

The accuracy of renal tumor biopsy: analysis from a national prospective study

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Abstract

Objective To assess preoperative renal tumor biopsy (RTB) accuracy.

Materials and methods As part of the prospective NEPHRON study, data from 1,237 renal tumors were collected, including the use and results of RTB and final histology following nephrectomy. During the 6 months period of inclusion, 130 preoperative biopsies were performed. We used the kappa coefficient of the McNemar test to

determine the concordance between the biopsy and the nephrectomy specimen (NS) regarding four parameters: malignant/benign status, histological subtype, Fuhrman grade and microscopic necrosis.

Results Preoperative biopsies were performed in 9.7 and 11.4 % of the 667 radical and 570 partial nephrectomies, respectively. Tumor biopsy was inconclusive in 7.7 % of the cases. In 117 cases, a comparison between RTB and NS was available. Benign tumors accounted for three (2.6 %) and five (4.3 %) of the RTB and NS, respectively ($\kappa = 0.769$, good). With seven (6 %) discordant results in

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terms of histological subtype characterization between RTB and final pathology, RTB accuracy was considered excellent ($\kappa = 0.882$). In 33 cases (31.7 %), Fuhrman grade was underestimated at biopsy resulting in an intermediate concordance level ($\kappa = 0.498$). Tumor microscopic necrosis was identified in 12 RTB (10.4 %) versus 33 NS (28.4 %) ($\kappa = 0.357$, poor).

Conclusions RTB provides good to excellent diagnostic performance for discriminating malignancy and tumor histological subtype. However, its performance is intermediate or even poor when considering prognostic criteria like Fuhrman grade or microscopic necrosis. Thus, this possible inaccuracy should be taken into consideration when using RTB for accurate guidance of treatment strategy.

Keywords Renal cell carcinoma · Biopsy · Nephron sparing surgery · Diagnosis · Prognosis

Introduction

The widespread use of modern imaging increased the detection of asymptomatic small renal tumor and led to the need to reassess minimal invasive and non-surgical strategies [1]. At the same time, new systemic treatments have radically modified the management of renal metastatic disease [2]. These changes have given a rationale for expanding the indications for renal tumor biopsy (RTB).

The percutaneous biopsy ability for distinguishing benign from malignant lesions is excellent with a perfect match between RTB and surgical specimens found in many studies [3–8]. Numerous studies also reported good

accuracy for determining tumor histological subtype from 77 to 100 % [3–12].

Nevertheless, in addition to histological subtype, here is a need for prognostic histological data to guide the treatment decisions particularly for active surveillance or neoadjuvant systemic therapy. RTB accuracy in determining Fuhrman nuclear grade has been reported between 31 and 93 %, and no study has evaluated the ability for RTB to diagnose microscopic intratumoral necrosis [4, 9, 10, 13–15].

As part of the National Observational Registry on the Practices of Haemostasis in Partial Nephrectomy (NEPHRON), this study was aimed to prospectively evaluate the concordance between RTB and the final specimen pathology.

Materials and methods

Data were obtained from a French, multicentre, prospective and observational study, the NEPHRON study, designed to evaluate the management of renal tumors in France [16]. The study and database were approved by the CNOM (Conseil National de l'Ordre des Médecins) and the CNIL (Commission Nationale de l'Informatique et des Libertés). Two hundred and forty-six French urologists from 56 centers were involved in this nationwide study. Sixty-three percent and 37 % of them were affiliated with public or private institutions, respectively.

Data from 1,237 nephrectomy cases between June 1 and December 31, 2010, have been prospectively registered via a web-based electronic case report form. The use and results of RTB and the definitive histology following

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nephrectomy were also registered. Tumor staging was done according to the 2009 International Union Against Cancer TNM classification of renal tumors [17]. Histological subtype was defined according to the World Health Organization 2004 classification [18]. Tumor grading was assessed according to the Fuhrman grading scheme [19].

Following the investigator usual practice, RTB was performed under ultrasonography or CT guidance using local anesthesia to attain 18-gauge needle cores for pathologic analyses. At each institution, pathologists trained to genitourinary malignancies evaluated the specimens.

Preoperative biopsies were compared to surgical specimens with respect to malignant/benign status, histological subtype, Fuhrman grade and microscopic necrosis.

We used the kappa coefficient of the McNemar test to determine the concordance between the histological result of the biopsy and final histology. The kappa coefficient was stratified as: excellent (0.81–1), good (0.61–0.80), intermediate (0.41–0.60) and poor (inferior to 0.41) [20]. In the intent to characterize the cases presenting with an upgraded Fuhrman category at final pathology, normality was assessed with the Kolmogorov–Smirnov test and the Wilcoxon–Mann–Whitney or Chi-square tests were, respectively, used for quantitative and categorical variables comparisons.

Results

During the 6-month enrollment period of the nationwide prospective NEPHRON study, a preoperative biopsy was performed in 65 (9.7 %) and 65 (11.4 %) cases of the 667 radical nephrectomies (RN) and 570 nephron sparing surgery (NSS), respectively. A preoperative biopsy was used by 33 centers accounting for 58.9 % of the totally 56 participating centers.

Tumor biopsy was conclusive in 120 (92.3 %) cases, and in 117 cases a comparison between RTB and nephrectomy specimen (NS) was possible, thereby defining our final study cohort. Patients were males in 65 % of the cases ($n = 76$), with a median age of 60 [21–83] and a median BMI of 26.4 [16.7–39.3] kg/m². Mean tumor size was 4.8 ± 2.8 cm but significantly different whether patients underwent a partial or a radical nephrectomy: 3 versus 6.5 cm, respectively. Eight tumors (6.8 %) were Bosniak type 4 cysts. RTB results according to the type of surgery are shown in Table 1. Table 2 describes the results on tumor type, histological subtype, Fuhrman grade and tumor necrosis assessments, based on RTB and NS analysis. Benign tumors accounted for 2.6 % ($n = 3$) and 4.3 % ($n = 5$) of the RTB and NS, respectively. Two cases diagnosed as primary renal cancers on RTB were finally reported as benign tumors on the definitive pathologic exam. The concordance between RTB and NS in determining the tumor type was

Table 1 Renal tumor core biopsy results in 117 patients according to treatment strategy: radical nephrectomy (RN) or partial nephrectomy (PN)

	RN [$N = 59$ (%)]	PN [$N = 58$ (%)]
<i>Tumor type</i>		
Primary renal cancer	58 (98.3)	55 (94.8)
Metastasis of a non-primary renal cancer	0	1 (1.7)
Benign renal tumor	1 (1.7)	2 (3.5)
<i>Histological subtype</i>		
Clear cell carcinomas	38 (64.4)	43 (74.1)
Papillary carcinomas	6 (10.2)	7 (12.1)
Chromophobe carcinoma	8 (13.5)	5 (8.6)
Undifferentiated carcinomas	3 (5.1)	0 (0)
Rare renal carcinomas	3 (5.1)	0 (0)
Oncocytoma	1 (1.7)	2 (3.5)
Lung adenocarcinoma	0 (0)	1 (1.7)

considered good ($\kappa = 0.769$). A discrepancy between histological subtype from RTB and final pathology occurred in 7 cases (6 %) (Table 3). The concordance between RTB and the final pathologic exam for precise histological subtype diagnosis was estimated as excellent with the McNemar test ($\kappa = 0.882$).

In determining Fuhrman grade, RTB and NS had an intermediate concordance level ($\kappa = 0.498$). Excluding non-primary renal cancers (benign tumors and metastases) and cases with at least one missing Fuhrman grade, a detailed comparison of the RTB and the NS analysis results was performed on a one to one basis. Among 104 cases, 65 had a perfect match (62.5 %). Thirty-three cases (31.7 %) were upgraded at final pathology with 16 (15.4 %) reclassified from low grade (I or II) to high Fuhrman grade (III or IV). Of 38 total high-grade tumors, 16 (42.1 %) were so falsely classified as low-grade tumors by RTB. At the same time, 6 cases (5.8 %) were downgraded. The detailed magnitude and direction of Fuhrman grade changes are shown in Table 4. No significant differences were observed in terms of tumor size ($p = 0.077$), histological subtype ($p = 0.474$) or ECOG classification ($p = 0.426$) was found between patients that were reclassified in the high Fuhrman grade category versus those that were not. Finally, microscopic necrosis was identified in 12 RTB (10.4 %) versus 33 NS (28.4 %), and the concordance was rated as poor ($\kappa = 0.357$) (Table 2).

Discussion

In contrast with the management of other neoplasms, RTB indications have been limited in renal cancer. RTB is

Table 2 Assessment of the concordance between RTB and NS pathology results available in 117 cases

	RTB [<i>N</i> = 117 (%)]	Nephrectomy specimen [<i>N</i> = 117 (%)]	McNemar test			
			<i>p</i>	Kappa coefficient		
<i>Tumor type</i>						
Primary renal Cancer	113 (96.6)	111 (94.9)	0.572	0.769 (good)		
Metastasis of a non-primary renal cancer	1 (0.9)	1 (0.9)				
Benign renal tumor	3 (2.6)	5 (5)				
<i>Histological subtype</i>						
Clear cell carcinomas	81 (69.2)	78 (66.7)	0.998	0.882 (excellent)		
Papillary carcinomas	13 (11.1)	15 (12.8)				
Chromophobe carcinoma	13 (11.1)	12 (10.3)				
Undifferentiated carcinomas	3 (2.6)	3 (2.6)				
Rare renal carcinomas	3 (2.6)	3 (2.6)				
Oncocytoma	3 (1.7)	4 (3.3)				
Angiomyolipoma	0 (0)	1 (0.9)				
Lung adenocarcinoma	1 (0.9)	1 (0.9)				
<i>Fuhrman grade</i>						
NR	10	9			0.002	0.498 (intermediate)
Grade 1	18 (16.8)	8 (7.4)				
Grade 2	63 (58.9)	61 (56.5)				
Grade 3	20 (18.7)	30 (27.8)				
Grade 4	6 (5.6)	9 (8.3)				
<i>Tumor Necrosis</i>						
NR	2	1	<0.001	0.357 (poor)		
No	103 (89.6)	83 (71.6)				
Yes	12 (10.4)	33 (28.4)				

Table 3 Detailed report of the seven cases with histological subtype inconsistency between RTB and NS

Histological subtype on RTB	Histological subtype at final pathology (NS)
Clear cell renal carcinoma	Chromophobe carcinoma
Clear cell renal carcinoma	Papillary carcinoma
Clear cell renal carcinoma	Angiomyolipoma
Clear cell renal carcinoma	Rare renal carcinoma
Chromophobe carcinoma	Oncocytoma
Chromophobe carcinoma	Clear cell renal carcinoma
Rare renal carcinoma	Papillary carcinoma

recommended for renal masses that are indeterminate on abdominal imaging, if suspicious for metastatic disease in the presence of a known extra-renal malignancy, or for patients who are potential candidates for active surveillance or minimally invasive ablative therapy and for patients with metastatic disease before systemic therapies [7]. In spite of those recommendations, RTB remains underused prior surgery. Consistent with our observation, 89.5 % of the surgical procedures were performed without preoperative

pathologic assessment. More surprisingly, although mean tumor size of those undergoing NSS was 3 cm, 88.4 % of the cases were performed without preoperative RTB. Is this because French urologists feel confident enough in performing PN believing in a low risk of kidney loss or because they're not convinced by the usefulness and accuracy in diagnosing benign tumors in this specific subset of small lesions [21]? However, in recent publications, the practice of RTB was shown to be safe, cost-effective and could change clinical management and particularly avoid overtreatment for benign lesions [3–12]. In our study RTBs were conclusive in 92.3 % of the cases and even if in two cases the tumor was falsely classified as a malignant lesion, we confirmed a good accuracy of RTB for distinguishing benign from malignant tumors ($\kappa = 0.769$).

We found an excellent correlation between RTB and final specimen ($\kappa = 0.88$) for the determination of histological subtype. This accuracy of RTB has also been reported in several studies [3, 6–12, 15]. This finding is of significant importance when electing a specific targeted therapy on the strength of a biopsy result.

There remains scenarios that require careful interpretation of the RTB's results. In case of multifocal renal masses,

Table 4 Concordance or magnitude and direction of Fuhrman grade changes between RTB and NS on 104 patients

		Fuhrman grade on Nephrectomy Specimen (n)				
		1	2	3	4	
Fuhrman grade on Renal Tumor Biopsy (n)	1	5	13	-	-	18
	2	3	43	15	1	62
	3	-	1	13	4	18
	4	-	1	1	4	6
		8	58	29	9	104

Gray zone = perfect match zone. Orange zone = upgrading at final pathology. Blue zone = downgrading at final pathology

Simhan et al. [22] reported that for malignant, benign and histological diagnosis the RTB concordance rates for multiple unilateral lesions were only of 77.2, 48.6 and 58.8 %, respectively. In the case of metastatic carcinoma, because of heterogeneity within the tumor and among metastases, RTB seems to have a limited ability to identify non-clear-cell histological subtype [13, 14]. Lastly, in the case of a cystic lesion, RTB gives a high rate of false-negative results and are difficult to interpret [23].

More than the histological confirmation of cancer diagnosis and its histological subtype, the purpose of RTB could also be to predict tumor aggressiveness and risk of progression to further discriminate patients requiring surgery from those who could be managed by active surveillance or ablative therapies. Indeed, the increasing number of patients diagnosed with small renal cancers could result in overtreatment. This is especially pertinent for small renal tumors in the elderly [24].

The Fuhrman grading system is the most accurate histological prognosticator. It was based on the degree of nucleolar prominence [19]. Recently, the International Society of Urological Pathology proposed a novel grading system for clear cell RCC in which microscopic necrosis added statistically significant information to predict cancer specific survival [25]. Moreover, necrosis demonstrated prognostic improvement when combined with Fuhrman grade, tumor size and TNM stage in the SSIGN nomogram that is probably one of the most accurate nomograms in renal cancer and at the ISUP conference 2012, there was consensus that for clear cell carcinoma the presence of necrosis should be routinely included in pathology reports [26, 27].

Like us, numerous studies have already shown a poor accuracy of RTB for Fuhrman grade determination with

a trend toward an underestimation [15]. Only Miller et al. reported an accuracy rate of 93 % for distinguishing low-grade tumors (I–II) and high-grade tumors (III–IV), but all the RTBs were performed in the same center and were all reviewed by a single skilled pathologist [10]. In contrast our multi-institutional study better estimates the general experience, specifically with a low RTB accuracy rate for Fuhrman grading—more than one-third of the patients were misclassified. Moreover, a 42.1 % rate of high-grade tumor underdiagnosis has to be taken into account when electing the most appropriate treatment strategy, including active surveillance.

To our knowledge, this is the first study to report on RTB accuracy of evaluating intra-tumoral microscopic necrosis. Unfortunately, identifying microscopic necrosis on RTB was associated with poor accuracy ($\kappa = 0.35$) and may not add clinical utility for enhancing tumor grading at the time of biopsy nor for individualizing necrotic tumors of poor prognosis. Obviously, the standard techniques of renal mass biopsy recommending avoidance of gross necrotic areas may in part explain the low concordance between RTB and final pathology for this specific purpose. Moreover, because biopsy represents a small regional sampling of the larger tumor, it bound to be misrepresentative in the face of intra-tumoral heterogeneity. This may also reasonably account for the significant discrepancies between biopsy and final specimen.

In summary, we confirmed the poor ability of RTB to very accurately discriminate tumors of poor prognosis. At least for the moment, RTB does not seem to be reliable enough to guide treatment decision-making based on prognostic parameters. In this context, the development of new molecular markers would be necessary to improve prognostic accuracy [28].

This study allows us to report on the accuracy of RTB, but no conclusion can be drawn in terms of practice or to determine the role of RTB in the management of kidney cancer. Indeed, the NEPHRON study was initially designed to assess the French surgical practice regarding partial nephrectomy. For this reason, non-operated patients were not included. We can therefore not determine the number of patients that were diagnosed with benign tumors and were consequently ruled out of surgery.

The second limitation of this study is its multicenter character leading to an heterogeneity in the RTB practices and the absence of centralized pathologic review. However, these results prospectively obtained in a short period of time, reflect a real-life general French experience with a significant part of the data coming from non-academic centers.

Conclusion

Renal tumor biopsy has a good to excellent diagnostic performance for the diagnosis of malignancy and tumor histological subtype determination. However, its performance is intermediate and even poor when considering prognostic criteria like Fuhrman grade or microscopic necrosis. Thus, these limitations should be taken into consideration when RTB is considered for guiding treatment strategy.

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Conflict of interest The authors declare that they have no competing interests.

Ethical standard The study and database were approved by the CNOM (Conseil National de l'Ordre des Médecins) and the CNIL (Commission Nationale de l'Informatique et des Libertés). All patients received oral information with exhaustive written notice about the objectives of the study and the potential use of confidential clinical data for statistical analysis and publication.

References

- Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK (2006) Rising incidence of small renal masses: a need to reassess treatment effect. *J Natl Cancer Inst* 20(98):1331–1334
- Motzer RJ (2011) New perspectives on the treatment of metastatic renal cell carcinoma: an introduction and historical overview. *Oncologist* 16(Suppl 2):1–3
- Wang R, Wolf JS Jr, Wood DP Jr, Higgins EJ, Hafez KS (2009) Accuracy of percutaneous core biopsy in management of small renal masses. *Urology* 73:586–590 discussion 90–91
- Menogue SR, O'Brien BA, Brown AL, Cohen RJ (2013) Percutaneous core biopsy of small renal mass lesions: a diagnostic tool to better stratify patients for surgical intervention. *BJU Int* 111:E146–E151
- Somani BK, Nabi G, Thorpe P, N'Dow J, Swami S, McClinton S (2007) Image-guided biopsy-diagnosed renal cell carcinoma: critical appraisal of technique and long-term follow-up. *Eur Urol* 51:1289–1295 discussion 96–97
- Vasudevan A, Davies RJ, Shannon BA, Cohen RJ (2006) Incidental renal tumours: the frequency of benign lesions and the role of preoperative core biopsy. *BJU Int* 97:946–949
- Volpe A, Mattar K, Finelli A et al (2008) Contemporary results of percutaneous biopsy of 100 small renal masses: a single center experience. *J Urol* 180:2333–2337
- Shannon BA, Cohen RJ, de Bruto H, Davies RJ (2008) The value of preoperative needle core biopsy for diagnosing benign lesions among small, incidentally detected renal masses. *J Urol* 180:1257–1261 discussion 61
- Neuzillet Y, Lechevallier E, Andre M, Daniel L, Coulange C (2004) Accuracy and clinical role of fine needle percutaneous biopsy with computerized tomography guidance of small (less than 4.0 cm) renal masses. *J Urol* 171:1802–1805
- Millet I, Curros F, Serre I, Taourel P, Thuret R (2012) Can renal biopsy accurately predict histological subtype and Fuhrman grade of renal cell carcinoma? *J Urol* 188:1690–1694
- Leveridge MJ, Finelli A, Kachura JR et al (2011) Outcomes of small renal mass needle core biopsy, nondiagnostic percutaneous biopsy, and the role of repeat biopsy. *Eur Urol* 60:578–584
- Lebret T, Poulain JE, Molinie V et al (2007) Percutaneous core biopsy for renal masses: indications, accuracy and results. *J Urol* 178:1184–1188 discussion 8
- Abel EJ, Culp SH, Matin SF et al (2010) Percutaneous biopsy of primary tumor in metastatic renal cell carcinoma to predict high risk pathological features: comparison with nephrectomy assessment. *J Urol* 184:1877–1881
- Abel EJ, Carrasco A, Culp SH et al (2012) Limitations of preoperative biopsy in patients with metastatic renal cell carcinoma: comparison to surgical pathology in 405 cases. *BJU Int* 110:1742–1746
- Blumenfeld AJ, Guru K, Fuchs GJ, Kim HL (2010) Percutaneous biopsy of renal cell carcinoma underestimates nuclear grade. *Urology* 76:610–613
- Sobin L, Gospodarowicz M, Wittekind C (eds) (2009) *UICC: TNM classification of malignant tumors*, 7th edn. Oxford, Wiley-Blackwell
- Pignot G, Mejean A, Bernhard JC et al (2014) The use of partial nephrectomy: results from a contemporary national prospective multicenter study. *World J Urol* (Epub ahead of print)
- Eble J, Sauter G, Epstein J, Sesterhenn IA (eds) (2004) *World health organization classification of tumours. In: Pathology and genetics of tumours of the urinary system and male genital organs*. IARCC Press, Lyon
- Fuhrman SA, Lasky LC, Limas C (1982) Prognostic significance of morphologic parameters in renal cell carcinoma. *Am J Surg Pathol* 6:655–663
- Jr Landis Gg Koch (1977) The measurement of observer agreement for categorical data. *Biometrics* 33:159–174
- Barwari K, de la Rosette JJ, Laguna MP (2012) The penetration of renal mass biopsy in daily practice: a survey among urologists. *J Endourol* 26:737–747
- Simhan J, Canter DJ, Sterious SN et al (2013) Pathological concordance and surgical outcomes of sporadic synchronous unilateral multifocal renal masses treated with partial nephrectomy. *J Urol* 189:43–47
- Fendler JP (2003) Non-radiological investigation of cystic renal tumours. *Prog Urol* 13:1402–1405
- Patel N, Cranston D, Akhtar MZ et al (2012) Active surveillance of small renal masses offers short-term oncological

- efficacy equivalent to radical and partial nephrectomy. *BJU Int* 110:1270–1275
25. Delahunt B, McKenney JK, Lohse CM et al (2013) A novel grading system for clear cell renal cell carcinoma incorporating tumor necrosis. *Am J Surg Pathol* 37:311–322
 26. Zigeuner R, Hutterer G, Chromecki T et al (2010) External validation of the Mayo Clinic stage, size, grade, and necrosis (SSIGN) score for clear-cell renal cell carcinoma in a single European centre applying routine pathology. *Eur Urol* 57:102–109
 27. Delahunt B, Cheville JC, Martignoni G et al (2013) The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol* 37(10):1490–1504
 28. Algaba F, Akaza H, Lopez-Beltran A et al (2011) Current pathology keys of renal cell carcinoma. *Eur Urol* 60:634–643