Accuracy of Percutaneous Core Biopsy in the Diagnosis of Small Renal Masses (≤4.0 cm): A Meta-analysis

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ABSTRACT

Objective: To use meta-analysis to determine the accuracy of percutaneous core needle biopsy in the diagnosis of small renal masses (SMRs ≤ 4.0 cm).

Materials and Methods: Studies were identified by searching PubMed, Embase, and the Cochrane Library database up to March 2013. Two of the authors independently assessed the study quality using QUADAS-2 tool and extracted data that met the inclusion criteria. The sensitivity, specificity, likelihood ratios, diagnostic odds ratio (DOR) and also summary receiver operating characteristic (SROC) curve were investigated and draw. Deek’s funnel plot was used to evaluate the publication bias.

Result: A total of 9 studies with 788 patients (803 biopsies) were included. Failed biopsies without repeated or aborted from follow-up/surgery result were excluded (232 patients and 353 biopsies). For all cases, the pooled sensitivity was 94.0% (95% CI: 91.0%, 95.0%), the pooled positive likelihood was 22.57 (95% CI: 9.20-55.34), the pooled negative likelihood was 0.09 (95% CI: 0.06-0.13), the pooled DOR was 296.52(95% CI: 99. 42-884.38). The area under the curve of SROC analysis was 0.959±0.0254.

Conclusion: Imaging-guided percutaneous core needle biopsy of small renal masses (SMRs≤4.0 cm) is highly accurate to malignant tumor diagnosis with unknown metastatic status and could be offered to some patients after clinic judgment prior to surgical intervention consideration.

KEY words:
Nephrostomy, Percutaneous; Biopsy; Carcinoma, Renal Cell

INTRODUCTION

Renal cell carcinoma (RCC) is in the top 15 most common malignancies of both men and women and incidence has steadily increased since 1975 (1). Increasingly, these malignant tumors are recognized more frequently as small masses (2). CT-guided and sonographically guided percutaneous biopsy of small renal masses seemed to be effective in early reports. Several studies of renal mass biopsy have demonstrated high degrees of accuracy between 86%-95.5% (2-5), with accuracy for the Fuhrman nuclear grade at 46%-85% (4, 5). The sensitivity and specificity have been high with values between 93%-100% (3, 4, 6). The accuracy of percutaneous biopsy on small renal masses (≤4 cm), however, has not been widely debated and might be owing to tumor mobility and difficult needle penetration. We still believe that there has been a paucity of data on biopsy performance for small renal masses that could be extracted and summarized.
No large randomized controlled trials comparing percutaneous to other methods of metastatic detection are available; we set out to review the available literatures on percutaneous renal mass biopsies. Therefore, this meta-analysis included only well-designed, comparative studies in order to mainly evaluate the safety and accuracy of percutaneous core needle biopsy in diagnosis of patients presenting with small renal masses (SMRs≤4.0 cm). The purpose of this meta-analysis is to determine the diagnosis accuracy of images-guided percutaneous needle biopsies of small renal masses in adult patients.

MATERIALS AND METHODS

Search strategy
A Medline search of the English-language Literature searches were performed to identify reviews of well-designed, comparative studies on the accuracy of percutaneous core needle biopsy in diagnosis of RCC in patients presenting with small renal mass. The search included words identified in the whole text as well as in the Medical Subjects Heading (MeSH) terms: ‘kidney’, ‘renal mass’, ‘renal cell carcinoma’, ‘percutaneous’, ‘needle’, ‘diagnosis’, ‘biopsy’, ‘accuracy’. The following databases were used: Pubmed (1966-March 2013), Embase (1974-March 2013), the Cochrane Library (2011 issue 5). No language restrictions were used. Publications addressing evaluated renal masses or recurrent disease after radiofrequency ablation or nephrectomy were excluded.

Eligibility criteria
Publications were included in the meta-analysis if the pre-set inclusion of below were met: (1) the renal lesions had to be limited in size (≤4cm) and location (kidney mass); (2) all histological diagnoses of large-core needle biopsy specimens had to be confirmed by either surgical pathology or follow-up (defined as a minimum of 12 months in at least 90% of the patients). (3) The absolute number of benign and malignant diagnoses had to be derivable; (4) Renal core biopsy was performed under ultrasonography or CT guidance using local anesthesia and an 18-G core biopsy gun. Exclusion criteria included masses >4.0 cm in any dimension and biopsy of tumor masses outside the kidney, lacking of confirmed by surgical pathology or adequate follow-up for the mass diagnosis, vague patients counting and different biopsy tools and methods, others which could not meet our eligibility criteria.

Data Extraction and Quality Assessment
A total of 744 papers were obtained in our initial search, 690 of which failed to meet our inclusion criteria. Of the 84 studies remaining, 75 publications were excluded for lacking follow-up data (22 papers), unsatisfactorily confirmed histological diagnoses on needle biopsy (16 papers), failed to allow absolute patient small mass number to be derived (≤4 cm)(37 papers). Only 9 studies (7-15) were included (Figure-1).

The aim of our study was to evaluate the accuracy of percutaneous core needle biopsy of small renal masses (≤4 cm), especially for the malignancy. The results of the percutaneous renal mass biopsy were defined as positive if the pathologic examination presented a RCC, a metastasis, or a specific extrarenal malignancy invading the kidney. In all other cases, the biopsy results were considered negative, including those specimens in which cytology revealed malignancy not otherwise specified (i.e. the malignant cells were found, but the type of tumor could not be specified).

All positive percutaneous renal mass biopsy results (i.e. identification of a specific malignancy) which were confirmed by surgical procedure, surgical pathology or follow-up information (individuals refusing surgery however proved malignancy in a follow-up) were considered true-positive. The false-positive rate was defined as zero because there usually no positive biopsy results would outcome benign mass. Studies were included if patients with negative percutaneous renal mass biopsies were followed up to confirm negative or metastasis.

If the malignancy was not identified or characterized, the results of percutaneous renal mass biopsies were still considered negative despite the resulting malignancy identification could lead to different management. If either surgical pathology or follow-up confirmed the percutaneous renal mass biopsy negative result, we characterized the
The biopsy result was defined as true-negative. If the final diagnosis and the diagnosis based on the initial results of the percutaneous renal mass biopsy were discordant, also including the malignancy not specified initially, the results of the biopsy were defined as false-negative. Our use of these methodological definitions is in accordance with a similar large prospective study (16).

Quality assessment of the study was assessed by using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist (17). Briefly, QUADAS-2 is a 4-domain tool, the last domain of which assists authors of systematic reviews in rating: 1) bias and 2) applicability. The risk of bias is assessed in four key areas: patient selection, index test, reference standard, and flow and timing. Concern for applicability is assessed in three key areas: patient selection, index test, and reference standard. For both categories, risk of bias and concern for applicability, the individual criteria were classified as low risk, high risk, or unclear and the results were presented using tables from the QUADAS web site (www.quadas.org) (Table-1 and Figure-2).

**Data analysis**

One author extracted the data from included studies and entered them into the data extraction form. A second reviewer checked the extracted data to ensure data quality. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, it was planned that corresponding author would decide.

The 2x2 data were summarized in forest plots of sensitivity and specificity for each study. We calculated and assessed the true positive rate (TPR, sensitivity), specificity, likelihood ratios, diagnostic odds ratio along with 95% confidence intervals (CI). Since the false positive rate was de-
fined as 0, a correction was required to make 2x2 tables rational. Thus, a correction value of ½ was added to all cells in the 2x2 matrix. Heterogeneity was assessed by means of the Cochran Q and $I^2$ test. Heterogeneity was classified as not like-
if present. To assess the diagnostic accuracy of the percutaneous core needle biopsies of small renal masses, we used the Rutter and Gastonis version of formulas for constructing summary receiver operating characteristic (SROC) curve. To identify if publication bias was present in our study, we calculated the diagnostic odds ratio inverse of the square root of the effective sample size from Deek’s funnel plots for all included studies.

Meta-analysis in this study was conducted with the Meta-Disc software package (Clinical Biostatistics Unit, Ramony Cajal Hospital, Madrid, Spain) (version 1.40) and Stata (version 11, College Station, TX, USA); probability values of less than 5% were considered significant.

RESULTS

Search results and characteristics of studies

Our initial search yielded 744 literatures and the process of study selection is summarized in Figure-1. In total, there were 1020 patients and 1156 percutaneous core needle biopsies in 9 studies. All failed biopsies without repeat biopsies or quit from follow-up/surgery result were excluded (232 patients and 353 biopsies). Finally, 788 patients and 803 percutaneous core needle biopsies were included in our meta-analysis and Table 2 summarizes the main characteristics of included studies.

Quality assessment

Table-2 and Figure-2 summarized the methodological quality of our nine studies assessment by QUADAS-2 tool. If the answers to all questions of a domain are judged as ‘yes’ indicating low risk of bias, then this domain will be judged to be at low risk of bias. In advert, if one judged as ‘no’ would indicate ‘high risk’, the potential bias might exist. ‘Unclear’ indicated insufficient information to determine whether partial verification was present.

Of the 9 studies’ risk bias, 8/9 provided clear definition of an exclusion criteria, one study just described the basic information about subjects without exclusion criteria and thus scored “high risk”. Two studies (8, 14) did not show enough information about the methods in details clearly, and also did not described an exact time of interval between the biopsies and follow-up of patients. Studies where language differences were thought to exist were scored ‘unclear’ in the index tests bias and patient flow and timing domains which we were not sure about in these studies. The remaining studies presented a clear interpretation in all the questions of domains and scored well. In relation to applicability, patient selection criteria in 2/9 studies were in accordance to our analysis inclusion criteria and scored well, the other 7 studies might have some different aims, neither some patients were not applicable for our inclusion criteria and were excluded from our analysis. So we considered it might have high risk bias in patient selection domain. The other two domains scored well for all studies.

Diagnostic accuracy

Because of our definition about the true positive, which is the specific malignancy biopsies could be confirmed by surgery procedure or follow-up final diagnosis, the false positive could not exist, that’s to say, if the cytopathology report of the biopsies defined a malignancy, the corrected benign results conducted from surgery procedure or follow-up would mostly never happen. So the specificity would be calculated as 100%.

The pooled sensitivity was 94.0% (95% CI: 91.0%, 95.0%, p=0.28), with I2 of 17.7% (no likely contributory), specificity was 100% (95% CI: 98.4%, 100%, p=1), with I2 of 0% (no likely contributory). The pooled positive likelihood was 22.57 (95% CI: 9.20-55.34, p=0.54), the pooled negative likelihood was 0.09 (95% CI: 0.06-0.13, p=0.13) (Figure-3).

The pooled DOR was 296.52 (95% CI: 99.42-884.38, p=0.36). The overall diagnostic accuracy according to the results of SROC curve analysis was 0.959±0.0254 and the overall diagnostic accuracy (Q*) was 0.903±0.037 (Figure-4). Thus, percutaneous core needle biopsies to diagnose malignancy in small renal masses (≤4 cm) is a highly accurate method.

Publication bias

Deek’s funnel plots of diagnostic odds ratio inverse of the square root of the effective sample size was constructed to assess the publication
Table 2 - Basic characteristics of the included studies of using 18 gauge needles biopsy on ≤4 cm renal mass.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country and published time</th>
<th>Research Time</th>
<th>Patients (eligible/all)</th>
<th>Biopsy (eligible/all)</th>
<th>Nondiagnostic biopsy</th>
<th>RB (≤4 cm)</th>
<th>Follow-up (months)</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>Excluded patients number and reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Volpe et al.7</td>
<td>Canada 2008</td>
<td>Jan 2000 - May 2007</td>
<td>40/91</td>
<td>40/100</td>
<td>16/100</td>
<td>2/16 (M:1/2)</td>
<td>22</td>
<td>20</td>
<td>0</td>
<td>2</td>
<td>18</td>
<td>51 pts lack surgery or follow-up confirmation</td>
</tr>
<tr>
<td>C.Thuillier et al.8</td>
<td>France 2008</td>
<td>Feb 1998 - Nov 2006</td>
<td>32/53</td>
<td>32/53</td>
<td>6/53</td>
<td>0/12</td>
<td>52</td>
<td>24</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>21 pts lack surgery or follow-up confirmation</td>
</tr>
<tr>
<td>Frank J. et al.10</td>
<td>U.S 2002</td>
<td>Oct 1990 - March 2001</td>
<td>31/113</td>
<td>31/115</td>
<td>NC</td>
<td>NC</td>
<td>32</td>
<td>21</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>82 pts tumors diameter &gt;4.0 cm</td>
</tr>
<tr>
<td>I. Eshed et al.11</td>
<td>Israel 2003</td>
<td>Jan 1996 - Aug 2001</td>
<td>6/22</td>
<td>7/22</td>
<td>1/6</td>
<td>1/1 (NC)</td>
<td>&gt;12</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>16 pts tumors diameter &gt; 4.0 cm</td>
</tr>
<tr>
<td>M. J. Leveridge et al.12</td>
<td>Canada 2011</td>
<td>Jan 2000 - Dec 2009</td>
<td>291/294</td>
<td>291/345</td>
<td>67/345</td>
<td>12/67 (M:8/12)</td>
<td>25</td>
<td>221</td>
<td>0</td>
<td>11</td>
<td>59</td>
<td>1 pts lost follow-up 57 biopsies unclear</td>
</tr>
<tr>
<td>Rou Wang. et al.13</td>
<td>U.S 2009</td>
<td>Feb 1999 - Oct 2006</td>
<td>90/106</td>
<td>93/110</td>
<td>10/110</td>
<td>1/10 (M:0/1)</td>
<td>13</td>
<td>60</td>
<td>0</td>
<td>1</td>
<td>32</td>
<td>9 pts quit and 7 pts lost follow-up (lack surgery or follow-up)</td>
</tr>
<tr>
<td>S. Rybikowski et al.14</td>
<td>France 2008</td>
<td>Jan 2001 - Oct 2006</td>
<td>63/65</td>
<td>68/70</td>
<td>12/70</td>
<td>4/12 (M:2/4)</td>
<td>19</td>
<td>52</td>
<td>0</td>
<td>5</td>
<td>7</td>
<td>2 pts lost follow-up</td>
</tr>
<tr>
<td>Stuart R. et al.15</td>
<td>Australia 2012</td>
<td>1998 - 2009</td>
<td>209/250</td>
<td>211/268</td>
<td>54/268</td>
<td>18/54 (M:10/18)</td>
<td>19-36</td>
<td>146</td>
<td>0</td>
<td>11</td>
<td>54</td>
<td>18 pts lost follow-up 23 pts diagnosis failed</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>788/1020</td>
<td>803/1156</td>
<td>NC</td>
<td>&gt;41</td>
<td>566</td>
<td>0</td>
<td>39</td>
<td>187</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

NC = not clear; M = malignancy; pts = patients; RB = repeat biopsy
Figure 3 - Forest plots of index.
bias of literature. The shape of the funnel plots revealed a bit asymmetry (p=0.00, Figure-5). An existing publication bias were indicated; the reason for this might be related to the presence of a potential publication bias, a language bias, inflated estimates in smaller studies, and the lack of publication of small trials with opposite results.

COMMENTS

Recent advances in radiological examinations have improved small renal mass malignancy diagnosis accuracy. In many cases, if an enhanced effect in radiographic appeared, renal lesions were assumed to be malignant and patients were directed toward surgery intervention mostly. However, some solid and complex cystic lesions cannot be well defined and diagnosed by images; and urologists still encounter some masses that cannot be definitively categorized as either benign or malignant, especially for small renal masses (≤4cm). Therefore, percutaneous needle core biopsy is becoming an efficient tool in the characterization of incidentally discovered SRMs in the diagnosis for some uncertain renal lesions. In our analysis, data of the pooled sensitivity, pooled positive likelihood, pooled
negative likelihood was similar to many literature reviews demonstrating that renal mass biopsy has an overall success rate above 90% (19, 20).

Accuracy might be defined by several variables, including the diagnostic ability to subtype/grade tissue, as well as the ability to obtain an interpretable tissue specimen to conduct a consistent diagnosis. The RCC subtype was not routinely provided; however available, the accuracy for RCC subtype is estimated at nearly 96.6% (13). Tissue grade, another diagnosis index, was not reported as high accuracy as the subtype reports. Some studies showed that the biopsies accuracy for the Fuhrman nuclear grade was lower at 46%-85% (4, 5).

In respect to the complication rates of the percutaneous biopsy, numerous studies (4-6) have already presented enough evidences that there is a very low complication rate. The most common complications observed are bleeding, syncope, flank pain, pneumothorax, etc. The most feared potential complication is tumor seeding, however, similar to several other analyses (4-7) no contemporary study has observed this complication. In the 9 included studies of our meta-analysis, the major complications and mortality reports were extremely low.

As observed in many meta-analysis of diagnostic test, the concept of the false negative remains a complex issue. Some patients received an indeterminate biopsy on their mass, which does not precisely determine subtype even it was a malignancy. Moreover, some patients' mass may be compounded by some existence of hybrid tumors containing elements of benign and malignant histology after surgical intervention, such as oncocytoma related to chromophobe RCC (21). In all such cases the event was defined as false negative. Only truly identified subtype of the benign/malignancy could be recognized as true negative/positive. This definition, while strict, is much in accordance with similar studies (10, 13).

In our analysis of 9 included studies, there were 71.5% biopsies (561/788) that were true positive malignancy and 29.7(233/788) truly benign, the ratio between malignancy and benign was 2.4:1 which agrees nicely to others' reports (5, 12, 13, 20). As the high morbidity of malignancy in SRMs suggests a probably trend toward over treatment of these mass with surgery intervention, some reports indicate that only one third of SRMs would become significant if managed conservatively (22). Some studies showed that biopsy could alter management in 41%-61% of cases (5, 6, 16).

If the patient receives an initially non-diagnostic biopsy, repeat biopsy is recommended. In our analysis, repeat biopsy was carried out in 41 patients and 23 patients were malignancy after repeat biopsies in 9 studies. Laguna and colleagues (23) analyzed published renal-mass biopsy series and determined that repeat biopsy or surgical resection of tumors followed indeterminate biopsy in 46.4% of cases, and that repeat biopsy identified cancer in 71% of cases. That means that if normal, insufficient tissue or necrosis obtained from the initial biopsy is caused by technical failure, a repeat biopsy is necessary with respect of 70% malignancy morbidity in SRMs.

Like other meta-analyses of diagnostic tests, our work has limitations. We have tried to identify and calculate all the studies about diagnosis accuracy of the percutaneous core needle biopsies of the small renal mass (≤4.0 cm). By means of an extensive Medline-based search, we aimed to retrieve and extract all published data available regarding SRM...
percutaneous core needle biopsy diagnosis of malignancy. Some published studies may have been overlooked due to our strict exclusion criteria. Given diagnostic accuracy studies require large sample numbers and long follow-up periods with which to facilitate metastatic events, it seems likely studies of this magnitude would miss follow-up data and generate bias. Furthermore, publication bias (a lower probability of the publication of negative results) was more difficult to avoid than it would have been in a meta-analysis of a randomized controlled trial. Future studies should follow the Standards for Reporting of Diagnostic Accuracy recommendations and also include enough subjects.

CONCLUSIONS

Our meta-analysis identified that imaging-guided percutaneous core needle biopsy of small renal masses (SMRs ≤ 4.0 cm) is highly accurate in differentiating benign from malignant tumors. We propose percutaneous core needle biopsies be offered to adapted patients prior to consideration of surgical intervention. Accordingly, a number of unnecessary nephrectomies might be avoided by tissues biopsy pathology.

CONFLICT OF INTEREST

None declared.

REFERENCES


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