Current management of small renal masses

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The incidence of small renal masses (< 4 cm) is increasing due to the widespread use of imaging studies. Many of these incidental lesions may remain asymptomatic or in fact be benign, and recent insight into their natural course has contributed to modifications in management. With improvements in biopsy technique and minimally invasive technologies, appropriate diagnosis and treatment of these masses are further being evaluated. Other contemporary approaches, including surveillance, laparoscopic partial nephrectomy, enucleation, ablative procedures, and high-intensity focused ultrasound, are weighed against open nephron-sparing surgery, the current gold standard for treatment. Here, we review currently available data on the efficacy of these treatment options. Additionally, we examine the natural history of small renal masses, the role of diagnostic biopsy, and follow-up strategies for proper management.

Key Words: renal cell carcinoma, nephron-sparing, nephrectomy, minimally invasive, ablation, diathermy, cryosurgery, enucleation, biopsy

Introduction

In 2007, there will be an estimated 51190 new cases of renal carcinomas in the United States amounting to 12890 deaths.[1] Since 1950, the incidence of renal cell carcinoma (RCC) has increased 126%,[2] while 5-year survival rates have risen from 51% in 1975 to 66% in 2002.[1] Extensive use of enhanced imaging modalities may attribute to the increased incidence and likely account for concomitant rises in the detection of small renal masses.

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Within a broad range of treatment options, diagnosis and management of these incidental findings can be challenging for several reasons. First, the majority of these masses are asymptomatic and the natural history has not been examined until recently. Second, since imaging is often unable to characterize these small masses and up to 40% are benign, the role of biopsy is being reconsidered. Third, the improvement of minimally invasive techniques provides options for patients potentially unsuitable for surgical intervention.

For accessible T1a tumors, nephron-sparing surgery (NSS) is now considered the standard of care. This method was initially reserved for imperative implications such as bilateral renal masses or tumor in solitary kidneys, but cancer control is now shown to be

equivalent to that of radical nephrectomy for tumors < 4 cm. Preservation of functional parenchyma, particularly with the 2%-3% risk of bilateral RCC, mandates the use of NSS when technically feasible. Yet recent data show that most small renal tumors are still being managed with removal of the entire kidney.[3,4] In settings of underutilization, especially in non-teaching and low-volume hospitals, treatment policies should be carefully reexamined. In this article we summarize the current management of small renal masses, including their natural history, a role for diagnostic biopsies, treatment options, and follow-up strategies.

The natural history

The emergence of active surveillance as an initial treatment option for select patients has helped to define the natural history of small renal masses. This characterization is important in determining biological behavior of the mass and necessity for intervention. Newer studies, although small and with short follow-up, are consistent in revealing an association of smaller renal masses with less metastatic risk and slower growth rates. Average growth rates of small renal masses are reported from 0.10 cm/year to 0.54 cm/year.[5-11]

The natural progression of incidentally detected small RCCs was examined by Kato et al.[11] Eighteen patients were initially observed for a median of 22.5 months prior to surgical removal. A mean tumor growth rate of 0.42 cm/year was noted, with grade 3 tumors growing significantly faster than grade 2 lesions (0.93 cm/year versus 0.28 cm/year). No significant difference in growth rate was observed between grades 2 and 1 (0.37 cm/year). As in other studies, growth rate was found to correlate with histological grade and apoptosis, as indicated by a positive TUNEL ratio.[12,13] A few prospective studies evaluating the natural history during active surveillance also conclude small renal masses grow relatively slowly.[14-16] Moreover, smaller tumor size is more likely to reflect benign etiology, but if malignant, associated with low grade and increased survival.[17] Therefore, assessing growth rate, as well as absolute size, may be helpful in managing small tumors.

The role of biopsy

Historically, a role for renal mass biopsy was limited, as over 90% were considered to be malignant and require removal. However, because up to 40% of small masses detected incidentally via imaging are in fact benign and many malignant tumors are indolent, a role for biopsy has rationale to potentially avoid unnecessary surgery.[18,19] However, biopsy also carries the possible risk of seeding, bleeding and infection, as well as substantial sampling error. In the past, these issues have raised concern as to whether biopsy is safe and useful prior to surgery. Today, the availability of newer treatment options and advances in diagnostic modalities such as imaging, interventional approaches, and cytologic techniques has led to a more useful role of biopsy in the management of small renal masses.

In a recent study, Neuzillet et al demonstrated that percutaneous fine needle biopsy for small renal masses can be performed with accuracy and low morbidity in an outpatient setting.[20] Eighty-eight patients with solid renal masses < 4 cm were biopsied with an 18-gauge core needle under CT guidance. Three biopsies were inadequately sampled and five were considered inconclusive due to fibrosis. Fourteen patients (15.9%) were found to have benign lesions, and biopsy results changed the management in 42 patients (47.8%). Biopsy had a reported accuracy of 92% in detecting histopathological tumor type and 69.8% in determining tumor grade, though no tumor was incorrectly graded by more than one point. Others have reported similar success rates,[18,21] degree of impact on treatment decision,[18,22] and high specificity in grading.[23-25]

Evidence supports a greater role for biopsy of small renal masses, and its use should be tailored to individual patients. For example, biopsy may be helpful in patients with metastatic disease or possible lymphoma by providing a definitive diagnosis, especially for inclusion in a clinical trial. On the other hand, lesions highly suspicious for malignancy on imaging and clinically appropriate for resection can forgo biopsy.

Treatment options

Surveillance

Based upon tumor size and grade, renal cancer may present as clinically insignificant disease and therefore never necessitate curative treatment within a patient's lifetime. This may especially apply to older patients. The greatest rise in incidence of small tumors presents in patients older than 70 years who quite often have concerning comorbidities.[26] Favorable results may be achieved with small renal tumors simply by providing active surveillance and intervention if necessary; still, strict observation is warranted since not all lesions remain indolent.[10,11] Some suggest that these tumors tend to grow slowly and the period of time from discovery to intervention may be wide enough to

warrant observation without adversely affecting the chance for cure.[27,28]

Kouba et al examined 43 patients with Bosniak IV renal masses on a watchful waiting protocol due to patient choice or comorbidity.[26] At a mean follow-up of 35.8 months, 74% of patients had an increase in tumor size (median 0.35 cm/year). Delayed intervention did not result in upstaging from initial pT1 in any of the 13 patients who underwent surgical removal, including those with rapidly growing tumors, and no patient experienced significant symptoms, disease progression, or cancer-specific mortality. Age ≤ 60 years strongly predicted for rapid growth rate and 13% of patients not undergoing definitive treatment died of unspecified causes other than RCC. These findings promote the use of surveillance in selected patients, especially the elderly and those at higher risk for mortality from other comorbidities. Indication for treatment intervention, including growth rate, absolute tumor size, and symptomatic progression, remains to be defined in clinical practice, and studies with longer follow-up would additionally confirm oncologic outcomes.

Open partial nephrectomy

Irrespective of a clinical indication to preserve renal function, open partial nephrectomy (OPN) is the established approach for localized renal tumors, setting the standard for comparison of newer minimally invasive techniques. Data from major cancer centers indicate elective NSS is analogous in providing curative treatment for single, localized tumors < 4 cm in diameter.[29-31] Not only has NSS proven to maintain equivalent efficacy, morbidity, and mortality rates in comparison with radical nephrectomy, but this approach has also been associated with a lower risk of developing renal insufficiency.[32-34] In reviewing open NSS results from nine comparative studies of 1262 patients,[30,31,35-41] Novick et al reported 88%-97.5% mean cancer-specific survival with a follow-up of 4-6 years,[42] Table 1. For tumors ≤ 4 cm, Fergany et al report cancer-specific survival rates of 98% and 92% at 5 and 10 years in their analysis of 107 patients undergoing OPN at the Cleveland Clinic.[43] Others have reported similar survival rates.[44] It should be noted that the appeal of minimally invasive procedures should not prompt the use of laparoscopic RN in lieu of NSS, since it does not replace the treatment objective.

Laparoscopic partial nephrectomy

Though OPN remains the standard of care, laparoscopic NSS is becoming more commonplace as similar outcomes have been reported. In the largest review of open versus partial nephrectomies for single, localized renal tumors, Gill et al reported on 1800 patients from three large referral centers.[45] LPN was reported to have shorter operative time, less blood loss, and shorter hospital stay, while intraoperative complications were similar to those of OPN, Table 2. Postoperative acute renal failure rates were equivalent despite increased warm ischemic time with LPN. Though patients undergoing OPN were considered to be at higher risk, 3-year cancer-specific survival rates were nearly identical in both groups with stage I disease: 99.3% and 99.2% after LPN and OPN, respectively. Similarly, Permpongkosol et al did not find any significant difference between 5-year disease-free and actuarial survival rates in 143 patients who underwent either LPN or OPN.[46] Differences between recurrence rates, metastatic occurrences, and positive surgical margins were also insignificant.

TABLE 1. **Outcome for patients undergoing nephron-sparing surgery for localized renal cell carcinoma. Adapted from Novick et al.[42]**

References	N of patients	Disease-specific survival (%)	Local recurrence (%)	Mean follow-up (months)
Moll et al[35]	142	98	1.4	34.8
Provert et al[36]	44	88	2	36
Lee et al[30]	79	96	0	40
Lemer et al[31]	185	89	5.9	44
Steinbach et al[37]	121	90	4.1	47
Hafez et al[38]	485	92	3.2	47
Barbalias et al[39]	41	97.5	7.3	39
Belldegrun et al[41]	146	93	2.7	74

TABLE 2. **Log transformed multivariate regression of select outcomes: LPN versus OPN. Adapted from Gill et al.[45]**

Covariate	Relative increase (95% CI)	p-value
Warm ischemia time	1.69 (1.62, 1.77)	< 0.0001
Operative time	0.78 (0.75, 0.81)	< 0.0001
Hospital stay	0.59 (0.56, 0.61)	< 0.0001
Intraop estimated blood loss	0.80 (0.74, 0.83)	< 0.0001

On the other hand, inexperience and technical difficulties with this approach may lead to increased morbidity. The former multicenter analysis also demonstrated significant increases in laparoscopic postoperative complications, especially urological, as well as increased incidence of postoperative hemorrhage and consequential procedures.[45] Other reports have revealed less morbidity, reduced narcotic use, and faster convalescence with laparoscopic techniques.[46-48] LPN may therefore only be appropriate under the care of an experienced surgeon, and efforts to refine techniques should persist.

Simple enucleation

Simple enucleation of small renal tumors, as elective NSS, allows for maximum preservation of renal parenchyma and a lower incidence of major bleeding and collecting system damage, thereby theoretically decreasing the incidence of complications such as urinoma and urinary fistula.[49] Despite these advantages, simple enucleation is not widely used because of the questionable adequacy of the thin 1-mm tumor margin. Traditional practice has been to excise a 1-cm margin of normal appearing parenchyma to prevent local recurrence, but current data demonstrate that narrower margins may be sufficient for low-stage RCC.[50] Additional studies indicate that margin width does not correlate with disease progression if complete excision is accomplished,[50-52] and the rate of disease recurrence with enucleation is reportedly similar to that in NSS.[49,53]

Carini et al reported the results of a retrospective analysis of 232 patients who underwent simple enucleation for T1a RCC followed for a mean of 76 months.[53] Five and 10-year cancer-specific survival rates were 96.7% and 94.7%, and progression-free survival rates were 96% and 94%, respectively. Approximately five percent of patients had blood loss requiring transfusion, 2.6% had prolonged urinary leakage requiring JJ stent insertion, and one patient developed a urinoma requiring aspiration, drainage, and a JJ stent. Overall, five patients experienced local recurrence, three of whom had tumor multifocality, and eight others were found to have metastatic progression. In all patients, the tumor was enucleated without excising an additional rim of normal tissue. These data are similar to others and comparable to those of nephrectomy with respect to postoperative complications, subsequent intervention, local recurrence rates, and survival outcomes.[44,54] Simple enucleation using a minimal margin of normal tissue may therefore be a safe and adequate approach for elective NSS.

Cryoablation

Renal tumor ablation is the least invasive treatment currently available and one form is cryoablation, which uses a liquid nitrogen-cooled cryoprobe to ablate normal and cancerous tissues at temperatures of -40ºC. Though histological proof of complete tumor eradication is not possible with this method, the ability to achieve real-time ultrasound imaging allows for precise targeting and ablation. Biopsy offers tissue sampling at lesion borders but may not provide an adequate assessment of lesion margins.

Deployment of cryoprobes can be accomplished either laparoscopically (LCA) or percutaneously (PCA). In a recent abstract, Landman et al compared the efficacy and complications of these two approaches.[55] Of the 53 patients who underwent PCA, 13.5% had minor complications; of the 35 patients treated with LCA, of which there were more anterior tumors, 11.4% experienced complications, including two major complications and one death. The LCA group also had increased EBL requiring transfusion. At a mean follow-up of 7 months, no recurrences were detected after LCA, while a 3.8% recurrence rate was demonstrated in the PCA group at 16 months. The authors concluded that both options appear to be viable, and although LCA was associated with a higher complication rate, it may prove to be more effective. Moreover, this approach may be most suitable for hilar or anterior tumors that pose considerable risk when accessed percutaneously.[56] Further intermediate data on the safety and efficacy of laparoscopic cryoablation are promising,[56,57] Table 3.

TABLE 3. **Select outcomes at 3-year follow-up in patients undergoing cryoablation**

Reference	N patients	Reduction in lesion size (%)	Undetectable lesions (%)	Local recurrence (%)	Cancer-specific survival (%)
Gill et al[57]	56	75	38	3.6	98*
Weld et al[56]	31	71	42	3.2	100

*in 51 patients who had a unilateral sporadic renal tumor

Analyses with longer follow-up will further define the role of cryosurgery in treating small renal neoplasms.

Radio frequency ablation

Radio frequency ablation (RFA) is an alternative ablative technique also under investigation, specifically in patients unsuitable for definitive nephrectomy. RFA approaches can be quite varied and allow for creativity within individualized treatment. Percutaneous means may not be suitable for certain tumors, namely those located in the left upper pole owing to splenic interference, those near the hilum due to heat sink, and those in the right upper pole adjacent the liver. A successful percutaneous transhepatic technique has been described in the literature by McGahan et al.[58] Using color ultrasonography, they were able to identify lesions and avoid hepatic and renal vessels without complications in four medically unstable or elderly patients unsuitable for prone positioning.

As tissue is not routinely acquired for analysis post-treatment, imaging every 3-6 months has been employed to measure successful tumor destruction. No evidence of growth, as well as < 10 HU contrast enhancement on CT or no qualitative evidence of enhancement with IV gadolinium on MRI, has implied cancer control. However, the adequacy of imaging surveillance is questionable. In a recent examination of 37 patients who underwent RFA, biopsy at 6 months was negative in only 64.8%, and nearly half the patients who had positive results had no enhancement on MRI.[59] In comparison, 97 cryoablated tumors revealed a 93.8% negative biopsy rate at 6 months with 100% of

TABLE 4. **Percutaneous RFA: initial outcomes. Adapted from Cambio and Evans.[66]**

Reference	N tumors	Mean tumor size (cm)	Complete tumor ablation, n/N (%)	Mean follow-up (months)	Complications
McDougal et al[60]	20	3.2	19/20 (95) with one session	55.2	One perinephric hematoma.
Merkle et al[61]	18	5.3 (cm^2)	16/18 (89)	16.1	Information not available.
Gervais et al[62]	42	3.2	36/42 (86)	13.2	One minor hemorrhage, two major hemorrhages + one ureteric stricture.
Su et al[63]	35	2.2	33/35 (94); Two patients required retreatment for residual enhancement on follow-up CT	9	Burn injury to liver. Resolved without further sequelae. Small asymptomatic perirenal hematomas identified in 8 patients by CT immediately after RFA, none required blood transfusion.
Pavlovich et al[64]	24	2.4	24/24	2	No major complications.
Ogan et al[65]	13	2.4	12/13, one tumor with persistent enhancing rim on CT	4.9	No major complications. One patient developed small perinephric hematoma that resolved without intervention.

positive biopsies demonstrating enhancement. These findings suggest that enhancement may not be an acceptable surrogate form of assessment and, although patients were not randomized to receive a specific treatment, RFA is potentially inferior to cryoablation. Only for high-risk patients in the setting of an IRB protocol do the authors recommended RFA with a follow-up protocol including biopsy.

Table 4 presents data from six studies reporting outcomes with RFA.[60-66] As with other novel therapies for the small renal mass, RFA will require larger studies to better define the indications and contraindications to ablative technologies. Furthermore, delivery of RF energy, including the method used, number of probes and duration of treatment, require further study to produce uniform results.[67]

Microwave thermal ablation

Microwave thermal ablation (MTA) is a new approach with potential advantages of technical ease and marked hemostasis. While this technique is useful in both OPN and LPN, some recommend restricting its use to small exophytic renal tumors to minimize serious damage to adjacent structures.[68,69]

Terai et al report on 19 patients who underwent laparoscopic MTA without renal pedicle clamping for tumors 1.1 cm-4.5 cm.[68] Mean operative duration was 240 minutes, with minimal blood loss in 14 patients and 100 ml-400 ml in four. One case was converted to an open procedure because of perirenal adhesions. No local or distant recurrence was observed by imaging at a median follow-up of 19 months. Complications included urine leakage, arteriovenous fistula, and renal pelvic stenosis. Others report similar, but rare, complications, most involving tumors located near the renal pelvis or hilum.[70-72]

High intensity focused ultrasound

A noninvasive, experimental approach to renal tumors is HIFU, which induces a well-defined area of coagulation necrosis by extracorporeally applying targeted ultrasound energy.[73] Theoretically, HIFU offers minimal procedure time, morbidity, and faster time to recovery. Investigational studies have demonstrated principle viability and safety of HIFU for renal lesions.[74-77] However, clinical studies are limited, and no substantial comparative results are available thus far.

A phase II clinical trial reported treating a total of 16 patients with HIFU.[76] Histological signs of tissue necrosis were identified in nine of the 14 surgically excised kidneys, and no significant side-effects were noted. One of the two tumors treated with curative intent exhibited a moderate reduction in size on MRI at 12 months. A similar phase II trial reported histological changes of thermal injury in 15 of 19 treated kidneys, though effects were variable and did not correspond to the intensity of treatment.[77]

Determining successful tumor destruction and appropriate follow-up are challenges with HIFU. Though the kidney is nicely imaged by ultrasonography, its two-dimensional nature, respiratory motion, and poor resolution present intraoperative limitations. Moreover, overlaying ribs absorb HIFU energy, making certain tumors difficult to ablate.[73] Duplex Doppler ultrasonography, CT and MRI are other methods currently under development for this application. Major technical improvements are mandatory to enable this technology as an effective treatment option for patients with small renal masses.

Follow-up

While NSS is clearly advantageous in preserving renal tissue, monitoring for recurrence is important. Local and metastatic recurrence rates after partial nephrectomy rise with increasing stage, reportedly 0%, 2%, 8.3% and 10.6%, and 4.4%, 5.3%, 11.5% and 14.9% for pathological stages T1, T2, T3a and T3bN0M0, respectively.[29] Surveillance guidelines are mandatory to adequately follow patients with different stage tumors. Table 5 presents such guidelines for localized RCC after partial nephrectomy.[78]

TABLE 5. **Guidelines for surveillance of localized RCC after partial nephrectomy. Adapted from Evans.[78]**

Pathological stage	Guidelines for surveillance
pT1-2 N0M0	Annual history, physical, systems review, chest radiograph, chem-20, complete blood count and urine analysis Abdominal CT or renal ultrasonography every 2 years
pT3N0M0	History, physical, systems review, chest radiograph, chem-20, complete blood count and urine analysis every 6 months for 2 years, then every 2 years Abdominal CT or renal ultrasonography every 6 months for 2 years, then every 2 years

Among nephron-sparing methods, only OPN, simple enucleation and LPN allow the tumor to be excised with margins that can be clearly reviewed by a pathologist. Therefore, imaging is used to follow ablative and HIFU techniques, with lack of enhancement or growth implying cancer control. Choice of imaging modality in addition to surveillance protocols after non-surgical techniques have yet to be determined.

Summary

In the absence of randomized studies, retrospective series of OPN from large-volume centers have set the standard intervention for small (< 4 cm), single, localized renal tumors. Among skilled laparoscopic surgeons, LPN is considered an equivalent option. With added insight to the natural history of small renal tumors, there now exists a role for observation, especially for non-surgical patients who have a short life expectancy and those with clinically insignificant, biopsy-proven low-grade lesions. Other minimally invasive techniques are also gaining acceptance, but have not replaced partial nephrectomy due to undetermined long-term outcomes. Possible indications need to be further examined, but may include poor surgical candidates with comorbidities, a ≥ 2-5 year life expectancy, biopsy-proven low grade disease, or those on protocol; von Hippel-Lindau lesions; and multifocal tumors ≤ 4 cm. As with all new techniques, validation requires large, uniform trials with long-term follow-up demonstrating decreased morbidity and outcomes equivalent to open partial nephrectomy. Figure 1 shows a decision tree, which proposes a model of the various treatment methods for managing small renal tumors.

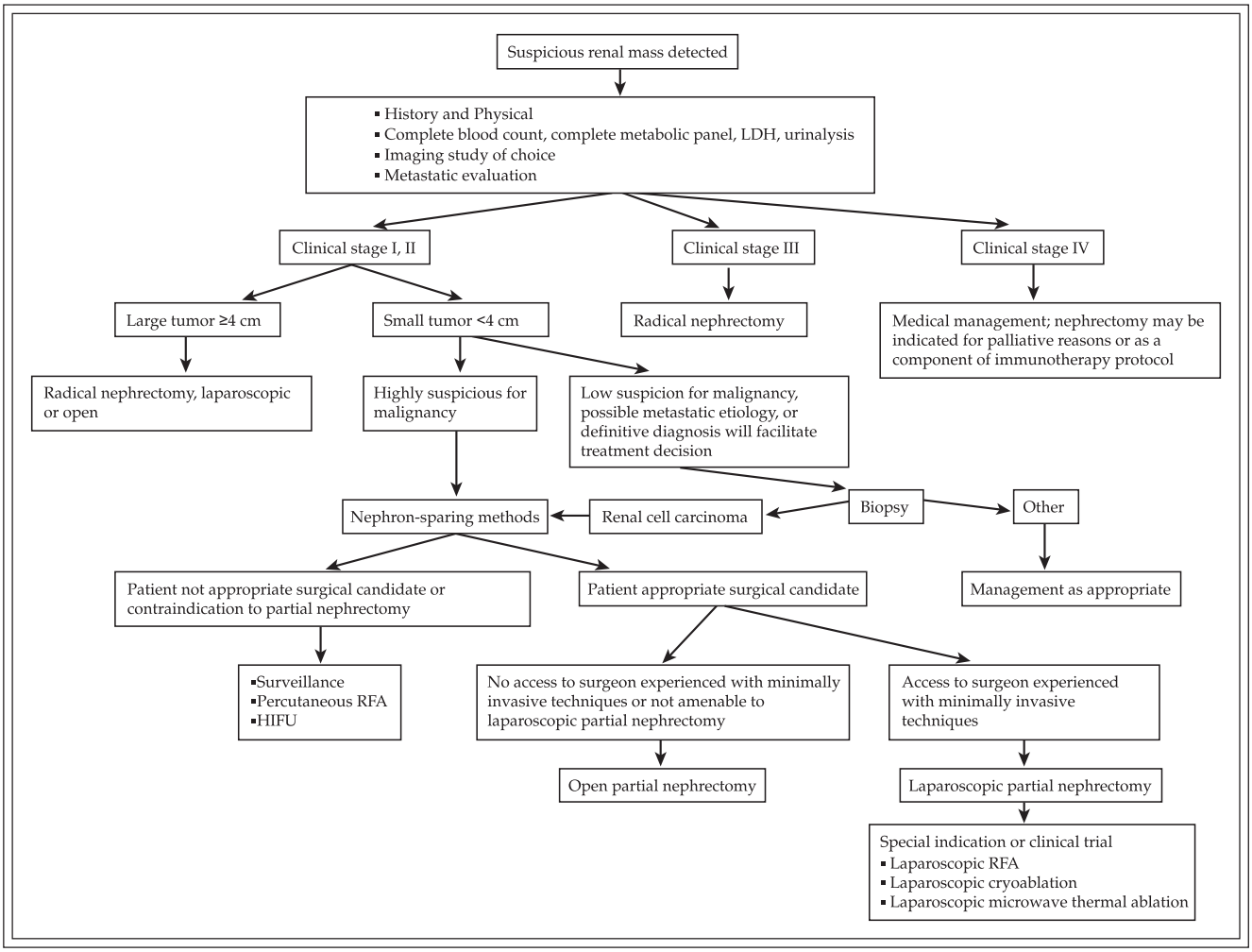

Figure 1. Decision tree for managing small renal tumors, assuming normal contralateral kidney. Adapted from Cambio and Evans, Copyright 2006 American Cancer Society.[66] This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Disclosure

Dr. Christopher Evans is a member of the Speakers' Bureau for Boehringer Ingelheim. He is on the advisory board for Boehringer Ingelheim and Astra Zeneca and an investigator for Astra Zeneca. □

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