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REVIEW ARTICLE

Percutaneous radiofrequency ablation of small renal cell carcinoma: technique, complications, and outcomes

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Summary

Imaging-guided radiofrequency ablation (RFA) is an option for treatment in patients with early-stage small renal cell carcinomas (RCCs). RFA has been introduced to treat focal renal tumors, particularly incidental lesions <3 cm in elderly patients and those with comorbid conditions. Other uses have included treatment in patients with von Hippel-Lindau syndrome and other diseases that predispose patients to multiple renal carcinomas, where renal parenchymal preservation is desired. It appears that this technique has a low complication rate, preserves renal function, is well tolerated by the patients, and, in a high percentage of patients, can eradicate small renal tumors. Techniques, patient selection, complications, and results are discussed.

Key words: radiofrequency ablation, small renal cell carcinoma, treatment

Introduction

RCC represents 2-3% of all cancers, with the highest incidence occurring in Western countries [1]. It is the commonest solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies [1]. Due to the increased detection of tumors by imaging techniques, such as ultrasound (US) and computerised tomography (CT), the number of incidentally diagnosed RCCs in asymptomatic patients has increased. These tumors are more often smaller and of lower stage. The traditional standard treatment for localized RCCs is partial or radical nephrectomy, but this method is not ideal for treating all tumors because some patients are unable or unwilling to undergo surgery or would have limited or no functional renal tissue remaining after standard therapy [1,2]. There is increasing evidence that image-guided, percutaneous ablative modalities, such as RFA and cryoablation, have become increasingly effective in certain patient groups, such as patients with multiple or bilateral tumors, predialysis patients, patients who are nonoperative candidates, and patients with syndromes that predispose them to metachronous lesions [3-5]. The European Association of Urology (EAU) guidelines of 2010 on the diagnosis and management of RCC list RFA as a treatment alternative to surgery [1]. Possible advantages of RFA include reduced morbidity, outpatient therapy, and the ability to treat high-risk surgical candidates.

Herein, we review the principles of RFA of renal tumors and the published data supporting its use in the treatment of RCC. We also describe patient selection, the techniques used for the ablation procedure, complications, and follow-up imaging after RFA of RCCs.

Pretreatment

In most practices patients are assessed by an urologist who decides if percutaneous RFA is appropriate. Pretreatment imaging is important for planning the ultrasound, magnetic resonance imaging (MRI), or CT-guided needle placement (Figure 1a, 3a). Pretreatment abdominal CT or MRI allows diagnosis of RCC and provides information on the function and morphology of the contralateral kidney, primary tumor extension

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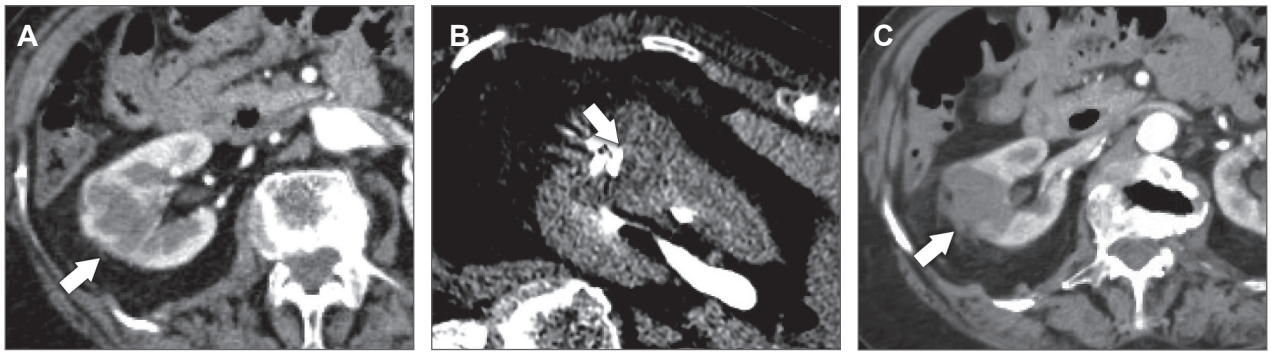

Figure 1. RFA of biopsy-proven RCC. **A:** CT image of a 3.5-cm exophytic solid renal mass (arrow) incidentally detected on ultrasound in an 85-year-old man with severe cardiovascular disease. The patient was deemed a poor candidate for surgery. Therefore, RFA was performed as a minimally invasive alternative. **B:** CT image demonstrates a single RF electrode in the mass (arrow). **C:** CT scan obtained 3 months after two overlapping ablations shows absence of contrast enhancement within the ablated lesion –there is no evidence of residual viable tumor (arrow).

with extrarenal spread, venous involvement, enlargement of locoregional lymph nodes, condition of adrenal glands and the liver and detailed information about the kidney vascular supply [6,7]. Important laboratory tests include prothrombin time, partial prothrombin time, complete blood cell count, creatinine, and screening for intravenous sedation or anesthesia. It is also important to obtain baseline measures of renal function. First, the ablation procedure will likely include ablating some normal renal parenchyma. Second, iodinated i.v. contrast material may be needed during a CT-guided ablation, either to define tumor margins before applicator placement or during the ablation to assess whether the tumor has been ablated completely or whether the collecting system is intact. Previously, renal mass biopsy (RMB) prior to treatment had a limited role. However, 20-25% of small renal tumors are benign, tract seeding and post-biopsy complications are very rare and the diagnostic accuracy of RMB is very high (sensitivity 89.7%, specificity 92.1%). Therefore, RMB for diagnosis prior to ablative treatment will become more important in the future [6].

Patient selection

At our institution, patients to be selected for RFA are those with known contraindications to partial or complete nephrectomy as a result of comorbid conditions or advanced age. Indications for RFA include small, incidentally found, renal cortical lesions in elderly patients, those with a genetic predisposition for developing multiple tumors, patients with bilateral tumors, and patients with a solitary kidney at high risk of complete loss of renal function following surgical tumor resection [1,8].

Tumor size and location are the two most important factors that govern whether RCCs can be treated successfully by the RFA. Because heat decreases exponentially from the RF source, large tumors (>5 cm) pose a significant challenge for RF ablation, especially because a 0.5-1.0 cm ablation margin surrounding the tumor is also preferred. In general, RCC tumors ≤4 cm in diameter or T1a tumors are ideal for ablation, with near-perfect success rates on postprocedural imaging [8-10]. In several studies using RFA, complete ablation was achieved in 100% of tumors <3 cm, 92% of tumors between 3 and 5 cm, and 25% of tumors >5 cm [4,5,7,8]. Tumor size also affects the number of separate ablation sessions necessary to achieve complete necrosis. Studies have shown that for tumors <3 cm, a single ablation session (with multiple overlapping ablations) can achieve complete necrosis in at least 92% of the cases, with 8% of tumors eradicated after two ablations. For tumors between 3 and 5 cm, 53% were ablated in one session, an additional 44% in two sessions, and the remaining 3% required a third session. For tumors >5 cm, all required more than one ablation session, 50% needed two sessions, and 50% needed three sessions [7,8].

The location of the tumor (exophytic, parenchymal, or central) also influences RFA results. Even larger exophytic tumors are almost always treated successfully, with ≥70% requiring only a single RF session (Figures 1a, 3a). Parenchymal tumors may be more difficult to treat, but centrally located tumors represent the largest obstacle for successful ablation. Central tumors are challenging because of their proximity to the collecting system, ureter, and central renal vasculature. Treatment of central tumors carries the potential for collecting system injury, including infundibular or ureteral strictures and urinomas. The presence of a central component in a tumor >3 cm is reported to be a significant predictor of failure [7,9-11]. Absolute contraindications for RFA include uncorrected

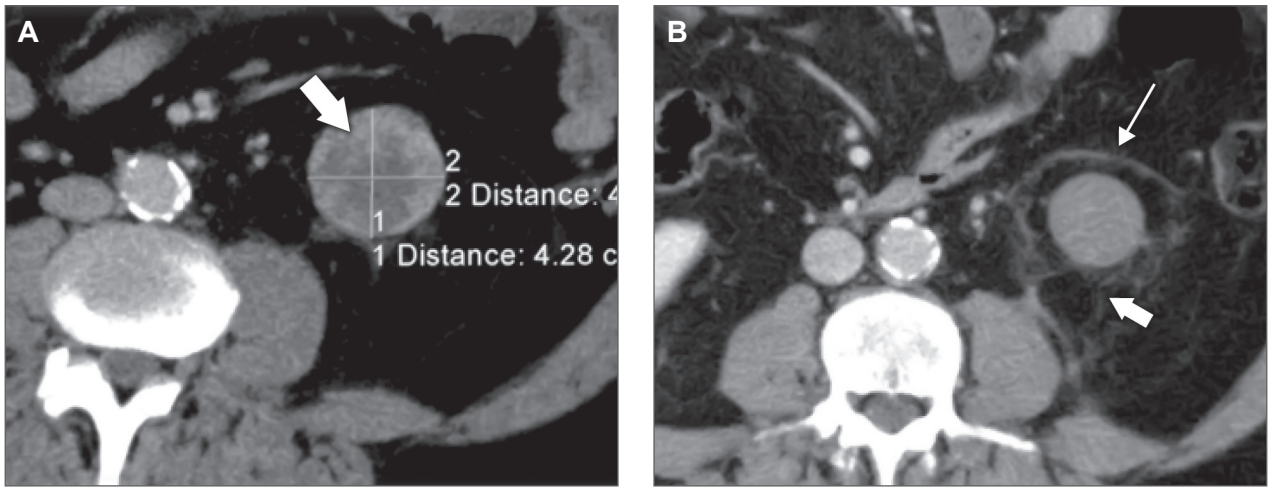

Figure 2. Solid renal masses prior and after RFA on CT. **A:** Contrast-enhanced CT scan shows an avidly enhancing 4-cm-diameter exophytic mass (arrow) arising from the left kidney. **B:** CT scan obtained 12 months after RFA shows absence of contrast enhancement within the ablated lesion (there is no residual viable tumor) with local perinephric stranding (thick arrow) and with organized periablation halo (thin arrow). The treated tumor is smaller than before treatment, which is a typical feature following RFA.

coagulopathy and acute illness such as sepsis [6,12,13]. Although many patients referred for RFA have serious comorbidities (e.g., chronic congestive heart failure), this should not be considered a contraindication to RFA ablation of the RCC.

Radiofrequency ablation

RFA can be performed surgically, laparoscopically and percutaneously. Although there is no evidence for supremacy of one approach in the literature, percutaneous approach (using CT or ultrasound guidance) is favorable as long as it is technically feasible (Figure 1b). Kidney RFA is commonly performed in a CT scanner suite. Patients undergo this procedure either under moderate sedation with pain relief or under general anesthesia. General anesthesia has the advantage of complete control over patient's breathing and motion that helps to accurately place the RFA electrode within the tumor.

Commercially available RFA units are broadly classified into temperature-based or impedance-based systems. This means that the computer-controlled generator provides energy to the probe based on either the average temperature achieved at the tines or the measured impedance of the tissue during ablation. Impedance rises towards infinity when tissues are desiccated during ablation or when there is charring. Another major classification in RFA technology is the differentiation between dry RFA and wet RFA. Wet RFA probes allow constant infusion of saline during ablation in order to mitigate the charring effect and premature rise in impedance. While there is a theoretical benefit to saline infusion, no randomized studies have compared these modalities [31]. The RFA electrodes come in various shapes, length and thickness, depending on the manufacturer.

During the procedure, tumor cells are destroyed by placing a needle (RFA electrode) within the center of the tumor using the guidance of images in the CT suite. Multiple CT images are taken to confirm the safe placement of RFA electrodes, and to avoid adjacent vital organs. Following placement, RFA electrodes are connected to an external RF generator. High-frequency alternating energy is then applied through the RF electrodes. This causes ionic agitation in tumor cells which raises tissue temperature. As the temperature increases above 45-50° C within the tumor, cellular proteins denature and cell structure disintegrates. This results in thermal coagulation in tumor cells, ultimately leading to tumor destruction. This usually occurs at temperatures between 52-100° C [6,12]. Each ablation takes about 8-12 min and the entire RFA procedure session usually takes 1-2 h or less. Following completion of therapy, track ablation is performed to avoid bleeding complications and tumor cell seeding. Subsequently, patients are closely observed for any post procedural complications. The shape of the resulting coagulation necrosis is mainly depending on probe configuration, but also of the presence of heat sink effects by cooling vessels (segmental arteries) and collecting system. Modern probes allow ablation of lesions between 2 and 5 cm in diameter. Increase of necrosis is achieved by superselective tumor embolization prior to ablation by particles or lipiodol, which is suggested in lesions exceeding 3 cm in size [9]. A further increase in the ablation volume

requires reposition of the probe. In order to avoid thermal collateral damage in adjacent structures like bowel or liver, an additional injection of carbon dioxide or 5% glucose is suggested in cases of exophytic tumors with broad contact to neighboring organs. Also, large blood vessels (> 3 mm) near a tumor constantly cool the tissue due to the flowing blood that takes heat away from the area being treated, commonly known as the heat sink effect [7,12]. As a result, tumors in continuity with large blood vessels may be suboptimally treated with RFA. Some electrodes are believed to produce necrosis measuring up to 4-5 cm in diameter. This allows for the treatment of a 3 cm lesion and a 1 cm margin. Tumors larger than 3 cm may require multiple electrodes to create overlapping tissue RFA zones.

After ablation, noncontrast CT is obtained to document any immediate complications, such as perinephric hemorrhage.

Post ablation imaging

The major reason for performing surveillance imaging after renal RFA is the early detection of residual or recurrent tumor. Imaging immediately after the procedure can be difficult to interpret because peripheral inflammation may mimic the appearance of viable tumor. The monitoring protocol after these procedures usually consists of dedicated contrast-enhanced CT of the kidneys performed within 1 month after the ablation and then at 3 and 6 months. Once the 1-year CT is reached, and no viable tumor has been demonstrated, then CT scans can be performed at 1-year intervals. Although the use of CT as the primary imaging modality is justified because of cost and availability issues, a substantial number of eligible patients cannot be exposed to iodine-containing contrast agents owing to pre-existing allergies or impaired renal function, with creatinine levels >2.0 mg/dL (176.8 mol/L). These patients are usually referred for contrast-enhanced MRI of the kidneys [11,13]. There is currently no role for conventional US in the detection of residual or recurrent disease, although US contrast agents (CEUS) may play a role in patient surveillance after thermal ablation. CEUS with second generation contrast agents can be useful in detecting complete ablation or recurrence of tumors after RFA of RCC in patients who cannot undergo CT [14]. Complete tumor necrosis is considered to have occurred when follow-up CT or MRI shows absence of contrast enhancement within an ablated lesion or at its periphery (Figures 1a, 3b). Any focal and nodular peripheral enhancement in the ablated lesion should be considered indicative of residual or recurrent tumor. Residual or recurrent disease (i.e., local tumor progression) is the most common at the margin of the ablation zone [13,14].

Complications

Major reported complication rates are remarkably low (0-4%) [15-21]. The most commonly reported major complication associated with percutaneous RFA is hemorrhage. Perinephric hematomas often look worse at imaging than at clinical examination and often resolve spontaneously without treatment (Figure 2). Hematuria occurs uncommonly, is self-limited, and resolves within 24 h of treatment [15,16]. Gross hematuria is causing obstruction and requires stent placement. Pyelocalyceal injury can lead to either urine leakage or stricture formation. Urinomas usually resolve with ureteral stenting, whereas strictures in the collecting system may require endopyelotomy or reconstructive surgery. Ureteral stent placement is used to protect the ureter from thermal damage during the ablation of central renal tumors. Retrograde placement of an end-hole ureteral stent by an urologist allows drip infusion of 5% dextrose in water, which protects the renal collecting system and ureter with either a heat- or cold-sink effect. The stent is typically removed at the completion of the ablation.

Because of the kidney's location, care must be taken to avoid thermal injury to the adjacent bowel. At a minimum, 5 mm of intervening fat should be present between bowel and the target tumor to avoid causing

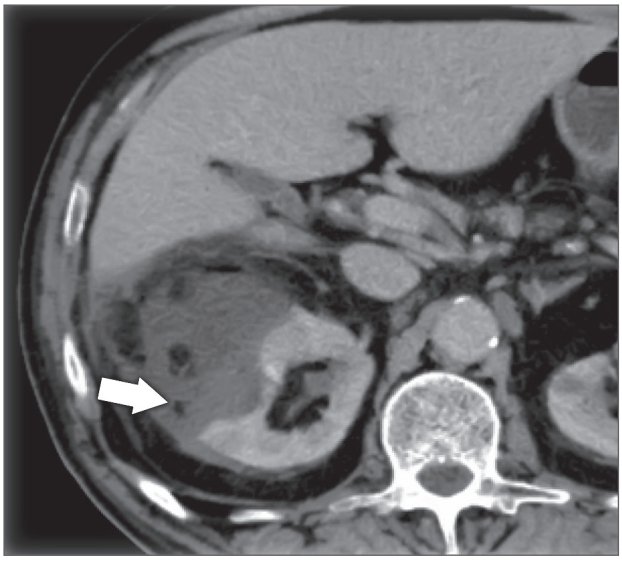

Figure 3. Contrast-enhanced CT scan obtained immediately after RFA shows a perirenal hematoma (arrow). The patient was observed in the hospital overnight and, owing to a decreasing hematocrit level, he was transfused with 2 units of blood. Hospitalization was prolonged over 2 days. Perirenal hematoma resolved spontaneously.

bowel necrosis [7,16]. Fat is an effective insulator, and 5 mm or more is thought to be adequate protection for the adjacent bowel. Hydrodissection is used to protect adjacent organs by moving them away from the ablation zone during treatment. It is performed by placement of a needle or sheath under imaging guidance into the perinephric space between the tumor and the critical organ, followed by infusion of sterile water.

Ablation of renal tumors adjacent to the adrenal gland can cause sudden release of vasoactive catecholamines. For ablation of these tumors, the operator should be prepared to administer α-adrenergic blocking medications. The risk of clinically significant thermal injury to the liver or spleen, when ablating an RCC, is thought to be insignificant. Even in the treatment of central tumors, the development of clinically important pelvicalyceal damage has been rarely reported [15,16].

Literature review

Surgical resection is considered the standard of care for clinically localized RCC because of the favorable prognosis associated with surgery [1]. The 5-year cancer-specific survival (CSS) for patients after nephrectomy is 97% and 87% for pT1a and pT1b tumors, respectively, and only 20% for pT4 disease. Similarly, patients who undergo partial nephrectomy (nephron-sparing surgery-NSS) demonstrate 5- and 10-year rates CSS of 92 and 80%, respectively, across all pathologic stages and 96 and 90%, respectively, for tumors < 4 cm. Similarly, early data on laparoscopic partial nephrectomy are favorable, with a 100% CSS rate reported at a 3-year median follow-up [21-26]. Although oncologic outcomes after NSS are durable, the morbidity profile is not insignificant, even in the hands of experienced laparoscopic and open-operation surgeons.

Meta-analyses, case series, and retrospective reviews support the safety and efficacy of RFA as a minimally invasive treatment option for patients with renal masses who are poor surgical candidates [3-5,7-10,16-19]. Data for long-term oncological outcomes for small RCCs treated with RFA are limited. Currently, there are 6 published cohorts of patients with renal masses managed by RFA with a minimum follow-up of 5 years [3,27-30]. Local recurrence-free survival rate at 5 years ranged from 88-93% and 5-year disease-free survival (DFS) ranged from 83-91% [3,27,29,30]. Metastasis-free 5-year survival rate ranged from 95-100%, which is comparable to metastasis-free survival rate of 98% for patients with small tumors treated with partial nephrectomy [27]. Progression-free survival (PFS), CSS and overall survival (OS) rates at 5 years in different studies ranged from 79.9-93.8%, 98-100% and 58.3-85%, respectively [28]. Therefore treatment of small RCC with RFA results in durable local tumor control and prolonged OS and DFS. Our own recently published institutional data confirm those reported in the literature by other authors [12].

Other studies have compared RFA to cryoablation and/or to radical and/or partial nephrectomy. In a systematic review of renal tumor ablation including RFA and cryotherapy, Hui et al. stated that there are no comparative data to suggest that cryoablation is more effective than RF ablation in the treatment of RCC [31]. In a retrospective review, Hegarty et al. reported a 3-year median follow-up CSS rate following cryoablation of 98% compared to a median 1-year follow-up of 100% following RFA [32]. In a retrospective review, Stern et al. reported that there was not a statistically significant difference (p=0.674) in the 3-year recurrence-free rate following treatment of renal masses with RFA (n=40; 93.4%) compared to partial nephrectomy (n=37; 95.8%) [33].

Another primary benefit of ablative therapy for renal tumors is the potential for preservation of renal function. However, to our knowledge, few studies to date have examined the effects of kidney ablation on renal function. In a retrospective comparative review, Lucas et al. reported on the changes of renal function following radical nephrectomy (RN) (n=71), partial nephrectomy (PN) (n=85), and RFA (n=86) in patients with renal masses <4 cm in size (stage T1a). Following treatment, new onset of chronic kidney disease and a decrease in glomerular filtration rate were significantly more prevalent in the RN group compared to the PN or RFA group (p<0.001 each) [34].

Conclusion

Percutaneous imaged-guided RFA is a minimally invasive safe treatment option for RCC with low rate of recurrence and prolonged metastases-free and CSS rates at 5 years after treatment. Post ablation imaging is critical for the assessment of ablation success, and radiologists must be familiar with the appearance of necrotic tissue and viable tumor. At present, this therapy should only be reserved for smaller tumors in non-surgical patients because further longer-term studies are required to determine its long-term oncological outcome.

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