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ORIGINAL ARTICLE

Oncocytoma on renal mass biopsy: is it still the same histology when surgery is performed? Results from UroCCR-104 study

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Abstract

Purpose To describe clinical features of patients with oncocytoma on renal biopsy (RMB), correlation with final histology on surgically treated patients, and predictive factors of discrepancy between RMB and final histology.

Methods This was a retrospective study conducted in the framework of the UroCCR project (NCT03293563). All tumors with oncocytoma on RMB were selected and all pathological reports were reviewed. Patients with the RMB simultaneously performed with a focal treatment, synchronous bilateral tumors and ambiguous RMB report were excluded. Discrepancy between RMB and definitive histology was evaluated using a uni- and multivariable logistic regression analyses model.

Results Overall, 119 tumors with oncocytoma on RMB, from 15 centers, were included. Of those, 54 (45.4%) had upfront surgery and 65 (54.6%) had active surveillance (AS). In renal masses with initial active surveillance, with a median follow-up of 28 months, 23 (19.3%) underwent surgery, 4 (3.4%) received focal treatment and 38 (31.9%) remained on AS. On final pathology, only 51 of the 75 surgically treated tumors (68.0%) had oncocytoma, while 24 presented malignant tumors (mainly chromophobe carcinoma (19.2%), and hybrid oncocytic/chromophobe tumor (HOCT) (6.8%)) leading to a discrepancy of 32.0% between RMB and final pathology. The only predictive factor of a discrepancy between RMB and definitive histology was a biopsy done outside of the center (Odds ratio: 3.22 [95%-confidence interval: 1.08–9.61], $p=0.03$).

Conclusion Despite the increase of RMB in more and more centers, histologic discrepancy between RMB and definitive histology remains significant. This information should be discussed with patients and taken into consideration before treatment decision.

Keywords Renal mass · Renal mass biopsy · Oncocytoma · Partial nephrectomy · Active surveillance

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Abbreviations

RO	Renal oncocytoma
RMB	Renal mass biopsy
AS	Active surveillance
HOCT	Hybrid oncocytic/chromophobe tumor

Introduction

Renal oncocytomas (RO) are the most frequent surgical removed benign tumors, representing 5 to 15% of all lesions in surgical series [1, 2]. The proportion of RO is higher in small tumors [3], and in centers who do not practice routinely renal mass biopsy (RMB) [1].

The use of RMB in the management of renal masses is controversial, and varies substantially among centers and countries [4]. However, due to the good specificity and safety of this procedure [5], the increasing use of focal treatments [6] and active surveillance (AS) [7]), there is a progressive adoption of RMB for the management of small renal masses [8–10].

In case of a diagnosis of RO on RMB, patients could be offered either AS or active treatment [11]. On the one hand, more and more series showed that AS is a safe strategy [12–14]. On the other hand, the reliability of a diagnosis of RO on RMB is often questioned, because of a risk of hybrid oncocytic/chromophobe tumor (HOCT) [15]. Moreover histologic correlation in patients who will have surgery is far from being perfect: discrepancy is observed in one third of the patients in the largest meta-analysis [16]. This unresolved question is manifested by various strategies among urologists in a situation of suspected RO on RMB [17]. Despite the broadcasting of RMB among centers and improvement in characterization of RMB for oncocytic tumors [18], to the best of our knowledge, no studies re-examined the correlation between suspected RO on RMB and definitive histology since the meta-analysis from *Patel* et al. in 2017 (which was based on very small cohorts:maximum 13 patients by cohort, 48 patients overall) [16].

The aim of this study was therefore to analyze the correlation of RMB results with definitive histology in patients who had a suspicion of RO on RMB in a big multicenter database, and to try to find predictive factors of discrepancy.

Methods

Study design

This was a retrospective study conducted in the framework of the UroCCR project (French network of research on kidney cancer, NCT03293563), which is a French multi-institutional prospectively maintained database of patients treated for kidney tumors. All patients received oral and written information about the objectives and methodology of the UroCCR project, and written informed consent was obtained (CNIL authorization number DR-2013-206).

We reviewed the data of all RMB with a diagnosis of oncocytoma ($n=141$) between January 2007 and September 2021. We then excluded the patients who had RMB in the same procedure than a focal treatment ($n=8$), patients with no follow-up ($n=2$) who had a synchronous bilateral tumors ($n=3$). Two patients with bilateral tumors were not excluded because the contralateral renal mass appeared and was biopsied during follow-up. Each center was contacted to review the RMB reports to be sure than there was no ambiguity about the conclusion of oncocytoma (exclusion if a diagnosis of low-grade oncocytic tumors (LOT) ($n=1$) doubt with chromophobe carcinoma ($n=6$), error in filling database ($n=2$)).

The protocol of RMB was quite similar according centers: it was performed under local anesthesia, with a 16–18 gage coaxial needle. The large majority of centers uses a CT guidance, one center uses routinely contrast ultrasound, and another center uses sometimes US guidance for well visible masses. The number of cores varied from 2 to 4 depending on centers, size of tumor and quality of cores realized. Annual amount of RMB performed on each center ranged from 20 to 200 procedures.

Data measurements

Based on the UroCCR database, we evaluated clinical characteristics of patients (age, sex, body mass index, size and side of tumor) and treatments (active surveillance, upfront surgery, upfront focal treatment). For patients who had surgery (upfront or after initial active surveillance), we evaluated pathological characteristics, especially histological subtype. Each center was contacted to know the indication of surgery (tumor size, patient's young age, tumor growth, surgeon's decision, multiple tumors, patient's preference).

Statistical analysis

The statistical analysis consisted of descriptive analyses of clinical data including median, range and percentages.

For the comparison of the different proportion of oncocytoma or malignant tumor according to clinical characteristics, chi-square test was used.

To evaluate potential predictors of discrepancy between RMB and definitive histology, we performed first univariable logistic regression analyses and then included the statistically significant factors in the multivariable logistic regression analyses model.

For all analyses, SPSS version 25.0 (IBM Corp., Armonk, NY, USA) was used. All p values were two-sided and the significance level was set at 0.05.

Table 1 Characteristics of lesions with oncocytoma on renal mass biopsy (119 lesions)

Characteristics	Value
Age (median)	64
Sex	
Male	63 (52.9%)
Female	56 (47.1%)
Side	
Right	74 (62.2%)
Left	45 (37.8%)
Obesity	
Yes	16 (13.4%)
No	96 (80.7%)
No information	7 (5.9%)
Size of tumor	
Median (cm)	4.0
< 4 cm	61 (51.2%)
≥ 4 cm	54 (45.4%)
No information	4 (3.4%)

Results

Patients' characteristics

Among the more than 12 000 patients included in uroCCR database, 119 renal masses (Table 1) from 15 centers were eligible and included (117 patients). The proportion of patients with RMB performed in the contributor centers ranged from 7 to 52%.

Renal masses flow chart is described in Fig. 1. Initially, the majority of lesions had active surveillance (AS) (65 patients, 54.6%), and 54 patients (45.4%) upfront surgery. Median size of the tumor was 4.0 cm. There were 63 (52.9%) males, and 16 (13.4%) obese patients. Median follow-up was 28 months for patients initially in AS.

Surgically treated renal masses are described in Table 2. The main indication of surgery were the tumor size (24 patients, 32.0%) and tumor growth (22 patients, 29.3%). Most patients had partial nephrectomy, except for 4 patients treated by radical nephrectomy. The concordance with definitive histology was 68.0%. In case of discrepancy, the most frequent tumor was chromophobe

Fig. 1 Study flow-chart

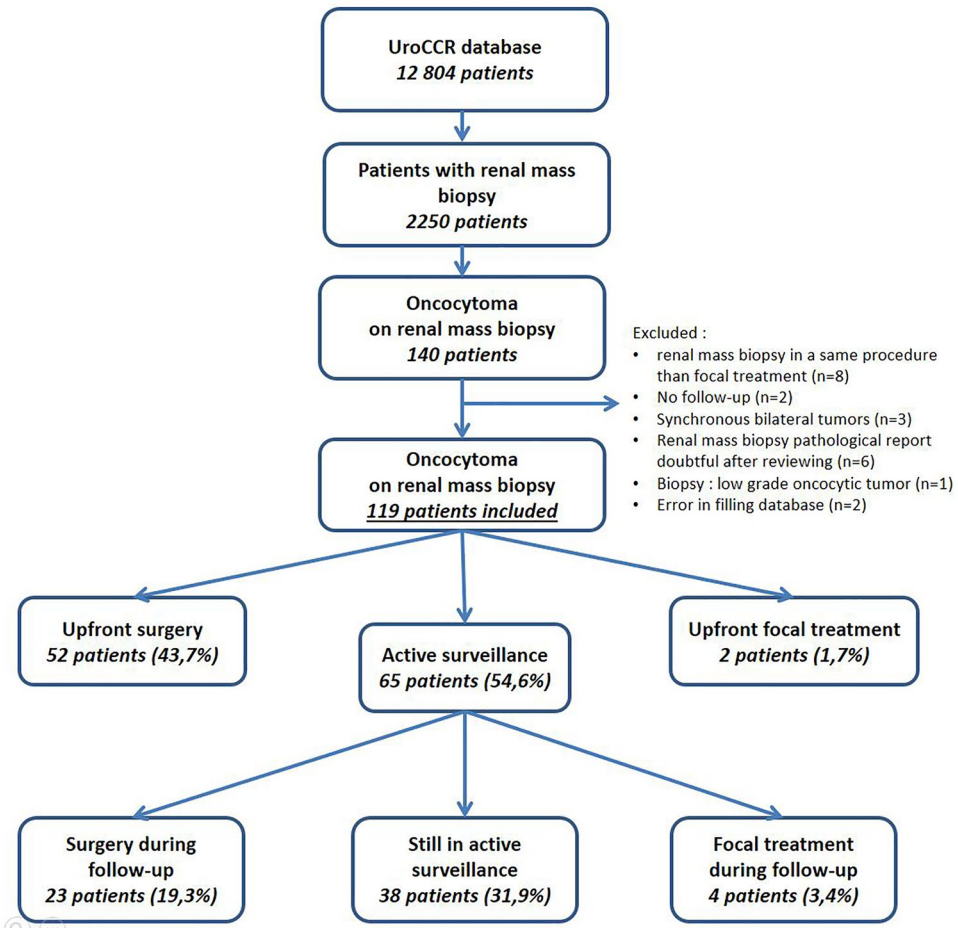

Table 2 Characteristics of tumors with oncocytoma on renal mass biopsy, surgically treated (75 lesions)

Characteristic	Value
Age	
Time between RMB and surgery	
If upfront surgery (median, in month)	3
If first active surveillance (median, in month)	26
Sex	
Male	34 (45.1%)
Female	41 (54.9%)
Side	
Right	50 (69.0%)
Left	25 (31.0%)
Size tumor	
Median (cm)	4.5
< 4 cm	25 (31.0%)
≥ 4 cm	50 (69.0%)
Indication of surgery	
Tumor size	24 (32.0%)
Tumor growth	22 (29.3%)
Surgeon's decision	17 (22.7%)
Patient's young age	6 (8.0%)
Multiple tumors in the kidney	3 (4.0%)
Patient's preference	3 (4.0%)
Surgery	
Partial nephrectomy	71 (94.4%)
Total nephrectomy	4 (5.6%)
Robotic surgery	50 (69.0%)
Histology	
Oncocytoma	51 (68.0%)
Chromophobe carcinoma	14 (19.2%)
Hybrid oncocytic/chromophobe tumor	5 (6.8%)
Clear cell renal carcinoma	2 (2.7%)
Oncocytic papillary renal cell carcinoma	2 (2.7%)
Unclassified renal cell carcinoma	1 (1.4%)
Surgical margins	
Negative	73 (97.3%)
Positive	2 (2.7%)

carcinoma (14 patients; 19.2%) and HOCT (5 patients, 6.8%).

Regarding the sixty five patients in AS, with a median follow-up of 28 months, more than half (58.5%, 38 patients) remained in AS at last follow-up.

Discrepancy between RMB and definitive histology

Table 3 summarizes clinical features of patients with or without discrepancy between RMB and definitive histology. When biopsy was done outside of the center, the proportion of patients who had a malignant tumor on definitive histology was 52% versus 20.8% when RMB was done in the center ($p = 0.004$). Male sex was also associated with discrepancy: 47.1% versus 19.5% on females ($p = 0.006$). Age, size of tumor, upfront surgery or any other indication of surgery were not associated with discrepancy.

Table 3 Renal masses with oncocytoma on biopsy surgically treated: discrepancy between renal mass biopsy and final histology according to patient characteristics

Characteristic	Oncocytoma on histology	Malignant tumor on histology	p
All patients	51 (68.0%)	24 (32.0%)	
Age			0.35
< 60 years	26 (63.4%)	15 (36.6%)	
≥ 60 years	25 (73.5%)	9 (26.5%)	
Size of the tumor			
< 4 cm	19 (76.0%)	6 (24.0%)	0.29
≥ 4 cm	32 (64.0%)	18 (36.0%)	
Sex			
Male	18 (52.9%)	16 (47.1%)	**0.004**
Female	33 (80.5%)	8 (19.5%)	
Obesity (body mass index ≥ 30)			
No	43 (69.4%)	19 (30.6%)	0.23
Yes	5 (50.0%)	5 (50.0%)	
Biopsy			
Done in the center	38 (79.2%)	10 (20.8%)	**0.006**
Outside of the center	12 (48.0%)	13 (52.0%)	
Missing	1	1	
Indication of surgery			
Tumor size	17 (70.8%)	7 (29.2%)	0.71
Tumor growth	15 (68.2%)	7 (31.8%)	0.89
Surgeon's decision	10 (58.8%)	7 (41.2%)	0.35
Patient's young age	5 (83.3%)	1 (16.7%)	0.40
Multiple tumors in the kidney	2 (66.7%)	1 (33.3%)	0.96
Patient's preference	2 (66.7%)	1 (33.3%)	0.96
Upfront surgery			
Yes	36 (69.2%)	16 (30.8%)	0.73
No	15 (65.2%)	8 (34.8%)	

In multivariable logistic regression analysis, only biopsy outside the center remained a significant predictive factor: OR 3.22 [1.08–9.61]; $p = 0.03$, (regarding male sex, OR was 2.78 [0.94–8.29], $p = 0.06$).

Median follow-up since the time of RMB was 20 months for all patients. Regarding patients who had a malignant tumor, no patients had a metastatic recurrence and one patient had a local recurrence treated by focal treatment. Regarding other patients, 3 had a recurrence, all in contralateral kidney (one treated by surgery (oncocytoma again), 2 in active surveillance).

Discussion

Our study showed that almost one third of tumors with a suspected diagnosis of RO on RMB appeared malignant on final histology, and biopsy performed outside of the center was the only predictive factor of discrepancy.

Despite the widespread use of RMB among centers and increasing experience in pathologists, this proportion of discrepancy is still surprisingly high, and comparable to Patel et al. [16]. However, the repartition of histological subtypes is quite different with a majority of chromophobe carcinoma and HOCT. Only 3 patients (4.1%) of patients had non-oncocytic tumors. This seems more logical than a majority of renal cell carcinoma described in the meta-analysis (where no pathological or pathological reports were reviewed). Despite rigorous selection of patients after reviewing pathological reports in our study, the discrepancy between RMB and definitive histology remained comparable (32.0%).

Several explanations could be proposed to explain the discrepancy. First, affirming a diagnosis of RO on small samples of RMB can be challenging and need expertise [18–20]. This expertise could be related to technical aspects of sampling done by the radiologist (accuracy of guidance, number of cores taken), or the analyzes and experience of the pathologist. Sub typing of renal tumors is done even more easily and with a high level of certainty since the sampling of the tumor is important. This is valid for surgical and biopsies specimens. Small mass size was reported in the literature to be the most predictive factor of a non-diagnostic biopsy [21].

The exhaustivity of sampling allows to see the histological morphology of different components but also to have enough tissue material for immunohistochemical (IHC) and genetic analyzes. Another reason for the difficulty of pathological diagnosis, moreover on biopsy, is the evolution of the classification [22], with new entities described, modification of the definitions of entities and the recommendation to use new diagnostic tools (IHC, genetics). All these factors could explain the highest discrepancy observed when biopsy was done out-of-institution in our study.

Second, this surgical cohort may be associated to a selection bias, with an increased proportion of malignant tumors in comparison with AS cohorts of RO found on RMB (93% of accordance described in 14 patients by Deledalle et al. 100% of accordance described in 5 patients by Liu et al. [23]). Third, because of tumor's heterogeneity in HOCT, RMB could not catch the whole characteristics of the tumor [15].

This study shouldn't be interpreted as an advocacy to reject RMB strategy in the management of renal masses. Despite of these results, several arguments advocate in favor of AS strategy concerning RO on RMB. Indeed, in small renal masses, AS has been proven to be a safe option in biopsy proven malignant tumors [7]. Moreover, chromophobe carcinomas have a low aggressive profile and small probability to develop metastasis in the majority of the cases, especially if they do not harbor sarcomatoid features [24].

AS can also be considered in confounding entities. WHO 2022 classification introduce the "Other oncocytic tumors of the kidney" subgroup [22].This subgroup is define as a heterogeneous tumor group of oncocytic tumors not classifiable as oncocytoma, chromophobe renal cell carcinoma (ChRCC), or other tumor types with eosinophilic features. Authors precise that these tumors are typically indolent.

Furthermore, AS is the best way to prevent overtreatment, as Neves et al. reported a complication Clavien–Dindo grade 3 or more in 4% of patients with RO managed by surgery [25]. In addition, renal function does not seem to be impaired in AS for RO [13].

In light of the results of our study, honest but not too much alarmist information should be given to patients, namely that a malignant tumor cannot be strictly ruled out by a result of RO on RMB, but AS remains a safe option. Treatment strategy should be then decided considering multiple cofactors (such as patient age, comorbidities, anxiety, tumor size and growth) to assess the benefit/risk ratio, in a shared-decision making process. Besides, if AS is chosen, the window of the possibility of conservative treatments options (partial nephrectomy, focal treatments) should not be missed during follow up if tumor size is increasing [26].

To improve the reliability of a diagnosis of RO on RMB, other tools could be added to strengthen the probability of a benign tumor such as MRI [27], 99mTc-sestamibi SPECT/CT [28], or artificial intelligence [29]. On the one hand, although interesting results are published, data are still preliminary and these devices are not very implemented. On the other hand, these tools have been rather developed to avoid RMB.

Furthermore, as expertise in renal biopsy seemed the only predictive factor of discrepancy in our study, second pathological opinion review of the specimen should be proposed when RMB report is doubtful or seem insufficient (no immunohistochemistry), especially when management could be different depending on tumor malignity (surgery versus AS for example).

Our study has several limitations. First, there was no centralized pathological review of the RMB. However, all pathological reports were reviewed again to ensure that there was no ambiguity regarding the finding of oncocytoma. Moreover, patients with a diagnosis of low grade or high grade oncocytic tumors on RMB were excluded as these entities were only recently added [30]. Second, the

number of patients is rather small, but comparable or even higher than previous studies. This may be due to the fact that most patients with small renal masses are still offered upfront surgery for either diagnosis and therapeutic purpose. Patients with suspected RO on RMB are also often proposed AS. Third, surgical cohorts drive an indisputably bias of selection. Clinical and pathological features of this cohort may not be the same compared to all patients with a suspected RO on RMB. However, in our study, there was no difference between patients according to the time of surgery (upfront or after AS) or to the indication of surgery (surgeon's decision, size, growth). Fourth, no precise data were available about tumors growth, to find an association between high tumor growth and malignant histology. Fifth, a significant disparity in the correlation between RMB and biopsies was observed between centers. Caution is warranted to generalize the results.

Conclusion

Despite the increase of RMB in more and more centers, histologic discrepancy between RMB and definitive histology remains significant (32.0%) and similar to older studies. However, most of the time if a malignant tumor was found, it had a low aggressive profile (chromophobe carcinoma or HOCT). This information should be discussed with patients and taken into consideration before treatment decision.

Author contribution BN: protocol/project development, data collection or management, data analysis, manuscript writing/editing. BP: data collection or management, manuscript writing/editing. PG: manuscript writing/editing. LV: Data analysis. AF: data collection or management, manuscript writing/editing. PB: data collection or management. DN: data collection or management. BM: data collection or management. XE: data collection or management, manuscript writing/editing. BR: data collection or management, manuscript writing/editing. RM: data collection or management. CC: data collection or management. NF: data collection or management. LH: data collection or management. CT: data collection or management. AD: manuscript writing/editing. MR: data collection or management. BK: data collection or management. BJ-C: data collection or management.

Data availability The data that support the findings of this study are available from the corresponding author, Nicolas Branger, upon reasonable request.

Declarations

Conflicts of interest None.

Research involving human participants and/or animals This was a retrospective analysis, no interventional actions were done, only data collection.

Informed consent All patients gave informed and written consent, in accordance to the UroCCR project (French network of research on kidney cancer, NCT03293563).

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