ORIGINAL PAPER

Diagnostic significance of biopsies in renal masses

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Introduction We investigated the reliability and mapping of percutaneous needle core biopsies in the kidney in histopathological diagnosis of renal masses particularly for those with suspicious radiologic appearance in an attempt to prevent unnecessary nephrectomies.
Material and methods Overall, 96 cases were included in our study that underwent radical nephrectomy or partial nephrectomy due to renal mass between November 2007 – March 2010. *Ex–vivo* biopsies 1 cm apart were obtained from the peripheral region of the mass. Additionally, half of these peripheral biopsies were obtained from the central region of the mass. Diagnostic yield of the biopsy cores were correlated. Sensitivity and specificity of peripheral and central biopsies in differentiating benign and malignant tissues were calculated.
Results Sensitivity and specificity in differentiating malignant lesions were 93% and 87%, and 90% and 93% for peripheral and central biopsies, respectively. Positive and negative predictive values were 97% and 68%, and 98% and 64% for peripheral biopsies and central biopsies, respectively. Hazard ratio for cigarette smoking and presence of necrosis on CT scans were 4.76 (CI 1, 6–14.3; p = 0.04) and 3.32 (CI 1,2–9.2; p = 0.017) and 3.71 (CI 1.3–10.7; p = 0.013) and 3,51 (CI 1.3–9.6; p = 0.012) for peripheral and central biopsies, respectively.
Conclusions Kidney biopsies can be performed in suspicious renal masses of central and peripheral biopsies with similar efficacy.

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INTRODUCTION

There has been an increase in recent years in the incidence of detection of incidental renal masses, due to the widespread clinical use of radiological imaging techniques [1, 2, 3]. The increase in the incidence of asymptomatic masses smaller than 4 cm brings about difficulties in determining their malignant potential [1]. Although kidney needle biopsy has often been used in medical kidney diseases and in follow–up after kidney transplantation, it is not frequently preferred in the diagnosis of renal masses because of the risks of hematoma in the surgical specimen, diagnostic failure and tumour seeding. However, recent studies have reported that renal needle biopsies have high specificity and sensitivity in the diagnosis of masses [4, 5, 6]. Percutaneous renal biopsies have been performed for histopathological diagnoses in elderly patients in order to plan medical or oncological treatment. In addition, renal needle biopsy is recommended in cases such as solitary kidney, suspicion of metastasis to the kidney and bilateral renal masses.

The aims of this clinical study are to examine the accuracy and validity of percutaneous core needle biopsy in histopathological diagnosis and grading in order to determine the correct location for biopsy, which is necessary for a correct diagnosis, and to avoid unnecessary nephrectomies performed for malignant renal masses.

MATERIAL AND METHODS

Patient population

Ninety–eight patients who had undergone partial or radical nephrectomy due to renal mass at our clinic between 2007 and 2010 were included in this study. Two patients were excluded from the study because no tissue was observed on biopsies taken from the masses. Demographic data, clinical symptoms, findings on current imaging, physical examination and method of surgical operation were recorded for all patients. Abdominal computed tomography (CT) scans were available to all, and Doppler ultrasound, magnetic resonance imaging, positron emission tomography and CT of the chest were performed when needed in some patients.

Postoperative renal mass biopsy and pathological examination

Needle biopsy samples were obtained *ex vivo* from specimens of the patients after partial or radical nephrectomy, with an 18–gauge automatic biopsy gun (GTA International Medical Devices). The samples were collected at 1–cm intervals at the periphery through the long axis of the mass as detected by preoperative CT; in the centre, samples were taken of half the number of biopsies taken from the periphery (Figure 1). The biopsy specimens were evaluated by a single pathologist who was unaware of the pa-
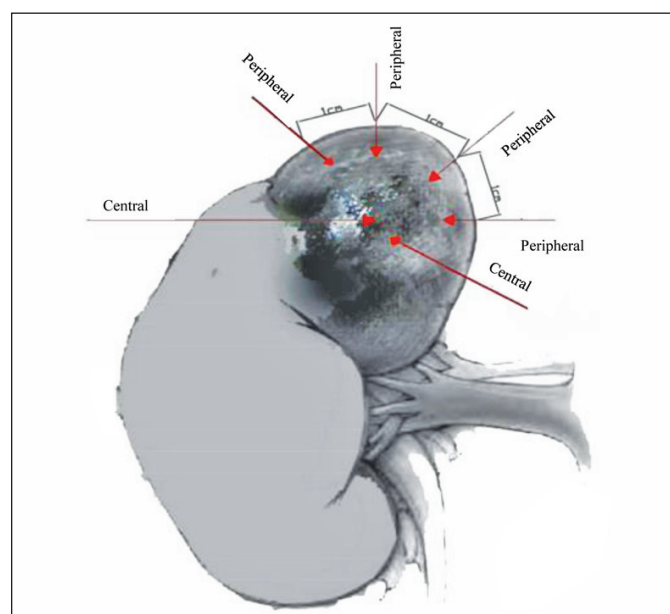
tient's characteristics or the final histological diagnosis of each pathological specimen. The pathological findings of each biopsy specimen were compared with the pathologic findings of the excised specimen, and correlated with the demographic data of the patient and the mass characteristics as defined by imaging techniques.

Figure 1. *The samples were collected by 1 cm intervals in the periphery and in the center and by half the number of biopsies taken from periphery.*

Table 1. *Patients characteristics and descriptive statistics*

	n	%
Number of patients	96	100
Age mean ±(SD)	58.5 ±11.2 (32–82)	
Sex		
Male	68	70.8
Female	28	29.2
Symptoms (%)		
No symptoms	41	42.7
Local symptoms	44	45.8
Flank pain	34	35.4
Hematuria	10	10.4
Systemic symptoms	11	11.5
weakness – loss in weight	9	9.4
nausea – vomiting	2	2.1
History of smoking (%)		
Yes	54	56.2
pack per year (mean)	28.6 ±18.9 (1–80)	
No	42	43.8
Tumor side (%)		
Right	54	56.2
Left	42	43.8
Exophytism (%)		
Yes	65	67.7
No	31	32.3
Tumor size		
Median tumor size (mm) ±(SD)	69.3 ±44.1 (15–236)	
≤4 cm (%)	27	28.1
>4 cm (%)	69	71.9
Palpable mass on physical examination (%)		
Yes	8	8.8
No	88	91.2
Presence of necrosis on imaging (%)		
Yes	59	61.5
No	37	38.5
Operation type		
Radical nephrectomy	63	65.6
Open	59	61.5
Laparoscopic	4	4.1
Partial nephrectomy (open)	33	34.4
Number of peripheral biopsy cores ±(SD)	6.67 ±4.3 (1–24)	
Number of central biopsy cores ±(SD)	3.32 ±2.3 (1–12)	

Statistical analysis

Following the Kolmogorov–Smirnov test, one of the following tests were utilised when appropriate: Wilcoxon test, cross–table statistics (Chi–square and kappa), Spearman correlation analysis, Kendall's tau–b statistics and logistic regression analysis. The statistical significance limit was taken as P <0.05.

RESULTS

The demographic data, characteristics of the masses, types of surgery and biopsy features of 96 patients are given in Table 1. In 41 patients (42.7%), the masses were detected incidentally. Of the masses, 27 (28.1%) were smaller than 4 cm, 35 (36.5%) were 4–7 cm, 34 (35.4%) were larger than 7 cm and 65 (67%) were exophytically located. The pathological diagnoses of the biopsies are given in Table 2.

Detailed explanations of the histological diagnoses of malignant and benign pathologies in the biopsies are shown in Table 3. Between the two groups, the malignant and benign masses did not differ in terms of histological diagnosis 95% of the time.

Necrosis was detected in the specimens of 50 out of 81 patients (61.7%) diagnosed with cancer, whereas this number was 34 (42%) and 31 (38.3%) in peripheral and central biopsy samples, respectively. The concordance between the central and peripheral biopsies in terms of detecting necrosis was calculated at 61% (kappa = 0.615 ±0.174, P = 0.001). The concordance of necrosis detected on the peripheral and central biopsies of the specimens was calculated at 62% (kappa = 0.619 ±0.154, P = 0.001) and 46% (kappa = 0.462 ±0.166, P = 0.001), respectively. There was no difference in terms of the prevalence of necrosis in both groups.

The distribution of the pathological examinations of the nephrectomy specimens is presented in Table 4. When Fuhrman changes were considered, 72% concordance was observed with peripheral and central biopsies (Kendall's tau–b = 0.719 ±0.101, P = 0.001). Neither the peripheral nor the central biopsy is superior to the other in predicting the Fuhrman grade. The changes in Fuhrman grade according to the final pathology are presented in Table 5.

Evaluation of all the patients revealed that the sensitivity and specificity in differentiating malignant from benign masses were 93% and 87% for peripheral biopsies and 90% and 93% for central biopsies, respectively. Positive predictive value and negative predictive value were calculated at 97% and 68% for peripheral biopsies and 98% and 64% for central biopsies, respectively (kappa = 0.715, P = 0.001). The concordance of peripheral and central biopsies

in detecting malignancy accurately was found to be 90.7% (kappa = 0.907, P = 0.001).

For tissue masses of 4 cm and smaller, the sensitivity and specificity of peripheral biopsy were 95% and 83% in differentiating malignant from benign masses, whereas they were 90% and 83% for central biopsies, respectively. Positive predictive value and negative predictive value were 95% and 83% for peripheral biopsies and 71% and 95% for central biopsies, respectively. No difference was observed between the two groups in differentiating malignant from benign masses. For masses larger than 4 cm, the sensitivity and specificity rates in differentiating malignant from benign masses were 92% and 89% for peripheral biopsies and 90% and 100% for central biopsies, respectively. Positive predictive value and negative predictive value were 98% and 62% for peripheral biopsies and 60% and 100% for central biopsies, respectively. No difference was observed

Table 2. *Pathological diagnosis in the specimens and biopsies*

Diagnosis	Surgical (n)	Surgical (%)	Peripheral (n)	Peripheral (%)	Central (n)	Central (%)
Malignant	81	84.4	77	80.2	74	77.1
Clear cell RCC	66	68	58	60.4	58	60.4
Non–Clear Cell RCC	9	9.3	8	8.3	7	7.3
Papillary RCC	7	7.2	5	5.2	5	5.2
Chromofobe cell RCC	2	2.1	3	3.1	2	2.1
Other cancer types	6	6.1	6	6.2	6	6.2
Squamous cell Ca	2	2.1	2	2.1	2	2.1
Collecting duct Ca	1	1	1	1	1	1
Transitional cell Ca	1	1	1	2.1	1	1
Leiomyosarcoma	1	1	1	2.1	1	1
Mucinous spindle and tubular cell Ca	1	1	1	1	1	1
Benign	15	15.6	19	19.8	22	22.9
Angiomyolipoma	6	6.2	4	4.2	5	5.2
Oncocytoma	4	4.1	3	3.1	4	4.1
Other benign	5	5.2				
Chronic pyelonephritis	2	2.1	3	3.1	2	2.1
Simple cyst	3	3.1				
Normal renal tissue			6	6.2	6	6.2
No diagnosis			1	1	5	5.2
Pathological staging						
To	15	15.6				
T1a	22	22.9				
T1b	18	18.8				
T2	8	8.3				
T3a	21	21.9				
T3b	6	6.2				
T3c	–	–				
T4	6	6.2				

Table 3. *Histological diagnosis in the malignant and benign masses with the bx*

	Malignant				Benign			
	True	False	Kendall's tau–b	p	True	False	Kendall's tau–b	p
Peripheral Bx	67 (89.3%)	8 (10.7%)	0.629 ±0.215	0.001	12 (92.3%)	1 (7.7%)	0.596 ±0.529	0.034
Central Bx	65 (89%)	8 (11%)	0.611 ±0.215	0.001	11 (78.6%)	3 (21.4%)	0.851 ±0.215	0.001

Table 4. *The distribution of pathological examinations of nephrectomy specimens*

	Specimen n (%)	Peripheral biopsy n (%)	Central biopsy n (%)
Fuhrman grade 1	9 (11.8%)	9 (12.9%)	9 (13%)
Fuhrman grade 2	28 (36.8%)	29 (41.4%)	31 (44.9%)
Fuhrman grade 3	24 (31.6%)	23 (32.9%)	20 (29%)
Fuhrman grade 4	15 (19.7%)	9 (12.9%)	15 (13%)
Total	76	70	69

Table 5. *Comparison of the Fuhrman Grades between specimen and bx pathologies*

Fuhrman Grade	Peripheral bx n (%)	Central bx n (%)
Unaltered	52 (74.3%)	45 (65.2%)
Changed		
Increased	12 (17.1%)	17 (24.7%)
Decreased	6 (8.6%)	7 (10.1%)
Total	70	69

Peripheral bx–specimen Fuhrman grade; Kendall's tau–b=0.730 ±0.133, p=0.001
Central bx–specimen Fuhrman grade; Kendall's tau–b=0.725 ±0.103, p=0.001
Peripheral bx–central bx Fuhrman grade; Kendall's tau–b=0.719 ±0.101, p=0.001

Table 6. *Positive tumor rates in peripheral and central biopsies with pathological specimen*

	Peripheral bx	Central bx
Number of patients Bx (+)	75	73
Biopsy number (mean) (total)	7 ±4.6 (525)	3.5 ±2.4 (256)
(+) bx number (mean) (total)	5 ±3.3 (375)	2.5 ±1.8 (185)
(+) bx proportion (mean)	0.80 ±0.2	0.79 ±0.3
(+) bx percentage (%)	80	79

between the two groups in the differentiation of malignant and benign masses.

The positive tumour rates in peripheral and central biopsies with pathological specimen malignity are shown in Table 6.

Other factors associated with malignancy in peripheral and central biopsies were a history of smoking and the presence of necrosis on imaging. No effects were observed for age, gender, tumour side, tumour location, presence or absence of exophytic tumour, symptoms, physical examination findings or the number of biopsies.

Logistic regression analysis revealed that a history of smoking (P = 0.04) and the presence of necrosis on imaging correlated positively (P = 0.013) in peripheral biopsies. Cigarette smoking and the presence of necrosis on imaging were shown to increase positive biopsy rates 4.76–fold (CI 1.6–14.3) and 3.71–fold (CI 1.3–10.7) in peripheral biopsies and 3.32–fold (CI 1.2–9.2, P = 0.017) and 3.51–fold (CI 1.3–9.6, P = 0.012) in central biopsies, respectively.

Peripheral and central biopsy cores missed the correct diagnosis in only two patients, which resulted in a very strong correlation for both biopsy strategies (Pearson's R = 0.943).

DISCUSSION

There has been an increase in the incidence of detecting incidental renal masses with the widespread clinical use of radiological imaging techniques in recent years, which has also brought about difficulties in determining diagnostic and treatment methods for these masses that are asymptomatic and smaller than 4 cm in diameter [1, 3]. Many entities, such as inflammatory pseudotumours, metastatic masses, abscesses and hematomas, which are treated with different methods, may imitate renal cell carcinoma (RCC). Therefore, in some special clinical cases, such as those that could not be diagnosed by radiological imaging and patients who are high–risk for anaesthesia, the assessment of solid renal masses with biopsy may be of importance for determining treatment modality [4, 7, 8].

Currently, nephron sparing surgery is the most commonly used surgical approach for patients with single, easily removable, small masses [9]. It has been reported in recently published large studies that 28–34% of specimen pathologies after laparoscopic and robotic partial nephrectomy are of a benign histology [10, 11]. Needle biopsy can be performed in lesions suspicious for malignancy that cannot be defined decisively with imaging methods.

Recently published studies reported that the sensitivity of needle biopsy was between 70% and 100%, specificity was nearly 100% and accuracy was above

90% [5–8, 12–15]. In addition, sensitivity and specificity, diagnostic accuracy and accurate histological typing rates were reported to be 93–100%, 67–100%, 91–98% and 73–98%, respectively [4, 12, 13, 15–19]. Similar to the literature, our study found that sensitivity and specificity for peripheral and central biopsies were 90% and 93%, and 87% and 93%, respectively. Sensitivity and specificity were 90% and 83% for peripheral and 95% and 83% for central biopsy cores in renal masses smaller than 4 cm, while they were 92% and 89% for peripheral and 90% and 100%, respectively, for central biopsy cores in renal masses larger than 4 cm in diameter. The findings suggest that renal biopsy can successfully differentiate malignant from benign cores.

Currently, the success of percutaneously obtained renal mass biopsy specimens in detecting tumour degree is still controversial. The ratio of accuracy for preoperatively obtained biopsies in the detection of the degree of tumour is lower than the accuracy of grading obtained by examination of the specimens. In 2005, in an *ex vivo* study including 250 renal mass biopsies, the degree of tumour biopsy was reported to have 85.2% accuracy [19]. The degree of compliance of needle biopsy and surgical specimen in demonstrating the Fuhrman grade was reported to be 74–76% [15, 17]. This ratio was reported to be 69.8% for tumours smaller than 4 cm [13]. Breda et al. and Lebret et al. found that the concordance between the degree of needle biopsies and that of pathology specimens was 40–46% [18, 20]. In our study, we observed that Fuhrman grading was done correctly in 74% of peripheral biopsies and 65% of central biopsies, and there was a significant concordance between the two groups. The concordances between Fuhrman grading of the specimen and of the central and peripheral biopsies were 72% and 73%, respectively. Intratumoural heterogeneity may exist in RCC, which may affect treatment decisions [21]. Severe heterogeneity even within a single tumour has been demonstrated in 25% of RCCs. It should not be ignored that the Fuhrman grading system has been done subjectively in assessing this issue. Volpe and colleagues re–examined 43 clear–cell RCC specimens smaller than 3 cm to determine the incidence of heterogeneity, and they found heterogeneity of grade to be 16% [22]. Positive tumour biopsy rates for peripheral and central cores were 80% and 79%, respectively, for patients who had a diagnosis of renal tumour on the surgical specimen. Absence of tumour in some of the quadrants is thought to be due to heterogeneity in tumour tissue. False–negative results from needle biopsies may largely be caused by an insufficient amount of tissue sampling, delivering samples through necrotic or haemorrhagic areas, or sampling through normal kidney tissue [4, 23]. With small needles, failure is much more likely due to inadequate focussing of the needle [11]. These biopsies are called 'biopsies inadequate for diagnosis' or 'failure due to technique'. This ratio varies between 0% and 21% in the published studies [4, 5, 12, 13, 18, 23]. In our study, necrosis was seen in both the peripheral and the central biopsies at similar rates (42% and 38%), which did not affect diagnosis.

Rybicki et al., in their large study published in 2003, reported a false–negative biopsy rate of 2.3%. This was found to be 13–37% for tumours between 1 and 3 cm, and 9–12% for larger tumours [17, 24]. Negative and positive predicted values were reported to be 75–100% and 96–100%, respectively [15, 18]. In our study, the false–negative rates of peripheral and central biopsies were found to be 10% and 7.5%, respectively. The positive and negative predictive values were 97% and 68% for peripheral and 98% and 64% for central biopsies, respectively.

Currently, most small renal tumours are diagnosed incidentally and because of comorbidity, and most are detected in elderly patients with high preoperative morbidity and mortality. Significantly high rates of benign pathologies have been reported in recent studies on the results of operations performed for small renal masses. A retrospective study at the Mayo Clinic on the final pathological analysis of radical and partial nephrectomies performed due to renal masses smaller than 4 cm in diameter between the years 1970 and 2000 reported that approximately 30% of the masses were benign and approximately 87% of RCCs were found to be low–grade [25]. In Johns Hopkins and Cleveland Clinic studies, it was reported that the rates of benign pathologies after laparoscopic partial nephrectomies performed for small renal masses were 30% and 33.6%, respectively [26, 27]. These results imply the importance of distinguishing benign and malignant renal masses preoperatively. Unnecessary treatments for benign masses can be prevented by needle biopsy performed with modern techniques. Neuzillet et al. did not implement any surgical treatment in patients with renal masses whose pathology results from preoperative needle biopsy were reported as benign, and no malignancy was detected on follow–up. As a result, 15.9% of unnecessary surgeries were avoided [13]. Wood et al. reported this rate as 44% [4].

Currently, the diagnosis of oncocytoma (which is generally considered benign) with percutaneous renal mass biopsy is still controversial [28]. Although it is claimed that unnecessary surgical procedures in patients with a definite diagnosis of oncocytoma can be avoided because the histological diagnosis of onco-

cytoma with biopsy can be confused with papillary–type RCC, the benefit in planning treatment and follow–up remains limited [29]. In our study, 15.6% of the patients operated on for renal masses had benign masses. The accuracy of histological differentiation of benign masses is 92.3% in peripheral biopsies and 78.6% in central biopsies. The accuracy of differentiation of the histologic type of cancer was 95.5% and 98.1%, and 96% and 100%, respectively, for peripheral and central biopsies larger than 4 cm in diameter [19]. In our study, the accuracy of differentiating the histological type of malignant masses was found to be high, at 89.3% in peripheral biopsies and 89% in central biopsies.

We investigated the factors affecting the detection of malignancy by both peripheral and central biopsies of renal masses, and correlated them with smoking history and detection of necrosis on preoperative imaging studies. Due to the high rates of success in detection of malignancy, we have concluded that biopsy can be safely performed in patients who are suspected to have a renal malignancy and who have a solitary kidney or are high–risk for treatment, and follow–up can be planned in accordance with the results. Our results also indicated that no difference was seen between peripheral and central biopsies in the detection of malignancy.

Despite the high sensitivity rate of renal mass biopsy, it should be considered with hesitation because of the risk of false–negative results, especially in young, healthy patients. However, if adequate techniques are available and the biopsy results might change the treatment plan, renal mass biopsy should be performed in small renal masses and in renal masses for which a clear differentiation between benign and malignant cannot be made preoperatively, especially in elderly patients with high morbidity and for whom no surgical treatment is planned. Biopsy can be performed in metastatic RCC, after which an immunotherapy or cytoreductive therapy may be planned accordingly.

Renal mass biopsies may also be used for evaluation of the efficacy of targeted therapy, which is being studied contemporarily. Negative biopsies should suggest follow–up rather than treatment. As a result, patients with benign masses may be protected from a morbidity such as nephrectomy, which could cause major problems in the future. Similarly, the cost of unnecessary treatment will be eliminated. Today, studies are focused on the molecular and genetic characteristics of tumours. Through this, the characteristic features and prognoses of tumours may be evaluated in the future, and on the basis of these data, clinicians may define treatment protocols in order to prevent morbidity and to reduce financial burden.

CONCLUSIONS

This study was performed as an *ex vivo* model because a large number of preoperative biopsies is not ethically appropriate. Correlation of *ex vivo* and *in vivo* biopsies obtained by modern techniques in the future may help preoperative biopsies take their place in the algorithm of the definitive diagnosis of renal masses.

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