Early-Stage Renal Cell Carcinoma Locoregional Therapies: Current Approaches and Future Directions

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ABSTRACT: Renal cell carcinoma (RCC) is the most common primary renal malignancy. Prevalence of RCC in developed countries has slowly increased. Although partial or total nephrectomy has been the first-line treatment for early-stage RCC, improved or similar safety and treatment outcomes with locoregional therapies have challenged this paradigm. In this review, we explore locoregional techniques for early-stage RCC, including radiofrequency ablation, cryoablation, and microwave ablation with a focus on procedural technique, patient selection, and safety/treatment outcomes. Furthermore, we discuss future advances and novel techniques, including radiomics, combination therapy, high-intensity focused ultrasound, and catheter-directed techniques.

KEYWORDS: Renal cell carcinoma, locoregional therapy, ablation, high-intensity focused ultrasound, radiomics, SIRT

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Introduction

Renal cell carcinoma (RCC) has seen a gradual increase in incidence in developed countries in recent decades. Locoregional treatments have grown from carving a niche to occupying a significant space in the treatment realm for RCC, particularly with early-stage disease in appropriately selected patients. In this comprehensive review, we discuss the current locoregional treatment strategies, and the outcomes and future directions in the minimally invasive management of RCC.

Epidemiology

The incidence of renal cancer in developed countries has been slowly increasing since the early 2000s, likely due to a combination of slowing birth rates and an aging population.[1] RCC accounts for more than 90% of all renal cancers and 5-year survival rates hover around 75%.[2] Most RCCs occur sporadically, with tobacco use and obesity continuing to be the most correlated risk factors.[1]

Out of the several subtypes, clear cell RCC is the most prevalent, accounting for 70% to 80% of cases and is known for its aggressive nature and lower survival rates.[3] The next most prevalent subtype, papillary RCC, accounts for 10% to 15% of cases and has a generally better prognosis. Finally, chromophobe RCC accounts for most of the remaining 5% of cases, typically diagnosed at an earlier stage, thus with better survival outcomes than clear cell.[3]

Although the classic triad of hematuria, flank pain, and palpable mass are associated with RCC, most cases are asymptomatic and diagnosed incidentally on abdominal imaging. Currently, available evidence suggests only screening high-risk individuals such as those with familial history of *VHL* or *MET* gene mutations.[4,5]

Staging

The American Joint Committee on Cancer (AJCC) TNM system is the most widely used staging paradigm for RCC.[5-7] Staging helps determine the prognosis and guide treatment, whether it be surgical, minimally invasive, medical, or a combination. Per the AJCC, Stage I and II tumors are both locally confined to the renal parenchyma and separated by size smaller or larger than 7 cm in maximum dimension. Stage I/II tumors are categorized as early-stage disease. Prognosis is generally more favorable than late-stage disease and treatments are more available. Stage III tumors include those that involve adjacent major venous structures (e.g. renal vein, inferior vena cava) or involving immediate lymph nodes. Stage IV tumors are those that have invaded beyond Gerota's fascia or have metastasized. Stage III/IV tumors are categorized as late-stage disease.

Treatments

Surgery has been the gold standard for management of early-stage, resectable disease. Surgical resection may be partial or radical, open, or laparoscopic/robotic depending on certain tumor characteristics, involvement of adjacent structures, status of the contralateral kidney, etc. Indeed, partial nephrectomy (PN) is preferred for tumors that are smaller without evidence of local invasion. However, for tumors that have lymph node involvement are locally invasive in the surrounding perirenal fat, or multifocal, radical nephrectomy is typically performed.[8] Finally, for patients with later stage or metastatic disease, medical management with systemic immunotherapy or targeted agents against vascular endothelial growth factor (VEGF) or mechanistic target of rapamycin (mTOR) is the mainstay.[9] Newer systemic therapies are developing which show improved survival, particularly in combination with other immunotherapeutic agents.

The idea of active surveillance has been studied for early-stage cancer. Mir et al[10] examined risk trade-offs of active surveillance in clinically localized renal masses and found that surveillance can be a safe initial option for tumors smaller than 2 cm, particularly in the elderly and comorbid patients. However, since most RCCs are of the clear cell subtype, they often progress and lead to some form of therapy.

Although surgical resection remains the gold standard for early-stage disease, locoregional and catheter-directed therapies have been cultivating an increasing role in the treatment of RCC, especially for patients who are not surgical candidates or prefer a less aggressive treatment. Considering this, careful preoperative assessment of patient comorbidities is crucial as higher frailty indices are associated with increased postoperative complications following PN.[11] Consequently, percutaneous, image-guided thermal ablation is now recommended by the American Urological Association (AUA) as an alternative for tumors less than 3 cm likely given short hospital admission and less detriment to renal function.[12,13]

Locoregional Therapies

Thermal ablation techniques are compelling alternatives to surgery for the treatment of early-stage RCC. The 3 primary percutaneous methods of thermal ablation are radiofrequency (RFA), microwave (MWA), and cryoablation (CA), although high-intensity focused ultrasound (HIFU) and laser (LTA) are increasingly moving from the experimental arena to the clinical realm. The primary goal of thermal ablation is to induce coagulative necrosis and tissue destruction within the tumor while sparing surrounding tissue.[14,15] These procedures are particularly well suited for patients who are deemed poor candidates for surgery due to factors, such as advanced age, multiple comorbidities, or the small/slow-growing nature of a lesion. Table 1 summarizes the different locoregional techniques, their mechanisms, ideal patient/tumor characteristics, efficacy outcomes, and disadvantages.

Radiofrequency ablation

In RFA (Figure 1), a needle electrode is advanced into the center of the tumor under image guidance, usually ultrasound or computed tomography (CT). Once in place, high-frequency alternating current (HFAC) within the 400 to 460 kHz range induces ionic oscillation increasing the temperature in the field to a goal of 80°C to 90°C. The electrode is maintained at target temperatures usually for several minutes. Not only does the heat destroy tumor cells but also provides a cauterization effect of the often neovascularized tumor. Energy is emitted from the electrode, which creates a thermal field destroying tumor and a margin to ensure complete effect.[16,17]

RFA may be indicated when tumor size is < 3 cm since larger tumors require a greater thermal field which may be more injurious to surrounding unaffected renal parenchyma.[18] Also, smaller tumors are more likely to be completely ablated instead of leaving residual tumor. A peripheral location of the tumor is another indication since they are more percutaneously accessible and are farther away from critical vascular and urinary tract structures. Another reason to consider RFA over resection includes patients who are not suitable for surgery secondary to advanced age, significant medical comorbidities, or other perioperative risk factors that might make recovery prolonged. Finally, patients who have a solitary kidney might be at high risk for poor renal function following partial resection; thus, RFA can provide a safer alternative.[18,19]

Excellent outcomes have been reported for patients undergoing RFA across major parameters, including local tumor control, preservation of renal function, complication rates, recurrence rates, and survival.[14-19,23] For lesions < 4 cm, technical success rates approach 100%, matching PN, however with fewer complications, reduced hospital stays, decreased readmission rates, and better 90-day mortality.[14-19,23,24] In addition, 5-year cancer-specific survival has been reported near 90% to 95% in appropriately selected patients.[14-19,23]

Microwave ablation

MWA (Figure 2) entails the utilization of microwave energy to induce controlled thermal injury within the tumor, thereby facilitating its eradication. The core elements of MWA include the deployment of specialized microwave antennas, typically coaxial or helical in design, that are precisely positioned within the tumor under the guidance of ultrasound or CT. Once positioned, these antennas emit electromagnetic microwaves, usually at a frequency of 915 MHz or 2.45 GHz, which generate rapid oscillations of water molecules within the target tissue. These oscillations result in frictional heat generation and rapid heating of the tumor to temperatures exceeding 60°C to 100°C. This, in turn, induces coagulative necrosis and protein denaturation, ultimately leading to the devitalization of the cancerous tissue.[15,17]

Several technical considerations are vital to the success of MWA for RCC. Precise antenna placement within the tumor is paramount to maximize energy delivery to diseased tissue. Factors such as antenna size and power settings are adjusted based on tumor characteristics, size, and location. Careful attention must also be paid to cooling mechanisms, often involving internally cooled antennas or temperature monitoring probes, to prevent overheating of adjacent healthy renal tissue. Post-procedural imaging is essential to assess the completeness of ablation.[15,17] Still, MWA requires shorter ablation time and less sedation dosage than RF and CA, conferring a major technical advantage.[20]

Patient selection is mostly like that of RFA described above with some notable differences. First, MWA is considered for larger tumors > 4 cm since it achieves high target temperatures quicker than RFA, has better 10-year overall survival than RFA

Table 1. Comparison of locoregional techniques.

LOCOREGIONAL TECHNIQUE	MECHANISM	IDEAL PATIENT/TUMOR CHARACTERISTICS	KEY EFFICACY OUTCOMES	DISADVANTAGES
RFA	• 1 or more ablation probes are advanced into tumor under CT or US guidance. • Thermal energy is used to induce tumor necrosis.	• Ideal for peripherally located masses that are < 3 cm in size. • May be suitable for patients with solitary kidney.	• 90% to 95% 5-year cancer-specific survival[13-19] • Lower complication rates than PN while achieving similar treatment outcomes for lesions < 3 cm.[13-19]	• Less precise ablation zones. • Lower success rates for lesions > 3 cm.
MWA	• 1 or more antenna probes are advanced into tumor under CT or US guidance. • Probes generate oscillations in water molecules and generate frictional heat energy.	• Ideal for lesions > 4 but less than 7 cm and located peripherally. • Less heat sink effect than RFA, making it more ideal for vascular tumors.	• 87.4% 5-year cancer-specific survival[20] • MWA resulted in better 10-year overall survival and local control for CT1a tumors compared with RFA.[20]	• Less ideal for tumors near the renal hilum compared with CA.
CA	• 2 or more cryoprobes placed into tumor under CT or US guidance. • Liquid nitrogen or argon gas is used to freeze tumor. Helium gas is used to thaw tumor to induce hemorrhagic necrosis.	• Ideal for tumors near critical structures (ex. renal hilum) due to real-time visualization of ice ball. • Can consider this technique for patients with multiple lesions in a single kidney. • Excellent treatment success and safety outcomes for tumors 3 to 5 cm.[21]	• 98% local recurrence-free survival and 88% overall survival at 3 years[19] • CA resulted in excellent recurrence-free survival (82.4% at 5 years) and overall survival (91.0% at 5 years).[22]	• Longer procedural time than RFA and MWA.

Abbreviations: CA, cryoablation; MWA, microwave ablation; PN, partial nephrectomy; RFA, radiofrequency ablation.
This table details the mechanisms, ideal patient and tumor characteristics, efficacy outcomes and disadvantages of using different ablative modalities, including RFA, MWA, and cryoablation.

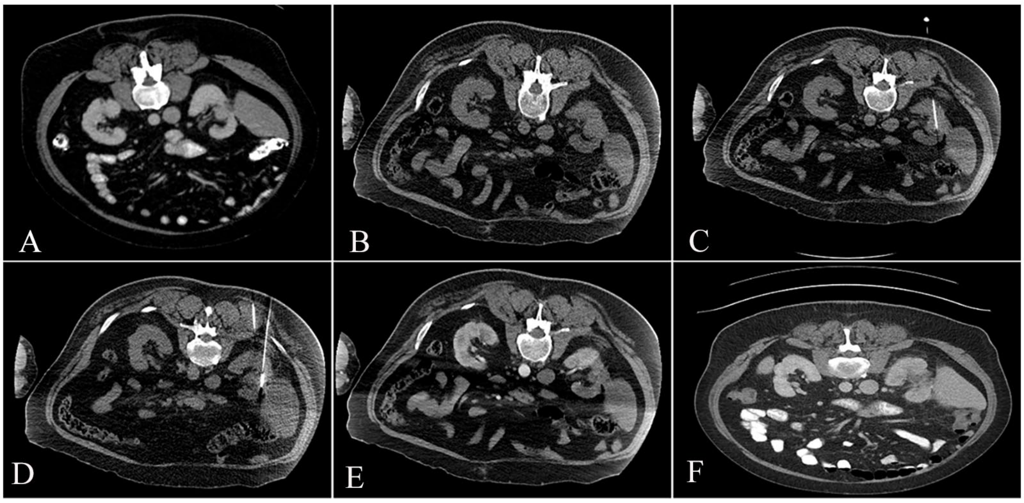

Figure 1. RFA for RCC. Images show prone, cross-sectional imaging of a 66-year-old man with biopsy-proven RCC. (A) Preoperative contrast-enhanced CT shows an enhancing right interpolar lesion, measuring up to 2.4 cm. (B) 6 months pre-treatment non-contrast-enhanced CT redemonstrates this lesion. (C) The first RFA probe is inserted within the superior portion of the lesion. Ablation was performed at 65 W for 8 minutes at this superior probe. (D) The second ablation probe is inserted at the inferior margin of the lesion, where ablation was performed at 65 W for 8 minutes. The more superior probe is partial visualized. (E) Post-procedural contrast-enhanced arterial (shown) and venous phase (not shown) images were obtained, revealing no perfusion to the ablated right interpolar renal mass. (F) It is a contrast-enhanced CT obtained 3 months after ablation which does not show enhancement at the post-treatment bed to suggest viable lesion as compared with the initial contrast-enhanced CT in panel (A).

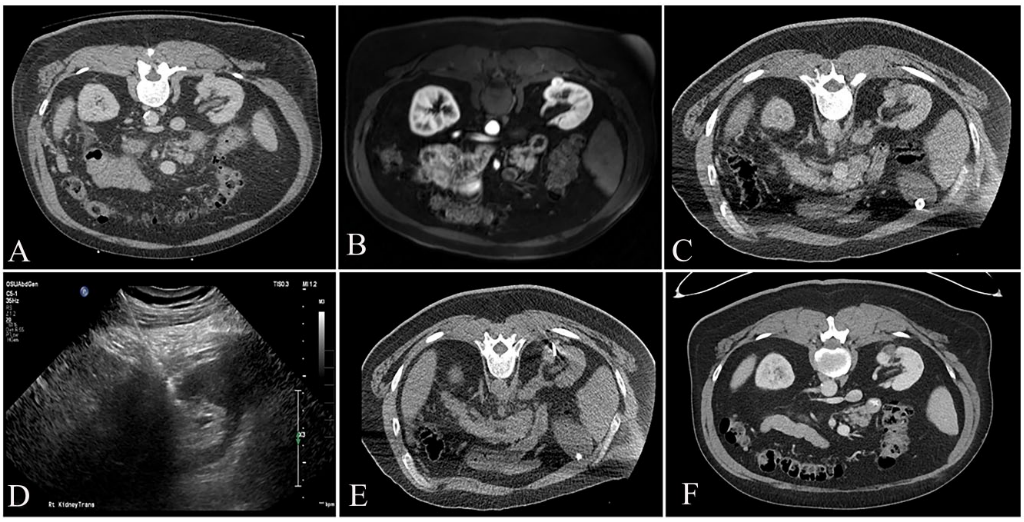

Figure 2. MWA for RCC. Images show prone, cross-sectional imaging of a 58-year-old man with biopsy-proven RCC. (A) Contrast-enhanced CT shows the initial finding of an enhancing posterior exophytic right interpolar lesion. (B) Post-contrast fat-suppressed T1-weighted MRI 6 months after the initial CT redemonstrates the enhancing lesion, measuring up to 1.7 cm. (C) 3 months later, pre-treatment non-contrast-enhanced CT shows the posterior exophytic lesion. (D) It shows real-time ultrasound guided placement of the MWA antenna probe within the posterior right interpolar renal lesion while monitoring for gas bubble formation. (E) Intraprocedural CT was performed after the first ablation to re-confirm probe placement. (F) is a contrast-enhanced CT obtained 1 year after ablation which does not show enhancement at the post-treatment bed to suggest viable lesion as compared with the initial contrast-enhanced CT in (A).

while having promising results for tumors 4 to 7 cm.[25] Also, the heat sink effect is less pronounced with MWA; thus, it makes this modality better for highly vascular tumors (e.g. clear cell subtype) or those lesions that are perivascular. Considering this, CA is still preferred for lesions near the renal hilum.

Patient survival and local tumor control outcomes are similar to that of nephron-sparing surgery, however, with fewer complications and shorter hospital stays.[20,26]

Cryoablation

Cryoablation (Figure 3) is a technique that uses extreme cold to destroy tissue. During the procedure, probes are placed into the tumor. These cryoprobes release a freezing gas, often liquid nitrogen or argon, to create ice crystals inside the tumor cells, which leads to cell death. The procedure is typically performed under general anesthesia or conscious sedation with the use of imaging guidance from CT and ultrasound. Once a small skin

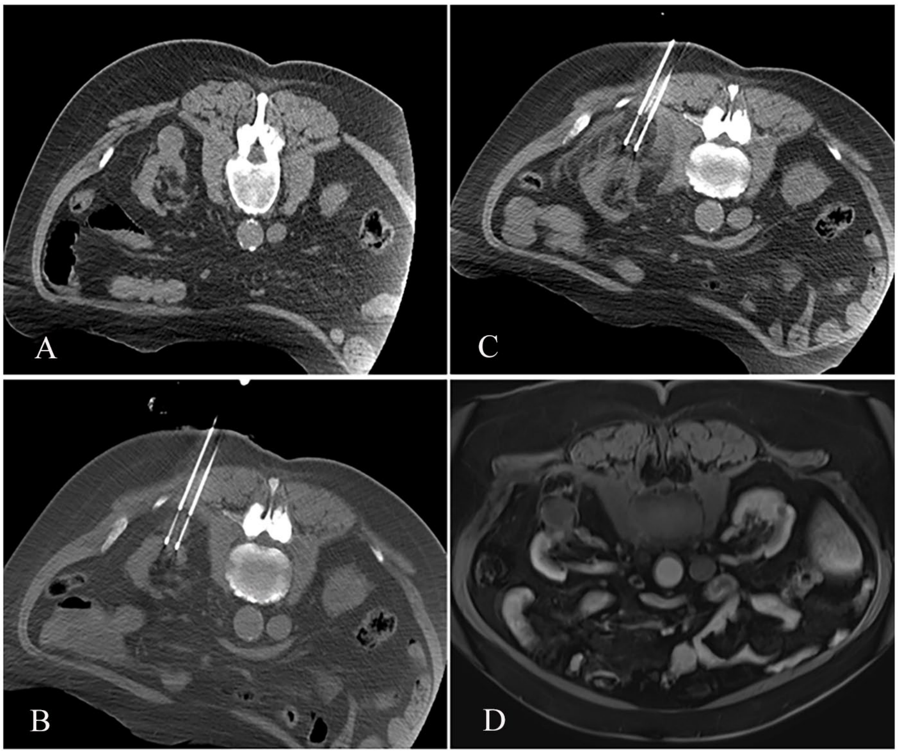

Figure 3. Cryoablation for RCC. Images show prone, cross-sectional imaging of a 62-year-old man with biopsy-proven RCC. (A) Pre-treatment non-contrast CT shows left renal posterior exophytic tumor. (B) It shows 2 cryoprobes with a smaller, intervening hydrodissection probe inserted via a posterior approach. Saline hydrodissection was performed prior to cryoablation to provide adequate space for ablation and reduce risk of injury to surrounding posterior abdominal wall/paraspinal musculature. (C) It shows the ice ball formation. (D) It is a post-contrast fat-suppressed T1-weighted MRI obtained 6 months after ablation demonstrating devascularized tumor bed without residual or recurrent tumor.

incision is made and the cryoprobes are inserted into the tumor, a freezing phase begins lasting anywhere from 5 to 30 minutes followed by a similar length-thawing phase. This cycle can be repeated multiple times to ensure adequate tumor ablation.[15]

Similar to the aforementioned locoregional modalities, patient selection and appropriate indications are important to achieving a high procedural success rate. Indications for cryoablation include small, localized tumors measuring < 4 cm, multiple tumors within a solitary kidney, tumor recurrence after prior partial resection or other ablation, poor surgical candidates due to comorbidities, or patient preference of a minimally invasive option.[16,24,27] Although cancer-specific mortality for RF and CA are similar for tumors < 3 cm, Sorce et al[26] revealed that heat-based thermal ablations such as RF have a 2-fold higher cancer-specific mortality for tumors 3.1 to 4 cm compared with CA. Thus, as suggested by our proposed treatment algorithm, CA may confer an advantage for tumors > 3 cm (see Figure 4). Technical considerations include tumor proximity to critical vascular or urinary structures, number of probes to achieve adequate coverage, and angle of approach to ensure that a tumor margin is not included. Typically, 2 freeze-thaw cycles are performed under real-time ultrasound visualization to assess the ice ball formation and confirm no significant injury to surrounding structures. Some institutions or operators may use temperature probes to monitor these surrounding structures and hydro- or pneumodissection to provide a barrier between target and non-target tissue.[22] This is demonstrated in Figure 1.

Outcomes for cryoablation demonstrate exceedingly high success rates above 90%, especially for RCCs smaller than 3 cm. Thompson et al[23] conducted a prospective study comparing PN with percutaneous ablation, both RFA and cryoablation, from 2000 to 2011 which found that metastases-free survival was significantly improved after cryoablation as compared with RFA. Stacul et al[22] also conducted a retrospective long-term follow-up study evaluating recurrence-free and overall survival in patients treated with CA, which revealed excellent recurrence-free survival (90.5% at 3 years; 82.4% at 5 years) and overall survival (96.0% at 3 years; 91.0% at 5 years). Indeed, cryoablation may be complicated by a urine leak or fistula formation if the ice ball involves the collecting system. In addition, post-ablation syndrome, a self-limiting flu/cold-like syndrome is experienced by some patients. Nonetheless, the significantly reduced hospital stay and overall postoperative complication rate have made cryoablation an attractive alternative to surgical resection.[22,28,29]

The preservation of renal function after cryoablation is notable and particularly beneficial for patients with compromised renal function, bilateral renal disease, or solitary kidney, which is often the case in this patient cohort. Studies of eGFR have demonstrated significant postprocedural maintenance when compared with surgical resection or RFA.[30] Finally, the

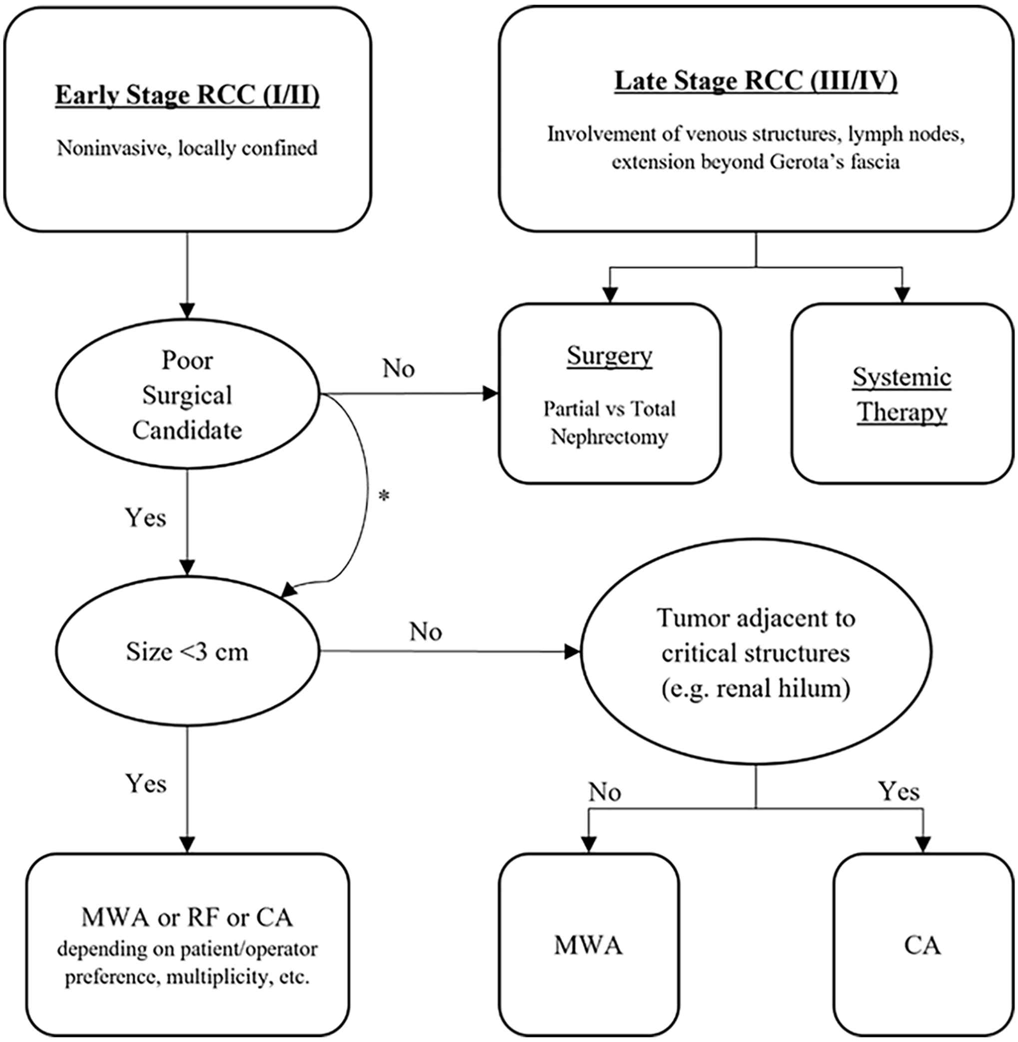

Figure 4. Proposed algorithm for locoregional therapy in RCC.
*Implies that for patients with T1a tumors and who are good surgical candidates either locoregional therapy or PN is a viable option after multidisciplinary discussion with oncology, urology, and interventional radiology, and patient preferences.

health care economic burden of percutaneous cryoablation is far inferior to that of PN. Multiple, single-center studies have demonstrated a substantial decrease in overall cost of renal cryoablation, hovering between 40% and 60%, or approximately US$4500 to US$7000 when compared with PN (open or robot-assisted). Although the device cost was higher in the cryoablation groups, the considerable reductions in hospital stay, laboratory/pathology fees, management of complications, intensive care unit admission, and procedural room time and staffing all contributed to this substantial improvement in cost-effectiveness.[31-33]

The appropriate treatment modality for the appropriate patient can be complex. As such, the authors have proposed an algorithmic approach to RCC locoregional management in Figure 4.

Cost-Effectiveness and Procedural Times

Locoregional techniques are more cost-effective than partial nephrectomies for T1a tumors (Table 2). In a retrospective study of 279 patients (165 MWA vs 114 PN), Yeaman et al[33] revealed that MWA (US$6470) has significantly lower total costs compared with PN (US$20 536). Models accounting for factors such as procedural complications, hospital stay, and local recurrence rates have also shown that CA and RFA were also more cost-effective than PN.[34-36,29]

A large retrospective study on the locoregional techniques revealed that MWA confers significantly less overall procedural time, ablation time, and mean number of ablations compared with RFA and CA.[25] RF and CA are grossly similar regarding these factors (see Table 2). In practice, CA usually has longer procedural times due to more probes being inserted percutaneously and the need to monitor the ice ball progression intraprocedurally.

Procedural Details, Complications, and Role of Imaging

General overview

Locoregional therapies are performed with either general anesthesia (GA) or conscious sedation. GA is generally done for

Table 2. Comparison of procedural costs and duration times of locoregional techniques.

LOCOREGIONAL TECHNIQUE	COST RELATIVE TO PN	MEAN TOTAL PROCEDURE TIME (MIN)	MEAN ABLATION TIME (MIN)
RFA	US$75 000 per QALY for RFA versus US$1 115 529 QALY for PN.[34]	132	35
MWA	US$6470 MWA versus US$20 536 PN[35]	57	7
CA	US$20 491 CA and US$26 478 PN[36]	142	31

Abbreviations: CA, cryoablation; MWA, microwave ablation; PN, partial nephrectomy; QALY, quality-adjusted life-years; RFA, radiofrequency ablation.
This table details the total and relative costs of locoregional techniques relative to PN. Also, it highlights mean procedural times and mean ablation times for each ablative modality.

patient comfort and comorbidities which require anesthesiology support (ex. chronic heart failure, BMI > 30, severe chronic obstructive pulmonary disease [COPD]).

Patients are typically placed in a prone position, however, in a small number of patients, a lateral decubitus position is chosen depending on the location of tumor or variant renal anatomy. Patients are placed in CT and initial non-contrast images are obtained. The ablation probes are initially placed percutaneously with either US or CT guidance. Intraoperatively, either imaging modality can be used to monitor progress of procedure. At the end of procedure, the probes are removed.

These locoregional therapies are usually performed in an outpatient setting. Following the procedure, there is a 2-hour observation period. If there are no perioperative complications, patients are discharged same day, obviating the need for hospital admission.

Pre-procedural planning and patient preparation

As mentioned above, the choice of GA or conscious sedation is based on patient preference and comorbidities. Risk satisfaction models for elective procedures and multidisciplinary discussion with ordering providers may be used to aid this decision. Scoring systems, such as RENAL nephrometry, have been used to predict outcomes following PN; however, literature remains sparse pertaining to similar scoring in regard to locoregional techniques. Li et al[37] attempted to investigate this scoring system in patients treated with MWA, but they did not find the system to have consistent predictive utility.

Contrast-enhanced cross-sectional imaging (CT or MRI) is performed in the preoperative setting to evaluate the size of lesion and location with respect to the renal hilum and adjacent organs (ex. bowel). These factors ultimately guide locoregional treatment choice and adjunctive maneuvers to facilitate the procedure (discussed below).

Patient should be nothing by mouth (NPO) at least 8 hours prior to the procedure. Relevant laboratories (CBC, INR) should be obtained within 30 days of procedure. INR goal is < 1.5, while platelets goal is > 50,000. If patient is on Plavix, this should be held for at least 5 days prior to the procedure. Oral anticoagulants such as apixaban should have 4 to 6 doses held prior to procedure. Warfarin should be held 5 to 7 days prior to the procedure.

Intra-operative phase

In RFA, 1 or more ablation probe (s) are advanced into the tumor under CT or US guidance (see Figure 3). Thermal energy is then used to induce tumor necrosis. As mentioned prior, RFA has less accurate ablation zones than MWA and may sometimes require multiple ablation probes. This is demonstrated in Figure 3, where successful RFA was performed using 2 ablation probes.

MWA uses 1 or more antenna probes, which are also advanced into the tumor under CT or US guidance. These probes generate oscillations in water molecules and induce frictional heat energy to induce tumor necrosis. At our institution, the United States is typically used to monitor for gas bubble formation and gauge the ablation zone (Figure 2D). As mentioned previously, MWA confers a technical advantage regarding total ablation time. For example, successful MWA for the patient in Figure 2 was performed at 60 W for 10 minutes.

CA differs in that at least 2 or more cryoprobes are advanced into tumor under CT or US guidance. Liquid nitrogen or argon gas is used to freeze tumor and induce necrosis. At our institution, a 10-minute freeze cycle is followed by a 8-minute passive thaw cycle and another 10-minute freeze cycle and a 3- to 4-minute passive thaw cycle. The formation of an ice-ball is monitored interprocedurally with either US or CT. Thus, the insertion of more probes and monitoring the ice ball progression may result in longer average procedural times for CA compared with RFA and MWA. At the end of the procedures mentioned above, the probe (s) are removed, and sterile dressing is applied to the site.

Postoperative phase, management of complications and follow-up imaging

At the end of the procedure, CT or US images are obtained to ensure there are no immediate postoperative complications. Patients are typically monitored for 2 hours and discharged home if there are no suspicious clinical or imaging findings. Locoregional techniques are minimally invasive, and patients rarely report significant postprocedural pain.

If perirenal hematomas are identified or there is clinical suspicion for bleed, hemoglobin is obtained and trended. The patient is clinically monitored, and a CTA abdomen/pelvis may be obtained to determine the presence of active bleed. In this scenario, the patient would be admitted as an inpatient and coil embolization may be performed if hemoglobin continues to downtrend or if there is significant drop in blood pressure (ex. < 90 mm Hg systolic).

Although careful selection of locoregional therapy and adjunctive maneuvers (discussed above) may decrease the risk of collecting system injuries, the risk is not zero. Urinary system fistulas, leaks or strictures may be evaluated with CT cystography, where contrast is instilled in a retrograde fashion into the patient's bladder. CT images and 3D reconstructions are also obtained for detailed evaluation of the collecting system. If urinary leak is identified, patient may undergo surgical repair or minimally invasive ablation, depending on location/type of fistula.

Finally, bowel perforation with subsequent fluid collection/abscess is another complication which may require hospital admission. In this scenario, patient is initiated on antibiotics and a percutaneous drain is placed at the site of the collection. Re-imaging and removal of drain is considered based on clinical improvement and decreased/absent drain output.

Large retrospective studies have employed a 3-, 6-, 12-, 18-, and 24-month follow-up protocol, with annual follow-up thereafter if no evidence of disease recurrence.[25] At our institution, follow-up imaging is initially performed 1-month post-ablation with contrast-enhanced CT or MRI to establish a new baseline. Thereafter, the patient's oncology team typically performs a 3-, 6-, and 12-month follow-up surveillance protocol. If no evidence of recurrence, an annual surveillance schedule is used.

Adjunctive Maneuvers and Clinical Scenarios

Pyeloperfusion

Centrally located lesions pose unique challenges to thermal ablation techniques (RFA and MWA). Due to the heat sink phenomenon and narrow safe zones of ablation from the target to adjacent collecting system, potential damage to the collecting system (ex. fistula, leaks, strictures) is a clinical scenario proceduralists routinely face. Pyeloperfusion mitigates this risk by employing a retrograde catheter which is placed in the renal pelvis with the aid of Urology.[36] Refrigerated saline is then used to perfuse the collecting system interprocedurally and provide a cooling buffer while thermal ablation is performed.

Hydrodissection

Retroperitoneal targets may be surrounded by adjacent bowel and pose a technical challenge for the path of the ablation probe. In this scenario, hydrodissection may be used for intraprocedural troubleshooting (see Figure 1B). A hydrodissection probe is placed between adjacent bowel and the target, then saline is infused to "push" the bowel away and create a potential space for safe ablation.

Concomitant biopsy and ablation

Although imaging plays a significant role in identifying renal masses and, initially, raising the suspicion for RCC, there is a growing trend of obtaining biopsies to further characterize lesions and personalize treatment algorithms.[38] At times, both a biopsy and ablation with curative intent may be selected. For this unique clinical scenario, the ablation probe(s) are first inserted into the lesion. Subsequently, the biopsy probes are inserted, and concomitant ablation and biopsy are performed.

Future Directions

Investigations are underway to improve the survival and expedite the detection of RCC. Exciting developments in radiomics, tumor immunology, high-intensity-focused ultrasound including histotripsy, combination strategies, and catheter-directed therapies are coming to the forefront and expanding the treatment arsenal for RCC. The following sections provide an overview of some of these developments.

Radiomics

Radiomics refers to the extraction of many advanced quantitative features from medical images, potentially capturing tumor heterogeneity and providing insight into the tumor's biology and behavior. In RCC, radiomics can improve diagnostic accuracy, prognostic prediction, and therapeutic response assessment. Radiomic analyses, when applied to CT, MRI, or other imaging modalities, can help differentiate between various RCC subtypes, predict aggressiveness, and monitor treatment response.[33,39] Integrating these advanced image-derived data with clinical, genetic, and other biomarker data can provide a comprehensive patient profile, paving the way for personalized treatment approaches for RCC. As a relatively new field, continued research, standardized methodologies, and validation in larger cohorts are essential for radiomics to be fully integrated into clinical decision-making for RCC.[28]

Combination therapies

RCC has been a target for various combination therapies, especially in advanced and metastatic settings. The rationale for combination therapies stems from the heterogeneous nature of RCC.[40] Targeting multiple pathways simultaneously may increase synergism and overcome resistance. For example, Motzer et al[41] demonstrated promising results including improved survival outcomes in advanced cases when combining immune checkpoint inhibitors nivolumab and ipilimumab. Other therapies such as tyrosine kinase inhibitors (TKIs) and mTOR inhibitors show variable efficacy but are often hindered by their meaningful adverse effects.

Combining immunotherapy with ablation techniques is an even newer area of investigation demonstrating potential in late-stage disease. For example, Campbell et al[42] published a recent pilot study of tremelimumab with and without adjuvant cryoablation in 29 patients with metastatic RCC which found a demonstrable increase in post-ablation immune cell infiltration and increased ratio of T effector cells to T regulatory cells within the tumor microenvironment. Toxicity profiles were not statistically different in either arm. Kroeze et al[43] investigated RFA with and without interleukin-2 in a murine model of RCC, which found significant increase in natural killer cells, CD4+ and CD8+ T cells in tumor tissue in addition to significant decrease in lung metastatic formation and size when compared with interleukin-2 alone.

High-intensity focused ultrasound

Similar to previously discussed ablative modalities, HIFU produces coagulative necrosis in target tissue by a thermal effect achieved via mechanical vibrations in a focused ultrasound beam. Both extracorporeal and intracorporeal systems have been used for experimental studies. A systematic review conducted by Nabi et al[44] showed promising outcomes with pathologic necrosis in all target renal lesions when a laparoscopic/intracorporeal method was used. However, in an early clinical trial, only 15% to 35% of target tissue was histologically damaged when exposed to the highest HIFU intensities.[21]

Histotripsy is a type of HIFU wherein microbubble formation under pressure causes mechanical tissue lysis.[40] This technique involves the formation of a predetermined microbubble area within the targeted tissue site. The ultrasonic waves cause necrotic cavitation of the tissue with complete resorption of necrotic debris in 2 months. The most exciting advantages of histotripsy are the sparing of collagenous tissue, such as vascular and collecting system structures and the continued permeation of immune cells into the disrupted tumor microenvironment which facilitates further tumor cytoreduction.[45]

As with many emerging treatments, challenges such as selecting ideal candidates, optimizing treatment parameters, and standardizing post-procedure monitoring need to be addressed.[46] Continued clinical trials and larger, longer-term studies will be essential in solidifying the position of HIFU and histotripsy in RCC management.

Catheter-directed therapies

Catheter-directed therapies are minimally invasive procedures that deliver treatments directly to the tumor site using catheters, allowing for targeted therapy. Although these techniques are more commonly associated with liver or lung tumors, they have been explored in the treatment of RCC as well. Several catheter-directed therapies have been used or investigated for RCC, including radioembolization, chemoembolization, and bland embolization. Radio- and chemoembolization have been shown to reduce tumor size and limit progression;[47] however, not enough data are available on RCC when compared with HCC or other solid organ tumors. Side effects are also more systemic than ablative modalities. With this in mind, a recent development involves selective internal radiation therapy using yttrium (Y-90) microspheres to target RCC tumors. In a phase I study, de Souza et al[48] revealed promising results regarding local control of the tumor at 12 months while maintaining adequate safety and toxicity profiles. Bland embolization has carved a niche in palliation with studies showing improved postprocedural patient quality of life.[49,50] Overall survival varies based on patient selection, tumor characteristics, and specific modality.[51,52]

Conclusions

This review sheds light on the evolving landscape of RCC management, emphasizing the shift toward minimally invasive approaches. Surgical interventions, particularly nephron-sparing techniques such as PN, remain crucial for resectable disease. However, locoregional therapies are gaining prominence, offering viable options for patients who are not surgical candidates or prefer less aggressive treatments. Locoregional ablation techniques have reduced overall costs and shorter hospital stays while offering comparable local recurrence rates and metastasis-free survival compared with conventional surgical interventions. However, the choice of the specific ablation modality depends on various factors, including tumor size, location, and the patient's overall health. Looking forward, continued research into HIFU, catheter-directed, histotripsy, and combination therapies promises to expand the arsenal of minimally invasive options. Challenges such as patient selection, optimal parameters, and standardized protocols need to be addressed to harness the full potential of these techniques.

Author Contributions

UK reviewed and organized available literature, wrote the manuscript, and contributed to the final edits. BH created relevant figures and tables, and contributed to additional literature review and edits. MSM originated the idea for the article, provided guidance, reviewed article organization and provided edits, and contributed technical expertise of the discussed locoregional therapies.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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