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SYSTEMATIC REVIEW

Diagnostic accuracy of ^{18}F -FDG PET or PET/CT for the characterization of adrenal masses: a systematic review and meta-analysis

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Objective: We aimed to explore the role of the diagnostic accuracy of ^{18}F fluodeoxyglucose PET (^{18}F -FDG PET) or PET/CT for characterization of adrenal lesions through a systematic review and meta-analysis.

Methods: The MEDLINE, EMBASE, and Cochrane Library database, from the earliest available date of indexing through 30 April 2017, were searched for studies evaluating the diagnostic performance of ^{18}F -FDG PET or PET/CT for characterization of adrenal lesions. We determined the sensitivities and specificities across studies, calculated positive and negative likelihood ratios (LR+ and LR-), and constructed summary receiver operating characteristic curves.

Results: Across 29 studies (2421 patients), the pooled sensitivity for ^{18}F -FDG PET or PET/CT was 0.91 [95% CI (0.88–0.94)] with heterogeneity ($\chi^2 = 141.8$, $p = 0.00$) and a pooled specificity of 0.91 [95% CI (0.87–0.93)] with heterogeneity ($\chi^2 = 113.7$, $p = 0.00$). Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 9.9 [95% CI (7.1–13.7)] and negative likelihood ratio (LR-) of 0.09 [95% CI (0.07–0.13)]. The pooled diagnostic odds ratio was 105

[95% CI (63–176)]. In metaregression analysis, study design, publication year, study location (western vs others), interpretation criteria of PET or PET/CT images, quantification of PET or PET/CT [SUV_{max} (maximum standardized uptake value) vs SUV (standardized uptake value) ratio], patient group, and analysis method (patient-based vs lesion-based) were the sources of the study heterogeneity. However, in multivariate metaregression, no definite variable was the source of the study heterogeneity.

Conclusion: ^{18}F -FDG PET or PET/CT demonstrated good sensitivity and specificity for the characterization of adrenal masses. At present, the literature regarding the use of ^{18}F -FDG PET or PET/CT for the characterization of adrenal masses remains still limited; thus, further large multicenter studies would be necessary to substantiate the diagnostic accuracy of ^{18}F -FDG PET or PET/CT characterization of adrenal masses.

Advances in knowledge: ^{18}F -FDG PET or PET/CT showed good sensitivity and specificity for the characterization of adrenal masses and could provide additional information for that purpose.

INTRODUCTION

Adrenal incidentaloma is defined as an adrenal mass detected incidentally with a size of 1 cm or larger and could be detected in approximately 4–6% of the patients who received imaging studies such as CT or MRI.¹ Although most incidental lesions are adenomas, the adrenal gland is common site for metastasis in patients with cancer with the rate of metastasis being between 25 and 75% depending on the type and size of the primary tumour.² Hence, accurate differentiation of adrenal lesions of cancer patients could be

essential for prognostication and treatment choices, especially when such lesions are the only abnormality detected.³

Non-invasive anatomical imaging techniques have been used to differentiate metastases from benign adrenal adenoma. CT has ability to measure attenuation, on both unenhanced images and on delayed contrast-enhanced images, to differentiate benign from malignant lesions.⁴ However, the diagnosis based on attenuation measurement is often not feasible in unenhanced or delayed

contrast-enhanced CT.⁵ Better diagnostic accuracy could be expected when chemical shift MRI is used, but the signal intensity of benign and malignant lesions overlaps considerably.^{6,7}

¹⁸F-fluodeoxyglucose (FDG) PET/CT is a functional imaging modality that could help characterize these adrenal lesions. Several previous reports have shown the usefulness of ¹⁸F-FDG-PET/CT to differentiate benign from malignant adrenal lesions.^{8,9} However, some studies reported that benign adrenal adenomas could demonstrate variable activity of attenuation and these findings could yield false positive diagnoses for malignancy.^{10–12}

Several studies have evaluated the diagnostic accuracy of ¹⁸F-FDG PET or PET/CT for the characterization of adrenal incidentaloma and/or masses, reporting wide range of sensitivity and specificity. The purpose of our study is to meta-analyse published data on the diagnostic accuracy of ¹⁸F-FDG PET or PET/CT for the characterization of adrenal incidentaloma and/or masses, in order to provide more evidence-based data and to address further studies in the evaluation of adrenal masses.

METHODS AND MATERIALS

Data sources and search strategy

We conducted electronic English language literature searches of MEDLINE via PubMed, Embase and Cochrane Library database from the earliest available date of indexing through 30 April 2017. We also handsearched the reference lists of identified publications for additional studies. We used a search algorithm based on a combination of terms: (1) “PET” OR “positron emission tomography” OR “positron emission tomography/computed tomography” OR “PET/CT” “positron emission tomography-computed tomography” OR “PET-CT”; and (2) “Adrenal mass” OR “Adrenal incidentaloma” OR “Adrenal lesions”.

Study selection

The inclusion criteria for relevant studies were as follows: whole-body ¹⁸F-FDG PET or PET/CT had been used to identify and characterize the adrenal lesions (incidentaloma or masses); sufficient data to reassess sensitivity and specificity of ¹⁸F-FDG PET or PET/CT in characterizing the adrenal masses or absolute numbers of true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) data had been presented; and no data overlap.

Studies were excluded if fewer than 10 patients had been included. In addition, duplicate publications were excluded, as were publications such as review articles, case reports, conference papers, and letters, which do not contain the original data. Two researchers independently reviewed titles and abstracts of the retrieved articles, applying the above-mentioned selection criteria. Articles were rejected if clearly ineligible. The same researchers independently evaluated the full-text of the included articles to determine their eligibility for inclusion of the current review.

Data extraction and quality assessment

Information about basic study (authors, year of publication, and country of origin), study design (prospective or retrospective), patients' characteristics and technical aspects were collected.

Each study was analysed to retrieve the number of TP, TN, FP, and FN findings of ¹⁸F-FDG PET or PET/CT for the characterization of adrenal masses, according to the reference standard. Only studies providing such complete information were finally included in the meta-analysis.

The overall quality of the included studies in this review was critically appraised by two authors independently, based on 15-item modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS2).¹³ Discrepancies between the researchers were resolved by discussion.

Data synthesis and analysis

All data from each eligible study were extracted. The primary objective was to estimate the sensitivity and specificity, and the positive and negative likelihood ratios (LR+ and LR-, respectively) with 95% confidence intervals (CIs), and diagnostic odds ratios (DORs) with 95% CIs. A DOR can be calculated as the ratio of the odds of positivity in a disease state relative to the odds of positivity in the non-disease state, with higher values indicating better discriminatory test performance.¹⁴ Between-study statistical heterogeneity was assessed using I^2 and the Cochrane Q test on the basis of the random-effects analysis.¹⁵ Publication bias was examined using the effective sample size funnel plot and associated regression test of asymmetry described by Deeks and colleagues.¹⁶ We used the bivariate random-effects model for analysis and pooling of the diagnostic performance measures across studies, as well as comparisons between different index tests.^{17,18} The bivariate model estimates pairs of logit transformed sensitivity and specificity from studies, incorporating the correlation that might exist between sensitivity and specificity. Each data point of the summary receiver operator characteristic (SROC) graph comes from an individual study; then, the SROC curve is formed based on these points to form a smooth curve to reveal pooled accuracy.¹⁹ When statistical heterogeneity was substantial, we performed metaregression to identify potential sources of bias.²⁰ Pooled estimates were also calculated for subgroups of studies that were defined according to specific study designs. Two-sided $p \leq 0.05$ was considered statistically significant. Statistical analyses were performed with commercial software programs (STATA, v. 13.1; StataCorp LP).

RESULTS

Literature search and selection of studies

After the comprehensive computerized search was performed and references lists were extensively cross-checked, our research yielded 465 records, of which 40 records (non-human studies 15, conference abstract 25) were excluded after reviewing the title and abstract. Also, non-relevant 370 abstracts were excluded. Remaining 55 full-text articles were assessed for eligibility and 26 articles were excluded due to insufficient data (24 studies) for the calculation of sensitivity and specificity of ¹⁸F-FDG PET or PET/CT for the characterization of adrenal masses and two non-English articles. Finally, 29 studies were selected and were eligible for the systematic review and meta-analysis and no additional studies were found screening the references of these articles.^{21–49} The characteristics of the included studies are presented

in Table 1. The detailed procedure of study selection in the meta-analysis is shown in Figure 1.

Study description, quality, publication bias

We conducted all analyses based on per-patient data and/or per-lesion data analysis. Among those 29 studies included in the current review, 9 studies conducted patient based analysis of ^{18}F -FDG PET/CT.^{23,35,37,41,45–49} Others conducted lesion-based analysis. There were a total of 2421 patients and 2795 adrenal lesions in the included studies, and the age ranged from 1.5 to 88 years. A total of 1017 patients were male, and 720 patients were female. The seven studies did not report the number of male and female patients in their population.^{29,35,40,45–47,49} Of all 30 studies, 28 studies^{21–26,28–42,44–49} enrolled patients retrospectively; 2 studies^{27,43} enrolled patients prospectively. Four studies^{23,25,35,47} used PET and other studies used PET/CT as imaging device in their studies. Four studies^{27,35,39,48} investigated the diagnostic role of ^{18}F -FDG PET or PET/CT in the incidentally detected adrenal masses to differentiate benign and malignant adrenal lesions. Other 25 studies^{21–26,28–34,36–38,40–47,49} examined the role of PET or PET/CT to detect adrenal metastasis in cancer patients. The visual analysis group included nine studies.^{24,25,27,30–32,37,38,40} The quantitative analysis group included the 20 studies that used the SUV_{max} , SUV ratio, and total lesion glycolysis (TLG) as quantitative indices. In extended subgroup analysis, 13 studies^{22,26,28,29,33–36,39,43–46} used the SUV ratio as quantitative index (12 studies; adrenal to liver SUV ratio; 1 study; adrenal to spleen SUV ratio) and 1 study used the TLG as quantitative index. Six studies^{21,23,42,47–49} used the SUV_{max} as quantitative index. The principal characteristics of the 29 studies included in the meta-analysis are included in Table 1. To assess a possible publication bias, Deeks's funnel plot asymmetry tests were designed. The non-significant slope indicates that no significant bias was found. The p -value was 0.86 (Figure 2).

Methodological quality assessment

Figure 3 shows the risk of bias and applicability concerns summary and overall, the quality of the included studies was deemed satisfactory.

Characterization of adrenal masses

In most included studies of the current review, the characterization of adrenal masses was confirmed by one of the following methods. (1) Histopathological confirmation (2) in cancer patients, adrenal lesions considered as metastases when the lesions showed sequential aggravation on the following CT scans. (3) Adrenal lesions were regarded as benign when the sequential CT or FDG PET/CT scans did not exhibit any change during the follow-up period of 6 months. (4) An adrenal mass with a mean non-contrast attenuation value of <10 Hounsfield unit (HU) was also classified as a benign adenoma.

Diagnostic accuracy of ^{18}F -FDG PET or PET/CT

The diagnostic performance results of ^{18}F -FDG PET or PET/CT in the 29 included studies in the meta-analysis are presented in Table 2 and Figure 4. The pooled sensitivity for ^{18}F -FDG PET or PET/CT was 0.91 [95% CI (0.88–0.94)] with heterogeneity ($\chi^2 = 141.8$, $p = 0.00$) and a pooled specificity of 0.91 [95% CI

(0.87–0.93)] with heterogeneity ($\chi^2 = 113.7$, $p = 0.00$). Likelihood ratio (LR) syntheses gave an overall LR+ of 9.9 [95% CI (7.1–13.7)] and LR– of 0.09 [95% CI (0.07–0.13)]. The pooled DOR was 105 [95% CI (63–176)]. Forest plots of the sensitivity and specificity of ^{18}F -FDG PET for the characterization of adrenal lesions are shown in Figure 4. Figure 5 shows hierarchical summary receiver operating characteristic (ROC) curve and indicates that the areas under the curve was 0.96 [95% CI (0.94–0.98)] indicating good diagnostic accuracy.

Heterogeneity evaluation and metaregression analysis

Between-study heterogeneity was present for sensitivity and specificity among studies of ^{18}F -FDG PET or PET/CT for the characterization of adrenal lesions. A metaregression analysis was performed to explore other sources of heterogeneity in the studies of ^{18}F -FDG PET or PET/CT. In metaregression analysis, study design, publication year, study location (western vs others), interpretation criteria of PET or PET/CT images, quantification of PET or PET/CT (SUV_{max} vs SUV ratio), patient group, and analysis method (patient-based vs lesion-based) were the sources of the study heterogeneity. However, in multivariate metaregression, no definite variable was the source of the study heterogeneity.

Subgroup analysis according to interpretation criteria of ^{18}F -FDG PET or PET/CT

We conducted the subgroup analysis according to the used interpretation criteria of ^{18}F -FDG PET or PET/CT for characterization of adrenal masses (visual and quantitative analysis) and also extended the subgroup analysis of quantitative analysis into SUV_{max} group and SUV ratio group. In quantitative subgroup analysis, we excluded one study⁴¹ which used TLG as quantitative index in their study to minimize the heterogeneity of the results. The results are presented in Table 3. The pooled sensitivity and specificity of visual analysis were 0.91 [95% CI (0.83–0.95)] and 0.92 [95% CI (0.86–0.95)], respectively. The pooled DOR was 114 [95% CI (48–273)]. The pooled sensitivity and specificity of quantitative analysis were 0.92 [95% CI (0.87–0.95)] and 0.90 [95% CI (0.85–0.94)], respectively. The pooled DOR was 101 [95% CI (53–192)]. The pooled sensitivity and specificity of SUV ratio analysis were 0.89 [95% CI (0.83–0.93)] and 0.91 [95% CI (0.85–0.95)], respectively. The pooled DOR was 83 [95% CI (35–195)]. The pooled sensitivity and specificity of SUV_{max} analysis were 0.95 [95% CI (0.86–0.98)] and 0.91 [95% CI (0.81–0.96)], respectively. The pooled DOR was 185 [95% CI (76–451)]. Figure 6 showed the comparison of HSROC of visual, SUV ratio, and SUV_{max} for the characterization of adrenal masses. The areas under s of visual analysis, SUV ratio, and SUV_{max} were 0.97 [95% CI (0.95–0.98)], 0.96 [95% CI (0.93–0.97)], and 0.98 [95% CI (0.96–0.99)], respectively.

DISCUSSION

The adrenal incidentaloma usually is benign adenomas even in patients with known malignancy.⁵⁰ Although the most incidental adrenal mass is a benign lesion, it is crucial to characterize the lesion and exclude malignancy to ensure appropriate management, especially in cancer patients. The capability of

Table 1. Characteristics of the included studies

Authors	Year	Country	Device	Analysis	Patient no	Lesion no	Age	M/F	FDG dose (MBq)	Interpretation criteria	Diagnosis of AM	Cut-off	Study design
Metser U	2006	Israel	PET/CT	LB	150	175	63.2	89/61	370–666	SUV _{max}	H, HU, IM-FU	3.1	R
Blake MA	2006	USA	PET/CT	LB	38	41	66	21/17	555	ATL SUV ratio	HU, IM-FU	>1	R
Han SJ	2007	Korea	PET	PB	105		55	70/35	370	SUV _{max}	H, IM-FU	NA	R
Park BK	2007	Korea	PET/CT	LB	14	20	59	12/2	8.1 kg ⁻¹	Visual	H, IM-FU	≥Liver	R
Sung YM	2008	Korea	PET/CT	LB	42	61	62	38/4	370	Visual	H, C-FU	≥Liver	R
Vikram R	2008	USA	PET/CT	LB	96	112	NA		444–740	ATL SUV ratio	H, IM-FU	>1	R
Tessonnier L	2008	France	PET/CT	LB	37	41	NA	22/15	4 MBq kg ⁻¹	Visual	H	≥Liver	P
Boland GWL	2008	USA	PET/CT	LB	150	165	60	78/72	555	ATL SUV ratio	H, IM-FU	>1	R
Okada M	2009	Japan	PET/CT	LB	30	35	NA	NA	3 MBq kg ⁻¹	ATL SUV ratio	IM-FU, HU	>1.8	R
Lu Y	2010	China	PET/CT	LB	87	110	61	49/38	370	Visual	H, C-FU	≥Liver	R
Ansquer C	2010	France	PET/CT	LB	78	81	55	37/41	4 MBq kg ⁻¹	Visual	H, C-FU, IM-FU	≥Liver	P
Gratz S	2010	Germany	PET/CT	LB	109	218	NA	NA	0.2 mCi kg ⁻¹	Visual	HU	≥Liver	R
Perri M	2011	Italy	PET/CT	LB	93	117	67.2	61/32	370–444	ATS SUV ratio	H, IM-FU	1.77	R
Cho AR	2011	Korea	PET/CT	LB	51	61	60	40/11	370	ATL SUV ratio	H, IM-FU	1.3	R
Gust L	2012	France	PET	PB	51		54	NA	4 MBq kg ⁻¹	ATL SUV ratio	H	1.7	R
Kara PO	2011	Turkey	PET/CT	LB	81	104	61.5	55/26	370	ATL SUV ratio	H, IM-FU, HU	1.68	R
Uemura S	2012	Japan	PET/CT	PB	150		70.5	48/102	190–300	Visual	H	≥Liver	R
Evans PD	2013	USA	PET/CT	LB	105	132	66	49/56	5.2 MBq kg ⁻¹	Visual	H, IM-FU, HU	≥Liver	R
Kunikowska J	2014	Poland	PET/CT	LB	85	102	63.8	47/38	300–370	ATL SUV ratio	H	1.53	R
Park SY	2014	Korea	PET/CT	LB	68	68	63.2	NA	8.1 MBq kg ⁻¹	Visual	H, C-FU	>Liver	
Kim Y	2014	Korea	PET/CT	PB	52		56.4	34/18	5.1 MBq kg ⁻¹	TLG	H	12	R
Launay N	2015	France	PET/CT	LB	67	67	56.5	33/34	5 MBq kg ⁻¹	SUV _{max}	H	3.7	R
Nakajo M	2015	Japan	PET/CT	LB	40	41	66	18/22	3.7 MBq kg ⁻¹	ATL SUV ratio	H, HU, IM-FU, C-FU	1.08	P
Watanabe H	2013	Japan	PET/CT	LB	41	45	66.4	31/10	184–244	ATL SUV ratio	H, HU, IM-FU	1.37	R
Xu B	2012	China	PET/CT	PB	260		61.7	181/79	5.5 MBq kg ⁻¹	ATL SUV ratio	H, IM-FU, C-FU	>1.25	R
Kim JY	2013	Korea	PET/CT	PB	147		NA	NA	370–444	ATL SUV ratio	IM-FU, C-FU	2.5	R
Pitts A	2013	USA	PET	PB	129		NA	NA	370	SUV _{max}	H, IM-FU	3	R
Cistaro A	2015	Italy	PET/CT	PB	68		44.1	36/32	4.6 MBq kg ⁻¹	SUV _{max}	H	NA	R

(Continued)

Table 1. (Continued)

Authors	Year	Country	Device	Analysis	Patient no	Lesion no	Age	M/F	FDG dose (MBq)	Interpretation criteria	Diagnosis of AM	Cut-off	Study design
Kim BS	2014	Korea	PET/CT	PB	48		56.1	NA	5.2 MBq kg ⁻¹	SUV _{max}	IM-FU	2.39	R

AM, adrenal mass; ATL, adrenal to liver; ATS, adrenal to spleen; C-FU, clinical information follow-up; H, histopathology; HU, measurement of Hounsfield unit from non-enhanced CT; IM-FU, imaging follow up; LB, lesion-based; NA, not available; P, prospective; PB, patient-based; R, retrospective; SUV, standardized uptake value; SUV_{max}, maximum standardized uptake value; TLG, total lesion glycolysis.

Figure 1. Flow chart of the search for eligible studies on the diagnostic performance of ^{18}F -FDG PET or PET/CT for characterization of adrenal lesions. FDG, fludeoxyglucose.

CT to detect and differentiate adrenal adenomas has shown usefulness because of its ability to measure attenuation, on both unenhanced images and on delayed contrast-enhanced images.⁴ A recent meta-analysis concluded that an attenuation threshold of 10 HU on unenhanced CT had a sensitivity of 71% and a specificity of 98% for the diagnosis of adrenal adenoma.⁵¹

¹⁸F-FDG PET or PET/CT has become increasingly used for differentiating adrenal lesions in cancer patients. Previous studies reported that ¹⁸F-FDG PET could be used for the differentiation of benign and malignant adrenal lesions in cancer patients, with

Figure 2. Results of Deeks's funnel plot of asymmetry test for publication bias. Non-significant slope indicates that no significant bias was found. ESS, effective sample size.

Figure 3. Risk of bias and applicability concerns summary.

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Ansquer 2010	?	+	+	+	+	+	+
Blake 2006	+	+	?	?	?	?	+
Boland 2009	?	+	+	+	+	+	+
Cho 2011	?	+	+	+	?	?	+
Cistaro 2015	+	+	?	?	+	+	?
Evans 2013	?	+	+	+	?	+	+
Gratz 2010	+	?	+	?	?	?	+
Gust 2012	+	+	+	?	?	+	+
Han 2007	+	?	+	?	+	+	+
Kim 2013	?	+	+	+	?	+	+
Kim 2014	?	+	+	+	?	+	+
Kim 2015	+	+	+	+	+	+	?
Kunikowska 2014	?	+	+	+	?	+	+
Launay 2015	+	+	+	+	+	+	+
Lu 2010	+	+	+	+	?	+	+
Metser 2006	?	+	+	+	?	+	+
Nakajo 2015	+	+	+	+	+	+	+
Okada 2009	+	+	+	+	?	+	+
Ozcan 2011	?	+	+	+	?	+	+
Park 2007	?	+	+	+	?	+	+
Park 2014	?	+	+	+	+	+	+
Perri 2011	?	+	+	+	+	+	+
Pitts 2013	+	+	+	?	+	?	+
Sung 2008	?	+	+	+	?	+	+
Tessonnier 2008	+	+	+	+	+	+	+
Uemura 2013	+	+	+	+	+	+	+
Vikram 2008	+	+	+	+	?	+	+
Watanabe 2013	?	+	+	+	?	+	?
Xu 2012	+	+	+	?	?	+	+

High
 Unclear
 Low

a sensitivity of 92–100% and a specificity of 80–100%.^{10–12} Most studies used the visual criteria for diagnosis of malignant adrenal lesions, and PET findings were positive if the adrenal FDG uptake was greater than or equal to that of the liver or if the lesion uptake was greater than those of the blood pool, background, and spleen activities. However, these visual assessments would be subjective

and could lead to some FP or FN findings for characterization of adrenal lesions.

A recent meta-analysis and systematic review found that the overall sensitivity and specificity of ¹⁸F-FDG PET/CT in differentiating malignant and benign adrenal disease in patients with known primary malignancy were 97 and 91%, respectively. In our meta-analysis, the results reported show that ¹⁸F-FDG PET or PET/CT has excellent diagnostic accuracy for the characterization of adrenal lesions, with an area under the ROC curve of 0.95 [95% CI (0.93–0.97)]. ¹⁸F-FDG PET or PET/CT demonstrated a sensitivity of 0.90 [95% CI (0.87–0.92)] and a specificity of 0.88 [95% CI (0.85–91)]. This result was also consistent with the results of other well-designed studies. Blake et al investigated the diagnostic accuracy of ¹⁸F-FDG PET/CT for characterization of adrenal lesions.²² The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy on lesion-based analysis were 100, 93.8, 81.8, 100, and 95.1%, respectively. Boland et al performed a retrospective review of 150 consecutive patients who underwent ¹⁸F-FDG PET/CT scans for the post-treatment surveillance of cancer patients and used three different method for interpretation of ¹⁸F-FDG PET/CT images.²⁸ The absolute adrenal SUV value of 2.31 demonstrated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for characterization of adrenal lesions to be 100, 94, 76, 100, and 95%, respectively. The adrenal to liver SUV ratio >1 showed the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for characterization of adrenal lesions to be 100, 97, 87, 100, and 98%, respectively. The visual assessment (FDG activity scores of 2 or greater) demonstrated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for characterization of adrenal lesions to be 100, 99, 93, 100, and 99%, respectively.

However, some studies included in the current review reported low sensitivity of ¹⁸F-FDG PET or PET/CT for characterization of adrenal masses. Kim et al evaluated the clinical usefulness of the various interpretation methods obtained with ¹⁸F-FDG PET/CT for differentiation malignant and benign adrenal incidentaloma in 52 patients.⁴¹ They demonstrated the sensitivity, specificity, positive-predictive value, negative-predictive value, and accuracy of ¹⁸F-FDG PET/CT for characterization of adrenal incidentaloma to be 92.1, 64.3, 87.5, 75, and 84.6% with SUV_{peak}. With use of SUV_{mean}, the sensitivity, specificity, positive-predictive value, negative-predictive value, and accuracy of ¹⁸F-FDG PET/CT were 65.8, 85.7, 92.6, 48, and 71.2%. In their study, TLG was the best parameter in distinguishing the intermediate- to high-risk adrenal incidentaloma. The TLG demonstrated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ¹⁸F-FDG PET/CT were 92.1, 78.6, 92.1, 78.6, and 88.5%.

Recently, Wu et al reported the meta-analysis of the utility of ¹⁸F-FDG PET/CT for the diagnosis of adrenal metastasis in lung cancer patients.⁵² They included 9 studies involving 707 lung cancer patients with 810 adrenal masses and showed the

Table 2. Diagnostic performance of ^{18}F -FDG PET or PET/CT for the characterization of adrenal masses

Authors	Test results, number of patients or lesions				Sensitivity (95% CI)	Specificity (95% CI)
	True-positive	False-positive	False-negative	True-negative		
Metser U	70	8	1	96	0.99 (0.92–1.00)	0.92 (0.85–0.97)
Blake MA	17	4	2	18	0.89 (0.67–0.99)	0.82 (0.60–0.95)
Han SJ	60	7	4	34	0.94 (0.85–0.98)	0.83 (0.68–0.93)
Park BK	7	3	1	9	0.88 (0.47–1.00)	0.75 (0.43–0.95)
Sung YM	28	3	7	23	0.80 (0.63–0.92)	0.88 (0.70–0.98)
Vikram R	25	12	5	70	0.83 (0.65–0.94)	0.85 (0.76–0.92)
Tessonnier L	12	4	0	25	1.00 (0.74–1.00)	0.86 (0.68–0.96)
Boland GW	26	4	0	135	1.00 (0.87–1.00)	0.97 (0.93–0.99)
Okada M	17	0	3	15	0.85 (0.62–0.97)	1.00 (0.78–1.00)
Lu Y	74	3	2	31	0.97 (0.91–1.00)	0.91 (0.76–0.98)
Ansquer C	24	13	3	41	0.89 (0.71–0.98)	0.76 (0.62–0.87)
Gratz S	103	6	3	106	0.97 (0.92–0.99)	0.95 (0.89–0.98)
Perri M	38	8	4	67	0.90 (0.77–0.97)	0.89 (0.80–0.95)
Cho AR	38	0	7	16	0.84 (0.71–0.94)	1.00 (0.79–1.00)
Gust L	21	1	1	28	0.95 (0.77–1.00)	0.97 (0.82–1.00)
Kara PO	63	3	7	31	0.90 (0.80–0.96)	0.91 (0.76–0.98)
Uemura S	3	2	1	94	0.75 (0.19–0.99)	0.98 (0.93–1.00)
Evans PD	28	3	7	94	0.80 (0.63–0.92)	0.97 (0.91–0.99)
Kunikowska J	31	6	2	63	0.94 (0.80–0.99)	0.91 (0.82–0.97)
Park SY	14	4	3	47	0.82 (0.57–0.96)	0.92 (0.81–0.98)
Kim Y	36	3	3	10	0.92 (0.79–0.98)	0.77 (0.46–0.95)
Launay N	49	3	2	13	0.96 (0.87–1.00)	0.81 (0.54–0.96)
Nakajo M	11	9	0	21	1.00 (0.72–1.00)	0.70 (0.51–0.85)
Watanabe H	22	0	1	22	0.96 (0.78–1.00)	1.00 (0.85–1.00)
Xu B	113	12	49	86	0.70 (0.62–0.77)	0.88 (0.80–0.94)
Kim JY	80	14	17	36	0.82 (0.73–0.89)	0.72 (0.58–0.84)
Pitts A	36	22	0	71	1.00 (0.90–1.00)	0.76 (0.66–0.85)
Cistaro A	36	0	12	20	0.75 (0.60–0.86)	1.00 (0.83–1.00)
Kim BS	13	1	2	32	0.87 (0.60–0.98)	0.97 (0.84–1.00)
Combined	1095	158	149	1354	0.91 (0.88–0.94)	0.91 (0.87–0.93)

CI, confidence interval; FDG, fludeoxyglucose.

pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and DOR of ^{18}F -FDG PET/CT were 0.887 [95% CI (0.852–0.917)], 0.908 [95% CI (0.875–0.934)], 8.552 [95% CI (6.197–11.802)], 0.090 [95% CI (0.039–0.211)], and 96.825 [95% CI (40.402–232.05)], respectively. In addition, the area under the curve was 0.9622 and the overall diagnostic accuracy (Q* index) was 0.9077, suggesting excellent performance.

In cancer patients, it is essential of accurate characterization of adrenal lesions. It is generally accepted that CT and MRI are non-invasive methods for the characterization of adrenal masses.^{53,54} The differential diagnosis of adrenal adenoma is

based on the CT attenuation value (HU) with threshold value of 0–20 HU of unenhanced CT.⁵¹ It is well known that a cut-off value of 10 HU is useful because lipid-rich adenoma is diagnosed in lesions with a value of <10 HU of unenhanced CT.⁵¹ Okada et al reported the comparison of diagnostic value of CT and ^{18}F -FDG PET/CT in patients for cancer screening, staging, and post-therapeutic evaluation.²⁹ In characterizing of adrenal lesions, with a CT threshold of 10 HU showed a sensitivity of 57%, specificity of 94%, accuracy of 74%, positive predictive value of 92% and negative predictive value of 65%. The SUV_{max} cut-off value of 2.5 revealed a sensitivity of 89%, specificity of 94%, accuracy of 91%, positive predictive value of 94% and negative predictive value

Figure 4. Forest plot of pooled sensitivity and specificity of ^{18}F -FDG PET or PET/CT for characterization of adrenal lesions. FDG, fludeoxyglucose.

of 88%. Also, using T/L SUV_{max} ratio cut-off value of 1.8 had a sensitivity of 85%, specificity of 100%, accuracy of 91%, positive predictive value of 100% and negative predictive value of 83%.

Figure 5. HSROC curves for the characterization of adrenal lesions of ^{18}F -FDG PET or PET/CT. FDG, fludeoxyglucose; HSROC.

Heterogeneity between studies may represent a potential source of bias. The included studies were statistically heterogeneous in their estimates of sensitivity and specificity. This heterogeneity is likely to arise through diversity in methodological aspects between different studies (Table 1). The baseline differences among the patients in the included studies (Table 1) may have contributed to the observed heterogeneity of the results too. Also, major limitation was the considerable heterogeneity of the PET or PET/CT parameters for characterization of adrenal lesions used in the included studies. In subgroup analysis of the current review, the quantitative criteria (SUV_{max} vs SUV_{min} ratio) in this study did not provide significant increase of the diagnostic accuracy data and some sources of heterogeneity. Furthermore, the small sample size and bias were the potential source of limitations of the current review. To minimize bias in the selection of studies and in the data extraction, reviewers who were blinded to the journal, author, institution, and date of publication independently selected articles based on the inclusion criteria, and scores were assigned to study design characteristics and examination results by using a standardized form that was based on the QUADAS2 tool. Also, publication bias is a major concern in all meta-analyses as studies reporting significant findings are more likely to be published than those reporting non-significant results. We assessed the publication bias in our analysis by using funnel plots which showed no definite asymmetry ($p = 0.86$).

CONCLUSION

^{18}F -FDG PET or PET/CT demonstrated good sensitivity and specificity for the characterization of adrenal masses. At present, the literature regarding the use of ^{18}F -FDG PET or PET/CT for

Table 3. Subgroup analysis for the diagnostic accuracy of ^{18}F -FDG PET or PET/CT for characterization of adrenal masses according to used interpretation criteria

Variable	Number of studies	Sensitivity	Specificity	PLR	NLR	DOR
		(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Visual analysis						
	9	0.91 (0.83–0.95)	0.92 (0.86–0.95)	11.1 (6.4–19.1)	0.1 (0.05–0.18)	114 (48–273)
Quantitative analysis						
All	20	0.92 (0.87–0.95)	0.90 (0.85–0.94)	9.3 (6.2–14.0)	0.09 (0.06–0.14)	101 (53–192)
SUV ratio	13	0.89 (0.83–0.93)	0.91 (0.85–0.95)	9.8 (5.8–16.6)	0.12 (0.07–0.19)	83 (35–195)
SUV _{max}	6	0.95 (0.86–0.98)	0.91 (0.81–0.96)	10.6 (4.8–23.5)	0.06 (0.02–0.15)	185 (76–451)

DOR, diagnostic odds ratio; FDG, fludeoxyglucose; NLR, negative likelihood ratio; PLR, positive likelihood ratio; TLG, total lesion glycolysis; 95% CI, 95% confidence interval.

The subgroup analysis of quantitative analysis of ^{18}F -FDG PET or PET/CT exclude one study which used TLG as quantitative index to minimize the heterogeneity of the results.

the characterization of adrenal masses remains still limited; thus, further large multicentre studies would be necessary to substantiate the diagnostic accuracy of ^{18}F -FDG PET or PET/CT characterization of adrenal masses.

ETHICAL APPROVAL

Institutional review board approval was not required because we only performed data analysis based on the published studies.

Figure 6. Comparison of HSROC curves for the characterization of adrenal lesions of ^{18}F -FDG PET or PET/CT according to interpretation criteria. (a) visual analysis; (b) SUV ratio; (c) SUV_{max}. FDG, fludeoxyglucose; HSROC, Hierarchical summary receiver operating characteristic; SUV, standardized uptake.

INFORMED CONSENT

Written informed consent was not required for this study

because it is a meta-analysis based on the studies that have been published.

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