REVIEW

The current role of percutaneous biopsy of renal masses

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MALLY AD, GAYED B, AVERCH T, DAVIES B. The current role of percutaneous biopsy of renal masses. The Canadian Journal of Urology. 2012;19(3): 6243-6249.

Introduction: *There has been an increased incidence of small renal masses with a majority incidentally discovered in elderly patients or patients with several comorbidities. The historic role of renal biopsy has been limited due to initial concerns about accuracy and safety. This review analyses the current role of percutaneous renal biopsy.*

Materials and methods: *A comprehensive literature review of PubMed and MEDLINE for reports of percutaneous needle core biopsy and fine needle aspiration of renal tumors that were published from 1977 to 2012.*

Results: *With the adoption of new biopsy techniques, there is a very low risk of tumor seeding. Symptomatic complications are relatively low; less than 2% require any form of intervention. The accuracy has dramatically improved over the past decade. While about 10%-15% of small renal mass biopsies are indeterminate, the rate of false negative renal biopsies is only 1% in contemporary series. Recent studies suggest that biopsy results can be improved by combining histological and molecular analysis.*

Conclusions: *In contemporary series, renal mass biopsies (RMB) have a low complication rate and significantly improved accuracy. RMBs can better stratify patients into an active surveillance protocol and therefore potentially decrease the over treatment of small renal masses, especially in the elderly or patients with comorbidities.*

Key Words: renal mass biopsy, renal tumors, fine-needle aspiration, active surveillance

Introduction

The incidence of renal tumors has been increasing in the United States with 64,770 new cases and 13,570 deaths estimated in 2012.[1] The Surveillance Epidemiology End Results database has demonstrated a 52% increase in the incidence of kidney cancer between the years 1983 and 2002. The largest increase was noted in tumors less than 4 cm in maximal diameter with tumors < 2 cm in maximal diameter increasing by 285% and tumors 2 cm-4 cm in maximal diameter increasing by 244%.[2] In fact the majority of (≤ 60%) of renal tumors are small (≤ 4 cm) and found incidentally on imaging in asymptomatic patients. Half of these tumors were found in patients greater than 65 years.[3] These are elderly patients with numerous comorbidities that are undergoing imaging as a result of their medical problems and incidentally found to have a small renal mass discovered.

The standard of care for these small renal masses is surgical extirpation. Percutaneous renal biopsy for renal masses has been limited in the past due to concerns of safety and accuracy. Though, with improved technique both safety and accuracy have improved over the past decade and research suggests that percutaneous renal biopsy should be employed more frequently in the future to aid in clinical management of patients with these renal masses.

Historically, renal biopsy has been used to aide in the diagnosis of patients with suspected lymphoma, metastatic disease, infection and in patients that have an increased surgical risk.[4] Due to concerns with regards to safety and accuracy, renal biopsies have rarely been utilized outside of these select indications. However, there has been a dramatic increase in the diagnosis of incidentally discovered small renal masses (SRM). Approximately one third of SRMs are benign on final surgical pathology and if malignant, the majority are low grade.[5] With increased use of molecular profiling

Accepted for publication March 2012

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to diagnose SRMs and increased minimally invasive options now available for the treatment of SRMs, there is a renewed interest in renal biopsy. We reviewed the literature to analyze the current role of percutaneous core needle biopsy and fine needle aspiration of renal masses.

Materials and methods

A comprehensive literature review of PubMed and MEDLINE for reports of percutaneous needle core biopsy and fine needle aspiration of renal tumors that were published from 1977 to 2012. Exclusion criteria included non-English language and renal mass biopsies (RMB) performed for reasons other than SRMs.

Results

Biopsy concerns

Renal biopsy is routinely performed on renal transplant patients. However, it is very infrequently performed in patients with a small renal mass largely due to concerns of tumor seeding, bleeding, concern for AV fistula, infection and pneumothorax. There is also concern for biopsy inaccuracy, whether there is sufficient tissue to make a diagnosis, inability to type and grade the biopsy tissue, heterogeneity of the tumor leading to misdiagnosis and lastly the biopsy leading to only minimal change in clinical management.

Indications for biopsy

The standard of care for the treatment of SRMs is surgical resection. However, certain SRMs should not be treated with surgical extirpation and to obviate this aggressive approach, renal biopsy would be beneficial. Established indications for biopsies and where they have been used historically include patients with a renal mass and known extrarenal primary malignancy. Lymphoma is treated with chemotherapy rather than surgical extirpation, but radiographically it can mimic renal cell carcinoma (RCC). Infection can also mimic RCC and if abscess is suspected, biopsy can potentially prevent aggressive surgical management. Finally, renal masses in patients with significant surgical comorbidities may be benign or low grade and therefore these patients may be candidates for less aggressive management ranging from active surveillance to minimally invasive ablative options.[4]

Potentially the most common indication for renal mass biopsies in the future would be to ascertain suitable candidates for active surveillance. Imaging of renal masses gives us tumor size, which is only one prognostic factor to predict malignant potential. Without a renal biopsy, three main prognostic indicators in RCC are still unknown: grade, histologic subtype and pathologic stage. This is an obvious limitation to any observational protocol. Table 1 lists several large series on active surveillance of SRMs, which revealed 72% of patients remained on active surveillance without

TABLE 1. **Series on active surveillance of small renal masses**

Reference	No. of renal masses	Median follow up (months)	Median age (years)	Median tumor diameter at presentation (cm)	Median growth rate (cm/ year)	% underwent RMB	% remain on active surveillance/ no intervention	% develop metastasis
Wehle et al[6]	29	32 (mean)	70 (mean)	1.8	0.12	NA	79	0
Rosales et al[7]	223	35	71	2.8	0.34	19	93	1.9
Crispen et al[8]	124	26	73	2.0	0.21	NA	64	1.4
Kunkle et al[9]	106	29	72	2.0	0.19	0.9	60	1.1
Kouba et al[10]	46	36 (mean)	67	2.9	0.35	NA	70	0
Crispen et al[11]	87	14	66	2.0	NA	62	33	0
Beisland et al[12]	65	37	79	3.5	0.66 (mean)	12	86	3.2
Youssif et al[13]	44	41	74	2.2	0.17	NA	77	2.9
Abouassaly et al[14]	110 (patients)	24	81	2.5	0.08	5	96	0
Crispen et al[15]	172	24	71	2.0	0.15	NA	61	1.3

NA = not available; RMB = renal mass biopsy

intervention, and progression to metastatic disease occurred in 1.2% of cases. Unfortunately, most of these studies on active surveillance did not comment on the use of RMBs, and when implemented, RMBs were performed in only 0.9%-62% of the cases.[6-15] Renal biopsy has the potential to more accurately determine suitable candidates for active surveillance. Active surveillance is suitable only in a subset population. For patients that are good surgical candidates, surgical extirpation is still the gold standard.

Other potential future indications for renal biopsies include patients with renal masses considered for percutaneous ablation and patients with indeterminate cystic renal mass. It should be emphasized that biopsy should only be considered in patients who have a range of management options ranging from observation to surgery. Patients who are not going to change their management after a renal biopsy are not candidates for renal biopsy.

Biology of SRMs

There are numerous studies that have compared pathological features of renal masses in relation to tumor size. In one of the larger series, they retrospectively examined 2770 resections of solid renal masses over a 30 year period and reported 46.3% of tumors that were ≤ 1 cm were benign.[5] There was increased risk of malignancy with increasing size of the renal mass. They found that 30% of renal lesions ≤ 4 cm that were removed by radical or partial open nephrectomy were benign at final pathological evaluation.[5] At Johns Hopkins and Cleveland Clinic, 33.6% and 30% of SRMs were found to be benign after surgery.[16,17] The American Urological Association (AUA) guidelines state that 20% of clinical stage T1 renal masses may represent benign disease and could be considered for less aggressive management.[18] If the SRM is found to be malignant, it should be noted that 87% of RCCs less than 4 cm were low grade. Fuhrman's seminal paper has shown nuclear grade is the most significant prognostic factor for malignant potential for RCC.[19]

Based off of a recent meta-analysis of the world literature of observed enhancing renal masses that included 234 SRMs, the mean growth rate was 0.28 cm/yr. However, the mean growth rate for RCC confirmed renal masses was 0.4 cm/yr. Progression to metastatic disease occurred in 1% of the cases (3 of 286 cases). Of note, all 3 of those patients were symptomatic upon presentation and did not have an incidentally discovered renal mass. It is important to note that 30% of RCC confirmed renal masses had no growth.[20]

The biology of SRMs suggests that they could potentially be managed with less aggressive care. About 30% of SRMs are benign and, if found to be malignant, the majority are low grade.[5] In order to implement a more conservative approach, it would be beneficial to separate indolent from more aggressive diseases. This would allow for more precise counseling and allow the patient to make a more informed decision.

Accuracy of core needle biopsies and fine-needle aspiration (FNA)

Without renal biopsy for surveillance of SRMs, we are limited to radiographic follow up to determine growth rate. However, studies have shown that growth rate does not necessarily correspond with malignancy. Even with tumor growth, the mass may be benign. Conversely, stable renal masses that do not increase in size may still be malignant.[20] Renal biopsy would allow us to more accurately follow patients with SRMs in comparison to serial imaging.

The accuracy of renal biopsy whether obtained under computerized tomography (CT) or ultrasonography (US) has yet to be directly compared against each other. While there are advantages and disadvantages to each, there appears to be no difference with regards to accuracy.[21,22] There is a wide range of results reported with regards to the accuracy of renal mass biopsy, whether core needle biopsy or FNA. A recent review of the literature reanalyzed the results of 2,474 RMBs for suspected RCC in studies published before 2001. Accurate diagnosis was obtained 80.9% of the time.[23] It is important to emphasize studies after 2001 since the advances in imaging and biopsy technique have dramatically improved. Table 2 summarizes RMBs for SRMs in our contemporary literature. A benign diagnosis was established in 26.8% of the biopsies, with a 51.9% change in clinical management.[24-30] It should be noted that in many of these studies the default was to perform a radical nephrectomy, and clinical management was altered to partial nephrectomy if the biopsy revealed cortical, low grade, clear cell or chromophobic RCC. As a result of this outdated management preference, RMBs were more likely to change the treatment type. However, based off of the current AUA guidelines the preference for the management of most clinical stage T1 masses is a partial nephrectomy.[31] The sensitivity of core needle biopsies range from 70%-100% and the specificity is reported to be 100%. The accuracy in all of the series reviewed after 2001 appears to be superior to 90%.[22,24,32-37] The sensitivity of FNA's range from 76%-97% and specificity ranging from 97%-100%.[38-42] The accuracy of FNA is variable and dependent on the interpretation. The concordance of grading accuracy in recent series ranges from 46%-70%.[24,25,43-45] The rate of technical failure where there is insufficient tissue to make a

TABLE 2. **Contemporary series of small renal mass biopsies**

Reference	Renal mass biopsied	Needle size (gauge)	Benign (%)	Nondiagnostic biopsy (%)	Diagnostic accuracy (%)	Grade accuracy (%)	Complications (%)	Change clinical management (%)
Neuzillet et al[24]	88	18	15.9	3.4	92	70	0	47.8
Volpe et al[25]	100	18	21.4	16	100	68	3	NA
Shannon et al[26]	235	18	25	22	98	NA	0.9	NA
Wang et al[27]	110	18	35	9.1	100	NA	7.2	NA
Lebret et al[28]	119	18	20.1	21	100	46	0	30.4
Veltri et al[29]	150	18, 21-22	24.8	14	92.2	NA	5.3	68.9
Maturen et al[30]	152	18	40	4	100	NA	1.3	60.5

NA = not available

diagnosis is about 5% in recent studies. The incidence of indeterminate or inaccurate pathological findings has decreased to about 4% in recent studies.[23] It appears that core needle biopsy and FNA are complementary and this is especially evident when analyzing soft, high grade tumors where the diagnostic yield is higher with FNA than with core needle biopsy.[46]

One of the major concerns of renal biopsy is tumor heterogeneity. Hybrid oncocytomas are one of the primary reasons for unsatisfactory biopsies, where RCC cells are scattered. This phenomenon is seen in up to 18% of oncocytomas.[23] Therefore, it is recommended that patients diagnosed with oncocytoma have close follow up to exclude the possibility of malignancy. Since the radiographic clues to detecting oncocytoma are neither sensitive nor specific, it may be prudent to obtain a repeat biopsy.

The future of improving the accuracy of renal biopsies lies in advances in molecular analysis. Through the subtitles of molecular fingerprinting, we can more accurately identify benign versus malignant masses as well increase subtyping accuracy. It has been shown that the diagnostic accuracy of exvivo renal mass biopsies has increased from 87% with histopathology alone to 95% with the use of florescence in situ hybridization to evaluate chromosomal abnormalities.[47] The addition of polymerase chain reaction on the expression of select genes in addition to standard histological analysis has improved the subtyping accuracy from 90% to 95%.[48] Molecular profiling of several molecular factors has shown to have potential prognostic significance.[49] There is more research needed in molecular analysis as it increases the accuracy of renal biopsies,[46,50] and will allow us to stratify the aggressiveness of the disease.

Complications of renal biopsy

It is important to emphasize contemporary series, since as a result of improved technique and technology dramatic advances have been made in both the safety and the accuracy of renal biopsy. Symptomatic complications from renal mass biopsy are very low, with only less than 2% requiring any form of intervention.[51] Mortality from renal biopsy is very rare, as there are no cases reported of mortality as a result of a renal mass biopsy.

Currently one of the most feared complications of renal biopsies is tumor seeding of the needle track. But the overall estimated risk is less than 0.01%.[52] There have only been six reported cases of tumor seeding with the cases being reported from 1977 to 1994.[53-58] Upon review of these reports, surprisingly needle size was not associated with tumor seeding. Rather, it was associated with the number of needle passes and the use of noncutting needles. There are no cases of tumor seeding that have been reported in over a decade, likely due to improved technique and the widespread use of guiding cannulas which have led to a statistically significant 15% increase in the biopsy success rate without a detectable change in the complication rate based off of cannula use in extra-thoracic sites.[55] The risk of tumor seeding is minimized since this coaxial technique allows multiple needle passes into the renal mass with only one pass through intervening normal tissues.[55] There is an increased concern for tumor seeding in patients with transitional cell carcinoma (TCC) and therefore, biopsy should be considered very carefully in someone with a renal mass suspected to be TCC with a positive urine cytology.

In 1987, 91% of patients had mild perirenal or subcapsular hematomas on immediate post biopsy

CT.[31] That number decreased by greater than half (44%) in 2000.[32] No hematoma had clinical significance in several recent large series and upon review of older studies, renal hemorrhage necessitating hospital observation or blood transfusion occurred in only 1%-2% of cases.[24,51,59]

Needle passage for posterior approach increases risk of pneumothorax, especially in patients with intercostal access. There is a less than 1% risk of a clinically significant pneumothorax and subcostal needle placement further decreases the risk of penetration of pleura.[60] AV fistula's are uncommon and present with persistent bleeding. They may have a delayed presentation and can usually be treated with arterial embolization.

While there are some risks associated with renal biopsy, they have been dramatically ameliorated with new techniques as less than 2% of RMBs results in a complication that requires intervention.[51]

Discussion

Historically RMBs have been avoided due to early studies showing only 40% of FNAs yielded sufficient quantities of malignant cells for definitive diagnosis with only 32% concordance with final nuclear grade.[42] This led to the conclusion that the diagnostic yield was not sufficient to warrant the potential morbidity of this procedure. However, with our improved understanding of the biology of many SRMs to be indolent even if malignant, our increased armamentarium of minimally invasive options and improvements in the safety and accuracy of RMBs has forced us to reevaluate the indications for renal biopsy. With the adoption of new biopsy techniques, tumor seeding is rare. Less than 2% of RBMs result in a complication that requires intervention.[51] The rate of false negative renal biopsies is only 1% in the contemporary series.[61] However, these high success rates are primarily seen in high volume centers. Decreased accuracy with regards to grading is still a limitation that has a large impact on clinical management.

While nephrectomy has great oncologic outcomes, the benefit may be overshadowed by the cost of renal impairment. While we are diagnosing and treating more serendipitously discovered SRMs, the effect of aggressive surgical management on renal tumors with low predicted oncologic potential has not been elucidated with regards to overall survival. In fact, it has been shown that for clinical T1 renal tumors in patients ≥ 75 years, surgical management has not been associated with increased overall survival. This was presumably due to nephrectomy accelerating renal dysfunction, which was a significant predictor of cardiovascular mortality.[62] In fact, increased detection and treatment of renal tumors has not been associated with a corresponding decrease in age specific renal cancer mortality rates in the United States.[63] This data suggests that the current treatment algorithms for serendipitously discovered SRMs may be too aggressive and lead to over treatment of renal tumors, especially in the elderly with comorbidities.

In accordance with the AUA guidelines, renal biopsy is appropriate for patients who have a wide range of management options including observation and active surveillance is appropriate in elderly patients with multiple comorbidities and decreased life expectancy.[31] Renal biopsy can better stratify patients into an active surveillance protocol and therefore potentially decrease the over treatment of SRMs. From a financial perspective, a recent cost effectiveness analysis of RMBs for incidentally discovered SRMs found it to be a cost effective treatment strategy.[64] A recent meta-analysis evaluating nephron sparing surgery (NSS), cryoablation, radio frequency ablation and observation for SRMs revealed that there was no significant difference in progression to metastatic RCC for lesions regardless of treatment modality (NSS or ablation) or lack of treatment, suggesting potential over treatment of SRM's.[65]

As a phase II, prospective, multi-center trial on active surveillance of SRMs has revealed that the average growth rate of these masses did not differ from zero (0.35 mm/yr; $p = 0.08$).[66] There appears to be a low risk of size or stage progression for most patients on a sensible period of active surveillance while maintaining most therapeutic options.[52] Renal biopsy has the potential to more accurately determine suitable candidates for active surveillance. It should be emphasized that renal biopsies should not be performed if it is not going to alter clinical management. It should not be utilized in healthy patients who want surgical extirpation regardless of the results or in elderly patients who only want conservative management.

Conclusions

Our understanding of the biological potential of SRMs in conjunction with our improved renal biopsy techniques, and the incorporation of molecular analysis will likely lead to the increased adoption of RMBs in the management of SRMs. Long term studies are still needed to elucidate the outcomes of RMBs performed on patients in active surveillance protocols and to get a better understanding of how often it truly alters clinical management. □

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