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Renal Biopsy: Appraisal of the Methods

Ogochukwu Okoye

Abstract

Renal biopsy is an invasive specialized test aimed at obtaining renal tissue for histologic diagnosis of a variety of kidney diseases. Common indications for renal biopsy in practice include adult nephrotic syndrome, steroid resistant or clinically atypical nephrotic syndrome in children, glomerulonephritis, acute kidney injury (AKI) of unknown aetiology, systemic diseases with renal involvement, and persistent proteinuria or haematuria with reduced renal function. Over the years there has been continuous refinement of renal biopsy techniques. It is now mostly performed percutaneously using imaging guidance and more sophisticated spring-loaded needles of varying sizes. Other non-percutaneous techniques such as transjugular, laparoscopic and open renal biopsy are also being performed especially in patients with contraindications to the percutaneous approach. Percutaneous ultrasound guided approach is standard care for biopsy of non-focal lesions. The CT-guided method can be used in obese patients and other patients who are unable to lay prone, patients with complex anatomy, and when the kidneys are not sufficiently visualised by ultrasound scan. The transjugular technique is most popular for combined liver and kidney biopsy. The major advantages of the laparoscopic and open biopsy techniques are the opportunity for direct visualization of the kidney and good intra-operative haemostasis.

Keywords: renal biopsy, transjugular biopsy, percutaneous renal biopsy, open renal biopsy

1. Introduction

Renal biopsy is an invasive specialized test aimed at obtaining renal tissue for histologic diagnosis of a variety of kidney diseases. Kidney biopsy is generally indicated when, (1) the cause of kidney disease cannot be sufficiently determined or predicted clinically or by less invasive diagnostic procedures, (2) clinical features suggest parenchymal disease that can be diagnosed by pathologic evaluation and (3) the differential diagnosis includes diseases that have different treatments, prognosis or both [1].

Common indications for renal biopsy in practice include adult nephrotic syndrome, steroid resistant or clinically atypical nephrotic syndrome in children, glomerulonephritis, acute kidney injury (AKI) of unknown aetiology, systemic diseases with renal involvement, and persistent proteinuria or haematuria with reduced renal function. Sometimes diagnosis of kidney disease is clinically apparent, however a biopsy may be required for confirming diagnosis, assessing disease activity, chronicity and severity, e.g. in systemic lupus erythematosus [2].

Renal biopsy may be associated with complications such as bleeding, pain, infections, injury to contiguous structures, and very rarely loss of a kidney or death of the patient. The safety and usefulness of renal biopsy in the diagnosis, monitoring and treatment of renal parenchymal diseases largely depends upon correct selection and adequate preparation of the patient, the skillfulness of the operator, and the technique used.

Over the years there has been a continuous refinement of renal biopsy techniques. It is mostly performed percutaneously using imaging guidance and more sophisticated soft-tissue needles (**Figure 1a-c**) of varying sizes. Other
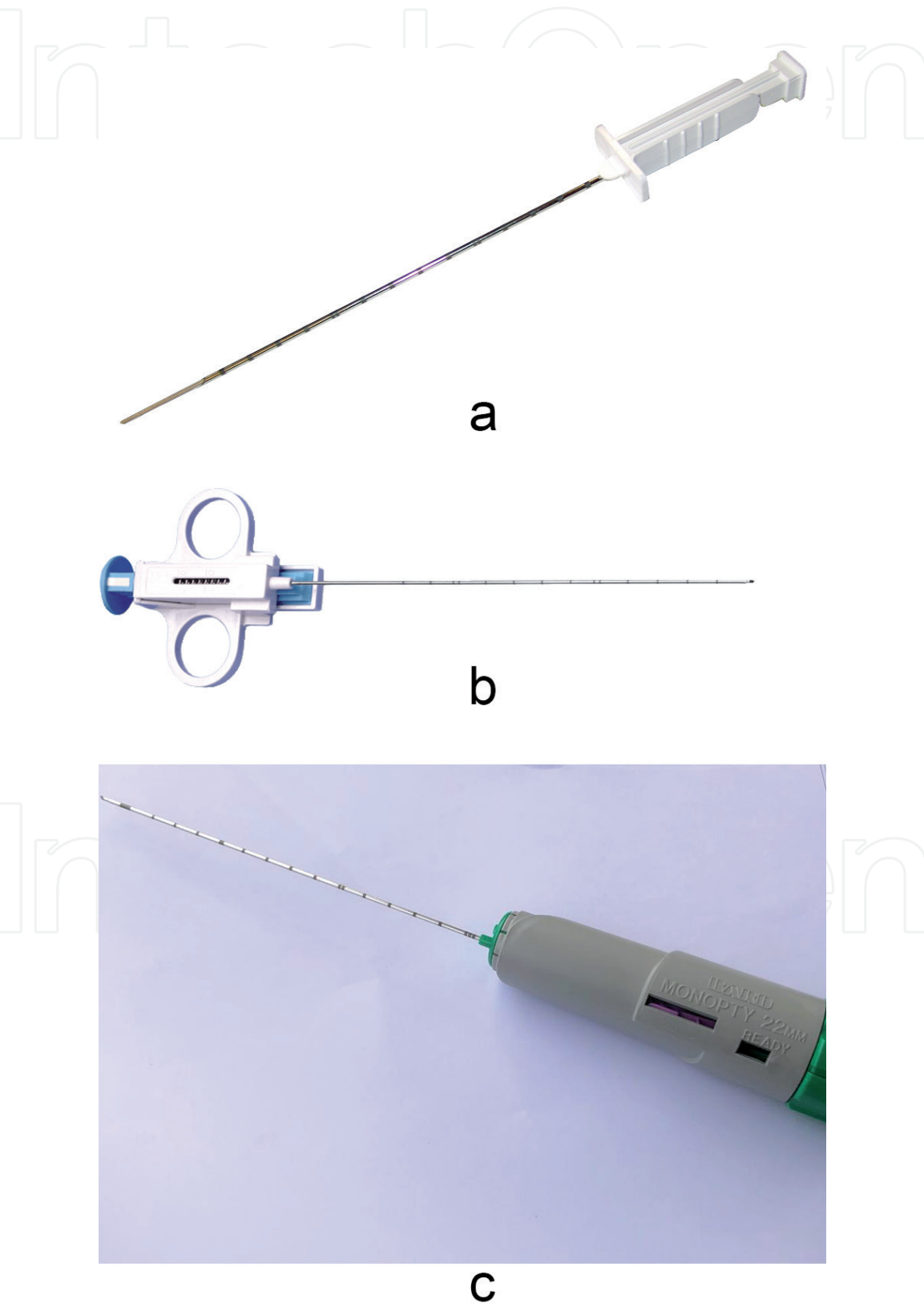

Figure 1.
Soft tissue biopsy needles: (a) Tru-Cut, (b) semi-automated biopsy needle, and (c) automated biopsy needle.

non-percutaneous techniques such as transjugular renal biopsy, laparoscopic and open renal biopsy are also being performed especially in patients with contraindications to the percutaneous approach.

2. Methods of renal biopsy

Iversen and Brun introduced percutaneous renal biopsy (PRB) of native kidneys in 1951, when they performed the procedure in a sitting patient using an aspiration needle after localizing the kidney with intravenous pyelography [3]. Although this innovation revolutionized the nephrology practice at the time, the tissue yield was inadequate in up 47% of the biopsies they performed over time [3]. Since then other percutaneous methods have been introduced and practiced with better tissue yields of up to 95–99% in some series [4–6]. Despite these encouraging figures, the tissue obtained is sometimes not diagnostically useful. This can be due to poor patient selection, wrong or poor technique, and inappropriate tissue handling, i.e., division of tissue for the different histopathologic examinations, and storage. The nephrologist should be adequately knowledgeable of indications, contraindications and complications of renal biopsy, and the several techniques available. This will significantly help to improve the usefulness of this procedure in terms of individual patient care and outcome.

Renal biopsy may be performed by one of the following approaches: percutaneous blind, blind after localisation with ultrasound scan, percutaneous real-time ultrasound guided, percutaneous CT guided, transjugular renal biopsy, laparoscopic renal biopsy, and open renal biopsy. The choice of technique among physicians often depends on skillfulness, availability of equipment and compelling indications in the patient. The techniques are briefly described below.

2.1 Percutaneous blind

This technique is now obsolete in advanced countries, but still being practiced in some centres in low and low-middle income countries. The patient is placed in the prone position with a pillow or towel under the abdomen; the lower pole of the kidney to be biopsied is localised using the anatomic landmark (the tip of the twelfth rib posteriorly). Thereafter the skin is prepped, draped, and local anaesthetic is used to infiltrate the skin down to the kidneys. Either the manual (Tru-Cut) or spring-loaded biopsy needle is inserted through a nick made on the anaesthetized skin, and advanced towards the renal capsule while patient breaths gently. When the needle just pierces the renal capsule (signified by a give and swinging of the biopsy needle with respiratory excursions), the patient is instructed to hold the breath, and the biopsy cut is taken. Patient is observed usually for at least 6–8 hours, but may require longer admission depending on the presence of complications. This technique can be cumbersome and potentially associated with complications; tissue yield is often not optimal and several passes may be required to obtain adequate tissue.

2.2 Percutaneous ultrasound guided

Percutaneous ultrasound guided biopsy is the standard of care [7]. This technique can be performed blind after localizing the kidney with an ultrasound probe, or performed with real-time ultrasound guidance. The patient is placed in a prone position with a towel or pillow beneath the abdomen to ensure proper positioning and to stabilize the kidney. The lower pole of the

kidney is localized using the ultrasound probe placed around the renal angle posteriorly (**Figure 2**). The area of skin overlying the lower pole can be marked and the probe removed (blind) or the probe is used to guide the biopsy needle throughout the procedure (real-time). From this point on the procedure is similar to the blind technique.

The use of ultrasound guidance is now universally available in most countries globally, except for some centres in low and low-middle income countries where the ultrasound machine may not be available in the centre or to the nephrologist. The implication of this is that nephrologists in such centres may not have the skill required and this contributes to declining practice of renal biopsy in many of such centres.

2.3 CT guided percutaneous

CT guided PRB may be the primary imaging technique or is indicated in obese patients, patients with complex kidney anatomy (e.g. vascular anomaly, horse-shoe kidney), focal lesions, those in whom kidneys are not well visualized on ultrasound and in patients who have difficulty lying prone [7, 8]. Interventional nephrologists or radiologists perform this procedure in the CT suite. Patients are usually fasted for 8 hours to allow for administration of conscious sedation. An intravenous line is secured for fluid administration and monitoring equipment for vital signs and pulse oximetry are attached to patient [9]. Patient with difficulties lying prone are placed in the ipsilateral side-up position, however the location of a focal lesion also influences the position chosen, e.g. lesions along the lateral edge of the kidney may be difficult to access with an ipsilateral side-up approach [9].

After adequately positioning the patient, a localizing grid is placed and pre-liminary CT images at 5 mm axial slices covering the entire length of the kidney is obtained. Thereafter, the shortest and safe route is chosen, the skin overlying kidney is prepped, draped and anaesthetized with 1% lidocaine. A coaxial needle is advanced to the kidney with CT guidance and core biopsy samples or fine needle aspirates are collected [9]. Once all samples are collected the needle is removed and post-care is given, including a post-procedure imaging to exclude haemorrhage.

2.4 Transjugular renal biopsy

Mal who intended to carry out a liver biopsy but accidentally also obtained renal tissue first performed this procedure in 1989 [10]. Thereafter he further explored the feasibility of the procedure and it has since been practiced with success. Transjugular renal biopsy (TJRB) is performed in a radiology suite by either an interventional nephrologist or radiologist with fluoroscopy guidance.
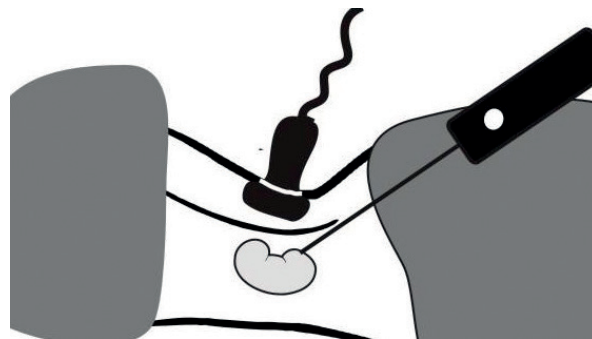

Figure 2.
Percutaneous ultrasound guided renal biopsy.

	US-guided biopsy	**CT guided biopsy**	**Laporoscopic**	**Open biopsy**	**Transjugular biopsy**
Compelling indications	None	Obese Complex anatomy Focal lesions Poor USS visualization	Obese Complex anatomy Bleeding diathesis Poor visualization Failed PRB Solitary kidney Cystic kidneys High kidney location	Obese Complex anatomy Bleeding diathesis Poor visualization Failed PRB Solitary kidney Cystic kidneys High kidney location	Morbidly obese Bleeding diathesis Liver + kidney biopsy
Contraindications	Hypertension Obesity Small kidneys Bleeding diathesis Solitary kidney Infection Obstructed kidney	History of allergic reaction to contrast	*	Religious grounds	History of allergic reaction to contrast
Tissue yield	Good	Excellent	Excellent	Excellent, abundant	Good
Routine admission required	No	No	Yes	Yes	Yes
Complications	Pain Bleeding Injury to structures Infections	Pain Bleeding Injury to structures Infections Radiation contrast nephropathy	Surgical risks	Surgical risks	Capsular perforation Contrast nephropathy
Skill requirement	+	++	+++	+++	++
G. A	No	No	Yes	Yes	No
Cost	+	++	+++	+++	++

*Patient's refusal or uncooperative patients are universal contraindication to all approaches.

Table 1.
Comparing the biopsy techniques.

The aspiration needle or core biopsy approach may be used and the main difference between the two approaches is the biopsy instrument.

The right internal jugular vein is often preferred due to its straighter course to the inferior vena cava. Following injection of local anaesthetic to skin and subcutaneous area, the vein is punctured with an 18-guage needle just above the thyroid cartilage medial to the sternal head of the sternocleidomastoid [11]. A guide wire is inserted and then a venous sheath is introduced over it. Next the catheter is advanced under fluoroscopic guidance through the IVC into the right renal vein. Lastly, the TRJB needle, pre-filled with normal saline and attached to a 20 ml luer

lock syringe, is advanced down the catheter to obtain the tissue core (core biopsy technique) [11]. More than one pass is usually possible to improve tissue yield.

2.5 Laparoscopic and open biopsy

Laparoscopic biopsy is usually performed by a urologist mostly via the retro-peritoneal approach but can be approached transperitoneally. The patient receives general anaesthesia, is placed in full right or left flank position, prepped and draped. Using a two-port technique, firstly the retroperitoneum is entered in the posterior axillary line, halfway between the ribs and iliac crest [12]. The lower pole of the kidney is then localized by blunt dissection with the laparoscopic lens to create a space posterior to the kidney. Next a 5 mm trochar is inserted under direct vision in the anterior axillary line at the level of the iliac crest to identify the kidney; the biopsy is taken using a laparoscopic biopsy forceps [12]. Multiple biopsies can be taken and thereafter haemostasis is secured. In uncertain cases, intraoperative ultrasonography can be performed via a laparoscopic probe, to confirm renal tissue before biopsy [12, 13].

Open biopsies can be performed in patients with contraindication to PRB, or during open abdominal surgeries for other renal indications, e.g. taking a biopsy during a partial nephrectomy. Some patients refuse open biopsies on religious grounds (Jehovah's witness refusing blood transfusion) [12], so the laparoscopic technique becomes the preferred option (**Table 1**).

3. Specimen handling and processing

The manner in which the biopsy core collected is handled and processed contributes to the diagnostic and prognostic usefulness. The tissue core should be gently removed from the biopsy needle using an 18G needle, or washed from the needle onto a Petri dish, using a slow jet of normal saline. A magnifying lens or a dissecting microscope should be used immediately to confirm it is kidney tissue, and whether it is cortex or medulla. The renal cortex appears pale pink to tan with reddish blushes depicting the glomeruli, while the medulla usually contains straight red striations representing vasa recta [14].

The biopsy operator must be knowledgeable of effective ways of dividing the renal core obtained when needed, and the right fixative to use. This ensures that adequate samples are delivered to the pathologist, for the different processing and fixation methods required for light microscopy (LM), immunohistochemistry (IHC) and electron microscopy (EM). At least three cores are required, one each for LM, IHC and EM. The need for dividing tissue core arises if the number of cores obtained is inadequate, e.g. if only one core is obtained, 1 mm cuts are made from both ends for EM, while the remainder is cut in two, the larger of which is used for LM while the other for IHC [14]. Specimen should be placed quickly in appropriate fixatives and accompanied with adequate clinical information to guide the pathologist in interpreting the findings.

3.1 Light microscopy

The fixative for LM is buffered 10% aqueous formaldehyde solution. The tissue is examined using a light microscope which employs focused visible light to magnify objects viewed. Stains are used to enhance characterization of the tissue; common stains are H&E, periodic acid-Schiff (PAS), Silver, and Trichrome. Light microscopy (LM) shows predominantly proliferative lesions, and occasionally

membranous features and crescents. It gives limited magnification and so there is often a need for EM and or IHC to avoid missed diagnosis.

3.2 Immunohistochemistry

This includes immunofluorescence (IF) and immunoperoxidase (IP). The choice of which to use often depends on the pathologist and resources available. Immunoperoxidase (IP) requires no special fixation, since a tissue pre-fixed in formalin for LM can be used for IP depending on the question to be answered. It produces well-developed antigen retrieval and results are reproducible [14]. Immunofluorescence is the choice of most renal pathologist. The fixation used is Zeus solution (modified Michel's tissue fixative). IF produces accurate location of deposits with the aid of dark field microscopes, and excellent resolution when fluorescence microscopes with epifluorescence attachments are used. Routine examinations during IF include immunoglobulin's (IgG, IgM, IgA), complements (C3, C1q, C4) fibrin, kappa and lambda chains. Other antibodies may be examined depending on the question to be answered, e.g. C4d in allograft biopsies.

3.3 Electron microscopy

The fixative for EM is 2–3% glutaraldehyde or 1–4% paraformaldehyde. Electron microscopy (EM) aids in visualizing the ultrastructure and cross section of the kidney tissue including the glomerular basement membrane, mesangium, capillary loops, tubulointerstitium, vessels. Immune deposits are also well visualized.

Ideally all three histopathologic examinations discussed above should be performed on all individual patient's specimens received to avoid missed diagnosis. Diagnosis such as light chain-associated disease, IgA nephropathy, anti-glomerular basement membrane disease may be missed without IHC, while diagnosis such as minimal change disease, fibrillary glomerulopathy, immunotactoid glomerulopathy, dense deposit disease, Alports, and thin glomerular basement membrane nephropathy may be missed without an EM.

4. Appraisal of the methods

The image guided percutaneous techniques are successful in terms of tissue yield in majority of cases. Furthermore, image guidance is particularly instrumental to the safe performance of focus biopsies in cases of cystic kidneys and solid renal masses [9]. Apart from methods described earlier, newer imaging techniques, such as, CT fluoroscopy and fusion ultrasonography may apply to renal biopsy in the future [15].

Percutaneous ultrasound guided approach is standard care for biopsy of non-focal lesions [7]. The real-time ultrasound guided technique has been compared to the blind technique after localisation with ultrasound, and no significant difference in tissue yield was noted [16]. Both techniques have similar potential complications and can be used in similar patients. The rates of complications associated with PRB are difficult to compare across studies because of the heterogeneity of studies in terms of technique and needle used, operator and definitions of complications, e.g. bleeding [7]. These procedures are however done routinely without need for overnight admission except severe complications arise.

Tissue diagnosis may not be successful in about 6% of ultrasound guided biopsies in some series and common reasons are due to operator's technique, type/size of biopsy needle, and patient factors (reduced GFR, small atrophic kidneys,

anatomically complex kidneys). Some comparative studies have reported that automated needles provide superior yield and lower major complication rates than older, hand-driven (Tru-Cut) systems [17, 18]. A 14- or 16-gauge needle provides larger cores and the tissue yields are comparable however, the 14-gauge needle is reportedly associated with more bleeding complications [19, 20]. The 18-gauge needle on the other hand is smaller and some studies report a lower tissue yield [19, 20]. A study by Kriegshauser et al. found that operator experience, taking multiple specimens, and using the cortical tangential approach significantly improved the pathologic material obtained during native renal biopsies [21]. It also helps to have a light microscope available during renal biopsy procedure, to visualize biopsy core immediately after it is obtained.

The CT-guided method can be used in obese patients and other patients who are unable to lay prone, patients with complex anatomy, and when the kidneys are not sufficiently visualised by ultrasound scan [8]. This procedure has been associated with 100% success in some reports [22]. Biopsy of focal lesions is more successful with CT-guidance using either core biopsy or aspiration needle, although some authors have reported increased diagnostic yield when a combination of both needles are used [9]. Unlike the ultrasound-guided technique, it is not performed real-time and patients are exposed to some radiation. Most patients will usually require conscious sedation but can be discharged a few hours after the procedure provided there are no major complications.

Contraindications to PRB such as uncontrolled severe hypertension, morbid obesity, uncontrolled bleeding diathesis, solitary kidney, small kidneys, complex kidney anatomy (e.g. high location, horse-shoe kidney), and renal impairment; are often reasons for selection of alternative techniques. Additionally, failed percutaneous biopsy, poor visualization on imaging, cystic kidney with rapidly progressing GN, and high location of the kidneys are some indications for a laparoscopic or open biopsy [13]. The major advantages of the laparoscopic and open biopsy techniques are the opportunity for direct visualization of the kidney and good intra-operative haemostatic control of the biopsy site [13]. The tissue yield is often abundant and diagnostically useful, however the risks of general surgery/anaesthesia, need for special surgical skill, overnight admissions and high costs are some of the disadvantages.

The transjugular technique is most popular for combined liver and kidney biopsy, and in patients with certain contraindications to PRB (bleeding, inability to lie prone due to obesity, ascites or respiratory difficulty) in whom pathological diagnosis might alter clinical management. Diagnostic yield is comparable with PRB, but differs slightly depending on the approach used, 73–95% diagnostic yield has been reported for the aspiration needle approach [23–26] compared with 89–96.5% for the core biopsy needle [27, 28]. Although judged to be a safe and efficient procedure, there is the risk of contrast induced nephropathy and capsular perforation, which might require coil embolisation. Major complications are seen in 1–18% of cases when using the aspiration needle [23–26], compared to 2.7–27% with the core biopsy technique [27, 28]. Rathod et al. in India reported capsular perforation in five out of nine patients who had TRJRB using the core biopsy approach, although none had major event requiring intervention (blood transfusion or embolisation) [11]. Contrast nephropathy is a concern given that a significant proportion of patients undergoing this procedure have baseline renal impairment, but only 15–30 ml of contrast is used. There is usually no need for overnight stay as patient can be discharged as early as 4 hours post procedure.

Finally, regardless of the renal biopsy method selected, the nephrologist must ensure adequate pre- and post-care of the patient and obtain informed consent. Biopsy protocols should ideally exist in every centre carrying out renal biopsies,

and should be strictly adhered to. It is standard practice before kidney biopsies to check patient's vital signs, obtain a complete blood count, international normalized ratio/prothrombin time, activated partial thromboplastin time, serum creatinine, urine culture, and group/crossmatch blood. Medications should be reviewed for drugs that may increase bleeding risk. Intravenous access is needed and anxious, uncooperative, and/or pediatric patients may require conscious sedation or general anesthesia. Biopsy tissue histology must only be interpreted by experienced and competent pathologists.

5. Conclusion

Renal biopsy can be an indispensable tool in the diagnosis, monitoring, treatment, and prognosis, of patients with non-focal or focal renal parenchymal disease or systemic diseases with renal manifestation. The diagnostic usefulness significantly depends upon the operator's ability to select and prepare the patient based on in depth knowledge of the indications, contraindications and complications. The operator's skill, choice of technique and instruments are key factors that will determine the safety and efficacy of the procedure.

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Conflict of interest

The author declares no conflict of interest.

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