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TOPIC PAPER

# Renal tumor biopsy: indicators, technique, safety, accuracy results, and impact on treatment decision management

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## Abstract

**Context** Renal tumor biopsy (RTB), as distinct from the more common renal biopsy for medical renal disease, is an option for patients with renal masses. It is mainly used for small renal masses (SRM) but it may also be indicated for larger masses and even in the presence of metastatic disease. Its main indication in SRM is to avoid intervention for benign kidney tumors but increasingly enables more personalized treatment for kidney cancer patients.

**Objective** The objective of this paper is to provide a comprehensive review of the most recent literature available for RTB including the indications, the technique and also the possible complications.

**Results** The urological community continues to optimize the indications for RTB. Non-operative treatment modalities, such as active surveillance, ablative modalities, and immunotherapy, may have different results influenced by tumor histology. Continuing concern regarding complications and accuracy and, therefore, the utility of RTB has been addressed. Recent reports support the potential benefit of RTB, safely avoiding a significant number of interventions with good results and minimal complications.

**Conclusion** Urologists should be aware of the benefits of RTB and develop experience with this technique to optimize the results. This diagnostic strategy should be discussed with patients and adopted as it has been with other solid tumors.

**Keywords** Kidney cancer · Active surveillance · Small renal mass · Renal tumor biopsy

## Introduction

### Indications for renal tumor biopsy

Incidental renal lesions are found in 13–27% of abdominal imaging studies [1], but most are small, simple cysts. However, many of the rest are clinically significant. Most tumors that are suspicious of malignancy, particularly the smaller ones, are frequently benign or low-grade tumors [2] and RTB can define the histology. The role for RTB can be considered in multiple additional scenarios, including patients with larger renal masses and even metastases. For small renal masses ($SRM^x$—the superscript x can be added to identify those that have not undergone a diagnostic biopsy), the indications for RTB vary among centers. It can be used for treatment decision making, e.g., by characterizing as benign, low-risk malignant, or high-risk malignant [3], to exclude lymphoma or an abscess (specially if the imaging look infiltrative) [4, 5] or to confirm success after an ablative modality [6]. When the RTB is done at the time of radiofrequency ablation (RFA) (without previous histologic diagnosis), it may help to tailor the surveillance strategy. Approximately 2–5% of the SRMs are in fact "non-renal" malignancies (metastasis), for which the treatment will be largely different [7, 8].

For patients who have comorbidities with high surgical risk, avoidance of unnecessary procedures is particularly relevant, even in larger kidney masses, RTB may be useful. In larger malignant tumors (T1b-2), a biopsy yielding high-risk pathology could result in a more aggressive approach (radical nephrectomy) for cancers with high-risk features, whereas in low-risk tumors, the approach could be more conservative (active surveillance (AS) or nephron sparing surgery). If neoadjuvant therapy is employed (not yet

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standard of care), different responses can be expected with different histologic types [6].

In metastatic patients, indications include primary histologic diagnosis as well as histological characterization of a metastatic site. In up to 5% of SRMs presenting with apparent lung metastases, the lung lesion is a primary lung cancer and the SRM is a metastasis [7, 9, 10]. The choice of systemic agents for metastatic RCC (mRCC) may vary with the histologic type [6]. Since the benefit of cytoreductive nephrectomy was described [11, 12], the preoperative evaluation of high-risk features has been used to assist to establish prognosis [13]. Unfortunately, in mRCC, the accuracy of RTB for the diagnosis of high vs. low-grade, non-ccRCC histology, and the presence of sarcomatoid features in the final surgical specimen can be low [10, 14]. In a more recent study, Abel et al. [15] describe improved sensitivity for the detection of sarcomatoid features (86.7 vs. 25%) using a "multi-quadrant" biopsy technique (sampling at least four separate solid enhancing areas of the tumor) compared to the classic technique. Furthermore, the platelet-to-lymphocyte ratio may help to identify a non-renal origin in metastatic patients, but at this point, we still need the RTB [16].

Contraindications for RTB include the presence of uncorrected coagulopathy and cases when the result will not change management; particularly, those with reduced life expectancy in whom best supportive care will be offered [6, 17]. Patients with $SRM^{x}$ and hereditary renal tumor syndromes may not need biopsy, as the histological diagnosis can be surmised [17]. Some anatomical tumor locations, patient habitus, and concomitant conditions/anatomic variations should be assessed, as they may lead to technical challenges.

## Technique for renal tumor biopsy

Our recommendations have been previously described [18]. The following are important for preparation:

- Assessment of bleeding risk. International normalized ratio (INR), platelet count, and partial thromboplastin time (PTT) should be measured within a month of the procedure. We recommend suspending aspirin, clopidogrel, and nonsteroidal anti-inflammatory medications 7–10 days before the procedure, and suspend warfarin until normal INR values are obtained.
- Rule out urinary infection clinically or with urinalysis [19].
- Plan the procedure including the needle track and optimal imaging technique. Ultrasound and CT are the usual imaging modalities for guidance, while MRI is limited by the cost and need for special equipment such as non-ferromagnetic biopsy needles and large bore. Decisions should be individualized according to the patient and the mass [13], as well as personal experience.

### Fine needle aspiration (FNA)

This technique utilizing a 21-gauge needle, and an insertion cannula (coaxial sheath), appears to improve outcomes and perhaps decreases the risk of seeding through the needle tract [13]. In addition, the use of a cannula may decrease discomfort and facilitate multiple samples. Once the cannula is in place, a syringe is attached to the external end of the needle to apply negative pressure. With constant negative pressure, 15–20 passes are done through the tumor without penetrating further than, where the tumor is; then, the needle is extracted and the obtained material is sent for histopathological analysis. The "Zajelda's technique" is similar but without negative pressure, resulting in reports of similar outcomes; we recommend the latter technique for the cases when we obtain only blood after the first "pressurized" attempt. It is useful to have a cytotechnologist present to confirm the quality of the sample obtained. The preferred stain is the modified Diff-Quick® Romanowsky–Giemsa stain, but hematoxylin and eosin can also be used. When a biopsy is done for a cystic lesion, we recommend injecting contrast into the cyst after the biopsy to better characterize the cyst. If a significant solid component is visualized, it should be biopsied in the same procedure.

### Core biopsy

An automated biopsy gun is used to obtain 18-gauge [20] cores of tissue though a coaxial sheath, as described above with the FNA technique. Imaged areas of necrosis should be avoided. We try to obtain at least one central and one peripheral sample, since peripheral samples have a better diagnostic yield, particularly with larger masses [6]. In smaller masses, central biopsies are representative [21]. Ideally, cores should be 10 mm long and inspected once obtained, to corroborate size and the presence of non-necrotic tissue [6]. In tumors > 4 cm in diameter, multiple samples are suggested given the known heterogeneity in large RCC [22]. Hematoxylin and eosin staining is the primary technique, but specific stainings can be done for RCC subtypes or in cases of suspected metastasis from a non-renal malignancy.

Both types of biopsies can be performed in an outpatient setting including the office with local anaesthesia and ultrasound guidance [23]. The sensitivity and specificity of core biopsies are reported to be superior to FNA (99.1 and 99.7% vs. 93.2 and 89.8%, respectively) and this is our preferred approach [24]. Our experience is that the core biopsy is not only more frequently diagnostic but delivers sufficient tissues for correlative studies and research. However, there is

at least one report that the combination of both techniques is superior [25].

For cystic lesions, the diagnostic yield is lower than for solid masses, but increases in those complex cysts with a solid component. Nonetheless, in our series, we obtained a histological diagnosis in up to 80% of the cases, which can reduce unnecessary treatment. Of Bosniak IIF–IV cysts (those who have a solid nodule that can be sampled) [6], tumor location can also influence biopsy success. Anterior, perihilar, and endophytic tumors in the upper or mid-pole are more difficult to access.

### Safety

Complications associated with RTB are infrequent, but include tumor cell seeding along the tract (rare with RCC but can occur with urothelial carcinomas), bleeding, fistula, pseudoaneurysm, infection, and pneumothorax. Reported mortality is extremely infrequent (0.031%) [18, 26]. In a recent systematic review [27], complications included hematoma in 4.9%, clinically significant pain in 1.2%, hematuria 1%, pneumothorax in 0.6%, and haemorrhage in 0.4%. Using a coaxial technique appears to reduce complications, as well as improving visual guidance throughout the whole procedure [26]. Major complications (e.g., pseudoaneurysm, need of embolization) occur in < 1% of the RTB [24, 28, 29].

## Accuracy, results, and impact on treatment decision making

The major impact of RTB is to identify SRM that are benign before treatment, and allow AS with reduced intensity of follow-up instead of ablation or surgery. In a retrospective analysis of 1175 $SRM^{x}$ treated with PN in five academic centers [30], 52% were either benign (23%) or amenable to AS (29%) (including favourable risk SRM or intermediate risk < 2 cm SRM); if a preoperative biopsy had been done (and assuming 100% concordance with final pathology), more than half of these surgeries could have been avoided at least initially. Furthermore, when the authors accounted for comorbidities and surgical risk, the number of candidates of AS increased considerably. In a recent retrospective analysis using the same decision algorithm [31] in 202 patients with preoperative biopsy and surgical resection, Osawa et al. [3] reported a benign pathology in 12 (5.9%), of whom one had a malignant pathology after surgical resection. Out of the 53 (26%) patients assigned to surveillance, 9 (4.5% of the total SRM analyzed) were incorrectly assigned and were candidates for the initial treatment based on the final surgical pathology. In the multivariate analysis, they were unable to identify features that improve the algorithm. These findings differ from our own. In our published series of RTB-based AS, 41% of the patients avoided surgery based on the result of the RTB [2]. In a recent Canadian multi-institutional registry publication, 61% of the patients with RTB for $SRM^{x}$ underwent surgery or ablation treatment, so almost 40% avoided initial treatment [32]. Together, these results show the potential impact of pre-treatment histological diagnosis.

Biopsy in only indicated if the results of biopsy will change management. Even if low-grade $SRM^{ccRCC}$ and other $SRM^{RCC}$ subtypes are going to be managed by initial AS in a given patient, RTB results may contribute. A benign result may reduce the intensity of follow-up and imaging, while more aggressive pathology could be an indication for treatment. Patient comorbidities are a factor in the decision to biopsy. Charlson Comorbidity Index and increasing age are associated with the other cause mortality. In patients with poor performance status or limited life expectancy, surgical resection of the tumor might not have an impact due to competing comorbidities [6]. If that is the case, and the patient is not amenable for ablative therapies, the biopsy might not offer any benefit.

As observed with prostate biopsy, RTB Fuhrman nuclear upgrading has been reported in approximately 15% when compared with surgical pathology, which is less frequent than in prostate cancer. Data are limited and not all biopsied patients go on to surgery, which may bias the results. Fuhrman grade in SRM is usually low (> 70% of the RTB for SRM), and the concordance between the RTB and the final specimen is 62.5% (IQR 52.1–72.1%) using the 4-tier classification, but 87% (IQR 71–98%) when stratifying to low and high grades only [24]. Our reported concordance was 94% [2]. In addition, in highly experienced centers, the diagnostic rate and the concordance between the RTB and the nephrectomy diagnosis are better, indicating a room for improvement in low volume centres [2]. Simply stratifying Fuhrman grades into low/high grade seems to have good prognostic accuracy compared to the classic 4-tier classification [33]. The significant intratumoral heterogeneity in kidney tumors [34, 35] could explain the difficulties in defining the Fuhrman nuclear grade with a RTB. Perhaps, increasing the number of samples/passes could improve the concordance with the resected tumor pathology ("multi-quadrant" biopsy technique). In the presence of multiple tumors, a biopsy of each should be considered because of possible discordance. Not only may there be different subtypes of RCC, but there may be coexistence of benign and malignant/hybrid tumors in the same patient (approximately, 3%), particularly with oncocytic tumors and chromophobe histology [6, 36].

Experienced pathological services are important for accurate diagnosis. Processing and interpretation of the samples are of utmost importance. The limited amount of tissue provided by RTB in oncocytic tumors can challenge pathologists attempting to provide a definitive diagnosis of oncocytoma vs. chromophobe or other RCC [37]. However, the

safety of initial AS for SRM$^{onc}$ has been recently reported with both oncocytomas [mean follow-up 34 months] and chromophobe tumors [mean follow-up 25 months]), suggesting that initial AS is safe [38].

A non-diagnostic biopsy can occur due to both tumor and patient characteristics, including cystic tumor (non-diagnostic rate up to 39.8%), non-enhancing tumors (non-diagnostic rate up to 42.1%), smaller tumor size, and skin-to-tumor distance > 13 cm (non-diagnostic rate of 26.9%) [39, 40]. Awareness of these characteristics will improve outcomes and should be explained to patients as part of informed consent. Repeat biopsy has the same non-diagnostic rate as the first biopsy, suggesting that a non-diagnostic biopsy result is usually due to a miss. Together, first and repeat RTB (if indicated after a non-diagnostic first-RTB) result in a diagnostic rate of > 90% (94% in experienced centers) [2, 29, 32, 40].

The appropriate indications for delayed treatment of an SRM initially managed by AS are poorly understood. Upper size limit (≥ 3 or 4 cm) and growth kinetics (rapid doubling) are the usual triggers [41]. Repeat biopsy may be indicated if the initial biopsy was benign or equivocal and rapid growth is observed.

In larger masses (> 4 cm), histologic confirmation of malignancy may also be useful. In a recent study by Daugherty et al. [42], the metastatic potential of chromophobe tumors up to 7 cm was similar to SRM$^{ccRCC}$ and SRM$^{pap}$ (< 3%). This suggests that such tumors could be treated with AS or delayed nephrectomy even when they are > 4 cm. If partial nephrectomy is planned, but the RTB reveals an aggressive tumor type, radical nephrectomy might be a safer option to ensure oncological success, whereas for more indolent tumor, a partial nephrectomy can be sufficient.

Despite evidence that RTB can have a positive impact on clinical decision making, some groups argue against the utility of routine RTB [43]. Nevertheless, we believe that it is not only useful now, but that the benefits of histologic confirmation are only going to increase. The increasing evidence for AS, use of ablative techniques, and rate of approval of new systemic therapies, all of which have outcomes that vary between histological subtypes (being tested even in neoadjuvant scenarios) [9], support histological characterization of tumors by RTB.

Limitations of the RTB include the rate of non-diagnostic samples and the low but real rate of discordance between biopsy and surgical pathology. In current series, the PPV of RTB is > 99%, and the non-diagnostic rate is 8–14.7%, according to recent systematic reviews (range 0–22.6% for core biopsies and 0–36% for FNA). The NPV for patients who had a biopsy followed by resection of the tumour (non-malignant biopsy confirmed as non-malignant in the final surgical specimen) is 70% [24, 27]. We should remember that the numbers of these calculations are limited and the reasons for surgery are not well established.

In a recent cost-effectiveness analysis [44] with limited data regarding the use of RTB, biopsy before treatment decision seems to perform better than immediate surgical intervention, even considering the possibility of surgical intervention afterwards.

## Future directions

While there has been a gradual increase in adoption of RTB, there are many urologists who remain concerned about safety and accuracy. Treating a renal mass as a cancer without tissue diagnosis remains an anomaly in GU oncology care. There are some promising developments in predicting the presence of cancer and its subtype. Several strategies are being developed to improve diagnosis and, therefore, avoid RTB [43]. Better imaging studies (molecular imaging) [45] targeting transmembrane protein carbonic anhydrase IX with several molecules such as girentuximab have promising results for RCC [46]. For the diagnosis of oncocytomas and hybrid tumors, the use of the 99TC-sestamibi SPECT/CT is being studied based on its accumulation in mitochondria [47]. Nephrometry scoring has been proposed to predict unfavourable malignancies (R.E.N.A.L. score > 8, size > 3 cm and male sex) [48], but RTB outperforms nephrometry scores, albeit at the cost of being invasive [49]. Finally, very good results using MRI to predict the histopathology of renal masses have been described, opening another window for improvement in patient care [50–52]. Gene expression and molecular marker studies are underway [13, 53, 54] and may augment the findings of RTB.

There are other uses of RTB tissues. Successful attempts to create tumor xenografts and implant them in mouse models using RTB samples have been reported [55]. These xenografts can reproduce the response of the tumor to systemic therapies. In the future, this technology may help to tailor treatments in different stages of RCC [55]. Molecular classifications could also serve as response predictors in metastatic RCC, and perhaps in localized RCC too in the setting of neoadjuvance [56–59].

Finally, we believe that the use of AS will expand and will be applied to more patients. Even patients who are fit for surgery could be managed initially with AS, and the information obtained with the RTB will help in that decision. Furthermore, in patients who are not fit for surgery due to temporary conditions, the RTB can determine those who need an immediate ablative procedure in comparison with those who can have a delayed intervention if the comorbidities improve. Until we develop a better (perhaps non-invasive) diagnostic strategy, RTB should be at least discussed with the patients, since it can have an important therapeutic impact.

## Conclusions and renal tumor biopsy challenges

RTB is not yet widely adopted as a diagnostic strategy [60, 61]. Many remain unconvinced about its utility to change management. RTB is a "team sport" requiring expertise in imaging, pathology and urology. We currently biopsy all SRM larger than 1 cm if the result will change management. We do this to avoid overtreatments and also to establish how urgent is the treatment and what type of procedure is ideal in a given patient [62].

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## Compliance with ethical standards

**Conflict of interest** The authors have no conflicts of interests for the present work. The authors declare that they have no conflict of interest.

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