Intra-tumor Doppler flow patterns do not predict malignancy of renal masses in a United States population

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Introduction: *Increased use of nephron sparing surgery has revealed a small but significant percentage of benign tumors. Improved imaging techniques have aided in diagnosis, but are still unable to differentiate benign from malignant tumors. We sought to evaluate whether the intra-tumor Doppler flow pattern could predict the presence of renal cell cancer (RCC).*

Materials and methods: *Standard grayscale ultrasound (US) and Power Doppler ultrasound (PDUS) were performed on 40 patients referred to our clinic for suspicious renal masses diagnosed by CT or MRI from December 2007 to May 2010. PDUS findings were used to classify tumors according to vascular patterns as proposed by Jinzaki et al, where pattern 0, 1, or 2 are considered diagnostic of benign renal lesions while patterns 3 and 4 predict malignancy. Clinical and pathological data were reviewed; ultrasound findings were correlated with histopathology.*

Results: *Of the 40 patients included for analysis, 13 underwent active surveillance, 24 underwent partial or radical nephrectomy, and 3 underwent ablative procedures. Twenty-seven (67.5%) patients had pathological specimens available for review, of which 22 patients had RCC and 5 had benign pathology. Intra-observer (kappa 0.46-0.70) and inter-observer (kappa 0.41-0.56) reliability were reasonable, but ratings didn't correlate with pathologic outcomes (all kappa < 0).*

Conclusions: *Our results suggest that PDUS may not be helpful in the diagnosis of malignant renal masses detected by CT or MRI. Further studies are needed to elucidate a preoperative tool useful in diagnosing malignancy in renal masses.*

Key Words: renal mass, Doppler ultrasound

Introduction

Historically, non-fat containing enhancing renal masses on cross sectional imaging were thought to represent renal cancer. Renal cell carcinoma is a potentially curable disease, particularly for small lesions, and the gold standard for treatment has been surgical excision. However, not all renal lesions are malignant, and smaller masses are less likely to be malignant.[1] In modern partial nephrectomy series, there is a rate of benign findings after surgery in 10%-30% of cases.[2] This results in unnecessary loss of renal function and exposure to potential surgical morbidity for those patients with benign tumors.[3]

Another trend in urologic practice is the increasing utilization of nephron sparing procedures (i.e. partial nephrectomy, cryoablation, and radio frequency ablation) in the treatment of renal tumors. It has been demonstrated that nephron sparing leads to a lower risk of end stage renal disease and lower overall mortality.[4] Concomitantly, a tremendous interest has

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developed for the utilization of active surveillance in small renal masses. Active surveillance is based on the assumption that small renal masses are either benign tumors or low grade cancers with slow growth rates and low risk of metastasis. However, we lack reliable and affordable tests of malignant potential of these small renal masses.

Because of the difficulty in accurately diagnosing the malignant potential of renal masses with CT and MRI, other imaging modalities have been investigated. Recent reports have studied the utility of Power Doppler ultrasound (PDUS), specifically evaluating the Doppler flow patterns of vessels within and surrounding small renal masses.[5-7] Jinzaki et al proposed using a scale of patterns numbered 0-4, Figure 1, and showed that no tumors exhibiting patterns 0-2 harbored malignancy on final pathology. In another report, Ascenti et al found good sensitivity and specificity with grayscale ultrasound and Doppler flow patterns, though ultrasound contrast did not increase the value of the test.[6] Finally, Raj et al, found that patients with clear cell renal cell cancer had a very high prevalence of intra-tumoral flow compared to other histologic subtypes of renal cancer.[5] Therefore, PDUS holds much promise as a useful measure of tumor malignant potential.

We sought to evaluate the utility of PDUS in determining the pathological behavior of renal masses in an American population in the office setting. We hypothesized those vascular patterns within the tumor, as assessed by flow pattern could discriminate benign from malignant lesions. To test the hypothesis, we evaluated Doppler flow patterns in patients referred to our clinic with suspicious renal masses diagnosed by CT or MRI.

Methods and materials

Between December 2007 and May 2010, 40 patients with suspicious renal masses were prospectively evaluated with standard grayscale and power Doppler ultrasound. Of the 40 lesions "suspicious for malignancy" on CT or MRI prior to undergoing ultrasound evaluation, 11 lesions (27.5%) were detected by MRI, 20 lesions (50.0%) by CT, 4 lesions (10.0%) by both MRI and CT, and in 5 patients (12.5%) we were unable to obtain the CT or MRI records for review.

Renal ultrasound

Patient assessment included bilateral renal ultrasonography with the patient in the lateral decubitus position. All US examinations were performed with a commercially available scanner (LOGIQ P5; GE Medical Systems) at 5.2-5.5 Hz and a dynamic range of 60-75 dB. All ultrasound examinations were performed by a single licensed ultrasonographer to minimize variability. The volume of the lesion was calculated by the following equation for an ellipsoid (4/3) x pi x (R1 x R2 x R3) = volume (cm^3).

Doppler ultrasound

The presence of hypervascularity and the vascular distribution in the masses were evaluated. The vascular distribution in a lesion was classified and recorded by the ultrasonographer in the method described by Jinzaki et al, see Figure 1. Pattern 0 represented no signal pattern, which indicated no detectable vessels; pattern 1, represented intratumoral focal pattern, which indicated persistent focal color

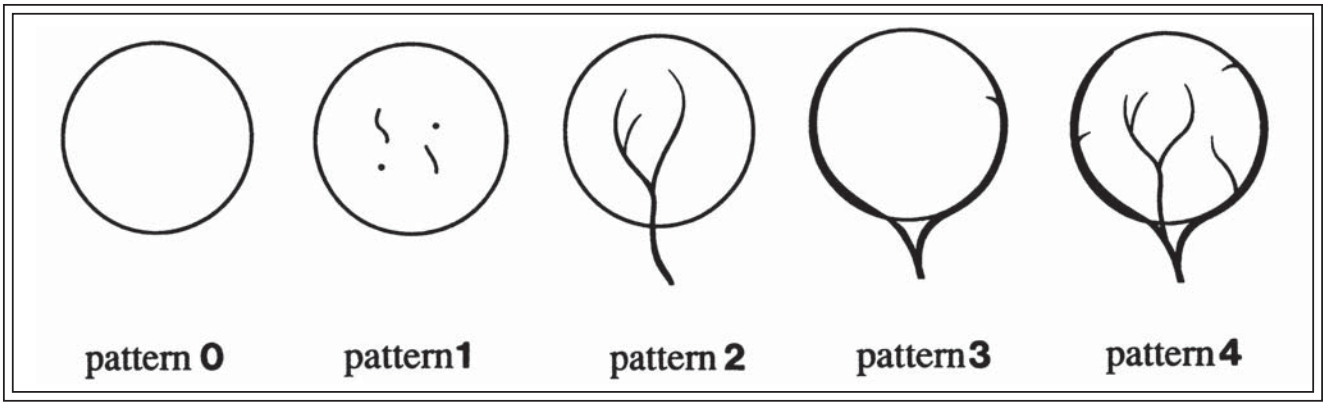

Figure 1. Schematic representing vascular flow pattern as proposed by Jinzaki et al. Pattern 0, no signal; pattern 1, intratumoral focal; pattern 2, penetrating pattern; pattern 3, peripheral; pattern 4, mixed penetrating and peripheral. Figure taken from Jinzaki et al., 1998.[7] Reprinted with permission.

flow signal that did not extend to the margins; pattern 2 was a penetrating pattern, which indicated that blood vessels arose outside the lesion and coursed toward the center; pattern 3 was a peripheral pattern, which indicated blood vessels arose outside the lesion and surrounded the lesion; and pattern 4 was a mixed penetrating and peripheral pattern (pattern 2 plus pattern 3).

Treatment decisions were made by attending urologists who were blinded to the results of the Doppler flow patterns. In the 27 lesions that that were surgically treated, findings from both grayscale and power Doppler US were correlated with histopathologic findings.

Interpretation reliability

The 27 studies with known pathology were reviewed independently by two attending urologists and an attending radiologist who were all blinded to pathology results. Studies were reviewed twice separated by a span of at least 2 weeks. Intra-observer was calculated by the kappa coefficient. Inter-observer reliability was measured by the kappa coefficient and comparisons were pairwise. Kappa coefficient are reported as ranges of the three pairwise comparisons (radiologist to first urologist, radiologist to second urologist, and first urologist to second urologist). All raters were then compared to pathologic outcomes as the standard.

Statistical analysis

Descriptive statistics were calculated. All results were expressed as mean ± standard deviation unless otherwise indicated. Inter-observer reliability was determined by dichotomizing the flow patterns into benign (patterns 0, 1, or 2) versus malignant (pattern 3 or 4). Standard comparison was done to the final pathology specimen. Normal distribution was tested with a Shapiro-Wilk W test. For those data not normally distributed a Wilcoxon test for non-parametric data was utilized. For those continuous variables with a normal distribution, student t-tests were used to compare means. Categorical variables were compared using Pearson chi-square tests if there were more than five individuals in each category. For those with less than five individuals per category, a Fisher's Exact Test was used, with a one-tailed assumption used for those with no patients in a category and a 2-tailed assumption used for those with 1-5 patients in a category. All analysis was done with Microsoft Excel (Microsoft, WA) and JMP (SAS Institute, Cary, NC).

Results

Patients

Our total patient cohort comprised 40 patients with 40 renal masses. The mean age was 58.4 ± 14.6 years old. The average BMI was 30.2 ± 6.4. The population was 67.5% (27/40) male and 32.5% (13/40) female. Seventy percent (28/40) of patients were white, 20.0% (8/40) black, and 10.0% (4/40) unknown. Sixty-five percent (26/40) of patients had hypertension, 27.5% (11/40) were diabetic, 37.5% (15/40) reported current or previous smoking, and 32.5% (13/40) reported diuretic use.

Grayscale ultrasound patterns

On ultrasound, the average renal length was 11.3 cm ± 1.5 cm. The average longest diameter of the renal lesions was 3.8 cm ± 1.4 cm and the median volume (with standard deviation) was 30.8 cm^3 ± 31.4 cm^3. Twenty-eight masses were solid appearing on ultrasound while 14 were solid with some cystic components to the mass.

Patient treatment and pathology

Twelve patients underwent active surveillance, 3 patients underwent ablative procedures, 13 patients had partial nephrectomy, and 12 patients underwent radical nephrectomy. Of the 27 patients (67.5%) with pathologic results, 22 patients had RCC (14 clear cell, 4 papillary, 2 chromophobe, and 2 RCC NOS), 2 patients had an angiomyolipoma, 2 patients had oncocytomas, and 1 patient had necrotizing granulomatous inflammation, Table 1. Tumors with US patterns 0-2 were cancer in 88.2% (15/17) of cases, while tumors with patterns 3 and 4 were cancer in 70% (7/10) of cases. None of the RCC lesions had angiolymphatic invasion. The prevalence

TABLE 1. **Histopathology of 27 patients with available information and their Jinzaki classification**

	Type of tumor			
Jinzaki pattern	RCC	Angiomyolipoma	Oncocytoma	Granulomatous inflammation
0	4	0	0	0
1	5	1	0	0
2	6	0	0	1
3	5	0	0	0
4	2	1	2	0

TABLE 2. **Characteristics of patients when stratified by Jinzaki classification 0-2 (benign) versus 3-4 (malignant)**

Characteristic	Jinzaki class 0-2 (n = 28) Mean (SD)		inzaki class 3-4 (n = 12) Mean (SD)		p-value
Age (years)	59.9 (14.3)		54.8 (15.1)		0.31
Body Mass Index	30.3 (6.4)		30.0 (6.6)		0.89
	N	**%**	**N**	**%**	
Sex					
Male	20	71.4%	7	58.3%	0.41
Female	8	28.6%	5	41.7%	
Race					
White	19	67.9%	9	75.0%	0.90
Black	6	21.4%	2	16.7%	
Other or unknown	3	10.7%	1	8.3%	
Smoking	10	35.7%	4	33.3%	1.00+
Hypertension	19	67.9%	7	58.3%	0.56
Diabetes	7	25.0%	4	33.3%	0.70+
Diuretic use	8	28.6%	5	41.7%	0.41
Pathology*					
Benign	2/17	11.8%	3/10	30.0%	0.33+
Malignancy	15/17	88.2%	7/10	70.0%	

+two-tailed Fisher's exact test
*for those patients with known pathology

TABLE 3. **Patient characteristics stratified by final pathology**

Characteristic	Benign (n = 5) Mean (SD)		Malignant (n = 22) Mean (SD)		p value
Age (years)	45.8 (17.5)		57.2 (12.3)		0.22
Body Mass Index	26.0 (6.3)		31.6 (6.3)		0.12
	N	**%**	**N**	**%**	
Sex					
Male	1	20%	20	90.1%	0.0006*
Female	4	80%	2	9.1%	
Race					
White	4	80%	17	77.3%	1.0*
Non-white	1	20%	5	22.7%	
Smoking	1	20%	9	40.9%	0.62*
Hypertension	1	20%	17	77.3%	0.03*
Diabetes	2	40%	5	22.7%	0.58*
Diuretic use	2	40%	8	36.4%	1.0*

*two-tailed Fisher's exact test

of malignancy in our cohort was 81.5% (22/27). The sensitivity of using a pattern 3-4 to predict malignancy was 31.8% and the specificity was 40%. The positive predictive value was 70.0% and the negative predictive value was 11.7%.

Patients were then stratified by by Jinzaki class (0-2 versus 3-4) and there was no significant difference between the groups in terms of age, BMI, sex, race or smoking history, Table 2. When stratified by final pathology, 9.1% (2/22) of patients with malignant lesions were female, while 80% (4/5) of those with benign lesions were female (p = 0.0006). In addition, a much higher percentage of patients with malignancy had hypertension at presentation (77.3% versus 20%, p = 0.03). However, there were no significant differences in age, BMI, race, or smoking history, Table 3.

Interpretation reliability

There was strong intra-observer agreement when films were reviewed at least 2 weeks apart (kappa 0.46-0.70) and reasonable inter-observer agreement (kappa 0.41-0.56) between observers. However, there was no significant correlation of any observers grading with the final pathology (all kappa values < 0).

Discussion

A number of groups have evaluated PDUS in the evaluation of renal masses. Jinzaki et al proposed a system of characterization of vascular flow patterns and found that the presence of patterns 0, 1 or 2 had a 100% positive predictive value for benign pathology.[7] We hypothesized that if the Jinzaki system proved accurate in our patient population, we would be able to non-invasively spare patients unnecessary treatment for small, enhancing renal masses if they had a Jinzaki pattern of 0, 1, or 2.

Our results show that Doppler renal ultrasound and specifically intra-tumor flow patterns do not reliably predict the presence of malignancy in renal masses. Therefore, clinical decisions should not be made based on Jinzaki flow patterns alone. While, Jinzaki et al found that no cancer presented with a pattern 0-2, we have actually found that no pattern predicted benign disease.

It is interesting that Jinzaki et al found such a high positive predictive value of Doppler flow patterns while we did not. Perhaps, our inability to reproduce these results in a racially heterogeneous American population speaks to the differing genetics of this disease in the two populations. Fujii et al examined the incidence of benign pathologic lesions at partial nephrectomy for presumed RCC in 176 Japanese patients.[8] The authors found a lower incidence of benign tumors (11%) compared to that reported in multiple Western cohorts (20%-30%). One possible reason for the lower incidence of benign histology was the low incidence of oncocytoma in Japanese patients (2.8%) compared to Western studies (6%-13%).

Limitations of our study include its small numbers. Also, these are outpatient transabdominal ultrasounds performed in the urology department. Perhaps, ultrasound at the time of laparoscopic therapy or open therapy for these lesions would provide for higher frequency and more sensitive ultrasound. Another weakness is that we did not have a radiologist present during the actual studies, nor did a radiologist interpret the grayscale US since this was a study to evaluate the usefulness of this system as an outpatient urologic diagnostic tool.

Conclusions

We have evaluated the usefulness of PDUS and intra-tumor blood flow patterns in the assessment of patients with suspicious renal masses. While previous reports had indicated that intra-tumor flow patterns may be able to identify benign lesions, we did not find that PDUS predicted pathology in our American patient population. Further studies are needed to elucidate a preoperative tool useful in diagnosing malignancy in renal masses. □

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