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Provisional chapter

Renal Tumor Biopsies: A Shift towards Improving Outcomes in the Management of Small Renal Masses

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Abstract

This chapter reviews the current literature in view of varying clinical practices surrounding the diagnostic role of renal tumor biopsies of small renal masses. Surgical management of small renal masses without pretreatment biopsy is a routine strategy in many urological centres around the world. This is in spite of improvements in techniques, accuracies and biomarkers to diagnose the neoplasm. Apart from its effectiveness, renal tumor biopsies avoid the risks of surgically treating benign renal masses and may also prove cost-effective to healthcare systems. Interdisciplinary communication between urologists, interventional radiologists and pathologists will facilitate the process of making this biopsy-driven management the standard of care.

Keywords: active surveillance, biopsy, diagnostic accuracy, intratumour heterogeneity, kidney neoplasms, renal cell carcinoma, renal tumor biopsy, partial nephrectomies, renal mass biopsy, small renal mass

1. Introduction

The surgical disposition towards partial nephrectomies and ablative techniques in the management of small renal masses (**SRMs**) urges the use of biopsies to overcome preoperative misclassifications.

SRMs are defined to be T1a tumors ≤4 cm in greatest dimension, limited to the kidneys. With improved medical imaging, the incidence of patients with SRMs has been rising. These patients tend to be asymptomatic and show a good prognosis. The current European Association of Urology (**EAU**) guidelines promote nephron-sparing techniques, especially

partial nephrectomies (**PN**) in the management of T1a tumors. Other approaches such as radiofrequency ablation (**RFA**), cryotherapy and active surveillance (**AS**) are also considered.

However, it has been shown that a large proportion of SRMs treated are benign incidentalomas. Twenty percent of surgically removed SRMs have proven to be benign [1, 2] (angiomyolipoma, oncocytoma, metanephric adenoma, etc.), with the figure rising to 29% for tumors <2.5 cm [3]. Thus, it is necessary for current practices to be reevaluated to avoid unnecessary overtreatment.

Surgical management based on CT imaging, without pretreatment biopsy, is considered appropriate in most centres. Such an approach not only leads to the patient undertaking unnecessary surgical risks but also places a significant burden on the healthcare system. Premanagement renal tumour biopsies (**RTBs**) have the potential to not only offer holistic approach to their management but can equally be cost-effective.

Opponents to RTBs believe that concordance rates of the final pathology with radiological imaging, false-negative rates and potential seeding make this an unreliable procedure. However, the safety and outcomes of RTBs have improved significantly over the last decade. Improved imaging techniques allow for a specific localized tissue to be biopsied. Samples taken from percutaneous needle biopsies also now utilize biomarkers that can lend further insights to the heterogeneous nature of renal neoplasms.

It is important to recognize that avoiding unnecessary surgical treatments is more cost-effective and negates associated risks. In this chapter, we will discuss the improvements of RTBs and the merits of incorporating them to deliver better outcome measures.

2. Protocol of SRM management

It is estimated that 60% of all diagnosed renal cell carcinomas (**RCCs**) are SRMs that are discovered as incidentalomas on ultrasound and/or abdominal CT scans [4]. The current protocol in many urological renal centres, following the discovery of a SRM, is to offer the patient treatment options without a biopsy. Generally, unless contraindicated, these options include PN, RFA, or AS. This approach to treating a SRM is done without a clear histological diagnosis.

There should be a paradigm shift on how SRMs are approached. In some centres, RTBs are now performed upon the discovery of an incidentaloma. Here, patients are referred to an interventional radiologist who will then perform a RTB before their consultation with their urologist. Following the biopsy results from the pathologist, the urologist will meet the patient and offer better informed treatment options.

3. Contemporary indications and contraindications for biopsy

The EAU guidelines recommend RTBs to be performed for AS on selected patients with SRMs, prior to ablative treatments and patients suffering from renal metastatic disease before embarking on systemic treatment.

The American Urological Association (**AUA**) guidelines stipulate that biopsies should be considered when a renal mass is suspected to be metastatic, hematological, inflammatory or infectious. RTBs are also expected to be performed before ablative procedures.

Historically, absolute contraindications to RTBs include uncontrolled severe hypertension, inability to cooperate with biopsy, solitary kidney and uncontrollable bleeding diathesis [5]. Relative contraindications may include a lack of a safe pathway to the lesion and pregnancy where imaging guidance involves ionizing radiation.

4. Prevalence of biopsies

Recent studies have shown that RTBs are still not widely adopted among urologists in clinical practice. A survey in 2010 by Barwari et al. [6] showed that 73% of urologists never take biopsies and only 9% take biopsies in more than 25% of cases. Another survey in 2016 by Richard et al. [7], investigating the prevalence of biopsies for SRMs, showed that only 12% perform RTBs in >75% of cases, while 53% never perform or perform RTBs in <25% of cases.

In both surveys the main reasons urologists cited for not performing biopsies were the lack of influence in clinical management, the risk of false negatives and safety. There is also a radiology-related concern of a lack of expertise with RTBs [7]. These concerns will have to be tackled.

4.1. Prevalence of RTBs in active surveillance

In current literature, many patients undergoing AS have not had a biopsy [8–10]. AS is usually indicated for elderly patients with significant comorbidities or those refusing surgery. Though considered a safe option for patients with SRMs, the risk of developing metastatic disease during surveillance is not ruled out. A systematic review performed by Prins et al. [9] showed that though 1.12% (0–3.2%) of the pooled AS population (968 patients) incurred delayed intervention, only a small proportion of the said population had undergone a RTB. If a biopsy had been performed, it could have led to an earlier appropriate intervention [11]. A systematic review performed by Smaldone et al. [10] looked at the incidence of metastases in AS strategies. In this review of 880 patients, 18 patients (2.05%) progressed to metastatic disease. Unfortunately, only three of these patients had undergone a RTB.

RTBs can also pave the way for a more refined AS strategy and are strongly recommended [8, 10, 12, 13]. If the SRM proves to be histologically benign, a less stringent follow-up protocol can be adopted, or the patient may even be discharged. Higher metastatic potential masses that are better suited for surgical intervention can also be identified. Thus, RTBs can stratify patients into a low-risk or high-risk surveillance strategy.

4.2. Prevalence of RTBs in radiofrequency ablation

In some centres performing RFA, RTBs are either done at the time of the procedure or not performed at all [14–16]. These patients continue to be treated with a presumptive diagnosis of renal cancer based on CT/US imaging. This increases the rate of RFA performed for benign

or indeterminate pathology [15]. Performing RTBs prior to ablative techniques can also be used to stratify patients—where those with unfavorable histology can be triaged to surgery instead.

5. Addressing barriers

In order to facilitate the shift in managing SRMs (be it in AS, RFA or systemic treatment), it is important for us to address these barriers in adopting RTBs. We will now assess the reliability and improvements of RTBs.

5.1. Improved techniques for biopsy

RTBs are performed percutaneously under local anesthesia. It can be with needle core biopsy or fine needle aspiration (FNA) with US or CT guidance.

Core needle biopsies yield a higher diagnostic rate and a more accurate histological examination over FNA. This was exemplified by a systematic review performed by Marconi et al. [17] (57 studies recruiting 5228 patients)—showing superior sensitivities and specificities over diagnostic FNAs. A coaxial technique allows multiple biopsies to be taken through a coaxial canula, avoiding potential tumor seeding. Comparing needle sizes used, 18-gauge needles are preferred over 14- and 20-gauge needles—showing safer and more accurate histological results [18, 19].

With regard to imaging modalities, US and CT possess their own merits. CT has the advantage of a better resolution that is ideal to locate lesions that are in proximity to critical structures. US has the advantage of lower radiation and lower cost. More importantly it allows real-time needle placement that is suited for nonfocal renal lesions [20].

In spite of acknowledging preferred techniques of RTBs, there are other technical factors that affect their success: amount of adipose tissue in the patient, echogenicity and location of lesion. The challenge of performing a successful biopsy can thus vary from lesion to lesion. Effective communication between the interventional radiologist and urologist is necessary to ensure that a RTB would be reliable in managing a specific SRM.

5.2. Improvements in accuracy

Recent literature lends support to the diagnostic accuracies of RTBs, challenging the notions some urologists believe. The meta-analysis performed by Marconi et al. [17] showed that initial RTBs yielded a diagnosis in >90% of cases. Core biopsies showed a high sensitivity and specificity of 99.1 and 99.7%, respectively. In cases where both a RTB and surgical pathology were available, good concordance ($k = 0.683$) for tumor histotype and fair concordance ($k = 0.34$) for tumor grade were shown.

A systematic review by Patel et al. [21] (including 20 studies with 2979 patients) showed a high diagnostic accuracy of RTB with a sensitivity of 97.5% and a specificity of 96.2%. There

was also a high histological concordance observed. Patel's study highlighted the concern of a reasonable non-diagnostic rate (14.1%).

However, repeat biopsy led to diagnosis in 80% of previously undiagnostic biopsies. It is reported that following a non-diagnostic biopsy, a repeat biopsy has a high rate of rendering a diagnosis—ranging from 67 to 85% [22]. Therefore, in the case of a non-diagnostic biopsy, there is merit in performing a repeat biopsy.

With overall improved diagnostic accuracies of RTBs, urologists should be more reassured about their successes.

5.3. Managing complications

Reported concerns regarding the safety of RTBs stem from the risks of bleeding, pneumothorax and tumor seeding [7]. Rising literature appraising the choice of gauge needles, imaging modality and preference for core biopsies over FNA have improved the safety of RTBs.

In Patel's et al. study [21], complication rates observed were quite low. The rate of haematomas was 4.9%, while the occurrence of any clinically significant pain was 1.2%. Pneumothorax was only detected in 0.6% of cases, and no study reported any cases of tumor seeding. In Marconi's et al. study [17], the median complication rate was 8.1% with only three Clavien grade ≥2 complications to be reported.

Tumor seeding along the needle tract is anecdotal and very rare. As per the EAU reported guidelines, to avoid any such complication, coaxial sheaths should be used. This allows multiple passes through the renal mass with only one through surrounding tissue.

5.4. Discerning tumour heterogeneity

Despite the high concordance rates in identifying tumor subtypes (as mentioned above), the heterogeneous nature of RCC in itself is an identified barrier in adopting RTB. It is essential for clinicians to identify the challenges in discerning between specific tumor subtypes in order to have a comprehensive grasp on the reliability of a RTB.

The four main subtypes of RCC include clear cell RCC (**ccRCC**), papillary RCC (**pRCC**), chromophobe RCC (**chRCC**) and collecting duct carcinoma (**CDC**). There are over 10 such subtypes with many inherited syndromes [23]. Each subtype is associated with its own prognostic factors from clinically indolent (pRCC type 1, chRCC) to highly metastatic (pRCC type 2 or ccRCC). Thus, it is valuable for a subtype to be distinguished from benign lesions and also to be reliably identified for a more tailored management.

Another systematic review by Patel et al. [24] investigated the success of identifying oncocytomas. Of the 48 lesions that were diagnostic of oncocytoma on RTB, 64.6% was in concordance with analysis following surgical treatment. Meta-analysis determined the PPV of oncocytoma on RTB to be 67% with a notable proportion to be identified as chRCC. Histologically, they are hard to distinguish as both have an eosinophilic cytoplasm. Clinical diagnostic dilemmas between chRCC and oncocytomas still remain. Clinicians should factor this in tailoring an altered AS for oncocytomas.

6. Investigating biomarkers

Recent studies have explored the merits of molecular biomarkers to improve diagnostic classification of RTBs. A recent systematic evaluation by Gulati et al. [25] assessed cancer-specific survival (**CSS**) in 350 ccRCC patients with 28 published genetic biomarkers. Seventeen of these genetic and transcriptomic prognostic ccRCC markers were validated as predictors of CSS. A comprehensive review article by Farber et al. [26] shows the many other areas where biomarkers are being developed: PET imaging, MRI, serum biomarkers, urine biomarkers, liquid biopsy and immunohistochemistry. Of particular interest is the staining method for CK7 that is expressed in both chRCC and oncocytoma. In the former it is strongly and diffusely positive, while in the latter, only focal positivity or no staining is observed [18, 26, 27]. With further prospective clinical studies, a combinatorial approach can be adopted to discern the heterogeneous nature of renal lesions.

7. Cost-effectiveness

It is critical to stress on the cost-effectiveness of integrating RTBs in the management of SRMs. A cost-effectiveness study by Pandharipande et al. [28] showed that a strategy of pretreatment biopsies of SRMs leads to a minimally greater difference of quality-adjusted life expectancy (4 days) than empiric surgery. This is at a lower lifetime cost of ($3466). Avoiding unnecessary surgery in cases of resecting indolent SRMs is in the interests of both the patient and the healthcare system. With similar outcomes and lower cost, the use of biopsy to triage patients facilitates this.

8. Conclusion

RTBs have the strong potential to avoid unnecessary surgeries, preventing treatment-related morbidities in patients and saving healthcare costs. RTBs have high diagnostic accuracies, high concordance rates and low complication rates. Therefore, RTBs should be integrated in the pretreatment management of SRMs when their results can alter the treatment options for the patient. Further studies in improving diagnostic biomarkers are worthwhile in supplementing the classification of RCC subtypes.

This shift in management away from empiric surgical treatment requires support from interventional radiologists, histopathologists and urologists. An interventional radiologist would be suited in identifying the preferred imaging modality for a specific RTB and explaining the difficulty to obtain an adequate amount for a reliable diagnosis. A histopathologist can raise concerns on potential misclassifications of specific tumor subtypes.

Integrated clinical communication between these disciplines can optimize the effective use of a RTB in crafting a well-suited treatment plan for the patient.

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