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Radiofrequency Ablation for Renal Tumor, Past, Present and Future

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1. Introduction

Cancer of the kidney is the third most common cancer of the urinary tract and accounts for 3.5% of all malignancies. With an estimated 51,190 new cases occurring in 2007 and 12,890 deaths attributable to the disease, renal cell carcinoma (RCC) is the most lethal of all genitourinary tumors (1).

The clinical diagnosis of RCC is radiographic, and effective imaging of the kidneys can be achieved by ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) (2). Because of the increased use of diagnostic imaging for the evaluation of patients with abdominal symptoms, incidentally discovered small renal masses (SMRs) are being diagnosed with greater frequency (3) and may account for up to 66% of RCC diagnoses (4). Thus, an increased incidence of RCC over the last 30 years has been associated with stage migration and a concurrent rise in rates of surgical intervention (5). Unfortunately, despite earlier diagnosis and treatment, cancer-specific survival (CSS) and overall survival have not improved significantly, this could be due to the fact that we deliver less treatmentfor solid kidney tumorsthan in the past (6).

Surgical resection remains the standard of care for clinically localized RCC because of the favorable prognosis associated with surgery and the relative ineffectiveness of systemic therapy. Patients who undergo radical or partial nephrectomy for SRMs (tumors classified as pathologic T1a [pT1a], tumors 4 cm) exhibit 5-year CSS rates in excess of 95%. Laparoscopic approaches to partial nephrectomy have produced similarly favorable early results (7).

Recently, minimally invasive ablative technologies have emerged as potential treatment options for clinically localized RCC. The question of whether in situ ablative technologies (8) can replace excision for the treatment of small renal tumours remains unanswered. The reported advantages of ablative approaches over extirpative techniques include reduction of perioperative morbidity, shorter hospital stay and faster recovery time. The main advantage of ablative techniques, however, would be to offer treatment to patients who are otherwise not candidates for invasive extirpative techniques. Radiofrequency ablation (RFA) is a

minimally invasive treatment for localized cancer in which a small needle attached to a device that delivers radiofrequency energy is inserted into a tumour to destroy the cancerous tissue while the patient is sedated or under general anesthesia. The procedure is usually performed percutaneously with image guidance using computed tomography (CT) or ultrasonography (9). Although these newer nephron-sparing techniques appear to be promising, the majority of published studies are single-institution series with relatively few numbers of patients.

Although treatment options for low-stage RCC have expanded in recent years, their proper application and their affect on the biology of SRMs has yet to be defined fully. Here we analyze the combined published data regarding RFA as treatment of SRMs.

2. History of RFA

Minimally invasive tumor ablation therapy for focal malignancies encompasses several specific objectives. Most importantly, through the application of energy or chemicals, the primary goal of most ablation procedures is to eradicate all viable malignant cells within a designated target volume. As such, one substantial advantage of percutaneous ablative therapies over conventional surgical resection is the potential to remove or destroy only a minimal amount of normal tissue. This is also useful when nephron-sparing treatments are needed in patients with von Hippel–Lindau syndrome, who are prone to the development of multiple renal cell carcinomas and in patients with primary lung malignancies in the setting of extensive underlying emphysema and limited lung function.Currently Indications for minimally invasive techniques, including RFA, are: small, incidentally found, renal cortical lesions in elderly patients; patients with a genetic predisposition for developing multiple tumours; patients with bilateral tumours; patients with a solitary kidney at high risk of complete loss of renal function following surgical tumour resection (LE: 2b). Contraindications to the above-mentioned procedures include: poor life expectancy of < 1 year; multiple metastases; low possibility of successful treatment due to size or location of tumour. In general, tumours > 3 cm or tumours in the hilum, near the proximal ureter or the central collecting system are not typically recommended for ablative techniques via a percutaneous approach. (10). RFA of an exophytic renal mass before open radical nephrectomy was described first in 1997 (11) and the first report of RFA as sole treatment for a renal tumor was published in 1999 (12). Although RFA has been applied using open, laparoscopic, or percutaneous approaches under ultrasound, CT, or MRI guidance, the current literature describes percutaneous access in approximately 94% of patients who underwent renal RFA.

3. RFA electrodes and generators

Three types of RF electrodes are currently available commercially: two brands of retractable needle electrodes (model 70 and model 90 Starburst XL needles, RITA Medical Systems, Mountain View, CA, USA; LeVeen needle electrode, Boston Scientific, Boston, MA, USA) and an internally cooled electrode (Cool-Tip RF electrode; Radionics, Burlington, MA, USA) (13).

The needle electrodes of RITA consist of a 14-gauge insulated outer needle that houses nine retractable curved electrodes of various lengths. When the electrodes are extended, the device assumes the approximate configuration of a Christmas tree. Nine of the electrodes

are hollow and contain thermocouples in their tips in order to measure the temperature of adjacent tissue. The alternating electric current generator comes in a 250-W model at 460 kHz (Model 1500X RF Generator, RITA Medical Systems). The ablation algorithm is based on temperature at the tips of the electrodes. After the ablation cycle is completed, a temperature reading from the extended electrodes in excess of 50°C at 1 min is considered to indicate satisfactory ablation.

Another RFA device (LeVeen Needle Electrode; Radiotherapeutics. OWL universal RF System URP-3AP: figure I) has retractable curved electrodes and an insulated 17-gauge outer needle that houses 10 solid retractable curved electrodes that, when deployed, assume the configuration of an umbrella. The electrodes are manufactured in different lengths (2- to 4.0-cm umbrella diameter). The alternating electric current generator is 200 W operated at 480 kHz (RF 3000; Boston Scientific). The ablation algorithm is based on tissue impedance, and ablation is considered successful if the device impedes out.

The third RFA device (Cool-Tip radiofrequency electrode; Radionics) has an insulated hollow 17-gauge needle with an exposed needle tip of variable length (2- or 3-cm). The tip of the needle contains a thermocouple to record the temperature of adjacent tissue. The shaft of the needle has two internal channels to allow the needle to be perfused with chilled water. In an attempt to further increase the size of the ablation area, the manufacturer placed three of the cooled needles in a parallel triangular cluster with a common hub. The generator has a peak power output of 200 W and is operated at 480 kHz (CC-1; Radionics). The ablation algorithm is based on tissue impedance, and ablation is considered successful if the device impedes out. As a result, successful ablations usually increase the temperature of the ablated tissue to above 60°C.

Fig. 1. RF generator: OWL universal RF System URP-3AP

4. Mechanism of action

Radiofrequency (RF) energy can be used to rapidly create highly localized lesions via a temperature-based or an impedance-based system. Both systems rely on the creation of a closed electrical circuit. The cytotoxic mechanism in both involves desiccation due to high intracellular temperatures. High-frequency current flows from a needle electrode to the

surrounding tissue, resulting in ionic agitation, which leads to accelerated molecular friction, which producesheat. Heat induces immediate cellular damage, leading to coagulative necrosis. Energy returns to the RF generator via a return pad that com- pletes the circuit.

The macroscopic and microscopic findings following RF treatment correlate (14). Macroscopically, after RF treatment, kidneys demonstrate a gray-white area of necrosis surrounding a central cavity containing both areas of hemorrhage and necrotic debris.

Clear demarcation exists between the induced lesion and the surrounding normal parenchyma. Shortly after RF ablation, intense stromal and epithelial edema with marked hypereosinophilia and pyknosis are present, accompanied by microvascular thrombosis and coag- ulative necrosis. Chronic lesions demonstrate dense fibrosis.

5. Technique

Monopolar needles are coupled with secondary hooks to create spherical lesions (Figure II-III). An insulating shaft protects normal tissue. Tissue temperature measurements are made via thermo-couples located at the tip of the needles. Electrode temperatures at approximately 100°C are generally required in order to assure temperatures of at least 60°C at the periphery of the ablated lesion (15). Multiprobe, hooked, and bipolar arrays; intraparenchymal saline injection; and internally cooled electrodes have all been developed to increase the size of the lesion created. Polascik and colleagues (16) introduced the modified technique of saline perfusion of tissue during RFA.
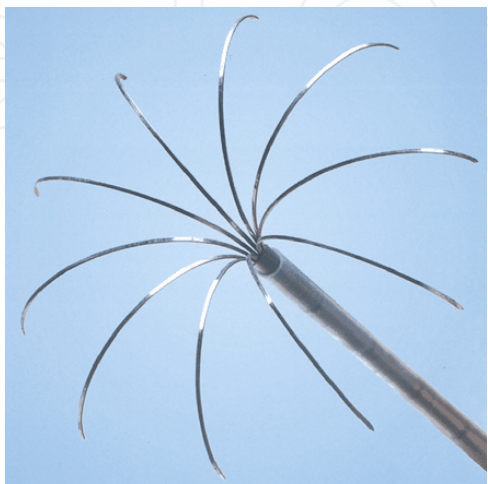
Fig. 2. Monopolar needles

Fig. 3. Monopolar needles

5.1 Electrodes
Most RF ablation systems today operate in a monopolar mode by using two different types of electrodes: interstitial electrodes (hereafter, electrode) and dispersive electrodes on the skin surface (also known as ground pads). The electrode delivers energy to the tumor, creating a volume of high current density and localized heating.

Monopolar electrode designs include both straight insulated needles with an exposed metallic tip and multitined electrodes. Internally cooled electrodes use a single needle, in which fluid is circulated inside the electrode's active tip, and temperatures at the electrode-tissue interface are reduced. Internally cooled needles are now used by the Cool-tip system (Valleylab by Covidien, Boulder, Colo).

In contrast, electrodes with multiple tines emanating from a single electrode sheath or handle assembly aim to distribute energy spatially (17).

Crowley and colleagues (18) showed minimal morbidity and allowed monitoring and control of ablation with impedance-based system in a porcine model.

The ability to monitor the lesioning process during RFA using real-time ultrasound is debatable. Some authors (19) reported that in a saline-infused RFA, a bubbling effect in the area of the treatment may be ultra-sonographically imaged as an area of increased echogenicity. Ultrasound is not useful for intraoperative monitoring. Posttreatment lesions appeared as a distinct hyperechoic zone, an area of bright echogenic foci, or a heterogeneous area of mild hyperechogenicity.

6. What about clinical outcomes?

6.1 Predictive factors for success of RFA
Tumor size is an important predictor of successful treatment in RF ablation of renal tumors. Despite advances in electrode design, the successful ablation of tumors, greater than 4 cm in diameter, has been a challenge (20). Therefore, smaller renal tumors are ideal candidates for an RF ablation. On the other hand, the larger tumors require multiple overlapping ablations and, in some cases, return visits for additional ablation sessions (20).
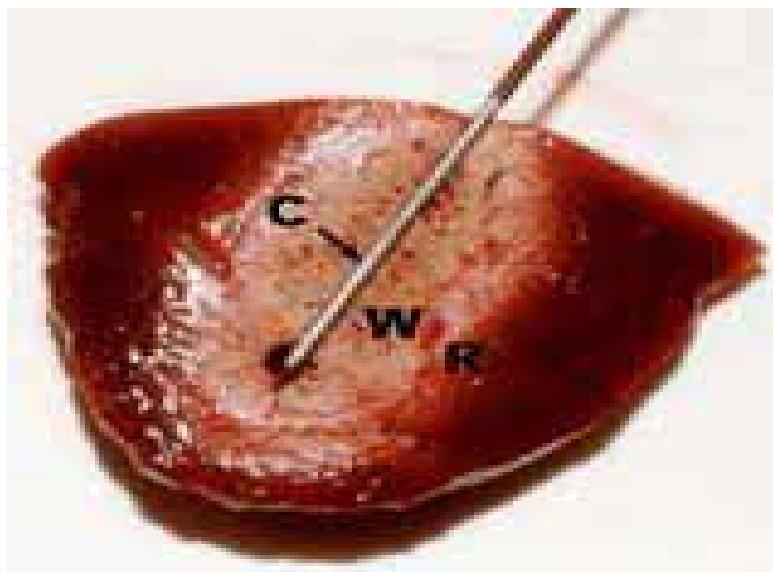

Fig. 4. "Owen effect": "R": red zone=kidney; "C": center of the lession; "W":white zone=fibrotic capsula

The location of the tumor within the kidney may also play an important role in the efficacy of the RF ablation treatment for renal masses, and may influence the success of an ablation. A central tumor ablation fails more frequently because of a heat sink effect, in which a regional vascular flow reduces the extent of the thermally induced coagulation (21). By contrast, exophytic lesions are surrounded by perirenal fat, which serves as a heat insulator and allows the achievement of higher temperatures during RF ablation. This phenomenon was first described in liver tumors and referred to as the "owen effect" (Figure IV) where hepatic tumors surrounded by a fibrotic capsule and surrounding cirrhotic liver tissue are more easily treated (22). As a result of this phenomenon, exophytic renal tumors have an increased likelihood of successful ablation. Therefore, size and location are good predictors of success, with small exophytic renal tumors being the most suitable candidates for RF ablation (23).

6.2 Clinical outcomes

Stern et al. (24) published their results in 37 ASA 1-2 patients. Only one patient had a local recurrence in a period over 2 years and he was treated by radical nephrectomy without recurrence after 1 year follow- up. The same author compared intermediate-term results of partial nephrectomy and radiofrequency ablation and concluded that 3-year oncological outcomes were similar (25).

Gervais and colleagues (26) published a series of 85 patients with the treatment of 100 tumors percutaneously. One local recurrence was seen. Indeed, 100% of the tumors smaller than 3 cm achieved complete ablation while only 25% of tumors greater than 5 cm were completely treated. Another paper of the same group, a cohort of 16 patients was reported with the longest term follow-up available (4.6 years). Five patients died of unrelated causes and the 5-year cáncer specific survival was 100%. Zagoria et al. (27) obtained complete ablation (absence of contrast enhancement in the tumors on CT or MRI) in 96% of tumors altough residual tumors were observed in 30% of those larger than 3.7 cm in a follow-up of 13.8 months.

Lucas et al (28) found a 6.97% of local recurrence and it was higher than in Bensalah´s serie (29) with a global rate of 2.63% of local recurrence, Weight et al (30) described a radiographic success in 85% and no mailgnant cells on biopsy after RFA in 65% of patients and Breen et al (31) an overall technical success rate of 90.47%.

Traver et al. (32) recently reported outcomes of 73 renal tumours in 65 patients treated with PRFA under CT guidance. Mean tumor size was size 2.9 cm. Although initial tumour control was obtained in 84.9%, 5 of 11 initial treatment failures were successfully retreated, 4 were followed conservatively, 1 required nephrectomy, and 1 patient died of unrelated causes. In patients with initial tumour control, recurrence occurred in 8.1%. Matsumoto et al. (33) got better results in a serie of 109 small renal tumours (91 patients) treated with CT-guided percutaneous . Mean tumour size was 2.4. The initial ablation was successful in 98% with two incomplete ablations successfully re-ablated. With at least 1 yr of follow-up, 60% had preoperatively biopsy proven RCC. In this group, one local recurrence was detected during a mean follow-up of 19.4 months and in those with known RCC, none had evidence of distant progression. The local recurrence was successfully re-ablated such that all 109 cases had no clinical or radiographic evidence of disease at last follow-up. Gallego et al. (34) presented a serie of 11 renal tumors in 9 patients. Mean tumor size was higher than in most of the papers reported previously (3.5 cm). In 2 patients two new RF session was needed. 9 tumors with treatment considered effective. Mean follow-up was 17.5 months (3-52 months).

One patient had local recurrence at 14 months and needed a laparoscopic radical nephrectomy and two patients developed lung metastases 41.5 months after RF. There were no clinically relevant complications.

RFA performed intraoperatively immediately before surgical nephrectomy using standard machines and ablation proto- cols did not result in complete cell kill, with persistence of viable tumor cells based on NADH staining varying from 50% to 100% in 2 small series (35). Recently, Klingler et al. (36) found incomplete ablation in 4/17 (14%) renal tumors receiving LRFA before undergoing LPN and concluded that RFA failures can occur also with modern high-energy equipment, thus limiting the indication of this MI thermoablative T to selected high risk patients.

6.3 Follow-up

Radiographic follow-up after RFA is currently the most common means of assessing treatment effect (37). Enhancement on postcontrast imaging is considered evidence of incompletely treated disease. Some centers have performed biopsy after ablation to assess for viable disease, whereas others have relied solely on radiographic evaluation (Figure V)(38). Although the presence of macroscopically viable disease may be detectable on follow-up imaging immediately after ablation, microscopic disease may require a longer duration of surveillance to become apparent. This may explain recent data suggesting that viable tumor may be present on postablation biopsy despite lack of radiographic enhancement. The Working Group on Image-Guided Tumor Ablation has used the term local tumor progression to indicate incomplete tumor destruction regardless of the time it takes for enduring disease to become evident clinically (39). Thus, the ultimate rate of treatment failure after salvage ablation remains to be fully defined. Furthermore, it is likely that ablation techniques have undergone refinement with increased experience; therefore, published series may not truly reflect contemporary results.

When comparing the rates of local disease persistence it is important to consider that nonuniform criteria may have been used to define recurrence after ablation. Although the majority of series used contrast-enhanced imaging to determine treatment effect, the definition of ablative success has been called into question by studies that have demonstrated viable tumor on postablation biopsy despite a lack of enhancement on imaging (40). Perhaps the true rate of local disease progression could be determined more accurately if biopsy were included routinely in postablation surveillance protocols.

The context in which the technical success of renal ablation is evaluated must include consideration of the emerging body of data regarding the observation or active surveillance of SRMs in elderly or infirm populations. Although published series addressing the natural history of small renal tumors under active surveillance report some variability in the clinical behavior of observed SRMs (growth rates of 0.09-0.86 cm per year), a meta-analysis of clinically localized tumors determined an overall median growth rate of 0.28 cm per year for observed lesions across multiple published series (41). Moreover, it has been reported that from 26% to 33% of enhancing renal masses demonstrate zero net growth when observed over a median of 29 months (42). It is note-worthy that only 1% of lesions reported in the active surveillance literature have demonstrated progression to metastatic disease in the absence of treatment. This information raises the possibility of an over-treatment bias for SRMs and suggests that treatment may not have an impact on the biologic potential of many lesions (43), but it is clear that today, with the availability of minimal invasive techniques

like percutaneous RFA only in patients who have competing health risks, radiographic **surveillance** may be an acceptable initial approach, and delayed intervention may be reserved for patients who have tumors that exhibit significant linear or volumetric growth. (44)
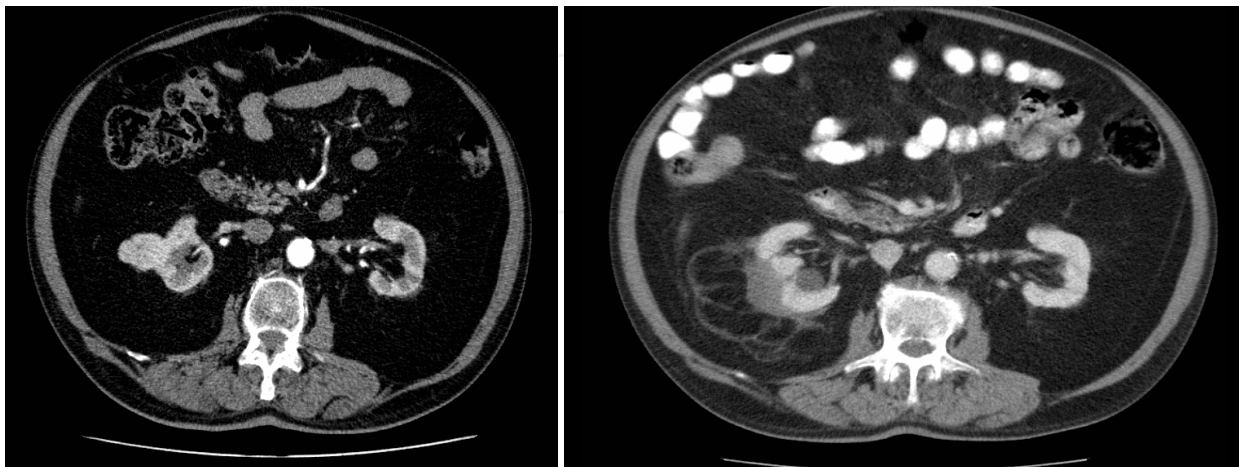

Fig. 5. Renal tumor previous and after RF ablation, after RF there is no contrast enhacement at CT scan

6.4 Effects on renal function

In addition to their minimally invasive nature, another primary benefit of ablative therapy for renal tumors is the potential for preservation of renal func- tion. However, to our knowledge, few studies to date have examined the effects of kidney ablation on re- nal function. Gill et al (45) examined 56 patients with 3- year follow-up after renal cryoablation and reported preoperative and postoperative serum creatinine levels of 1.2 mg/dL and 1.4 mg/dL, respectively. In 10 patients who had solitary kidneys in that series, the mean preoperative and postoperative serum creatinine levels were 2.2 mg/dL and 2.6 mg/dL, respectively, and 13 patients with baseline renal insufficiency demonstrated levels of 3 mg/dL and 2.7 mg/dL, respectively (46). In another series of 14 patients who underwent cryoablation in a solitary kidney, no adverse effect on renal function was noted, although 3 lesions required repeat treatment for incomplete ablation (41). A serie that examined the effects of RFA on 16 patients with a solitary kidney demonstrated a decrease in the mean glomerular filtration rate from 54.2 mL per minute per 1.73 m2 preoperatively to 47.5 mL per minute per 1.73 m2 at last follow-up (47). Similarly, Jacobsohn et al (48) studied 16 patients who underwent RFA in a solitary kidney and demon- strated a 13.3% change in creatinine clearance within 1 week after ablation and a 9.1% change at a mean follow-up of 15.3 months with 1 patient developing chronic renal failure. The ability to spare nephrons maximally remains a careful balance against the possibility of insufficient tumor destruction.

6.5 Complications

Recent data have revealed that two potential serious renal complications associated with RFA are urinoma and a proximal ureteral stricture. Traver et al. (49) reported 2 cases of ureteral strictures from a series of 73 tumours treated with percutaneous RFA: Matsumoto et

al. (33) in 1 case of 91, and Weizer et al. (50) in 1 case of 24 patients, respectively. Another major complication that has occurred is colon injury as described by Weizer et al. (50) in 2 of 24 patients undergoing percutaneous RFA. Other minor complications reported are a small perinephric haematoma and pneumothoraces (51).

7. Future

Ablation research has historically focused on creating larger or more uniform zones of ablation that are reproducible in many situations through device and application development, but device engineering is always constrained by the physiology of the target. New approaches to augment device performance by altering the underlying tissue physiology, optimizing energy delivery, or combining ablative therapies with other treatments, such as radiation or drug therapies, to increase ablation size, uniformity, or treatment specificity have been described.

Many recent investigations have centered on altering underlying tumor physiology as a means to advance thermal ablation. Most studies to date have focused on the effects of tissue characteristics in the setting of temperature-based therapies in general, such as tissue perfusion and thermal conductivity, and system-specific characteristics, such as electrical conductivity for RF-based ablation.

7.1 Tissue perfusión

The foremost factor limiting thermal ablation of tumors continues to be tissue blood flow, which acts as a heat sink and reduces the volume of tissue heated to target temperature, either through large blood vessels or capillary-mediated perfusion. Promising antiangiogenic therapies, such as sorafenib, are also starting to be studied as combination therapies with ablation, with similar encouraging results in animals (52).

7.2 Thermal conductivity

Increased thermal conductivity, such as that in cystic lesions, results in fast heat transmission (ie, heat dissipation), with potentially incomplete and heterogeneous tumor heating. Different tumor and organ characteristics may also make a 1-cm ablative margin difficult to achieve (53).

7.3 Electrical conductivity

Altering the electrical environment immediately around the RF electrode with ionic agents can increase electrical conductivity prior to or during RF ablation, allow greater energy deposition, and, therefore, increase coagulation volume (54).

7.4 Combining percutaneous ablation with other therapies

While substantial efforts have been made in modifying ablation systems and the biologic environment to improve the clinical utility of percutaneous ablation, limitations in clinical efficacy persist. For example, with further long-term follow-up of patients undergoing ablation therapy, there has been an increased incidence of detection of progressive local tumor growth for all tumor types and sizes despite initial indications of adequate therapy, suggesting that there are residual foci of viable untreated disease in a substantial number of cases (55). The ability to achieve complete and uniform eradication of all malignant cells remains a key barrier to clinical success, and therefore, strategies that can increase the

completeness of tumor destruction with RF ablation, even for small lesions, are needed. Investigators have sought to improve results by combining thermal ablation with adjuvant therapies, such as radiation and chemotherapy (56).

RFA qith chemotherapy: The underlying mechanisms of this synergy are multifactorial. Improved intratumoral drug delivery occurs with use of a liposomal carrier owing to increased circulation time, increased drug release with thermosensitive liposome types, and the well-documented vascular effects of sublethal hyperthermia in the peripheral treatment zone (57). Additionally, the cytotoxic effects of the chemotherapy agent combine with the heat-induced reduction in cellular reparative mechanisms to increase apoptosis (58). Finally, study results suggest that there are independent heat-related cytotoxic effects of the liposome itself (58). This preliminary success with combination therapy may be augmented by the development of new targeting vehicles, including several polymer-based temperature-dependent delivery systems currently under investigation (59).

RFA with radiation therapy: Previous data in the literature have demonstrated increased tumor destruction with external beam radiation therapy and low-temperature hyperthermia (60, 61). Findings in experimental animal studies have demonstrated increased tumor necrosis, reduced tumor growth, and improved animal survival with combined therapy when compared with either therapy alone (62). Preliminary clinical studies in primary lung malignancies confirm the synergistic effects of these therapies. Potential causes for the synergy include the sensitization of the tumor to subsequent radiation owing to the increased oxygenation resulting from hyperthermia-induced increased blood flow to the tumor (63). Future research is needed to identify the optimal temperature for ablation, the optimal radiation dose, and the most effective method of administering radiation therapy (eg, external beam radiation therapy, brachytherapy, or yttrium microspheres) on an organ-by-organ basis.

8. Conclusions

Excision remains the reference standard for the treatment of the small renal mass. Most studies pertaining to probe ablation provide level 3–4 evidence. RFA is a suitable and promising therapy in patients with small renal tumours (< 4 cm) who are considered to be poor candidates for more involved surgery. Long-term data on oncological control is lacking and more rigorous head-to-head trials are needed to determine the exact role of RFA in the treatment algorithm of small renal masses.

Concerns about residual tumour and local recurrences after RFA need to be addressed. As we have seen there are no sistematic follow-up strategies after RFA of renal tumors. Usually, local recurrence and development of metastasis are assessed by images and many definitions of radiographic success is being used. This arbitary method of follow up has been inadequate for determining complete ablation since positive biopsies have been reported. In future, molecular markers will also be considered for this purpose. Ideally, surveillance after ablations as well as reporting of outcomes, technique and histological confirmation should be standarized to make posible as better follow up and comparision of RFA series with surgery.

9. Acknowledgment

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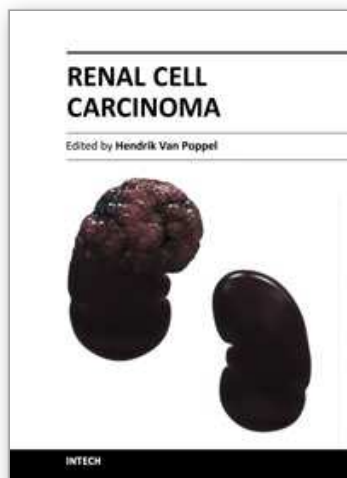
Renal Cell Carcinoma

Edited by Dr. Hendrik Van Poppel

Surgical and medical oncologists have been unable to decrease renal cell carcinoma mortality for uncertain reasons, although a lot of progress has been made in diagnosis and imaging, recognition of different genetic and pathological entities, management of localized disease and in the research on new drug treatments for advanced stages of the disease, potentially combined with surgery. The purpose of this book, which tackles a number of separate interesting topics, is to provide further insight into the disease and the management of early and advanced renal cell carcinoma. The volume is divided into different parts; the first part covers the characterization of renal masses and the second part covers rare distinct pathological entity. In the management section, active surveillance, partial nephrectomy and radiofrequency ablation are presented. A separate chapter reviews the management of Von Hippel Lindau disease, and finally, conventional and aberrant signaling pathways are explored.

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