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Meta-Analysis

The Diagnostic Value of ^{18}F-FDG PET/CT Scan in Characterizing Adrenal Tumors

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Abstract

Context: Imaging plays an important role in the characterization of adrenal tumors, but findings might be inconclusive. The clinical question is whether ^{18}F fluodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is of diagnostic value in this setting.

Objective: This meta-analysis was aimed at the diagnostic value of ^{18}F-FDG PET/CT in differentiating benign from malignant adrenal tumors discovered either as adrenal incidentaloma or during staging or follow-up of oncologic patients.

Data sources: PubMed, EMBASE, Web of Science, and Cochrane Library were searched to select articles between 2000 and 2021.

Study selection: We included studies describing the diagnostic value of ^{18}F-FDG PET/CT in adult patients with an adrenal tumor. Exclusion criteria were 10 or fewer participants, insufficient data on histopathology, clinical follow-up, or PET results. After screening of title and abstract by 2 independent reviewers, 79 studies were retrieved, of which 17 studies met the selection criteria.

Data extraction: Data extraction using a protocol and quality assessment according to QUADAS-2 was performed independently by at least 2 authors.

Data synthesis: A bivariate random-effects model was applied using R (version 3.6.2.). Pooled sensitivity and specificity of ^{18}F-FDG PET/CT for identifying malignant adrenal tumors was 87.3% (95% CI, 82.5%-90.9%) and 84.7% (95% CI, 79.3%-88.9%), respectively. The pooled diagnostic odds ratio was 9.20 (95% CI, 5.27-16.08; $P < .01$). Major sources of heterogeneity (I^2, 57.1% [95% CI, 27.5%-74.6%]) were in population characteristics, reference standard, and interpretation criteria of imaging results.

Conclusions: ^{18}F-FDG PET/CT had good diagnostic accuracy for characterization of adrenal tumors. The literature, however, is limited, in particular regarding adrenal incidentalomas. Large prospective studies in well-defined patient populations with application of validated cutoff values are needed.

Key Words: adrenal tumor, ^{18}F-FDG, diagnostic accuracy, systematic review, meta-analysis

Abbreviations: ^{18}F-FDG, ^{18}F fluorodeoxyglucose; CT, computed tomography; PET, positron emission tomography; SUV, standard uptake value; VOI, volume of interest.

Characterization of an adrenal tumor detected during an imaging study can be challenging at times. The adrenal tumor might be a serendipitous finding on a scan performed for other reasons than evaluation of an adrenal disorder, representing an adrenal incidentaloma. Based on computed tomography (CT) studies, the prevalence of adrenal incidentalomas ranges from 1.9% to 7.3% (1, 2). Alternatively, an adrenal tumor is frequently demonstrated in patients with a current or past history of an extra-adrenal malignancy who have undergone several types of imaging procedures for staging or follow-up purposes. In these circumstances, the adrenal tumor is often also designated an adrenal incidentaloma. This is, however, a misnomer as the very goal of such imaging procedures in oncologic patients is to detect metastases, which may occur in the adrenal glands with a frequency varying from 3% to 58% depending on the primary tumor (3, 4).

An important question in case of an adrenal tumor detected by either of these clinical scenarios is whether the tumor is benign or malignant. The malignancy rate in adrenal incidentalomas has been reported to range from 1.2% to 11% (median 8.0%) for adrenocortical carcinoma and from 0% to 18% (median 5.0%) for metastasis (5), whereas in oncologic patients with an adrenal mass, the probability that it represents a metastatic adrenal tumor may vary from 52% to 70% (6, 7). Radiological features are often used to differentiate between benign and malignant adrenal tumors. Characteristics suggestive of a benign mass on a CT with delayed contrast protocol are a diameter less than 4 cm, homogeneous texture, an unenhanced attenuation value of less than or equal to 10 Hounsfield units (HU), and an absolute or relative postcontrast washout of 60% or 40%, respectively (8). In a recent study, however, it was shown that an adrenal washout CT

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had only moderate diagnostic value at these cutoff values (9). Thus, there is an urgent need for a better noninvasive diagnostic test that enables reliable discrimination between a benign and malignant adrenal tumor.

^{18}F fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT has proven to be very useful in the clinical examination of neoplastic tumors, based on the phenomenon that many types of cancer cells demonstrate a higher tracer uptake, usually expressed as the standard uptake value (SUV) of a particular mass (10).

Two meta-analyses studying the diagnostic efficacy of ^{18}F-FDG PET/CT have been published, reporting good diagnostic accuracy for detecting malignant adrenal tumors (11, 12). Since then, additional studies have appeared describing the diagnostic performance of ^{18}F-FDG PET/CT in the characterization of adrenal tumors. We aim to provide an updated systematic review and meta-analysis on the diagnostic value of ^{18}F-FDG PET/CT for the characterization of adrenal masses.

Materials and Methods

Data Sources and Searches

The search engines PubMed, EMBASE, Web of Science, and Cochrane Library were consulted for relevant articles August 31, 2021. Additionally, all reference lists of relevant articles were cross-checked to find additional literature. The search strategy included 3 search strings, which were set up in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (13). These consisted of (i) synonyms for "adrenal neoplasm" and "adrenal incidentaloma," (ii) for "[^{18}F] FDG PET scan" and (iii) NOT "thyroid" OR "animals." The full search strategy is shown in Supplementary Fig. S1 (14). This review was conducted in agreement with the PRISMA for Diagnostic Test Accuracy (Supplementary Tables S1 and S2) (15-19).

Study Selection

Studies were selected to include adults (age ≥18 years) with an adrenal mass on CT or magnetic resonance imaging who had also undergone an ^{18}F-FDG PET/CT scan. Masses were either detected through imaging, performed for other reasons than for screening of adrenal disease, thus representing a "true" adrenal incidentaloma, or masses were detected during follow-up, or staging of patients with an extra-adrenal malignancy. Adrenal masses detected in patients who were in remission for at least 5 years were also regarded as adrenal incidentalomas. To determine the diagnostic accuracy of the ^{18}F-FDG PET/CT scan, only studies fulfilling the following criteria for the reference standard were included: (i) studies in which more than 50% of the malignant tumors were histologically proven, and at least 50% of benign masses were classified through either histology or imaging-based follow-up of at least 6 months, (ii) studies in which more than 90% of the masses were histologically proven.

Furthermore, studies needed to describe outcomes such as ^{18}F-FGD-PET/CT imaging results (eg, SUV_{max} or SUV ratios), pathological findings, and clinical follow-up. We excluded conference papers, letters, case reports, and review papers. In addition, we excluded studies with 10 or fewer participants and those not written in English. We aimed to exclude adrenal masses associated with hormonal hypersecretion, as hyperactivity in itself might result in higher ^{18}F-FDG uptake (20). Last, studies using stand-alone PET scanners or published before 2000 were excluded to ensure application of PET/CT systems with CT anatomic coregistration (21).

Studies were categorized in accordance with a previous meta-analysis on the imaging of incidentally discovered adrenal masses (22). For each study the main reason for assessment with ^{18}F-FDG PET/CT was determined, that is, whether 50% or more or 90% or more of the adrenal masses were investigated as incidentally detected tumors, or as adrenal tumors discovered in patients with current or prior extra-adrenal malignancy. Separate analyses were performed for the resulting subgroups, with no overlap between groups.

The title and abstract of each study were independently screened according to the selection criteria by at least 2 reviewers (M.S., A.H.B., A.M.B., M.N.K.). After retrieval of full-text articles, the articles were assessed for eligibility by 2 independent reviewers. Discrepancies were resolved by a third reviewer, who was blinded from previous decisions.

Data Extraction and Quality Assessment

Data extraction was performed by one reviewer (M.S.) and carefully analyzed for accuracy by a second reviewer. For each study 2×2 contingency tables were constructed, incorporating the number of true positives, false positives, true negatives, and false negatives per adrenal mass. Methodological quality of the studies was evaluated by at least 2 independent researchers (M.S., A.H.B., A.M.B., M.N.K.) using the 15-item Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (23).

Data Synthesis and Analysis

Basic information about the studies, such as author, publication year, study design, and time of follow-up were collected. Similarly, patient characteristics were collected to check for variability between patient groups. Imaging parameters related to the ^{18}F-FDG PET/CT scans, such as type of scanner, injected dosage, tumor size, outcome of visual analysis, and quantification parameters, such as SUV_{max} and SUV ratios, were retrieved. The maximum SUV (SUV_{max}) is a single voxel with the highest tracer uptake within a volume of interest (VOI) (24). SUV ratios are also used, calculated as the adrenal SUV_{max} divided by background SUV_{max} or SUV_{mean} (eg, liver, spleen, blood pool) (25). Uptake of the radioactive tracer in the adrenal gland can also be visually compared to the uptake in a reference organ, usually the liver. Also, the performance characteristics of ^{18}F-FDG PET/CT to determine the risk of malignancy in terms of sensitivity, specificity, positive predictive value, and negative predictive value were collected.

A data set was prepared by pooling the diagnostic parameters of ^{18}F-FDG PET/CT of the included studies. When multiple interpretation criteria were reported (eg, SUV_{max}, SUV_{ratio} or visual assessment), a rank order was applied with the adrenal-to-liver ratio as the preferred measure. A ratio-based analysis is considered to be the most robust variable as it is less sensitive to noise and placement of VOI compared to SUV_{max} (26). Second to the adrenal-to-liver ratio, the SUV_{max} was used for analysis. Finally, if semiquantitative measures were not reported, the diagnostic parameters of visual assessment were used. Therefore, the pooled results consisted of the most optimal SUV parameter available, according to the previously mentioned rank order. One study consisted of 2 independent study populations, a training

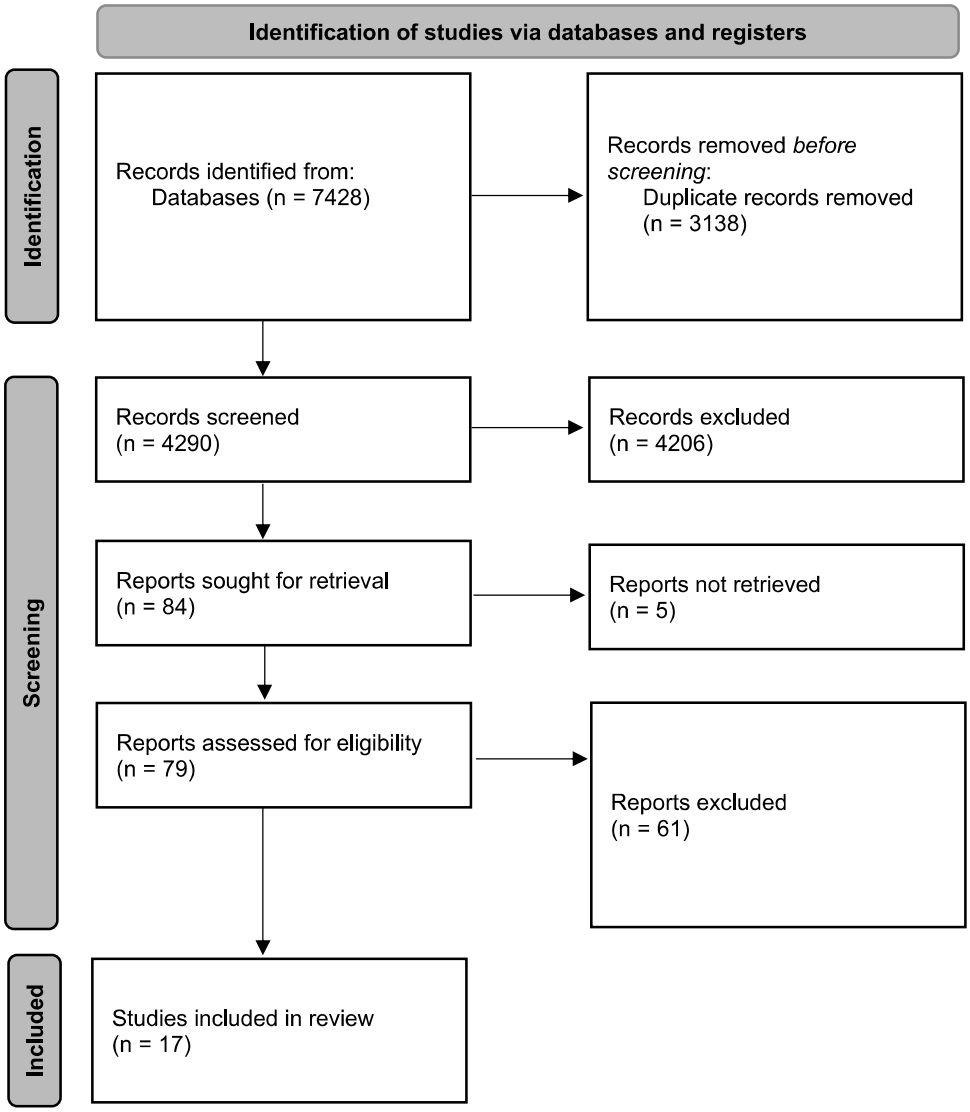

Figure 1. Flowchart of study selection and inclusion (13).

cohort and a validation cohort, and these 2 cohorts were analyzed separately (27).

Descriptive statistics were used for continuous data, and frequencies were reported for categorical data. Results were documented as either mean (±SD) or median (interquartile range) in normally, or nonnormally distributed data, respectively. Publication bias was visually established by Deeks funnel plot (28). Between-study variation was statistically assessed by the inconsistency index squared (I^2) and the DerSimonian-Laird method. To explore possible sources of heterogeneity, a hierarchical summary receiver operating curve was constructed. All analyses were performed using R (version 3.6.2), including the packages "Mada" and "Meta."

Results

Literature Search and Study Selection

The literature search yielded 7428 results across 4 search engines. After removing duplicates, 4290 articles remained (Fig. 1). Initial screening of title and abstract resulted in the exclusion of 4206 articles. The full-text screening included 84 articles, of which 67 were excluded. Finally, 17 studies were selected for the systematic review and meta-analysis (27, 29-44). No additional articles were found during the cross-reference search of the included articles.

Study Characteristics

The basic study characteristics are presented in Table 1. There were 9 retrospective and 8 prospective studies. All studies aimed to discriminate a benign from a malignant adrenal mass using ^{18}F-FDG PET/CT. A total of 1227 patients were included across all studies, representing 1262 adrenal masses. The sample size varied from 23 to 117 patients (mean, 68 ± 24). Mean age, mentioned in 10 out of 17 studies, ranged from 54.0 to 63.8 years (29, 30, 34, 35, 37-39, 41, 43, 44), SD was reported in only 3 studies (37-39). Nine articles (n = 570) reported the number of female and male patients (49% and 51%, respectively) (29-31, 34, 37, 38, 41, 43, 44). In total, the 17 studies comprised 707 benign (56.0%) and 555 malignant adrenal tumors (44.0%).

In 10 studies the reference diagnosis was defined by histopathology in 100% of the adrenal masses (27, 29, 32, 33, 35, 37-41). In 7 studies the reference diagnosis was based on

Table 1. Basic study characteristics

First author	Year	Study design	Country	Indication for ^{18}F-FDG PET/CT	No. patients	No. masses	Reference standard	Cutoff value SUV_{max}/ATL ratio	Mean age, y	M/W
Altinmakas (29)	2016	R	USA	≥90% EAM	59	61	H	3.47/0.83	61	36/23
Amodru[a] (30)	2019	R	France	≥90% AI	81	81	H, FU	ND/1.5	57.6	36/45
Ansquer (31)	2010	P	France	≥50% AI[b]	78	81	H, FU	3.3/ND	ND	37/41
Delivanis (32)	2018	R	USA	≥90% EAM	89	89	H	4.5/1.8	ND	ND
Groussin (33)	2008	P	France	≥50% AI	77	77	H	3.4/1.45	ND	ND
Guerin[a] (34)	2017	P	France	≥90% AI[b]	87	87	H, FU	4.1/1.5	55	34/53
Gust (35)	2012	R	France	ND	51	51	H	ND/1.7	54	ND
He (36)	2021	R	USA	≥90% AI[c]	117	117	H, FU	ND/2.5	ND	ND
Kim (37)	2014	R	S-Korea	≥50% AI	52	52	H	5.0/1.2	56.4	38/18
Kunikowska (38)	2014	R	Poland	≥90% EAM	85	102	H	5.2/1.53	63.8	47/38
Launay (39)	2015	R	France	ND	43	43	H	3.7/1.29	56.5	ND
Mohamed (40)	2018	P	Egypt	≥90% EAM	45	54	H	2.97/1.6	ND	ND
Nunes (41)	2010	P	France	≥50% AI	23	23	H	ND/1.6	54.1	6/17
Park (42)	2014	R	S-Korea	≥90% EAM	68	68	H, FU	ND	ND	ND
Salgues (43)	2020	P	France	≥50% AI[c]	64	64	H, FU	ND/1.5	58.3	33/31
Tessonnier[a] (44)	2008	P	France	≥90% AI[c]	37	41	H, FU	ND/1.8	58	22/15
Vos (T/V) (27)	2020	P	USA	≥90% EAM	96/75	96/75	H	4.6/ND	ND	ND

Abbreviations: ^{18}F-FDG, ^{18}F fluorodeoxyglucose; AI, adrenal incidentaloma; ATL, adrenal to liver; CT, computed tomography; EAM, extra-adrenal malignancy; FU, follow-up; H, histopathology; M, men; ND, not described; P, prospective study design; PET, positron emission tomography; R, retrospective study design; S-Korea, South Korea; SUV, standard uptake value; T/V, training cohort/validation cohort; USA, United States of America; W, women.
[a]Studies considered "true incidentaloma studies," including patients with only nonfunctioning adrenal incidentalomas and sufficiently excluding concurrent EAM, according to the authors.
[b]Studies including patients with a history of EAM in remission for at least 1 year.
[c]Studies including patients with a history of EAM in remission for at least 5 years.

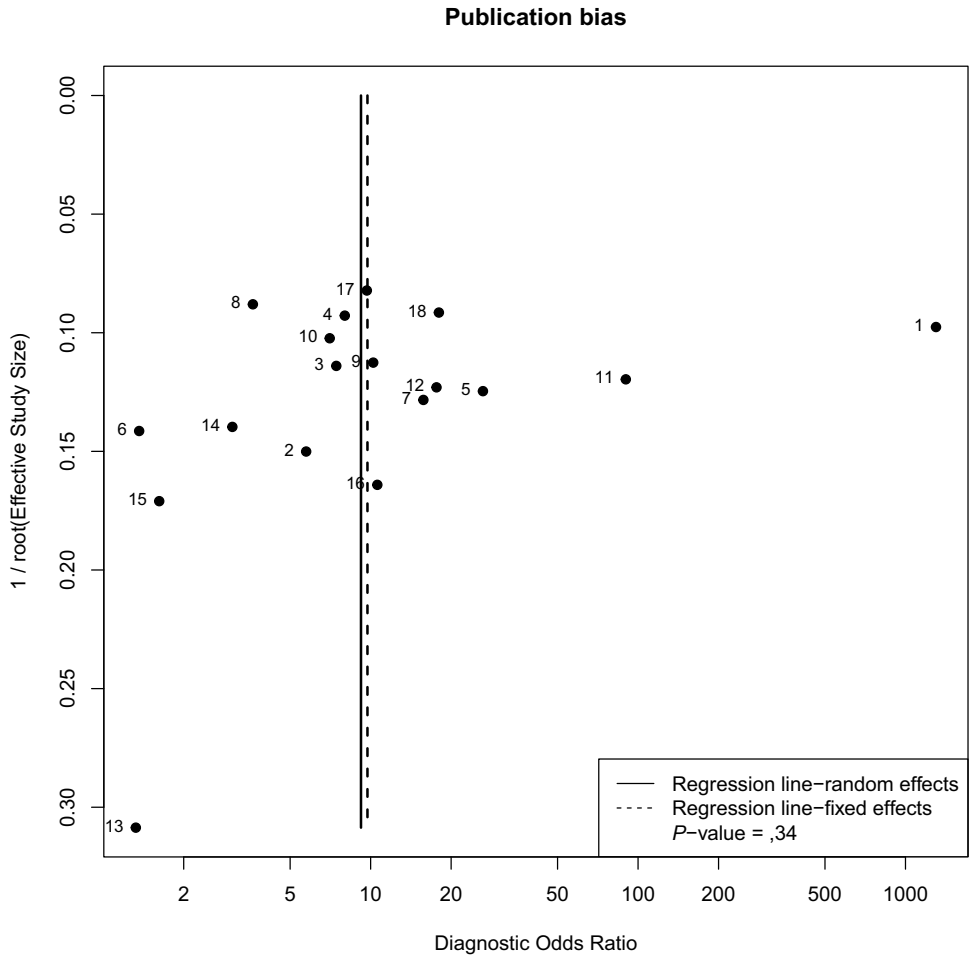

Figure 2. Funnel plot with regression lines and corresponding *P* value. Dots indicate individual study populations. Eighteen dots are displayed because 1 study included 2 independent study populations (17, 18).

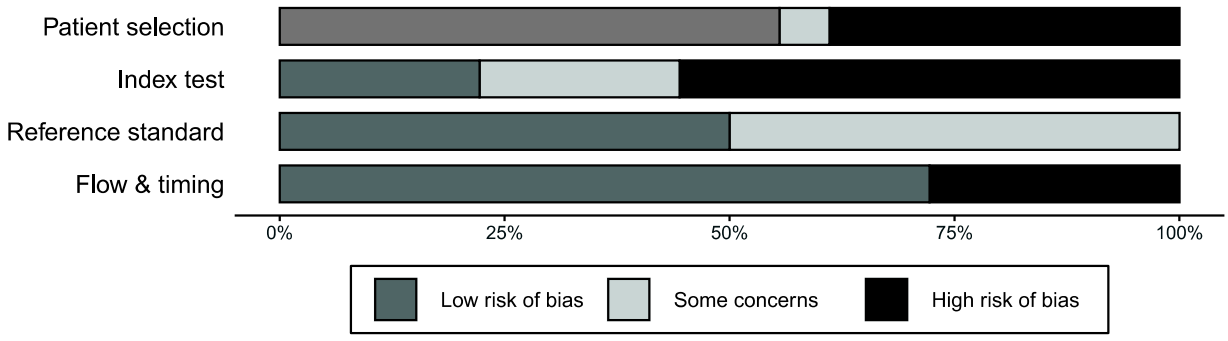

Figure 3. Visualization of results of QUADAS-2 tool performed on included studies.

either histopathology or clinical follow-up (30, 31, 34, 36, 42-44). Time of follow-up ranged from 6 to 61 months. Five studies reported using stability in size over time as criteria for benign masses (34, 36, 42-44); 2 studies additionally accepted an increase in diameter of no more than 15% compatible with a benign tumor (34, 43). Only 2 studies reported the size of each included adrenal mass (data not shown).

Hormonal assessment in adrenal incidentalomas was often performed in agreement with guideline recommendations (5). Only studies with tumors rendered inactive were considered adrenal incidentaloma studies. Oncologic patients with an adrenal tumor often did not undergo endocrine evaluation.

Only 3 studies included solely patients with an adrenal incidentaloma in whom hormone hypersecretion and a history of extra-adrenal malignancy had been specifically excluded (30, 34, 44).

In 6 studies 90% or more of the patients underwent follow-up from a previous extra-adrenal malignancy, demonstrating a pooled sensitivity and specificity of 86.5% (95% CI, 77.2%-92.4%) and 78% (95% CI, 60.2%-89.3%), respectively (27, 29, 32, 38, 40, 42). In 4 studies 90% or more of the patients were evaluated for an adrenal incidentaloma, showing a pooled sensitivity and specificity of 86.4% (95% CI, 77%-92.3%) and 89.1% (95% CI, 84.3%-92.6%),

respectively (30, 34, 36, 44). In 5 studies between 50% and 90% of patients were imaged because of the detection of an adrenal incidentaloma, showing a pooled sensitivity and specificity of 86.3% (95% CI, 74.9%-93.1%) and 82.8% (95% CI, 72.9%-89.7%), respectively (31, 33, 37, 41, 43). Two studies did not specify the reason for ^{18}F-FDG PET/CT scanning (35, 39).

Ten articles reported the number of patients with a history of extra-adrenal malignancy (n = 255) (30-34, 36, 38, 40-42), and in 4 studies the origin of the extra-adrenal malignancy was specified (n = 165) (Supplementary Table S3) (45). The majority of these patients had a history of either lung cancer (33.9%) or colon cancer (20.6%). In the 3 adrenal incidentaloma studies (209 adrenal masses), 8 metastatic tumors were diagnosed (30, 34, 44). Across all studies, 324 adrenal metastases were reported.

Deeks funnel plot asymmetry tests demonstrated a nonsignificant slope ($P = .34$), indicating that no statistically significant bias was present (Fig. 2).

Methodological Quality Assessment

The overall quality of the included studies was considered satisfactory (Fig. 3). The highest risk of bias was observed in the index test, as most studies did not use a prespecified threshold, but the threshold was determined according to the best diagnostic performance of ^{18}F-FDG PET/CT. In addition, most articles did not indicate whether the radiologist or nuclear medicine physician who was assessing the images was blinded to the clinical outcome of the patient.

Positron Emission Tomography/Computed Tomography Protocol

All studies used hybrid PET/CT systems, 3 studies reported using a standard dose of ^{18}F-FDG (range, 300-555 MBq) (27, 32, 38), and 11 studies used a weight-adjusted dose (range, 2.5-51.8 MBq.kg^{-1}) (30, 31, 33, 35, 37, 39-44). The method of ^{18}F-FDG dosing was not specified in 3 studies (Table 2). A variety of PET/CT systems were used across the studies (data not shown).

Diagnostic Parameters of ^{18}F-FDG Positron Emission Tomography/Computed Tomography

Study-specific 2 × 2 tables were constructed according to the described sensitivity and specificity per mass (Table 3). Assessment of the ^{18}F-FDG PET/CT scans was performed by semiquantitative methods in 11 studies. In 5 studies both qualitative and semiquantitative methods were used for interpretation (31, 34, 36, 39, 44), whereas 1 study was based solely on visual assessment to characterize the adrenal masses (42). Semiquantitative outcomes for benign and malignant adrenal masses are separately displayed in Table 4.

The adrenal-to-liver SUV_{ratio} was used as a cutoff value in 14 studies, varying from 0.83 to 2.5 (29, 30, 32-41, 43, 44). Only one study used a predetermined cutoff value of the adrenal-to-liver ratio of 1.7 or greater, based on previous literature (39). Sensitivity and specificity for the adrenal-to-liver SUV_{ratio} ranged from 78.9% to 100% and 22% to 100%, respectively. A predetermined SUV_{max} cutoff value (≥1.45) to distinguish malignant from benign adrenal masses was used in one study (35). Ten studies determined the cutoff value of SUV_{max}, ranging from 2.97 to 5.20 (27, 29, 31-34, 37-40).

Table 2. ^{18}F-FDG PET/CT protocol characteristics of included studies

First author	Time fasting, h	Time to scan, min	Glucose before ^{18}F-FDG	Fixed dose, MBq, or weighted based, MBq/kg
Altinmakas (29)	6	120	<150 mg/dL	ND
Amodru (30)	6	60	Normoglycemic	Weight based (4)
Ansquer (31)	6	60-80	Normoglycemic	Weight based (4-7)
Delivanis (32)	ND	60	ND	Fixed dose (555)
Groussin (22)	12	60	<150 mg/dL	Weight based (2.5/5.5)
Guerin (34)	6	60	ND	ND
Gust (35)	6	60	ND	Weight based (4)
He, (25)	ND	ND	ND	ND
Kim (37)	6	60	ND	Weight based (51.8)
Kunikowska (38)	6	60	<150 mg/dL	Fixed dose (300-370)
Launay (39)	12	60	<150 mg/dL	Weight based (5)
Mohamed (40)	6	60	<150 mg/dL	Weight based (2.5-5.2)
Nunes (41)	6	60	<110 mg/dL	Weight based (5)
Park (42)	4	60	<140 mg/dL	Weight based (8.1)
Salgues (43)	6	60	ND	Weight based (3)
Tessonnier (44)	6	60	ND	Weight based (4)
Vos[a] (27)	ND	60	ND	Fixed dose (370)

Abbreviations: ^{18}F-FDG, ^{18}F fluorodeoxyglucose; CT, computed tomography; ND, not described; PET, positron emission tomography.
[a]Training cohort; validation cohort did not describe ^{18}F-FDG PET/CT protocol procedures.

The sensitivity and specificity for SUV_{max} ranged from 60.5% to 100% and 33% to 95.2%, respectively. Sensitivity and specificity of visually assessed ^{18}F-FDG uptake ranged from 88.2% to 100% and 43% to 95.2%, respectively (31, 34, 36, 39, 42, 44) (Table 5).

Adrenal-to-liver ratio was used in all adrenal incidentaloma studies with sensitivities and specificities ranging from 86.7% to 100%, and 86.1% to 100%, respectively (30, 34, 44). Pooling of the 3 adrenal incidentaloma studies resulted in a sensitivity of 92.4% (95% CI, 73.8%-98.1%) and specificity of 90.5% (95% CI, 81.5%-95.4%). One out of 3 adrenal incidentaloma studies used SUV_{max}, reporting a sensitivity of 86.7% and a specificity of 75% (34). Visual assessment was also reported in 2 studies with a sensitivity and specificity ranging from 93.3% to 100% and 68.1% to 86%, respectively (34, 44).

The pooled sensitivity and specificity for all studies of ^{18}F-FDG PET/CT was 87.3% (95% CI, 82.5%-90.9%) and 84.7% (95% CI; 79.3%-88.9%), respectively (Fig. 4). The pooled diagnostic odds ratio using a random-effects model was 9.20 (95% CI, 5.27-16.08; $P < .01$). The positive likelihood ratio ranged from 1.26 to 58.28; the negative likelihood ratio from 0.025 to 0.344. The area under the curve was 0.92. A weighted forest plot for indicating the diagnostic odds ratios of the included studies is displayed in Fig. 5.

Table 3. Reported ^{18}F-FDG PET/CT performance to detect malignant adrenal masses

First author	Type of assessment used for MA	Cutoff value	True positive	False positive	False negative	True negative	Sensitivity	Specificity
Altinmakas (29)	ATL ratio	0.83	51	7	1	2	98	22
Amodru (30)	ATL ratio	1.5	13	5	0	63	100	92.3
Ansquer (31)	SUV_{max}	3.3	25	12	2	42	93	78
Delivanis (32)	ATL ratio	1.8	41	7	6	35	87	84
Groussin (22)	ATL ratio	1.45	22	5	0	38	100	88
Guerin (34)	ATL ratio	1.5	13	10	2	62	86.7	86.1
Gust[a] (35)	ATL ratio	1.7[a]	21	1	1	28	95	97
He (25)	ATL ratio	2.5	40	7	7	63	85	90
Kim (37)	ATL ratio	1.2	30	3	8	11	78.9	78.6
Kunikowska (38)	ATL ratio	1.53	30	6	2	64	93.8	91.4
Launay[a] (39)	ATL ratio	1.29[a]	30	2	1	10	96.7	83.3
Mohamed (40)	ATL ratio	1.6	23	0	1	30	97.1	100
Nunes (41)	ATL ratio	1.6	3	2	0	18	100	90
Park (42)	VA	NA	15	14	2	37	88.2	72.5
Salgues (43)	ATL ratio	1.5	9	4	1	50	90	92.6
Tessonnier (44)	ATL ratio	1.8	12	0	0	29	100	100
Vos-T (27)	SUV_{max}	4.6	56	4	18	18	76	82
Vos-V (27)	SUV_{max}	4.6	48	3	16	8	75	55

A total of 18 study populations are displayed because 1 study consisted of 2 independent study populations (T and V) (27).
Abbreviations: ^{18}F-FDG, ^{18}F fluorodeoxyglucose; ATL, adrenal to liver; CT, computed tomography; MA, meta-analysis; NA, not applicable; PET, positron emission tomography; SUV, standard uptake value; T, training cohort; V, validation cohort; VA, visual assessment.
[a]Studies using predefined cutoff values, not based on population described in study.

Heterogeneity and Subgroup Analysis

The analysis of heterogeneity using the DerSimonian-Laird method yielded an I^2 of 57.1% with a CI of 27.5% to 74.6%. Meta-regression analyses were executed to explore sources of heterogeneity. Variables of interest were year of publication ($P = .67$), study design ($P = .38$), and sample size ($P = .15$). Twenty-four percent of the difference in true effect size can be attributed to sample size; however, this finding was not statistically significant.

Discussion

In the present meta-analysis, we assessed the diagnostic performance of ^{18}F-FDG PET/CT for the evaluation of adrenal tumors presenting either as an adrenal incidentaloma or as an adrenal mass detected in oncologic patients. Our main finding was that ^{18}F-FDG PET/CT demonstrated fairly good diagnostic accuracy to discriminate between benign and malignant adrenal tumors. The included studies, however, showed substantial heterogeneity and there were insufficient data to determine its diagnostic utility in case of an adrenal incidentaloma.

The diagnostic accuracy of ^{18}F-FDG PET/CT in the differentiation of adrenal tumors has been evaluated before in 2 meta-analyses, reporting a sensitivity and specificity for malignancy ranging from 95% to 97% and 88% to 91%, respectively (11, 12). These estimates are higher than the sensitivity and specificity of 87.3% and 84.7%, respectively, found in the present study. In contrast to these previous 2 meta-analyses, we determined for each study the main presenting clinical scenario of assessment, that is, whether the mass was detected as an adrenal incidentaloma or as part of the follow-up or staging in a patient with a past history of an extra-adrenal malignancy. In addition, we defined a minimal set of criteria for the reference standard to be met with regard to duration of follow-up and the proportion of histopathological diagnoses to minimize the risk of misclassification of the adrenal tumor. Moreover, we were able to incorporate the results of additional studies published after the inclusion period of the most recent meta-analysis.

In clinical practice, ^{18}F-FDG PET/CT is commonly used to characterize an adrenal mass in patients with a previous or concurrent extra-adrenal malignancy (3). In the literature adrenal masses detected in patients with an extra-adrenal malignancy are sometimes inappropriately referred to as adrenal incidentalomas (5). Such misclassification may obviously confound the performance results of any diagnostic test that aims to determine the biological behavior of an adrenal incidentaloma. Moreover, several studies comprised a mixture of patients with an adrenal mass discovered incidentally or as part of an oncologic diagnostic workup, thereby further complicating extrapolation of those study findings to the respective patient groups encountered in clinical practice. Importantly, the pretest probability for malignancy is significantly higher in oncologic patients compared to individuals with an adrenal incidentaloma, which directly affects the calculated positive predictive value of the ^{18}F-FDG PET/CT. Therefore, in an effort to circumvent this problem, we categorized the patients with an adrenal mass described in these papers according to the clinical route of discovery. For a reliable assessment of the diagnostic value of ^{18}F-FDG PET/CT, it is imperative that future studies maintain a strict separation of these 2 populations.

Table 4. Semiquantitative results of ^{18}F-FDG PET/CT imaging in patients with adrenal incidentaloma

First author	SUV_{max} benign	SUV_{max} malignant	SUV_{ratio} benign	SUV_{ratio} malignant
Altinmakas (29)	6.1 (ND) (2-14.7)	11.4[ND] (3.2-52.4)	1.7 ± ND (0.6-3.6)	3.3 (0.6-18.4)
Amodru (30)	ND	ND	ND	ND
Ansquer (31)	ND (1.2-11.7)	11 (ND) (1.6-26)	ND	ND
Delivanis (32)	3.7 (ND) (1.4-24.5)	10 (ND) (2.3-29.4)	1.2 (ND) (0.5-6.61)	3 (ND) (0.7-13.4)
Groussin (33)	3.3 ± 1.5 (1.7-7.8)	11.1 ± 5.4 (3.5-26.2)	1.0 ± 0.3 (0.6-2.4)	4.6 ± 2.9 (1.6-15.4)
Guerin (34)	ND	ND	1.3 ± 1.7 (0.4-13.6)	3.2 ± 4.1 (0.8-17.7)
Gust (35)	ND	7.3 ± ND (4-21.8)	0.9± (0-1.6)	3.7 ± ND (1.7-10.2)
He (36)	3.7 (ND) (1.6-28.6)	13.3 (ND) (2.3-70.8)	1.4 (ND) (0.6-18.1)	6.2 (ND) (0.9-30)
Kim (37)	3.1 ± 1.4	8.9 ± 8.2	1.4 ± 0.6	4.6 ± 5.0
Kunikowska (38)	3.7 ± 3.0	13.0 ± 7.1	1.0 ± 0.9	4.2 ± 2.6
Launay (39)	3.2 ± 1.6 (1.7-4.8)	ND (4.9-14.1)	1.3 ± 0.8 (0.6-2.1)	ND (1.7-5.3)
Mohamed (40)	2.9 ± 0.5 (1.2-5.3)	6.8 ± 2.8 (3.8-10.4)	1.0 ± 0.4 (0.1-2.1)	3.7 ± 1.9 (1.2-6.7)
Nunes (41)	3.7 ± 1.6 (1.3-6.3)	8.5 ± 3.9 (5.8-13)	1.1 ± 0.7 (0.3-2.7)	2.6 ± 0.5 (2.1-3.0)
Park (42)	ND	ND	ND	ND
Salgues (43)	4.8 ± 8.2 (0.4-58.5)	12 ± 5.4 (6.2-21.5)	1.1 ± 1.8 (0.1-13.3)	2.9 ± 1.2 (1.2-4.4)
Tessonnier (44)	2.6 (ND) (1.3-4.23)	11.1 (ND) (1.1-24)	0.9 (ND) (0.5-1.7)	5 (ND) (2.0-71)
Vos-T (27)	3 (2.4-3.8)	8.3 (4.7-13.7)	ND	ND
Vos-V (27)	4.1 (3.3-13.3)	ND	ND	ND

A total of 18 study populations are displayed because 1 study consisted of 2 independent study populations (T and V) (27). Mean ± SD or median. Interquartile ranges are indicated for different SUV indices for individual study populations.
Abbreviations: ^{18}F-FDG, ^{18}F fluorodeoxyglucose; ATL, adrenal to liver; CT, computed tomography; ND, not described; PET, positron emission tomography; SUV, standard uptake value; T, training cohort; V, validation cohort.

Table 5. Reported diagnostic values in relation to applied interpretation criteria ^{18}F-FDG PET/CT

First author	ATL ratio cutoff value	Sensitivity	Specificity	SUV_{max} cutoff value	Sensitivity	Specificity	VA sensitivity	VA specificity
Altinmakas (29)	0.83[a]	98	22	3.47	96	33	ND	ND
Amodru (30)	1.5[a]	100	92.3	ND	ND	ND	ND	ND
Ansquer (31)	ND	ND	ND	3.3[a]	93	78	89	76
Delivanis (32)	1.8[a]	87	84	4.5	87	69	ND	ND
Groussin (22)	1.45[a]	100	88	3.4	100	70	ND	ND
Guerin (34)	1.5[a]	86.7	86.1	4.1	86.7	75	93.3	68.06
Gust (35)	1.7[a]	95	97	ND	ND	ND	ND	ND
He (25)	2.5[a]	85	90	ND	ND	ND	98	43
Kim (37)	1.2[a]	78.9	78.6	5.0	60.5	92.9	ND	ND
Kunikowska (38)	1.53[a]	93.8	91.4	5.2	90.6	90	ND	ND
Launay (39)	1.29[a]	96.7	83.3	3.7	96.7	83.3	ND	ND
Mohamed (40)	1.6[a]	97.1	100	2.97	100	95.2	100	95.2
Nunes (41)	1.6[a]	100	90	ND	ND	ND	ND	ND
Park (42)	ND	ND	ND	ND	ND	ND	88.2[a]	72.5
Salgues (43)	1.5[a]	90	92.6	ND	ND	ND	ND	ND
Tessonier (44)	1.8[a]	100	100	ND	ND	ND	100	86
Vos-T (27)	ND	ND	ND	4.6[a]	76	82	ND	ND
Vos-V (27)	ND	ND	ND	4.6[a]	75	55	ND	ND

A total of 18 study populations are displayed because 1 study consisted of 2 independent study populations (T and V) (27).
Abbreviations: ^{18}F-FDG, ^{18}F fluorodeoxyglucose; ATL, adrenal to liver; CT, computed tomography; ND, not described; PET, positron emission tomography; SUV, standard uptake value; T, training cohort; V, validation cohort; VA, visual assessment.
[a]Method of ^{18}F-FDG PET/CT interpretation used during pooling of the results.

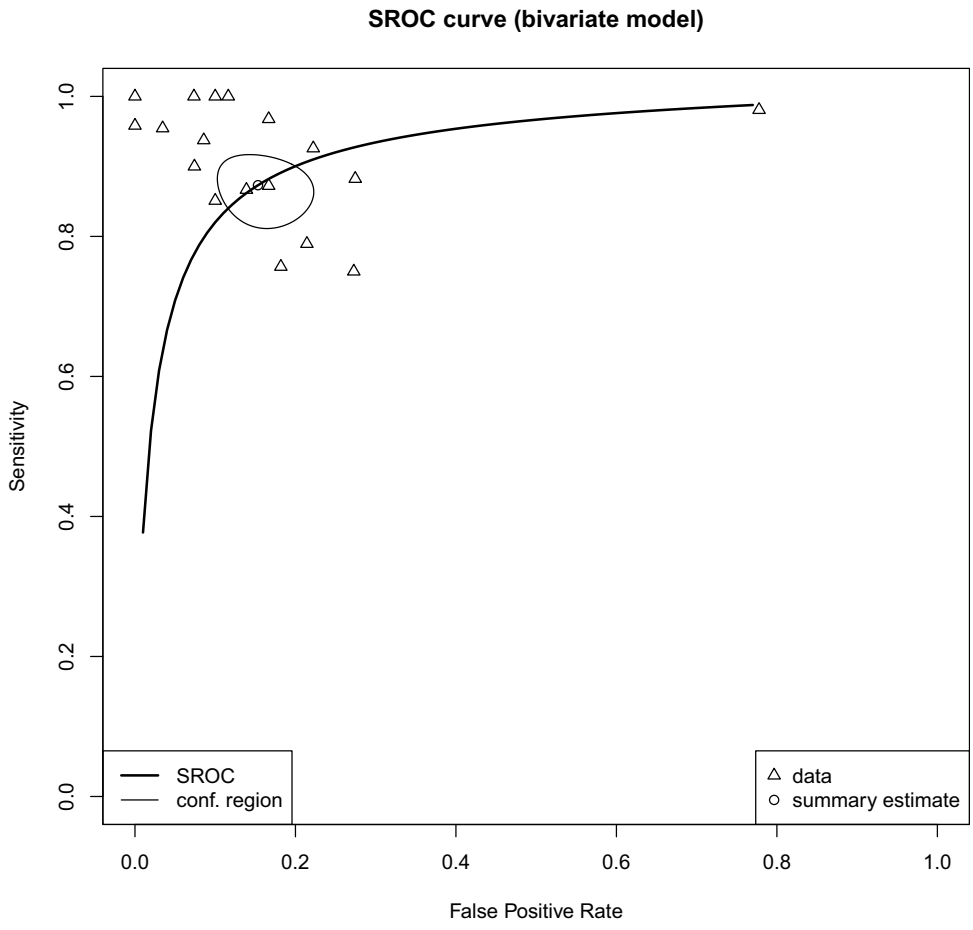

Figure 4. Summary receiver operating curve (SROC) of sensitivity and false positive rate. Eighteen data points are displayed because 1 study consisted of 2 independent study populations; both are displayed.

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight (common)	Weight (random)	Diagnostic Odds Ratio MH, Fixed + Random, 95% CI
1	51	52	2	53	0.1%	3.6%	1300.50 [114.31 - 14796.35]
2	13	13	63	76	2.1%	2.8%	5.74 [0.32 - 102.58]
3	25	27	42	67	5.5%	6.2%	7.44 [1.62 - 34.12]
4	41	47	35	76	10.5%	8.5%	8.00 [3.04 - 21.08]
5	22	22	38	60	1.4%	2.9%	26.30 [1.52 - 454.78]
6	13	15	62	75	8.5%	5.9%	1.36 [0.27 - 6.78]
7	21	22	28	49	2.4%	4.4%	15.75 [1.96 - 126.62]
8	40	47	63	103	18.1%	8.9%	3.63 [1.48 - 8.88]
9	30	38	11	41	6.9%	8.2%	10.23 [3.61 - 28.99]
10	30	32	64	94	6.3%	6.3%	7.03 [1.58 - 31.37]
11	30	31	10	40	0.9%	4.3%	90.00 [10.84 - 747.56]
12	23	24	30	53	2.4%	4.4%	17.63 [2.22 - 140.37]
13	3	3	18	21	2.2%	2.4%	1.32 [0.06 - 31.71]
14	15	17	37	52	6.6%	5.9%	3.04 [0.62 - 14.95]
15	9	10	50	59	4.5%	4.2%	1.62 [0.18 - 14.40]
16	12	12	29	41	1.7%	2.8%	10.59 [0.58 - 193.11]
17	56	74	18	74	13.5%	9.5%	9.68 [4.57 - 20.51]
18	48	64	8	56	6.6%	8.7%	18.00 [7.04 - 46.00]
Total (common effect, 95% CI)	**550**		**1090**		**100.0%**	**--**	**9.73 [7.07 - 13.39]**
Total (random effect, 95% CI)					**--**	**100.0%**	**9.20 [5.27 - 16.08]**

Heterogeneity: $Tau^2 = 0.7037$; $Chi^2 = 39.63$, df = 17 ($P < 0.01$); $I^2 = 57\%$

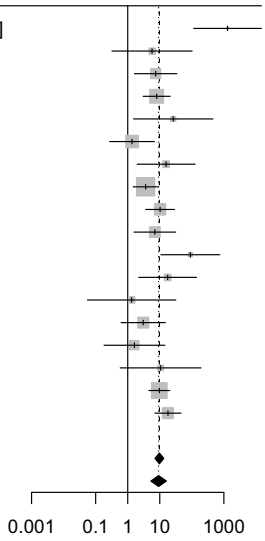

Figure 5. Weighted forest plot for diagnostic odds ratio (DOR) of individual studies. One study included 2 independent study populations; both were included separately (17, 18). MH, Mantel-Haenszel.

We also assessed the interpretation criteria of the ^{18}F-FDG PET/CT scans across the various studies, which varied from visual analysis only to the application of several semiquantitative SUV measurements. In nearly all studies the cutoff value to discriminate between benign and malignant adrenal tumors was not predefined, but rather established

afterward. This approach limits the external validity of the reported cutoff values, as the universally accepted method is to validate previously determined cutoff values through application to different study populations. Although the results of SUV_{max} are consistent across various software programs, it measures only a single voxel and is therefore most sensitive to noise. Alternatively, a metabolic parameter such as SUV_{peak}, which represents a single milliliter per cubic centimeter (mL/cm^3) in the VOI containing the highest activity, reduces noise bias and is therefore likely to decrease the risk of artifacts (36). None of the studies, however, provided information on SUV_{peak}. Another limitation of the included studies is the lack of standardization and harmonization of the various PET/CT systems that were used. It is important that in future studies calibration errors and variability in PET/CT performance be accounted for through participation of research centers in an accreditation program, for example as issued by the European Association of Nuclear Medicine Research Ltd (46). Tumor size has been shown to be positively correlated with the risk of malignancy, but detailed information on the diameter of the adrenal masses was absent in nearly all studies, thereby precluding further analysis between size and ^{18}F-FDG avidity of the adrenal tumor (5).

The heterogeneity in FDG PET/CT protocols and interpretation prevents adequate pooling of the results, therefore challenging the possibility of providing clear recommendations on the clinical utility of ^{18}F-FDG PET/CT in the assessment of an adrenal tumor. There are several other limitations of our meta-analysis. Definition of the reference diagnosis varied substantially between studies and was either based on histopathology or on clinical follow-up with various criteria to classify an adrenal tumor as either benign or malignant. In addition, some studies included patients with bilateral adrenal tumors, in which only the mass with CT characteristics most suspicious for malignancy was evaluated. This approach introduces the possibility for selection bias with overrepresentation of malignant tumors. The fact that more than half of the studies were retrospective in design represents yet another important limitation. Finally, it should be noted that in several studies oncologic patients were not screened for the presence of hormonal hypersecretion. This might have resulted in a false-positive outcome of the ^{18}F-FDG PET, as it has been suggested that hyperfunctioning adrenal tumors demonstrate higher ^{18}F-FDG uptake (20). The aforementioned limitations therefore preclude a definite and reliable positioning of the diagnostic value of ^{18}F-FDG PET/CT in the evaluation of an adrenal tumor, which is also reflected in the wide range of positive likelihood ratios. It is important that future studies on the diagnostic performance of ^{18}F-FDG PET/CT be conducted in a well-defined population of patients with an adrenal mass that is either a true incidentaloma or a finding on imaging studies performed in an oncologic setting. These studies should be prospective in design with application of standardized and harmonized protocols for PET scintigraphy and predefined interpretation criteria.

In conclusion, the present meta-analysis suggests that ^{18}F-FDG PET/CT might be useful to discriminate between benign and malignant adrenal tumors, depending on the clinical route of discovery. However, the true diagnostic value of this technique cannot be established because of substantial heterogeneity among the available studies. Future well-designed studies are needed to better define the diagnostic utility of ^{18}F-FDG PET/CT in the evaluation of adrenal masses.

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Disclosures

The authors have nothing to disclose.

Data Availability

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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