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Diagnostic Accuracy and Risks of Biopsy in the Diagnosis of a Renal Mass Suspicious for Localized Renal Cell Carcinoma: Systematic Review of the Literature

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Abstract

Purpose—Clinical practice varies widely on the diagnostic role of biopsy for clinically localized renal masses suspicious for renal cell carcinoma. Therefore, we performed a systematic review of the available literature to quantify the accuracy and rate of adverse events of renal mass biopsy.

Materials and Methods—MEDLINE®, Embase® and the Cochrane databases were searched (January 1997 to May 2015) for relevant studies. The systematic review process established by the Agency for Healthcare Research and Quality was followed. Nondiagnostic biopsies were excluded from diagnostic accuracy calculations.

Results—A total of 20 studies with 2,979 patients and 3,113 biopsies were included in the study. The overall nondiagnostic rate was 14.1% with 90.4% of those undergoing surgery found to have malignancy. Repeat biopsy led to diagnosis in 80% of patients. The false-positive rate was low (4.0%), histological and renal cell carcinoma subtype concordance was substantial, and Fuhrman upgrading notable (16%) from low grade (1 to 2) to high grade (3 to 4). Core biopsy was highly sensitive (97.5%, CI 96.5–98.5) and specific (96.2%, CI 90.7–100) when a diagnostic result was obtained, but most patients (~80%) did not undergo surgery after a benign biopsy. Among patients undergoing extirpation 36.7% with a negative biopsy had malignant disease on surgical pathology (negative predictive value 63.3%, CI 52.4–74.2). Direct complications included hematoma (4.9%), clinically significant pain (1.2%), gross hematuria (1.0%), pneumothorax (0.6%) and hemorrhage (0.4%).

Conclusions—Diagnostic accuracy was generally high for biopsy of localized renal masses with a low complication rate, but the nondiagnostic rate and negative predictive value were concerning. Renal mass sampling should be used judiciously as further research will determine its true clinical utility.

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Keywords

carcinoma; renal cell; biopsy; diagnosis; data accuracy; complications

KIDNEY cancer affects 65,000 new patients with more than 13,000 deaths annually.[1] Increasing incidental detection has led to the diagnosis of more asymptomatic, small and clinically localized renal masses, approximately 20% of which are benign at surgical resection.[2–6] It is estimated that 6,000 benign renal masses are removed each year.[7] Renal mass biopsy provides a potential route for tissue sampling to aid in histological and subtype diagnosis for risk stratification and management. However, clinical practice has varied widely due to uncertainty about diagnostic accuracy and potential harms of renal mass biopsy.

In 2009 the American Urological Association published the guideline used most widely by the United States urological community for the management of clinical stage 1 renal masses based on systematic review of observational studies available at the time and expert opinion.[8] According to the guideline renal mass biopsy was generally not indicated for healthy patients unwilling to accept uncertainty or older patients only considering conservative management options regardless of results. Data on renal mass biopsy were limited and numerous large institutional experiences have been reported in the last decade. Therefore, we performed a systematic review of the literature to quantify the diagnostic accuracy and rate of adverse events of biopsy for clinically localized renal masses suspicious for RCC.

MATERIALS AND METHODS

The methods of this systematic review follow the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[9] In an open process representatives of various stakeholder groups developed Key Questions, which are posted on the AHRQ web site for public comments (www.effectivehealthcare.ahrq.gov). The final review protocol was registered on PROSPERO (CRD42015015878, fig. 1). MEDLINE, Embase and the Cochrane Central Register of Controlled Trials were searched from January 1, 1997 through May 1, 2015.

The systematic review focused on 3 major topics, of which 1 topic included 2 questions on renal mass sampling for masses suspicious for stage I or II RCC. 1) What is the accuracy (eg sensitivity, specificity, positive and negative predictive value) of percutaneous renal mass sampling (using FNA with cytopathology or core biopsy with surgical pathology) in establishing a diagnosis (eg malignancy, histology, and grade)? 2) What are the adverse effects including direct complications (eg pain, infection, hemorrhage and radiation exposure) and harms related to false-positives, false-negatives or nondiagnostic results? Complete details are available in the full version of the EPC Report.[10]

Study Selection and Data Abstraction

Study selection was based on predefined eligibility criteria in a PICOT format (supplementary Appendixes 1 and 2, http://jurology.com/). Independent dual reviewer

abstract screening was used. Differences were resolved through consensus. We used DistillerSR (Evidence Partners 2010) to manage screening. Additional study exclusion criteria were applied at the full text stage (supplemental Appendix 2, http://jurology.com/). Full text articles underwent an additional independent review by paired investigators before data abstraction. One reviewer completed the abstraction and a second reviewer checked for completeness and accuracy. We resolved differences through discussion and, as needed, consensus among our team.

Statistical Methods

Studies varied in terms of which diagnostic test performance characteristics were reported and how these accuracy measures were calculated for renal mass biopsy. The terminology also varied. To standardize results we cross tabulated percutaneous renal mass biopsy results from the first attempted biopsy into contingency tables based on raw surgical pathology findings at biopsy from individual studies. Pooled estimates were aggregated from raw data to allow representative weights among studies, minimize heterogeneity and account for missing or unreported data from studies.

Benign biopsy results were classified as true negatives or false-negatives and malignant biopsy results were classified as true positives or false-positives. Biopsies were considered diagnostic if sufficient tissue was obtained to demonstrate etiology of the renal lesion and nondiagnostic if insufficient tissue for diagnosis was obtained or benign renal parenchyma was found without an etiology for the renal lesion (eg benign fibrosis). Nondiagnostic biopsies were not considered negative biopsies and were excluded from diagnostic accuracy calculations. Formal definitions were used for diagnostic performance characteristics (sensitivity, specificity, PFV, NFV, false-positive rate and false-negative rate) as defined in the EPC Report.[10] Analyses were conducted using STATA® version 12.0.

Risk of Bias Assessment, Strength of the Body of Evidence and Public Comment

Two reviewers independently assessed risk of bias for individual studies using a quality assessment tool (QUADAS-2).[11] We graded strength of evidence using the AHRQ EPC Methods Guide for Conducting Comparative Effectiveness Reviews scheme (supplementary Appendix 3, http://jurology.com/).[9] The draft report was peer reviewed and posted for public comment May 28, 2015 through June 25, 2015. Comments received from invited reviewers and public comment were compiled and addressed.

RESULTS

From 20,829 unique citations screened 20 related to renal mass biopsy were included in the study (fig. 2).[5,12–30] One evaluated FNA with cytopathology alone[12] and all other studies evaluated core needle biopsy with surgical pathology. There were 15 core biopsy studies that used 18G needles.[5,13,15,16,18,20,21,23–30] Eleven studies included biopsies performed using multiple imaging modalities (primarily CT or ultrasound). Radiation exposure from CT guidance occurred in 44.3%.

Study Characteristics

Four studies were prospective cohorts and all 20 were single center experiences.[12,24,28,29] Ten included consecutively performed biopsies.[5,12,20,21,23–26,28,29] Overall 9 were performed in North America,[5,12,14–17,26,27,30] 5 in Europe,[13,19,20,28,29] and 3 each in Asia[21,22,24] and Australia.[18,23,25] One study was an update[23] of a previously published series.[25]

Population and Tumor Characteristics

A total of 2,979 unique patients were included in the study (supplementary table 1, http://jurology.com/). Overall 3,074 tumors were biopsied, with 11 studies focused specifically on localized clinical T1a tumors[5,13,14,16,18–22,26,27] and another 3 focused on tumors 5 cm or smaller.[12,23,25] Among these studies mean tumor size ranged from 2.3 to 3 cm (supplementary table 2, http://jurology.com/).

Biopsy Histology

Ultimately 3,113 biopsies were performed (supplementary table 3, http://jurology.com/).[16,17,23] Of the eligible biopsies 67.6% were reported as malignant and 19.0% benign. The proportion of nondiagnostic biopsies was 14.1% overall and 13.9% when limited to core biopsy studies. Clear cell RCC was the most common diagnosis, ranging from 30.4% to 80.0% of biopsies, depending on nondiagnostic rates. Other histological results are shown in supplementary tables 3 and 4 (http://jurology.com/).

Fuhrman Grade

Twelve studies provided data on Fuhrman grade at biopsy (supplementary table 5, http://jurology.com/).[5,12,14,16,18–22,24,26,29] Grades were assigned for 67.3% of biopsies showing RCC. Biopsies showed 688 (87.8%) patients with low grade (1 to 2) and 96 (12.2%) with high grade (3 to 4) tumors. Surgical pathology was available for 489 tumors. Ten studies reported tumor upgrading from low to high grade, with an overall proportion of 16.0% upgraded at surgical pathology.[5,12,14,18–21,24,26,29] The accuracy of grades between biopsy and surgical pathology results varied, with studies reporting concordance from 51.5%[24] to 75.9%.[29]

Diagnostic Accuracy

Among 1,710 malignant biopsies 965 (56.4%) cases proceeded to surgery with available pathology, among which 2 (0.21%) were false-positives. In contrast, only 79 (16.9%) of 468 benign biopsies had surgical pathology available with 29 (36.7%) false-negatives. The false-negative rate was 3.1% (29 of 931) and the false-positive rate was 4.0% (2 of 50). Of note is that nondiagnostic biopsies are not used to calculate these parameters and only diagnostic biopsies were considered. Among 73 (22.3%) nondiagnostic biopsies with surgical pathology available 90.4% of tumors were malignant.

The study evaluating FNA had a sensitivity of 62.5%.[12] Two studies included consecutive patients undergoing core biopsy with surgical pathology available for all tumors, including one with 78 patients (sensitivity 95.2%, specificity 100%, PPV 100%, NPV 81.3%)[29] and

another with 42 patients (sensitivity 91.4%, specificity 75.0%, PPV 97.0%, NPV 50.5%).[24] Supplementary table 6 (http://jurology.com/) presents pooled diagnostic accuracy estimates for all diagnostic biopsies and the core biopsy subset. Core biopsy had a sensitivity of 97.5% (median 100, 95% CI 78–100), specificity of 96.2% (median 100, 95% CI 75–100), PPV of 99.8% (median 100, 95% CI 97–100) and NPV of 68.5% (median 100, 95% CI 13–100). NPV indicates the percentage of negative (nonmalignant) biopsies confirmed negative (nonmalignant) on surgical pathology. The positive likelihood ratio was 25.3 and the negative likelihood ratio was 0.026.

However, likelihood ratios are derived only from sensitivity and specificity, which are prone to verification bias among included studies due to missing gold standard surgical pathology for most benign biopsy results. Given that studies appear to include a representative prevalence of small renal mass histologies, predictive values from the data may be more clinically relevant than likelihood ratios. A subset analysis of core biopsy studies judged to be at low risk for bias showed similar diagnostic accuracy estimates with a sensitivity of 96.3%, specificity of 96.0%, PPV of 99.6% and NPV of 72.7%.[14,24,28,29]

Histological Concordance and Repeat Biopsies

Histological concordance was generally high. Three studies reported 100% histopathology concordance,[19,26,27] and 1 each reported 94.7%,[29] 93%,[5] 92%[20] and 77.5%.[24] RCC subtype concordance was also substantial, with studies reporting concordance in 53 of 58 masses,[29] 28 of 29 masses,[27] 27 of 29 masses[17] and a final study reporting a kappa of 0.69.[16]

There was variation in the performance and reporting on repeat biopsies. Repeat biopsies were reported for 84 of 411 (20.4%) nondiagnostic biopsies. A single repeat biopsy helped diagnose 19 of 24,[30] 20 of 24,[5] 6 of 9,[22] 10 of 12,[16] 9 of 12[23] and 3 of 3[21] initially nondiagnostic lesions among studies for an overall rate of 67 of 84 (79.8%).

Direct Adverse Events

Direct complications were infrequent (supplementary table 7, http://jurology.com/). The most common were hematoma (4.9%) and clinically significant pain (1.2%). The definition of hematoma varied among studies but the majority of patients underwent CT to check for procedure related complications, including the development of hematoma. No study reported tumor seeding.

Gross hematuria (1.0%), pneumothorax (0.6%) and hemorrhage (0.4%) were rare events but were noted in some patients. Three studies specifically referenced Clavien grading.[5,16,30] One study found Clavien 1 complications in 10.1% and a single Clavien 3a complication (0.3%).[16] The Clavien 3a complication involved gross hematuria leading to urinary retention due to the formation of clots. A second study revealed a Clavien 3b complication (percutaneous angioembolization)[5] and a third study showed a Clavien 3a complication (selective renal artery embolization for bleeding leading to hemodynamic instability).[30]

Risk of Bias and Strength of Evidence

Of the 20 studies 5 were at low risk for bias (fig. 3).[12,14,24,28,29] All studies were at low risk for bias for the reference standard test and index test, and the majority (17 of 20) for patient selection. However, assessment of flow and timing showed 14 of 20 studies had a high potential risk due to missing reference standard evaluations (surgical pathology) among patients with benign biopsy results limiting tabulation of data on true and false-negatives. Strength of evidence was moderate for diagnostic accuracy and low for Fuhrman grade and harms (see table).

DISCUSSION

The systematic review identified 20 articles comprising biopsies of more than 3,000 clinically localized renal masses, the majority of which were cT1a tumors. Evaluation of diagnostic biopsies with available surgical pathology revealed excellent sensitivity and specificity. However, an ideal analysis of a diagnostic test would require the gold standard reference (surgical specimen pathology) to be available for all lesions to prevent verification bias. While negative biopsies are informative, many studies presume the results to be true even though they are not pathologically confirmed. The limitation of the literature has been previously acknowledged but addressed for the first time in the current systematic review by cross tabulating raw data from individual studies.[6]

For the clinically relevant scenario of a patient with a renal mass biopsy result, a positive biopsy was associated with a high PPV compared to the gold standard, indicating strong confidence in a positive result. On the other hand, a negative biopsy result led to greater uncertainty with 36.7% of those undergoing extirpation found to have malignant disease. Although an individual study such as that by Richard et al may reveal a 100% NPV,[5] the percentage is based on only 3 biopsied tumors with benign results that were found to be benign on surgical pathology. Reasonably the most suspicious tumors with benign biopsy results may be the ones selected to undergo extirpation and lead to a lower than anticipated NPV. To address this we performed a subset analysis of core biopsy studies judged to be at low risk for bias (surgical pathology was available for benign biopsy results). The subset analysis revealed potentially more valid but similar diagnostic accuracy estimates (sensitivity 96.3%, specificity 96.0%, PPV 99.6% and NPV 72.7%).[14,24,28,29]

Furthermore, 14.1% of biopsies were nondiagnostic with the majority malignant at surgical pathology, a proportion possibly slightly higher than the baseline frequency of malignancy among localized renal masses as the most suspicious tumors likely proceeded to surgery. We found repeat biopsy can potentially lead to diagnosis in 80% of patients with initially nondiagnostic results. The nondiagnostic rate was similar to the previously reported range of 10% to 20%,[6] but the rate of malignancy at extirpation among nondiagnostic biopsies has not been previously reported to our knowledge. Also, relative to prior reviews of the literature, we excluded series with large renal masses that were not stated to be localized, as well as biopsy studies before ablation procedures.

Harms were infrequent but not negligible. While case reports indicate a risk does exist, tumor seeding was not reported in any modern renal mass biopsy series for localized

disease. A small proportion of patients experienced harm due to renal mass biopsy, with hematoma (4.9%) being the most common direct complication, followed by clinically significant pain, gross hematuria, pneumothorax and hemorrhage. Few studies provided Clavien grading and strength of evidence was determined to be low because studies were inconsistent in which harms, if any, were reported.

Based on the current clinical paradigm, localized renal masses suspicious for RCC are assumed to be malignant, and generally treated based on patient preference and risk factors. Grade heterogeneity and Fuhrman upgrading at surgery lead to uncertainty about the metastatic potential of a tumor after a positive biopsy result. The NPV of 72.7% based on studies at low risk for bias confers some uncertainty about the accuracy of a negative biopsy result. The ideal diagnostic test would need to precisely identify patients at extremes of malignant risk to confer confidence on a benign result but also differentiate aggressive from indolent malignancies to aid in consideration for active surveillance, where the role of biopsy still needs to be determined.

Therefore, clinicians and policy makers should strive to identify patients most likely to benefit from biopsy, and where it might change management in light of our findings for judicious and appropriate use of medical resources. American Urological Association guidelines currently recommend biopsy for patients undergoing thermal ablation and those with the possibility of lymphoma, abscesses or metastasis.[8] Biopsy could change management or help determine appropriate followup and treatment efficacy in these situations or in cases with a solitary kidney. Importantly, molecular correlates may help to improve the diagnostic performance of biopsy and warrant investigation in the future.

The main limitations of the evidence base include the lack of detail on tumor location (anterior, posterior, hilar), variation in protocols, single center experience and absence of surgical pathology for most tumors with benign biopsies. Risks and harms from withholding anticoagulation were not reported and it is not known if perirenal hematomas complicated or delayed subsequent interventions. Lastly the absence of complete biopsy result reporting from all studies precluded formal area under the curve meta-analysis. Standardization and detailed publication of biopsy protocols, reporting of tumor location and tabulation of all pathology results, including negative and inconclusive results, would be helpful in future studies. A prospective study with biopsy before surgery would provide the most valid assessment of renal mass biopsy accuracy.

CONCLUSIONS

Based on the available evidence it is not possible to conclude that renal mass biopsy is a universal prerequisite to clinical decision making. Diagnostic accuracy is generally high for renal mass biopsy for localized renal masses, but the nondiagnostic rate and NPV were concerning. Gold standard pathology was missing for most benign biopsies. This summary of the evidence should help to guide clinical decisions about the use of biopsy in patients with a small renal mass suspicious for RCC. Additional research is needed to better define the clinical utility of renal mass biopsy in such patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
CT	computerized tomography
EPC	Evidence-Based Practice Center
FNA	fine needle aspiration
NPV	negative predictive value
PPV	positive predictive value
RCC	renal cell carcinoma

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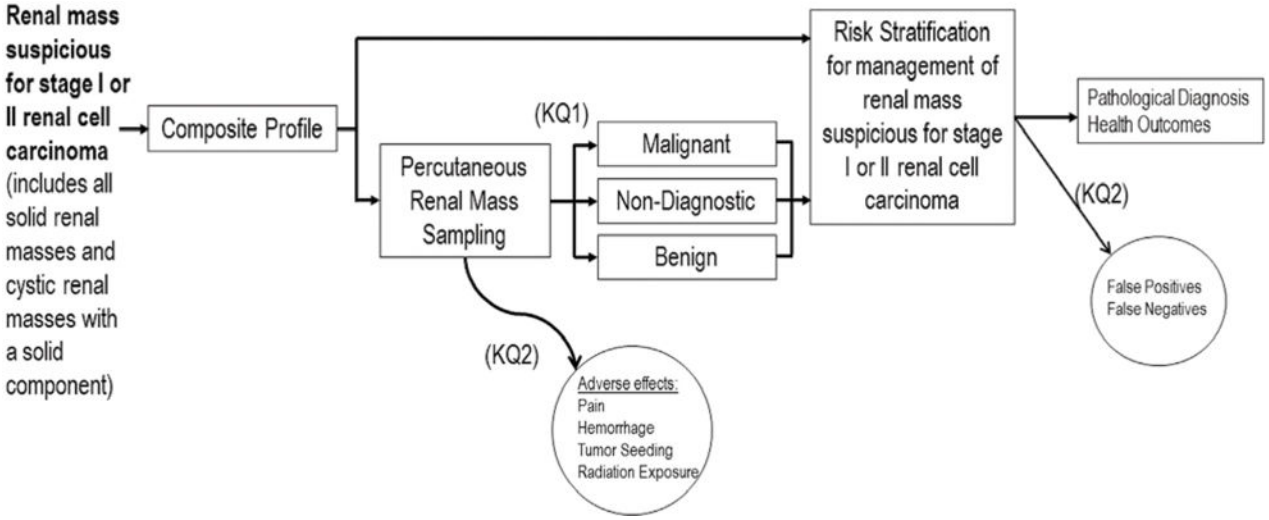

Figure 1.

Analytic framework for systematic review of role of renal mass biopsy in diagnosis of renal masses suspicious for localized kidney cancer. *KQ*, key question.

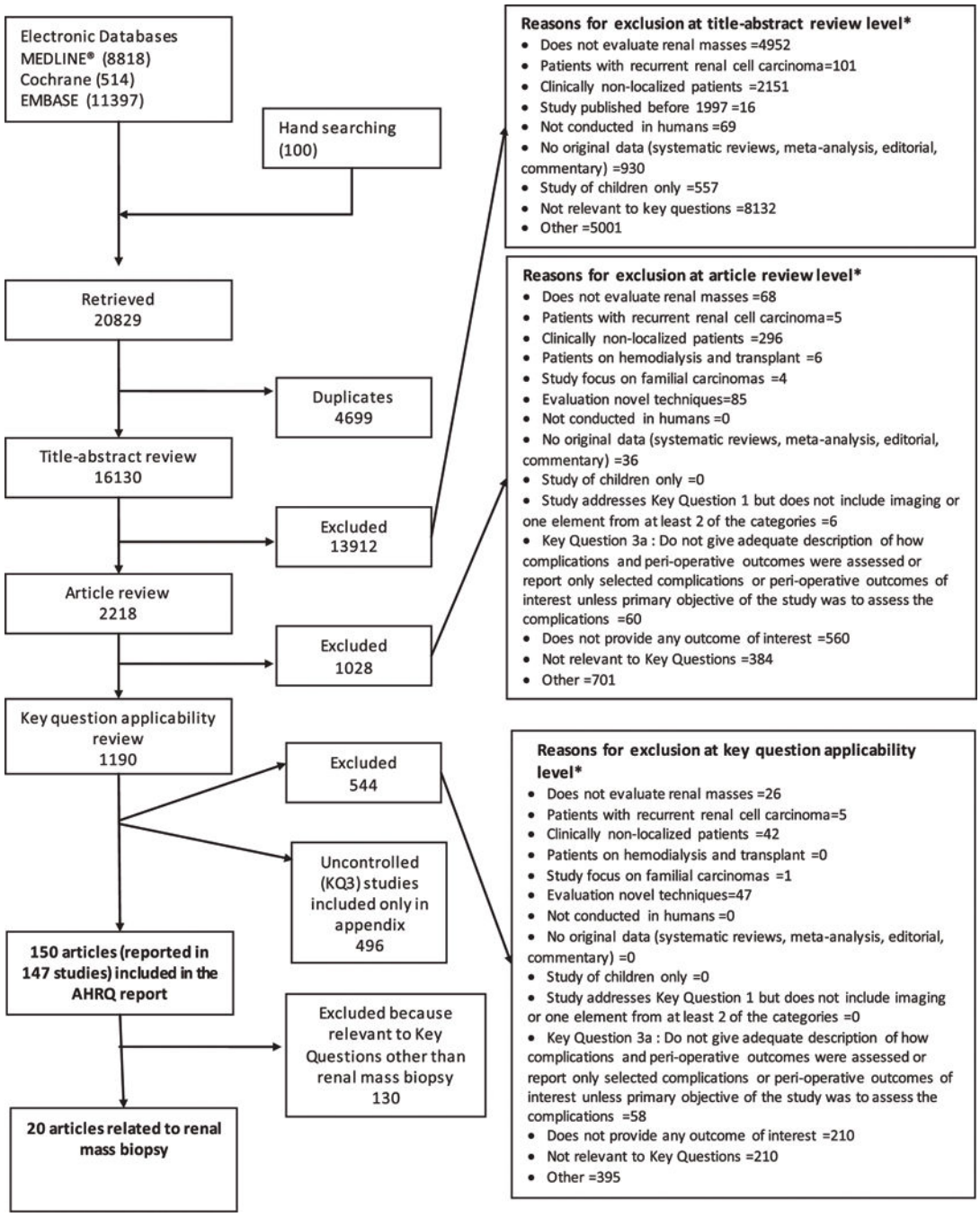

Figure 2.
Summary of literature search

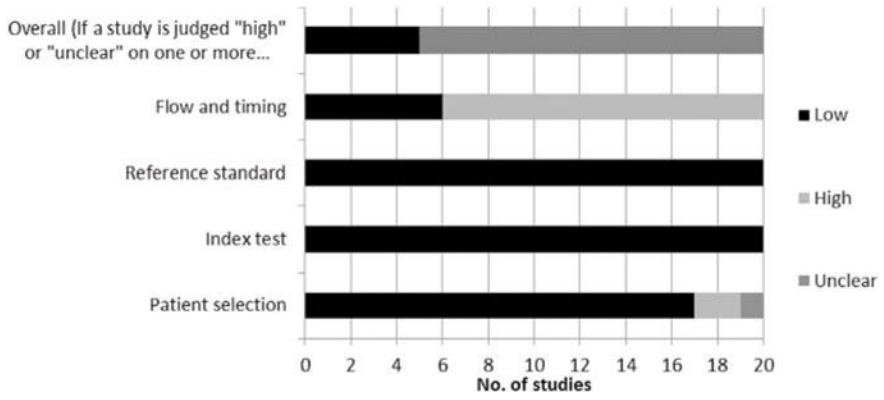

Figure 3.
Risk of bias assessment for studies evaluating percutaneous renal mass sampling

Strength of evidence for renal mass biopsy outcomes

Key Outcomes	No. Studies (No.)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence Finding
Diagnostic accuracy	18 (2,203)	Medium	Direct	Consistent	Precise	Undetected	Moderate: Renal mass biopsy has high PPV (99.8%) for diagnosis of renal malignancy but also notable nondiagnostic (~14%) rate and low NPV (less than 70%). Primary limitation is absence of surgical pathology for benign biopsies, but sensitivity and specificity of diagnostic biopsy result appear to be more than 90% based on available data.
Fuhrman grade	12 (1,999)	High	Direct	Consistent	Imprecise	Undetected	Low: Fuhrman upgrading on final pathology occurred in 16.0% of biopsies but many studies did not provide data on grade concordance.
Harms	16 (2,422)	Medium	Direct	Inconsistent	Precise	Undetected	Low: Small but notable proportion of pts experience harm due to renal mass biopsy with hematoma (5%) being most common direct complication. Studies were inconsistent in which harms, if any, were reported.