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The Diagnostic performance of adrenal biopsy: A Systematic Review and Meta-Analysis

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Abstract

Objective: To perform a systematic review of published literature on adrenal biopsy and assess its performance in diagnosing adrenal malignancy.

Methods: Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trial were searched from inception to February 2016. Reviewers extracted data and assessed methodological quality in duplicate.

Results: We included 32 observational studies reporting on 2174 patients (39.4% women, mean age 59.8 years) undergoing 2190 adrenal mass biopsy procedures. Pathology was described in 1621/2190 adrenal lesions (689 metastases, 68 adrenocortical carcinomas , 64 other malignant, 464 adenomas, 226 other benign, 36 pheochromocytomas, 74 other). The pooled non-diagnostic rate (30 studies, 2030 adrenal biopsies) was 8.6% (CI 6.1%-11%). The pooled complication rate (25 studies, 1356 biopsies) was 2.4% (CI 1.5%-3.3%). Studies were at a moderate risk for bias. Most limitations related to patient selection, assessment of outcome and adequacy of follow up. Only 8 studies (240 patients) could be included in the diagnostic performance analysis with sensitivity and specificity of 87% and 100% for malignancy; 70% and 98% for adrenocortical carcinoma ; and 87% and 96% for metastasis.

Conclusions: Evidence based on small sample size and moderate risk of bias suggests that adrenal biopsy appears to be most useful in the diagnosis of adrenal metastasis in patients with a history of extra-adrenal malignancy. Adrenal biopsy should only be performed if the expected findings are likely to alter the management of the individual patient and after biochemical exclusion of catecholamine-producing tumors to help prevent potentially life-threatening complications.

Introduction

Widespread use of imaging has resulted in an increased discovery of incidental adrenal masses described in around 5% of abdominal imaging studies[1, 2] While most adrenal tumors are benign, many have indeterminate imaging characteristics as the specificities for diagnosing malignancy is suboptimal for the most commonly employed imaging modalities, computed tomography (CT) and magnetic resonance imaging (MRI) [3, 4]. Pre-test probability of an indeterminate adrenal mass being malignant is much greater in a patient with a history of extra-adrenal malignancy, in some series described as high as 50-75%[5-10]. Justifiably, in such circumstances, additional investigations are warranted, especially if a definitive diagnosis alters the management in the patient concerned. Other indicators of possible underlying malignancy are adrenal mass size and accelerated interval tumor growth, however their predictive value has been either insufficiently investigated or found to have low specificity[11, 12]. The current approach to patients with a newly discovered adrenal mass in the context of a history of extra-adrenal malignancy includes follow up interval imaging to assess tumor growth, additional imaging studies such as FDG-PET and/or referral for image-guided adrenal biopsy.

Pathologists regularly struggle to differentiate a benign from a malignant adrenocortical or adrenomedullary mass even when having the entire tumor specimen available, therefore an adrenal biopsy usually does not have a role in the differential diagnosis of true adrenal incidentalomas. However, in the context of patients with a history of an extra-adrenal malignancy undergoing follow-up monitoring or diagnostic work-up, an adrenal biopsy can confirm an adrenal metastasis without delay. Much more rarely, a diagnostic adrenal biopsy may avoid unnecessary surgery by identifying other underlying pathologies such as primary adrenal lymphoma, infection or hemorrhage. However, adrenal biopsy is an invasive, expensive procedure with a potential for non-diagnostic results and complications. Rates of non-diagnostic adrenal biopsy rates have been reported to vary widely[8, 13-15]

though it is unclear what factors influence this outcome. Adrenal biopsy complications vary in severity with both immediate and delayed onset complications previously described[16-18]. In addition, if clinicians fail to biochemically exclude the presence of pheochromocytoma prior to biopsy, an unplanned biopsy of a catecholamine-producing tumor can result in severe complications[19, 20].

The performance of adrenal biopsy in making the diagnosis of malignancy is unclear. Published studies investigating diagnostic parameters of adrenal biopsy include a small number of participants and employ a variety of adrenal biopsy techniques. Moreover, the results of adrenal biopsy are compared to a reference standard that varies considerably between studies, thus making any confident conclusions impossible.

Our objectives were:

1) To systematically review published literature on adrenal biopsy with a special attention to patient populations, indications of adrenal biopsy procedural descriptions.
2) To quantify the rate of non-diagnostic adrenal biopsies.
3) To describe and quantify complications ensued from the adrenal biopsy procedure.
4) To establish the performance of adrenal biopsy in the diagnosis of malignancy.

Methods:

This systematic review was conducted based on standard methods recommended by the Cochrane Collaboration for Systematic Reviews of Diagnostic Test Accuracy [21] and followed a predefined protocol. This report follows the standards set in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [22] and reports on the diagnostic accuracy of adrenal biopsy in malignant adrenal masses and also on the non-diagnostic rates and complication rates for the adrenal biopsy procedure.

Data sources and Searches

A comprehensive search of several databases from each database's inception to February 24th, 2016, for English language articles was conducted. The databases included Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator (IB). Controlled vocabulary supplemented with keywords were used to search for original research of adrenal biopsy, percutaneous fine needle aspiration of adrenal mass, or core adrenal biopsy. The full search strategy is available in **Supplemental Table 1.** The reference lists from primary studies and narrative reviews were searched and we included any manually identified additional references that might have been missed by our initial search strategy.

Reviewers working independently and in duplicate reviewed all abstracts and selected full-text manuscripts for eligibility. Disagreements at full text screening were resolved by consensus.

Study Selection

We searched for randomized clinical trials, observational studies and case series describing experience with adrenal biopsy procedure in patients with adrenal tumors and reporting one or more of the following outcomes: (i) complication rate of adrenal biopsy procedure, (ii) non-diagnostic rate of adrenal biopsy procedure (failure to obtain sufficient tissue material to make histological diagnosis), and/or (iii) diagnostic performance of adrenal biopsy. We included only studies in English that reported data on more than 10 patients undergoing any kind of adrenal biopsy procedure. Case reports and case-control studies were excluded. Adrenal biopsy was defined as non-diagnostic when the amount of tissue material generated from the adrenal biopsy that was insufficient to obtain a histopathological or cytological diagnosis. We accepted any definition of complications reported by the authors.

For the diagnostic accuracy analysis of adrenal biopsy, we included only studies fulfilling the following criteria:

(i) Reference standard

a. includes either 1) histology following adrenalectomy or autopsy, 2) imaging follow up after 3-12 months, or 3) or clinical follow up for at least 2 years.

b. is reported for at least 50% of patients with malignant adrenal masses (disease positives) and at least 50% of patients with benign adrenal masses (disease negatives) undergoing adrenal biopsy

(ii) Studied population included fewer than 30% patients in whom the adrenal lesion could not be conclusively classified as either benign or malignant.

Data extraction

Data extraction was carried out independently and in duplicates by independent pairs of reviewers (IB, DD, ST, MS, FA) using DistillerSR software from Evidence Partners [23] to collect information from each eligible study. For each study the following were collected: last name of first author and year of publication, the country where the study was conducted, study objective, type of study, study population, time interval of patient enrolment, inclusion and exclusion criteria, patient age and gender, number of patients who underwent biopsy, number of adrenal biopsies (CT guided, US guided, endoscopic US guided, others), needle gauge, number of needle passes, non-diagnostic biopsies, adrenal mass characteristics related to malignant and benign categories and subcategories (number, tumor size, reference standard, complications) and diagnostic accuracy parameters for adrenal biopsy. Discrepancies in data extraction were resolved by consensus or by a third reviewer.

Quality assessment

Authors working independently and in duplicates analyzed the full text of articles eligible for diagnostic accuracy to assess the reported quality of the methods. For the studies selected for diagnostic accuracy analysis, we assessed the risk of bias and the applicability of findings related to patient selection, index test, reference standard using QUADAS-2, the current best tool for quality assessment of studies of diagnostic accuracy in systematic reviews, tailored to the review topic. Patient flow, timing and exclusion, a part of QUADAS-2, was not assessed as it was not relevant to our topic.

Patient selection was regarded at high risk of bias if either consecutive or random selection was not used, or patients were selected from an adrenalectomy database, or case control design was used, or patients were inappropriately excluded based on tumor size or specific imaging characteristics or difficult to diagnose patients. Index Test (adrenal biopsy) interpretation was considered at high risk of bias when it was reviewed knowing the results of the reference standard. Reference standard implementation was considered at high risk of bias if the final diagnosis of malignancy was reached without histopathology or if any benign diagnosis was reached by imaging follow up of less than 6 months (in patients without histopathology).

High concern about applicability was noted for studies where adrenal biopsy procedure and interpretation was not described in sufficient detail to allow replication or if some patients could not be disaggregated (more than 10% pheochromocytomas or neuroblastomas, etc) in the disease negative group, and/or up to 10% of ‘benign’ tumors (cysts, myelolipomas, etc) were included as disease positive.

For observational studies reporting complications, quality was assessed for several parameters: representativeness of patient sample, ascertainment of complication, and the length and adequacy

of follow up were noted for each study. An overall judgment for each of these elements of low, moderate, or high risk of bias was made.

Data Synthesis and Statistical Analysis

We investigated the relation of complications and non-diagnostic adrenal biopsies to the experience at the institute (the number of biopsies per year as a surrogate marker) by liner regression model. Heterogeneity between studies was assessed using the I2 statistic.

Meta-analysis was conducted by fitting a two-level mixed logistic regression model, with independent binomial distributions for the true positives and true negatives within each study, and a bivariate normal model for the logit transforms of sensitivity and specificity between studies. The analysis was done using STATA, version 14 (StataCorp, College Station, TX). We estimated sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratios (DORs), with 95% confidence intervals (CIs).

Results

Included Studies

A total of 173 references were identified with the initial database screening. Reference list screening of the primary studies yielded two more references. Of the 175 studies, 95 were excluded based on abstract screening and 80 full text papers were reviewed. Of these, 32 studies [7-10, 13, 16, 17, 21, 22, 24-43] reported at least one outcome of interest and were included. Studies were primarily excluded due to no outcome of interest (n=19), <10 patients (n=12), abstract only without subsequent full paper publication (n=8), patient overlap (n=7), ex-vivo biopsy (n=1) and case-control study (n=1). Only 8 studies[8, 13, 32, 33, 36-38, 43] were included for the diagnostic accuracy analysis, reasons for exclusion being lack of any or optimal reference standard for at least 50% patients (n=20) or more than 30% patients with adrenal lesions that could not be classified as either benign or malignant in benign

cohort (n=4), **Supplemental Figure 1**. The chance-adjusted inter-reviewer agreement was calculated using the statistic for abstract (kappa = 0.64) and for full-text screening (kappa=0.97).

The summary characteristics of the included studies are presented in **Table 1**. A total of 2174 patients (13-188 per study) were reported to undergo adrenal biopsy. Patients' age ranged between 1.2 to 88 years[16, 31], though mainly included older patients (mean 59.8 years), women representing 39.4% (722/1832 patients of the 29 studies that reported sex). The study population included mainly patients with established or suspected extra-adrenal malignancy (15 studies, 1110 patients), selected populations with either indeterminate masses, specific size thresholds and patients undergoing adrenalectomy (5 studies, 198 patients) and all comers (12 studies, 866 patients). However, even in "all comers" prevalence of malignant adrenal masses ranged between 18% and 70%[13, 25, 26, 28, 30, 32, 42], suggesting a highly selected population (**Table 1)**.

Information on a total of 2190 adrenal biopsies (13 to 277 per study) was reported in 32 studies, **Table 2**. Most of the biopsies were performed either in the United States (n=1390, 63%; 15 studies) or Europe (n=731, 33%; 13 studies). Mean diameter of the mass was 3.9 cm. Adrenal biopsy was performed under Computed Tomography (CT) guidance in 985 (45%) patients (17 studies), under ultrasound (US) guidance in 265 (12%) patients (11 studies), through endoscopic ultrasound in 300 (13.7%) patients (5 studies), and a mixture of CT or US guidance in 48 (2.2%) patients. In 592 (27%) procedures, type of image guidance was not reported (**Table 2**). Needle gauge used for adrenal biopsy ranged from 16 to 25 gauge, though 22 gauge was most frequently employed. Number of needle passes ranged from 1 to 7 passes per procedure, with most studies reporting 3 to 4 passes on average per procedure.

The pathology of adrenal lesions (confirmed by reference standard where available) was reported only for 1621/2190, 74% cases. Out of these, 828 (51%) were classified as malignant lesions, 718 (44%) as benign while the remaining 75 (5%) were not classified as either benign or malignant.

Of the 828 malignant lesions, the majority were metastases of an extra-adrenal malignancy (n=689, 83%), with the rest representing adrenocortical carcinomas (n=68, 8%), primary adrenal lymphomas (n= 17, 2%), neuroblastomas (n=7,<1%) other malignant lesions (n=4, <1%) or not specified (n=43, 5%). The specific extra-adrenal primary tumor from which the adrenal metastases originated was reported in 517 cases: lung (n=348, 67.3%), kidney (n=39, 7.6%), melanoma (n=16, 3%), 12 (2.3%) each from liver, breast and colon, 11 (2.1%) from esophagus, 6 (1.2%) from bladder and 5 (1%) from pancreas. The remaining metastases (56, 10.8%) were from unknown primary, squamous cell carcinoma, multiple myeloma, stomach, pancreas, osteosarcoma, ovary and stomach. After excluding lung cancer only studies, in 17 studies reporting on the origin of 409 metastatic lesions, the three most common malignancies were lung (234, 57%), gastrointestinal (43, 10.5%) and kidney (42, 10%) cancers (**Table 3).**

Of the 718 benign lesions, 464 (65%) were reported to be adrenocortical adenomas, 12 (1.7%) were myelolipomas, 7 (1%) were cysts, 5 (<1%) were ganglineuromas, 4 (<1%) were hematomas, while 226 (31%) were reported as “benign”, but the underlying distinct pathology was not specified by authors (and possibly included benign adrenal lesions other than adrenocortical adenomas).

The remaining 75/1621 (%) lesions that were not classified as either benign or malignant adrenal lesions included pheochromocytomas (n=36), infection (n=29; histoplasmosis n=15, tuberculosis n=14), and other (n=10), **Table 1**.

The pooled non-diagnostic rate derived from 30 studies (2030 adrenal biopsy procedures) was 8.7% (CI 6.2%-11.2%; I^2 = 84%, p<0.001) **Figure 1**. Correlation with needle gauge or number of passes used was not possible due to under-reporting and variability of techniques used. No relationship of non-diagnostic rates to the number of adrenal biopsies performed in a year (reflecting center experience) was observed (R2= 0.0175).

The pooled overall complication rate derived from 25 studies (1356 biopsies) was 2.5% (CI 1.5%-3.4%; I^2 = 19%, p=0.195) **Figure 2**. Reported practices for detection and monitoring of complications varied in the studies. Major complications (those requiring hospitalization/intervention) were adrenal hematoma (n=7), pancreatitis (n=2), pneumothorax requiring chest tube placement (n=2), hemothorax (n=1), perirenal hematoma (n=1), duodenal hematoma (n=1), hypertensive crisis (n=1) and minor complications (self-limiting/ not needing intervention or hospitalization) included pneumothorax (n=12), hematomas [perinephric (n=2), intra hepatic (n=2), subcapsular (n=1), other (n=3)], self-resolved pain (n=4), hypertensive episodes (n=2), abdominal discomfort (n=2), asymptomatic self-limited hypotension and bradycardia (n=2), nausea (n=1), mild hematuria (n=1), hemothorax (n=1), severe pain requiring analgesics (n=1).). All three hypertensive events were described in patients with pheochromocytomas (two of which were apparently non-secreting). Only one study reported a delayed onset complication (needle track metastasis seeding (n=1))[16]. None of the four studies using endoscopic ultrasound (EUS) and providing information on complications, recorded any complications (**Table 2).** No relationship of the complication rate to the number of adrenal biopsies performed in a year was observed (R2= 0.0055).

Diagnostic Accuracy Analysis

An appropriate reference standard was reported for 1096 adrenal masses and included pathology after adrenalectomy or autopsy in 308 (28%) and either imaging or clinical follow up of 1 to 60 months (when reported), **Table 1**. The diagnostic performance of adrenal biopsy was calculated using the data from the 8 studies (240 adrenal biopsy procedures) meeting pre-established eligibility criteria. Diagnostic performance was calculated separately for adrenocortical carcinoma and metastases of an extra-adrenal primary tumor when disaggregation of patient data was possible.

The accuracy was assessed for diagnosing adrenocortical carcinoma (4 studies, n=107), metastasis of an extra-adrenal primary tumor (5 studies, n=131) and for overall malignancy (7 studies, n=217).

The sensitivity of adrenal biopsy for diagnosing any malignancy was 87% (78%-93%) and specificity was 100% (76%-100%). For diagnosing adrenocortical carcinoma, the sensitivity was 70% (42%-88%) and specificity 98% (86%-100%). For diagnosing metastasis of an extra-adrenal primary malignancy, sensitivity was 87% (74%-94%) and specificity 96%. Additional diagnostic accuracy measures (likelihood ratios and diagnostic odds ratios are given in **Table 4.**

Methodological quality

Methodological quality was assessed by the QUADAS-2 tool in the 8 studies included in diagnostic accuracy meta-analysis **(Supplemental figure 2).** Limitations of the studies were not including consecutive or random patient population for biopsy studies and inappropriate exclusion of patients. These limitations increased the likelihood of bias in patient selection. The risk of bias for index test was low and risk of bias for reference standard was low to unclear for most of the included studies. The concerns for applicability in index test and the reference standard were low in majority of the studies.

The quality of studies assessed by the Newcastle Ottawa quality assessment tool for studies reporting complications suggested the studies to be at a moderate risk for bias, most limitations related to patient selection, assessment of outcome and adequacy of follow up of the study population.

Discussion:

We present a systematic review of published experience with adrenal biopsy. Notably, while 32 studies report at least one outcome of adrenal biopsy, mainly due to suboptimal reference standard we were only able to use data from 8 studies (240 biopsies) to calculate the diagnostic accuracy parameters for adrenal biopsy.

Based on these limited numbers we estimated that adrenal biopsy has 87% sensitivity and 100% specificity for the overall diagnosis of malignancy. Similar performance was noted for the diagnosis of metastases (sensitivity 87%, specificity 96%). Lower performance of adrenal biopsy in diagnosing adrenocortical carcinoma (sensitivity 70%, specificity 96%) could be explained by the well-known difficulties and challenges in differentiating between adrenocortical adenoma and carcinoma even when the entire tumor specimen is available. In addition, in the case of a biopsy it is more likely that tissue material is insufficient to apply all criteria for applying the Weiss score system that is usually used for discriminating benign from malignant adrenocortical masses. All estimates are based on data derived from a fairly small sample size and 95% confidence intervals are wide. In addition, high risk of bias was observed especially in the patient selection domain of quality assessment raising concerns with applicability of these findings. Moreover, it is important to note that all diagnostic performance estimates are based only on “diagnostic” adrenal biopsies (where sufficient amount of cells was obtained).

The rate of non-diagnostic biopsy varied significantly between studies from 0% to 28%with quite a high pooled rate of 8.7%. In the majority of cases a repeat adrenal biopsy was not performed. It is likely that the experience of the radiologists, adrenal biopsy technique and type of tumor biopsied influenced the likelihood of non-diagnostic biopsy (although we could not prove this in our analysis). However, it is obvious that additional factors (such as lack of applying the Weiss score upon pathological assessment) are also important, as illustrated in the *ex-vivo* study by Saeger et al where 10% of biopsies were non-diagnostic[44].

The pooled rate of complications was relatively low at 2.5%. However, most studies failed to describe in detail the information on how complications were collected and assessed. It is also likely that the retrospective nature of included studies contributed to the low pooled rate of complications. Adrenal biopsy is an invasive procedure and in some studies the rate of adverse events such as pneumothorax, pain and adrenal hemorrhage was as high as 13.6%[13, 39]. We have not found a

correlation between the adrenal biopsy volume/year (as a surrogate marker for radiologist's experience) and the number of complications. In addition, adrenal biopsy technique could play a role, though we could not perform this analysis based on the data provided. Of note, in 4 out of 5 studies done by the EUS-FNA technique, there were no complications related to the procedure. However, again the sample size was limited with a total of 300 biopsies.

Inadvertent biopsy of pheochromocytomas can release catecholamines that may lead to severe adverse events[20]. A significant number of patients presenting with chromaffin tumors were reported in our review. Most lacked biochemically screening for exclusion of pheochromocytoma prior to the adrenal biopsy resulting in several clinically significant hypertensive episodes. Endocrine evaluation prior to the adrenal biopsy (or at least biochemical screening with metanephrines) should be instituted as standard of care as the adrenal biopsy procedure in a patient with pheochromocytoma is both unnecessary and dangerous.

Strengths and limitations

This is the first systematic review addressing the performance of adrenal biopsy. The strengths of this systematic review include an in-depth comprehensive literature search, a focused review question, duplicate review, pre-planned analysis and stringent inclusion criteria in terms of reference standard for diagnostic accuracy analysis to reduce bias.

We acknowledge that our review has several limitations. The study population and adrenal biopsy procedure described in the studies included in our review were heterogeneous, which lowers our certainty in meta-analytic estimates. Another significant limitation was that most of the studies did not have optimal reference standard. The histological diagnoses included in the "benign adrenal biopsy" category varied in between studies. We limited this bias by excluding studies with more than 30% of lesions that could not be classified as benign (such as pheochromocytomas) in the benign cohort.

Definition and reporting of complication rates and non–diagnostic rates was inconsistent among the studies. We were not able to perform the subgroup analyses as we had planned related to needle gauge, number of passes and imaging technique used to perform biopsies due to heterogeneity and insufficient information available.

It is important to note that most of the included studies were performed in large medical centers and could potentially overestimate performance of adrenal biopsy, however authors' opinion is that such a procedure should indeed be limited to highly specialized adrenal centers.

Conclusion

Adrenal biopsy should be sparingly applied as it is an invasive procedure with variable diagnostic performance, an appreciable non-diagnostic and complication rate. Adrenal biopsy appears to be most useful for the diagnosis of adrenal metastasis in patients with a newly detected adrenal mass and a history of extra-adrenal malignancy. The recommendation of the recent European Society of Endocrinology Guideline Panel on the management of adrenal incidentalomas is that an adrenal biopsy should only be performed if the expected findings are likely to alter the management of the individual patient and after biochemical exclusion of catecholamine-producing tumors to help prevent potentially life-threatening complications[20]. Prospective multi-center studies with detailed recording of adrenal biopsy procedures and outcomes following a pre-agreed diagnostic algorithm would be highly valuable to more accurately determine the diagnostic performance and factors determining the rates of non-diagnostic biopsies and complications associated with the procedure.

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References:

1. Grumbach MM, Biller BM, Braunstein GD, Campbell KK, Carney JA, Godley PA, Harris EL, Lee JK, Oertel YC, Posner MC, et al. Management of the clinically inapparent adrenal mass ("incidentaloma"). *Annals of internal medicine* 2003 **138** 424-429.
2. Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y & Bornstein SR. The clinically inapparent adrenal mass: update in diagnosis and management. *Endocrine reviews* 2004 **25** 309-340.
3. Herrera MF, Grant CS, van Heerden JA, Sheedy PF & Ilstrup DM. Incidentally discovered adrenal tumors: an institutional perspective. *Surgery* 1991 **110** 1014-1021.
4. Kasperlik-Zeluska AA, Roslonowska E, Slowinska-Srzednicka J, Migdalska B, Jeske W, Makowska A & Snochowska H. Incidentally discovered adrenal mass (incidentaloma): investigation and management of 208 patients. *Clinical endocrinology* 1997 **46** 29-37.

5. Lenert JT, Barnett CC, Jr., Kudelka AP, Sellin RV, Gagel RF, Prieto VG, Skibber JM, Ross MI, Pisters PW, Curley SA, et al. Evaluation and surgical resection of adrenal masses in patients with a history of extra-adrenal malignancy. *Surgery* 2001 **130** 1060-1067.
6. Frilling A, Tecklenborg K, Weber F, Kuhl H, Muller S, Stamatis G & Broelsch C. Importance of adrenal incidentaloma in patients with a history of malignancy. *Surgery* 2004 **136** 1289-1296.
7. Schwartz LH, Ginsberg MS, Burt ME, Brown KT, Getrajdman GI & Panicek DM. MRI as an alternative to CT-guided biopsy of adrenal masses in patients with lung cancer. *The Annals of thoracic surgery* 1998 **65** 193-197.
8. Porte HL, Ernst OJ, Delebecq T, Metois D, Lemaitre LG & Wurtz AJ. Is computed tomography guided biopsy still necessary for the diagnosis of adrenal masses in patients with resectable non-small-cell lung cancer? *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 1999 **15** 597-601.
9. Bodtger U, Vilmann P, Clementsen P, Galvis E, Bach K & Skov BG. Clinical impact of endoscopic ultrasound-fine needle aspiration of left adrenal masses in established or suspected lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2009 **4** 1485-1489.
10. Eloubeidi MA, Black KR, Tamhane A, Eltoum IA, Bryant A & Cerfolio RJ. A large single-center experience of EUS-guided FNA of the left and right adrenal glands: diagnostic utility and impact on patient management. *Gastrointestinal endoscopy* 2010 **71** 745-753.
11. Angeli A, Osella G, Ali A & Terzolo M. Adrenal incidentaloma: an overview of clinical and epidemiological data from the National Italian Study Group. *Hormone Research* 1997 **47** 279-283.
12. Mantero F, Terzolo M, Arnaldi G, Osella G, Masini AM, Ali A, Giovagnetti M, Opocher G & Angeli A. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. *The Journal of clinical endocrinology and metabolism* 2000 **85** 637-644.
13. Quayle FJ, Spitler JA, Pierce RA, Lairmore TC, Moley JF & Brunt LM. Needle biopsy of incidentally discovered adrenal masses is rarely informative and potentially hazardous. *Surgery* 2007 **142** 497-502; discussion 502-494.
14. Burt M, Heelan RT, Coit D, McCormack PM, Bains MS, Martini N, Rusch V & Ginsberg RJ. Prospective evaluation of unilateral adrenal masses in patients with operable non-small-cell lung cancer. Impact of magnetic resonance imaging. *The Journal of thoracic and cardiovascular surgery* 1994 **107** 584-588; discussion 588-589.
15. Dusenbery D & Dekker A. Needle biopsy of the adrenal gland: retrospective review of 54 cases. *Diagnostic cytopathology* 1996 **14** 126-134.
16. Mody MK, Kazerooni EA & Korobkin M. Percutaneous CT-guided biopsy of adrenal masses: immediate and delayed complications. *Journal of computer assisted tomography* 1995 **19** 434-439.
17. Silverman SG, Mueller PR, Pinkney LP, Koenker RM & Seltzer SE. Predictive value of image-guided adrenal biopsy: analysis of results of 101 biopsies. *Radiology* 1993 **187** 715-718.
18. Williams AR, Hammer GD & Else T. Transcutaneous biopsy of adrenocortical carcinoma is rarely helpful in diagnosis, potentially harmful, but does not affect patient outcome. *European journal of endocrinology / European Federation of Endocrine Societies* 2014 **170** 829-835.
19. Osman Y, El-Mekresh M, Gomha AM, Mohsen T, Taha N, Hussein N & Eraky I. Percutaneous adrenal biopsy for indeterminate adrenal lesion: complications and diagnostic accuracy. *Urologia internationalis* 2010 **84** 315-318.
20. Vanderveen KA, Thompson SM, Callstrom MR, Young WF, Jr., Grant CS, Farley DR, Richards ML & Thompson GB. Biopsy of pheochromocytomas and paragangliomas: potential for disaster. *Surgery* 2009 **146** 1158-1166.

21. Macaskill P GC, Deeks JJ, Harbord RM, Takwoingi Y. Analysing and presenting results. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Version 10. The Cochrane Collaboration, 2010:

Chapter 10.

22. Moher D, Liberati A, Tetzlaff J & Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open medicine : a peer-reviewed, independent, open-access journal* 2009 **3** e123-130.

23. https://distillercer.com/products/distillersr-systematic-review-software/.

24. Deville WL, Buntinx F, Bouter LM, Montori VM, de Vet HC, van der Windt DA & Bezemer PD. Conducting systematic reviews of diagnostic studies: didactic guidelines. *BMC medical research methodology* 2002 **2** 9.

25. Puri R, Thandassery RB, Choudhary NS, Kotecha H, Misra SR, Bhagat S, Paliwal M, Madan K, Saraf N, Sarin H, et al. Endoscopic ultrasound-guided fine-needle aspiration of the adrenal glands: analysis of 21 patients. *Clinical endoscopy* 2015 **48** 165-170.

26. Martinez M, LeBlanc J, Al-Haddad M, Sherman S & DeWitt J. Role of endoscopic ultrasound fine-needle aspiration evaluating adrenal gland enlargement or mass. *World journal of nephrology* 2014 **3** 92-100.

27. Welch TJ, Sheedy PF, 2nd, Stephens DH, Johnson CM & Swensen SJ. Percutaneous adrenal biopsy: review of a 10-year experience. *Radiology* 1994 **193** 341-344.

28. Rana C, Krishnani N & Kumari N. Spectrum of adrenal lesions on fine needle aspiration cytology. *Indian journal of pathology & microbiology* 2012 **55** 461-466.

29. Hussain S. Gantry angulation in CT-guided percutaneous adrenal biopsy. *AJR. American journal of roentgenology* 1996 **166** 537-539.

30. Wu HH, Cramer HM, Kho J & Elsheikh TM. Fine needle aspiration cytology of benign adrenal cortical nodules. A comparison of cytologic findings with those of primary and metastatic adrenal malignancies. *Acta cytologica* 1998 **42** 1352-1358.

31. de Agustin P, Lopez-Rios F, Alberti N & Perez-Barrios A. Fine-needle aspiration biopsy of the adrenal glands: A ten-year experience. *Diagnostic cytopathology* 1999 **21** 92-97.

32. Lumachi F, Borsato S, Brandes AA, Boccagni P, Tregnaghi A, Angelini F & Favia G. Fine-needle aspiration cytology of adrenal masses in noncancer patients: clinicoradiologic and histologic correlations in functioning and nonfunctioning tumors. *Cancer* 2001 **93** 323-329.

33. Lumachi F, Borsato S, Tregnaghi A, Basso SM, Marchesi P, Ciarleglio F, Fassina A & Favia G. CT-scan, MRI and image-guided FNA cytology of incidental adrenal masses. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2003 **29** 689-692.

34. Paulsen SD, Nghiem HV, Korobkin M, Caoili EM & Higgins EJ. Changing role of imaging-guided percutaneous biopsy of adrenal masses: evaluation of 50 adrenal biopsies. *AJR. American journal of roentgenology* 2004 **182** 1033-1037.

35. Kocijancic K, Kocijancic I & Guna F. Role of sonographically guided fine-needle aspiration biopsy of adrenal masses in patients with lung cancer. *Journal of clinical ultrasound : JCU* 2004 **32** 12-16.

36. Lucchi M, Dini P, Ambrogi MC, Berti P, Materazzi G, Miccoli P & Mussi A. Metachronous adrenal masses in resected non-small cell lung cancer patients: therapeutic implications of laparoscopic adrenalectomy. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2005 **27** 753-756.

37. Lumachi F, Borsato S, Tregnaghi A, Marino F, Fassina A, Zucchetta P, Marzola MC, Cecchin D, Bui F, Iacobone M, et al. High risk of malignancy in patients with incidentally discovered adrenal masses:

accuracy of adrenal imaging and image-guided fine-needle aspiration cytology. *Tumori* 2007 **93** 269-274.

38. Tsitouridis I, Michaelides M, Stratilati S, Sidiropoulos D, Bintoudi A & Rodokalakis G. CT guided percutaneous adrenal biopsy for lesions with equivocal findings in chemical shift MR imaging. *Hippokratia* 2008 **12** 37-42.

39. Osman Y, El-Mekresh M, Gomha AM, Mohsen T, Taha N, Hussein N & Eraky I. Percutaneous adrenal biopsy for indeterminate adrenal lesion: complications and diagnostic accuracy. *Urologia internationalis* 2010 **84** 315-318.

40. Mazzaglia PJ & Monchik JM. Limited value of adrenal biopsy in the evaluation of adrenal neoplasm: a decade of experience. *Archives of Surgery* 2009 **144** 465-470.

41. Schuurbiers OC, Tournoy KG, Schoppers HJ, Dijkman BG, Timmers HJ, de Geus-Oei LF, Grefte JM, Rabe KF, Dekhuijzen PN, van der Heijden HF, et al. EUS-FNA for the detection of left adrenal metastasis in patients with lung cancer. *Lung cancer* 2011 **73** 310-315.

42. Tyng CJ, Bitencourt AG, Martins EB, Pinto PN & Chojniak R. Technical note: CT-guided paravertebral adrenal biopsy using hydrodissection--a safe and technically easy approach. *The British journal of radiology* 2012 **85** e339-342.

43. Tirabassi G, Kola B, Ferretti M, Papa R, Mancini T, Mantero F, Scarpelli M, Boscaro M & Arnaldi G. Fine-needle aspiration cytology of adrenal masses: a re-assessment with histological confirmation. *Journal of endocrinological investigation* 2012 **35** 590-594.

44. Saeger W, Fassnacht M, Chita R, Prager G, Nies C, Lorenz K, Barlehner E, Simon D, Niederle B, Beuschlein F, et al. High diagnostic accuracy of adrenal core biopsy: results of the German and Austrian adrenal network multicenter trial in 220 consecutive patients. *Human pathology* 2003 **34** 180-186.

Figure 1: Non-diagnostic adrenal biopsies*

Figure 2: Adrenal biopsy related complications

Supplemental Figure 1: Prisma Flow diagram

Supplemental Figure 2: QUADAS2 for 8 studies included in the diagnostic accuracy analysis

Table 1: Characteristics of included studies reporting on adrenal biopsy experience

Author, year	Country	Type of study*	Time interval	Population (details)	Patients (N)	Aged y/o	Women (n/N)	Malignant	Benign	Other	Reference standard
Tikkakoski, 1991	Finland	RCS	1985 - 1990	Mainly patients with known malignancy (70%)	56	54.3 (22-87)	28/56	22 metastases 1ACC 1 lymphoma	20 adenomas	3 hematoma 1 pheochromocytoma 1 lymph node 5 adrenal cysts	Adrenalectomy (n=13) Autopsy (n=2) Imaging follow up at 2 months-5 years (n=39)
Kane, 1991	USA	RCS	1984 - 1989	Patients with left adrenal mass	47	Not reported	Not reported	Not reported			Not reported
Gillmas 1992	UK	RCS	1985 - 1990	Patients with lung cancer	16	66 (51-74)	Unclear	5 metastases	8 “benign”	0	Death or imaging follow up 21-29 months (n=7) No follow up (n=6)
Silverman, 1993	USA	RCS	Period not reported (9 years)	Mainly patients with known malignancy (68%)	97	Not reported	Not reported	36 metastases 2 lymphomas 1 multiple myeloma 3 “malignant”	41 “benign”	0	Adrenalectomy (n=8) Imaging follow up mean 16 months (n=16) Clinical follow up (n=8) Not reported (n=51)
Dusenbery, 1994	USA	RCS	1985-1994	All-comers	53	61 (34-79)	25/53	3 ACCs 18 metastases 1 lymphoma	12 adenomas	1 “splenosis” 1 myelolipoma	Adrenalectomy (n=6) Clinical follow up 1-60 months (n=22) No follow up (n=6)
Saboorian, 1994	USA	RCS	1986 - 1992	Patients with known malignancy	188	24-84	68/188	9 ACCs 77 metastases 3 lymphomas	63 adenomas	5 pheochromocytomas 2 myelolipomas 2 histoplasmosis granulomas	Adrenalectomy (n=7) Not reported (n=154)
Welch, 1994	USA	RCS	1982 - 1991	Mainly patients with	270	31-84	102/270	78 metastases#	59 “benign”#	0	Clinical follow up of at least 1 year

				known malignancy							
Burt, 1994	USA	PCS	Not reported	Patients with lung cancer	20	Not reported	Not reported	4 metastases	6 adenomas	0	Not reported
Mody, 1995	USA	RCS	1985 - 1993	Mainly patients with known malignancy (78%)	78	61 (28-88)	32/78	31 "malignant"	47 "benign"	0	Not reported
Hussain, 1996	USA	RCS	1990 - 1994	All-comers	23	63	17/23	Not reported			Not reported
Wu, 1998	USA	RCS	1990 - 1996	All-comers	162	Not reported	Not reported	6 ACCs 73 metastases 1 lymphoma 9"malignant"	50 adenomas	2 pheochromocytomas 2 histoplasmosis granulomas 1 adrenal cyst 1 abscess	Not reported
Schwartz, 1998	USA	RCS	1993 - 1996	Patients with lung cancer	42	67 (41-83)	17/42	18 metastases	24 adenomas	0	Not reported
Porte, 1999	France	RCS	1991 - 1997	Patients with lung cancer	32	43-74	2/32	18 metastases	14 adenomas	0	Adrenalectomy (n=9) Imaging follow up 6 months (n=23)
De Agustin, 1999	Spain	RCS	1988 - 1997	All-comers	169	59 (1.2-76)	24/169	55 metastases, 1 lymphoma + unclear number of ACCs as a part of "22 primary adrenal tumor" group	34 "negative" + unclear number of other as a part of "22 primary adrenal tumor" group	5 neuroblastoma 1 pheochromocytoma + unclear number of other nonadenomas as a part of "22 primary adrenal tumor" group	Adrenalectomy (n=16) Clinical follow up unclear length (n=153)
Lumachi, 2001	Italy	Unclear	Not reported	No history of malignancy:	73	49 (17-80)	44/73	10 ACCs 4 metastases	49 adenomas	7 pheochromocytomas	Adrenalectomy (n=68) Imaging follow up (n=2)

				functioning and nonfunctioning adrenal masses							
Lumachi, 2003	Italy	PCS	1999 - 2001	Patients with incidentaloma >2 cm	34	47 (26-80)	28/34	4 ACCs 2 metastases	24 adenomas	3 ganglioneuromas 1 pheochromocytoma	Adrenalectomy (n=19) Imaging follow up 12 months (n=15)
Paulsen, 2003	USA	RCS	1998 - 2002	Patients with known or suspected malignancy	50	26-86	20/50	4 ACCs 32 metastases 1 sarcoma, 1 lymphoma, 1 extraadrenal leiosarcoma	6 adenomas	3 pheochromocytomas	Adrenalectomy (n=1) Imaging follow up 23 months (n=3) Not reported (n=56)
Kocijančič30, 2004	Slovenia	RCS	1991 - 2001	Patients with lung cancer	64	59 (42-82)	18/64	52 metastases	6 adenomas	0	Not reported
Lucchi, 2005	Italy	RCS	1993 - 2003	Patients with lung cancer	13	65.7 (50-78)	1/13	10 metastases	3 adenomas	0	Adrenalectomy
Lumachi, 2007	Italy	PCS	2001 - 2003	Patients with unilateral incidentaloma >3 cm	42	54 (25-75)	24/42	8 ACCs 4 metastases	26 adenomas	2 ganglioneuromas 2 pheochromocytomas	Adrenalectomy
Quayle, 2007	USA	RCS	1997 - 2006	All-comers	22	60 (31-80)	10/22	3 ACCs 3 metastases	7 adenomas	4 pheochromocytomas 1 paraganglioma 1 hemorrhagic cyst 1 hematoma 2 myelolipomas	Adrenalectomy (n=21) Imaging characteristics (n=3)
Tsitouridis, 2008	Greece	RCS	2000 - 2005	All-comers with indeterminate adrenal masses (56% with	57	58.8 (33-82)	27/57	3 ACCs 29 metastases 2 lymphoma	20 adenomas	1 pheochromocytoma	Adrenalectomy (n=4) Imaging follow up 6-12 months (n=20) Not reported (n=31)

				history of malignancy)							
Osman, 2009	Egypt	RCS	1992 - 2005	All-comers with indeterminate adrenal masses	15	33.3 (7-65)	7/15	5 ACCs 1 metastasis	0	1 cystic teratoma 5 pheochromocytomas 1 schwannoma	Adrenalectomy
Mazzaglia, 2009	USA	RCS	1997 - 2007	All-comers	154	66 (12.5)	59/154	unclear	unclear	0	Not reported
Bodtger, 2009	Denmark	RCS	2000 - 2006	Patients with lung cancer and a left adrenal mass	40	63 (38-79)	20/40	10 metastases 1 myosarcoma	28 adenomas	1 teratoma	Clinical follow up for 21-86 months
Eloubeidi, 2010	USA	Unclear	2000 - 2007	Patients with known malignancy	59	63.8 (47-49)	22/59	22 metastases	37 “benign”	0	Presence of or suspected primary malignancy at another site and/ or imaging and /or clinical follow up
Schuurbiers, 2011	Netherlands	RCS	2001 - 2009	Patients with lung cancer and an FDG-PET positive left adrenal mass	85	65 (37-86)	34/85	1 ACC 54 metastases	25 adenomas	0	Clinical and radiological follow up for benign only
Tyng, 2012	Brazil	RCS	2009 - 2010	All-comers	13	64 (48-84)	2/13	9 metastases	4 adenomas	0	Follow up imaging at 6 months (n=4)
Tirabassi, 2012	Italy	RCS	1990 - 2010	All-comers who subsequently underwent adrenalecto	50	53.4	29/50	9 ACCs 15 metastases	19 adenomas	2 pheochromocytomas 5 myelolipomas	Adrenalectomy

				my							
Rana, 2012	India	RCS	2002 - 2009	All-comers	35	48.9 (17-83)	10/35	1 ACC 7 metastases 5 lymphomas	0	2 neuroblastoma 1 pheochromocytoma 1 angiomyolipoma 1 myelolipoma 9 histoplasmosis granulomas 4 tuberculosis granulomas	Adrenalectomy (n=10) Clinical follow up (n= 25)
Martinez, 2014	USA	RCS	1997 - 2011	All-comers (42% with history of malignancy)	94	66 (32-86)	45/94	1 ACC 24 metastases	58 adenomas	1 pheochromocytoma 1 paraganglioma	Clinical follow of unclear length (n=24), Adrenalectomy (n=6) Imaging follow up of at least 6 months (n=28) Other (n=3) No follow up (n=36)
Puri, 2015	India	PCS	2010 - 2013	All-comers	21	56 (12.2)	7/21	7 metastases	0	1 myelolipoma 1 lipoma 10 tuberculosis granulomas 2 histoplasmosis granulomas	Unclear: imaging characteristics, clinical follow up for 3 years

*Retrospective cohort study: RCS, Prospective cohort study: PCS, #Reported for lung cancer patients only

Table 2: Description of the adrenal biopsy procedure, non-diagnostic rates and complications

Author, year	Biopsies (N)	Adrenal biopsy procedure	Needle gauge	Number of passes	Adrenal mass diameter (cm)	Nondiagnostic rate n1/N	Complication rate n2/N	Complications in details
Tikkakoski, 1991	56	CT-guided (11) US - guided (45) (fine needle biopsy)	Not reported	Not reported	Not reported	2/56	0/56	
Kane, 1991	33	CT-guided, anterior approach, left adrenal only (tandem needle technique)	20-22	1-6	Not reported	1/33	2/33	Pancreatitis leading to 11-13 days hospitalization (n=2)
Gillmas 1992	16	CT-guided (FNA)	18,20	3	2.6 (1.1 - 8)	3/16	1/16	Small pneumothorax (n=1)
Silverman, 1993	101	CT-guided (86) US-guided (15) (unclear technique)	19-22	Not reported	Not reported	18/101	9/101	Mild abdominal discomfort (n=2) Nausea (n=1) Mild hematuria (n=1) Asymptomatic self-limited hypotension and bradycardia (n=2) Pneumothorax (n=2), one patient requiring tube placement Hemothorax, requiring chest drainage (n=1)
Dusenbery, 1994	54	Not reported ((FNA in 43, core in 11)	Not reported	Not reported	Not reported	18/54	Not reported	
Saboorian, 1994	188	Not reported (FNA)	18-22	Not reported	Benign: 2.4(0.8) ACC: 10.6(6) Metastases: 5(2.5)	27/188	Not reported	
Welch, 1994	277	CT-guided (271) US - guided (6) (unclear technique)	16-23	Not reported	3.8 (1-12)	10/147 (provided only for lung cancer patients)	8/277	Only major complications reported (requiring hospitalization or intervention): Perirenal hematoma (n=1) Adrenal hematomas (n=7)

Burt, 1994	20	CT-guided (needle aspiration)	Not reported	Not reported	2.2 (1.2-7.1)	10/20	Not reported	
Mody, 1995	83	CT-guided (79) US-guided (4) (FNA for all + biopsy gun for 2)	18-22	1-7	3.5	5/83	7/83	Pneumothorax requiring tube placement (n=1) Self-resolved pneumothorax (n=1) Perinephric hematoma (n=2) Intra-hepatic hematoma (n=1) Subcapsular hematoma (n=1) Needle-track metastasis seeding (n=1)
Hussain, 1996	26	CT-guided (angle gantry technique)	18-22	3	1.25 (0.6-4)	6/26	0/26	
Wu, 1998	162	Not reported FNA	20-23	3	Not reported	17/162	Not reported	
Schwartz, 1998	42	CT-guided (?core)	22	Not reported	Benign: 1.9 (1-4) Malignant 4.3 (1-7.6)	0/42	3/42	Pneumothorax not requiring hospitalization (n=3)
Porte, 1999	32	CT-guided (?core)	19,22	Not reported	Not reported	0/32	0/32	
De Agustin, 1999	169	CT-guided FNA	22	Not reported	Not reported	47/169	unclear	"no serious complications observed"
Lumachi, 2001	73	CT-guided (52), US-guided (18) FNA	21-23		4.23 (1.71)	3/73	3/73	Self-resolved pneumothorax (n=2) Hematoma (n=1)
Lumachi, 2003	34	CT-guided (14) US-guided (20) FNA	21-23	Not reported	Benign: 4.3(1.4) Malignant: 6.3(2.2)	Not reported	1/34	Self-resolved pneumothorax (n=1)
Paulsen, 2003	50	CT-guided (41) US-guided (9) FNA (3) and core (47)	16-22	3	4.9 (1.5–16)	2/50	0/50	
Kocijančič30, 2004	64	US-guided FNA	22	Not reported	5.6 (2.5-13)	6/64	4/64	Self-resolved pain (n=4)
Lucchi, 2005	13	CT and US-guided FNA	Not reported	Not reported	4.6 (2-10)	Not reported	0/13	

Lumachi, 2007	42	CT-guided (11) US-guided (31) FNA	23	Not reported, cit 4	6.9 (5.1)	2/42	2/42	Self-resolved pneumothorax (n=1) Severe pain requiring analgesic therapy (n = 1)
Quayle, 2007	22	Not reported (needle biopsy)	Not reported	Not reported	5.1 (3-10)	6/22	3/22	Hepatic hematoma (n=1) Hemothorax (n=1) Duodenal hematoma requiring hospitalization (n=1)
Tsitouridis, 2008	57	CT-guided (technique varied)	16- 22	Not reported	3.9 (1.3 -7.8)	2/57	3/57	Self-resolved hematoma (n=2) Self-resolved pneumothorax (n=1)
Osman, 2009	15	CT-guided (12) US-guied (3) (biopsy gun technique)	18		7.7 (1-15)	2/15	2/15 Hypertensive episode (n=2)	
Mazzaglia, 2009	163	Not reported	Not reported	Not reported	3.9 (2.2)	2/163	unclear	"few" complications including one described hematoma and pain
Bodtger, 2009	40	Endoscopic US-guided FNA, left adrenal only	22	1-3	2 (0.6-6)	2/40	0/40	
Eloubeidi, 2010	59	Endoscopic US-guided FNA	22	3 (1-4)	Benign: 2.3 Malignant: 3.1	0/59	0/59	
Schuurbiers, 2011	85	Endoscopic US-guided FNA, left adrenal only	22	3 (1-6)	2.86 (1.91)	5/85	0/85	
Tyng, 2012	13	CT-guided, paravertebral hydrodissection technique	17, 18	Not reported	4.1 (1.3-8.4)	0/13	0/13	
Tirabassi, 2012	50	US-guided FNA	22		Benign: 5.4 ACC: 4.6 Metastases: 5	11/50	2/50	Pneumothroax (n=1) Hypertensive crisis (n=1)
Rana, 2012	35	CT and US-guided FNA	18-22		Not reported	4/35	0/35	
Martinez, 2014	95	Endoscopic US-guided FNA	19, 22 or 25	mean 3.2 ± 1.4	Right: 3.5 (0.88) Left: 2.72 (1.36)	9/95	Not reported	
Puri, 2015	21	Endoscopic US-guided FNA	22	median 4(range 3-7)	2.4	0/21	0/21	

*FNA – fine needle aspiration

Table 3: Origin of Adrenal Metastases reported in included studies*

Author, year	Metastases (n)	Lung	Gastro-intestinal	Kidney	Melanoma	Breast	Prostate	Bladder	Other + unknown primary
Tikkakoski, 1991	22	15	2	3	1				1
Dusenbery, 1994	18	8	4	1	1			1	3
Saboorian, 1994	77	55	4	7	5	1		1	4
Wu, 1998	82	40	9	14	2	1		1	15
De Agustin, 1999	55	26	4	1	2	1	1	1	19
Lumachi, 2001	4	4							
Lumachi, 2003	2	2							
Paulsen, 2003	32	22	4	2	1				3
Quayle, 2007	3			2	1				
Tsitouridis, 2008	29	18	3	2	1	4			1
Osman, 2009	1							1	
Eloubeidi, 2010	22	17	1		2			1	1
Tyng, 2012	9	2	1	3					3
Tirabassi, 2012	15	7		3	1	3			1

Rana, 2012	7	2	1	2			1	1	
Martinez, 2014	24	10	9	2	1	1			1
Puri, 2015	7	6	1						
TOTAL	**409**	**234**	**43**	**42**	**18**	**11**	**2**	**7**	**52**

*studies performed exclusively on lung cancer patients were excluded

Table 4: Diagnostic performance of adrenal biopsy

	Diagnosis of malignancy# (7 studies, 217 patients)			Diagnosis of ACC* (4 studies, 107 patients)			Diagnosis of metastasis (5 studies, 131 patients)		
	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
Sensitivity	87%	78%	93%	70%	42%	88%	87%	74%	94%
Specificity	100%	76%	100%	98%	86%	100%	96%	89%	98%
LR+	229.4	2.9	18145.3	100.43	8.10	1245.43	19.8	7.4	53.1
LR-	0.13	0.07	0.23	30.86	4.16	228.80	0.13	0.06	0.28
DOR	1775	22	142702	0.31	0.14	0.70	151	41	560

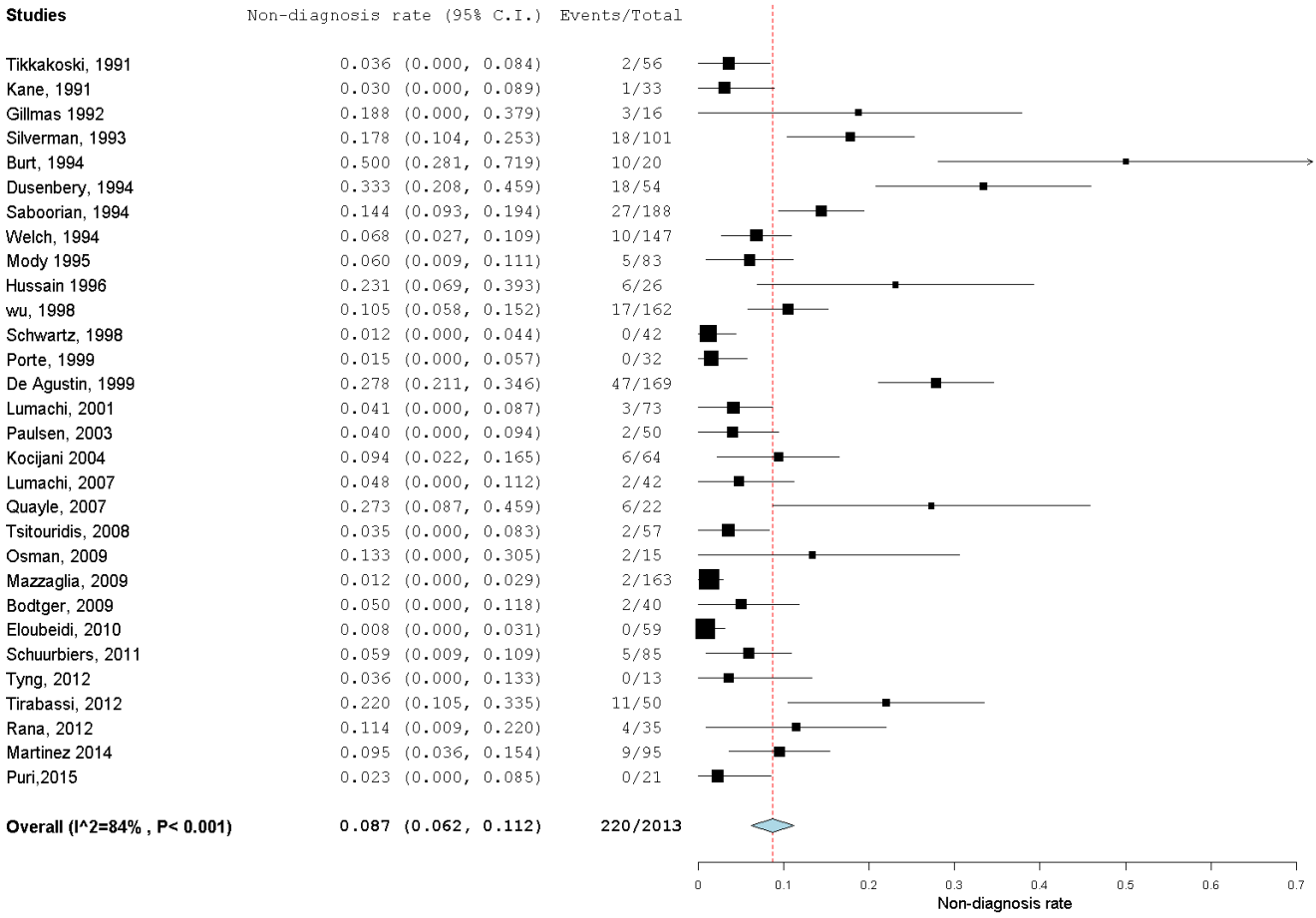
#includes metastases, adrenal cortical carcinoma and other adrenal malignancies (lymphoma, sarcoma, etc)

*ACC: Adrenocortical Carcinoma

DOR: Diagnostic odds ratio

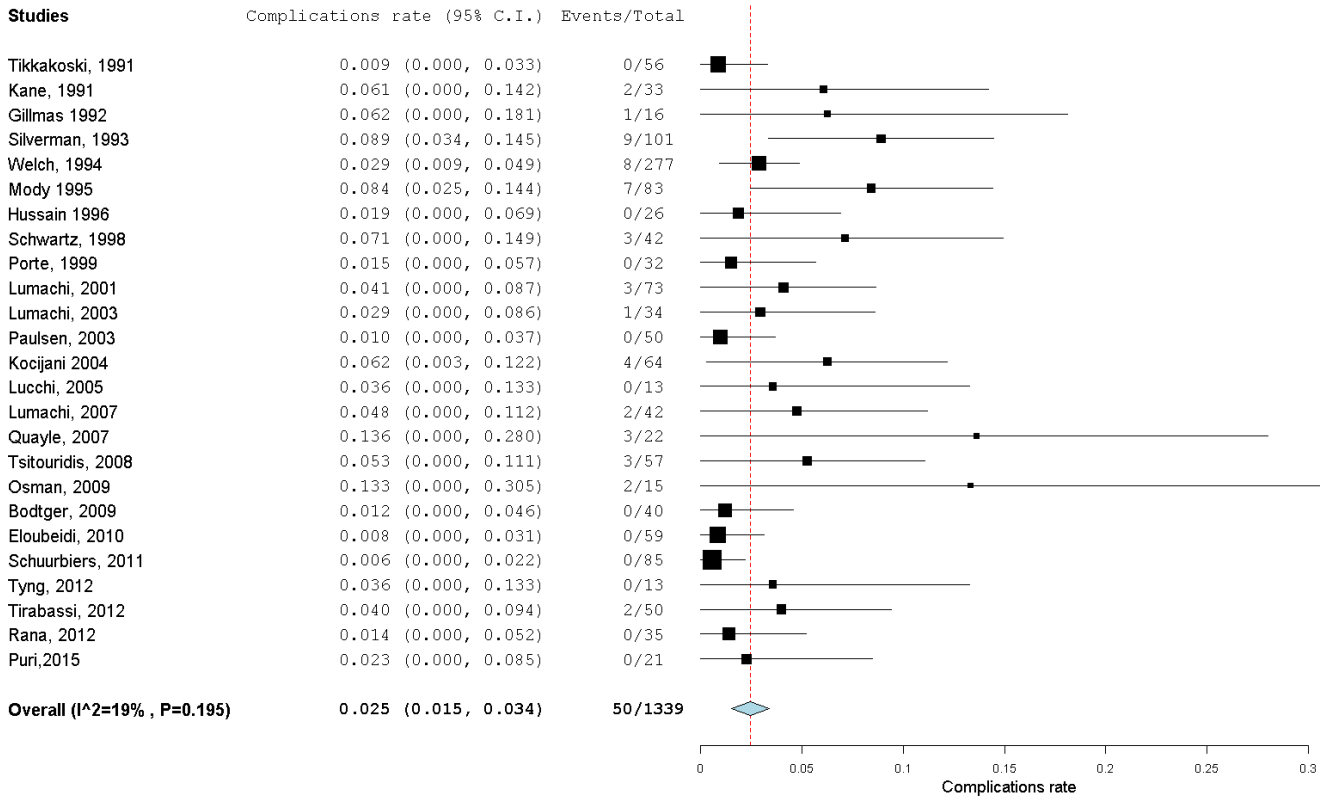
LR: likelihood ratio

Figure 1: Non-diagnostic adrenal biopsies*

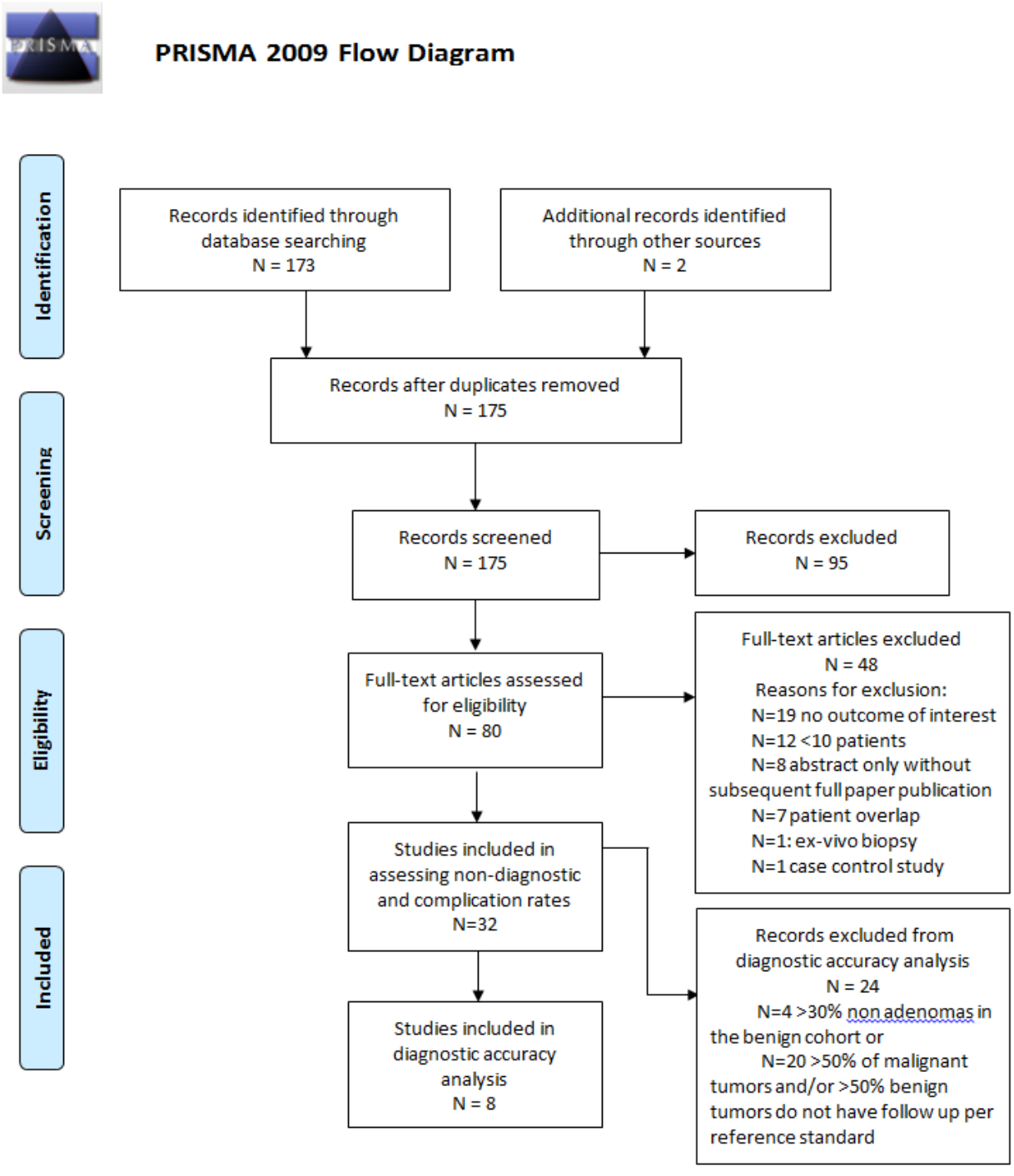


*defined as failure to obtain sufficient amount of cytology material to make a diagnosis

Figure 2: Adrenal biopsy related complications



Supplemental Figure 1: Prisma Flow diagram



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Supplemental Figure 2: QUADAS2 for 8 studies included in the diagnostic accuracy analysis