Interventional Ultrasound: Biopsy of Renal Masses

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13.1 Introduction

Percutaneous biopsy of renal tumors has been historically used with limited indications: (1) differential diagnosis of lymphoma and renal abscesses, (2) diagnosis of metastatic renal disease in the presence of known extrarenal malignancy, and (3) diagnosis of a renal primary tumor in the presence of disseminated metastases or surgically unresectable retroperitoneal tumors.

Beyond these indications, biopsies of renal tumors have been rarely used for a number of uncertainties in terms of (1) safety, for the potential risk of tumor seeding along the needle track and hemorrhagic complications, (2) diagnostic rate and accuracy, and (3) effectiveness in terms of impact on clinical decisions, due to the perception that all solid renal masses have malignant potential and should be removed surgically up front.

Many of these uncertainties have now been overcome due to the growing experience of urologists and interventional radiologists in performing biopsies, to the growing experience of pathologists in interpreting biopsy specimens, and to the growing confidence of urologists in using biopsy information to support the clinical decisions.

The increasing incidence of small renal masses (SRMs), the development of alternative treatments for these lesions in selected patients, and the development of effective biological therapies for metastatic disease have increased the awareness that pretreatment histological information are necessary to choose the best-suited treatment for each individual patient [1].

13.2 Rationale of Percutaneous Renal Tumor Biopsy

Percutaneous biopsy can today provide important information for clinical management of renal tumors, with major impact on clinical practice.

13.2.1 Decrease of Surgical Indications for Benign Tumors

SRMs are benign tumors in a non-negligible proportion of cases, with a probability that significantly increases with decreasing tumor size [2–4].

Conventional radiology (CT, MRI, CEUS) does not allow an accurate diagnosis of oncocytoma. In fact, the typical appearance of the oncocytoma as a homogeneous hypervascular mass

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with a central starry scar is observed only in few cases. No other radiological feature is sufficiently reliable for the diagnosis of this benign tumor [5, 6].

Moreover, although most angiomyolipomas are easily recognizable at CT scan for the characteristic fatty content, fat-free angiomyolipomas (leiomyoma-like and epithelioid variants) cannot be properly diagnosed at imaging [7]. Overall, Remzi et al. observed that only 17 % of benign tumors are correctly characterized at preoperative CT [8].

Performing a percutaneous biopsy before treatment decision can therefore decrease the number of unnecessary surgery for benign tumors, especially in elderly and comorbid patients.

13.2.2 Support of Treatment Decision-Making for Localized Renal Tumors

A significant proportion of SRMs are benign tumors or low-grade RCC with a relatively indolent biological and clinical behavior [9, 10]. Furthermore, most SRMs are incidentally detected in older patients, in whom comorbidities are more frequent and the risk of competitive mortality is higher [11].

Surgical resection is the gold standard treatment for SRMs, but focal ablative therapies and active surveillance are alternative options in patients with advanced age, reduced life expectancy, or high surgical risk [12]. Renal tumor biopsy can be useful to select patients who are good candidates for a conservative management. In fact, active surveillance is more suitable for low-grade tumors, with limited risk of progression. A biopsy may also help to decide the intensity of follow-up for patients in active surveillance. In fact, benign tumors can be followed with a less rigid scheme, reducing the risks of radiation exposure and the costs for the health-care system.

Percutaneous biopsy can also be performed for larger localized renal lesions (T1b–T2). Although the decision to perform a radical or partial nephrectomy depends essentially on patient's characteristics and tumor's radiological features, the histological characterization of the renal mass may favor a radical surgical treatment in case of aggressive disease and a conservative treatment even in highly complex cases in case of benign or indolent histology.

13.2.3 Support to Define the Oncological Outcomes of Focal Ablative Therapies

Although the outcomes of cryoablation and radiofrequency ablation are encouraging, the persistence of viable tumor cells after these ablative procedures is not infrequent [13]. The guidelines of the American Urological Association recommend a percutaneous biopsy of renal tumors after ablation if recurrence or persistent disease is suspected at follow-up imaging. Routine biopsies after treatment can allow the histological confirmation of the success of minimally invasive therapies and check for local recurrences [14].

13.2.4 Support of Treatment Decision-Making for Metastatic Renal Tumors

Percutaneous biopsies of renal tumors can be useful for treatment decision-making in the setting of metastatic disease. The presence of sarcomatoid differentiation predicts a poor prognosis, with limited response to systemic therapy and less benefit of cytoreductive nephrectomy, which should not be performed to avoid unnecessary morbidity [15, 16].

In addition, molecular targeted drugs have different response rates according to RCC histology. Studies have shown that mTOR inhibitors have better activity in the treatment of chromophobe RCC than tyrosine kinase inhibitors. Similarly, foretinib demonstrated good responses in the treatment of papillary RCC, particularly in cases with MET germline mutations [17, 18].

Currently, biopsy is required to characterize primary renal tumors before starting systemic therapy for metastatic disease. In particular, percutaneous biopsy is recommended when cytore-

ductive nephrectomy is not indicated or when a neoadjuvant systemic therapy is planned [12].

13.3 Current Indications of Percutaneous Renal Tumor Biopsy

Percutaneous biopsy of renal tumors can be useful in several clinical settings and is currently recommended for the histological characterization of:

- Indeterminate renal masses at abdominal imaging (including Bosniak IV cystic lesions)
- Small incidental renal masses in patients who are candidates for active surveillance or minimally invasive ablative therapy
- Radiological suspicion of local recurrence after ablative therapy
- Renal masses which are suspicious for metastatic disease in the presence of a known extrarenal tumor
- Retroperitoneal tumors involving the kidney when surgery is not feasible or indicated
- Metastatic primary renal tumors in patients who are not candidates for cytoreductive nephrectomy or when a neoadjuvant systemic therapy is planned [12]

13.4 Technique of Percutaneous Renal Tumor Biopsy

13.4.1 Preparation

Before biopsy of a renal mass, a screening for the presence of coagulative disorders (assessment of PTT, INR, and platelet count) should be performed. Antiplatelet drugs should be stopped 5–7 days before biopsy, and anticoagulants should be discontinued in time to achieve acceptable INR values. Anticoagulants are generally replaced with low molecular weight heparin which are then continued for a few days after biopsy.

13.4.2 Anesthesia

Percutaneous renal biopsy can be performed in an outpatient or day hospital setting and is generally well tolerated under local anesthesia with lidocaine 2%. Local anesthesia should be ideally performed on the selected needle track (Fig. 13.1). Sedation is indicated only in selected patients who are particularly anxious. In fact, patient's consciousness is generally useful to perform biopsies of upper pole masses under deep inspiration.

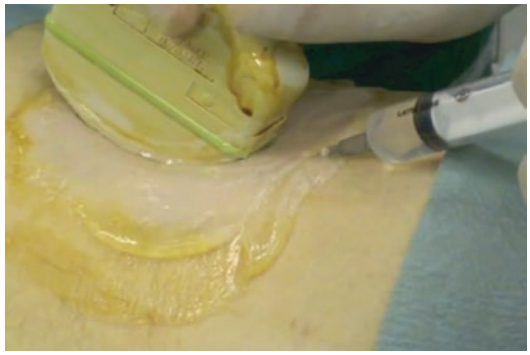

Fig. 13.1 Local anesthesia

13.4.3 Radiological Guidance

Biopsies can be performed under ultrasound, CT, or MRI guidance. The choice of the imaging guidance depends on the operator's experience and habits, on tumor size and location, and on patient's habitus. MRI is rarely used for the high costs and the need of ferromagnetic needles. Ultrasound guidance is used in most cases, since it allows a real-time puncture, avoids radiation exposure, and is associated with lower costs (Fig. 13.2). However, in some obese patients, CT guidance should be preferred, since the presence of significant subcutaneous and perivisceral fat can hinder a clear ultrasound visualization of the renal mass, which is essential to perform an accurate biopsy. Renal masses located at the upper pole or on the anterior face of the kidney and smaller than 15 mm in size are also more likely to be sampled under CT guidance (Fig. 13.3). A major limitation of CT guidance is that it does not allow biopsies in real time. This can be overcome with the use of modern techniques such as CT fluoroscopy.

At present there is no solid evidence of the superiority of the ultrasound or CT guidance. In a large series of biopsies of SRMs performed at the University of Toronto, no significant difference was observed between the detection rates of biopsies performed with the two approaches [19, 20].

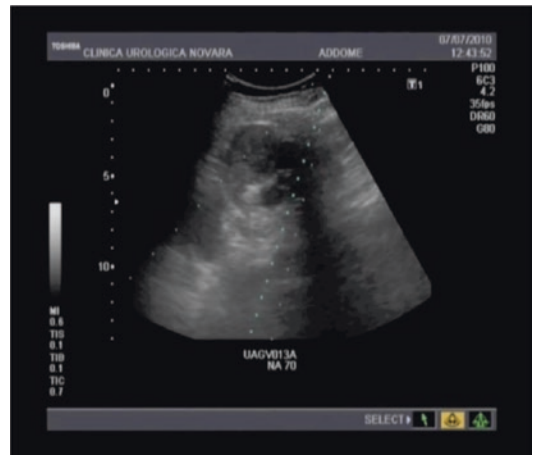

Fig. 13.2 Biopsy of a renal mass under ultrasound guidance

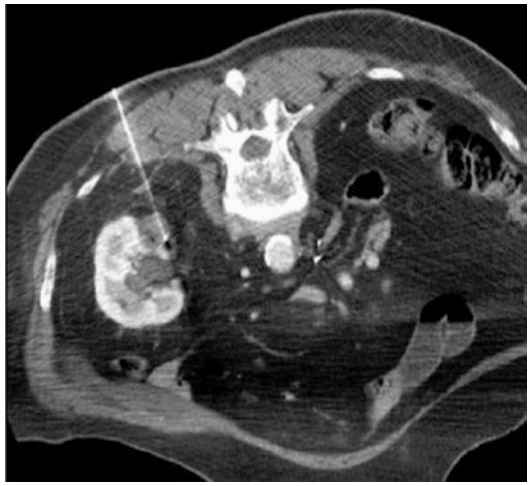

Fig. 13.3 Biopsy of a small renal mass under CT guidance

13.4.4 Biopsy Needles

Biopsies are usually performed with a Tru-Cut 18-gauge needle loaded on an automatic biopsy gun, which achieves the best compromise between safety and detection rate (Fig. 13.4a). The biopsy is generally performed coaxially to a 17-gauge cannula which is previously placed near or just inside the renal mass (Fig. 13.4b). The use of full-core needles seems to allow better results both in terms of diagnostic rate and accuracy.

Fine-needle aspiration (FNA) for cytology is performed instead with smaller (≤21 G) needles.

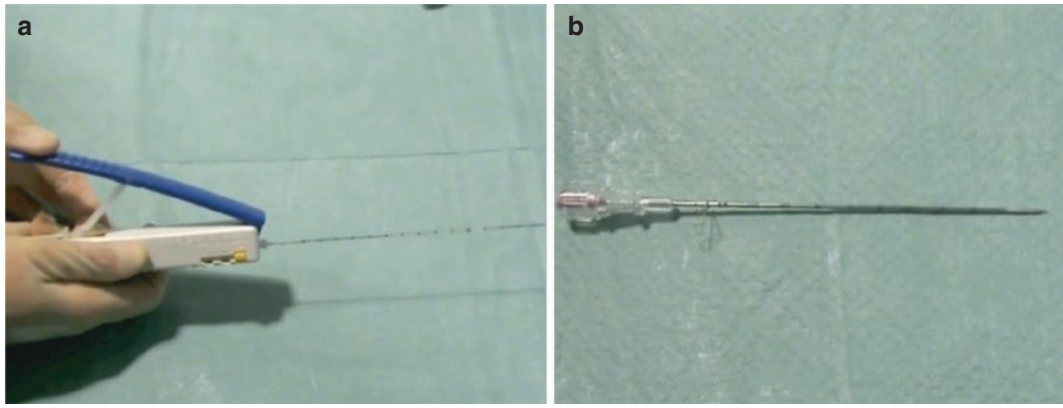

Fig. 13.4 (**a**) Full-core 18-gauge needle loaded on an automatic biopsy gun; (**b**) 17-gauge cannula through which the biopsy needle is introduced

13.4.5 Biopsy Technique

The patient is generally placed in a lateral decubitus, but a prone or semiprone position can be also used based on the characteristics of the renal lesion and on the selected imaging guidance. After performing local anesthesia, the most appropriate biopsy track is chosen, and a guided cannula is inserted percutaneously to approach the lesion (Fig. 13.5).

The puncture can be performed "freehand" or with the use of an ultrasound guide that directs the needle in a predetermined angle within the plane of view of the transducer (Fig. 13.6). The freehand technique requires more experience, but has the advantage of greater flexibility by allowing subtle adjustments that can compensate for improper needle trajectory and patient movement.

Once the lesion is reached, the stylet is removed, and the needle core biopsy or FNA is performed through the guiding cannula (Fig. 13.7). The biopsy can be performed after removal of the ultrasound guide or under real-time ultrasound guidance based on operator's preference. Multiple biopsies can be obtained through the guiding cannula which is finely repositioned within the lesion to allow sampling of different areas of the tumor. This technique is called "coaxial" and is useful to reduce the risk of tumor seeding along the needle track, since it minimizes the potential risk of contact of the needle with the healthy tissues interposed between the skin surface and the renal mass.

When a FNA is planned together with a core biopsy, it should be performed first to limit the risk of hemorrhagic contamination of the sample, which makes the cytological diagnosis more challenging. The quality of the FNA sample should be checked by a cytologist during the procedure (Fig. 13.8). This increases the diagnostic yield and confirms the proper placement of the cannula through which the core biopsies will be then performed.

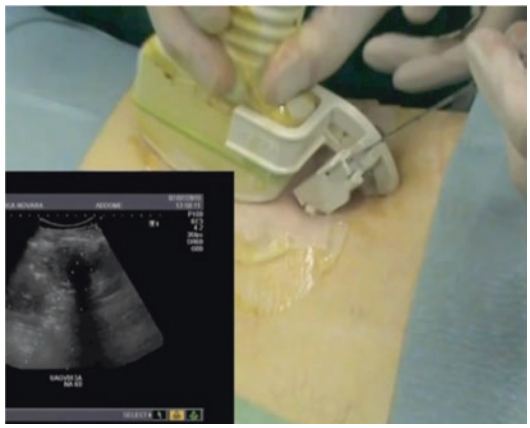

Fig. 13.5 Skin puncture and advancement of the guiding cannula to reach the tumor capsule under ultrasound guidance

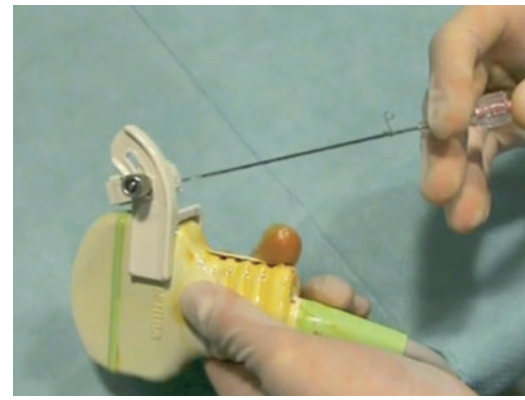

Fig. 13.6 Ultrasound guide for percutaneous biopsy

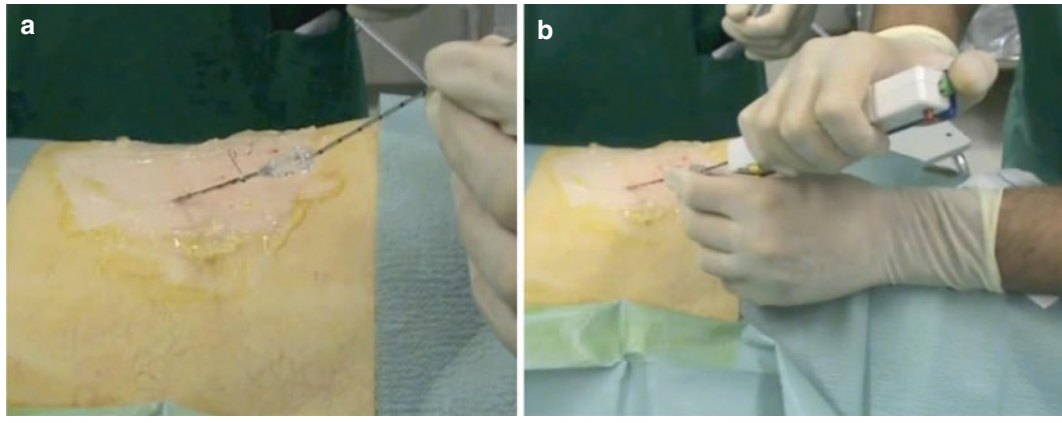

Fig. 13.7 (**a**) Coaxial introduction of the 18G needle in the guiding cannula to perform the biopsy of a renal mass. (**b**) The sampling is performed with the automatic biopsy gun

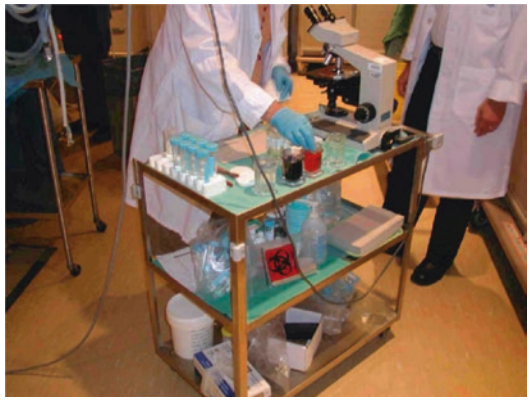

Fig. 13.8 Check of the quality of the cytologic specimen during the procedure

13.4.6 Biopsy Pattern

At present, the ideal biopsy pattern to sample renal masses of different sizes is not standardized. However, at least two good quality samples should be always obtained from different areas of the tumor, avoiding areas of necrosis. A good quality core is at least 1 cm long and not fragmented. Wunderlich et al. observed a poorer diagnostic accuracy for central biopsies in tumors >4 cm, likely due to the higher likelihood of necrosis in the central portion of larger tumors [21]. Based on these results, it is currently generally recommended to obtain at least a central and a peripheral core in <4 cm tumors and two peripheral cores in larger tumors.

13.4.7 Biopsy Processing

To favor an optimal histological assessment, every biopsy should be placed between two sponges in a single histological cassette (Fig. 13.9).

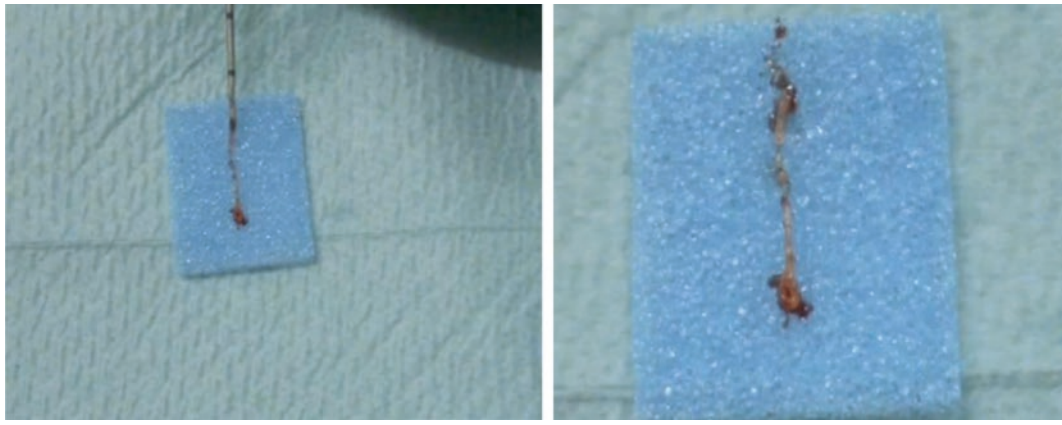

Fig. 13.9 Release of the core biopsy on a dedicated sponge for the following histological processing

13.4.8 Patient Management

Patients should be monitored for at least 4 h after the biopsy. The vital parameters and a cell blood count should be assessed. Post-procedural ultrasound and CT scans are generally not required in the absence of clinical or laboratory signs of active bleeding.

13.5 Safety

Complications after renal tumor biopsy are infrequent with the use of proper biopsy techniques and are mainly represented by immediate or delayed bleeding, since renal tumors are generally hypervascularized. However, significant bleedings requiring hospitalization and/or blood transfusion are rare in experienced centers (<1 %) [1].

The risk of tumor seeding along the needle track is anecdotal. Only seven cases of seeding of renal parenchymal tumors have been reported to date in the literature. Most of these cases were observed before 2001 when the biopsy was performed with different instruments and techniques [22]. The use of the coaxial technique is particularly important to avoid tumor seeding. In fact, the only case of seeding that has been recently described was not carried out with a coaxial technique [23].

Other possible rare complications of biopsy are pneumothorax in case of biopsies of upper polar lesions with a posterior approach and infections [24].

13.6 Diagnostic Rate and Accuracy of Renal Tumor Biopsies

Renal tumor biopsy has been shown to have a good diagnostic rate (78–97 %) and a high specificity (98–100 %) and sensitivity (86–100 %) for the diagnosis of histological malignancy in several large series from experienced centers [1].

A recent systematic review and meta-analysis of the literature observed that the overall median diagnostic rate of renal tumor biopsy is 92 %. The sensitivity and specificity of diagnostic core biopsies and FNAs were 99.1 % and 99.7 % and 93.2 % and 89.8 %, respectively [25].

The risk of a nondiagnostic biopsy remains a concern for clinicians. When a biopsy is not diagnostic in the presence of suspicious radiological findings for malignancy, a repeat biopsy or surgical exploration should always be recommended [12].

The accuracy of the biopsy for the diagnosis of histological subtype is high (86–100 %) [1, 25]. The evaluation of the tumor grading on biopsy is challenging for pathologists. The accuracy for the assessment of Fuhrman grade (I–IV) is only fair (43–75 %), but can be increased using a simplified grading system (high grade vs. low grade) [1, 25].

Percutaneous biopsies have a lower detection rate for cystic renal masses and should not be recommended for characterization of these lesions, except for Bosniak IV lesions which have a visible and targetable solid area in their context [12]. The combination of needle core biopsy and FNA can obtain complementary results especially for the characterization of complex cystic masses [26, 27].

13.7 Limitations and Future Perspectives of Renal Tumor Biopsies

Prospective studies with larger series are needed to confirm the good results of percutaneous biopsy of renal masses, to establish the role of the repeat biopsy in nondiagnostic cases, criteria for quality control of biopsy samples, and guidelines for the standardization of pathological results.

The accuracy of renal tumor biopsies is limited by factors that are intrinsic to the procedure (risk of insufficient sampling), by factors related to histology of renal tumors (difficult differential diagnosis between different histological subtypes such as oncocytoma and chromophobe RCC, difficult assessment of tumor grade, the presence of intratumoral heterogeneity), and by factors relating to the interpretation of biopsy specimens (intra- and interobserver variability).

Intratumoral heterogeneity in terms of histological type is not frequently found, but 18 % of oncocytomas can show patterns of chromophobe RCC. Recent studies indicate that the oncological outcomes of surgery for these hybrid tumors are similar to those obtained for pure oncocytomas [28]. The differential diagnosis between oncocytoma, eosinophilic variant of chromophobe RCC, oncocytic papillary RCC, and clear-cell RCC with granular cytoplasm remains the most difficult challenge for pathologists in the interpretation of biopsy. In a recent study, Kummerlin et al. observed a good intraobserver and interobserver agreement in the histologic assessment of renal tumor biopsies performed on the bench after surgery. However, the diagnosis was less reproducible for chromophobe RCC when only the classical hematoxylin-eosin staining was used [29].

The challenging definition of tumor grade on biopsy samples represents a limitation when grading is used for treatment decision-making. The assessment of grading is also limited by the potential presence of intratumoral heterogeneity, which is reported in 5–25 % of renal tumors [1].

The detection rate and accuracy of biopsies of renal masses could be optimized by the definition of standardized biopsy protocols. Further studies are therefore needed to define the optimal number of cores and the ideal location where the samples should be taken according to tumor size.

Finally, the use of cytogenetic and molecular markers on biopsy samples has the potential to provide more diagnostic and prognostic information, thereby further increasing the utility of percutaneous biopsy in the management of renal neoplasms.

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