TITLE: World Health Organization (WHO)/International Society of Urological Pathology (ISUP) Grading in Fine Needle Aspiration Biopsies of Renal Masses

RUNNING TITLE: WHO/ISUP Grading of RCC on FNA Biopsy

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ABSTRACT AND KEY WORDS:

ABSTRACT (limit 250 words)

Background: Utilization of fine needle aspiration (FNA) biopsy for the evaluation of renal masses has been increasing at our institution due to improvements in image-guided biopsy techniques and changes to clinical guidelines.

Methods: A search of the pathology database identified all renal FNAs that were performed during an 11-year period (2006-2017). Corresponding core biopsy and resections were identified. Cases with a diagnosis of primary renal neoplasia on FNA, core biopsy, and/or resection were included. Two pathologists reviewed all cases and assigned a World Health Organization (WHO)/International Society of Urological Pathology (ISUP) grade to each FNA, core biopsy, and resection case.

Results: A total of 162 FNAs of the kidney were identified (2006-2017). Primary renal neoplasia was diagnosed in 137 cases on core biopsy and/or resection. Among diagnostic FNAs of clear cell RCC and papillary RCC with corresponding core biopsy and/or resection specimens available for re-review (n=52), reviewers assigned a concordant WHO/ISUP grade to 83%

(43/52) of cases. Among the 9 cases with discrepant scores, they all had a discrepancy of 1 grade, and all were undergraded on FNA. Using a two-tier grading system (low versus high grade), reviewers assigned a concordant grade to 88% (46/52) of cases. Among the 6 cases with discrepant scores, all were classified as low grade (WHO/ISUP grade 2) on FNA versus high grade (WHO/ISUP grade 3) on resection.

Conclusion: The WHO/ISUP grade assigned on FNA shows good concordance with subsequent resection/core specimens (83%), with all discrepant cases being undergraded by one grade.

KEYWORDS (3 to 6 key words)

Renal cell carcinoma, fine needle aspiration, cytology, nuclear grading, Fuhrman grade, WHO/ISUP grade

BODY OF ARTICLE:

INTRODUCTION

Renal cell carcinoma (RCC) is the most common malignant neoplasm of the kidney in the United States. Its incidence has been increasing, which is largely attributed to improvements in the ability of imaging techniques to detect small renal lesions. Likewise, utilization of core biopsy and fine needle aspiration (FNA) biopsy of renal masses is on the rise. Management guidelines including those published by the European Association of Urology (EAU), the American Urological Association (AUA), and the National Comprehensive Cancer Network (NCCN) outline scenarios in which performance of a biopsy is an appropriate component of the work-up of a renal lesion. These scenarios include biopsy prior to ablation/cryosurgery/radiofrequency, during active surveillance, if the lesion is central and urothelial carcinoma enters the differential diagnosis, and if a renal mass is suspected of being hematologic, metastatic, inflammatory, or infectious.[1-3] Renal mass biopsy can guide treatment in several scenarios. If an oncocytic renal neoplasm is present then surgery can be delayed or avoided altogether.[4] In addition, in small renal masses in patients who are poor surgical candidates, a histologic diagnosis of low grade clear cell RCC or papillary RCC, type 1 may help guide a patient and urologist when deciding between active surveillance or surgical resection.[5, 6]

Notably, while nuclear grade is routinely assigned to needle core biopsies with RCC, this is not common practice for FNA biopsies.

The utility of core biopsy versus FNA biopsy of solid renal masses remains somewhat debatable. Several publications report comparable rates of sensitivity and diagnostic accuracy of FNA biopsy versus core biopsy. The AUA and the EAU both state that multiple core biopsies are preferred over fine needle aspiration (FNA) biopsy of a solid renal mass, however they also acknowledge the benefit of rapid on-site evaluation of adequacy during a FNA biopsy and state that this may help to obtain a higher proportion of diagnostic core biopsies.[1, 7]

Core biopsy has been shown to be a reliable diagnostic tool in the work-up of renal lesions in terms of assigning an accurate diagnosis.[5, 8-12] While some studies have indicated only moderate concordance between grade assignment on needle core biopsy and resection specimens, assignment of a nuclear grade to core biopsies is still common practice at many institutions including our own.[8, 11-13] In contrast, assignment of a nuclear grade is not routine for FNA biopsies from primary renal lesions. There are only a few studies which address the topic of assigning a nuclear grade to an FNA biopsy of a renal lesion the literature, all of which indicate either moderate agreement with resection grade or moderate interobserver variability using a four-tier grading system.[14, 15] These same studies state that there is higher agreement when a two-tier grading system is applied (low versus high grade), which is not unexpected and has also been proven to be true in core biopsies.[14, 15]

At our institution, it is routine to perform FNA biopsy with rapid on-site assessment of adequacy prior to core biopsy for all renal masses. There are occasional instances in which the material on direct smears is superior to that in the cell block and core biopsy, as well as instances in which the radiologist chooses not to proceed with core biopsy (renal mass is too small, lesion starts bleeding, unable to proceed for safety reasons due to change in patient's status). Therefore, we aim to study the reproducibility of the application of the World Health Organization (WHO)/International Society of Urological Pathology (ISUP) grading system to direct smears prepared from FNA biopsy of primary renal clear cell RCC and papillary RCC. We present the largest series to date comparing the WHO/ISUP grade in clear cell and papillary RCC FNA biopsy versus subsequent core biopsy and/or resection specimens.

MATERIALS AND METHODS

This study was approved by the institutional review board (IRB) committee at Indiana University and by the Ethics Committee. A search of the pathology database identified all renal FNAs that were performed during an 11-year period (2006-2017). Cases with a diagnosis of primary renal neoplasia on FNA biopsy, core biopsy, and/or resection were included. FNA biopsies were performed using ultrasound or computed tomography (CT) imaging guidance and using 22-gauge or 25-gauge needles. Paired air-dried (Diff-Quik stain) and ethanol-fixed (Papanicolaou stain) specimens were prepared. Rapid on-site evaluation for adequacy was performed in each case by either a cytopathologist and/or a cytotechnologist. Ideally, at our institution we now collect 2 to 5 passes for direct smears, 2 to 4 directed passes for cell block, and at least 2 needle

core biopsies were obtained immediately following FNA biopsy. All material is collected during the same procedure, and the radiologists at our institution utilize the same sheath to guide the FNA needle and core biopsy needle (18-gauge) to ensure that they are performing core biopsy of the same location that the FNA passes are taken from. Touch preparations are performed in a subset of cases depending on the preferences of the cytopathologist, cytotechnologist, and radiologist performing the procedure. We do not consider touch preparation of core biopsies routine protocol at our institution given that in our experience the core used for the touch preparation does not yield good morphology on routine H&E staining and is at times destroyed, and we prefer to preserve tissue for permanent section in the even that immunohistochemical stains are required. Of note, at the beginning of this study this procedure was not standardized and collection of cell block and core biopsy were performed at the discretion of the cytopathologist/cytotechnologist and radiologist present at procurement. Furthermore, if collection is deemed unsafe to the patient for any reason (i.e. significant bleeding, lesion located close to a vessel), the procedure was stopped regardless of the quality of material collected until that point, which sometimes meant that only direct smears from the initial FNA biopsy were obtained. Finally, some of the cases included in this study were consultation cases, therefore cell block and core biopsy was not always included in the materials provided for review. These details account for the absence of a cell block and core biopsy in every case.

A chart review was performed and pertinent data was collected including patient age, sex, kidney laterality, treatment (no resection, partial nephrectomy, radical nephrectomy), survival status, and the presence/absence of metastases. All available slides from FNA biopsies, core biopsies, and resections were re-reviewed. Two pathologists (CMP, HHW) reviewed all cases

independently and confirmed the diagnoses. Diagnoses were considered non-diagnostic (benign kidney, necrosis, blood, hypocellular, etc.) or diagnostic (including atypical cells, suspicious for malignancy, and malignant). They subsequently assigned both independent and consensus WHO/ISUP grades to each FNA biopsy, core biopsy, and resection case with clear cell RCC or papillary RCC (**Fig 1**). They followed the guidelines for grading outlined in a 2013 ISUP consensus paper and in the most recent *WHO Classification of Tumours of the Urinary System and Male Genital Organs*.[16, 17] While the guidelines are outlined for formalin-fixed, paraffin-embedded tissue sections, the goal of this study was to determine if they also applied to Diff-Quik and Papanicolaou-stained direct smears, therefore the same guidelines were applied when grading the direct smears. There is a subspecialized genitourinary pathology service at our institution which applies these same guidelines (four tier system) to all core biopsies and resections of both primary renal clear cell RCC and papillary RCC.

RESULTS

A total of 162 FNA biopsies of the kidney from 157 patients were identified (2006-2017). Among all 162 FNA cases, 35 were non-diagnostic, 10 atypical, 6 suspicious, and 111 neoplastic (12 benign neoplasm, 99 malignant). Primary renal epithelial neoplasia was diagnosed in 137 cases on FNA biopsy, core biopsy, and/or resection specimen. The remainder of the diagnoses included high grade urothelial carcinoma (10), malignancies from other sites (metastases or local invasion 10), benign cysts (3), abscess (1), and other (2) (note: 1 case contained both papillary RCC and high grade urothelial carcinoma). In comparison, core biopsy was non-diagnostic in 7

cases out of 100 total cases and non-diagnostic in 6 out of 85 cases of primary renal epithelial neoplasia. Of the 29 non-diagnostic FNA cases of primary renal epithelial neoplasia, core biopsy was performed in 24 cases and was not performed in 5 cases.

Among all 137 FNA cases of primary renal epithelial neoplasms confirmed by FNA, core biopsy, and/or resection, core biopsy was performed in 100 total cases and partial or radical nephrectomy was performed in 110 cases (only core biopsy 27 cases, only nephrectomy 46 cases, both core biopsy and nephrectomy 64 cases). Among these 137 cases, FNA biopsy was diagnostic in 108 cases. Among diagnostic FNA biopsies with primary renal neoplasia and a corresponding core biopsy and/or resection specimen (n=108), 68 cases had slides from all specimens available for re-review. Among these 68 cases, 63 had concordant and 5 had discordant diagnoses (**Table 1**). The most common discrepancy was the presence of an oncocytoma/oncocytic cells on FNA biopsy versus a final diagnosis of RCC, unclassified (n=2) or papillary RCC, type 1 (n=1) on resection. Three discrepant cases were completely excluded from analysis, as they were not primary renal epithelial lesions on resection (1 leiomyosarcoma, 1 diffuse large B-cell lymphoma, 1 malignant melanoma).

TABLE 1 Discrepant diagnoses

Case #	FNA Diagnosis	Core Biopsy Diagnosis	Resection Diagnosis
1	oncocytoma	NA	RCCU
2	atypical spindle cells	CCRCC	RCCU
3	oncocytic renal neoplasm	oncocytic renal neoplasm	RCCU

4	oncocytic cells	PRCC type 1	PRCC type 1
5	CCRCC	CCRCC	translocation associated RCC

NA, not applicable; CCRCC, clear cell renal cell carcinoma; PRCC, papillary renal cell carcinoma; RCCU, renal cell carcinoma unclassified

Among diagnostic FNA biopsies of clear cell RCC and papillary RCC with corresponding core biopsy and/or resection specimens available for re-review (n=52), reviewers independently assigned identical WHO/ISUP scores to 92% (48/52) of FNA biopsies, 97% (34/35) of core biopsies, and 95% (39/41) of resection cases. Among the 4 FNA cases with discordant WHO/ISUP scores, 2 cases had a discrepancy of grade 1 versus 2, and 2 cases had a discrepancy of grade 2 versus 3. The only core biopsy case with a discordant WHO/ISUP score had a discrepancy of grade 2 versus 3. Among the 2 resection cases with discordant WHO/ISUP scores, both had a discrepancy of grade 2 versus 3. The final consensus scores for each specimen type were assigned by 2 reviewers while simultaneously double scoping.

Among diagnostic FNA biopsies of clear cell RCC and papillary RCC with corresponding core biopsy and/or resection specimens available for re-review (n=52), reviewers assigned a concordant consensus WHO/ISUP grade to 83% (43/52) of cases on FNA versus core biopsy and/or resection (**Table 2**). Among the 9 cases with discrepant WHO/ISUP scores, all had a difference of only 1 WHO/ISUP grade (WHO/ISUP grade 2 versus 3 in 6 cases, WHO/ISUP grade 3 versus 4 in 3 cases). In comparison, WHO/ISUP grade assigned to core biopsy was identical to that assigned to the corresponding resection specimen in 92% (22/24) of cases.

Among the 2 discrepant cases, both had a discrepancy of 1 WHO/ISUP grade (grade 3 versus 4). In all discrepant cases, the WHO/ISUP grade assigned on FNA and core biopsy was less than that assigned on the resection specimen.

TABLE 2 WHO/ISUP grade assigned to FNA, core biopsy, and resection specimens

	Total Cases (n)	Agree	Disagree	2 vs. 3	3 vs. 4
FNA versus Core/Resection	52	43	9	6	3
FNA versus Resection	41	32	9	6	3
FNA versus Core Biopsy	35	34	1	1	0
Core Biopsy versus Resection	24	22	2	0	2

Some prior publications have suggested the use of a two-tier grading system, with WHO/ISUP grades 1 and 2 corresponding to low grade and grades 3 and 4 corresponding to high grade. If a two-tier system were to be applied to this study, reviewers assigned a concordant WHO/ISUP grade to 88% (46/52) of cases on FNA biopsy versus resection. All 6 discordant cases would have been placed in the low grade category on FNA biopsy (WHO/ISUP grade 2), but were high grade after resection (WHO/ISUP grade 3). Using the two-tier system, all cases would have been assigned a concordant WHO/ISUP grade on core biopsy and resection.

DISCUSSION

Guidelines for the management of small renal masses are changing and surveillance is now an acceptable approach in certain clinical scenarios. As a reflection of these changing guidelines, the utilization of core biopsy and FNA biopsy of renal masses is on the rise. While assignment of a WHO/ISUP nuclear grade to needle core biopsies with primary renal clear cell RCC or papillary RCC is standard of care at some institutions, it is not common practice to include this information in cytopathology reports of FNA biopsies. Prior studies note that the ability to provide a histologic diagnosis and assign a nuclear grade to a renal mass biopsy provides additional data to the urologist and oncologist for prognostication.[18] This is helpful when patients have benign tumors on biopsy and in patients who are elderly with multiple comorbidities who are poor surgical candidates and are found to have a low grade malignancy on biopsy.[18] There are times when the FNA direct smears obtained at our institution are more cellular than the cell block or core biopsy, or when a cell block and/or a core biopsy were unable to be obtained due to complications such as bleeding, therefore accurate diagnosis and grading of the smears is the only opportunity to provide clinicians with this information.

It is well established that both FNA and core biopsy of renal masses are diagnostically accurate. In this study, the non-diagnostic rate of FNA was 21% (29/137) and of core biopsy was 7% (6/85) in cases of primary renal epithelial neoplasia. Of note, in this series most non-diagnostic FNA biopsies of primary renal epithelial lesions were followed up by a core biopsy (83%, 24/29). The remainder of the core biopsies (n=56) were performed after a diagnostic FNA biopsy.

The well-known Fuhrman grading scheme for RCC was initially proposed in 1982. The authors of this algorithm used nuclear size, nuclear irregularity, and nucleolar prominence to assign 4 grades to resection specimens. They showed a statistically significant inverse relationship between nuclear grade and 5 year survival (grade 1 versus combined grades 2 and 3 versus grade 4). They also showed a statistically significant difference in the rate of metastases between grade 1 tumors versus the combined rate of metastases in grade 2, 3, and 4 tumors.[19] Of note, at the time of this study the numerous histologic subtypes of RCC were not recognized.[16]

Since the initial publication of the Fuhrman grading system RCC has become an increasingly complex and heterogeneous category of tumors. As a result, the reliability of Fuhrman grading became a topic of debate.[20] The ISUP published a consensus statement in 2013 which stated that nuclear grade should only be applied to clear cell RCC and papillary RCC and that the most emphasis should be placed on nucleolar prominence when assigning a grade.[16] The WHO/ISUP grading system outlined in the 2016 *WHO Classification of Tumours of the Urinary System and Male Genital Organs* encompasses these guidelines.[17] The WHO/ISUP grading system has been validated in the literature to show a statistically significant difference in cancer-free survival between grades 2 versus 3 and between grades 3 versus 4 (grade 1 excluded from analysis because no tumors had recurrence/metastases).[21]

Despite the fact that a nuclear grade is commonly applied to core biopsy and resection specimens, this practice is not widely utilized in cytopathology specimens. There have been very few studies that have compared assignment of a nuclear grade to a cytology specimen versus a

resection specimen of a primary renal tumor. Nazer et al. compared nuclear grade of 18 cases of RCC on FNA biopsy (2 FNA biopsies performed ex vivo) versus resection. They assigned a concordant nuclear grade to 78% (14/18) cases. Among the 4 discordant cases, all were a discrepancy of 1 grade; 2 cases were grade 1 on cytology and grade 2 on resection, and 2 cases were grade 4 on cytology and grade 3 on resection. If a two-tier system would have been utilized, there would be no discrepancy of the grades (low versus high) assigned on FNA biopsy versus resection.[14] Bishop et al. compared nuclear grade of 33 cases of RCC on FNA biopsy versus resection. They did not provide the exact grades assigned to each FNA biopsy and resection in their study. However, they stated that using a four-tier system they found higher diagnostic sensitivity for better-differentiated tumors, and higher diagnostic specificity and accuracy for less differentiated tumors. Using a two-tier system they found that low grade tumors had sensitivity 100%, specificity 44%, and accuracy 84%, while high grade tumors had sensitivity 44%, specificity 100%, and accuracy 84%.[15] Gilani et al. compared nuclear grade of 21 cases of RCC (14 primary kidney tumors, 7 metastases) on FNA biopsy versus resection. Diagnostic accuracy was 60-70% for cases which were grade 2 on resection, 50-70% for cases which were grade 3 on resection, and grade 4 cases were all undergraded. Differences in grade assigned to cytology versus resection specimens were never more than 1 grade.[22]

While there have only been 3 previously published studies comparing nuclear grade assigned on cytology versus resection specimens, they have suggested at least moderate concordance in the grading of FNA versus resection. Likewise, we assigned a concordant WHO/ISUP nuclear grade on FNA biopsy and resection of primary renal clear cell RCC or papillary RCC to 83% of cases. All 9 discordant cases had a grade difference of 1. As some previously published studies have

suggested, had we employed a two-tier grading system (low versus high grade), we would have had an improved concordance rate of 94% between FNA biopsy and resection. In all discordant cases in our study, the grade assigned on FNA biopsy was less than that assigned on resection. We attribute this difference to both sampling bias and specimen preparation. FNA biopsy samples only a small portion of the tumor, whereas multiple blocks of tumor are submitted from resection cases. Given that the WHO/ISUP grade is based on the highest grade identified in an entire tumor, there will be inherent differences of grading in cases in which high grade features are only focally present in the lesion. Furthermore, there are some differences when assigning a grade based on direct smears versus a hematoxylin and eosin-stained slide from a resection. We did find it difficult to evaluate nucleoli on the Diff-Quik stained slides, and assessment of nucleoli is the crux of the most recent WHO/ISUP grading system.

A recent abstract compared interobserver variability when assigning an ISUP grade to RCC based on cytology specimens. They had 5 experienced cytopathologists assign both an ISUP grade and a Fuhrman grade to 26 cases of RCC (18 clear cell RCC, 8 papillary RCC). When they analyzed the results using a two-tier system, they found that there was slightly better concordance between ISUP grades in comparison to Fuhrman grades.[23] We also found a high rate of concordance between WHO/ISUP score assigned to each FNA biopsy (88%) when a two-tier system was utilized, with all 6 discordant cases having a discrepancy of 1 grade (grade 2 on FNA biopsy versus grade 3 on resection).

In conclusion, given the increasing rate of FNA biopsy of primary renal tumors the question of whether or not assignment of a nuclear grade to cytologic material would provide an accurate

prediction of subsequent grade on core biopsy/resection is relevant. There is a paucity of data in the literature that addresses this topic, which we attribute to the infrequent utilization of FNA biopsy of renal masses in the past. We found that the WHO/ISUP grade assigned to FNA biopsies of clear cell RCC or papillary RCC correlated with the grade on core biopsy and/or resection in the majority of cases. There are FNA biopsies of primary renal clear cell RCC and papillary RCC which have hypocellular/acellular cell blocks and which may not have corresponding core biopsies. Our results offer support that providing a WHO/ISUP grade based on the direct smears would provide the clinician with useful information for prognostication. Therefore, we recommend the addition of a WHO/ISUP score to cytopathology reports of FNA biopsies of primary renal clear cell RCC and papillary RCC.

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FIGURE LEGENDS:

FIGURE 1 WHO/ISUP Grade in Fine Needle Aspiration Biopsy of Clear Cell Renal Cell Carcinoma and Papillary Renal Cell Carcinoma

A. WHO/ISUP grade 1 (X400, Diff Quik stain).

B. WHO/ISUP grade 2 (X400, Papanicolaou stain).

C and D. WHO/ISUP grade 3 (X400, Diff Quik stain and Papanicolaou stain).

E and F: WHO/ISUP grade 4 (X400, Diff Quik stain and Papanicolaou stain).