DIAGNOSIS OF ENDOCRINE DISEASE

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 to assess its performance in diagnosing adrenal malignancy.

Methods: Medline In-Process and 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 malignancies, 464 adenomas, 226 other benign, 36 pheochromocytomas, and 74 others). The pooled non-diagnostic rate (30 studies, 2013 adrenal biopsies) was 8.7% (95%CI: 6–11%). The pooled complication rate (25 studies, 1339 biopsies) was 2.5% (95%CI: 1.5–3.4%). Studies were at a moderate risk for bias. Most limitations related to patient selection, assessment of outcome, and adequacy of follow-up. Only eight studies (240 patients) could be included in the diagnostic performance analysis with a sensitivity and specificity of 87 and 100% for malignancy, 70 and 98% for adrenocortical carcinoma, and 87 and 96% for metastasis respectively.

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.

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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).

Although 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, 6, 7, 8, 9, 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, 14, 15), although it is unclear what factors influence this outcome. Adrenal biopsy complications vary in severity with both immediate and delayed-onset complications as described previously (16, 17, 18). In addition, if clinicians fail to biochemically exclude the presence of pheochromocytoma before 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 with a reference standard that varies considerably between studies, thus making any confident conclusions impossible.

Our objectives were as follows:

1. To systematically review the 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 the 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 24 February 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 principle investigator (IB) of the study. Controlled vocabulary supplemented with keywords was 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 [Supplementary Table 1](#), see section on [supplementary data](#) given at the end of this article. 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 language that reported data on more than ten 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 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:

1. Reference standard
 - (a) includes either (i) histology following adrenalectomy or autopsy, (ii) imaging follow-up after 3–12 months, or (iii) 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.
2. 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 (I B, D D, S T, M S, and F A) using DistillerSR software from Evidence Partners (23) to collect information from each eligible study. For each study, the following were collected: last name of the first author and year of publication, the country where the study was conducted, study objective, type of study, study population, time interval of patient enrollment, 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, and 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, and 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, and 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, were not assessed, as they were not relevant to our topic.

Patient selection was regarded at a high risk of bias if 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 a high risk of bias when it was reviewed knowing the results of the reference standard. Reference standard implementation was considered at a 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 were 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.

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

Reference	Country	Type of study*	Time interval	Population (details)	Patients (N)	Aged y/o (22–87)	Women (n/N)	Malignant	Benign	Other	Reference standard
(47)	Finland	RCS	1985–1990	Mainly patients with known malignancy (70%)	56	54.3 (22–87)	28/56	22 metastases 1 ACC 1 lymphoma	20 adenomas	3 hematomas 1 pheochromocytoma 1 lymph node 5 adrenal cysts	Adrenalectomy (n=13) Autopsy (n=2) Imaging follow-up at 2 months to 5 years (n=39) Not reported
(45)	USA	RCS	1984–1989	Patients with left adrenal mass	47	Not reported	Not reported	Not reported			
(44)	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) Adrenalectomy (n=8) Imaging follow-up mean 16 months (n=16) Clinical follow-up (n=8) Not reported (n=51)
(17)	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=6) Clinical follow-up 1–60 months (n=22) No follow-up (n=6) Adrenalectomy (n=7) Not reported (n=154) Clinical follow-up of at least 1 year
(15)	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) Adrenalectomy (n=7) Not reported (n=154) Clinical follow-up of at least 1 year
(46)	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 histioplasmosis granulomas	Adrenalectomy (n=7) Not reported (n=154) Clinical follow-up of at least 1 year
(27)	USA	RCS	1982–1991	Mainly patients with known malignancy	270	31–84	102/270	78 metastases [#]	59 “benign” [#]	0	
(14)	USA	PCS	Not reported	Patients with lung cancer	20	Not reported	Not reported	4 metastases	6 adenomas	0	Not reported
(16)	USA	RCS	1985–1993	Mainly patients with known malignancy (78%)	78	61 (28–88)	32/78	31 “malignant”	47 “benign”	0	Not reported
(29)	USA	RCS	1990–1994	All comers	23	63	17/23	Not reported	Not reported	2 pheochromocytomas	Not reported
(30)	USA	RCS	1990–1996	All comers	162	Not reported	Not reported	6 ACCs 73 metastases 1 lymphoma 9 “malignant”	50 adenomas	2 histioplasmosis granulomas 1 adrenal cyst 1 abscess	Not reported

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(7)	USA	RCS	1993–1996	Patients with lung cancer	42	67 (41–83)	17/42	18 metastases	24 adenomas	0	Not reported
(8)	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)
(31)	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 non-adenomas as a part of “22 primary adrenal tumor” group	Adrenalectomy (n=16) Clinical follow-up unclear length (n=153)
(32)	Italy	Unclear	Not reported	No history of malignancy: functioning and non-functioning adrenal masses	73	49 (17–80)	44/73	10 ACCs 4 metastases	49 adenomas	7 pheochromocytomas	Adrenalectomy (n=68) Imaging follow-up (n=2)
(33)	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)
(34)	USA	RCS	1998–2002	Patients with known or suspected malignancy	50	26–86	20/50	4 ACCs 32 metastases 1 sarcoma, 1 lymphoma, 1 extra-adrenal leiomyosarcoma	6 adenomas	3 pheochromocytomas	Adrenalectomy (n=1) Imaging follow-up 23 months (n=3) Not reported (n=56)
(35)	Slovenia	RCS	1991–2001	Patients with lung cancer	64	59 (42–82)	18/64	52 metastases	6 adenomas	0	Not reported
(36)	Italy	RCS	1993–2003	Patients with lung cancer	13	65.7 (50–78)	1/13	10 metastases	3 adenomas	0	Adrenalectomy
(37)	Italy	PCS	2001–2003	Patients with unilateral incidentaloma	42	54 (25–75)	24/42	8 ACCs 4 metastases	26 adenomas	2 ganglioneuromas 2 pheochromocytomas	Adrenalectomy
(13)	USA	RCS	1997–2006	All comers >3 cm	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)
(Continued)											

(Continued)

Table 1 (Continued)

Reference	Country	Type of study*	Time interval	Population (details)	Patients (N)	Aged y/o	Women (n/N)	Malignant	Benign	Other	Reference standard
(38)	Greece	RCS	2000–2005	All comers with indeterminate adrenal masses (56% with the history of malignancy)	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)
(19)	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
(39) (9)	USA Denmark	RCS RCS	1997–2007 2000–2006	All comers Patients with lung cancer and a left adrenal mass	154 40	66 (12.5) 63 (38–79)	59/154 20/40	unclear 10 metastases 1 myosarcoma	unclear 28 adenomas	0 1 teratoma	Not reported Clinical follow-up for 21–86 months
(10)	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
(40)	The 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
(41)	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)
(43)	Italy	RCS	1990–2010	All comers who subsequently underwent adrenalectomy	50	53.4	29/50	9 ACCs 15 metastases	19 adenomas	2 pheochromocytomas 5 myelolipomas	Adrenalectomy
(28)	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 angiomylipoma 1 myelolipoma 9 histioplasmosis granulomas 4 tuberculosis granulomas	Adrenalectomy (n=10) Clinical follow-up (n=25)

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(26)	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-up of unclear length (n = 24), Adrenalectomy (n = 6) Imaging follow-up of at least 6 months (n = 28) Others (n = 3) No follow-up (n = 36) Unclear: imaging characteristics, clinical follow-up for 3 years
(25)	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	

*RCS, retrospective cohort study; PCS, prospective cohort study. #Reported for lung cancer patients only.

Data synthesis and statistical analysis

We investigated the relationship between complication 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 the studies was assessed using the I^2 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 the studies. The analysis was done using STATA, version 14 (StataCorp). 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 the remaining 80 full-text papers were reviewed. Of these, 32 studies (7, 8, 9, 10, 13, 16, 17, 19, 21, 22, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42) 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 eight studies (8, 13, 32, 33, 36, 37, 38, 42) were included for the diagnostic accuracy analysis, reasons for exclusion being lack of an 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 ($n=4$), [Supplementary Fig. 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 (13–18 per study) were reported to undergo adrenal biopsy. Patient age ranged between 1.2 and 88 years (16, 31), although mainly included older patients (mean 59.8 years), women representing 39.4% (722/1832 patients of the 29 studies).

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

Reference	Biopsies (N)	Adrenal biopsy procedure	Needle gauge	Number of passes	Adrenal mass diameter (cm)	Non-diagnostic rate n1/N	Complication rate n2/N	Complications in detail
(47)	56	CT-guided (11) US-guided (45) (fine-needle biopsy)	NR	NR	NR	2/56	0/56	
(45)	33	CT-guided, anterior approach, left adrenal only (tandem-needle technique)	20–22	1–6	NR	1/33	2/33	Pancreatitis leading to 11–13 days of hospitalization (n=2)
(44) (17)	16 101	CT-guided (FNA) CT – guided (86) US-guided (15) (unclear technique)	18, 20 19–22	3 NR	2.6 (1.1–8) NR	3/16 18/101	1/16 9/101	Small pneumothorax (n=1) 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)
(15)	54	NR (FNA in 43, core in 11)	NR	NR	NR	18/54	NR	
(46)	188	NR (FNA)	18–22	NR	Benign: 2.4 (0.8) ACC: 10.6 (6) Metastases: 5 (2.5) 3.8 (1–12)	27/188	NR	
(27)	277	CT-guided (271) US-guided (6) (unclear technique)	16–23	NR		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)
(14)	20	CT-guided (needle aspiration)	NR	NR	2.2 (1.2–7.1)	10/20	NR	
(16)	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)
(29)	26	CT-guided (angle gantry technique)	18–22	3	1.25 (0.6–4)	6/26	0/26	
(30) (7)	162 42	NR (FNA) CT-guided (7core)	20–23 22	3 NR	NR Benign: 1.9 (1–4) Malignant 4.3 (1–7.6)	17/162 0/42	NR 3/42	Pneumothorax not requiring hospitalization (n=3)

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(8)	32	CT-guided (?core)	19, 22	NR	NR	0/32	0/32	unclear	"No serious complications observed"
(31)	169	CT-guided FNA	22	NR	NR	47/169	47/169		Self-resolved pneumothorax (n=2)
(32)	73	CT-guided (52), US – guided (18) FNA	21–23		4.23 (1.71)	3/73	3/73		Hematoma (n=1)
(33)	34	CT-guided (14) US-guided (20) FNA	21–23	NR	Benign: 4.3 (1.4) Malignant: 6.3 (2.2)	NR	NR	1/34	Self-resolved pneumothorax (n=1)
(34)	50	CT-guided (41) US-guided (9) FNA (3) and core (47)	16–22	3	4.9 (1.5–16)	2/50	2/50	0/50	
(35)	64	US-guided FNA	22	NR	5.6 (2.5–13)	6/64	6/64	4/64	Self-resolved pain (n=4)
(36)	13	CT- and US-guided FNA	NR	NR	4.6 (2–10)	NR	NR	0/13	
(37)	42	CT-guided (11) US-guided (31) FNA	23	NR, cit 4	6.9 (5.1)	2/42	2/42	2/42	Self-resolved pneumothorax (n=1)
(13)	22	NR (needle biopsy)	NR	NR	5.1 (3–10)	6/22	6/22	3/22	Severe pain requiring analgesic therapy (n=1)
(38)	57	CT – guided (technique varied)	16–22	NR	3.9 (1.3–7.8)	2/57	2/57	3/57	Hepatic hematoma (n=1)
(19)	15	CT-guided (12) US-guided (3) (biopsy gun technique)	18		7.7 (1–15)	2/15	2/15	2/15	Duodenal hematoma requiring hospitalization (n=1)
(39)	163	NR	NR	NR	3.9 (2.2)	2/163	2/163	unclear	Self-resolved hematoma (n=2)
(9)	40	Endoscopic US-guided FNA, left adrenal only	22	1–3	2 (0.6–6)	2/40	2/40	0/40	Self-resolved pneumothorax (n=1)
(10)	59	Endoscopic US-guided FNA	22	3 (1–4)	Benign: 2.3 Malignant: 3.1	0/59	0/59	0/59	Hypertensive episode (n=2)
(40)	85	Endoscopic US-guided FNA, left adrenal only	22	3 (1–6)	2.86 (1.91)	5/85	5/85	0/85	
(41)	13	CT-guided, paravertebral hydrodissection technique	17, 18	NR	4.1 (1.3–8.4)	0/13	0/13	0/13	"Few" complications including one described hematoma and pain
(42)	50	US-guided FNA	22		Benign: 5.4 ACC: 4.6 Metastases: 5	11/50	11/50	2/50	Pneumothorax (n=1)
(28)	35	CT and US-guided FNA	18–22		NR	4/35	4/35	0/35	Hypertensive crisis (n=1)
(26)	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	9/95	NR	
(25)	21	Endoscopic US-guided FNA	22	Median 4 (range 3–7)	2.4	0/21	0/21	0/21	

FNA, fine-needle aspiration; NR, not reported.

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that reported sex). The study population included mainly patients with established or suspected extra-adrenal malignancy (15 studies, 1110 patients); selected populations with indeterminate masses, specific size thresholds, and patients undergoing adrenalectomy (five studies, 198 patients); and all comers (12 studies, 866 patients). However, even in “all comers,” the prevalence of malignant adrenal masses ranged between 18 and 70% (13, 25, 26, 28, 30, 32, 41), suggesting a highly selected population (Table 1).

Information on a total of 2190 adrenal biopsies (13–277 per study) was reported in 32 studies (Table 2). Most of the biopsies were performed either in the USA ($n=1390$, 63%; 15 studies) or in Europe ($n=731$, 33%; 13 studies). The 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 and US guidance in 48 (2.2%) patients. In 592 (27%) procedures, the type of image guidance was not reported (Table 2). Needle gauge used for adrenal biopsy ranged from 16 to 25 gauge, although 22 gauge was most frequently employed. Number of needle passes ranged from 1 to 7 passes per procedure, with most studies reporting 3–4 passes on an 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, six (1.2%) from bladder, and five (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, seven (1%) were cysts, five (<1%) were ganglioneuromas, four (<1%) were hematomas, while 226 (31%) were reported as “benign”; however, 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

Table 3 Origin of adrenal metastases reported in included studies*.

Reference	Metastases (n)	Lung	Gastrointestinal	Kidney	Melanoma	Breast	Prostate	Bladder	Other+unknown primary
(47)	22	15	2	3	1				1
(15)	18	8	4	1	1			1	3
(46)	77	55	4	7	5	1		1	4
(30)	82	40	9	14	2	1		1	15
(31)	55	26	4	1	2	1	1	1	19
(32)	4	4							
(33)	2	2							
(34)	32	22	4	2	1				3
(13)	3			2	1				
(38)	29	18	3	2	1	4			1
(19)	1							1	
(10)	22	17	1		2			1	1
(41)	9	2	1	3					3
(42)	15	7		3	1	3			1
(28)	7	2	1	2			1	1	
(26)	24	10	9	2	1	1			1
(25)	7	6	1						
TOTAL	409	234	43	42	18	11	2	7	52

*Studies performed exclusively on lung cancer patients were excluded.

included pheochromocytomas ($n=36$), infection ($n=29$), histoplasmosis $n=15$ and tuberculosis $n=14$), and others ($n=10$) (Table 1).

The pooled non-diagnostic rate derived from 30 studies (2013 adrenal biopsy procedures) was 8.7% (CI: 6.2–11.2%; $I^2=84\%$, $P<0.001$) (Fig. 1). Correlation with needle gauge or number of passes used was not possible due to underreporting and variability of the techniques used. No relationship between non-diagnostic rates and the number of adrenal biopsies performed in a year (reflecting center experience) was observed ($R^2=0.0175$).

The pooled overall complication rate derived from 25 studies (1339 biopsies) was 2.5% (CI: 1.5–3.4%; $I^2=19\%$, $P=0.195$) (Fig. 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 ($n=1$), and hypertensive crisis ($n=1$), and minor complications (self-limiting/not in need of intervention or hospitalization) included pneumothorax ($n=12$), hematomas (perinephric ($n=2$), intra-hepatic ($n=2$), subcapsular ($n=1$), and others ($n=3$)), 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 ($n=1$), and 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 ($R^2=0.0055$).

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.

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 1–60 months (when reported) (Table 1). The diagnostic performance of adrenal biopsy was calculated using the data from the eight 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 (four studies, $n=107$), metastasis of an extra-adrenal primary tumor (five studies, $n=131$), and for overall malignancy (seven studies, $n=217$). The sensitivity of adrenal biopsy for diagnosing any malignancy was 87% (78–93%) and the specificity was 100% (76–100%). For diagnosing adrenocortical carcinoma, the sensitivity was 70% (42–88%) and specificity was 98% (86–100%). For diagnosing metastasis of an extra-adrenal primary malignancy, sensitivity was 87% (74–94%) and specificity

was 96%. Additional diagnostic accuracy measures (likelihood ratios and diagnostic odds ratios) are presented in Table 4.

Methodological quality

Methodological quality was assessed by the QUADAS-2 tool in the eight studies included in diagnostic accuracy meta-analysis (Supplementary Fig. 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.

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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	18 145.3	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	142 702	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.

Discussion

We present a systematic review of published experience with adrenal biopsy. Notably, although 32 studies report at least one outcome of adrenal biopsy, mainly due to suboptimal reference standard, we were only able to use data from eight 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% and specificity 96%). Lower performance of adrenal biopsy in diagnosing adrenocortical carcinoma (sensitivity 70% and 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 the 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 the 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.*, in which 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, although we could not perform this analysis based on the data provided. Of note, in four out of five 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 biochemical screening for exclusion of pheochromocytoma before the adrenal biopsy, resulting in several clinically significant hypertensive episodes. Endocrine evaluation before the adrenal biopsy (or at least biochemical screening with metanephrines) should be instituted as a 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 were 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 the performance of adrenal biopsy; however, the 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 performances and 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 (48) 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.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-0297>.

Declaration of interest

The authors have no conflicts of interest to declare. I B, W A, and M F are the members of the European Society of Endocrinology and European Network for the Study of Adrenal Tumors Clinical Guideline Panel.

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Author contribution statement

S T and D D contributed to data extraction, data analysis, and manuscript writing. M S and F A contributed to data extraction and data analysis. M H M contributed to data analysis, manuscript writing, and overall guidance with expertise in methodology. W A and M F contributed to conceptual design, subject matter expertise, and manuscript writing. I B provided overall project supervision, contributed to conceptual design and subject matter expertise, as well as contributed to data extraction, data analysis, and manuscript writing.

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