Optimal Management of Small Renal Masses

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Small renal mass, kidney cancer

Abstract
The incidence of small renal masses is increasing. Limited data suggest that although most are malignant, they are also likely to show indolent behavior. The tendency of these tumors to occur in older patient populations with multiple comorbidities raises important issues. Retrospective and prospective studies suggest that a substantial proportion of these small renal masses can be observed without compromising the opportunity for cure or subjecting patients to invasive procedures that might impact negatively on quality of life. Less-invasive treatment modalities, including partial nephrectomy and energy ablation techniques, provide multiple options for some patients. This article reviews selected aspects of the management of small renal masses, including their natural history, imaging, diagnostic biopsies, and treatment options. (JNCCN 2006; 4:1083–1088)

Background
Renal cell carcinoma (RCC) is the most common malignancy of the kidney, accounting for 3% of all cancers. An estimated 38,890 new cases of RCC will be diagnosed and 12,480 deaths will occur in the United States in 2006. The incidence of RCC has steadily increased over the past 30 years, with a prominent increase in older patients (i.e., 70–90 years of age). This increased incidence has been partially attributed to the incidental detection of asymptomatic small renal cell masses (< 4 cm) during imaging studies performed for unrelated reasons. However, at least one study noted an increased incidence throughout all stages of disease. Incidentally discovered renal masses have been estimated to constitute from 48% to 66% of all renal masses, in many instances as a consequence of ultrasonography performed during the evaluation of renal insufficiency.

Although the survival of patients treated surgically for small renal tumors is excellent, with 5-year survival rates exceeding 85% for early-stage tumors, small renal masses are challenging to diagnose and manage for several reasons. Some important aspects to consider when determining optimal management of small renal masses include imaging techniques for diagnosis, diagnostic versus excisional biopsy, and treatment versus observation. Thus, similar to prostate cancer, patient and tumor characteristics are important to consider when determining the best management approaches.

Correlation of Size with Etiology of Small Renal Masses
Tumor size has been consistently linked to survival. However, a smaller mass is also more likely to have a benign etiology, including adenoma, angiomyolipoma, and oncocytoma. In one of the largest retrospective reviews, the pathology of 2935 renal tumors resected in 2770 patients indicated that a smaller size was associated with a greater likelihood of benign etiology, papillary histology (compared with clear cell), and low-grade differentiation. In this series, among masses less than 4 cm, 30% were benign and 87% of those found to be clear cell RCC were low-grade.

Imaging of Small Renal Masses
Imaging studies have the advantage of being noninvasive, and some are comparatively inexpensive. Although the sensitivity of current imaging modalities for detecting a renal mass can be good, specificity may be suboptimal.
However, combining imaging studies can frequently provide sufficient information to help determine the likelihood of malignancy.

Ultrasonography is relatively inexpensive and readily available, making it one of the most common modalities used to identify renal masses. As many as 40% or more of incidentally encountered renal masses have been found by ultrasonography. An analysis of renal ultrasonography in 45,905 patients, of which 41,364 lacked signs or symptoms of urinary tract malignancy, found renal lesions in 355 asymptomatic patients (0.858%), 39 lesions in 1667 patients with microscopic hematuria (2.3%), and 75 in 2874 symptomatic patients (2.6%). A sonoluent lesion with a smooth wall and distal acoustic enhancement strongly suggests a simple cyst. Other findings, such as internal echoes, mural nodules, or lack of distal acoustic enhancement, are more likely seen in neoplasms.

Computed tomography (CT) is becoming the most common modality used to diagnose renal masses. Significant contrast enhancement correlates with renal neoplasm. Small increases in attenuation may be caused by partial volume averaging. Other CT criteria suggestive of malignancy include central calcification, marginal irregularity, and inhomogeneity. These characteristics may be difficult to identify in masses smaller than 1 cm, and therefore serial CT may be better. Fat content noted on CT may indicate an angiomyolipoma, providing an important clue to the origin of a renal mass.

Magnetic resonance imaging (MRI) is an important tool for evaluating indeterminant renal masses and for staging. MRI has better sensitivity than CT or ultrasonography for showing locally advanced disease such as extrarenal extension or vascular invasion in larger tumors. For smaller masses, MRI can show fat content more precisely and may better identify angiomyolipoma compared with CT. Gadolinium must be used to show enhancement of a solid mass. One disadvantage of MRI compared with CT imaging is its inability to show calcification.

In a retrospective review of 66 patients who had undergone positron emission tomography (PET) scans for suspected or known RCC, Kang et al. found that PET exhibited a 60% sensitivity and 100% specificity for detecting primary RCC versus 91.7% and 100%, respectively, for abdominal CT scan. Sensitivity and specificity varied between the 2 tests depending on the site of metastatic disease. However, PET was unable to identify RCC lesions in 39 scans performed on 32 patients. Thus, the usefulness of PET scans in this setting is limited by its low sensitivity, although its superior specificity may be beneficial when the origin of a primary renal mass cannot be determined with other imaging modalities. This study did not comment on the correlation of tumor size with PET results. A smaller study of 19 patients with suspected RCC based on conventional imaging techniques found an overall sensitivity and specificity for F-18 FDG PET of 86% and 84%, with a positive predictive value of 92% and a negative predictive value of 60%. Thus, the role of PET in excluding RCC was limited. This study also did not discuss the association between mass size and PET results.

### Biopsy and Histologic Assessment

Current interventional techniques make diagnostic biopsies feasible and relatively safe. However, enthusiasm for percutaneous biopsies has been tempered by anecdotal reports suggesting a risk for seeding the needle tract and concern for bleeding and infectious complications. Although these are valid concerns, the reliability of the histologic diagnosis is probably a more pertinent issue. Several studies have reported a wide spectrum of results with sensitivities ranging between 62% and 100% and specificity between 0% and 100%

Wunderlich et al. compared the results of needle core biopsies performed ex vivo on 250 partial or radical nephrectomy samples with the histopathologic results of whole tumor samples. In renal tumors less than 4 cm in diameter, a central biopsy correctly diagnosed malignancy in 83.3% of cases versus 75% for a peripheral biopsy. When one central and one peripheral biopsy were combined, the correct diagnosis approached nearly 97%. The ability to correctly assess tumor grade and cell growth pattern was less impressive (84%–90%).

Neuillet et al. reported the results of 88 consecutive biopsies performed on 88 patients using CT guidance. Median tumor size was 2.8 cm and at least 2 cores were obtained on each patient. Of the 88 biopsy specimens, 3 were inadequate (3.4%). Of the remaining 85 successful biopsies, 14 (16%) were found to be benign, 5 inconclusive, and 66 malignant (65 RCC, 1 lymphoma). Biopsy had a reported accuracy of 92% for diagnosing malignancy. A meta-analysis by Chawla et al. reached similar conclusions regarding
the feasibility of observing small renal masses. Metastatic disease developed in only 3% of patients, and initial tumor size did not correlate with growth rate.

Reporting on 66 percutaneous biopsies, Shah et al.\(^\text{24}\) found that the average tumor size was 2.9 cm and a mean of 4.5 core biopsies were sampled. Of 66 biopsies, 52 were adequate for assessment (79%). Of these 52 biopsies, 51 rendered a definitive diagnosis (98%). Of the biopsies considered inadequate for assessment, most (11 of 14) were because only benign parenchyma was found.

Two different pathologists determined the accuracy of intraoperative frozen needle biopsies of renal masses in 103 consecutive patients. Limiting the analysis to small renal masses (< 4 cm) raised the proportion of benign histology to 22%. Overall, the positive and negative predictive values were 94% to 96% and 69% to 73%, respectively.\(^\text{25}\)

Molecular techniques have been applied to RCC samples for diagnostic and prognostic purposes. Various studies can provide prognostic information, such as nuclear grading (Fuhrman grade) and DNA ploidy.\(^\text{26}\) Several investigators have shown that global gene microarray expression can differentiate among histologic subtypes of RCC, and have occasionally subdivided clear cell RCC into distinct prognostic categories based on a selected group of genes.\(^\text{27,28}\)

In general, percutaneous needle biopsies can render a correct diagnosis in approximately 75% of patients. Although reasonably good results can be achieved, the contribution of a pretherapy biopsy to the overall management of a patient with a small renal mass depends on several factors, including underlying morbidities and patient choice of therapy. However, with the increasing detection of smaller-sized masses, the likelihood of a benign etiology also increases. Rendon and Jewett\(^\text{29}\) reported that as many as 40% of small renal masses resected in partial or radical nephrectomies were benign and that elderly patients with these masses were 3.5 times as likely to have benign lesions as younger patients. Thus, the use of diagnostic biopsies may become more prevalent in managing patients with small renal masses.

**Management**

**Natural History and Observation**

Management of small renal masses is being reconsidered for several reasons. Patients diagnosed with small renal masses tend to be asymptomatic from the standpoint of the renal mass. Many of these patients have comorbidities that may dictate their overall prognosis more than the renal tumor. The increasing availability of minimally invasive techniques and other modalities (e.g., endoscopic partial or total nephrectomy, energy ablation modalities) provide a welcome expansion in options to treat patients with small renal masses, but the lack of comparative studies further complicates the decision-making process. To better select the most appropriate approach for a given patient, the natural history of small renal masses must be understood.

Although few studies have prospectively evaluated the history of small renal masses, independent retrospective studies have reached similar conclusions. Volpe and Jewett\(^\text{30}\) reviewed the outcome of 6 studies examining active surveillance of small renal masses. The average follow-up in most studies was greater than 2 years. Tumor growth averaged between 0.1 and 0.54 cm/y. In 2 studies, all patients ultimately underwent surgical excision, but in the remaining 4, surgical excision was undertaken in 65% or fewer of the patients.

In a prospective study, Volpe et al.\(^\text{31}\) followed-up 32 masses in 29 patients using serial abdominal imaging. Mean follow-up was 38 months and surgical excision was performed on 9 masses (8 patients) because of surgeon or patient concern about an enlarging mass. No patient progressed to metastatic disease. Criteria for defining rapid growth included a mass reaching 4 cm or a doubling of tumor volume in 12 months. Only 11 of the masses (34%) fulfilled 1 of these criteria.

In a different population, Lamb et al.\(^\text{32}\) followed-up 36 elderly patients with renal cancer who were managed expectantly because of severe comorbid conditions that precluded surgical excision. Mean age at diagnosis was 76.1 years and the median tumor size was 6 cm. At a median follow-up of 24 months, 13 patients had died: 8 from unrelated illness and 5 from unknown causes but without radiologic evidence of progression. Only 1 patient developed metastatic disease (at 132 months follow-up). Of these patients, 11% developed hematuria that was managed conservatively or with embolization. Although the tumor sizes in this study were larger than those in other studies, the findings confirm that incidentally diagnosed renal masses seem to have a slow growth rate.

A study by Ozono et al.\(^\text{33}\) found that tumor growth rate was significantly associated with initial tumor size.
only if the tumor was greater than 4 cm in diameter, but neither Volpe et al. nor Lamb et al. reached that conclusion.

Thus, the indolent behavior of selected small renal masses creates the option for observation. This option is clearly best suited for older patients or patients with severe comorbid conditions that either make surgical excision a risky endeavor or whose life expectancy is limited because of associated comorbidities. Studies are currently hampered by the lack of long-term follow-up and by the fact that many of the slow-growing masses were never biopsied to confirm the presence of malignancy. These issues need to be considered when selecting appropriate patients for this management approach. For those patients in whom observation is not prudent (e.g., young patients, symptomatic patients, those with fast-growing lesions, patients unwilling to choose observation), numerous options are available. Surgical excision has been the gold standard for treating renal cancer. The cancer-specific survival for patients with surgically excised small renal tumors is excellent. Recent advances in energy ablation techniques, minimally invasive surgery, gene therapy, and targeted agents have been or will soon be investigated in this patient population.

Surgical Excision
Historically, radical nephrectomy has been the preferred technique for achieving long-term cancer control in patients with localized renal cancer. In recent years, nephron-sparing surgery (NSS) or partial nephrectomy has been established as a safe option. Furthermore, in patients with small renal tumors (< 4 cm), several series have shown the equivalency of NSS compared with radical nephrectomy in achieving long-term cancer-specific survival. Open partial nephrectomy has demonstrated cancer-specific survival that is equal to radical nephrectomy, with disease-specific survival upwards of 95% beyond 5 years for tumors less than 4 cm. However, the use of laparoscopic partial nephrectomy is less prevalent, partly because of technical difficulties such as achieving proper homeostasis, although at least 1 study has shown it to be feasible in patients with a unilateral exophytic mass.

Partial nephrectomy likely has some benefits over total nephrectomy. Several studies have reported quality of life data on patients who underwent a partial nephrectomy compared with those who underwent total nephrectomy. Self-reported physical health was better in patients who underwent partial nephrectomy compared with those who underwent total nephrectomy. A separate study showed a benefit favoring partial nephrectomy in terms of higher scores on physical functions, fatigue, sleep disturbance, pain, or constipation.

Preservation of renal parenchyma is a clear benefit of partial nephrectomy. Patients with RCC who develop end-stage renal disease have worse survival rates compared with patients that develop end-stage renal disease for other reasons. Furthermore, patients who undergo a partial nephrectomy for RCC are more likely to progress to chronic renal insufficiency than those who undergo partial nephrectomies for nonmalignant reasons. Miller et al. recently reported Surveillance Epidemiology and End Results (SEER) registry data showing that although the use of partial nephrectomy to resect renal tumors measuring less than 7 cm increased from 4.6% in 1988 to 17.6% in 2001, its use in the smallest tumors was still less common. For the most recent year reported (2001), partial nephrectomy was used 42% of the time for tumors measuring less than 2 cm, whereas for tumors measuring 2 to 4 cm, partial nephrectomy was used 20% of the time. The authors suggested that the underuse of partial nephrectomy is a potential concern in terms of quality of care. Based on these data, it is evident that partial nephrectomy has clear advantages over total nephrectomy in the treatment of small renal masses and should be the preferred surgical approach in appropriate patients.

Energy Ablation Technique
The primary energy ablation modalities available include hyperthermic and hypothermic ablation, with either modality involving the use of probes inserted into tumor tissue, usually percutaneously. Thus, a distinct advantage of this technique over surgical resection is the minimally invasive approach with less risk for complications. However, despite the attractive potential benefits of these ablation techniques, widespread implementation in clinical practice must be restrained until a more extensive and longer-term follow-up is obtained on patients treated with any of these modalities.

Various techniques of hyperthermic ablation have been used, including radiofrequency ablation (RFA), laser-induced thermotherapy, and microwave ablation. RFA has been the most widely studied hyperthermic modality. Gervais et al. reported their experience in
100 tumors treated with RFA in 85 patients. All 52 small (< 3 cm) and 68 exophytic tumors underwent complete necrosis, although some exophytic tumors larger than 3 cm required a second ablation session. Small size and noncentral location were independent predictors of complete necrosis after a single session. Six patients died of unrelated causes. The median follow-up of the surviving patients was 2.3 years (range, 3.5 months to 6 years). No patient with localized disease developed metastasis during follow up, and only 1 patient developed local recurrence. Similar results were obtained in another short-term follow-up study (2 years) involving 60 tumors in 49 patients.45

Cryoablation, which has been performed using both open and laparoscopic techniques, can help minimize complications by decreasing blood loss. As with RFA, data are limited in terms of large studies, long-term follow up, and prospective analysis. However, several studies have shown reasonably good results with this approach.

In a follow-up study of 56 patients who underwent laparoscopic cryoablation, Gill et al.46 reported that 3.6 cm was the mean intraoperative size of the cryolesion, for a mean tumor size of 2.3 cm. At a mean follow up of 3 years, cancer-specific survival was 98%, with postoperative needle biopsy in 2 patients showing persistent or recurrent tumor. A larger retrospective analysis of 85 patients reported by Schwartz et al.47 included both open and laparoscopic approaches, although most were performed laparoscopically (80%). Median follow-up was only 10 months in this study (range, 3–36 months), with 2 patients showing postoperative abnormal enhancement on imaging. Only 1 patient had a viable tumor on histologic sampling. Notably, malignant biopsy was confirmed in only 59% of patients.

These early results show promise for minimally invasive energy ablation techniques in the treatment of small renal masses. However, validation of these procedures is hampered by the lack of longer follow up, and the lack of histologic confirmation (both pre- and postablation). Therefore, these options should be reserved for patients who are not surgical candidates but are not suitable for observation (because of more rapid growth rate of the renal mass).

Conclusions
The approach to a patient with a small renal mass must be thoughtful, considering overall patient conditions and tumor characteristics. One or more imaging modalities may be needed for correct diagnosis. Percutaneous biopsies should be strongly considered if observation is an option, which it may be in patients who are unsuitable for surgery or have a shorter life expectancy, particularly those with low-grade tumors. Partial nephrectomy minimizes long-term morbidity and yields comparable results to radical nephrectomy for appropriate candidates. Although energy ablation techniques seem promising and are excellent options for carefully selected patients, their use should currently be limited to patients for whom surgical excision is not an option.

References