Correlation of pathology with tumor size of renal masses

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Objective: *The current standard of care for radiographically identified enhancing renal lesions is surgical removal. However, some of these lesions prove to be benign and did not truly warrant extirpation. Mass size has been traditionally described as a parameter to predict the malignant potential. We compiled our experience with surgically treated renal masses and correlated lesion size with final pathology.*

Materials and methods: *We performed a retrospective analysis of extirpative renal surgery and resultant renal mass pathology from 1998- January 2006. Nephrectomies performed for non-malignant disease or transitional cell carcinomas were excluded. Renal tumors were staged by the 2002 TNM classification system.*

Results: *Three hundred ninety-four patients with 460 lesions were identified. Overall, 24% of masses were determined to be benign and 76% were malignant. Three hundred forty-three malignant lesions were renal cell carcinoma (98%). Masses were stratified by size. Two hundred thirty masses were smaller than 4 cm and 72 (31.3%) of these were benign. There were 166 lesions between 4 cm and 7 cm with an 18% benign rate. Sixty-four lesions were > 7 cm in size. Only eight of these were benign (12.5%). Chi square testing revealed the 31.3% benign rate of the < 4 cm group to be significantly different than the benign rates of the other groups.*

Conclusions: *The preponderance of renal lesions removed for benign pathology occurs when lesion size is small, typically less than 4 cm. This information may be useful in deciding to offer expectant management of an otherwise surgical lesion in a patient who is a poor candidate to undergo an operative procedure.*

Key Words: kidney, renal cell carcinoma, pathology, surgery, renal masses

Introduction

The increased use of abdominal imaging with computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography, has resulted in a higher rate of incidentally found, small renal masses.[1-3] However, imaging alone is unreliable in characterizing the malignant potential of these lesions.[4-8] Similarly, the role of percutaneous biopsy is limited, and often does not alter medical decision making.[9] Therefore, the current standard of care remains surgical extirpation of any suspicious renal parenchymal mass.

Surgery is not always feasible given the extensive list of comorbidities a patient may have accrued by the time a renal mass is detected. The median age of diagnosis of renal cell carcinoma is approximately 65 years of age.[10,11] While the majority of renal lesions which are removed due to radiographic suspicion are malignant, there is a proportion of these masses which are benign. This rate has historically ranged from 6.1% to 16.9 %.[12,13] For those patients with benign disease, surgery results in unnecessary risk and nephron loss. These risks are only slightly lessened by the use of ablative therapies such as cryotherapy and radiofrequency ablation.

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Ideally, benign lesions would be screened out prior to surgical intervention based on preoperative imaging characteristics. One of these important characteristics is lesion size. The data regarding the potential for malignancy based on mass size is limited. In this paper, we review the pathology of renal masses obtained at a single institution over the past 7 years to determine the percentage of benign lesions, and correlate the size of the lesion with final pathology obtained after surgical intervention.

Materials and methods

We performed a retrospective review, approved by the institutional review board of the extirpative renal surgery carried out at our institution between 1998 and January 2006. The procedures performed included: radical nephrectomy, simple nephrectomy, partial nephrectomy and nephroureterectomy, via open and laparoscopic techniques. All surgical specimens were examined in our pathology department, with each lesion found analyzed separately. We excluded those cases in which no mass was present or those where the nephrectomy was performed for known transitional cell carcinoma (TCC), adrenal mass, infection, or nephrolithiasis. The size of the lesion was considered to be the largest dimension reported by the pathologist. Based on the revised 2002 TNM staging system, the lesions were divided into those measuring less than 4 cm, 4 cm-7 cm, and greater than 7 cm. Chi square testing was performed to assess statistical significance with $p < 0.01$ set as significant.

Results

A search of our surgical database yielded a total of 494 patients with 574 lesions. Of these cases, 100 patients with 114 renal lesions were excluded due to either no mass found or the procedure was performed for known transitional cell carcinoma, adrenal mass, infection, or nephrolithiasis. Three hundred ninety-four patients with 460 lesions remained, and were analyzed. Demographic data is listed in Table 1. The mean patient age was 57.1 years. By size there was no difference in age between those with benign versus malignant tumors. In our series, 33 patients were under 40 years old and 66% of them had malignant renal masses. One hundred ninety-eight were between 40 and 60 and 229 patients were older than 60. Seventy-seven percent of the subjects over 40 had malignant renal masses. There was no statistically significant difference between the age groups older and younger than 40 years old, even when separated by gender.

TABLE 1. **Patient demographics**

Total patients	394
Total lesions	460
Male	228 (57.9%)
Female	166 (42.1%)
Mean age	57.1 (22-91)
Male	57.7 (22-91)
Female	56.5 (26-86)

Two hundred twenty-eight patients (57.9%) were men and 166 (42.1%) were women. There were 140 malignant tumors in women and 210 in men. Compared to 75.3% of women, 87.2% of men had malignant tumors ($p = 0.0225$). For lesions less than 4 cm in size, the malignancy rates were 65.1% in women compared to 71.7% in men ($p = 0.3187$). Tumors between 4 cm and 7 cm had an 85.7% malignancy rate in women and 79.2% in men ($p = 0.3130$). Of masses greater than 7 cm, 64.7% were malignant in women but 96% in men ($p = 0.0032$).

Histologic examination revealed that a total of 110 lesions were benign (24%) and 350 (76%) were malignant, Table 2. Renal cell carcinoma (RCC) accounted for 343 (98%) of the malignant lesions, of

TABLE 2. **Pathology of renal lesions**

Malignant masses of kidney (n = 350, 76%)	
Pathology diagnosis	**Number of masses**
RCC (total)	343 (98%)
Clear cell	225* (65.6%)
Papillary	76* (22.2%)
Chromophobe	27* (7.9%)
Unspecified	8* (2.3%)
Wilm's tumor	1 (0.3%)
Metastatic (lung, 2; ovarian, 3; melanoma,1)	6 (1.7%)
Benign masses of kidney (n = 110, 24%)	
Pathology diagnosis	**Number of masses**
Oncocytoma	41 (37.3%)
Angiomyolipoma	15 (13.6%)
Benign cyst	48 (43.7%)
Adrenal adenoma	2 (1.8%)
Xanthogranuloma	3 (2.7%)
Benign tumor schwann-like	1 (0.9%)

*Percentage of renal cell carcinoma

TABLE 3. **Malignant potential by size**

Mass diagnosis	Size of mass (cm)		
	< 4	**4-7**	**> 7**
Benign (24%, n = 110)	72 (31.3%)	30 (18.1%)	8 (12.5%)
Malignant (76%, n = 350)	158 (68.7%)	136 (81.9%)	56 (87.5%)
Total masses (n = 460)	230 (50%)	166 (36.1%)	64 (13.9%)

which the clear cell subtype was most prevalent (n = 225, 65.6%). The majority of benign pathology consisted of cysts (n = 48, 43.7%), oncocytoma (n = 41, 37.3%) and angiomyolipoma (AML) (n = 15, 13.6%).

Evaluating the lesions by size, Table 3, 230 lesions were smaller then 4 cm and 72 (31.3%) of those were benign. One hundred sixty-six lesions were between 4 cm and 7 cm, of those 30 (18%) were benign. Sixty-four lesions were greater than 7 cm, of those only 8 (12.5%) were benign. Using a two sided Chi Square test, the benign rate was found to be significantly different between masses smaller than 4 cm and those between 4 cm-7 cm, and greater than 7 cm ($p = 0.003$, and $p = 0.0028$ respectively). Statistical significance was not detected when comparison was made between the benign rates of lesions between 4 cm-7 cm and those greater than 7 cm ($p = 0.31$).

Discussion

With the increase in frequency of abdominal imaging the urologist is faced with evaluating and managing a greater number of incidentally discovered small renal masses.[2,14-17] A significant proportion of these patients undergo surgical intervention for these lesions, with pathology revealing benign disease. Historically, this rate has ranged form 6.1% to 16.9 %.[12,13,18] More recently, the prevalence of small, incidentally detected lesions has spurred re-evaluation of the incidence of benign pathology as related to tumor size. Our series shows that small renal masses (< 4 cm) have a statistically lower probability of malignancy than those greater than 4 cm. Review of the recent literature revealed several series evaluating this trend.[19-22]

In a large series from the Mayo clinic, 2,935 renal lesions surgically resected between 1970 and 2000 were evaluated.[20] The overall rate of benign disease was 12.8%. For lesions less than 4 cm in size, the rate of benign pathology increased to 23.3%. In our series the overall rate of benign disease was 24%, and increased to 31.3%, when considering only lesions less than 4 cm. The Mayo series displays a lower percentage of benign disease than our series. This difference may be accounted for by the fact that their data spans at least two different eras in the diagnosis of renal masses. Early in their series (1970s-1980s), lesions were diagnosed due to their presentation with symptoms. In more recent years small lesions are usually found incidentally. Since symptomatically discovered masses are more likely to be malignant, this mode of detection seen prior to the modern era, may artificially depress the true benign rate.[23]

A more recent series evaluated 186 renal lesions removed between 1999-2002.[19] Within this smaller but more contemporary patient sample, the overall rate of benign lesions was 14%. Importantly, for those lesions less than 4 cm, 20% of the masses proved to be benign. This series offers a look at a modern patient population comparable with our own. Within this unique population, our rate of benign disease in lesions smaller than 4 cm is notably higher, 31.3% versus 20%. Although the rates of overall benign pathology in these two series are higher than the Mayo series, our larger sample size may explain why two comparable series have different rates of benign disease.

A third series, from Vienna Austria, examined their institution's experience with open partial nephrectomy by evaluating the pathology of 129 renal lesions that were resected between 1996 and 2002.[21] The mean lesion size was 4 cm with standard deviation of 2.4 cm. In this series, benign pathology was found in 32.6% of the masses. Though this series was not limited to lesions smaller than 4 cm, a high rate of benign lesions was seen. Interestingly, patients less than 40 years of age had benign lesions almost 70% of the time compared to the overall benign rate of 32%. This suggests that patient age may contribute to preoperative classification of renal masses, in addition to lesion size. When we analyzed the mass size and rates of malignancy by age, our data does not show that there is a difference.

Recent literature reports that gender and age may play a role in the risk of malignancy. Snyder et al show that women have an approximate 2:1 chance of having a benign tumor compared to men for lesions under 7 cm.[22] Our data support this trend; however, in comparing malignancy rates by gender the differences

did not reach statistical significance. Nor was statistical significance reached in comparing patients whose age was younger or older than 40 years, as the recent study by Marszalek et al suggests.[21] In that study, patients under 40 years old had a lower rate of malignancy compared to those older than 40. Marszalek et al report a benign histology rate of 69%; our rate is lower at 44%. This may be an underestimation of the true rate of benign renal masses due to the low volume of patients in that age category (n = 33).

It is well established and indeed reflected in the recently revised TNM staging system that oncological outcome is related to tumor size, with tumors < 4 cm in size portending better prognosis.[24,25] To allow a shift in treatment approach for small renal lesions, the risk of surgery must be balanced against the risk of stage progression and metastases under observation. The standard of care is to extirpate all suspicious renal lesions; therefore little data exists on observation of smaller lesions.

The data that does exist is well summarized by a recent review article.[26] Ten series were identified regarding the natural history of untreated localized enhancing renal lesions. A total of 286 lesions were identified, of which 234 lesions were included in the meta-analysis. The mean lesion size on presentation was 2.6 cm. Meta-analysis revealed a mean growth rate of 0.28 cm/yr at a mean follow up of 34 months. Tissue pathology was available in 46% (131/286), and confirmed 92% (120/131) as RCC variants. The authors did not analyze malignancy rates stratified by lesion size. Progression to metastatic disease was identified in only 1% (3/286) of lesions during follow up. The authors concluded that the majority of small enhancing renal masses grow at a slow rate when observed and that the metastatic and cancer specific death are low. They did however caution that serial radiographic data alone are insufficient to predict the true natural history of these lesions. Their data may challenge the current dogma of aggressive surgical management in patients with small renal masses, especially when they are poor surgical candidates.

Studying the natural history of renal masses in the von Hippel-Lindau disease (VHL) population is also useful. In a prospective study of hereditary renal cancer, Walther et al showed that of 52 patients with VHL and a tumor < 3 cm, no one developed metastases.[27] However, of the 44 patients with tumors larger than 3 cm, 25% (n = 11) developed or had metastatic renal cell carcinoma. These findings may be applicable to sporadic clear cell renal carcinoma given the underlying common association of the VHL gene.

Some authors have dismissed treating small renal masses initially with observation due to the lack of effective systemic therapies for metastatic RCC.[28] It is true that even with aggressive surgical and immunological therapy, metastatic RCC has a dismal survival.[29] However, small renal masses grow slowly and tend not to metastasize.[26,30,31] For this reason, combined with our observation that over 30% of patients with small renal masses undergo surgery for benign pathology, we believe a larger prospective trial of watchful waiting may be justified.

The role of percutaneous biopsy remains controversial in the diagnosis and treatment of renal masses. Scant literature exists to support the role of biopsy in changing management of small renal masses when compared to basing management on the image characteristics of the masses alone. Fine needle aspiration (FNA) biopsy has poor sensitivity.[9] Thin needle biopsy has improved sensitivity over the FNA technique; however, the results are still variable and the practice has not been widely adopted by the urology community.[32,33] A recent study by Barocas et al suggests thin needle biopsy, combined with molecular analysis, may improve sensitivities to 100%.[34] This study is limited by the fact that the biopsies were taken from surgical specimens, not via a percutaneous approach using image guidance.

Our study was limited by the fact that the patients were evaluated and brought to surgery by several different surgeons. Lesions were included based on search of a database in a retrospective fashion, looking for renal lesions which had been surgically removed. Each surgeon has individual practice patterns, and biases in interpreting radiographic data in terms of what they classify as a suspicious lesion. Therefore, all lesions were deemed to require surgical treatment, but these criteria may not have been entirely uniform.

Overall, there will always be a percentage of lesions with benign pathology when renal lesions are removed based on radiographic imaging characteristics alone. What are truly lacking are biomarkers which would determine the malignant potential of a lesion which is seen on radiography. In the absence of such markers, combined with the evidence that the growth rate and malignant potential of small lesions is limited, and the chance that a small lesion may be benign, observation may be indicated in poor surgical candidates. However, one should bear in mind that the majority (> 70%-92%) of small lesions are malignant, with potential for growth and metastasis, and therefore should be removed or ablated as dictated by the current standard of care.

Conclusions

Mounting data, including the series reported herein, suggest a trend that small renal lesions presenting for surgical removal have an increasing incidence of benign pathology. As current diagnostic trends continue, an even higher proportion of patients may undergo surgery for benign disease. Furthermore, many small renal malignancies may not pose a significant metastasis risk. We believe these conclusions justify a prospective investigation of watchful waiting of small renal masses in those with greater surgical risk. □

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