Original Article

Sequential liquid-based cytology based on exfoliative cells of 18-gauge core needle groove to improve renal mass core needle biopsy yield: a real-world observational study

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Background: Renal mass biopsy (RMB) has regained clinical interest in recent years due to the pursuit of individualized and precision medicine. Renal mass core needle biopsy (RMCNB) for histopathology (HP), with or without liquid-based cytology (LBC), has been used increasingly in our hospital. This study investigated factors influencing the HP diagnostic yield of RMCNB, and compared the diagnostic rate between HP alone and HP plus LBC.

Methods: In this retrospective cross-sectional study, a total of 134 patients who underwent ultrasound-guided percutaneous RMCNB in the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College between January 2015 and May 2022 were enrolled. All biopsies were performed using an 18-gauge core needle biopsy gun, and the sampling tissues and exfoliative cells of 18-gauge core needle groove were delivered for HP and LBC diagnosis, respectively. The patient demographics, clinical indications, tumor characteristics, number of biopsies, final pathological diagnosis, and follow-up data were reviewed. Univariate and multivariate logistic regression analyses were performed to evaluate the association between variables and

HP diagnostic yield of RMCNB. The diagnostic rate between HP and HP plus LBC was compared using McNemar's test and agreement was evaluated using the Kappa score.

Results: The most common indication of RMCNB was renal masses with a radiological diagnosis of locally advanced disease or distant metastasis (86.6%). The HP diagnostic yield was established in 88.1% (118/134) of cases, and the diagnostic rate of HP plus LBC was 94.0% (126/134). Logistic regression analyses revealed that non-enhanced area exceeding 50% [odds ratio (OR): 0.021, 95% confidence interval (CI): 0.003–0.134, P<0.001] and number of core biopsies (OR: 9.479, 95% CI: 1.528–58.794, P=0.016) were associated with the HP diagnostic yield of RMCNB. The diagnostic rate of HP plus LBC was significantly higher than that of HP alone (94.0% *vs.* 88.1%, P=0.008), and they showed substantial agreement (Kappa =0.638, P<0.001). Meanwhile, in the non-enhanced area ≥50% subgroup, the diagnostic rate between HP plus LBC and HP alone was significantly different (86.7% *vs.* 60%, P=0.008), and the agreement was fair (Kappa =0.375, P=0.009).

Conclusions: RMCNB has a high diagnostic yield with a minimum of two high-quality core biopsies, LBC can improve the diagnostic yield of HP alone, especially in masses with large non-enhanced area.

Keywords: Renal mass; core needle biopsy (CNB); histopathology (HP); liquid-based cytology (LBC)

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Introduction

The incidence of renal cell carcinoma (RCC) has rapidly increased worldwide over the past decades, possibly due to an increased aging population, the Western lifestyle, and the widespread use of non-invasive radiological techniques (1). Meanwhile, management strategies for localized and advanced renal neoplasms have evolved with an increased understanding of histologic subtype, molecular tumor biology, and variation in prognosis and natural history. However, in most circumstances, surgical excision is still a preferred treatment for renal neoplasms. Furthermore, unlike the standardized clinical practice of most other organ-based neoplasms, urologic practice does not include pretreatment biopsy before surgical interventions.

The role of renal mass biopsy (RMB) has been historically controversial due to concerns related to its safety, diagnostic accuracy, and the perception that biopsy results would not alter management decisions (2). However, with the advent of personalized medicine, determining the histology of renal masses plays an important role in understanding the aggressiveness of the tumor and ultimately guiding clinical management. According to recently published literature, RMB shows a high degree of diagnostic accuracy with low complication rates, and the use of RMB has increased progressively over the past 20 years (3). Meanwhile, it should be noted that researchers have mainly applied RMB to patients with metastases and patients treated with ablative therapy (4). In addition, there has been debate regarding the auxiliary value of fine needle aspiration (FNA) to core needle biopsy (CNB) (5). In view of these findings, we summarized our clinical experience with ultrasound-guided RMB at a tertiary cancer hospital in Beijing, China, and analyzed its indications, techniques, and diagnostic yield. We present this article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-972/rc).

Methods

Patients

We conducted a retrospective study of 190 patients who underwent ultrasound-guided renal mass core needle biopsies (RMCNBs) in the Department of Ultrasound, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College between January 2015 and May 2022. We retrieved patients' demographic, clinical, radiological [the most recent pre-RMB contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) images], RMB procedural, and

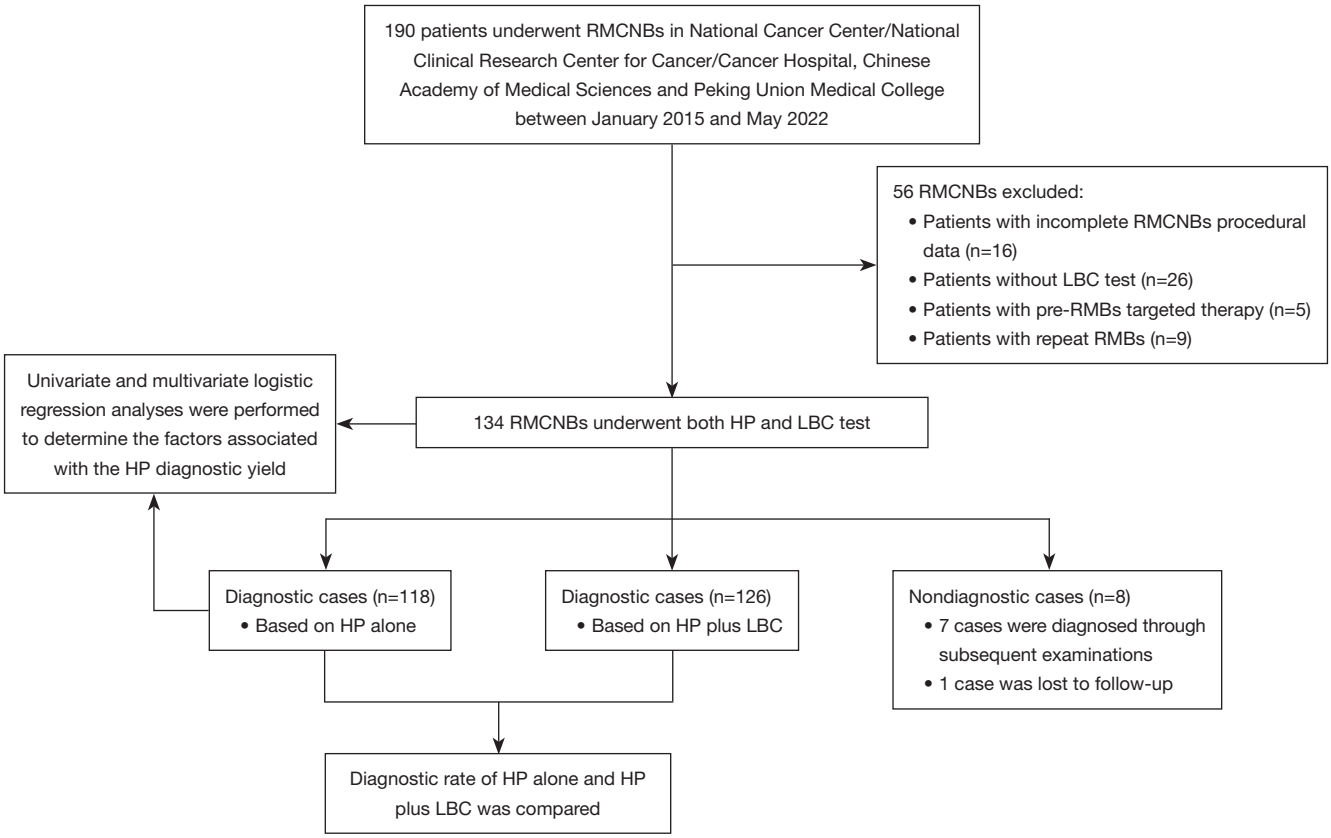

Figure 1 Flow chart of the patient enrollment and analysis process. RMCNB, renal mass core needle biopsy; RMB, renal mass biopsy; LBC, liquid-based cytology; HP, histopathology.

pathological details from the institutional Picture Archiving and Communication Systems (PACS) and electronic medical records. The exclusion criteria were as follows: (I) incomplete data, (II) liquid-based cytology (LBC) was not performed, (III) patients who had received targeted therapy, (IV) repeat RMBs. Ultimately, 134 patients who underwent both histopathology (HP) and LBC were included in the final analysis (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 21/108-2779), and the requirement for individual consent in this retrospective analysis was waived.

Peri-biopsy procedure

The standard pre-biopsy practice at our center includes stopping anticoagulation and antiplatelet medications for 7 days. Baseline bloodwork includes routine blood tests, coagulation function, and virus testing. If there is abnormal anticoagulation and/or local or systemic infection, the biopsy procedure is delayed or rescheduled. After the biopsy procedure, the kidney and perirenal space are scanned immediately to observe the presence of a hematoma. The patients are then required to compress the puncture site for at least 30 minutes and remain under observation for 1–2 hours. Patients who were without persistent pain or symptomatic hypotension are allowed to depart.

Biopsy procedure

During our study period, all biopsies were performed by 6 experienced senior radiologists using the freehand technique. All procedures were performed using a Philips iU-22 (Philips, Bothell, WA, USA), Philips EPIQ5 (Philips, Bothell, WA, USA), or Aloka Prosoundα10 (Aloka, Tokyo, Japan) with a convex array probe C5-2, C5-1, or C5-3. Greyscale and color Doppler ultrasound were routinely performed to evaluate the location of the renal mass, its size,

internal echo, and vascularity. Simultaneously, the operator designed the safest and shortest puncture route to avoid crossing additional organs, large vessels, or vital structures. The tumor peripheral solid areas were the preferred targets. The skin was sterilized, and a local anesthetic (1% lidocaine) was administered at the puncture site and along the pathway. Subsequently, a side-cutting automated or semi-automated biopsy gun with an 18-gauge needle was inserted into the renal mass to obtain the tumor tissues. The tissue samples were fixed in 10% formalin, and the biopsy needle cutting groove was rinsed into a vial of CytoLyt solution (Hologic Inc., Marlborough, MA, USA). The needle was disinfected 3 times with povidone-iodine before re-sampling. A total of 1–4 core biopsies were obtained depending on the quantity and color of the tissue specimens; ideally, the core should be an intact gray-white strip of at least 10 mm in length. Finally, the sampling tissues and cell solutions were sent for HP and LBC, respectively.

Pathological diagnosis

At our hospital, the HP and LBC are reported separately by 2 distinct sections of the Pathology Department. Both adopt the 2-level diagnostic system, wherein junior pathologists make initial diagnoses that are subsequently reviewed by senior pathologists, and the final reports are signed out by both pathologists. We reviewed the pathological reports from the electronic medical records directly. We classified the diagnoses into 6 categories: (I) negative (including sampling of normal renal tissue, fibrotic, degenerated, or necrotic tissues); (II) atypical cells or tissues; (III) neoplastic cells or tissues; (IV) malignant cells or malignancy; (V) RCC without classified subtype; and (VI) definite pathological subtype. For analysis, categories I–III were defined as nondiagnostic and IV–VI as diagnostic.

Statistics

Statistical analysis was performed using the software SPSS 26.0 (IBM Corp., Armonk, NY, USA). Continuous data with normal distribution were expressed as mean ± standard deviation (SD), otherwise as median and range, and categorical data were expressed as percentages. Univariate and multivariate logistic regression analyses were used to determine the factors associated with the HP diagnostic yield. Variables with P value <0.2 in the univariate analysis were included when performing multivariate analyses. The diagnostic rate of HP alone and HP plus LBC was compared using the McNemar's test, and the Kappa test was used to check the consistency. The statistical significance was set at $P<0.05$.

Results

Patient demographics, tumor and biopsy characteristics

Of the 134 patients, 97 (72.4%) were male and 37 (27.6%) were female, with a median age of 59 years (range, 23–85 years). The indications of the 134 RMCNBs were as follows: (I) 116 (86.6%) patients with a radiological diagnosis of locally advanced renal mass or with distant metastasis; (II) 14 (10.4%) patients with a prior history of extrarenal primary neoplasms or contralateral renal malignancy, including lung cancer, ovarian cancer, colorectal cancer, breast cancer, bladder cancer, contralateral renal pelvis cancer, or solid pseudopapillary tumor (SPT); (III) 1 (0.7%) patient with bilateral multiple renal masses; (IV) 1 (0.7%) patient with a history of contralateral nephrectomy due to aplasia, 1 (0.7%) patient with contralateral hydronephrosis, (V) 1 (0.7%) elderly patient with cardiovascular comorbidity. The tumor and biopsy characteristics are summarized in *Table 1*.

Pathological diagnosis

In the 134 RMCNBs, the diagnostic rate of HP was made in 88.1% (118/134), and the diagnostic rate of HP combined with LBC was 94.0% (126/134). *Table 2* summarizes the 126 pathological diagnoses. The remaining 7 nondiagnostic cases were subsequently diagnosed through nephrectomy, repeat RMB, or metastasis biopsy, and the other 1 case was lost to follow-up.

Logistic regression analysis for HP diagnostic yield

In the multivariate logistic regression analysis, non-enhanced scope [odds ratio (OR): 0.021, 95% confidence interval (CI): 0.003–0.134, $P<0.001$] and number of core biopsies (OR: 9.479, 95% CI: 1.528–58.794, $P=0.016$) showed a significant correlation with the HP diagnostic yield. The results are shown in *Table 3*.

A comparison of diagnostic rate between HP and HP plus LBC

The diagnostic rates for HP alone and HP plus LBC were

Table 1 The tumor and biopsy characteristics of the 134 cases

Characteristics	Value
Mass maximal diameter, mean ± SD, cm	8.5±3.2
Renal mass laterality, n (%)	
Right kidney	64 (47.8)
Left kidney	70 (52.2)
Location of the renal mass, n (%)	
Upper pole	42 (31.3)
Mid-pole	17 (12.7)
Lower pole	60 (44.8)
Diffuse/whole kidney	15 (11.2)
B-mode ultrasound, n (%)	
Solid	128 (95.5)
Cystic and solid mass†	6 (4.5)
Contrast-enhanced imaging, n (%)	
Large non-enhanced area‡	30 (22.4)
Inhomogenous enhancement	104 (77.6)
Number of core biopsies, n (%)	
1	23 (17.2)
2	70 (52.2)
3	32 (23.9)
4	9 (6.7)

†, continuous prominent anechoic areas exceeding 50% in the largest section; small, patchy, or spongy anechoic areas were not included. ‡, non-enhanced areas exceeding 50% in the largest section on contrast-enhanced CT or MRI. CT, computed tomography; MRI, magnetic resonance imaging; SD, standard deviation.

88.1% (118/134) and 94.0% (126/134), respectively. The diagnostic rate of the combined diagnoses was significantly higher than that of HP alone (P=0.008), and they showed substantial agreement (Kappa =0.638, P<0.001).

The study population was further divided into 2 subgroups according to enhanced scope. The diagnostic rate between HP and HP plus LBC was significantly different (60% *vs.* 86.7%, P=0.008) in the non-enhanced area exceeding 50% subgroup, and they showed fair agreement (Kappa =0.375, P=0.009). Meanwhile, there was no difference in the diagnostic yield in the inhomogeneous enhancement group (96.2% *vs.* 96.2%, P>0.99), and agreement was almost perfect (Kappa =1.000, P<0.001).

Table 2 Pathological diagnosis of the 126 diagnostic cases

Diagnosis	N (%)
Malignant	125 (99.2)
ccRCC	63 (50.0)
Papillary RCC	5 (4.0)
RCC with no specified subtype	22 (17.5)
Collecting duct carcinoma	1 (0.8)
Urothelial carcinoma	11 (8.7)
Metastases†	5 (4.0)
Lymphoma‡	2 (1.6)
Malignancy not otherwise specified	11 (8.7)
Others§	5 (4.0)
Benign	1 (0.8)
Oncocytoma	1 (0.8)

†, all 5 metastases originated from lung cancer; ‡, including 2 diffuse large B cell lymphoma; §, including 1 leiomyosarcoma, 1 liposarcoma, 1 DSRCT, 1 SPT, and 1 NET. SPT and NET were classified as malignant based on their medical history and radiologic findings. RCC, renal cell carcinoma; ccRCC, clear cell RCC; DSRCT, desmoplastic small round cell tumor; SPT, solid pseudopapillary tumor; NET, neuroendocrine tumor.

Discussion

Modern imaging techniques, such as ultrasound, CT, and MRI, have a high sensitivity for detecting renal masses. However, none of them can accurately and reliably characterize the masses in terms of growth rate, risk of malignancy, histological type, or prognosis. Despite attempts to evaluate the subtypes of RCC and its grading with imaging, the research data are currently derived from a single-center, retrospective, case-control series that lacks validity and reproducibility over a large scale (6,7) and have therefore not gained broad acceptance among urologists. Moreover, with the advent of personalized medicine, obtaining tumor tissues has gained even more importance in optimizing treatment decisions.

Although the utilization of RMB has increased progressively over the past 2 decades, there are no absolute criteria for when RMB is indicated, and the indications of RMB vary among centers. In our hospital, the most common indication was renal mass with a radiological diagnosis of locally advanced renal mass or distant metastasis suggestive of unresectable malignancy, and

Table 3 Variables affecting HP diagnostic yield of renal mass core needle biopsy

Variables	Subgroup	Univariate		Multivariate	
		OR (95% CI)	P value	OR (95% CI)	P value
Gender	Female	Reference			
	Male	1.222 (0.394–3.791)	0.729	0.501 (0.111–2.265)	0.369
Age (years)		1.010 (0.970–1.050)	0.633	1.006 (0.950–1.064)	0.848
Laterality	Right kidney	Reference			
	Left kidney	0.455 (0.149–1.389)	0.167	0.430 (0.106–1.744)	0.237
Location	Upper pole	Reference			
	Mid-pole	0.778 (0.171–3.546)	0.745	0.407 (0.051–3.248)	0.396
	Lower pole	1.500 (0.448–5.018)	0.510	1.375 (0.265–7.126)	0.704
	Diffuse/whole kidney	2.333 (0.257–21.168)	0.451	1.517 (0.095–24.131)	0.768
Renal mass size (cm)	4–10	Reference			
	≤4, and >10	0.457 (0.159–1.311)	0.145	0.427 (0.107–1.702)	0.228
B-mode ultrasound	Solid	Reference			
	Cystic and solid	0.246 (0.041–1.465)	0.123	0.725 (0.082–6.417)	0.773
Non-enhanced scope	Inhomogenous enhancement	Reference			
	Large non-enhanced area >50%	0.060 (0.017–0.207)	<0.001	0.021 (0.003–0.134)	<0.001
Number of core biopsies	1	Reference			
	≥2	2.525 (0.784–8.138)	0.121	9.479 (1.528–58.794)	0.016

HP, histopathology; OR, odds ratio; CI, confidence interval.

RMB was performed for histopathological confirmation before targeted or immunologic therapy (8,9). The second indication was prior history of extrarenal primary malignancy, and RMB was needed to determine whether the renal mass was a second primary malignancy, metastasis, or a benign renal mass, because management strategies differ (9,10).

The diagnostic yield of HP alone in our study was 88.1%, and that of HP plus LBC was 94.0%, which is comparable with the results from a meta-analysis that reported an overall diagnostic rate of 92% (11). There is some evidence that FNA is a complementary technique to CNB in renal masses (12), especially in necrotic lesions (13). Meanwhile, it has also been highlighted that the added value combined CNB and FNA should be weighed against time, complications, healthcare cost, and resources (14). Considering these views, we used the LBC based on exfoliative cells of rinsed tissue fragments in the core needle cutting groove as a substitute for FNA, which improved the overall HP diagnostic yield by 5.9% without increasing patient discomfort. Furthermore, the improvement of diagnostic yield was more significant in the non-enhanced area exceeding 50% subgroup (60% *vs.* 86.7%, P=0.008). Meanwhile, the agreement between HP alone and HP plus LBC in the subgroup analysis was fair (Kappa =0.375, P=0.009). Among the 8 cases with negative HP but positive LBC, the histopathologic diagnosis of 7 of the cases showed inviable tissue, such as proliferative, hyaline fibrous, and necrotic tissue, and the positive finding on LBC prevented the patients from undergoing repeat biopsy (*Figure 2*). In another case, it was suggested that a small amount of tumor tissue and further immunohistochemistry (IHC) was needed, but given that LBC had made a definite diagnosis of clear cell carcinoma, no further IHC was performed and the diagnostic time was shortened partly (*Figure 3*). Thus, LBC is helpful in

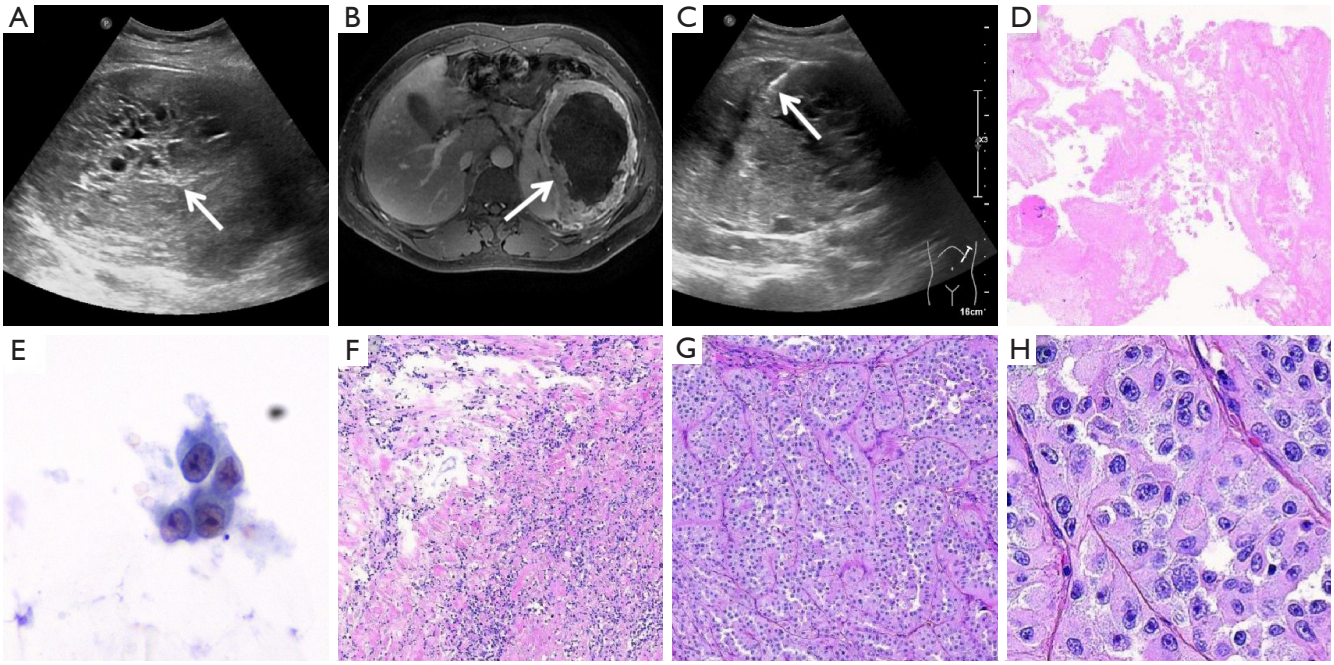

Figure 2 A large left renal mass with lymph node metastases in a 29-year-old man. (A) A grayscale ultrasound image showing a large ill-defined heterogeneous hypoechoic mass with a mesh-like anechoic zone in the center (arrow). (B) An MRI image showing peripheral ring-like enhancement with uneven thickness (arrow). (C) RMBs were performed with an 18-gauge core needle (arrow) guided by B-mode ultrasound focusing on the relatively solid area of the mass. Two core biopsies were performed. (D) The core needle biopsy histopathology (H&E stain; original magnification 4×) showing only proliferative and hyaline fibrous tissue and necrotic tissue. (E) The corresponding LBC (Pap stain; original magnification 400×) showing marked atypical epithelioid cells arranged in small cluster, with increased nuclear/cytoplasmic ratio, irregular nuclear, and prominent nucleoli. (F) Cytoreductive nephrectomy was performed after targeted and immunological therapy, and postoperative histopathology (H&E stain; original magnification 4×) showing severe treatment reaction. (G,H) A 1-year follow-up image showed recurrence, and postoperative histopathology [H&E stain; original magnification (G) 4×; (H) 20×] diagnosing RCC. MRI, magnetic resonance imaging; RMB, renal mass biopsy; H&E, hematoxylin and eosin; LBC, liquid-based cytology; RCC, renal cell carcinoma.

improving the HP, especially in renal masses with large inviable areas. This finding may help radiologists in determining whether to use HP alone or HP plus LBC for different renal masses with different imaging appearance in clinical workflow, striving for a balance between pathological diagnostic yield and healthcare cost.

The most common histologic subtype in our study was clear cell renal cell carcinoma (ccRCC), which is concordant with the natural prevalence of renal masses (15). The most common manifestation of ccRCC is a mixed enhancement pattern of both hypervascular soft-tissue components and low-attenuation areas that correspond to necrotic or cystic changes. In our study, the B-mode ultrasound predominantly showed a homogeneous or heterogeneous hypoechoic pattern that contained small patchy or spongy anechoic areas. Contrast-enhanced imaging was more advantageous in showing necrotic or cystic changes, and a non-enhanced area exceeding 50% in the largest section was an independent predictor of nondiagnostic HP. These results imply that we should be alert to non-liquid necrosis in case of contrast-enhanced imaging showing large areas without enhancement, and contrast-enhanced ultrasound (CEUS) guidance might be an effective technique to ensure viable tissue yield (16). The evaluation of the indications and efficacy of CEUS-guided RMB requires further research.

Unlike the prior studies that noted a significant correlation between smaller tumor size and nondiagnostic biopsy outcomes (17), there was no exact correlation in our study. Meanwhile, there was a trend toward increased non-diagnostic HP in the ≤4 and >10 cm subgroups (77.8% and 83.3%, respectively). The reason for non-diagnosis

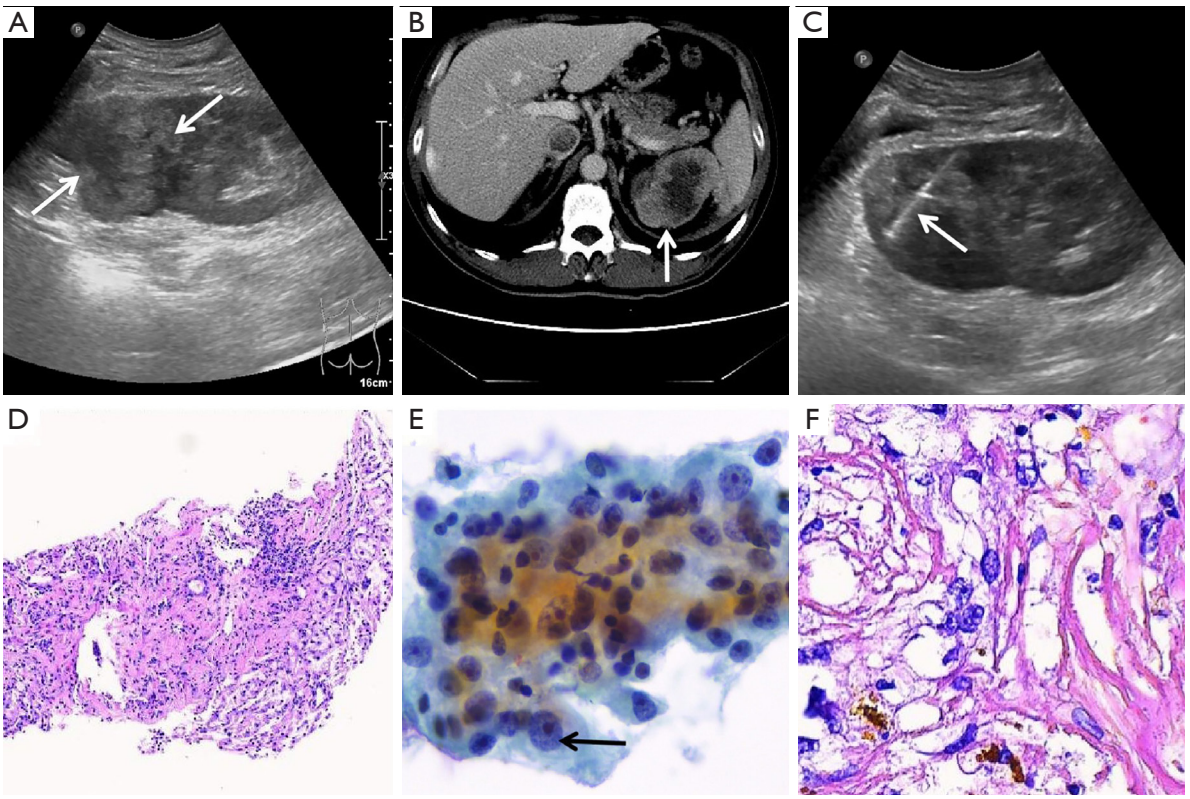

Figure 3 A mass in the upper pole of the left kidney with left renal vein and inferior vena cava tumor thrombus in a 49-year-old man. (A) A grayscale ultrasound image showing an ill-defined slightly hyperechoic mass in the upper pole of the left kidney (arrow). (B) CT image showing heterogeneous enhancement with non-enhanced necrotic area exceeding 50% (arrow). (C) RMBs were performed with an 18-gauge core needle (arrow) guided by B-mode ultrasound through the back puncture route. Two core biopsies were performed. (D) The core needle biopsy histopathology (H&E stain; original magnification 4×) showing only a small amount of tumor tissue. (E) The corresponding LBC (Pap stain; original magnification 400×) showing epithelioid cells arranged in group, with round nuclei, prominent nucleoli, and abundant cytoplasm. Cells with clear cytoplasm can be noted occasionally (arrow). (F) Cytoreductive nephrectomy performed after targeted and immunological therapy as well as postoperative histopathology (H&E stain; original magnification 20×) was ccRCC with mild treatment reaction. CT, computed tomography; RMB, renal mass biopsy; H&E, hematoxylin and eosin; LBC, liquid-based cytology; ccRCC, clear cell renal cell carcinoma.

in smaller masses (≤4 cm) might be missing of the target lesions. The non-diagnostic outcomes for the larger masses (>10 cm) might be due to an inadequate amount of tissue samples because of hemorrhagic, necrotic, or cystic changes. Interestingly, we discovered that LBC had greater value in improving the diagnostic rate in the >10 cm than ≤4 cm subgroup, from 83.3% to 91.7%. These findings confirm the view that cytology can improve the diagnostic rate to some extent, especially in partially cystic lesions (12).

There was no significant association between diagnostic rate and the location of the mass, which is in broad agreement with the literature (18,19). Seager *et al.* (20) reported that image-guided biopsy of upper pole small renal masses (SRMs) had a lower diagnostic rate (P=0.04). However, the renal masses in our study were relatively large, with a mean size of 8.5 cm, which reduced the impact of upper pole challenging anatomy. As the number of core biopsies increased, there was a theoretically increased diagnostic rate. However, more core biopsies may also increase the risk of bleeding and other complications. Among the 8 cases with both negative HP and negative LBC, there were 5 cases with only 1 and 3 cases with 2 in terms of number of core biopsies. Moreover, according to logistic regression analyses, ≥2 core biopsies were more likely to obtain positive HP (OR: 9.479, 95% CI: 1.528–58.794). Thus, a minimum of 2 high-quality core

biopsies is recommended (8,10).

The study had several limitations. First, the study was retrospective, the ultrasonograms retrieved from PACS were static sectional images, and the evaluation of cystic versus solid components inevitably had errors. Second, the sample size was determined by the number of cases in our hospital during the study period and therefore relatively small, and some clinical characteristics, such as skin-to-tumor distance and renal hilar involvement, were not included in the analysis. Third, all RMBs were performed using an 18-gauge biopsy needle, and we could not evaluate the efficacy of different biopsy needles. Finally, only 17/134 patients underwent subsequent surgical nephrectomy, thus, concordance analysis of RMCNB and surgical resection pathology was precluded.

Conclusions

RMCNB has a high diagnostic yield when a minimum of 2 high-quality core biopsies are collected, and LBC can improve the diagnostic yield of HP alone, especially in masses with large non-enhanced area.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-972/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-972/coif). YW serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 21/108-2779), and the requirement for individual consent for this retrospective analysis was waived.

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