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SYSTEMATIC REVIEW

Diagnostic accuracy of image-guided biopsies in small (<4 cm) renal masses with implications for active surveillance: a systematic review of the evidence

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Objective: To determine the safety and diagnostic accuracy of renal tumour biopsies in a defined population of small renal masses (SRMs) only <4 cm using 3 × 2 table, intention to diagnose approach. 3 × 2 table approach examines indeterminate results as a separate category rather than pushing these through traditional 2 × 2 table (four-cell matrix) approach.

Methods: A highly sensitive search was performed in the Cochrane Library, Database of Abstracts of Reviews of Effects; MEDLINE and MEDLINE in Process, EMBASE and conference proceedings (1966–2016) for the acquisition of data on the diagnostic accuracy and complications of RTB in patients with SRM <4 cm. Methodological quality and risk of bias was assessed using QUADAS-2. Test characteristics were calculated using conventional 2 × 2 contingency table analysis excluding non-diagnostic biopsies, and an intention-to-diagnose approach with a 3 × 2 table for pooled estimates of the sensitivity and specificity.

Results: A total of 20 studies were included with a total sample size of 974. The pooled estimates for sensitivity and specificity of RTB based upon univariate analysis using 2 × 2 table observed sensitivity 0.952 [confidence interval (CI) 0.908–0.979] and specificity 0.824 (CI 0.566–0.962). Using the 3 × 2 table and intention-to-diagnose principle, sensitivity 0.947 (CI 0.925–0.965) and specificity 0.609 (CI 0.385–0.803) decreased.

Conclusion: RTB in SRMs (<4 cm) is associated with a high diagnostic sensitivity but poor specificity when non-diagnostic results are included by a 3 × 2 table for analysis (intention to diagnose approach). Risk of non-diagnostic results and poor quality of research need addressing through future studies, preferably by a well-designed prospective study appropriately powered for diagnostic accuracy using valid reference standards.

Advances in knowledge: A comprehensive synthesis of literature on image-guided biopsies in SRMs using a different methodology and study design.

INTRODUCTION

Surgical series have demonstrated that 20–30% of small renal masses (SRMs) are benign upon final pathology assessment after excision,[1] and as a consequence it is ever pressing to obtain histological evidence to avoid over and unnecessary treatment. The role of renal tumour biopsy (RTB) has been acknowledged recently, but there many areas which remain poorly understood including its role in active surveillance of SRM <4 cm as a pre-defined patient group, and especially the handling of indeterminate results in evaluating the diagnostic accuracy of this technique.

Recent systematic review and meta-analyses[2,3] aimed to assess the diagnostic performance and safety of renal biopsy are both fraught with many methodological limitations. The studies included a large number of original papers which biopsied renal masses >4 cm with the largest biopsied mass of 32 cm.[4–7] In a sensitivity analysis limited to studies reporting on SRMs, (<4 cm), Marconi et al[2] failed to mention whether non-diagnostic results were treated as negative or were excluded from analysis in the included studies of their reported systematic review. Therefore, the generalizability of these findings to patients with SRMs less than 4 cm is limited and clinical challenge

in decision-making for indeterminate results remains a core issue in contemporary urological practice. It could be argued, that a larger biopsy target will improve sensitivity and accuracy outcomes because evidence suggests that tumour size plays a pivotal role, and small tumours are pushed by the biopsy needle instead of penetration to obtain adequate tissue.[8,9] With this in mind, a contrary view can put forward that that larger tumours are often necrotic and this could diminish accuracy, however no evidence has been provided to support this assertion in the previous reviews in this area.[4–7]

Simel et al[10] described a 3 × 2 contingency table approach to deal with non-diagnostic results (non-positive and non-negative)—a common scenario in RTB during clinical decision-making. The traditional approach has been to report outcomes of RTB using 2 × 2 tables (four-cell matrix) and making a number of assumptions such as treating non-diagnostic results as negative, excluding them from the analysis or treating these as positive. These approaches have the potential of leading to spurious diagnostic accuracy outcome for diagnostic tests, both sensitivity and specificity.[11] Figure 1 summarises the intention to diagnose principle used in this study. We considered, if the reference standard (histopathology of excised mass) proved to be positive for cancer, then an indeterminate RTB result was false-negative (FN) and, in contrast, if the reference standard showed no cancer (benign), then the indeterminate result was considered false-positive (FP). In other words if an indeterminate test missed a true-positive (TP), it was considered as FP and if it missed a true-negative (TN), it was considered as FP. This is similar to the approach used by Schuetz et al[11] in a meta-analysis of coronary CT angiography.

The primary objective of the study was to determine the diagnostic accuracy of percutaneous image-guided renal biopsy for detecting renal malignancy in individuals with only small (<4 cm), solid and enhancing renal masses employing the 3 × 2 table approach to minimize overestimation of diagnostic accuracy as described in the previous studies. The secondary objectives were to: (1) determine the rate of complications of the biopsy procedure such as post-procedural bleeding, infection (local or systemic), arteriovenous fistula formation, renal loss or seeding, and (2) establish the accuracy of the biopsy procedure to determine cancer grade and (3) establish the accuracy of biopsy procedure to determine pathological type of renal cell carcinoma (*e.g.* papillary, clear cell carcinoma).

METHODS AND MATERIALS

Types of studies

All observational studies reporting on image-guided biopsy in SRMs (<4 cm) were included. Studies with sufficient data to produce 2 × 2 and 3 × 2 contingency tables were included in the meta-analysis. Studies were excluded reporting on *ex vivo* kidney biopsies, non-image guided biopsies of renal masses such as those with the endoscopic (or laparoscopic) approach and those conducted on animals.

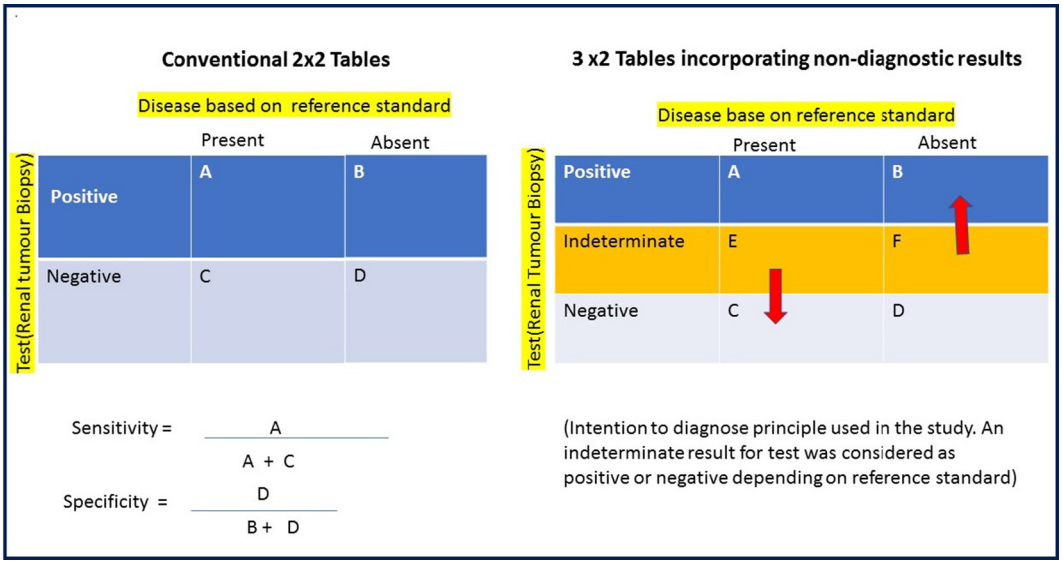
Participants

Safety and diagnostic accuracy of image guided biopsies was assessed in patients with SRMs in adults with small (<4 cm) solid renal mass and signs of contrast enhancement (CT, MRI). Studies were excluded with participants with known metastatic disease, either from renal cell carcinoma or other primary (*e.g.* breast cancer) cancers, and lesions >4 cm.

Index tests

Image-guided biopsy (obtaining a tissue sample using a needle under imaging guidance) in a renal mass which included renal core biopsies. Studies with indeterminate biopsy were also evaluated for patient outcomes. Inconclusive results were handled as a separate category as uninterpretable, intermediate and indeterminate. We also analysed these results as test–test strategy underpinned by clinical practice of repeating the index test in cases of inconclusive results.

Figure 1. Explanation of 3 × 2 table analysis for the non-diagnostic results.



Target conditions

Pathology-confirmed renal cell carcinoma.

Reference standards

We regarded histopathology of resection specimen (nephrectomy or partial nephrectomy) as the reference standard. In those studies where histopathology of the resected tissue was not available, we utilized long-term follow-up information (3 years) as an indirect assessment of the presence of malignant renal mass. The development of metastatic disease that is clinically determined to be of renal origin or the delayed surgical removal of the mass with confirmed malignancy was interpreted as evidence of a FN biopsy; the remainder were treated as TN. We excluded studies with no histopathological confirmation through subsequent resection of target condition or those with shorter follow up of less than 3 years. Growth in size alone was not used as a reference standard as benign lesions are known to exhibit growth upon serial imaging.

Search methods for identification of studies

Electronic searches

We performed an extensive electronic search to identify reports of relevant published and ongoing studies as well as grey literature, and recent meeting abstracts. A highly sensitive search strategy was developed using both appropriate subject headings and text word terms that reflect the clinical condition, interventional procedure (renal mass biopsy and subsequent management) and study designs that are within the scope of this project. Our search strategy is provided in Supplemental Table 1. This strategy was tested against a list of references to verify that these relevant records were found. The following databases were consulted: the Cochrane Library (Wiley) including the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Reviews of Effects (DARE); MEDLINE and MEDLINE in Process (Ovid SP) (from 1948 onwards); EMBASE (Ovid) including conference proceedings (from 1947 onwards); BIOSIS Citation Index (from 1985 onwards); and Web of Science including the ISI Science Citation Index and Index to Conference proceedings (http://ipscience. thomsonreuters.com) (from 1900 onwards). We applied no methodological filter to minimize any risk of missing relevant studies.[12]

Searching other resources

We searched for ongoing studies at ClinicalTrials.gov . We also searched for conference abstracts via the conference proceedings sections in the Web of Science and EMBASE searches. The research team screened the diagnostic database Medion as well as the Aggressive Research Intelligence Facility databases (http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/databases/index.aspx). An internet search included the websites of the American Urological Association (http://www.auanet.org/) and European Association of Urology (http://uroweb.org/) from the year 2010 onwards as well as manufacturers of biopsy equipment.

Data collection and analysis

Selection of studies

All observational studies reporting on image -guided biopsy in SRMs and with data sufficient to populate 2 × 2 and 3 × 2 tables for diagnostic accuracy assessment were included. Two review authors (CP, JG) screened titles and abstracts independently and in duplicate. All disagreements were resolved by discussion or by involving a third review author (GN) as an arbiter. A pre-defined electronic spreadsheet was used to assess and document studies for inclusion and exclusion according to the aforementioned selection criteria (criteria for considering studies for this review).

Data extraction and management

Four review authors (JG, CP, CSB, AA) independently performed data extraction of full-text papers using a pre-defined electronic spreadsheet. A fifth review author (GN) independently verified all the extracted data. Any discrepancy was resolved by discussions. Where necessary, we contacted study authors to obtain raw data. We used Cochrane statistical software[13] for further analysis. The reviewers abstracted information from all the included studies. The extracted information included: (a) the distribution of diagnoses in groups of patients with malignant and benign diseases; (b) the size of the SRMs; (c) the location of the lesions (upper, mid- or lower polar); peripheral or central in relation to renal parenchyma (d) the type of needle; (e) the type of radiological guidance; (f) whether a uropathologist was consulted during or prior to the procedure; (g) the reference standard utilised by the investigators (h) the type and number of complications (pneumothorax and bleeding) associated with the biopsy; and (i) the final results related to the accuracy of the test.

Assessment of methodological quality

Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)–2 quality checklist.[14–16] Four review authors (JG, CP, CSB, AA) independently scored each item as "yes", "no" or "unclear". All quality appraisal and any discrepancies were resolved by discussion with the fifth author (GN). Briefly, the included studies were assessed in four main key domains: (1) patient selection; (2) index test; (3) reference standard; (4) flow and timing. We evaluated study validity by systematically taking into account each of the potential sources of biases: work-up bias, by excluding patients from the analysis because they were not submitted to the reference standard procedure; review bias which is introduced when the test result was not verified by the reference standard procedure; and the test review bias which is introduced when the observers are aware of either the clinical condition of the patient or the final diagnosis.

Statistical analysis and data synthesis

The index test used in this review was to provide a binary outcome (presence of or absence of malignant condition). A univariate random-effects model was employed to obtain summary estimates of the sensitivity and specificity of the test.[17,18] Review Manager software[19] was for primary analyses and Meta-DiSc (http://www.hrc.es/investigacion/metadisc_en.htm), a publicly available software program for the diagnostic accuracy of tests and for secondary analyses.[20] We calculated summary diagnostic performance values including 95% confidence intervals (CIs) from standard data of a 2 × 2 table (after excluding indeterminate results) or the 3 × 2 table, including indeterminate results either in the "FN" or the "FP" cell of a 2 × 2 table according to the results of the reference standard (intention-to-diagnose principle). Where possible, the quality items relating to spectrum of

patients, technical problems in the conduction of index testing using different imaging modalities leading to verification and detection biases, and other domains in the QUADAS-2 tool were considered as potential covariates for sensitivity analysis.[12,14,15]

Assessment of reporting bias

The funnel plot was applied to determine the possibility of reporting bias and small study effects using plots of log diagnostic odds ratio *vs* 1/ESS1/2, where ESS is "effective sample size" defined as (4 *n* + n2)/(n1 + n2); moreover a test for asymmetry was assessed using regression and rank correlation tests.[21] However, testing for reporting bias and small study effects may not be especially useful in the context of studies of diagnostic tests.[22]

RESULTS

Results of the search

A total of 7212 titles and abstracts were identified by the literature search. Of the 85 full-text publications, 65 were excluded for the following reasons: renal lesions >4 cm;[23–31] no final histopathology as reference standard;[9,32–40] no description of tumour size,[41,42] RTB not performed,[43,44] not SRM's, and[45–54] descriptive narrative papers and one *ex-vivo* study[55] (Figure 1 for PRISMA). This list is available from the authors on request. The remaining 20 publications were reviewed in full: two prospective longitudinal studies and eighteen retrospective studies (Table 1). The included studies were carried out in a number of international centres, mainly located in European countries or in the USA (16/20; 80%). The data collection ranged between 1982 and 2013, mainly retrospective in design (19/20; 90%. The sample sizes ranged from 5 to 529, with a total sample size of 974 of participants that had final pathology available as a reference standard.

Operating characteristic of renal tumour biopsy in SRMs

Across all the included studies (Table 1) data was tabulated into TP, TN, FN, and FP, At the individual patient level, indeterminate biopsy results were tabulated as positive and negative (Table 2). Due to the small sample sizes of the available data as a reference standard it was not possible to conduct individual analysis of each of the primary studies.

Overall pooled sensitivity (0.952, CI 0.908–0.979) and specificity (0.824, CI 0.566–0.962) were considered to be at a satisfactory diagnostic rate when using a 2 × 2 table contingency. The pooled estimates for sensitivity and specificity of core biopsy based upon bivariate analysis significantly decreased for the 3 × 2 table contingency at a value of 0.945 (CI 0.920–0.960) and 0.609 (CI 0.397–0.800), $p < 0.001$, respectively (Figure 2). The median prevalence of non-diagnostic core biopsy was three patients [interquartile range (IQR 2–12)] across the patient series, and two studies did not report indeterminate biopsy numbers.[56,57] There were 171 patients with indeterminate results (171/974; 17.5%). The effects of different ways of handling indeterminate biopsies results upon pooled diagnostic accuracy values are depicted in Figure 3.

There is very limited available data on the accuracy of the subtype and Fuhrman grade of RTB when compared to final surgical histopathology. Four studies reported[58–61] grade concordance ranging from 90 to 98%, with a substantial agreement κ of 0.69 (substantial agreement), however, tumour grade accuracy assignment of SRM <4 cm was more challenging. Fuhrman grade was accurately assigned in 50/72 (69%) when compared to nephrectomy specimens, upgraded in 17 (25%) and downgraded in 5 (7%).[60] Data identifying tumours were graded erroneously as low (I or II) or high (III or IV), with accuracy for grade evaluation 69.8% (44/63).[61] Similar rates reported elsewhere 11/21 (52.3%).[58] Other series reported robust grade assignment with RTB at 93%.[56]

Complications

All the included studies reported on the prevalence of complications post-RTB, with the exception of a few.[8,56,62–64] Four studies reported no complications[57,61,65,66] with no seeding at mean follow up 18 months,[67] and longer at 28 months (IQR 11–53) or upon final histopathology.[1,63,65,68] One reported suspected seeding[69] over the course of follow up (2 years and 6 months) for a liposarcoma. Across the included studies, three patients (3/974; 0.3%) required blood transfusions[58,60] because of post-operative bleeding, one patient was admitted due to gross haematuria and urinary clots,[59] and one patient required percutaneous angioembolization,[57] though all recovered without sequelae. In another patient, a 2 cm intrarenal haematoma was mistaken for a tumour and excised at laparoscopic partial nephrectomy and subsequently, patient required to undergo a radical nephrectomy to remove renal (clear) cell carcinoma.[60] Minor complications included hypotension[59] pain[64,67,70] wound infection perirenal haematomas[1,64,65] and small pneumothorax[1,59] all managed conservatively. Minor complication rates ranged from 2.1%,[65] 8.5% 10.4%, to 20%.[64] No mortality was reported across all studies related to RTB.

Risk of bias and quality assessment

The methodology quality assessed by the QUADAS-2 tool across the 20 included studies is summarised in Table 3. Overall, there was a high risk of bias across all the included studies. The majority of the included studies were retrospective 19/20; 90%), and none of the included studies featured sample size calculations when estimating power for diagnostic accuracy in RTB. Most sample sizes were small, with a lack of clinical and demographic information to sufficiently characterise the patient population. Moreover, most studies did not detail the follow-up duration of the included participants over time, with the exception of,[66,67,70,76] with the longest follow-up of just over 2 years. Only one study reported the time interval of RTB to the date of surgery[72] (48 days, IQR 29–68), and the remaining studies were at risk of flow and timing bias. None of the included studies described the learning curve of the interventional radiologist or pathologist, which could inevitably influence RTB outcomes. 37.8% (974/2573) participants in the included studies had reference standards reported. However, more than half the participants (1546/2573; 62.2%) did not have reference standards listed; raising concerns of verification-bias as pathology of the resected SRMs was not available (opting for cryotherapy, RFA and AS), therefore the FP and FN rates remain unknown. Hence, these patients were excluded in the pooled sensitivity and specificity

Table 1. Characteristics of included studies

Author and year	Study design and level of evidence	Country and time period	Characteristics (n, gender, age, co-morbidities, performance status, BMI)	Tumour size (mean, SD, min and max)	Needle size	Guidance ultrasound scan , CT or MRI	Number of passes	Indeterminate biopsy n (%)	Complications
Abe and Saitoh (1992)	Retrospective C1	Japan (June 1982–May 1990)	n36. Gender: 23 males, 13 females; Age 39 to 78 years. No further clinical/demographic data. Duration of follow-up not reported.	n16 <4 cm, n20 >4 cm. Reference standard: n16	14G Tru-Cut biopsy needle, 15G Sure-Cut biopsy needle and 18G biopsy needle used (depending on patients)	Not clearly reported, ultrasound scan imaging mentioned.	Not reported.	n3 indeterminate (1 angiomyolipomasarcoma, 1 metastatic disease primary unknown, and 1 no information of outcome or follow up of patient)	No complications. Seeding suspected in 1 patients for recurrence reported following 2 years and 6 months post RTB
Halverson et al (2013)	Retrospective C1	USA (1999–2011)	n151. Age 59 (SD 14, range 22 to 84) years. No further clinical/demographic data provided. Duration between RTB and surgery 48 days (IQR 29–68)	Mean mass 2.8 (SD 0.8, 1.0 to 4 cm) Reference standard: n133	17-gauge introducer and an 18 gauge spring-loaded gun	CT or ultrasoundscan	≤2 cores	n14 indeterminate (outcomes of patients not reported)	Major complications < 1%
Wang et al (2009)	Retrospective C1	USA (1999–2006)	n110. Age 60.4 (SD 15.4, 28 to 91) years; n68 male, n38 female. Ethnicity: White n92, Africa-American n6, Asian n3, other n5. No further clinical/demographic data reported. 106 RTB <4 cm. Median f/up 1.1 years (0 to 4.7 years)	Mean mass 2.7 (0.5 to 4) cm Reference standard: n36	17-gauge introducer and an 18 gauge spring-loaded gun	CT n66 (60%) /ultrasoundscan n44 (40%)	≤2 cores. Median cores 4.	n10 indeterminate (n2 observed for 1 and 2 years with no change in mass size, n2 died due to unrelated causes, n1 chemo for TCC. n2 underwent surgical excision revealing chromophobe RCC and papillary RCC. n1 cryotherapy, n1 RFA, n1 surveillance benign angiomyolipoma)	n1 hypotensive during procedure and needed IV fluid resuscitation. n2 haematoma n5 flank pain or wound infection
Richard et al (2015)	Retrospective C1	Canada (January 2001–December 2013)	n529. Age 64 years. Sex: male n319 (60.3%), female n210 (39.7%); BMI: 27.3 (24.3–31.1) Duration of follow up not reported.	2.5 (1.8–3.2) cm Reference standard: n162	17-gauge coaxial sheath and an 18-gauge core needle.	ultrasoundscan n388 (73.4%)/CT n115 (21.7%), unknown n26 (4.9%)	1–2 n100 (18.9%), 3–4 n211 (39.9%),≥5 n203 (38.4%), unknown n15 (2.8%)	n4 indeterminate (all underwent surgery and all demonstrated malignancy)	n42 (8.5%). 75% perirenal haematomas, all classified as Clavien-Dindo Grade 1. Follow-up of 28 months not seeding reported.
Kroeze et al (2012)	Retrospective C1	Netherlands (August 2009–September 2010)	n13. Median age 74 (37.9 to 80.4) years. n9 solid masses, n2 bosniak III and n2 Bosnial IV. No further clinical demographic data reported. f/up 16 (6.4–19.8) months	Median tumour size 2.6 (range 1.0 to 14) cm. n9 <4 cm (of which 5 SRM, 4 cystic) , n4 >4 cm Reference standard: n9	17-gauge guiding	Real-time 3D fluoroscopy— CT	2 (1–4)	n3 indeterminate (all confirmed malignancy)	No complication during intervention. (Within 30 days, n1 experienced Grade 2 **Femoropopliteal** bypass occlusion due to stop of anticoagulants before biopsy)

(Continued)

Table 1. (Continued)

Author and year	Study design and level of evidence	Country and time period	Characteristics (n, gender, age, co-morbidities, performance status, BMI)	Tumour size (mean, SD, min and max)	Needle size	Guidance ultrasound scan , CT or MRI	Number of passes	Indeterminate biopsy n (%)	Complications
Park et al (2013)	Retrospective C1	Korea (June 2004–May 2011)	n58. Age 56.8 (24 to 79) years. Male n33, female n25. BMI 17.7–31.1 (23.5, SD 3.1). No further demographic data reported. Duration of follow up not reported.	1.2–3.9 (2.4, SD 0.7) cm Reference standard: n14	18-gauge 15 cm automatic core biopsy system	Ultrasoundscan	mean 3.5, median 4, min 1 max 6	n11 indeterminate (5 AS, 2 surgery [confirmed malignancy], 2 RFA, lost to follow-up 1, 1 re-biopsy, [had surgery confirmed malignancy])	n12 minor (9 perirenal haematoma, n3 pain).
Li et al (2012)	Retrospective C1	France (Jan 2004–Dec 2009).	n90. Sex: male n45, female 35. Age: mean 64.8 (27–88) Duration of follow up not reported.	FNA (n32, size 2.80 ± 0.18 cm), CB (n30, size 2.85 ± 0.19 cm). FNA + CB (n28, size 2.83 ± 0.16 cm) Reference standard: n59	Standard 18-gauge needle attached to 20 ml syringe. 18G	States usually CT guided, does not specify variation in imaging modality.	Not reported.	n2 indeterminate (underwent surgery and confirmed malignancy)	Not reported.
Leveridge et al (2011)	Retrospective C1	Canada (January 2000–December 2009)	n294. Age 25.7–89.5, median 64. Duration of follow up 25 months.	Median tumour size 2.5 cm (range: 0.6–4.0 cm). Reference standard: n77	17-gauge guiding cannula and an 18-gauge core needle. Core biopsies used in all cases.	US guided: 184 cases. CT guided: 60 cases. Both were used in 91 cases.	"Multiple" passes.	n58 indeterminate (32 AS, 9 re-biopsy, 17 RFA, 5 surgery,[confirmed malignancy] 1 lost to follow-up)	29 patients experienced complication, 22—small or moderate haematoma post-procedure or moderate bleeding through the coaxial sheath. 2 patients—small, asymptomatic pneumothoraces, 1 patient—post-biopsy syncope, 3 patients—gross haematuria (1 required admission for urinary retention due to clots). Complication data unavailable in 67 cases
Shah et al (2005)	Retrospective C1	USA (1999–2005)	n110. Further information not available. Duration of follow up not reported.	2.9 cm mean Reference standard: n16	18-Gauge biopsy needle gun	Not reported	4.5 cores (range 1–10 cores)	14 inadequate biopsies (outcomes not reported following advised re-biopsy)	Not reported
Salem et al (2012)	Retrospective C1	USA (10 year study period—dates not stated)	145 patients (99 Male, 46 Female). Mean age was 67.2 ± 11.6 years. Duration of follow up not reported.	Mean mass size 2.4 ± 2.1 cm) Reference standard: n14	16–20-gauge cutting Trucut or Temno needle	CT guided in all lesions	1–3 passes	19 (9 had repeat biopsy -->3 clear cell, 2 papillary, 1 unclassified, 5 RFA, and 5 AS).	Minor complications in 3 patients (2.1%)—2 developed sub capsular haematoma and 1 developed flank ecchymosis. No major complications

(Continued)

Table 1. (Continued)

Author and year	Study design and level of evidence	Country and time period	Characteristics (n, gender, age, co-morbidities, performance status, BMI)	Tumour size (mean, SD, min and max)	Needle size	Guidance ultrasound scan , CT or MRI	Number of passes	Indeterminate biopsy n (%)	Complications
Millet et al (2012)	Retrospective C1	France, 2006–2011	n187 (n60 treated by surgery, 30 male and 30 females, median age 60 years, range 20 to 85 years) Duration of follow up not reported.	Median size 3 cm (range 0.9 to 4). Reference standard: n73	17 gauge	8-multidetector CT scanner and CT fluoroscopic guidance	2–5 cores	Not reported	No complications
Walton et al (2012)	Retrospective C1	UK, 1999–2009	71 (54 males, 17 females), age ranged 61–76. Duration of follow up not reported.	≤4=25 patients (35.2%)>4=25 patients (35.2%) Reference standard: n36	18 gauge	Ultrasound in 69 (97.2%) patients and CT scan in 2 (2.8) patients	1–2 cores	n6 indeterminate (outcomes not reported)	Haematuria $n = 1$ (1.4%). Transfusion requirement $n = 1$ (1.4%)
Eshed et al (2004)	Retrospective C1	Israel, 1996–2001	23 patients (age range 36–89 years, mean 61; 15 males and eight females) Duration of follow up not reported.	>3 cm = 13≤3 cm=6 Reference standard: n18	18-gauge	CT Scan	Not reported	n1 non-diagnostic in obese patient	1 suspected bowel perforation
Granon et al (2014)	Retrospective C1	France, 2010–2013	26 patients (15 males and 11 females) with a mean age of 68 years (range 23–89 years). Duration of follow up median 18 months.	Mean size of tumour was 3.6 cm (range 0.6–9 cm). (There were 17 masses measured <4 cm and 9 masses measured >4 cm) Reference standard: n26	16 gauge	MRI	2 cores	Not reported	No complication
Hu et al (2015)	Retrospective C1	USA, 2008–2011	269 patients (74 females and 195 males), age ranged from 18 to 92 years with a median age of 66 years. Duration of follow up not reported.	Tumour size ranged between 0.5 to 24 cm with an average of 3.4 cm and a median of 2.6 cm 178 < 4 cm Reference standard: n55	Not reported	Not reported	Not reported	n3 indeterminate (follow-up outcomes not fully reported)	No complication
Menhadji (2013)	Prospective B3	USA, May–Dec 2012	n7, 5M and 2F, age 54–79, (mean 68.2) ASA - III (5), II (2), indication cancer (6), renal disease (1) BMI—not reported Duration of follow up not reported.	Right (2), Left (4). Mean size 2.55 (2.0–2.8 cm) Reference standard: n1	18 gauge, 1.5-inch biopsy needle gun, the device was 13.8 cm	Ultrasoundscan	Number of passes not reported. Mean biopsy cores 4.1 (3–6)	n1 indeterminate (outcome RFA)	No complications
Neuzillet (2004)	Retrospective C1	France, June 1995–March 2003	n88 , age 21–88 (mean 61.32, median 64) Duration of follow-up not reported.	2.8 cm (0.2–4 cm) Reference standard: n61	18 gauge allowing 1.7 × 0.1 cm core	Helical CT under LA, prone position	2 cores	n3 indeterminate (2 radical nephrectomy RCC, 1 lost to follow-up)	No complications and no tumour seeding reported.

(Continued)

Table 1. (Continued)

Author and year	Study design and level of evidence	Country and time period	Characteristics (n, gender, age, co-morbidities, performance status, BMI)	Tumour size (mean, SD, min and max)	Needle size	Guidance ultrasound scan , CT or MRI	Number of passes	Indeterminate biopsy n (%)	Complications
Chyhrai (2010)	Prospective B3	Germany, July 2004–February 2006 Mean follow-up 2 years	n25 Indication = non-cystic homogenous <4 cm SRM, old and multiple morbid patient. Mean age 63 ± 7.7 Mean follow up 2 years	2.5 cm (1.5 to 4 cm) Reference standard: n18	18 gauge, 1.7 × 0.1 cm specimen	Ultrasoundscan, repeat ultrasoundscan 2 h and next day post-RTB	3 cores	n2 indeterminate (1 surgery confirmed RCC, and 1 died before pre-operatively of myocardial infarction)	Bleeding 1
Volpe (2008)	Retrospective C1	Canada, Jan 2000–May 2007	91 patients. 100 bx, age 60 years (25–89) Duration of follow up not reported.	<4 cm Reference standard: n21	18 for bx, FNA = 22 gauge	44 ultrasoundscan + CT, 45 ultrasoundscan, 11 CT	2 cores	n8, (5 AS, 2 RFA, 1 partial nephrectomy—benign)	1 syncope. 1 flank pain
Menogue (2012)	Retrospective C1	Australia, 1998–2009	250 patients, mean age 64, (range 22–88) years Duration of follow up not reported.	2.5 (0.9–4 cm), 268 bx Reference standard: n129	18 G	Ultrasoundscan or CT	mean 2.7 cores (1–10)	n9 indeterminate (underwent surgery 8 malignant and 1 benign)	1 blood transfusion and 1 haematoma

AS, active surveillance; BMI, body mass index; FNA, fine needle aspiration; IQR, interquartile range; LA, local anesthetic; RCC, renal cell carcinoma; RFA, radiofrequency ablation; RTB, renal tumour biopsy; SRM, small renal mass; TCC, transitional cell cCarcinoma.

analysis. Finally, none of the included studies reported blinding of the outcome assessor/s.

Imaging modalities, needle gauges and number of biopsies

CT imaging modality and ultrasound scan was the most commonly reported approach to RTB,[1,58–60,62,69,74] real-time 3D fluoroscopy CT[56,76] and MRI.[67] The majority of studies used a 18G needle, with the biggest size report as 14G.[73] The number of cores ranged from 1 to 5 across of a number of studies.[60,63,72,74,77] Based on the small sample sizes, there was no usable data to conduct sensitivity analysis to explore the impact of procedural approaches on diagnostic yield. The procedural time and cost-consequence were not addressed in any of the included studies.

DISCUSSION

We set out to affirm the significance of the diagnostic accuracy of RTB in SRMs (<4 cm), specifically to address the existing bias and methodological problems of handling indeterminate results.[2] In a well-defined patient population of SRMs; RTB exhibited a high overall diagnostic rate (95%). However, specificity of the intervention remains low (61%) when we applied the intention-to-diagnose principle using a 3 × 2 table approach. From a clinical perspective, by transforming the 2 × 2 table into a 3 × 2 table, we reported all results accordingly and hence outcomes are fully transparent and summarised. This approach significantly altered diagnostic accuracy of RTB particularly in terms of specificity of the results. This may help in clinical decision-making and exploring the true clinical potential of RTB. Low rates of true negative (specificity) may raise a possibility of missing a malignant tumour using RTB which clinically is not acceptable as this provides false reassurance. Moreover, it limits choices of interventions and scope of discussion/options with patients diagnosed with incidental SRMs specifically for active surveillance. A strength of the current study was the definition of TP and TN because RTB's were only compared to final surgical specimen histopathology, and the intention-to-diagnosis principle using 3 × 2 table analysis (Figure 1). A summary of including indeterminate results as FPs or FNs according to reference standard offers transparent evidence for potential clinical use of the RTB test most adequately.

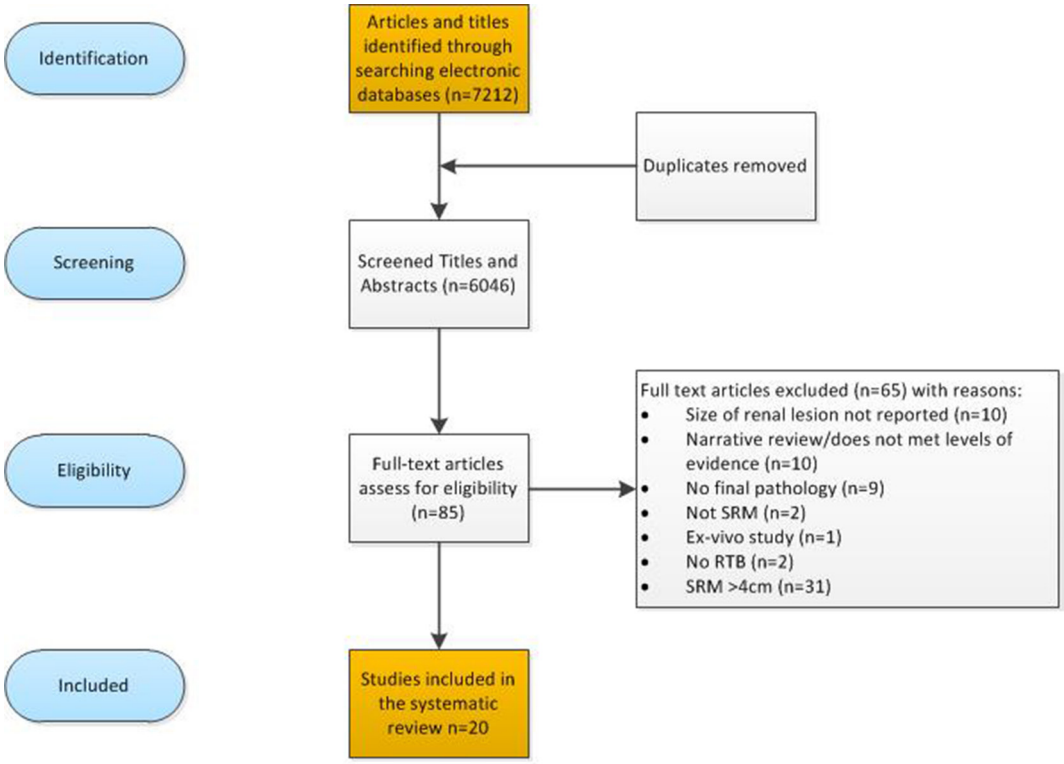
While it is clear that there is no agreed upon policy in the literature regarding how to handle indeterminate results of RTB, our review showed that 17.5% participants were reported to have indeterminate outcomes of first RTB attempts in 18 studies. Again, there was lack of clarity as to how these results were handled at the analysis level. Moreover, only 10 (10/20; 50%) of the included studies provided enough data to calculate alternative the 3 × 2 tables. None of the included studies used 3 × 2 table approach to analyse the outcomes of RTB.

Although overall, the diagnostic accuracy of RTB, RCC subtypes appeared to be reliable, the agreement between tumour grade at biopsy and upon the final surgical specimen had a much poorer performance, and this has been reported even in a meta-analysis with much larger tumour >4 cm targets.[2] Grade of tumour,

Table 2. Analysed studies with recalculated 3 × 2 tables including indeterminate results

2 × 2 table						Indeterminate at patient level	
Author and year	Handling of indeterminate biopsies at patient level	True-positive	False-positive	False-negative	True-negative	Indeterminate positive	Indeterminate negative
Abe and Saitoh (1992)	3 indeterminate patients excluded	8	0	1	7	–	–
Halverson et al (2013)	14 indeterminate patients excluded	122	3	2	6	–	–
Wang et al (2009)	10 indeterminate patients, of which 2 patients considered negative	34	0	0	0	2	0
Richard et al (2015)	4 indeterminate patients considered negative	155	3	0	0	4	0
Kroeze et al (2012)	3 indeterminate patients considered negative	6	0	0	0	3	0
Park et al (2013)	11 indeterminate patients, of which 3 considered negative	11	0	0	0	3	0
Li et al (2012)	2 indeterminate patients considered negative	57	0	0	0	2	0
Leveridge et al (2011)	58 indeterminate patients, of which 5 considered negative	70	2	0	0	5	0
Shah et al (2005)	14 indeterminate patients excluded	15	0	1	0	–	–
Salem et al (2012)	19 indeterminate patients excluded	14	0	0	0	–	–
Millet et al (2012)	Not reported	73	0	0	0	–	–
Walton et al (2012)	6 indeterminate patients excluded	30	0	5	1	–	–
Eshed et al (2004)	1 indeterminate patient excluded	14	0	4	0	–	–
Granon et al (2014)	Not reported	25	0	1	0	–	–
Hu et al (2015)	3 indeterminate excluded	55	0	0	0	–	–
Menhadji et al (2013)	1 indeterminate patient excluded	1	0	0	0	–	–
Neuzillet et al (2004)	3 indeterminate patients, 1 excluded, and 2 considered negative	56	0	3	0	2	0
Chyhrai et al (2010)	2 indeterminate patients, 1 excluded and 1 considered negative	14	0	3	0	1	0
Volpe et al (2008)	8 indeterminate patients, 7 patients excluded, and 1 patient considered positive	20	0	0	0	0	1
Menogue et al (2012)	9 indeterminate, 8 considered negative and 1 patient considered positive	117	0	3	0	8	1
Total	171	897	8	23	14	30	2

Figure 2. Flow of the diagnostic review.



a surrogate marker for tumour aggressiveness, is an independent and powerful prognostic predictor of cancer-specific outcomes.[77] Poor performance of RTB in our study may be based on variations in the level of expertise of the reporting pathologist, quality of biopsy material and operator of the RTB procedure.[56] In the included studies, very little or no information was detailed on these parameters. It is a common clinical observation that there is a learning curve for this intervention, which again was not estimated in any of the included studies. We pooled data from studies with available reference standard, however across the majority of patients in the included studies, they did not have their masses surgically removed and therefore, "definitively" determining the relationship between indeterminate or negative biopsy and the presence of cancer was impossible for these individuals. This summary of evidence should be considered while applying RTB in active surveillance of SRMs.

In the present study, we were unable to perform sensitivity analyses on the performance of RTB for the following factors: location of the tumour (anterior/posterior); lesion's echogenicity/enhancement; amount of adipose tissue; skin to tumour depth; expertise of radiologist/pathologist; imaging modality; number of passes and needle gauge; small sample size and lack of usable data. However, intuitively the diagnostic rate should increase with the number of biopsy cores. Across the vast majority of studies "multiple passes" were performed to achieve a histological diagnosis. However, this may increase the risk of complications, but evidence does not clearly delineate the number of passes

Figure 3. Diagnostic accuracy of image guided biopsies in small renal masses (<4 cm). CI, confidence interval.

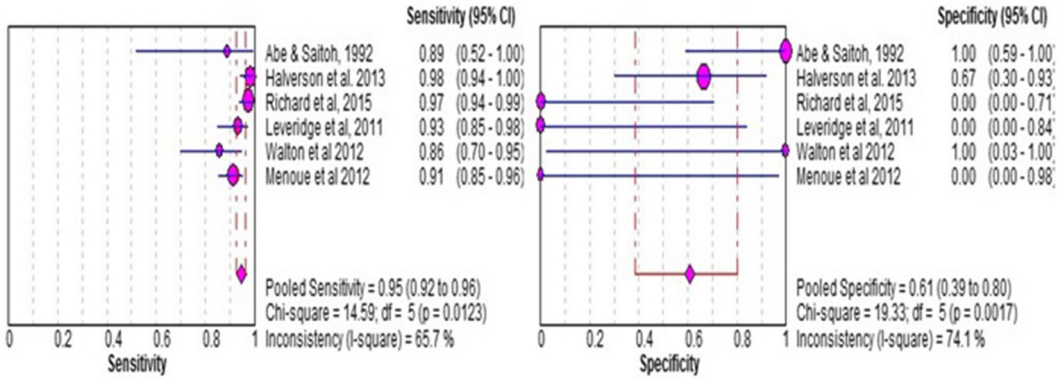


Table 3. Risk of bias summary

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Abe and Saitoh[71]	☺	☺	☺	☹	☹	?	?
Neuzillet et al[61]	☺	☺	☺	☹	☺	☺	☺
Eshed et al[8]	☹	?	☺	☹	☹	☺	☺
Shah et al[63]	?	?	☺	☺	☹	☹	☹
Li et al[65]	☺	?	☺	☹	☺	?	☺
Volpe et al[72]	☺	☺	☺	☺	☺	☺	☺
Wang et al[69]	☺	☺	☺	☹	☺	☺	☹
Chyhrai et al[73]	☺	?	☺	☺	☺	?	☺
Leveridge et al[59]	☺	☺	☺	☺	☺	☹	☹
Kroeze et al[74]	☺	☺	☹	☹	☺	☺	☺
Menogue et al[60]	☺	☺	☺	☺	☺	☺	☺
Salem et al[75]	☺	☺	☹	☺	☺	☹	☺
Millet et al[56]	☹	?	☺	☹	☹	?	☺
Walton et al[58]	☺	☺	☺	☺	☺	☺	☺
Halverson et al[73]	☺	☺	☺	☹	?	☺	☺
Park et al[71]	☺	☺	☺	☺	☹	?	☺
Garnon et al[69]	☹	?	☺	☹	☹	?	☺
Richard et al[70]	☺	☺	☺	☺	☺	☺	☺
Hu et al[64]	☹	?	☺	☹	☹	?	☹
Menhadji et al[66]	☹	☺	☺	☺	☹	?	☺

required or indeed the optimum technique or imaging modality. Multivariate analyses from previous studies have suggested factors that can predict diagnosis of SRM biopsy include tumour type, the presence of a cystic lesion, odds ratio of 13.9 (95% CI = 3.78–50.7; $p < 0.0001$) and tumour size, and for every 1 cm increase in diameter the odds ratio for diagnostic biopsy was 3.11 (95% CI = 1.54–6.28, $p = 0.002$).[59]

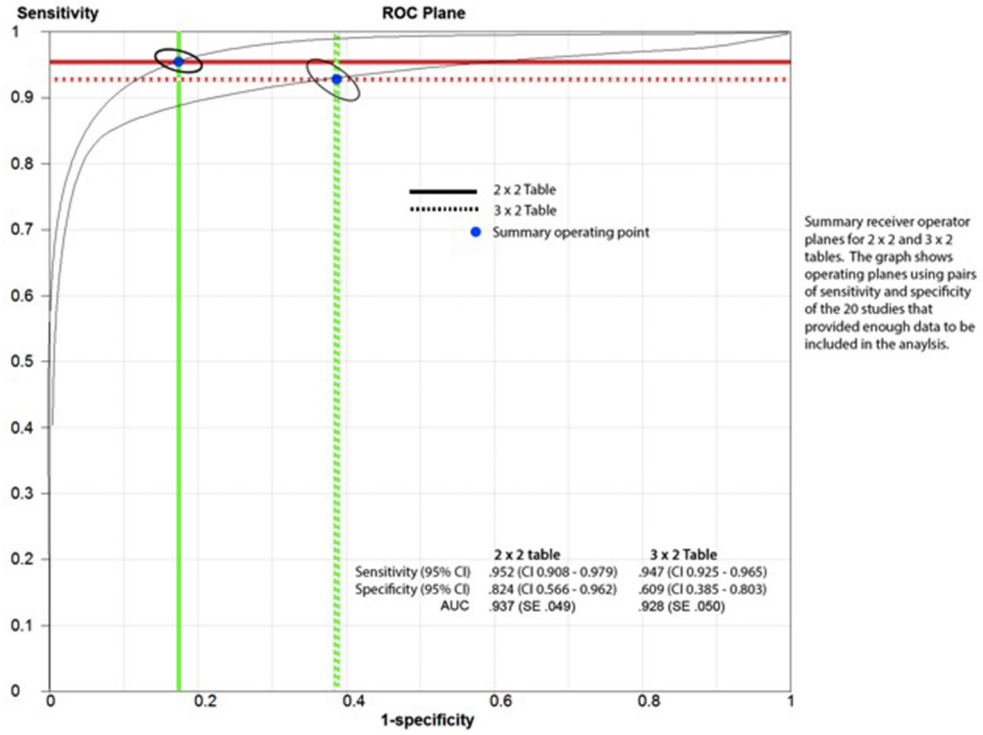
Unfortunately, the methodological quality of the included studies was poor, and the level of evidence underscores that despite many years of experience in RTB, there is a pressing need for a multicentre international collaboration to prospectively examine the RTB in SRM <4 cm. There were a number of patients who underwent AS and ablative therapies whereby, ultimately the prevalence of FP, FN will remain unknown. With a very limited follow-up, the median was reported at 25 months. Moreover, the majority were at risk of flow and timing bias, with only one study describing the duration between RTB procedure and surgery. Finally, studies were at risk of selection bias and through the use of different reference standards (differential-verification bias) including clinical and demographic differences in patients, clinical follow-up schedules, and RTB protocol-based approaches. Despite these limitations, we followed a robust, transparent methodology for reproducibility with strict study selection to address the role of RTB in SRMs, specifically <4 cm. We acknowledge that our findings are constrained because of the methodological limitations of the included studies. However, this systematic review has enabled a broad summary of the evidence, which facilitated refinement of future research directions and clinical implications.

Implication for clinical practice and future research

There are a number of uncertainties in the body of evidence of research to guide clinical practice:

(1) There are a number of studies focusing on outcome of intervention; mostly retrospective in design without prior protocols, power calculation and independent data assessors. Guidelines for clinical practice are mainly based on a large number of studies with risk of biases. Future improved designed prospective studies with better executions are necessary.

Figure 4. Receiver operating characteristic (ROC) analysis of the results..



(2) . None of the studies in the review defined accuracy of needle biopsies in relation to size of the target condition. The larger the mean size of the lesions, the more accurate the test is likely to be because large lesions tend to be easily accessible.
(3) Inconsistencies in "reference standard", duration of follow-up, number of cores needed for good quality tissue, and experience of interventional radiologist and pathologist exist in the present literature. This needs rectification in future research.
(4) Future research should also include data on patient experience, health economics and patients/public engagement. Data on these outcomes was lacking in the primary studies included in this review.
(5) Role of emerging ancillary methods to improve diagnostic yield of biopsies such as novel immunohistochemistry, cytogenetic and molecular markers as highlighted in some of the included studies require assessment.[30,62] Such novel approaches might aid and improve the biopsy accuracy and subtype identification for predicting disease-free survival. Extracting RNA and performing polymerase chain reaction has been shown to considerably increase the diagnostic accuracy of renal biopsy in defining histological subtypes.[73] Moreover, similar results have been observed when fluorescence *in situ* hybridization analysis was added to standard assessment.[74] Further studies have shown that integrating cytogenetic information to existing prognostic factors could lead to a nomogram having accuracy of 0.89 for predicting disease-specific survival.[75] If further confirmed, RTB might be used to guide more personalised management in the future.

CONCLUSIONS

RTB in SRMs (<4 cm) is associated with a high diagnostic sensitivity but poor specificity (TN). Following intention-to-diagnose principles, all results are transparent and provided heightened caution in the diagnostic performance of RTB. High risk of biases, risk of false negative and poor quality of research need addressing through future research efforts, preferably through well-designed prospective studies appropriately powered for diagnostic accuracy using valid reference standards.

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