Indications for biopsy and the current status of focal therapy for renal tumours

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Abstract: The increased detection of small renal masses (SRMs) has focused attention on their uncertain natural history. The development of treatment alternatives and the discovery of biologically targeted drugs have also raised interest. Renal mass biopsies (RMBs) have a crucial role as they provide the pathological, molecular and genetic information needed to classify these lesions and guide clinical management. The improved accuracy has improved our knowledge of the behaviour of different tumour histologies and opened the potential for risk-adapted individualized treatment approaches. To date, studies have demonstrated that percutaneous ablation is an effective therapy with acceptable outcomes and low risk in the appropriate clinical setting. Although partial nephrectomy (PN) is still considered the standard treatment for SRM, percutaneous ablation is increasingly being performed and if long-term efficacy is sustained, it may have a wider application for SRMs after biopsy characterization.

Keywords: Biopsy; focal therapy; renal tumours; surveillance

Introduction

The incidence of kidney cancer has been increasing, largely due to the increased use of imaging and the incidental detection of small renal masses (SRMs) (1,2). Not all SRMs are malignant and those that are, demonstrate heterogeneous pathology and behaviour. These features are not reliably predictable with conventional imaging or biomarkers (3). Early efforts to predict malignant pathology and tumor grade using tumor size and other clinical variables (such as age, gender, smoking history and presence of symptoms) are inaccurate, which limits their clinical utility (4,5). The presence of an enhancing renal lesion in CT imaging has traditionally been considered by the majority of the urologists as sufficient indication of surgery. Increasingly, renal tumour needle biopsy is being performed to characterize SRMs to assist in treatment decisions, as not all are malignant (3,6). Active surveillance and focal therapies are increasingly being considered as alternatives to partial and radical nephrectomy in selected patients. A multidisciplinary approach with experienced urologists, pathologists and radiologists is optimal for an accurate diagnosis and individualized renal mass management.

Renal mass biopsy (RMB) techniques, accuracy and safety

At least 20% of the SRMs are benign and these do not always require treatment. RMB/renal tumour biopsy (RTB) is increasingly being used to characterize renal masses.

RMB techniques

Several developments have been made in biopsy technique, imaging approaches, pathology evaluation and genetic testing in a way to improve renal mass characterization.

RMBs are performed as an outpatient or short-stay procedure using ultrasound or CT guidance with local

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anesthesia (7). MRI could also be used. There is no data to suggest superiority of one image guidance method over another (8). In experts' opinion, the imaging should be chosen based on the availability, expertise, patient and tumour characteristics (9). Preference should be given to US to limit exposure and cost (9).

The technique has evolved, but basically RMBs are performed using two methods; fine-needle aspiration (FNA) and needle core biopsy. The accuracy of FNA for the diagnosis of malignancy is inferior to that of core biopsies (10). Cytologic evaluation only permits diagnosis of tumour histology and grade in a minority of cases (11,12). Some authors imply that the two techniques can provide complementary results, increasing diagnostic rates and accuracy but we rely on needle cores (9,13).

We believe that co-axial sheathed needles are superior for needle core biopsies although there is variation in practice (7). The coaxial technique allows multiple biopsies through one tract with an increased likelihood of sampling the tumour with each pass, although the site sampled will not be as geographically distributed throughout the tumour. The use of the coaxial techniques appears to reduce the risk of tumour seeding along the needle track (14,15). The use of an 18-gauge needle is associated with low morbidity and provides sufficient tissue for diagnosis in the majority of cases. Needle cores provide a greater diagnostic yield and better accuracy for diagnosing malignancy and histological type in comparison with FNA. There is no consensus about the ideal number and location of core biopsies. It is accepted that at least two good quality cores (non-fragmented, >10 mm in length) should be obtained, and necrotic areas should be avoided to obtain a diagnostic specimen in up to 97% of cases (8,9,11,12,14-16). Regardless of the number of cores, the quality of the tissue retrieved seems to be the most important variable for biopsy success (17). Further studies are needed to define the ideal number, site and length of RMB, mostly based in the new upcoming methodologies for tumoral heterogeneity characterization.

RMB accuracy

A diagnostic rate of 80-94% including the identification of renal cell carcinoma (RCC) subtypes has been reported in larger series (6-8). Many studies published before 2001, reported false negative or non-diagnostic rates up to 25% (13,18). Of diagnostic biopsies, a benign diagnosis is obtained in 20-30% of cases.

One of the main concerns about RMB is the rate of non-diagnostic samples. A non-diagnostic biopsy is not a surrogate for benign pathology (8). These could represent samples with insufficient tissue, normal kidney parenchyma, or other situations where the renal mass cannot be described. Rates of non-diagnostic samples range between 0 and 47% and are more frequent in small and cystic lesions (3,8). Several authors have reported higher diagnostic rates for repeat core biopsies (83%) after a first non-diagnostic one (3,6,8,19).

Overall tumour size in particular, including the size of solid components of cystic tumours, and location correlate with diagnostic yield (3,7,20). The risk of cyst rupture with potential local seeding of tumour cells limits the role for biopsy in Bosniak IV cysts with enhanced solid areas (12,21,22). We manage tumours <1 cm in diameter by initial active surveillance until they reach 1 cm before an attempt to biopsy with increased diagnostic rate (8,12,23). Sampling error, tumour necrosis and tumour heterogeneity are responsible for most false-negative biopsy results (22).

Although tumour heterogeneity is a potential cause of sampling errors, concordance with dominant surgical pathology has been reported in approximately 100% of cases, and erroneous diagnosis of benign *vs.* malignant after adequate biopsy specimen is now rare (3,14,24). The infrequent hybrid tumours are difficult to adequately define using RMBs (25). It is possible to miss the malignant portion of a hybrid tumor and misclassify the lesion as being benign. Hybrid tumours have previously been reported to be present in up to 18% of oncocytomas diagnosed following RMB, although this has not been our experience (25,26).

The relative accuracy of grading renal cell cancers with percutaneous biopsy is controversial, with reported accuracy rates ranging from 43% to 75% (14). Grade concordance at surgery has traditionally been reported as low when evaluated grade by grade (12,27). However, in our recent series of 496 biopsied masses, when Fuhrman grades are pooled into low- and high-grade, the concordance is as high as 96.1% (6). Millet *et al.*, also found an increase in concordance and accuracy when combining low and high Fuhrman grades (as high as 93%) (27). Intratumoral grade heterogeneity has been reported in 5-25% of renal tumours, this may lead to an underestimation of the genetic complexity of a tumor when single-biopsy procedures are used (28).

Experience is required for pathological interpretation of biopsy specimens (29). Another limitation of RMB may occur in patients with multifocal renal lesions (both unilateral and bilateral) with possible discordance between different

tumours. Knowing the histology of one tumour does not necessarily reveal information about the histology of the other synchronous tumours (30). Thus, in patients with multiple lesions in which RMBs are being considered, each lesion should be biopsied to identify their respective histology.

Experienced multidisciplinary centers are more likely to achieve diagnostic outcomes with biopsy (3). Multidisciplinary expertise in urology, pathology and imaging is crucial to exploit the diagnostic yield of renal tumour biopsies.

At a genomic level, Gerlinger *et al.*, using whole-exome sequencing, found that somatic genetic mutations are not present ubiquitously within the primary tumor in cases with metastases (31). It is not surprising that intratumoral heterogeneity might be of concern clinically but the rate of clinically significant genomic alterations is still undetermined (32).

In the new era of personalized medicine, we believe that intratumoural heterogeneity is matter of concern. Potential tumour heterogeneity presents a considerable therapeutic challenge. A single tumor biopsy, currently the standard of tumor diagnosis, despite the high diagnostic rate, may not be representative of the landscape of genomic abnormalities in a tumour. Further studies and new markers will help us understand the role of heterogeneity in renal masses in treatment and follow-up.

Alternatives to needle biopsy are an appealing concept. New biomarkers and fluid biopsy (using blood and urine) are exciting prospects. Recently, Morrissey *et al.*, presented data updating their experience with the clinical utility of the urine biomarkers, aquaporin-1 (AQP1) and perilipin-2 (PLIN2), to screen for RCC (33). Elevated AQP1 and PLIN2 levels are associated with the presence of RCC and have potential utility in both general population screening and the SRM management setting to distinguish malignant from benign (33). Frantzi *et al.* reported a marker model based on urinary peptides, as a tool for the detection of RCC in selected patients at risk (34).

Safety

Major complications of biopsy are rare (<1%). A small amount of bleeding (minimal perirenal and subcapsular hematoma) is common (85% to 91%) based on post-biopsy CT imaging but haemorrhage necessitating blood transfusion is rare (13,18). The risk of bleeding appears to be greater with larger (<18-gauge) needles. Possible tumour seeding along the needle track is the greatest concern and is frequently raised by patients and physicians based on older literature and internet sources. However, only few cases of tumour seeding along the needle track have been reported and all were prior to 2001, probably due to improved techniques trough a coaxial guide or cannula (35-38). Other potential complications of RMB include infection, pneumothorax (<1%), and arteriovenous fistula (7).

Indications for RMB

The use of renal biopsies was historically indicated to diagnose secondary, metastatic renal tumours as well as benign non-tumour pathology such as renal abscess (28).

There is increasing acceptance in many centres that RMB should be offered to most, if not all (as we do) patients presenting with a SRM including those who are potential candidates for surgery or ablative therapy (pre-treatment) as well as active surveillance (39,40). Other indications include post ablative therapy for suspected recurrence, confirmation of a complete ablation and RCC subtype characterization of the primary in the setting of metastatic disease to select the optimal biological systemic therapy (particularly when a cytoreductive nephrectomy is not indicated). The role for biopsy of larger localized tumours (> T1b) is controversial but may be used increasingly when partial nephrectomy (PN) is being considered to rule out high grade tumours with theoretically higher risk of local recurrence and the not so rare, large oncocytoma or fat-poor component AML.

There are few contraindications for RMB. The only absolute one is un-correctable coagulopathy. Relative contraindications for RMB might include those in patients with short life expectancy who are not candidates for any surgical, ablative or medial treatment, as the results would not alter the management strategy.

Impact of RMB in clinical management

Treatment decision making for SRM's is an increasingly frequent and challenging clinical problem. The selection of the optimal treatment modality is based on patient age, clinical assessment of patient comorbidities and tumour characteristics (3). Non-adopters of routine RMBs have long argued that results will not affect the clinical management. However, recent study results suggest that this is not the case.

RMB can decrease the SRM surgical and ablation rate if benign disease is observed. Despite improvements in imaging, benign lesions cannot be accurately identified.

Frank *et al.* verified that 30% of renal lesions <4 cm that were removed by surgery (between 1970 to 2000) were benign (41). Rothman *et al.* proved that among patients with localized renal lesions, 84% of renal masses with <4 cm in size are low grade lesions (42). In the Toronto cohort, we have demonstrated that nearly 41% of our cohort avoided definitive treatment following biopsy either because they were found to have a benign tumor, favourable histology for active surveillance or because the RMB confirmed the presence of metastatic disease of another primary origin. Similarly, Maturen *et al.* have shown that biopsies can significantly impact clinical management in 60.5% of their cohort, which was defined as a change between surgery and no surgery (43). Oncocytomas and fat-poor angiomyolipomas with component are lesions that can frequently be misdiagnosed on imaging (27,44,45). In other series of percutaneous biopsies, surgery was avoided in 16-17% of patients after a histologic benign diagnosis (11,12,14).

Patients' life expectancy and performance status (Charlson Comorbidity Index) are predictors of overall survival (OS) (46). Thus, the perception that active treatment for SRMs may not improve OS as led to the development of conservative and minimally invasive treatments for selected elderly and surgically high-risk patients (47). For these patients, the characterization of their renal lesions is crucial and RTB can provide useful information.

RMB are also very useful for active surveillance protocols. The concept of active surveillance arose from the knowledge of the natural history of renal masses. In general, small low-grade lesions are indolent and non-harmful in the short term at least. The active surveillance protocols are built on tumour kinetics concept where non-growing or slow-growing tumours are amenable to follow-up with abdominal imaging and symptom evaluation. However, although tumour kinetics provide important information, the assessment of growth rate alone is not sufficient to determine malignancy. We have demonstrated that the initial growth rates of histologically benign and malignant lesions are not significantly different (48).

Minimally invasive treatments, such as radiofrequency ablation (RFA) and cryoablation (CA), are frequently used for SRMs in older patients with comorbidities and high surgical risk. Pre-ablation renal biopsy is often the only source of pathology in patients undergoing thermal ablation of a SRM. We recommend RMB before the treatment decision to reduce the risk of unnecessary ablation. Pre-ablation biopsy was shown to have a high diagnostic

yield of 94.2% in a multicentre series of RFA (49,50). Routine post ablation biopsy is not consistently done, however persistence of viable tumor after the procedure is possible and imaging may not detect viable tumor after thermal treatments (51,52). Weight *et al.* demonstrated that 46.2% of renal tumours with a post-ablation positive biopsy after RFA exhibited no enhancement on post-treatment CT or MRI (52). These results should stimulate urologists to define protocols for thermal ablation where pre-ablation and post-ablation biopsies are considered to monitor treatment success.

Another indication for RMB with potential impact is in metastatic RCC. The use of targeted therapies has increased the interest in renal tumours histologic characterization. The new era of targeted therapy enable urologists and medical oncologists to precisely target oncologic disease based on their histologic and genetic features. It is known that 20-30% of RCC present with metastatic disease and similar proportion of patients will develop metastases after surgical treatment of localized disease (53). Percutaneous biopsies can assess the presence of adverse prognostic factors and the histologic subtypes, both useful for selecting specific systemic treatment. Targeted therapies demonstrate different response rates in different histologic subtypes. Sunitinib and sorafenib showed low clinical responses when treating papillary lesions, though the efficacy of mammalian target of rapamycin (mTOR) inhibitor, temsirolimus, may be more effective among non-clear cell lesions and papillary subtype than in clear cell lesions (54,55).

We support adoption of RMB in the management of all solid, contrast enhancing SRMs (3).

Potential for histological, molecular and genetic characterization of renal tumours using biopsy material

Relevant information from RMBs with respect to biological aggressiveness is of great potential clinical value when making treatment recommendations. Sarcomatoid de-differentiation or histological necrosis correlates with decreased recurrence-free survival (56,57). It has been known for some time that carbonic anhydrase IX has prognostic implications for patient with localized and metastatic disease (58). However, subsequent advances in translational research have enabled increasingly relevant information from tissue sampling. Diagnostic and prognostic information can be obtained not only with immunohistochemistry (IHC), cytogenetic and molecular

analysis but also gene expression profiling (3).

An IHC antibody panel, including CD10, parvalbumin, a-methylacyl-coenzyme A racemase (AMACR), cytokeratin 7 (CK7), S100A1, cathepsin K, and carbonic anhydrase IX (CAIX) and others, seems to be the most promising (3). Some other studies have used RNA based assays; this molecular diagnostic algorithm increased the overall accuracy for histotype diagnosis from 83.3% to 95%, with sensitivity and NPV for diagnosing the clear cell variant at 100% (59).

Fluorescence in situ hybridization (FISH) studies, analyzing chromosomal abnormalities have shown to improve the accuracy of IHC. The addition of cytogenetic information to histology alone increased to 94% the diagnosis accuracy (59).

Several molecular and genetic tissue markers have been investigated as potential prognostic factors for RCC, including markers typically associated with renal cell carcinogenesis and progression [von Hippel-Lindau, hypoxia-induced factor 1 alpha (HIF-1α), VEGF, CAIX, pS6, phosphatase and tensin homolog] and markers described in other malignancies (p53, Ki67, CXCR3, CXCR4, matrix metalloproteinases 2 and 9, IGF II mRNA binding protein, epithelial cell adhesion molecule, vimentin, fascin, livin, survivin) (60). Microarray technology has demonstrated some ability to differentiate tumours by gene expression profiling (61). There is evidence that gene-expression profiles obtained with high-throughput microarray technology can identify histologic subtypes of RCC and predict clinical outcomes of the disease. Lane *et al*. recently identified a 44-gene expression profile that was able to distinguish two groups of ccRCCs with significantly different clinical behavior (62).

Overall, the results of studies with available molecular and genetic tissue markers are promising.

Clinical nomograms and their utility in SRM management

Clinical nomograms have been proposed to predict SRM malignancy prior to surgery as a substitute for RMB. Combining individual descriptors of the nephrometry score with patient characteristics (age, gender), Kutikov *et al*. developed a nomogram that could accurately define malignant RCC histology and high-grade features (5). Recently externally validated, these models represent the most accurate preoperative predictors of malignant potential of localized renal tumours to date, and their

accuracy for predicting tumor grade may match that of percutaneous core biopsy (63,64). Although early efforts have been encouraging, the role of statistical modeling for risk prediction during AS is likely to evolve and expand in the future (65).

Focal therapy for SRMs

During the last 20 years, minimally invasive and nephron sparing surgical approaches have become widely available. PN, more commonly done laparoscopically or robotically, remains the gold standard treatment for cT1 SRMs that are RCC (SRM^{RCC}). However, focal ablative therapies, CA and RFA are increasingly used. Microwave ablation, laser ablation and high-intensity focused ultra-sound are alternatives energy sources for ablation but are generally considered experimental techniques.

Patients considered candidates for percutaneous image-guided renal tumor ablation are typically evaluated jointly by an interventional radiologist and a urologist in our centre. We regularly perform pre-ablative biopsy and up to 37% of biopsied SRMs in this setting are benign oncocytomas or lipid-poor angiomyolipomas (41,66). In addition, pre-ablative biopsies can provide the interventional radiologists with a better understanding of how the patient will tolerate the ablation, the optimal position for ablation, the best percutaneous approach to the lesion, and how much IV sedation and analgesia might be required (67).

There is general consensus that ablative techniques are ideal for many SRM patients who are unfit for surgery, who are not candidates for active surveillance or who prefer these methods. Presently, the European Association of Urology (EAU) guidelines state that no recommendation can be made for RFA or CA due to the low quality of available data (19). The American Urological Association (AUA) guidelines state that ablation in general should be offered as an option but is not as a standard for high-risk patients (68). General limitations for focal ablative techniques are lesion dimensions (success is inversely related to size), lesion location (proximity with abdominal organs or vessels) and patient morbidities (malformations limiting access to the lesions, coagulopathies).

The advantages of CA include real-time imaging of the therapeutic ice-ball, uniformity of the ablation zone, the use of multiple probes simultaneously, outpatient therapy and repeat therapeutic cycles at the same setting. It is relatively safe which has encouraged the acceptance of this modality as an alternative to PN (19).

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CA is performed using either a percutaneous or a laparoscopic-assisted approach (under vision) with no difference in terms of overall complications (69). In a survey of 64 institutions performing ablative procedures for SRMs, Patel *et al*. identified laparoscopic CA as the most commonly performed ablative procedure (70). However, the percutaneous approach is associated with a shorter hospital stay and less morbidity (69).

Local disease control occurs in 85% to 99% of cases (lower than with PN) (71). The overall complication rate after laparoscopic CA ranges from 10% to 20%, and are generally minor. Bleeding (5%), urinary leakage (<0.5%) and adjacent organ injury (0.6%) are reported complications (72-77). Renal function is generally not affected by CA (72,73). Compared to PN, CA is associated with shorter operative times, less blood loss, shorter length of hospital stay but a higher risk of local and metastatic disease progression (78).

Percutaneous CA is generally done with CT guidance but US can also be used. Local control ranges from 84% to 97% (72,75,79,80). The results for local disease control are similar to CA techniques. Complication rates are around 20% (Clavien I and II) and are usually bleeding and hematoma (81). As in the laparoscopic approach, with percutaneous CA, measurable renal function is expected to be unaffected (82). One advantage of percutaneous ablation relative to laparoscopic is lower cost (83). Patients submitted to CA are followed by CT imaging with local recurrence or residual lesions appearing as enhancing lesions (84).

Recent data demonstrate that CA is a reasonable option for older patients, patients with several morbidities, solitary kidney or renal impairment, or patients in whom surgery is not felt to be feasible. Additional indications for CA are treatment of local recurrence, *de novo* tumours following ipsilateral PN or even metastatic lesions (85,86).

Zlotta *et al*. first used RFA in RCC patients in 1997, and demonstrated that this technique could be performed without damage to the surrounding healthy kidney (87). Since then, this methodology is increasingly used in urology departments and is currently the most commonly used and studied mode of ablation (67). RFA can be performed laparoscopic or percutaneously (guided either by US or CT) and is usually recommended for patients with lesions <3-4 cm, according to the EAU and AUA guidelines respectively, although some authors have reported successful treatment for pT1b lesions (88). There are no difference in terms of complication rate and type when comparing RFA performed laparoscopically with the percutaneous approach. RFA complications are generally minor but occur in up to 29% of patients (19).

As in other ablative techniques, clinician concern is related to the ability of these methods to achieve good oncological outcomes. A meta-analysis showed a 12.3% risk of local recurrence after RFA (89). However, more recent work shows a better oncological outcomes with local recurrences ranging from 2.5% to 9% for lesion <4 cm (90,91). A systematic review by Katsanos *et al*. showed that RFA of SRMs produces oncologic outcomes similar to nephrectomy and it is associated with significantly lower overall complication rates and importantly, less decline of renal function (92).

Recently RFA has been reported for the management of cT1b lesions with local control highly dependent on both tumour site and location (93). RFA is not recommended for central tumours with contact with the hilum, vessels or ureter due to heat sink effect (90).

Cryotherapy *vs*. radio frequency ablation

Two published studies comparing RFA and CA did not show significant differences in OS, cancer specific survival or recurrence-free survival (94,95). When considering local recurrence-free survival at five years, one study reported benefits for RFA and the other benefits for CA (94,95).

RFA is known to be effective in the treatment of small, peripheral renal masses (96,97). In contrast, CA appears more effective with tumours >3 cm or extending centrally into the kidney, though at the cost of increased complication rates (98).

A recent study evaluated the clinical outcomes of PN, percutaneous RFA, and percutaneous CA for the treatment of cT1 renal masses (93). Local control was similar among the three treatment groups, metastases-free survival was inferior for RFA, and OS was superior for PN. For patients with cT1b renal masses, local control and metastases-free survival were similar for PN and CA patients and OS favored PN patients (93). Kunkle and Uzzo reported that 12.9% and 5.2% of patients experienced local recurrence of their T1a tumor after RF ablation and CA, respectively, suggesting RF ablation to be the superior modality (89).

Microwave ablation is an experimental technique. It creates kinetic energy that is transformed into heat, leading to coagulation necrosis and cell death (99). Some studies have been published with success rates varying from 62% to 100% (100-103). In the Guan *et al*. study, a comparison between microwave ablation and PN showed that blood

loss, complications and postoperative decline of renal function is significantly better in the microwave ablation group (102). Recurrence-free survival at three years is not statistically different although the rates were 90.4% for microwave ablation and 96.6% for PN (102). Castle *et al.*, reported intra-procedural complications in 20% of patients, post-procedural complications in 40% of patients, and recurrence in 38% of patients followed to 17.9 months on average (101).

Laser interstitial thermotherapy, another experimental approach, utilizes an optical fiber inserted with US, CT or MRI guidance (104). Two different types of lasers have been used, Nd:YAG laser or diode laser, and both showed feasibility but further studies are needed for renal tumour treatment.

High-intensity focused ultrasonography (HIFU) is a therapeutic modality that induces heat by the absorption of focused ultrasound waves within targeted tissue, inducing cellular necrosis. Currently, there are two ways to perform HIFU treatment, extracorporeal or intra-corporeal. In contrast to CA and RFA, extracorporeal HIFU has the advantage of being a non-invasive treatment. It is also theoretically able to induce coagulation necrosis without damage in the surrounding healthy renal parenchyma and skin, because US beam intensities outside of the focal zone are much lower (105). There are no major complications related to HIFU (106). Marberger *et al.* performed a clinical phase II study which demonstrated that extracorporeal HIFU only covered 15-35% of the targeted lesion (107). Häcker *et al.*, also showed that the size of ablated lesions never reached the targeted volume (77). With intra-corporeal approach, different protocols have been used. Technical improvements have resulted in ablation zones reaching about 90-100% (108). A recent review of HIFU for RCC identified several limitations including technical and anatomic difficulties in delivery of HIFU beams to an SRM. Tracking the lesion during treatment showed non-uniform ablation, and clinical efficacies of only 57% to 67% (109). Additional technical advancements are necessary before HIFU is adopted in the treatment of SRMs.

Finally, the current limitations encountered when comparing RFA to CA also apply to the assessment of the newer ablative technologies.

Conclusions

SRMs are a heterogeneous group of benign and malignant entities (3). Although clinical judgment remains important, a risk stratification algorithm to help direct management

following RMBs has been proposed (110). Halverson *et al.* have demonstrated that biopsies were 96% sensitive and 100% specific in correctly assigning patients to intervention versus active surveillance. However, longer prospective studies will be required to validate this strategy. Despite new clinical evidence, there is no standard protocol for RMB. Generally, local practice patterns and research interests determine its use. Specific protocols for disease diagnosis, prognosis and follow-up are needed. Different protocols should address patient's clinical characteristics, histologic and molecular tissue characterization and treatments done.

With regards to tumour sampling, further research is needed to define the optimal number of cores and their location with an optimal biopsy pattern. It is crucial to obtain samples that allow a reliable and accurate evaluation of the tumour histology and grade and this should be addressed in future clinical research.

There are insufficient studies comparing outcomes among PN, RFA, and CA patients. Current AUA and EAU guidelines suggest the use of tumour ablation approaches in patients with several comorbidities, patients with genetic predisposition to develop multiple tumours, patients with bilateral tumours or solitary kidney.

Genetic and epigenetic studies are the next steps in tumour tissue evaluation. The ability to predict disease recurrence and determine disease aggressiveness is the key in the new era of personalized medicine. Molecular patterns within specific histological subtypes could soon be used to predict likelihood of recurrence (62). The capacity to stratify patients according to their disease phenotype will empower us to prescribe them the best possible and updated health care, ranging from active surveillance to targeted therapy passing through invasive and minimally approaches.

Known tumour suggests that a single biopsy specimen may not be representative of the landscape genomic alterations in a tumor. Probably the best future approach is to determine and identify baseline and common mutations in the stem of the phylogenetic tree of renal tumours.

Reliable diagnostic and prognostic serum and urine markers for RCC would greatly straightforwardness screening and management of patients with renal tumours by affording important diagnostic and prognostic information with a completely non-invasive approaches.

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Footnote

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