Evolving diagnostic paradigms for small Renal Masses: percutaneous Biopsy, why, when and how

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Authors: F. M. Danza, M. Falcione, A. Paladini, A. Bellieni, L. Bonomo; Rome/IT
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Learning objectives

To propose the use of percutaneous biopsy (PB) in diagnostic workup of small renal masses (SRM). To describe the most recent indications to the use of this procedure. To discuss materials and methods so as to perform the procedure in the right way to reduce the incidence of risks and complications.

In this poster we will analyze the role of PB on SRM, as far as prognosis and treatment are concerned.

Our aim is to make radiologists aware of the importance of a correct characterization of SRM so as to plan the right treatment according to new nephron-sparing philosophy.

This in order to identify the best treatment, aggressive or conservative, of Patients with an un-defined SRM.
Renal tumors often undergo surgery without an histological diagnosis. This attitude is unusual for all other body cancers, where a preoperative diagnosis is always obtained (such as: lung, colon, breast, pancreas, thyroid). It is not a coincidence that, in case of SRM (lesions with diameter less or equal to 4 cm) many Authors describes an incidence of benign lesions after surgical enucleation between 20 and 30%. What is emerging from literature is that renal parenchyma tumors are very different as far as histology is concerned. As a consequence, prognosis and spread capability are not the same. Nowadays, therefore, we need a new diagnostic approach that overcomes the concept of morphological imaging and identify the specific histotype of the mass in providing prognostic considerations and changes in therapeutic options. For this reason it is essential to discuss the use of pre-treatment biopsies of SRM.

This concept is even more important nowadays with small lesions because there are not official diagnostic guidelines. Keeping in mind that the gold-standard treatment is a nephron sparing surgery, we cannot forget that 20% of lesions are benign.

We should also consider that many patients are between 70 and 90 years old, as a consequence the risk of surgery and post-surgery complications is high. In this slice of Patients, therefore, a correct diagnosis of the disease would allow conservative treatment or a minimally invasive procedure (RFA, MW, CRIO, HIFU).

Nowadays, the renal biopsy is performed in presence of a primitive extra-renal cancer or in case of diffuse disease. The reasons for such a poor job reside in the stratified belief that biopsy may not be able to change the prognostic and therapeutic evaluation in addition of being risky. Furthermore, a lot of clinicians believe that histological diagnosis is burdened by a high percentage of false negatives.

PB can identify the specific histology of the mass, providing prognostic considerations and extending the range of treatment options. According to the current protocol, surgery is the gold standard treatment of SRM (radical or partial nephrectomy and enucleoresection). However, following this guideline, two out of ten times, surgeon deletes a kidney affected by a benign and not aggressive cancer (with a pattern of growth of 0.13 cm / year, on average)\(^1\) together with the healthy remaining parenchyma. This is a great waste of money and health for the patient. Moreover, only 9.2% of tumors < 2 cm\(^1\) appears highly undifferentiated in histological analysis. These dates, as a consequence, justify a mini-invasive therapy with less risk for Patient.

Nowadays, however, patient with SRM undergoes to radical or partial surgery so as to remove a mass whose nobody know histology or behavior (more or less aggressive) with all the surgical risks (lesion of the spleen, liver, pancreas, bowel; bleeding; septicemia; renal failure; pneumothorax). Although nephrectomy does not cause renal failure, the absence of a kidney will add more stress to the remaining kidney and progressive renal failure along years.
Moreover new surgical techniques - such as enucleation - have complication rates higher than simple nephrectomy (local or general: AMI, stroke, pulmonary embolism, thrombo-phlebitis).

According to target-therapy philosophy and nephron-sparing theories, biopsy has an important role in diagnosis and treatment planning of undefined masses.

Histological data are essential for the management and correct prognosis of SRM. Renal cancer, indeed, has different histological subtypes with different prognosis and treatment. For example, papillary renal cell carcinoma and chromophobe renal cell carcinoma have better prognosis than clear renal cell carcinoma and collecting duct carcinoma. As a consequence every subtype has a different treatment, and researches focused on the specific biology of each subtype so as to get a target therapy. Current medical therapy for renal cancer looks at radioimmunotherapy, antagonists of G250 (antigen expressed in some renal cell cancer), and inhibitor of the EGFR (Cetuximab).

The actual classification recognizes five different histological types of RCC, divided for morphology, bio-molecular characteristics, epidemiology and prognosis.

Histological data, predicting the cancer behaviour and prognosis, could guide clinician to the right therapeutic choice and it is the right key for personalized treatment in case of SRM.
Findings and procedure details

Nowadays, we obtain the presumptive diagnosis of the nature of the SRM only with imaging (through the study of morphological and functional elements of the lesion), but this approach is insufficient. According to current protocols, the renal biopsy should be performed in case of extra-renal primitive cancer (especially in case of small cell lung cancer), in case of clinical suspect of renal lymphoma (treated with medical therapy) or infection, and in case of Patient with an un-resectable tumor or severe co-morbidities\textsuperscript{[2]}. With the assumption that the choice of therapeutic plan (among drug therapy, surgery or active surveillance) could change on the basis of histology, the clinician needs a new approach to diagnosis that identifies the nature of the mass.

This preface is important to introduce emerging indications to the use of PB in case of SRM. Following these new indications, radiologist should perform renal biopsy:

- to differentiate a benign from a malignant SRM.
- in Patients with SRM eligible for percutaneous ablation.
- in Patients with renal complicated cysts. This is the case of cysts type III - Bosniak classification\textsuperscript{[3]} - with baffles and irregular calcifications.

Thanks to new biological therapies, PB on SRM will play an important role in treatment and management of SRM.

New functional imaging techniques together with studies on the molecular biology of cancer subtypes, could be useful for prognosis and treatment planning of patients.

Sampling procedures

The first step is to get an accurate medical history of the patient, paying attention to any haematological disease that can complicate the biopsy. Radiologist should evaluate a recent CBC and PT/INR. In case of severe heart disease (such as angina and heart failure) or breathing disease (emphysema, COPD), it would be better to have an anesthesiologist in the room during procedure. Patient should stop all anti-platelet therapy (aspirin and NSAIDs)\textsuperscript{[4]} from the week before biopsy, and stop the anticoagulation therapy five days before the sampling. A careful analysis of imaging is very important so as to choose the best approach to the lesion.

Types of sampling
A correct patient positioning is the first step for a good biopsy procedure (Fig.1), in primis depending on the nodule location. The patient can be:

1) Laid down and turned on one side, with the lesion on the side in contact with the table (ipsilateral side down position). This position reduces the movement of the kidney and moves up the ipsilateral pleural cavity.

2) Prone, with easier access to the kidney.

3) Laid down and turned on one side with the lesion on the side opposite to the table (ipsilateral side up position).

4) Supine, i. e. in case of biopsies on transplanted kidney.

Biopsy may be CT-guided (Fig. 2) or US-guided. CT provides an excellent resolution and a better visualization of the needle (especially in obese Patient or intra-parenchymal cancers), but it does not allow real-time procedure. Moreover, CT costs more than US and exposes Patient to a significative dose of radiation. Radiologists should always choose the shortest way to reach the target, trying to avoid adjacent organs.

After identifying the lesion, radiologist uses a co-axial needle to hit the target. The size of the needle depends on the size of biopsy needle and, consequently, on the amount of tissue to take. Coaxial needle permits multiple pass of biopsy needles, either fine or large cutting needles, without espanding the risk of complications. While the operator loads cutting needle on a biopsy-gun, coaxial needle remains in place moving together with the kidney during respiration. Furthermore, coaxial needle is very important to avoid the risk of seeding.

After the sampling, cutting needle is removed before the co-axial one.

Needles are very different as far as length, size and echogenic tip are concerned. Needles used are: cutting needles, pinching needles and suction needles. Pinching and suction needles can be: manual, semiautomatic or automatic. Semiautomatic and automatic models, compared to the manual, have a low risk of bleeding complications and are fast than manual models. Pathologists suggest radiologists should use 14 Gauge needles to obtain good samples, reducing the number of not diagnostic samples. The procedure ends with the manual compression of the wound and the application of a compressive bandage.

Guidelines suggest bed rest for 24 hours and blood analysis 4 hours after the procedure\textsuperscript{[5]}. Furthermore, Patient should avoid exercise and drugs concerning coagulation processes (aspirin, NSAIDs, anticoagulants, etc.) for the following 7 days.
**Analizing of sampling**

So as to get a better accuracy in frustules' analysis, radiologists should take two samples at least, one from the center and one from the periphery of the mass. Data\(^6\) show that a single sample in the central side of the mass has an accuracy of 83.3% while a single sample in the peripheral side has an accuracy of 75%. If radiologist take two samples from both sides, and this is easily obtained with the coaxial needle, biopsy will reach an accuracy of 96.7%. In case of cystic lesions, guidelines suggest we should sample the solid portion before the liquid one. Frustules are very small (1-2 cm x 2 mm on average) corresponing to 0.01-0.02% of the kidney volume.

Pathologists fix the sample with Solufix, that allows a distinction between chromophobe cancer and oncocytoma accentuating the folds of nuclear membrane in the chromophobe subtype. Anatomical evaluation of the sample is performed with Romanovsky-Giemsa (Diff-Quik), hematoxylin-eosin or Papanicolaou stain. Moreover, pathologists use specific colors so as to recognize specific subtypes of RCC, such as colors containing iron (Hale) for chromophobe tumor. Pathologic analysis ends with the Furham grading evaluation on the samples which can be achieved in 68% of biopsies (in 73% of cases the SRM is classified as grade I or II)\(^7\).

**Complications**

Risk of seeding is probably the main reason why biopsy of SRM has not been added to the diagnostic algorithm. According to literature, risk of seeding is 0.01%\(^8\) (only 6 cases described) and is real just for urothelial carcinoma. Moreover the seeding represents a complication after surgery and the its incidence after PB of SRM, as well as in tumors in other parts of the body, has been greatly reduced from the introduction of coaxial needle.

In conclusion the co-axial needle (Fig.3) has two important roles in the procedure:

1) it is a stable guide for the cutting needle to the target, allowing to obtain multiple specimens;

2) it reduce the risk of seeding

Bleeding has a very low incidence (1%)\(^9\), and it might be caused from breaking of normal vessels or vessels created by tumor angiogenesis. Bleeding is usually perinefric or rarely into the collecting system. In the great majority of cases, bleeding is self limiting, easily manageable with an external pressure (compressive bandage). In case of massive bleeding, radiologist can access to an angiographic embolization; other rare complications are.
Syncope, infection, post-operative pain in the lumbar region, arterio-venous fistula, and pneumothorax (incidence lower than 1%). It has not yet been demonstrated a direct proportionality between the size of the needle and incidence of complications.

In conclusion, it is important to underline that incidence of complications during biopsy of SRM is not higher than in other organs where the procedure is usually performed.
Fig. 1: Different positions of the Patient

**Fig. 2:** Cutting needle and target lesion

Fig. 3: Guide Needle equipped with cutting needle

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Conclusion

PB on SRM is a very accurate, sensitive and highly specific procedure to make diagnosis and identify the mass. It is important not only for radiologists but also for the clinician. In the last few years, indeed, it is increasingly important to combine a specific therapy to the specific histotype. As a consequence renal biopsy, together with pathological anatomy, can affect the clinical history of the patient.

In light of the high percentage of benign lesions that occur, the introduction of this technique in diagnostic protocol of SRM will avoid unnecessary surgery.

Thanks to the improvement of techniques and materials, the percentage of failed samples has been greatly reduced from 30% to 22% of cases, while the accuracy in differentiating a benign from a malignant mass, as well as the specificity and sensitivity, is more than 90%. Nowadays the biopsy on SRM could identify tumor histology in 98% of cases.

In addiction, biopsy technique is "universal" and can be applied in small centers, as in big one, with the same values of accuracy, sensitivity and specificity. From a prognostic and therapeutic point of view, therefore, biopsy of SRM is a safe, accurate and repeatable technique and it is very important for clinical history of Patients.

In the next years, the diagnostic power of biopsies may be increased by the support of molecular investigation and FISH$^{[10]}$. The specific gene-expression of a cancer subtype will provide a more accurate prognosis and a right target-therapy (similar to prostate and bladder cancer therapy).

In conclusion an active collaboration between urologists, pathologists and interventional radiologists is crucial to obtain the best results in the diagnosis of SRM. Never forget that the low risk of complications during biopsy is offset by risk of treating patients with incomplete information that could lead to the application of wrong treatments.
Personal information

Danza FM, Falcione M, Paladini A, Bellieni A, Bonomo L.

Department of Radiology, Università Cattolica del Sacro Cuore, Policlinico Universitario A. Gemelli, Largo Agostino Gemelli 8, 00168, Rome, Italy.

Mail to fmdanza@gmail.com
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