Contemporary management of small renal tumors

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The incidence of kidney cancer in the United States is rising because the increased use of cross-sectional imaging is resulting in more tumors being detected and because the population is aging. In addition, a stage migration in kidney cancer has been observed – again because of improved detection – with an increase in stage T1 tumors and a concomitant decrease in the number of stage T2 to T4 tumors. Recent studies have shown that up to 80% of small renal tumors (SRTs) either have an indolent course or are histologically benign. These findings raise the question of what the optimal management of SRTs should be. Radical nephrectomy, the traditional, most aggressive, and still most frequently used extirpative surgery, has been shown to increase the risk of chronic kidney disease. Therefore, during the past 2 decades there has been a shift toward nephron-sparing surgery in carefully selected patients as such procedures have demonstrated equivalent oncologic outcomes with a decrease in long-term renal-induced morbidities. More recently, thermal ablative techniques have evolved as a reliable minimally invasive option for SRTs that can provide adequate oncologic control with minimal morbidity. Finally, in patients with limited life expectancies, active surveillance may be a reasonable approach given the slow median growth rate of SRTs. In evaluating patients with SRTs, percutaneous renal biopsies are being used safely and with increasing accuracy, providing valuable histologic information that can be used to guide the management of SRTs. This article will explore the approaches to managing and treating this growing cohort of patients with SRTs, which are usually incidentally identified.

It is estimated that 63,920 Americans will be diagnosed with kidney cancer (parenchymal adenocarcinoma) in 2014.[1] The incidence of the disease is increasing because more cases are being detected with the use of cross-sectional imaging and because of an aging population with established risk factors such as smoking, hypertension, obesity, familial propensity for the disease, end-stage renal disease, and so on.[2,3] Coincident with the higher incidence of kidney cancer is a stage migration, with an increase in stage T1 tumors (organ confined, ≤ 7 cm) and a related decrease in stages T2-T4 (Figure 1). During 1993-2004, the size of stage T1 tumors decreased from a mean diameter of 4.1 cm to 3.6 cm. Excellent outcome data on the success of surgery in patients with lesions < 4 cm led to a subdivision of T1 cancers in 2002 to T1a for lesions ≤ 4 cm and T1b for those > 4 cm. Many small renal tumors (SRTs; T1a) pose little threat to patients (particularly older individuals) because about 60% may run a relatively indolent course[5] and up to 20% are histologically benign, most commonly oncocytomas or atypical variants of angiomyolipomas.[6] Most stage T1 lesions are identified radiographically in asymptomatic individuals and are found incidentally (often referred to as "incidentalomas").[4]

Data from the SEER (the Surveillance, Epidemiology and End Results program) show that during 1983-2008, the incidence of small kidney cancers (T1a, ≤ 4 cm) increased by 285% for lesions < 2 cm and by 244% for those of 2-4 cm[7] (Table 1). This was not unexpected because technological advances and use of radiographic imaging – ultrasound, computerized tomography (CT), and magnetic resonance imaging (MRI) – were able to detect clinically unsuspected kidney tumors, resulting in a rise in both the incidence and prevalence of the disease.[8] Concurrent with this rise has been a corresponding increase in the number of surgical procedures intended to eradicate the disease (Figure 2) based on the assumption that surgical removal will achieve optimal survival outcomes. However, the death rate from kidney cancer is not falling; in fact it seems to be rising (Figure 3). How is this possible if there is a stage migration to lower volume disease for which curative extirpative (surgery) is the mainstay of therapy? The answer is that overall mortality rates for patients with predominantly high tumor volume have been largely unaffected because in general, tumor size correlates with aggressiveness in tumor grade (Fuhrman grading system, based on nuclear changes and presence or absence of

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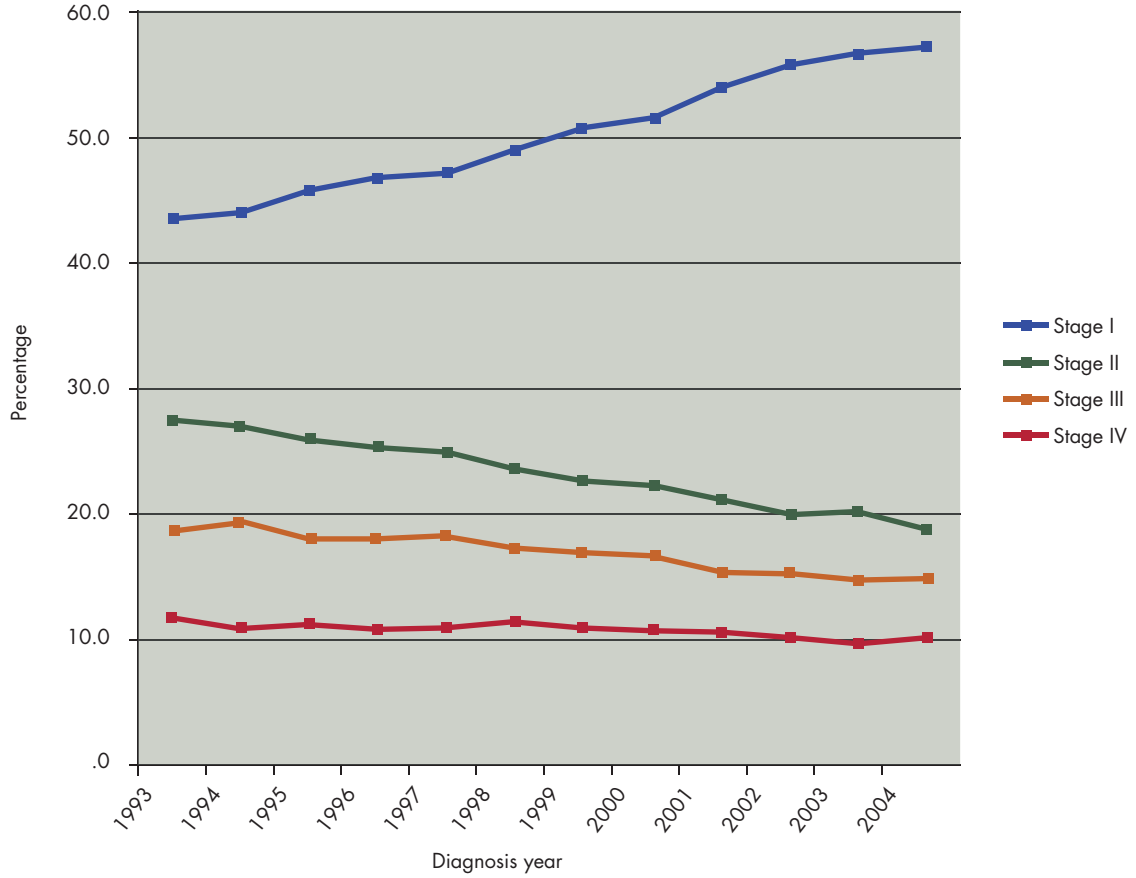

FIGURE 1 Renal cell cancer stage migration. Source: Cancer. 2008;113:78-83. Used with permission.

nucleoli), invasive phenotype, and adverse histological subtypes.[6] These unfavorable characteristics have a negative impact on prognosis with attendant increases in disease recurrence and decreases in disease-specific survival. In addition, although it seems that observational data has demonstrated increased survival in treated patients with low-volume disease, this improvement may be the result of length–time bias, yet advances in the use of VEFT-TKI and m-TOR inhibitors seem to have extended 5-year median survivals in patients with advanced disease from 7.3% during 1992-1995 to 12.3% during 2003-2009, according to a recent SEER database analysis.

With rare exceptions, kidney cancer can only be cured by using surgical extirpative or ablative techniques because there are few effective adjuvant treatments for locally recurrent or disseminated disease. There is no question that disseminated kidney cancer is lethal, and we must intensify our efforts to identify and better treat patients with high-volume, high-stage disease. Yet we also need to reassess how we are managing patients with low-volume disease because not every low-volume renal cancer poses a threat to every patient. In addition, up to 20% of small T1a renal tumors are histologically benign for which no treatment is necessary.

The scope of this review is to address the role of surgery, ablative therapies, active surveillance, and the use of percutaneous biopsy in the evaluation and management of SRTs, which are defined as parenchymal renal tumors ≤ 4 cm in diameter (stage T1a).

Surgery

Radical nephrectomy

Robson described the initial radical nephrectomy in 1963 as the surgical removal of the entire contents of Gerota's fascia, including the kidney, its surrounding fat, and the ipsilateral adrenal gland.[9] Whether the procedures are performed using an open or minimally invasive approach (ie, laparoscopic, robotic- or hand-assisted), the goals are identical – removal of the entire kidney. Radical nephrectomy has demonstrated improved survival over the previously popular pericapsular nephrectomy for patients with disease confined within Gerota's fascia (T1-T3a disease). It remains the gold standard as the most commonly performed surgical procedure for the treatment of patients with kidney cancer, although today the adrenal is often spared. Although radical nephrectomy does achieve high local control and cure rates for patients with localized

TABLE 1 Demographic and pathologic dataa for SEER renal cell carcinoma patients diagnosed during 1983-2002, by tumor size

Characteristic	Tumor size[b]				
	< 2 cm (n = 1,637)	2-4 cm (n = 9,676)	> 4-7 cm (n = 11,372)	> 7 cm (n = 11,818)	Missing (n = 6,310)
Patient					
Mean age (SD), y	60.7 (15.0)	63.5 (13.7)	63.2 (14.1)	59.4 (18.3)	65.6 (16.3)
Female,%[c]	38.3	38.1	37.6	36.3	37.8
Race, %[d]					
White	82	83.7	86.2	85.6	85
Black	13.4	11.4	8.8	9	10.7
Other	4.6	4.9	5	5.4	4.3
Tumor characteristics					
Right, %[c]	52.9	53.5	51.4	48.5	47.9
Organ confined, %[d]	88.1	85.1	66.3	40.1	27.4
Tumor histology, %[d]					
Clear cell	90.6	92	92.5	88.3	89.6
Papillary	3.3	2.4	1.5	1	0.9
Chromophobe	0.2	0.2	0.1	0.1	0
Oncocytoma	0.1	0.3	0.1	0.1	0.1
Other	5.8	5.1	5.8	10.5	9.4
Fuhrman grade, %[d]					
1	36.2	32.4	22.9	14.3	20.1
2	47.3	51.6	50.1	42.6	34.3
3	12.8	14	22	32.8	35.9
4	3.7	2	5	10.3	9.7

[a]From 9 Surveillance, Epidemiology, and End Results areas: San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, Metropolitan Atlanta. [b]For those cases with available tumor size data, chi-square tests were used to compare all categorical variables; Mantel–Haenszel chi-square tests were performed for all ordinal variables; generalized linear modeling was performed for continuous variables. [c]For $P < .05$. [d]For $P < .001$. Source: J Natl Cancer Inst. 2006;98:1331-1334. Used with permission.

disease, it is not without its consequences.

It is now appreciated that about 25% of patients who are being considered for surgical removal of a presumed kidney cancer, will demonstrate pre-existing grade 3 chronic kidney disease (CKD) with an estimated glomerular filtration rate (GFR) of < 60 mL/min per 1.73 m^2 despite having a radiographically normal opposite kidney and a normal serum creatinine. In addition, the development of grade 3 and higher CKD (GFR < 45 mL/min per 1.73 m^2) is much greater in patients who undergo radical nephrectomy than in those who undergo partial nephrectomy.[10] Several large studies have documented the adverse implications of CKD, including cardiovascular events, anemia, bone health issues, sexual dysfunction, and death.[11, 12] Despite the potential deleterious multisystem concerns, the appeal of radical nephrectomy is its excellent cure rate, long track record of use, and familiarity of the procedure to urologic surgeons. However, there has been a progressive decline in the popularity of radical nephrectomy for T1 lesions (< 7 cm) owing to the near equivalent oncologic and improved morbidity outcomes of nephron-sparing procedures.

Partial nephrectomy

Over the last 2 decades, nephron-sparing surgery has emerged as the standard of care for relatively small (T1 < 7 cm), surgically amenable renal tumors. An adequate surgical margin and histologic diagnosis can be obtained, ensuring complete removal of the tumor. Historically, partial nephrectomy was typically reserved only in patients with a solitary kidney, bilateral tumors, familial renal cancer, or who refused dialysis. Its proven efficacy and safety, coupled with the urologic surgeon's increasing comfort level with this surgically more demanding procedure, has fostered its acceptance and growth. Indeed, partial nephrectomy offers properly selected patients oncologic outcomes that are comparable with radical nephrectomy, as measured

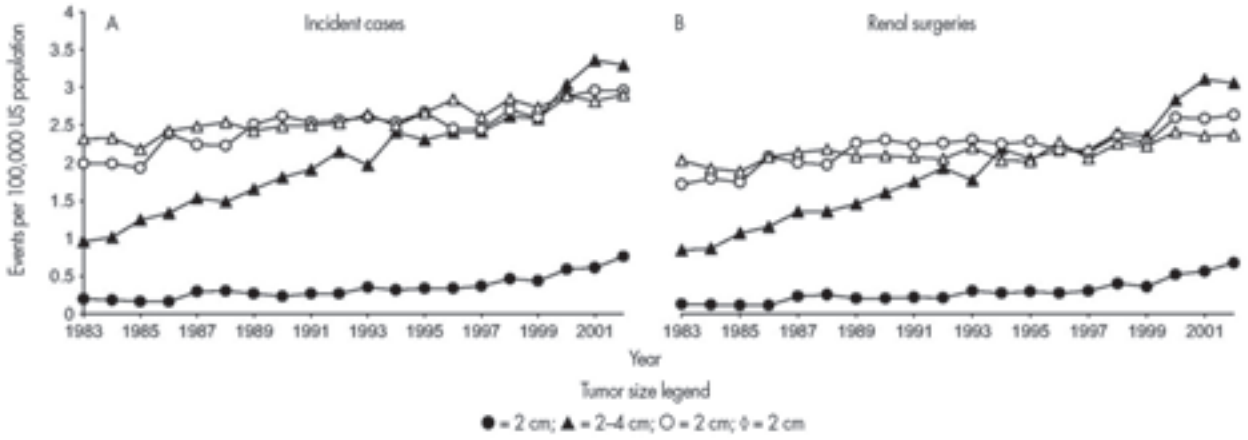

FIGURE 2 A, Age-adjusted (2000 US) annual kidney cancer incidence, and B, annual rates of renal surgery, stratified by tumor size. Rates are expressed as the number of events per 100,000 US population. The data used to calculate the incidence of kidney cancer and rates of renal surgery were obtained from 9 Surveillance, Epidemiology, and End Results areas: San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, Metropolitan Atlanta. Source: J Natl Cancer Inst. 2006;98:1331-1334. Used with permission.

by disease-specific survival, while preserving as much renal function as possible.[13,14]

Accurate radiographic assessment of renal tumor size and location are not only prognostically important but also essential in determining whether a lesion is amenable to partial nephrectomy.[15] The larger and more central a tumor is, the more likely it will be aggressively malignant and less amenable to nephron-sparing surgery, either on the basis of poor tumor control and/or high complication rates. Kutikov and Uzzo (Figure 4) established the RENAL Nephrometry Score, a standardized system to describe the anatomic features of renal tumors, including size, location, proximity to the renal hilum artery(s) and vein, and closeness to the collecting system. This comprehensive reproducible scoring system aids in clinical decision making and provides a tool for meaningful comparisons of the available invasive treatments. In general, the higher the nephrometry score the more technically difficult partial nephrectomy would be and the greater the potential for complications related to the procedure (score of 4-6 = low complexity for resection; 7-9 = moderate complexity; 10-12 = high complexity).

As with radical nephrectomy, technical advances in laparoscopic techniques and increasing surgeon familiarity with the procedure have led to an expansion in the use of minimally invasive surgical techniques for partial

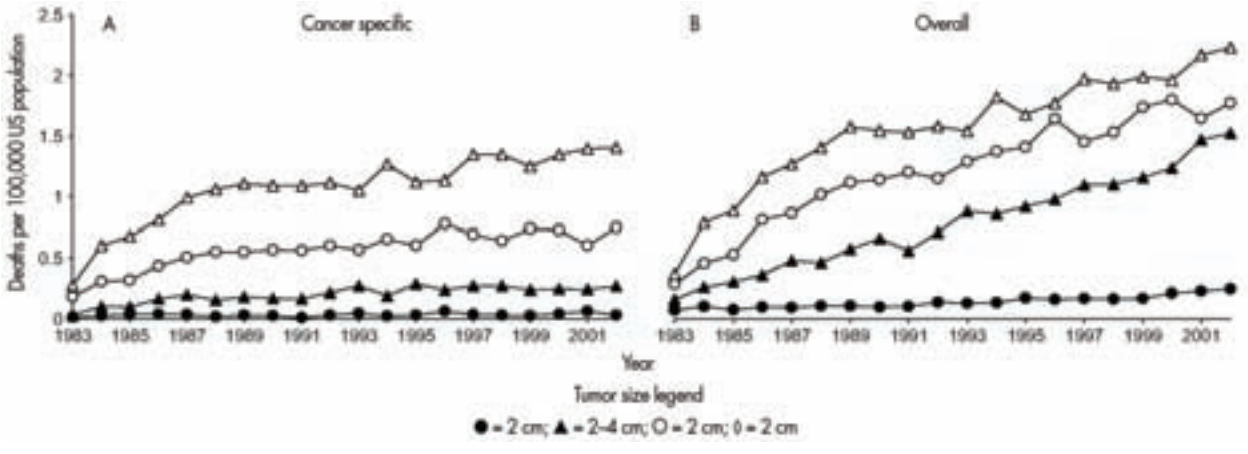

FIGURE 3 A, Age-adjusted (2000 US) kidney cancer–specific annual mortality rates, and B, overall annual cancer mortality rates, stratified by tumor size. Rates are expressed as the number of deaths per 100,000 US population. Data used for kidney cancer–specific mortality and overall mortality were obtained from 9 Surveillance, Epidemiology, and End Results areas: San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, Metropolitan Atlanta. Source: J Natl Cancer Inst. 2006;98:1331-1334. Used with permission.

A	1 pt	2 pts	3 pts
(R)adius (maximal diameter in cm)	≤ 4	> 4 but < 7	≥ 7
(E)xophytie/endophytic properties	≥ 50%	< 50%	Entirely endophytic
(N)earness of the tumor to the collecting system or sinus (mm)	≥ 7	> 4 but < 7	≤ 4
(A)nterior/Posterior	No points given. Mass assigned a descriptor of a, p, or x		
(L)ocation relative to the polar lines* *suffix "h" assigned if the tumor touches the main renal artery or vein	Entirely above the upper or below the lower polar line	Lesion crosses polar line	> 50% of mass is across polar line (a) *or* mass crosses the axial renal midline (b) *or* mass is entirely between the polar lines (c)

B

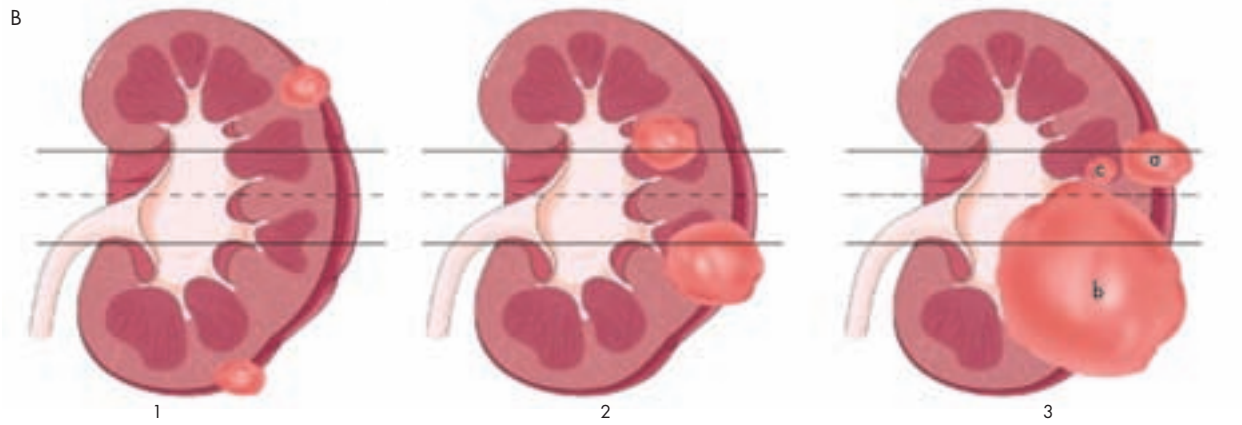

FIGURE 4 A, RENAL Nephrometry Score with B, scoring of Location (L) component. Polar lines (solid) and axial renal midline (broken) are depicted on each sagittal view of kidney. Numbers 1-3 represent points attributed to each category of tumor. J Urol. 2009;182:844-853. Used with permission.

nephrectomy. Laparoscopic partial nephrectomy has distinct advantages over open partial nephrectomy, including decreased operative blood loss and shorter length of hospital stay, but it has a higher complication rate. In general, urologic complications of partial nephrectomy include intraoperative or delayed hemorrhage; warm ischemia, in which the hilar vessels are not temporarily occluded and which may have an adverse effect on GFR; and urine leak. In addition, the surgical margins might be inadequate. Multiple surgical steps are necessary to reduce these morbidities which render partial nephrectomy, regardless of the approach, more challenging than a radical nephrectomy. These steps include attention to frozen section validation of negative margins, vascular control and selective clamping of the renal vessel(s) during tumor excision (with/without deep parenchymal suturing across the resected defect), use of various hemostatic sealants, and meticulous watertight closure of the collecting system. The need for transfusion, reintervention, and conversion to total nephrectomy is higher for partial nephrectomy compared with other definitive treatments.[13] Nonetheless, partial nephrectomy offers properly selected patients a disease-specific survival comparable with that of radical nephrectomy with a decreased risk of GFR reduction and its attendant morbidities.

Thermal ablation

Currently accepted energy-based modalities of thermal ablation include cryosurgery and radiofrequency ablation (RFA; Figure 5). The goal of this type of therapy is to deliver a lethal treatment to the tumor-bearing area without leaving viable tumor cells within the treated zone. Technically, the treating physician must be able to control the area of treatment by avoiding ablation of adjacent normal tissue. These modalities can be administered percutaneously, through an operative laparoscopic approach, or through an open surgical incision. The advantages of thermal ablation include a more rapid recovery and reduced morbidity compared with partial or radical nephrectomy. However, the incidence of local recurrence is expectedly higher than it is with radical or partial nephrectomy. This limitation is due to the difficulty in assessing recurrent/residual tumor on

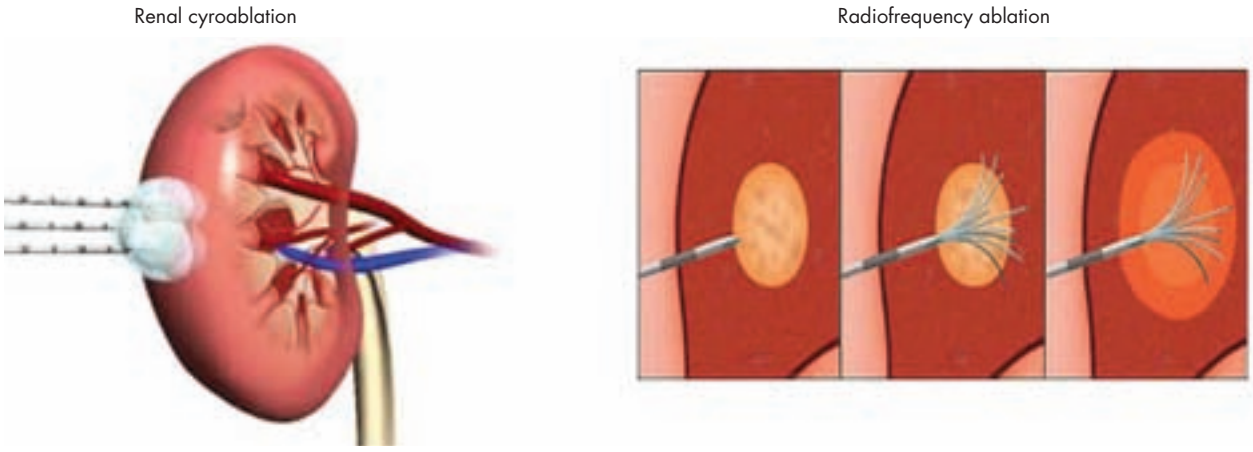

FIGURE 5 Thermal ablation: renal cyroablation and radiofrequency ablation. Source: Cartoon. Used with permission.

biopsy or radiographic imaging of posttreatment lesions, and the realization that the actual reporting of disseminated disease and disease-specific mortality is hampered in many series by the lack of pretreatment biopsies and long-term follow-up. Accordingly, these energy-based therapies are probably best suited for older patients, those with significant comorbidities, or those who develop a local recurrence after a thermal ablative procedure or partial nephrectomy. In addition, this form of treatment may be considered in patients with familial renal cancer or who present with multifocal lesions or choose this option despite appropriate counseling.

Thermal ablative treatments should be reserved for renal lesions ≤ 4 cm (T1a) that are readily accessible and predominantly exophytic. Risk factors for incomplete ablation include tumor size > 4 cm and hilar or endophytic lesions.[16] Treated areas need to be monitored for local recurrence after thermal ablation. Some decrease in the size of the treated lesion is often evident with cryoablation, but there is often no change in size after RFA. Persistent radiographic contrast enhancement of the ablated tumor-bearing area often suggests residual/recurrent disease although early postoperative enhancement of the treated area (< 12 months after ablation) should not be interpreted as a treatment failure.

Cryoablation

Cryoablation causes cell death through 2 mechanisms in the freeze–thaw cycle. The first is a 2-step process of chemical cellular damage that occurs when ice forms in the extracellular fluid compartment. This compartment becomes hyperosmotic, allowing fluid to enter from the intracellular compartment, which leads to hypersomolality and dehydration within the cell. The end result is desiccation trauma. With additional cooling, intracellular ice formation occurs, which causes cell organelle and cell membrane disruption, leading to cell death. The second mechanism takes place during the thaw cycle, which initiates microcirculatory arrest with a cascade of vasoconstriction, vascular congestion, and ischemia, leading to circumscribed necrosis.[17]

Most clinicians use 2 freeze–thaw cycles to effect a complete ablation. Studies with porcine models have confirmed that incomplete necrosis occurs at temperatures above about -20^{0}C and uniformly at temperatures < 40^{0}C.[18] Argon gas is used to generate temperatures of < -40^{0}C within the center of the ice ball. This temperature warms up considerably as the leading edge of the ice ball is approached so most clinicians extend this boundary 1 cm beyond the tumor. Most of the cryoablative studies reported to date have used laparoscopic means for placement of the probes.

Most of the studies that have evaluated the efficacy of cryoablation have been retrospective with small cohort sizes and relatively short-term follow-up. Nonetheless, cryoablation seems to achieve satisfactory local control as defined by the lack of local enhancement and diminution in size of the ablated area on CT.[19] On T2-weighted MRI, the ablated areas appear hypointense, demonstrating a change from high intensity on pre-ablation images. Weight and colleagues reported on a series of 192 lesions in 176 patients who underwent renal cryoablation.[20] At 6 months, the resultant fibrosis or scar formation on CT or MRI demonstrated absent enhancement in 90% of treated lesions. Subsequent biopsies failed to reveal any histologic malignant or atypical cells in 94% of treated lesions.

Complications of cryotherapy are uncommon and include hemorrhage, adjacent organ injury, renal fracture, ileus, and wound infection.

Radiofrequency ablation

RFA uses high-frequency electric current to create heightened ionic activity that results in heat and friction that

melts cellular membranes and denatures intracellular proteins. Cell death occurs with temperatures > 60^0C. Most therapies involve temperatures reaching 105^0C at the tip of the probe that is inserted directly into the tumor with a target zone of up to 4 cm. As with cyroablation, 2 treatment cycles (heat–cool down) are used with a desired ablated area of 5-10 mm from the tumor edge. Unlike cryoablation, there is no ice-ball, which makes it somewhat more difficult to monitor the treatment effect. Most RFA procedures on the kidney are performed percutaneously. Comparison with patients who have undergone cryoablation is difficult because of small study series and short follow-up, but patients selected for RFA seem to be somewhat older, are more likely to have a solitary kidney or a familial propensity for multiple tumors, and have more centrally located lesions than do those patients who have undergone cryoablation. In addition, patients treated with RFA also tend to undergo more secondary (salvage) ablations than do those who undergo cryoablation. This may be because of the relative ease of a repeat percutaneous RFA (compared with a laparoscopic cryoablation) and the tumor complexity selection. Complications are uncommon but include stricture of the ureteropelvic junction, acute renal failure, pancreatitis, and lumbar radiculopathy.[21]

Active surveillance

Active surveillance implies that intervention will be delayed until the benefit/risk of further monitoring, improvement in a patient's overall health, the patient's desire for definitive intervention, and/or change in tumor characteristics render continued observation an unattractive option. Active surveillance is a reasonable option for patients with an anticipated limited life expectancy and for those who are not amenable to and/or do not currently desire or require intervention. Patients who undergo active surveillance need to be apprised that the window of opportunity for definitive treatment may be lost and that there is a risk of cancer progression in those who harbor malignant tumors, with little effective therapy for malignant dissemination.

For some patients with small renal tumors, active surveillance may be appropriate. Bosniak and colleagues reported on 72 tumors (< 3.5 cm in diameter) in patients who were followed for a mean of 3.3 years (range, 2-10 years) that had CT characteristics consistent with renal cell carcinoma (solid, enhancing, homogeneous lesions). The median growth rate was 0.36 cm/year. Tumors in 32 patients grew to > 3 cm and were excised. All were T1a, low-grade renal cell carcinomas and no patient demonstrated metastatic disease during the period of observation.[22] Smaldone and colleagues performed a systematic literature review of small renal masses in patients who were under active surveillance. The investigators identified 6 cohort studies with available individual-level data totaling 284 masses in 259 patients. At a mean follow-up of 33.5 months, 87.1% of the tumors exhibited tumor growth, which was calculated at a rate of 0.31 cm (± 0.38) cm a year. Among the patients with available pathologic data, 88% of the tumors were malignant (predominantly clear cell histology); 10.3% were oncocytomas, and 1.7% angiomyolipomas. A broader review by these authors, incorporating data on 936 renal tumors in 880 patients from 18 published articles, identified 18 patients whose tumors progressed to metastasis. The mean time to progression was 40 months. Patients who progressed to metastasis were older than those who did not progress (75.1 vs 66.6 years, respectively) and they exhibited faster tumor growth rates (0.80 vs 0.30).[23]

The current stage migration of kidney tumors to a preponderance of incidentally found small lesions has allowed further observation of growth rates in some patients. Additional series confirm the slow growth rate (median, 0.28 cm/year) of many small tumors; however, the growth rate was often derived from a retrospective review of images in which the lesion was either initially missed or considered to have been inconsequential. In addition, many tumors were never biopsied and therefore had no histologic confirmation of being malignant. Frank and colleagues reported that tumor size matters.[6] They found that tumor diameter correlated with a likelihood of benign histology. Tumors < 2 cm had a 30% chance of being benign, whereas those between 2-3 cm and 3-4 cm had a 22% and 20% respective chance of a benign histology. In addition, many small malignant renal tumors were low grade, possibly suggesting a protracted indolent course. There are, however, occasional small tumors that may grow more rapidly. Volpe and colleagues have reported on the need for surgical intervention in tumors that grow to > 4 cm or doubled in size within a year.[24] Overall, 11 of 32 masses (34.3%) fulfilled these criteria. Nine masses were removed surgically at a mean follow-up of 38 months – 5 because of increased growth and 4 at the patient's request. The histological diagnosis was renal cancer (clear cell type) in 8 masses, and oncocytoma in 1; all of the tumors were organ confined and no patient had disease progression.

Long-term growth rates of many tumors seem to follow a linear rather than logarithmic progression. Accordingly, one monitoring approach for active surveillance is to obtain a CT or MRI as early as 6 months from the initial study and with annual follow-up imaging (ultrasound, CT, or MRI) in patients whose tumor growth rate is not of concern. It should be appreciated that with such an approach, several millimeters of inter- and intra-observer differences lie within the variability of measurement and should not necessarily be attributed to tumor growth.[25] The cumulative amount of ionizing radiation exposure with CT also must be appreciated.[26] Patients who, for whatever reason,

will never undergo intervention do not need follow-up imaging.

Needle biopsy

There is no clinically reliable test, short of histological confirmation, to determine if a renal tumor is benign, indolent, or aggressively malignant. Traditionally, renal tumor biopsy was commonly performed only to establish a tissue diagnosis in patients suspected of having metastatic disease, renal lymphoma, or atypical undiagnosed renal masses such as xanthogranulomatous pyelonephritis. Even in these circumstances, renal tumor biopsy was not routinely performed because of concern about a high false negative rate, biopsy complications, potential for needle-tract seeding, as well as the relatively high diagnostic accuracy of conventional imaging.

With 20% of T1 renal tumors being benign and the overall incidence of clear cell histology declining to 60%-66% in the past 20 years, there is an increasing likelihood that small malignant lesions may behave in an indolent manner.[27] This has engendered renewed interest in ascertaining a tumor's histology in many patients before embarking on active surveillance or definitive therapy.

There have been significant improvements in both the safety and the accuracy of renal tumor biopsy primarily owing to refinements in CT and MRI-guided techniques. Similarly, advances have been made in the interpretations of both core biopsies and fine-needle aspirates with improved specimen familiarity among pathologists and the use of in situ hybridization and immunohistochemistry to aid in obtaining a definitive diagnosis. The false negative rate of renal tumor biopsy is currently about 1%, and the incidence of symptomatic complications requiring some form of intervention is < 2%.[28] In addition, needle-tract seeding is extremely rare for parenchymal renal cell cancers and is reported at 0.01%. However, indeterminate (nondiagnostic) results of renal tumor biopsies before surveillance or treatment range from 10% to 15% in most series.

Complications of needle biopsy include hemorrhage and infection, which occur infrequently. Local bleeding after a renal biopsy may make subsequent intervention more difficult and a postbiopsy infection may delay definitive intervention. Patients who are unwilling to accept the possibility of uncertainty on a biopsy are usually managed based on clinical and radiographic considerations without biopsy determination. Similarly, biopsies are not recommended in patients who are not candidates for treatment or in those who, despite counseling, do not wish to undergo intervention. When there is concern about residual or recurrent disease after ablative therapies, postablation biopsies are sometimes difficult to interpret because of the resultant fibrosis and distorted growth pattern of tumor cells.

Discussion

The management of small renal tumors is evolving. Data is accumulating on tumor histology and the disease-specific and overall survival of patients who have SRTs. Knowledge of the natural history of SRTs is also accumulating through reported series of patients on active surveillance and has been enhanced by the expanding role of percutaneous biopsy. It is anticipated that the incidence of SRTs will continue to increase concomitant with the frequency of cross-sectional imaging and the aging population.

Not all small renal tumors are malignant and a relatively large percentage of tumors that are malignant may act in an indolent manner. Accordingly, it seems intuitive to consider knowledge of the histology of a small renal tumor before deciding on various treatment options, including active surveillance. We are becoming more comfortable in not only performing renal tumor biopsies but also in their safety and pathological interpretation. Patients should be counseled that percutaneous renal tumor biopsy is a well tolerated outpatient procedure with a very low risk of complication. Caution should be exercised with indeterminate biopsy results. Patients with these nondiagnostic interpretations should not construe that their biopsies are benign. For properly selected patients who are uncomfortable about undergoing percutaneous biopsy, surgical extirpation of small renal tumors remains the standard of care.

Ablative therapies are gaining in popularity as many of these are performed in an outpatient setting under conscious sedation with enhanced local anesthesia. At our institution, in the past 7 years, we have performed 52 renal tumor ablations on 50 patients. More than 90% of these procedures were cryoablations performed percutaneously. In our initial experience, we did not universally biopsy patients because of real-time imaging considerations concurrent to the virtual contemporaneous ablation. We now routinely perform core biopsies at the time of ablation. Of the tumors that we biopsied, 38% (13 of 34) had primary malignant renal pathology, 50% (17 of 34) had a benign diagnosis, and 12% (4 of 34) were indeterminate. The median diameter of the tumors was 2.4 cm and the median age of our ablated patients was 75 years.

Oncologic success encompasses local recurrence rates as well as the incidence of metastasis, cancer-specific deaths, and overall survival. Postablation recurrence-free survival is less than that of partial nephrectomy although the recurrence rate depends on its definition.[29] Most current clinical studies define local recurrence as persistent or new contrast enhancement of the ablated tumor bearing area. It is important to appreciate that, initially following ablation, most tumor-bearing areas demonstrate an increase in size and that maturation of the gross and cellular level ablated effect is not immediately apparent, often taking at least a year. Over time, tumor-bearing areas treated with

cryoablation generally regress in volume on imaging, in contrast to those treated with radiofrequency, which often do not. Routine histologic stains (hematoxylin and eosin [H&E]) of cryoablated tissue usually do not demonstrate viable cells, whereas RFA-treated tissue often demonstrates preservation of tumor architecture, shortly after ablation, as a result of heat fixation. The interpretation of these H&E stains may incorrectly imply the presence of such cells as viable persistent malignancy. However, delayed nicotinamide adenine dinucleotide diaphorase staining confirms nonviability.[21] Residual disease and/or recurrence, suggested by contrast enhancement of the ablated area, may be addressed with either another ablative procedure or a partial nephrectomy. Of note, there have been isolated reports of surgical technical difficulty in performing a partial nephrectomy after renal tumor ablation.[30]

When considering monitoring (active surveillance) patients with small renal tumors, 2 factors need to be appreciated. First, the behavior of small renal tumors is variable and often unpredictable. The heterogeneous group of T1 lesions averages up to 20% as histologically benign, about 60% as indolent cancers, and the remaining 20%-30% of lesions < 4 cm as potentially aggressive cancers.[31] Second, tumor growth rate is not indicative of malignant or benign histology as there are no reported differences in the presence of malignant cells in those renal tumors with a zero growth rate compared with those with a positive growth rate.[32] Nonetheless, it is true that tumor size does matter because the incidence of perinephric fat invasion, Fuhrman nuclear grade, and the development of synchronous renal and metastatic disease increases with increased tumor volume. However, there are a small number of T1a cancers (3.9%) that rapidly progress, disseminate, and result in an abbreviated disease specific survival.[33]

Most of the outcome studies on the management of small renal tumors are observational and therefore are limited by selection and other biases. However, some outcomes are apparent. Surgical removal of histologically proven malignant or indeterminate small renal tumors seems to offer properly selected patients the best chance for definitive tissue diagnosis with the highest recurrence-free and disease-specific survivals. Partial nephrectomy has a marginally higher incidence of postoperative hemorrhage requiring intervention or transfusion and a higher incidence of urinary leak (fistula) compared with radical nephrectomy. The relatively low conversion rate of laparoscopic partial nephrectomy to open surgical procedures reflects the technical advancements with laparoscopic techniques and their expanded familiarity among urologic surgeons. Specific reasons for conversion include bleeding, renal vessel or hilar tumor involvement, access limitations, positive margin status, and so on.[13]

Cancer-specific survival rates are relatively high across all types of interventions, including active surveillance for T1a lesions. This is likely a reflection of the indolent behavior of many stage T1a tumors, some of which are benign. Caution must be exercised in interpreting comparative treatment results as the interventions with the highest use often have the shortest follow-up, include smaller tumors, and/or are used more frequently in younger patients. Follow-up disease-specific survival studies are generally short (most ≤ 5 years), which further limits outcome interpretations.

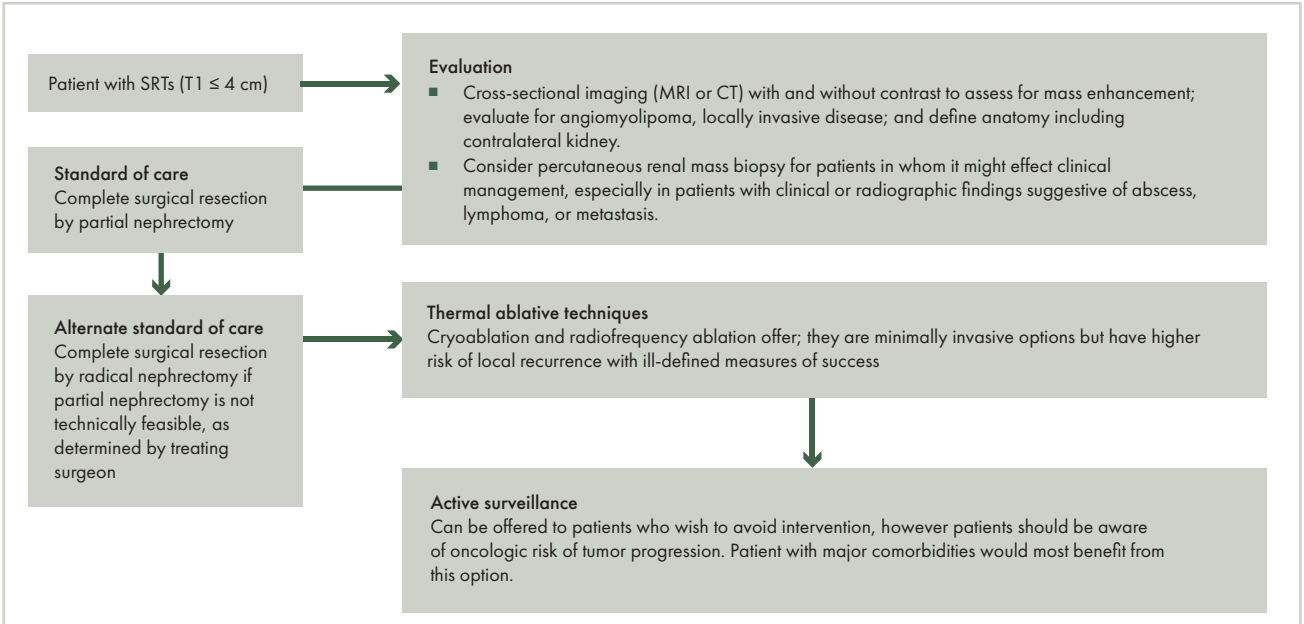

FIGURE 6 Algorithm for management of small renal tumors

Management of small renal tumors must be individualized because patient- and tumor-related factors influence management strategy (Figure 6). The overall health of the patient and his/her anticipated life expectancy are the primary considerations. Accurate knowledge of the histology of the tumor will often aid in considering definitive treatment and attendant follow-up. The deleterious effects of reduced GFR, as a result of intervention, must be weighed against cancer-specific survival in patients with malignant renal tumors.

Renal cell carcinoma was historically often referred to as the internist's tumor because of its not uncommon presentation as a paraneoplastic syndrome. Currently, stage migration via radiographic imaging would suggest that small renal tumors be subcharacterized as the radiologist's tumor because most tumors are discovered incidentally. As physicians, we need to temper our enthusiasm for extirpation of all small renal masses because many pose little threat to a given patient's survival and/or quality of life. Fortunately, we continue to accrue new knowledge on small renal tumor histology and use enhanced diagnostic and treatment modalities that facilitate the delivery of optimal care to our patients.

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