Percutaneous biopsy of small renal mass: can diagnostic accuracy be affected by hospital volume?

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Introduction High diagnostic performance and low morbidity for renal tumor biopsy (RTB) have been described in highly experienced centers. Here we present the five-year experience of our institute in performing RTB. The protocol used, the safety profile and the diagnostic accuracy obtained were analyzed.

Material and methods The study is a retrospective single-institution clinical data review of 84 consecutive RTB of small renal masses. Post-biopsy complications were reported using the Clavien-Dindo system. To measure the concordance between biopsy and nephrectomy specimens regarding histological subtype and International Society of Urological Pathology/World Health Organization (ISUP/WHO) renal cell carcinoma grade, the kappa coefficient of Cohen was used.

Results Median (IQR) follow-up time was 44 (29–58) months. In total, 94% of RTB procedures were free of complications; when complications did occur, 80% were grade I and 20% were grade II. No cases of tumor seeding were observed. Combining the first and repeated biopsies the overall diagnostic rate was 85.8%. Overall, 79.1% of diagnostic RTB were malignant. In 42 surgically treated patients, the concordance between the histological results of biopsies and surgical specimens was very good for histological subtypes (k = 0.87) and moderate for tumor grade (k = 0.51).

Conclusions RTB resulted in a high safety profile. The overall diagnostic rate was 85% and an unnecessary intervention was avoided in 21% of patients. RTB showed a very good accuracy in determining the histological subtype of renal cancer while it was moderate for the tumor grade. These results are similar to those reported in larger series and support feasibility of this procedure in low-volume centers.

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INTRODUCTION

In the last decades, the increasing number of abdominal imaging techniques performed in the general population for non-urological complaints in regimen of health prevention, oncological follow-up or due to the care of other medical conditions has led to a significant increase in the diagnosis of small, asymptomatic renal tumors.

In the context of available diagnostic tools to predict the histological pattern of these lesions, contrast enhanced multi-phasic computed tomography (CT) and magnetic resonance imaging (MRI) have shown high diagnostic accuracy in predicting the malignancy risk for renal masses and complex renal cysts with solid pattern [1]. However, CT and MRI are unable to distinguish oncocytoma and fat-free angiomyolipoma from malignant renal neoplasms [2–5].

As a consequence, the malignancy of some renal lesions cannot be assessed with the use of imaging techniques alone leading to up to 30% of kidney masses, surgically managed, being benign at the final histological examination [6].

Percutaneous renal tumor biopsy (RTB) is a method that allows to obtain a histological report of radiologically indeterminate renal masses to plan the appropriate management and to avoid the risk of an over-treatment with the related collateral risks.

Strong recommendation for this procedure is to obtain histology before ablative treatments or systemic targeted therapy in the setting of metastatic disease without previous pathology [7].

Initial concerns about the oncological safety and the diagnostic performance of RTB have been significantly reduced in the last years by the evidence that this procedure, if performed in highly experienced centers, is able to guarantee a high accuracy in the diagnosis of malignancy and histologic subtype, with very low associated morbidity [8].

The aim of this article was to show the recent experience of a low-volume center in performing RTB since its introduction. The protocol used, the safety profile of the procedure and the diagnostic accuracy obtained were analyzed and compared with the available literature.

MATERIAL AND METHODS

The study is a retrospective single-institution review of 78 consecutive patients undergoing RTB between April 2013 and July 2018 at the Regional Hospital of Bellinzona, Switzerland. Inclusion criteria were patients with radiological diagnosis of indeterminate renal mass less than 4 cm in maximum diameter. Exclusion criteria were renal mass showing classic radiological appearance of an angiomyolipoma, cystic renal masses and patients with competing risk for whom watchful waiting was recommended.

The study was performed following the principles outlined in the Declaration of Helsinki and after institutional review board approval.

Medical histories of all patients were collected, including the body mass index and chronic pharmacological therapy [with particular concern to antiplatelet therapy (APT) or oral anticoagulant (OAC) use]. Comorbidities were scored using the American Society of Anesthesiologists [9] and the Charlson Comorbidity Index [10] scores. Lesions' characteristics were revised including laterality and size; the R.E.N.A.L. nephrometry score [11] was used as anatomical classification system. Post-biopsy complications were reported using the Clavien-Dindo system [12].

Renal tumor biopsy procedure

Before RTB the patients were screened for any coagulation defects. Patients were advised to discontinue APT 7 days before the procedure and OAC 5 days before with another pre-procedure blood coagulation control.

RTBs were performed in an outpatient setting, before the procedure antibiotic prophylaxis was performed by an intravenous single-dose of third-generation cephalosporin.

All biopsies were performed by a single radiologist (R.B.) experienced in percutaneous procedures.

Percutaneous sampling was performed under local anaesthesia and sedation. The procedures were performed under intermittent CT guidance, using a geometric grid placed over the patient's skin. The patient was positioned in a prone, semi-prone or lateral decubitus position, as appropriate.

The radiologist computed the distance of the lesion from the skin, the exact skin point of entry, the necessary length and inclination of the needle. For core biopsy (CB), an 18 or 20 G needle loaded in automated biopsy gun is used through a co-axial guiding cannula to obtain cores of 15 mm in minimum length and to avoid potential tumor seeding. The needle track is accurately designed to avoid major nerve trunks and blood vessels.

Multiple core tissue samples were performed (1 central and 1 or 2 peripheral biopsies) [13]. Necrotic or hemorrhagic areas in the context of a given mass were possibly avoided [14, 15]. Specimen quality was assessed by the operator and if not satisfactory, a further sample was taken. The CB samples are immediately fixed in 10% formalin solution; paraffin embedded blocks are obtained and three 4-Uμ levels are cut from each block, of which two are stained with hematoxylin and eosin.

After the procedure, the patients remained under observation and underwent an ultrasound check after a 4-hour interval. In the absence of clinical complications, the patients were then discharged.

Histological analysis

All pathologic specimens were processed according to standard protocol for surgical procedures (i.e. partial or total nephrectomy) and CB samples, as previously illustrated.

A dedicated genitourinary pathologist (J.B.) reviewed all histological preparations in accordance with the most recent World Health Organization (WHO) classification [16]. International Society of Urological Pathology/WHO (ISUP/WHO) grade was reported for clear and papillary renal cell carcinoma; when

different grades were present in the specimen, the highest was reported. The term 'undefined carcinoma/malignancy' was used when the histological subtype was not identifiable; samples containing only normal tissues or not permitting a definite diagnosis were labelled as 'non-diagnostic biopsy'. In resection specimens, where biopsy tract was macroscopically identifiable through suggestive features (such as fat necrosis, hemorrhage, fibrosis in the perinephric fat and hemorrhagic foci in the capsular tissue), the possible presence of tumor seeding was also examined [17].

Statistical analysis

Quantitative data were summarized as mean with standard deviation or median with interquartile range. Qualitative data were presented as absolute numbers with percentages. Comparisons of data between diagnostic and non-diagnostic RTB were performed by using the Mann-Whitney, chi-square or Fisher exact test, as appropriated. To measure the concordance between biopsy and surgical results, the kappa coefficient of Cohen (k) was used. The degree of agreement was considered poor for k <0.2, fair for k = 0.21–0.40, moderate for k = 0.41–0.60, good for k = 0.61–0.80 and very good for k >0.81. All tests were two-sided and p-value <0.05 was considered significant. All statistical analyses were performed with Stata 15 (StataCorp LP, College Station, TX, USA).

RESULTS

Table 1 shows the clinical features of patients and renal lesions. Table 2 shows technical and post-operative data with annual biopsy volume. Median (IQR) follow-up time was 44 (29–58) months. No intra-operative complications were recorded. One of five patients affected by post-operative peri-renal hematoma required antibiotic and analgesic therapy (Clavien grade II). One event occurred in a repeated biopsy. No cases of tumor seeding were identified on histological examination of nephrectomy specimens or observed during clinical follow-up.

The detailed list of RTB histological results is shown in Table 3. The first biopsy was non-diagnostic in 16/78 patients (20.5%). At the time of analysis, 5 of the 16 patients with first non-diagnostic biopsies underwent re-biopsy, which was found to be diagnostic in 4 (80%) cases (3 clear cell renal carcinoma and 1 oncocytoma). The patient with a second non-diagnostic biopsy underwent a third biopsy whose results were compatible with lymphoma. Combining the first and repeated biopsies, the overall diagnostic

Table 1. *Clinical data and renal mass characteristics of patients undergoing renal tumor biopsies (n = 78)*

Variable	
Age (years), mean ±SD	64.4 ±11.2
Gender, n (%)	
Male	60 (76.9)
Female	18 (23.1)
BMI (kg/m²), mean ±SD	27.1 ±4.7
Kidney biopsied, n (%)	
Right side	44 (56.4)
Left side	34 (43.6)
R, n (%)	
1	78 (100)
E, n (%)	
1	55 (70.5)
2	17 (21.8)
3	6 (7.7)
N, n (%)	
1	11 (14.1)
2	11 (14.1)
3	56 (71.8)
A/P, n (%)	
a	26 (33.3)
p	29 (37.2)
x	23 (29.5)
L, n (%)	
1	29 (37.2)
2	31 (39.7)
3	18 (23.1)
H, n (%)	
Yes	3 (3.9)
No	75 (96.1)
R.E.N.A.L. score, n (%)	
4	3 (3.8)
5	10 (12.8)
6	21 (26.9)
7	20 (25.6)
8	17 (21.8)
9	5 (6.4)
10	2 (2.6)
Tumor size (mm), median (IQR)	28 (24–32)
APT/OAC, n (%)	
No	48 (61.5)
APT	26 (33.4)
OAC	4 (5.1)
ASA score, n (%)	
0	1 (1.3)
1	18 (23.1)
2	23 (29.5)
3	22 (28.2)
4	14 (17.9)
CCI score, n (%)	
0	9 (11.5)
1	8 (10.3)
2	15 (19.2)
3	12 (15.4)
4	17 (21.8)
5	16 (20.5)
6	1 (1.3)

ASA – American Society of Anesthesiologists; APT – antiplatelet therapy; BMI – body mass index; CCI – Charlson comorbidity index; IQR – inter-quartile range; OAC – oral anticoagulants; n – number; SD standard deviation; R – radius; E – exophytic/endophytic; N – nearness to collecting system or sinus; A/P – anterior/posterior; L – location relative to polar lines; H – hilar tumor

Table 2. *Technical and post-operative clinical data of percutaneous renal tumor biopsy procedures (n = 84)†*

Variable	
Technique, n (%)	
CB	84 (100)
Type of imaging used, n (%)	
Computed tomography scan	84 (100)
Number of sampling performed, n (%)	
2	51 (60.7)
3	33 (39.3)
Size of needle, n (%)	
CB	
20G	71 (84.5)
18G	13 (15.5)
Procedures affected by complications, n (%)	
Yes	5 (6.0)
Perirenal hematoma	5
No	79 (94.0)
Clavien Grade, n (%)	
0	79 (94.0)
I	4 (4.8)
II	1 (1.2)
Biopsy procedures per year, n (%)	
1st	10
2nd	12
3th	18
4th	21
5th	23
Annual biopsy volume, mean ±SD	16.8 ±5.6

CB – core biopsy; G – gauge; n – number; SD – standard deviation; † – repeated biopsies included

Table 3. *Histological data*

Variable	
Percutaneous renal tumor biopsy procedures (n = 84)†	
Pathology, n (%)	
Benign	14 (16.7)
Malignant	53 (63.1)
Non-diagnostic	17 (20.2)
Samples' diagnosis, n (%)	
Clear cell carcinoma	30 (44.7)
Clear and papillary cell carcinoma	1 (1.5)
Papillary carcinoma	9 (13.4)
Colic adenocarcinoma	2 (3.0)
Oncocytoma	10 (14.9)
Chromophobe carcinoma	3 (4.5)
Undefined carcinoma	3 (4.5)
Angiomyolipoma	4 (6.0)
Melanoma	1 (1.5)
Lymphoma	3 (4.5)
Myeloma	1 (1.5)
Tumor grade, n (%)‡	
1	18 (45.0)
2	20 (50.0)
4	2 (5.0)
Patients undergoing renal surgery (n = 42)	
Nephrectomy, n (%)	
Partial	26 (61.9)
Total	16 (38.1)
Pathology, n (%)	
Benign	0 (0.0)
Malignant	42 (100)
Histological diagnosis, n (%)	
Clear cell carcinoma	25 (59.5)
Clear and papillary cell carcinoma	2 (4.8)
Papillary carcinoma	9 (21.4)
Colic adenocarcinoma	1 (2.4)
Chromophobe carcinoma	5 (11.9)
Tumor grade, n (%)‡	
1	9 (25.0)
2	21 (58.3)
3	4 (11.1)
4	2 (5.6)

n – number; †- repeated biopsies included; ‡- clear and papillary renal cell carcinoma

rate reaches 85.8% (67/78 patients). Considering the diagnostic biopsies, 79.1% (53/67 patients) results were malignant and 20.9% (14/67 patients) benign. Considering the outcome of the first biopsy, the diagnostic and non-diagnostic patients groups do not differ in any of the clinical variables described (Table 4).

A total of 6 of the 7 patients diagnosed with metastasis of extra-renal tumor were referred to medical oncologic therapy; one was diagnosed with metastatic colonic adenocarcinoma and underwent total nephrectomy.

Of the remaining 46 patients diagnosed with renal malignancy (3 with undefined carcinoma), 42 were treated in our institution with partial or total nephrectomy. The histological diagnoses performed on surgical specimens are shown in Table 3.

In the sub-group of patients undergoing surgery, the concordance between RTB histology and surgical pathology was 92.3% for histological subtype and 70.9% for tumor grade. The agreement between the histological results of biopsies and surgical specimens was found to be very good for the variable histological subtype [kappa coefficient 0.87 (95%-CI: 87.38 ±19.1)] while it was moderate as to the tumor grade [kappa coefficient 0.51 (95%-CI: 51.05 ±25.08)].

DISCUSSION

Since the last fifteen years the literature has reported increasingly more evidence that the RTB procedure is safe and has a high diagnostic rate in high-volume centers, even though the quality of evidence remains moderate [8]. The widespread current use of RTB is unquestionably associated with the clinical need for an efficient diagnostic tool in the presence of an increasing number of early diagnoses of small renal masses, by exploiting the current technical advances of interventional radiology.

This trend has also affected our center which, in recent years, has introduced and increasingly performed this procedure (Table 2). In our first five-year experience shown here, the overall diagnostic

Table 4. *Clinical characteristics of patients, tumors and procedures stratified according to the outcome of the first biopsy*

Variable	Diagnostic RTB N = 62	Non-diagnostic RTB N = 16	P-value
Gender, n (%)			
Male	49 (79.0)	11 (68.7)	0.38
Female	13 (21.0)	5 (31.3)	
Age (yrs), median (IQR)	66 (54–74)	68 (59–75)	0.81
BMI (kg/m², median (IQR)	26 (24–31)	26 (24–30)	0.27
R.E.N.A.L. score, median (IQR)	7 (6–8)	6 (6–7)	0.55
Tumor side, n (%)			
Left kidney	28 (45.2)	6 (37.5)	0.58
Right kidney	34 (54.8)	10 (62.5)	
Tumor location, n (%)			
Upper pole	21 (33.9)	5 (31.3)	
Middle	14 (22.6)	4 (25.0)	0.97
Inferior pole	27 (43.5)	7 (43.8)	
Tumor location, n (%)			
Anterior	22 (35.5)	4 (25.0)	
Posterior	22 (35.5)	7 (43.8)	0.73
No A/P	18 (29.0)	5 (31.3)	
Size of needle, n (%) CB			
20G	48 (82.8)	11 (100)	0.34
18G	10 (17.2)	0 (0.0)	
Number of sampling performed, n (%)			
2	41 (66.1)	9 (56.3)	0.46
3	21 (33.9)	7 (43.7)	
APT/OAC, n (%)			
No	41 (66.1)	7 (43.8)	0.17
APT/OAC	21 (33.9)	9 (55.7)	
ASA, n (%)			
0	1 (1.6)	0 (0.0)	
1	14 (22.6)	4 (25.0)	
2	18 (29.0)	5 (31.3)	0.39
3	20 (32.3)	2 (12.5)	
4	9 (14.5)	5 (31.3)	
CCI, n (%)			
0	8 (12.9)	1 (6.3)	
1	7 (11.3)	1 (6.3)	
2	13 (20.9)	2 (12.5)	
3	10 (16.1)	2 (12.5)	0.37
4	13 (20.9)	4 (25.0)	
5	11 (17.7)	5 (31.3)	
6	0 (0)	1 (6.3)	
Biopsy procedure year, n (%)			
1st	7 (11.3)	3 (18.7)	
2nd	9 (14.5)	1 (6.3)	
3th	15 (24.2)	3 (18.7)	0.68
4th	16 (25.8)	3 (18.7)	
5th	15 (24.2)	6 (37.6)	

APT – antiplatelet therapy; ASA – American Society of Anesthesiologists; BMI – body mass index; CB – core biopsy; CCI – Charlson comorbidity index; IQR – inter–quartile Range; OAC – oral anticoagulants; n – number; A/P – anterior/posterior

rate of the RTBs was 85.8%. This rate is lower than the median value of 92% reported in a recent meta-analysis [8] but still in the IQR range (80.6–96.8%). In this context, the literature on RTB diagnostic rate is limited by different definitions of non-diagnostic biopsy used and different rates of repeated biopsies performed.

For the purpose of our study we used a stringent definition of non-diagnostic biopsy, including biopsies with fibrin, fibrous tissue only or normal renal parenchyma.

As to the second issue, the role of repeat biopsy (i.e. its ability to increase the overall RTB diagnostic rate) is limited by the fact that in the literature only a small number of patients among those with an initial non-diagnostic biopsy underwent this procedure [18].

Among the most numerous published RTB series, Richard [19] reported a second biopsy diagnostic rate of 83% in 24, Hu [20] of 82% in 17 and Jeon [21] of 100% in 11 patients, respectively.

In the majority of cases the diagnosis was of malignancy. Similar data was shown by Leveridge [22] in a series of 345 patients (first RTB diagnostic rate 80.6%). Repeat biopsy was diagnostic in 83% (10/12) of cases, eight of which were malignant. Moreover, pathologic examination showed a malignant lesion in 11 (73%) of 15 masses referred to surgical treatment on the first biopsy. In our series, a second biopsy was repeated in 4 out of 16 (25%) patients, with a diagnostic rate of 80%. In 3 cases the diagnosis was of malignant tumor. Taken together, these data show that the first and second biopsy have similar diagnostic rate and, more importantly, that a non-diagnostic biopsy should not be considered a surrogate for the absence of malignancy.

Although in a recent series of 95 RTB Seager [23] reported a similar diagnostic rate in mass groups with ≤2, >2 – ≤3 and >3 – ≤4 cm in diameter, small tumor size (<2 cm [20, 22, 24, 25] or difference per 1 cm of mass increase [22]) resulted the most common described risk factors for non-diagnostic RTB outcome. Other described anatomical risk factors are anterior and upper pole location [26], exophytic growth [19] and cystic nature [21, 23, 25]. Regarding the latter, Prince [25] showed that cystic masses have the highest rate of non-diagnostic outcome (40%) and a recent meta-analysis confirmed that the sensitivity of RTBs for cystic renal masses is inferior to that for solid masses [8]. Furthermore, cystic RTB has the potential risk of tumor cells seeding resulting from cystic rupture during biopsy. Because of these concerns, as a protocol policy, RTBs of cystic lesions were not performed.

In this context, considering the outcome of the first biopsy, in our series we failed to identify possible patient or renal mass characteristics associated with diagnostic or non-diagnostic group.

As a quality index to investigate the agreement between RTB and surgical histology we used the kap-

pa value. In a meta-analysis Marconi [8] observed a good (median k value = 0.63) and fair (median k value = 0.34) agreement between histologic subtype and Fuhrman grade on RTB and surgical specimen, respectively. In our series, we reported better values than the median values calculated in this analysis for both the histological subtype and the ISUP/WHO tumor grade. Our results appear similar to those reported by Bernhard [27], which showed in 117 cases described an excellent result in terms of RTB histological subtype characterization (k = 0.88) while Fuhrman grade resulted in a moderate concordance level (k = 0.49). Likewise, in 61 patients, Millet [28] found a moderate agreement (k = 0.52) for Fuhrman nuclear grade between biopsy and surgery but a perfect biopsy-surgery agreement for histological subtype (k = 1). Likewise, in our series the concordance between RTB histology and surgical pathology was 92.3% for histological subtype and, using the most detailed four-grade system, 70.9% for tumor grade. In fact, tumor grade concordance between RTB and surgical specimen is different among studies depending on the classification system used. The median concordance was 66.7% but increased to 86.5% when a low (grade 1–2) and high (grade 3–4) grading system was used [9]; Blumenfeld [29] reports using a four-grade system that the biopsy may underestimate the grade of the tumor in up to 55% of cases. This is an important limitation to keep in mind when evaluating the RTB outcome in particular in the context of an active surveillance regimen. The likelihood of grading discordance seems to be independent of tumor size [23]. In the present series, the RTB procedures were burdened by a complication rate of 6% (5 cases), all represented by peri-renal hematoma treated conservatively and with spontaneous resolution (80% grade I

and 20% grade II). Our rate is lower than the median overall rate of 8% of the studies in which complications after RTB are reported and similar to the median incidence of 5% for peri-renal hematomas [9]. Of note, our protocol provides the execution of a routine post-RTB ultrasound imaging to detect the presence of this complication, not performed in some series [18].

The present study has many limitations. First, it is a single-institution retrospective data collection. Second, the sample size may have limited the achievement of significant results. However, the number of procedures performed is not negligible if contextualized in the clinical practice of a non-academic regional center.

Third, it was not possible to investigate the role of radiologist learning curve on RTB outcome or the inter-observer concordance for tumor grade assessment, found fair (k = 0.25) by other authors [30].

CONCLUSIONS

The present study shows the five-year experience of a single low-volume center performing percutaneous biopsies of small renal masses. The procedure resulted in a high safety profile in terms of morbidity. The overall diagnostic rate was 85% and an unnecessary intervention was avoided in 21% of these patients. The procedure showed a very good accuracy in determining the histological subtype while it was moderate for the ISUP/WHO grade. These results are similar to those reported in the literature, supporting the current feasibility of this procedure in low-volume centers.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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