Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy

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**TAKE HOME MESSAGE:**

RTB is safe and has a high diagnostic yield and diagnostic accuracy for the diagnosis of malignancy and RCC subtype. Higher quality studies are needed to address existing knowledge gaps.

**ABSTRACT**

**Context:** The role of percutaneous renal tumour biopsy (RTB) remains controversial due to uncertainties regarding its diagnostic accuracy and safety.

**Objective:** We performed a systematic review and meta-analysis to determine safety and accuracy of percutaneous RTB for diagnosis of malignancy, histological tumour subtype and grade.

**Evidence Acquisition:** MEDLINE, EMBASE and Cochrane Library were searched for studies providing data on diagnostic accuracy and complications of percutaneous core biopsy (CB) or fine needle aspiration (FNA) of renal tumours. A meta-analysis was performed to obtain pooled estimates of sensitivity and specificity for diagnosis of malignancy. Cohen’s kappa coefficient (κ) were estimated for the analysis of histotype/grade concordance between diagnosis on RTB and surgical specimen. Risk of bias assessment was performed (QUADAS-2).

**Evidence Synthesis:** 57 studies recruiting 5228 patients were included. The overall median diagnostic rate of RTB was 92%. The sensitivity and specificity of diagnostic CBs and FNAs were 99.1% and 99.7%, and 93.2% and 89.8%, respectively. A good (k=0.683) and a fair (k=0.34) agreement were observed between histological subtype and Fuhrman grade on RTB and surgical specimen, respectively. A very low rate of ≥ Clavien 2 complications was reported. Study limitations included selection and differential-verification bias.

**Conclusion:** RTB is safe and has a high diagnostic yield in experienced centres. Both CB and FNA have good accuracy for the diagnosis of malignancy and histological subtype, with better performance for CB. The accuracy for Fuhrman grade is fair. Overall, the quality of the evidence was moderate. Prospective cohort studies recruiting consecutive patients and using homogeneous reference standards are required.

**Patient Summary:** We systematically reviewed the literature to assess safety and diagnostic performance of RTB. The results suggest that RTB has good accuracy in diagnosing renal cancer and its subtypes, and appears to be safe. However, the quality of evidence was moderate, and better quality studies are required to provide a more definitive answer.

**INTRODUCTION**

The management of renal tumours has evolved, with the increasing use of non-extirpative therapies for small renal masses (SRMs) in selected patients and the advent of effective targeted drugs for metastatic disease [[1](#_ENREF_1)]. This has led to an increasing recognition of the importance of histological characterisation of renal masses before treatment in order to tailor therapy based on tumour histology either in the localized and metastatic setting [[2](#_ENREF_2)].

Percutaneous renal tumour biopsy (RTB) has been criticized due to concerns regarding its safety, diagnostic accuracy, and ability to distinguish tumour histologic subtypes and nuclear grade. Furthermore, although fine needle aspiration (FNA) and core biopsy (CB) have been used to sample renal tumours, the best technique has not been clearly defined [[3](#_ENREF_3)]. Although several recent studies have reported low complication rates and good diagnostic performance of RTB, most studies were limited by small sample sizes, heterogeneous populations, different biopsy techniques, and lack of standardized definitions for diagnostic accuracy [[4](#_ENREF_4)].

We performed a systematic review of the literature and meta-analysis to determine the diagnostic performance and safety of RTB in characterizing malignancy, histological subtype and grade of renal tumours.

**EVIDENCE ACQUISITION**

**Search strategy.** The review was performed according to PRISMA [[5](#_ENREF_5)] and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [[6](#_ENREF_6)]. Studies on percutaneous RTB (1st January 1946 to 1st September 2014) were identified by highly sensitive searches of electronic databases (MEDLINE, MEDLINE In-Process, Embase, Cochrane Controlled Trials Register and LILACS) and relevant websites [[7](#_ENREF_7)]. The search was complemented by the reference list of included studies and additional reports identified by the European Association of Urology Renal Cell Carcinoma (RCC) Guideline Panel. No language restrictions were imposed. Two reviewers (LM,SD) screened all abstracts and full-text articles independently. Disagreement was resolved by a third party (TL).

**Selection of studies.** Prospective or retrospective cohort studies providing data on accuracy for malignancy, tumour histotype and grade, and/or on complications of percutaneous CB or FNA of solid or cystic renal masses of any size in adult patients were included. Studies that fulfilled the following criteria were included for the evaluation of diagnostic accuracy for malignancy: (a) reference standard for tumour malignancy represented by pathology on surgical specimen of partial or radical nephrectomy performed after RTB, or clinical and radiological follow-up of at least 12 months showing presence or absence of tumour progression and/or onset of tumour-related symptoms; (b) availability of number of non-diagnostic biopsies; and (c) availability of number of diagnostic biopsies classified as true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN) either as group totals or by case-by-case enumeration of diagnoses. Studies that did not provide data on all 4 elements of diagnostic accuracy were excluded.

Studies that provided data to assess concordance between tumour grade and/or histological subtype between RTB and surgical pathology were included for the assessment of diagnostic accuracy for histological subtype and/or grade.

Studies reporting exclusively complications of RTBs were also included. Complications were graded according to the Clavien-Dindo classification [[8](#_ENREF_8)]. Studies on laparoscopic-assisted or ex-vivo RTBs were excluded.

**Data extraction**. A data extraction form was developed *a priori* to collect information on study design, patient characteristics (age, gender, indication for RTB, comorbidities) tumour features (size, solid or cystic pattern), RTB characteristics (needle size, image guidance, number of cores, biopsy technique), reference standard (surgery performed, follow-up length and protocol) and outcome measures (accuracy and complications).

**Quality assessment.** Risk of bias (QUADAS-2 tool [[9](#_ENREF_9)]) was assessed for studies included in the diagnostic accuracy meta-analysis and in the analysis of accuracy for tumour histotype and grade.

**Data analysis and statistical methods.** The rate of diagnostic biopsies (diagnostic yield) and non-diagnostic biopsies was assessed in all studies. When non-diagnostic cases were not reported by authors, the following definitions were used to define a non-diagnostic result: “normal renal tissue”, “extrarenal tissue”, “blood or necrosis only”, “inflammatory or fibrotic tissue only”, “insufficient material” or “non-adequate tissue”.

The accuracy for diagnosing malignancy was assessed on diagnostic RTBs. For each study, we built a two-by-two contingency table consisting of TP, FP, FN and TN based on concordance between biopsy result and surgical pathology or clinical/radiological follow-up. Meta-analysis was performed where appropriate on studies demonstrating homogeneity of population, outcome definition, and methods and timing of outcome measurement. The joint estimates of sensitivity and specificity and their 95% confidence intervals were modelled using the metandi command in Stata 13.1 (StataCorp, College Station, Texas, USA). The summary ROC curve was plotted from this procedure. The xmlelogit default was used, which fits a multilevel mixed effects logistic regression using quadrature convergence. The gllamm (generalised linear latent and mixed model) formulation with spherical quadrature was used in rare instances with numerical convergence issues. The pooled estimates for sensitivity and specificity were based on bivariate analysis. For univariate analysis, forest plots for both sensitivity and specificity were generated using the metan command.

Sensitivity analysis was performed for studies with low risk of selection and flow bias and for studies reporting exclusively on FNA, CB, small (<4cm) renal masses (SRMs) or cystic masses. Egger’s test was used to identify publication bias [[10](#_ENREF_10)] and funnel plots were generated. The influence of potential publication bias was assessed using the ‘trim-and-fill’ method [[11](#_ENREF_11)].

Regarding the analysis of complications and accuracy for histological subtype and grade, a narrative synthesis was provided using descriptive statistics. Cohen’s kappa coefficient(κ) was calculated to define agreement between histotype and grade on biopsy and surgical specimen. To calculate agreement for histotype, a 7x7 contingency table was constructed with the following histologic subtypes: clear cell RCC, chromophobe RCC, papillary RCC, other malignant tumour, oncocytoma, angiomyolipoma and other benign tumour. Regarding agreement for grade, a 4x4 contingency table was constructed with the 4 grade categories. The strength of agreement was considered poor for κ<0.2, fair for κ 0,21-0,40, moderate for κ0,41-0,60, good for κ0,61-0,80 and very good for κ>0.81.

**EVIDENCE SYNTHESIS**

**Quantity of evidence identified.** A thousand-five hundred articles were identified by the literature search. Of these, 153 articles were selected for full text screening and 57 (recruiting 5228 patients) were eligible for inclusion (Figure 1). Thirty-three studies recruiting 2867 patients [[12-44](#_ENREF_12)] were included in the meta-analysis of diagnostic accuracy for malignancy of FNA and CB. Nineteen studies were included in the analysis of accuracy for histotype and grade and 37 studies in the analysis of complications.

The main characteristics of the biopsied tumours in each study and the technical details about RTBs (needle size and type, image guidance, number of cores) are listed in Table 1.

**Risk of bias and quality assessment.** Figure 2 shows the risk of bias assessment for studies included in the analyses of diagnostic accuracy for tumour malignancy, histotype and grade. Overall, there was a high risk of bias across studies. Only 5 studies included in the meta-analysis were prospective,[[15](#_ENREF_15),[16](#_ENREF_16),[27](#_ENREF_27),[36](#_ENREF_36),[37](#_ENREF_37)] while the majority were retrospective case series, including studies reporting all RTBs performed at a single institution and studies reporting only RTBs performed in patients who ultimately underwent surgery (i.e. selection bias). There was only one prospective, not fully paired comparative study of CB versus FNA [[36](#_ENREF_36)]. The clinical setting of RTBs was heterogeneous within studies and across studies. There were concerns about differential-verification bias since pathology of the surgical specimen was available in all patients as reference standard only in 11 of 33 studies included in the meta-analysis. Of these, only 3 high-quality papers reported on consecutive patients [[15](#_ENREF_15),[36](#_ENREF_36),[37](#_ENREF_37)]. In the other 17 studies pathology was available in a proportion of cases (median 56%), and clinical and radiological follow-up was used as reference standard for the remaining patients. Finally, the proportion of patients who had surgical pathology as reference standard was not reported in 5 studies. A modest evidence of publication bias was found in the FNA studies (data not shown).

**Meta-analysis of accuracy of RTBs for diagnosis of malignancy**

The overall median rate of diagnostic RTBs was 92% [IQR80.6-96.8%].

Figure 3 shows the forest plot of the 17 studies on CBs [[14](#_ENREF_14),[16](#_ENREF_16),[18](#_ENREF_18),[20](#_ENREF_20),[21](#_ENREF_21),[26](#_ENREF_26),[29](#_ENREF_29),[30](#_ENREF_30),[33](#_ENREF_33),[35-38](#_ENREF_35),[40](#_ENREF_40),[42-44](#_ENREF_42)]. The rate of non-diagnostic biopsies was 0-22.6%. The estimates for sensitivity and specificity of diagnostic CBs based on bivariate analysis were 99.1% [95%CI 96.4-99.8%] and 99.7%[95%CI 93.7-100%], respectively.

Figure 4 shows the forest plot of the 18 studies on FNA [[12](#_ENREF_12),[13](#_ENREF_13),[15](#_ENREF_15),[17](#_ENREF_17),[19](#_ENREF_19),[22-25](#_ENREF_22),[27](#_ENREF_27),[28](#_ENREF_28),[31](#_ENREF_31),[32](#_ENREF_32),[34](#_ENREF_34),[36](#_ENREF_36),[39](#_ENREF_39),[41](#_ENREF_41),[42](#_ENREF_42)].The rate of non-diagnostic biopsies was 0-36%. The estimated sensitivity and specificity of diagnostic FNAs based on bivariate analysis were 93.2% [95% CI 83-97.5%] and 89.8% [95% CI 78.6-95.4%], respectively.

The sensitivity analysis for studies reporting RTBs of SRMs only (n=7) [[15](#_ENREF_15),[16](#_ENREF_16),[27](#_ENREF_27),[30](#_ENREF_30),[33](#_ENREF_33),[40](#_ENREF_40),[43](#_ENREF_43)] showed a sensitivity of 99.7% [95% CI 81.5-100%]) and a specificity of 98.2% [95% CI 83.3-99.8%]) (Figure 5). The sensitivity analysis of studies reporting RTBs of cystic masses only (n=4) [[13](#_ENREF_13),[21](#_ENREF_21),[25](#_ENREF_25),[41](#_ENREF_41)] showed a sensitivity of 83.6% [95% CI 33.8-98.1%] and a specificity of 98% [95% CI 80.9-99.8%] (Figure 5). The estimates of sensitivity and specificity of studies with a low risk of selection and flow bias were 92.9% [95%CI 79.6-97.8%] and 84.3% [95%CI 69.2-92.8%].

**Analysis of accuracy of RTBs for tumour histotype**

Five studies allowed the analysis of the agreement between tumour histotype on biopsy and surgical specimen with the Cohen’s kappa coefficient (κ) [[14](#_ENREF_14),[28](#_ENREF_28),[37](#_ENREF_37),[45](#_ENREF_45),[46](#_ENREF_46)]. Median κ value was 0.683 [IQR 0.52-0.95], indicating a good degree of agreement.

Overall, 14 studies reported the concordance of tumour histotype between RTB and surgical pathology [[12](#_ENREF_12),[17](#_ENREF_17),[26](#_ENREF_26),[28](#_ENREF_28),[30](#_ENREF_30),[33](#_ENREF_33),[36](#_ENREF_36),[37](#_ENREF_37),[40](#_ENREF_40),[43](#_ENREF_43),[45-48](#_ENREF_45)] (Table 1). The median concordance rate was 90.3% [IQR84-94.4%]. One study compared the concordance for histological subtype of CB and FNA with final pathology, showing no significant difference (91% vs. 86%, respectively; p=0.45) [[36](#_ENREF_36)]. The median concordance rate for the diagnosis of histotype in the 6 studies including SRMs only was 96% [IQR 90-100%]. Tumour subtype was not reported in studies including cystic masses only.

**Analysis of accuracy of RTBs for tumour grade**

Seven studies allowed the analysis of the agreement between tumour grade on biopsy and surgical specimen with the Cohen’s kappa coefficient [[14](#_ENREF_14),[15](#_ENREF_15),[24](#_ENREF_24),[26](#_ENREF_26),[37](#_ENREF_37),[45](#_ENREF_45),[49](#_ENREF_49)]. Median κ value was 0.34 [0.13-0.52], which indicates a fair degree of agreement. In 17 studies, the authors reported the concordance rate between grade on RTB and surgical specimen [[12](#_ENREF_12),[14](#_ENREF_14),[15](#_ENREF_15),[24](#_ENREF_24),[26](#_ENREF_26),[30](#_ENREF_30),[33](#_ENREF_33),[36](#_ENREF_36),[37](#_ENREF_37),[40](#_ENREF_40),[43](#_ENREF_43),[45](#_ENREF_45),[47-51](#_ENREF_47)]. Ten studies used the 4-tier Fuhrman system, 3 studies used a 2 or 3-tier grading system (high vs. low, or high vs. intermediate vs. low), and 4 studies used both the 4-tier and 2-tier grading system. (Table 1) The majority of patients in these series (72% [44,8-82%]) had low grade RCC (Fuhrman 1-2). Overall, the median concordance rate between grading on biopsy and surgical specimen were 62.5% [IQR52.1-72.1%] and 87% [IQR 71-98%] using the 4-tier and the 2-tier grading system, respectively. One study compared the concordance of CB and FNA with final pathology, showing a higher concordance rate for CB (76% vs. 28%; (p<0.05) [[36](#_ENREF_36)]. The 6 studies on FNA [[12](#_ENREF_12),[15](#_ENREF_15),[24](#_ENREF_24),[49-51](#_ENREF_49)] reported concordance rates of 31.7-87.5% and 58-100% using the 4-tier and the 2-tier Fuhrman grading system, respectively. The 10 studies on CBs reported concordance rates of 43-93% [[14](#_ENREF_14),[26](#_ENREF_26),[30](#_ENREF_30),[33](#_ENREF_33),[37](#_ENREF_37),[40](#_ENREF_40),[43](#_ENREF_43),[45](#_ENREF_45),[47](#_ENREF_47),[48](#_ENREF_48)]. The median concordance rate for tumour grade between RTB and surgical specimen in studies including SRM only (n=7) [[15](#_ENREF_15),[30](#_ENREF_30),[33](#_ENREF_33),[40](#_ENREF_40),[43](#_ENREF_43),[45](#_ENREF_45),[47](#_ENREF_47)] was 66.7% [IQR 60-69.8%], but increased to 86.5%[range 80-93%] when a 2-tier grading system was used. Accuracy for grading was not reported in studies including cystic masses only.

**Analysis of complications of RTBs**

Ten [[17-19](#_ENREF_17),[26](#_ENREF_26),[37](#_ENREF_37),[42](#_ENREF_42),[52-55](#_ENREF_52)] and 5 [[23](#_ENREF_23),[33](#_ENREF_33),[56-58](#_ENREF_56)] studies reported the absence of any complications and major complications after RTB, respectively.

In 22 studies at least one complication was reported. The median overall complication rate across these studies was 8.1% [IQR 2.7-11.1%]. Only 3 ≥ Clavien grade 2 complications were reported.

Protocol-mandated computed tomography or ultrasound imaging was routinely performed in order to assess the presence of post-procedural haematomas in 9 of the 37 series included in the analysis of complications.

Overall, perirenal haematomas were observed in 18 studies. In 16 studies, Clavien 1 haematomas were reported in a median of 4.3% [2.7-7.8%] of cases. Haematomas requiring blood transfusion (Clavien 2) occurred in 3 studies in a median of 0.7% of cases. Self-limiting haematuria (Clavien 1) was reported in 12 studies in a median of 3.15% [1.1-8.6%] of patients [[12](#_ENREF_12),[20](#_ENREF_20),[25](#_ENREF_25),[31](#_ENREF_31),[59-67](#_ENREF_59)]. One case of gross haematuria requiring admission for clot urinary retention and one of pseudo aneurysm treated with endovascular embolisation (Clavien 3a) were reported [[29](#_ENREF_29),[63](#_ENREF_63)].

Lumbar pain after the procedure was reported in 8 studies, [[16](#_ENREF_16),[20](#_ENREF_20),[30](#_ENREF_30),[59](#_ENREF_59),[60](#_ENREF_60),[64](#_ENREF_64),[66](#_ENREF_66),[68](#_ENREF_68)] with a median incidence of 3% [IQR 1-4.8%]. One case of septic shock after RTB in a pyelonephritic kidney was reported [[64](#_ENREF_64)]. All other studies did not observe any inflammatory complications after RTB. Two studies reported one case of simple pneumothorax (Clavien 1) [[36](#_ENREF_36),[63](#_ENREF_63)].

Only one case of seeding of a transitional cell carcinoma was reported in the studies in the analysis [[66](#_ENREF_66)]. The presence of seeding was generally determined by clinical and radiological follow-up. However, no evidence of seeding was found when the peritumoural and perirenal fat were routinely histologically assessed after tumour surgical removal [[26](#_ENREF_26),[33](#_ENREF_33)].

**DISCUSSION**

This is to our knowledge the first systematic review including a meta-analysis of studies on diagnostic performance of percutaneous RTB. The meta-analysis showed a high overall diagnostic rate for the procedure (92%), with higher estimates for sensitivity and specificity for CB compared to FNA. The accuracy of RTB for the diagnosis of RCC histological subtype was found to be good, while a fair agreement between tumour grade at biopsy and on the final specimen was observed.

The use of percutaneous sampling of renal tumours has been historically limited due to concerns about its safety, diagnostic yield and accuracy, and for the perceived little impact of RTBs on clinical management [[69](#_ENREF_69)].

However, the adoption of modern biopsy techniques and the growing expertise in performing biopsies, the progressively increased experience of pathologists in interpreting biopsy specimens, and the increased confidence of urologists in using biopsy results to support treatment decisions based on a better knowledge of the natural history of benign and malignant renal tumours, have led to increasing indications of this procedure for the histologic characterisation of small renal masses and metastatic primary renal tumours [[3](#_ENREF_3),[70](#_ENREF_70),[71](#_ENREF_71)]. The current EAU urological guidelines on RCC recommend that RTBs should be performed in patients in whom active surveillance is pursued and before ablative therapy and systemic therapy without previous pathology [[1](#_ENREF_1)]. However, despite the wider indications and the encouraging diagnostic performance reported in experienced centres, the use of RTBs still remains limited outside academic centres and institutions with a special focus on urologic oncology [[72](#_ENREF_72),[73](#_ENREF_73)].

Improving the quality of the evidence on RTB is crucial to better define the role of this procedure in the management of renal tumours. The current evidence base in this field is in fact limited by several factors. First, most studies on RTBs are retrospective, have relatively small sample sizes, and have heterogeneous populations. Second, the assessment of diagnostic accuracy of RTBs is hampered by the lack of surgical confirmation of the histology in a variable proportion of cases, by the use of different follow-up protocols to monitor the clinical behaviour of tumours that are not surgically removed after biopsy, by the adoption of different definitions for biopsy success and by the use of different biopsy techniques and protocols (CB vs. FNA, CT vs. US guidance, number and location of biopsies taken).

In the absence of large, prospective, multicentre studies using homogeneous biopsy techniques and standardized protocols for assessment of diagnostic outcomes, the present paper provides the best available evidence on diagnostic yield and accuracy of RTB. The clinical question we assessed in the review was prioritized by an expert panel of clinicians (EAU RCC Guideline Panel), and the PICO elements were developed in conjunction with the panel. The search strategy and entire review process adhered to PRISMA guidelines and Cochrane review on diagnostic test accuracy principles. The strict methodological criteria used also ensured the inclusion in the meta-analysis of studies with lower risks of bias and a low level of clinical and methodological heterogeneity.

Our results show that percutaneous sampling of renal tumours harbours a diagnostic yield of 92% for the diagnosis of malignancy, indicating that a properly performed RTB can provide information for treatment decision-making in the majority of cases. However, non-diagnostic biopsies constituted a variable, but non-negligible proportion of cases either for CB and FNA. This represents a matter of concern for clinicians, hence surgical exploration or repeat sampling are recommended when the biopsy of a radiologically suspicious renal mass is non-diagnostic [[1](#_ENREF_1)]. Repeat biopsies have been reported to be diagnostic in a high proportion of cases (83-100%) in several series [[38](#_ENREF_38),[44](#_ENREF_44),[63](#_ENREF_63),[74](#_ENREF_74),[75](#_ENREF_75)].

It should be acknowledged that a relevant proportion of non-diagnostic RTBs are in fact failed biopsies due to technical limitations (use of suboptimal technique, needle type or image guidance) and/or to the intrinsic challenge of the procedure (i.e. targeting a mass in an organ which moves with respiration).

The frequent, inappropriate allocation of failed biopsies containing only normal renal parenchyma, blood or fibrosis in the category of inaccurate biopsies has led to a potential underestimation of biopsy accuracy.

A fair evaluation of diagnostic accuracy of informative RTBs is crucial for the definition of their utility, safety and reliability in clinical practice, when histological information is used to make clinical decisions, such as supporting the choice of observation/active surveillance in the presence of a benign histology or a low grade RCC.

In our meta-analysis, CB was shown to have excellent estimates for sensitivity (99.1%) and specificity (99.7%) in the assessment of tumour malignancy. Lower estimates for sensitivity (93.2%) and specificity (89.8%) for the diagnosis of malignancy were observed for FNA. Based on this data, CB may therefore be favoured over FNA for percutaneous sampling of renal tumours. However, since some authors suggest that the two techniques can provide complementary results and eventually increase diagnostic rates and accuracy [[76](#_ENREF_76)], FNA may be performed in combination with core biopsy in selected cases. A potential advantage of FNA is that it allows the intra-procedural assessment of the cytological specimen, which can potentially confirm the appropriate location of the guiding cannula and increase the diagnostic yield of the subsequent CBs.

The sub-group analyses we performed showed excellent accuracy of RTB for diagnosing malignancy in SRMs, while the estimates for specificity and above all sensitivity of RTBs of cystic renal masses are significantly poorer compared with RTBs of solid masses (98% vs. 83.6%, respectively). These findings, together with the potential risk of spreading of tumour cells resulting from cystic rupture during biopsy, support the current trend to limit the indications of RTBs for cystic renal lesions. Percutaneous sampling may still be indicated for Bosniak IV cysts, where clear enhancing solid nodules are visible within the lesion [[1](#_ENREF_1)].

Our analysis also revealed a good degree of concordance between the diagnosis of RCC subtype on biopsy and on surgical specimens (90.3% in the overall population, improving to 96% in the analysis for SRMs; median k value 0.63). The diagnosis of RCC subtype on RTBs is therefore reliable in most cases and can be safely used for treatment decision-making. In fact, although an independent prognostic role for RCC histotype has not been clearly established, single-institution and multi-centre series showed significantly different oncologic outcomes among RCC histologic subtypes, with clear cell and papillary type 2 tumours showing worse outcomes than papillary type 1 and chromophobe histologies [[77](#_ENREF_77), [78](#_ENREF_78)]. Furthermore, the diagnosis of RCC subtype is useful for tailoring the best targeted therapy in systemic disease.

The assessment of tumour grade on RTBs is challenging [[33](#_ENREF_33), [36](#_ENREF_36), [43](#_ENREF_43), [63](#_ENREF_63)]. According to our analysis, the degree of concordance of tumour grade on RTBs and surgical specimens is only fair (median κ=0.34). The median reported concordance rate is 62.5%, improving to 87% when a simplified, two-tier system (Fuhrman 1-2 = low grade; Fuhrman 3-4 = high grade) is adopted. When only studies on SRMs are included in the analysis the concordance rate using the 4-tier system is slightly improved (66.7%), while the concordance is similar using the 2-tier system (86.5%). Accuracy in the evaluation of tumour grade is important for clinical decision-making, but is limited by tumour heterogeneity and inter-observer variability. Intra-tumoural grade heterogeneity has been reported in 5-25% of renal tumours [[36](#_ENREF_36), [69](#_ENREF_69)]. Its potential impact on biopsy accuracy can be reduced by performing multiple biopsies in different areas of the tumour. Although the accuracy of RTBs for tumour grade is not optimal, Jeldres et al. observed that models including other patient and tumour characteristics cannot reliably predict Fuhrman grade and therefore cannot substitute percutaneous biopsy for grade assessment [[79](#_ENREF_79)]. Improving our ability to obtain samples that allow a reliable and accurate evaluation of tumour grade is clearly one of the main future goals of clinical research on RTBs. Furthermore, the classification of grading of renal tumours is evolving and the recent International Society of Urological Pathology (ISUP) 2012 Consensus Conference accepted a new grading system with grades 1-3 of clear cell and papillary RCC being based on nucleolar prominence, and grade 4 being defined by the presence of extreme nuclear pleomorphism or sarcomatoid and/or rhabdoid differentiation [[80](#_ENREF_80)]. Future studies will have to assess the accuracy of RTBs for this newly proposed grading system.

Finally, the present study indicates that percutaneous RTB is a safe procedure, with a very limited risk of significant (≥ Clavien 2) complications. Only one case of seeding was reported in the eligible studies, also when peritumoural and perirenal fat were assessed after surgical removal. Although another case of seeding was recently published, [[81](#_ENREF_81)] most of the few case reports date back to the late 1980s-early 1990s, when different biopsy techniques were used [[3](#_ENREF_3)]. Some authors suggest that the risk of this worrisome complication is minimal with the use of the coaxial technique [[4](#_ENREF_4)] which should always be used in clinical practice. Other complications of RTB were mainly lumbar pain and haematomas/haematuria, which mostly resolved spontaneously without medical intervention. Although protocol-mandated CT or US imaging was not performed after biopsy in all included studies, the incidence of haematomas was relatively low (median 5%) and blood transfusions were required on average in only 0.7% of cases.

This study has several limitations. Included studies may potentially be affected by selection bias, and use of different reference standards (differential-verification bias), including variable clinical follow-up schedules for renal tumours which were not surgically removed. In spite of our efforts to standardise outcome definitions and measurements, clinical and methodological heterogeneity was inevitable, although it was minimised. The threshold for good quality studies for sensitivity analysis was based on only two domains of the QUADAS-2 RoB assessment tool (patient selection and flow/timing), because data were incomplete for all other domains. The duration of follow-up was also relatively short for the majority of studies, and this confers uncertainty regarding biopsy-negative cases being true negatives.

Nevertheless, this study represents the first meta-analysis of diagnostic accuracy of RTBs and is based on a robust methodology, with strict criteria for study selection which are rigorous, transparent and reproducible.

Due to the lack of data in the literature, the study does not provide information on the learning curve needed by urologists and pathologists to take and interpret biopsy specimens, and on the optimal number of cores and biopsy pattern that should be performed to maximize diagnostic performance. Presently there is agreement that at least two good quality cores should be obtained in each case, but increasing the number of cores may increase the diagnostic yield of the procedure [[33](#_ENREF_33)].

Further research is also needed to confirm whether biopsies of the peripheral part of the tumour should be preferred for larger lesions to avoid central necrosis, or if both central and peripheral biopsies should be performed for SRMs, as previously suggested [[82](#_ENREF_82)].

**CONCLUSIONS**

RTB has a high diagnostic yield and is associated with a very low risk of significant complications. Good estimates of sensitivity and specificity for the diagnosis of malignancy were found at meta-analysis either for CB and FNA, with better performance for CB. The accuracy of RTBs for the diagnosis of RCC subtype was found to be good, while accuracy for nuclear grade was fair and improves using a simplified system (low vs. high grade). However, the quality of the available evidence is moderate and well designed, prospective cohort studies including consecutive patients and using valid reference standards to assess RTB performance are required to corroborate these findings and address knowledge gaps.

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**FIGURE LEGENDS**

**Figure 1**. PRISMA flow diagram: search and study selection process for this review.

**Figure 2.** Risk of bias summary (green circle=low risk of bias; red circle=high risk of bias; Yellow circle=unclear risk of bias).

**Figure 3.** Forest plot of estimates of sensitivity and specificity of percutaneous core biopsy for the diagnosis of tumour malignancy (univariate analysis).

**Figure 4.** Forest plot of estimates of sensitivity and specificity of percutaneous fine needle aspiration for the diagnosis of tumour malignancy (univariate analysis).

**Figure 5**. Forest plot of estimates of sensitivity and specificity of percutaneous renal tumour biopsy for the diagnosis of tumour malignancy in studies including only small renal masses or cystic renal masses (univariate analysis).

**Figures**

**Figure 1:**

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Table 1. Tumor characteristics, biopsy technical features and diagnostic results of the studies included in the analysis of accuracy for malignancy, histologic subtype and Fuhrman grade.

NR- not reported; NA- Not applicable SD- Standard deviation; US- Ultrasound; CT- Computed Tomography; FNA- Fine Needle Aspiration; CB- Core Biopsy; C Clavien-Dindo; G- Gauge; k- Cohen’s kappa coefficient; No comp.- No complications were observed

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **N** | **Period** | **Tumor characteristics** | | **Technical characteristics** | | | | **Diagnostic biopsies** | | **Non diagnostic biopsies**  **N(%)** | **Grade concordance** | | **Histologic**  **Subtype**  **Concordance** | **Complications** |
| Size  *Mean (SD), \*median [range]* | Solid or Cystic | Type | Needle size(G) | N pass/core | Guidance | % Patology Reference Standard | Metaanalysis | Fuhrman Grade | High/Low Grade |
| Abel et al. [12] | 166 | 91-07 | 9.2 [3.0, 32.0] | NR | FNA or CB | 22  20 | NR | US  CT | 100% | Yes | 5.4% (9) | 31.5% (33/104) | 67.9% (74/109) | 94.4% (75/79) | NR |
| Al Nazer et al. [49] | 18 | 90-98 | NR | NR | FNA | [20-25] | [1-4] | US CT | 100% | No | - | 77.7% (14/18)  k=0.65 | 100% (18/18) | NR | NR |
| Bielsa Galli et al. [13] | 17 | 85-97 | NR | C(100%) | FNA | NR | Cyst aspiration | NR | 100% | Yes | NA | NR | NR | NR | NR |
| Bishop et al. [50] | 33 | 90-10 | NR | NR | FNA | 22G | NR | US | 100% | No | - | NR | 85% (28/33) | NR | NR |
| Blumenfeld et al. [14] | 81 | 04-08 | 5.3[1‐17] | NR | CB | 18G | 2 | US  CT | 100% | Yes | 2.5% (2) | 43% (29/67)  k=0.126 | - | 88% (71/81)  k=0.679 | NR |
| Campbell et al. [15] | 25 | 94-96 | 3.1\*2.7 [1.2-5.0] | Solid(100%) | FNA | 22G | 2 | CT | 100% | Yes | 36% (9) | 60% (6/10)  k=0.375 | 80% (8/10)\* | NR | Hematoma 40% |
| Chyhrai et al. [16] | 25 | 04-06 | 2.5[1.5‐4.0] | Solid(100%) | CB | 18G | 3 | US | 87% | Yes | 8%(2) | NR | NR | NR | Lumbar Pain 4%; Hematoma 4% |
| Cristallini et al. [17] | 79 | 81-88 | NR | NR | FNA | [21-22] | NR | USCT | 37.5% | Yes | 8.9% (7) | NR | NR | NR | No comp. |
| Eshed et al. [18] | 23 | 96-01 | NR | NR | CB | 18G | NR | CT | 82.4% | Yes | 21.7%(5) | NR | NR | NR | No comp. |
| Garcia-Solano et al. [19] | 31 | 00-06 | [2-18] | Solid(100%) | FNA | 25G | [1-2] | US CT | 100% | Yes | 19.4%(6) | NR | NR | NR | No comp. |
| Halverson et al. [47] | 151 | 99-11 | 2.8(0.8)[1-4] | NR | CB | 18G | >=2 | NR | 100% | No | - | 65% | NR | 94% | NR |
| Hara et al. [20] | 33 | 94-99 | NR | Solid (79%)  Cystic (21%) | CB | 18G | NR | US  CT | 45% | Yes | 0% (0) | NR | NR | NR | Lumbar Pain 12.10% Hematoma 6.10% Hematuria 9.10% |
| Harisinghani et al. [21] | 28 | 97-00 | NR | BosniakIII (100%) | Both | 22G +  18G | [4-8]  [4-6] | CT | 61% | Yes | 0%(0) | NR | NR | NR |  |
| Haubek et al. [22] | 169 | 82-88 | NR | Solid(%NR), Cystic(%NR) | FNA | 23G | NR | US | NR | Yes | 4.7% (8) | NR | NR | NR | NR |
| Juul et al. [23] | 301 | 71-83 | NR | Solid(100%) | FNA | 23G | [4-5] | US | NR | Yes | 5.3% (16) | NR | NR | NR | No comp. |
| Kelley et al. [24] | 43 | 89-93 | NR | Solid(100%) | FNA | NR | NR | US  CT | 26% | Yes | 2.3% (1) | NR | 58% (7/12)  k=0.091 | NR | NR |
| Lang et al. [25] | 199 | 84-98 | NR | CysticBIIF/III(100%) | FNA(84%) CB(14%) | 20,21,22G  18G | NR | CT  US | 18% | Yes | 10.1%(20) | NR | NR | NR | Hematoma 1% Hematuria 8.5% |
| Lebret et al [26] | 119 | 99-05 | 3.3; \*3.0; [1-10] | Solid(100%) | CB | 18G | [1-4] | CT | 65% | Yes | 21% (25) | 54% (28/52)  k=0.340 | NR | 86% | No comp. |
| Li et al [27] | 35 | NR | <4cm | Solid(100%) | FNA | 22G | NR | US  CT | 100% | Yes | 0% (0) | NR | NR | NR | NR |
| Masoom et al [28] | 31 | NR | 7.3[1.9-14] | NR | **FNA** | NR | NR | NR | 100% | Yes | 3.2% (1) | NR | NR | 90% (28/31)  k=0.890 | NR |
| Maturen et al. [29] | 152 | 99-05 | 4.1[1-13] | Solid(89%)  Cystic(11%) | CB | 18G | <=4 | US  CT | NR | Yes | 3.9% (6) | NR | NR | NR | Hematoma: 0.7%(CI) 0.7%(CII), Pseudoaneurism(CIIIa) |
| Menogue et al [30] | 250 | 99-09 | \*2.5[0.9-4] | Solid(100%) | CB | 18-G | 2.7\*2[1-10] | US  CT | 78% | Yes | 20.8%(52) | 69% (50/72) | NR | 98% (117/120) | Lumbar pain: 0.4% Hematoma:0.4%(CII) |
| Mignon et al [31] | 67 | 85-95 | 5.2[1.5-13] | NR | FNA | [16-21G] | 2 | CT | NR | Yes | 28.4% (19) |  |  |  | Hematoma:10.40% Hematuria:3% |
| Millet et al. [45] | 61 | 06-11 | 3[0.9-4] | Solid(100%) | CB | 17-G | [2-5] | CT | 100% | No | NA | 75% (46/61)  k=0.52 | 93%  k=0.71 | 100%  k=1 | NR |
| Mondal et al [32] | 92 | 84-90 | NR | Solid(100%) | FNA | 21G | NR | Di  US | 100% | Yes | 4.3% (4) | NR | NR | NR | NR |
| Mondal et al. [51] | 24 | 05-09 | [1.5-16] | NR | FNA | 22-G | NR | CT | 100% | No | - | 87.5% (21/24) | NR | NR | NR |
| Neuzillet et al. [33] | 88 | 95-03 | \*2.8[0.2-4] | NR | CB | 18G | >=2 | CT | 71% | Yes | 9.1% (8) | 69.8% (44/63) | NR | 92% (58/63) | No comp |
| Niceforo et al. [34] | 23 | 87-91 | NR | NR | FNA | 22G | [1-3] | CT | 26% | Yes | NC | NR | NR | NR | NR |
| Renshaw et al. [46] | 34 | 87-95 | NR | NR | FNA | NR | NR | NR | 100% | No | - | NR | NR | 74% (25/34)  k=0.683 | NR |
| Rybicki et al [35] | 115 | 90-01 | NR | Solid(86%)  Cystic(14%) | CB | [16G-22G] | [3-5] | CT  US  O | NR | Yes | NC | NR | NR | NR | Hematoma 2.7% |
| Schmidbauer et al [36] | 121 | 05-07 | 4(±1.8)\*3.9[0.8-9] | Solid(100%) | CB vs. FNA | 18G | [2-3] | CT | 100% | Yes | 2.6% (2) | NR | 76% (44/58) | 91% (53/58) | Hematoma: 3.4% Pneumotorax:0.8% |
| 11.4%(5) | 28% (8/29) | 86% (25/29) |
| Sofikerim et al. [37] | 42 | 01-08 | 6.39[2.5-14.0] | Solid(%NR)  Cystic(%NR) | CB | 18G | 2 | US | 100% | Yes | 4.8% (2) | 51.5% (17/33)  k=0.267 | NR | 77.5% (31/40)  k=0.364 | No comp |
| Somani et al. [38] | 70 | 96-06 | NR | Solid (%NR)  Cystic (%NR) | CB | 16-18G | [2-4] | US  CT | 56% | Yes | 12.9%(9) | NR | NR | NR | Hematoma: 1.5% |
| Strojan et al. [39] | 79 | NR | 2.8(2.18)\*3.4[1-13] | Solid (%NR)  Cystic (%NR) | FNA | 22G | NR | US | 100% | Yes | 12.7%(10) | NR | NR | NR | NR |
| Thullier et al. [40] | 53 | 98-06 | 2.57[1.3-4] | Solid(100%) | CB | 18G | NR | US  CT | 56% | Yes | 22.6% (12) | 60% | NR | 84% (27/32) | Hematoma:7.5% |
| Todd [41] | 41 | 88-96 | NR | Cystic(100%) | FNA | 18; 22G | [1-4] | US  CT | 37% | Yes | NC | NR | NR | NR | NR |
| Torp-Pedersen [42] | 134 | 84-87 | NR | Solid(100%) | CB vs. FNA | 21G | [1-3] | US | 61% | Yes | 20.9%(28) | NR | NR | NR | No comp |
| 23G | 2.2%(3) |
| Volpe et al. [43] | 100 | 00-07 | \*2.4[0.8-4.0] | Solid (91%) Cystic (9%) | CB | 18G | >=2 | US CT | 24% | Yes | 16% (16) | 66.7% (8/12) | NR | 100% (19/19) | - |
| Walton et al. [48] | 71 | 99-09 | NR | Solid (%NR)  Cystic (%NR) | CB | \*18G  [15-18] | \*1[1-6] | US  CT | 42% | No | - | 52.3% (11/21) | NR | 80% (24/30) | NR |
| Wood et al. [44] | 79 | 88-96 | 4.5\*3.3[1-20] | Solid(72%)  Cystic(28%) | FNA+CB | FNA: 22G  Core: 17-20G | NR | CT  US | 52% | Yes | 6.3% (5) | NR | NR | NR | Hematoma:5.5% |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Aribas et al. [56] | 120 | 93-10 | 8.8(4.9) | Solid(100%) | FNA  CB | 18G  20G | [1-3] | US | NA | NA | NA | NR | NR | NR | No major complications |
| Beland et al. [52] | 56 | 98-05 | 3.1[1-11] | Solid(100%) | CB | 20G,18G,16G | [1-5] | CT US | NA | NA | NA | NR | NR | NR | No comp. |
| Brierly et al. [53] | 49 | 95-97 | NR | Solid(85,7%) Cystic(14.3%) | FNA | NR | NR | US | NA | NA | NA | NR | NR | NR | No comp. |
| Elder et al [54] | 25(31) | 76-82 | NR | NR | FNA | 22G | NR | Flour | NA | NA | NA | NR | NR | NR | No comp. |
| Izumi et al. [59] | 37 | 89-09 | \*8.3 | NR | NR | NR | NR | CT US | NA | NA | NA | NR | NR | NR | Hematuria 5.4%  Pain 2.7%  Hematoma 2.7% |
| Johnson et al. [60] | 44 | 93-98 | NR | Solid(100%) | FNA± CB | 18, 20G | NR | US | NA | NA | NA | NR | NR | NR | Hematoma-4.6%  Hematuria-2.3%  Pain-2.3% |
| Karp et al. [61] | 23 | NR | NR | Solid (%NR)Cystic (%NR) | FNA | NR | NR | US | NA | NA | NA | NR | NR | NR | Hematuria-8.7% |
| Kroeze et al [57] | 13 | 09-10 | 2.6[1-14] | Solid  Cystic(30.7%) | CB | 18G | 2[1-4] | CT | NA | NA | NA | NR | NR | NR | No major complications  (clavien>2) |
| Leiman et al. [62] | 120 | NR | NR | Cystic(100%) | FNA | 22G | [1-5] | US  CT | NA | NA | NA | NR | NR | NR | Hematuria-2.5% |
| Leveridge et al. [63] | 279 | 00-09 | \*2.5[0.6-4] | Solid(%NR)  Cystic(%NR) | CB | 18G |  | US  CT  Both | NA | NA | NA | NR | NR | NR | Hematoma-7.9%  Pneumothorax-0.7%  Syncope-0.36%  Hematuria C3a-0.36%  HematuriaC1-0.7% |
| Li et al [58] | 90 | 04-09 | <4 | Solid(100%) | FNA  CB | 18G | [1-3] | CT | NA | NA | NA | NR | NR | NR | No major complications |
| Nadel et al. [64] | 30 | NR | 4.6[1-11] | Solid(%NR)  Cystic(%NR) | FNA | 18,20G | [1-4] | CT  US | NA | NA | NA | NR | NR | NR | Hematuria 3,3%  Hematoma(C2) 3,3%  Pain 3,3%  Infection 3,3% |
| Pilotti et al. [65] | 132 | 80-84 | NR | Solid(%NR)  Cystic(%NR) | FNA | 22G | NR | CT  Flour | NA | NA | NA | NR | NR | NR | Hematuria9.1% |
| Richter et al. [55] | 517 | 67-96 | NR | Cystic (60%)  Solid (40%) | FNA  CB | 18G, [20-22G] | NR | Flou  US  CT | NA | NA | NA | NR | NR | NR | No comp. |
| Tikkakoski et al. [66] | 180 | 82-88 | 4.7[1.5-20] | Cystic(%NR)  Solid(%NR) | FNA | >20G | NR | US | NA | NA | NA | NR | NR | NR | Seeding:0.6%  Pain:0.6%  Hematuria:0.6% |
| Veltri et al. [67] | 145 | NR | 3.4[1-15] | Solid(%NR)  Cystic(%NR) | FNA± CB | 18G, 21,22 | NR | US  CT | NA | NA | NA | NR | NR | NR | Hematoma 4%  Hematuria:0.7%  AV fistula:0.7% |
| Park et al. [68] | 59 | 04-11 | 1.9[1.1-3.5] | Solid(%NR)  Cystic(%NR) | CB | 18G | \*4[1-6] | US | NA | NA | NA | NR | NR | NR | Hematoma15.3%  Pain 5.1% |