older and more comorbid population. This has facilitated the option of IGA as a sound alternative treatment in patients especially those unsuitable for surgery. At present, there are no prospective randomized studies looking at percutaneous RFA or CRA directly against PN for SRMs. CRA, although technically more challenging, has been shown to be more suited toward larger SRMs and centrally located tumors than RFA.

Compliance with ethical standards

Conflicts of interest No conflicts to report.

Human and Animal Rights Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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