Does Preoperative Doppler Ultrasound and Resistive Index Measurement Predict the Solid Renal Masses Histopathology?

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ABSTRACT:

BACKGROUND:

Renal masses have different histologic types and subtypes, aggressiveness and metastatic potential, depending on the changes in angiogenesis.

OBJECTIVE:

To differentiate between benign and malignant renal masses and predicate renal tumors histopathological subtypes by using non invasive methods (Doppler ultrasound and resistive index).

PATIENTS AND METHODS:

Sixty-eight patients with a renal mass prepared for surgical intervention were involved in this prospective study. Every patient was underwent Doppler ultrasonography by single operator. By gray and color Doppler ultrasound the site, location, dimensions, echogenicity and the vascularity of the renal mass were assessed. Then by spectral Doppler ultrasound specific vascular wave parameters from intra tumor vessels which include a Peak systolic velocity, end diastolic velocity and Resistive index was checked. All those patients underwent partial or radical nephrectomy and the histopathological result, were collected.

RESULTS:

It had been found that the mean RI in patients with clear RCC was 0.59 ± 0.09 and it was significantly higher than that of Wilms tumor (mean = 0.49 ± 0.05, (P. value = 0.029), and significantly higher than oncocytoma (0.42 ± 0.06) (P. value = 0.025).

Patients with malignant renal mass had significantly higher mean RI than that of benign renal mass, 0.58±0.11vs 0.42±0.06,(P-Value =0.021) . The optimal cutoff point of RI was 0.47 which gives the higher sensitivity and specificity of 88.9% and 100% respectively with an accuracy of 94.5%, (PPV) was 100% and (NPV) was 90%.

CONCLUSION:

The usage of color spectral Doppler US parameter (Resistive index) is considered as an excellent predictor to differentiate between benign and malignant renal masses, but failed to differentiate and predicate the malignant renal tumors subtypes.

KEYWORDS: Renal mass, Resistive index, Color Doppler

INTRODUCTION:

The increased utilization of radiologic studies has resulted in increased incidental imaging findings, frequent renal lesions. Currently, the major roles of imaging in renal mass management are in characterizing the detected mass, including differentiation benign from malignant lesions if possible, and in staging and preoperative planning. Multiphase CT is currently the imaging modality of choice for initial diagnosis, staging, and preoperative planning [(1)].

Sonography can be helpful in determining the cystic nature of a lesion when a lesion has slightly higher density than fluid on CT. However, its use for characterization is generally hampered by low sensitivity for small lesions, operator dependence, and technical limitations, depending on patient body habitus and bowel gas [(2)].

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Abbreviations

NPV	Negative predicative value
PPV	Positive predictive value
AUC	Area under the curve
RI	Resistive index

Several studies have investigated differentiation of renal tumor subtypes using US [3]. Despite most RCCs <3 cm being hyperechoic, this finding is not pathognomic because it mimics the appearance of an angiomyolipoma. Angiomyolipoma mainly appears as strongly hyperechoic on US due to its fatty content [3,4]. Also the US characteristics found in case of oncocytoma, which can vary greatly, cannot reliably distinguish oncocytoma from RCC. The typical oncocytoma central scar has only sporadically been described on US [5]. Overall, the echogenicity of the tumor does not differentiate between histologic subtypes and cannot reliably distinguish benign from malignant conditions [3].Additional techniques to conventional gray-scale US have been studied recently to support detection and characterization of renal tumors.

Contrast-enhanced US (CEUS) is a technique in which a contrast medium consisting of gas microbubbles is administered intravenously. This contrast changes renal parenchyma into brighter tones on the grey-scale images [6]. This technique provides information on the micro-circulation, unlike Doppler US, which concerns macro-circulation. The contrast agents used for CEUS are not nephrotoxic [7]. CEUS is more sensitive in detecting hypovascular solid lesions not distinguishable with Doppler US, and in which CT may show no vascularization [8]. One large CEUS diagnostic performance study showed a negative and positive predictive value of 100% and 94.7% for characterization of renal tumors as benign or malignant based on enhancement pattern [9]. However, the majority of the lesions were cystic. The enhancing pattern of angiomyolipoma and oncocytoma on CEUS does not differentiate these entities from RCC [10].

Color Doppler US showed added value in case of isoechoic endophytic tumors, which can be hard to detect using grey-scale US alone. Doppler US can show vessels with high velocity due to neovascularization in case of RCC. In tumors, the additional use of Doppler US has been described to aid in differentiating subtypes based on the vascular distribution pattern, especially in case of angiomyolipoma. One study found up to 78% of the 64 tumors investigated (26 RCC, 34 angiomyolipoma, 2 oncocytoma, 2 pseudotumors) were correctly diagnosed using a combination of grey-scale and Doppler US [11].

This study proposed a scoring system for the vascular distribution pattern of renal tumors that could aid information in assessing the nature of renal tumors. A validation study for this scoring system failed to show the ability to predict malignancy of renal tumors [12].There are many studies to differentiate tumors by Doppler ultrasound with spectral waveform by using the vascular wave characteristic of the tumors (**resistive index**) like in breast tumors[13,14], ovarian tumors[15], gynecologic tumors[16], lung tumors[17], and oral tumors[18] . All these studies were depending on the tumor angiogenesis. Angiogenesis is the early change that differentiates normal from cancerous tissue. Angiogenesis is an important predictor of the biologic behavior of certain cancers. In particular, the prediction and monitoring of response to treatment can be improved by the use of effective, non-invasive methods to detect early changes in the tumor blood supply. The aim of this study to differentiate between benign and malignant renal masses, and to differentiate and predicate renal tumors histopathological subtypes by using non-invasive methods (Doppler ultrasound and resistive index).

PATIENTS AND METHODS:

Sixty eight patients with renal mass prepared for surgical intervention involved in this prospective study. There were 37 males and 31 females with their ages ranging from 1 to 80 years. Exclusion criteria included cystic renal masses and absent vascularity in the Doppler ultrasound.

All patients had undergone renal ultrasound which includes gray scale, color Doppler and spectral Doppler by a single operator (expert radiologist), and the ultrasound device used was GE Voluson E6 unit, Austria.

Data collected from the gray scale renal ultrasound procedure include site, location, dimension and echogenicity of the renal mass. By color Doppler ultrasound the vascularity of the mass is assessed and by spectral Doppler ultrasound specific vascular wave parameters which include: Peak systolic velocity, end diastolic velocity, Resistive index (R.I).Resistive index was calculated as (peak systolic velocity-end diastolic velocity) / peak systolic velocity.

The RI of the renal mass lesion was measured twice for confirmation. All those wave parameters were calculated from intra tumor vessels.

All patients underwent radical nephrectomy, partial nephrectomy or nephroureterectomy. The histopathological analyses were performed by expert pathologists. Data were entered and analyzed using the statistical package for social sciences (SPSS) version 25, descriptive statistics were presented as mean, standard deviation, ranges, frequencies and proportions (%).Analysis of variances (ANOVA) was used to compare mean values of the Doppler parameters across the histopathology, least significant difference (LSD) test used for multiple comparisons of mean values of Doppler parameters in between different histopathological types. Receiver operating characteristics (ROC) curve analysis was used to assess the validity of Doppler parameters to predict histopathology types. The accuracy of the test depends on how well the test separates the groups being tested into those with and without the outcome under study (histopathology type). Accuracy is measured by the area under the ROC curve.

RESULTS:

Tumors' dimensions have a mean of 6.8cm x 5.5cm with small renal masses ≤4 cm in 18 patients (26.47 %). The echogenicity of the tumors in the studied group was hypoechoic in 30 masses (44.1%), while 18 masses were hyperechoic (26.5%), 14 masses were isoechoic (20.6%) and the remaining 6 masses were heterogenous (8.8%).

The histopathology of the masses were clear RCC in 44 patients (64%), papillary RCC in 8 patients (11.8%), transitional cell carcinoma (TCC) in 5 patients (7.4%), Wilms tumors in 5 patients (7.4%), oncocytoma in 2 patients (2.9%) and others* tumors found in 4 patients (5.9%). The 4 other tumors include 1 sarcomatoid RCC, 1 clear cell sarcoma, 1 RCC thyroid like follicular carcinoma and 1 Chromophob RCC.

The mean values and standard deviations of the Doppler parameters are demonstrated for each of peak systolic velocity (PSV), end diastolic velocity (EDV) and resistive index (RI), furthermore these values are compared across the histopathological types It had been significantly found that the mean RI in patients with clear RCC was 0.59 ± 0.09 and it was significantly higher than that of Wilms tumor (mean = 0.49 ± 0.05), (P. value = 0.029), and significantly higher than oncocytoma (0.42 ± 0.06) (P. value = 0.025).Moreover, the mean RI in oncocytoma was significantly lower than that of TCC and others*. RI in Wilms tumors was significantly lower than that in others*, (P<0.05). The mean PSV was significantly higher in oncocytoma than that of Wilms tumor and TCC, (P<0.05). From other point of view, the mean EDV of Oncocytoma group was 26.00± 5.66 and it was significantly higher than that in each Wilms tumor , Papillary RCC, TCC and Others*, (P< 0.05).More details about the mean values of these parameters and the multiple comparisons are shown in tables(1,2).

Table (1): Distribution and comparison of mean values of Doppler parameters (PSV, EDV and RI) according to the histopathology of the renal masses .

Histopathology	PSV		EDV		RI	
	Mean	SD	Mean	SD	Mean	SD
Clear RCC	29.16	14.55	12.99	10.33	0.59	0.09
Papillary RCC	21.30	8.91	6.85	0.21	0.63	0.18
TCC	17.33	0.58	6.33	2.31	0.62	0.14
Wilms tumor	18.95	6.02	9.51	3.00	0.49	0.05
Oncocytoma	44.50	4.95	26.00	5.66	0.42	0.06
Others*	32.97	17.16	9.62	7.27	0.67	0.19
ANOVA (P.value)	0.168		0.23		0.03	

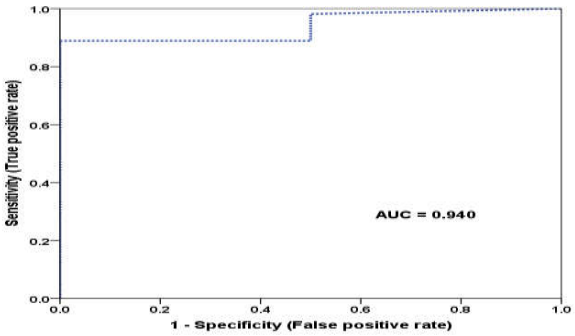
* The 4 other tumors include 1 sarcomatoid RCC, 1 clear cell sarcoma, 1 RCC thyroid like folicular carcinoma and 1 Chromophob RCC.

Patients with malignant renal mass has significantly higher mean RI than that of benign renal mass, 0.58±0.11 vs 0.42±0.06, (P.value =0.021) as shown in table(2).

Table (2): Comparison of resistive index (RI) between malignant and benign renal masses

Renal mass	No.	RI		P. value
		Mean	SD	
Malignant	66	0.58	0.11	**0.021**
Benign	2	0.42	0.06	

Furthermore, ROC curve analysis reveals that AUC=0.940 which indicates that RI was an excellent predicator and can differentiate malignant from benign renal mass as shown in figure (1).



Figure(1): Receiver operating characteristic (ROC) curve for the validity of RI in differnatation of benign from malignant

Patients with Clear RCC have significantly higher mean RI than that of oncocytoma, 0.59±0.9 vs 0.42±0.06, P.value =0.025 as shown in table (3).

Table (3): Comparison of resistive index (RI) between clear RCC and oncocytoma

Histopathology	**Number of Patients**	**RI**		P. value
		Mean	SD	
Clear RCC	**44**	**0.59**	**0.09**	**0.025**
Oncocytoma	2	0.42	0.06	

Furthermore, the validity of RI to differentiate the clear RCC from oncocytoma was assessed and revealed that RI succeeds to differentiate between those two histopathological types ((AUC =0.960)). The optimal cutoff point was 0.465 which yield the higher sensitivity, specificity and accuracy 93.2%, 100%, 96.6% respectively. Furthermore, other cutoff point revealed lower value of the validity parameters as shown in Figure (2) .

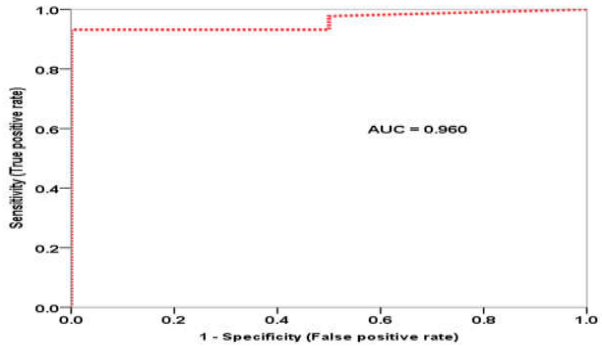


Figure (2): Receiver operating characteristic (ROC) curve for the validity of RI in differnatation of clear RCC from oncocytoma

From other point of view, assessment of validity of RI in differentiation between the remaining tumor types rather than the aforementioned types revealed that RI failed in differentiating between these histopathological types as shown in table (4).

Table (4): Summary AUCs of RI and interpretation the ability to differentiate between renal tumors types.

Histopathology	AUC	Interpretation
Clear RCC vs. Papillary RCC	0.452	Failed to differentiate (AUC<0.600)
Clear RCC vs. TCC	0.434	Failed to differentiate (AUC<0.600)
Papillary RCC vs. TCC	0.450	Failed to differentiate (AUC<0.600)

DISCUSSION:

In the current study the mean R.I of clear RCC was 0.59±0.09 and for papillary RCC was 0.63±0.18. In Sureka et al study, the mean R.I of the clear RCC and papillary RCC were 61±0.26, 0.70±0.34 respectively and this approximately agreed with our study results[19].

On the other hand, the mean R.I of the patients with malignant mass was significantly higher than those with benign mass, 0.59 vs. 0.42 respectively ((P. value < .005)) The R.I depend on PSV and EDV and those related to tumors blood flow and vascular resistance in a tumor bed, low vascular resistance in malignant tumors may be related to the deficiency of vasomotor control (lack of smooth muscle in intra tumor vessels wall) and arteriovenous shunting, and this may explain the cause of higher mean R.I of the malignant tumors than benign in current study [20-22].

Further analysis was performed to assess the validity of R.I and to differentiate the malignant masses from benign ones using ROC curve. Analysis revealed that RI was an excellent predictor and can differentiate malignant from benign renal masses with sensitivity of 88.9% specificity 100%, accuracy 94% PPV 100% and NPV 90% when using an optimal RI cutoff point of 0.47.

From other point of view increased RI cutoff point lead to decreased in sensitivity, accuracy and NPV, therefore the optimal RI cutoff point 0.47 produced the higher validity proportion and the surgeons have to be aware of the RI cutoff point that will be used in differentiation and the balance in validity parameters was very important.

Unfortunately, no previous study available that concerns the validity of RI in differentiation and predication of renal mass histopathology. On the other hand, in the present study the use of R.I failed to differentiate between malignant renal tumors subtypes and this may be due to overlap between R.I values.

CONCLUSIONS:

The usage of color spectral Doppler US parameter (Resistive index) is considered as an excellent predictor to differentiate between benign and malignant renal masses but failed to differentiate between malignant renal tumors subtypes.

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