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Diagnostic accuracy of F-18 FDG PET/CT for characterization of colorectal focal FDG uptake: a systematic review and meta-analysis

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Abstract

Introduction: We aimed to explore the role of the diagnostic accuracy of F-18 fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) for characterization of incidental colorectal focal FDG uptake through a systematic review and meta-analysis.
Methods: The MEDLINE, EMBASE, and Cochrane Library database, from the earliest available date of indexing through April 30, 2018, were searched for studies evaluating the diagnostic performance of F-18 FDG PET/CT for characterization of incidental colorectal focal FDG uptake. 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 8 studies (1451 patients), the pooled sensitivity for F-18 FDG PET/CT was 0.87 (95% CI 0.82–0.90) without heterogeneity (χ^2 = 10.84, p = 0.37) and a pooled specificity of 0.83 (95% CI 0.76–0.89) with heterogeneity (χ^2 = 130.1, p = 0.00). Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 5.2 (95% CI 3.6–7.4) and negative likelihood ratio (LR−) of 0.16 (95% CI 0.12–0.22). The pooled DOR was 32 (95% CI 20–51).
Conclusion: F-18 FDG PET/CT demonstrated good sensitivity and specificity for characterization of incidental colorectal focal FDG uptake. At present, the literature regarding the use of F-18 FDG PET/CT for characterization of incidental colorectal focal FDG uptake remains still limited; thus, further large multi-center studies would be necessary to substantiate the diagnostic accuracy of F-18 FDG PET/CT for characterization of incidental colorectal focal FDG uptake.

Key words: Positron emission tomography—PET/CT—Colonic uptake—Incidental

Colorectal cancer (CRC) is the third common type of cancer and the second leading cause of cancer-related death in men and the third in women in the United States [1]. In 2017, an estimated 71,420 men and 64,010 women will be diagnosed with CRC and 27,150 men and 23,110 women will die of the disease [1].

It is widely accepted that the most CRCs develop from preformed adenomatous polyp which is referred to as adenoma-to-carcinoma sequence [2]. Also, the colorectal adenomatous polyps are known to be the precursors of the majority of CRCs. The early detection and excision of these pre-malignant lesions is crucial for the prevention of development of CRC and the reduction of mortality of CRCs [3].

F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) has been reported to be an functional and useful imaging modality for tumor staging in different cancers [4, 5]. Also, F-18 FDG PET/CT had an improved diagnostic accuracy and is now considered an important technique in cancer imaging [6]. In CRC, F-18 FDG PET/CT is known to be useful for assessment of colorectal cancer in the fields of initial diagnosis, staging, and detection and staging of recurrence [7]. Moreover, F-18 FDG PET/CT has new potential indications, such as initial pre-therapeutic staging and risk stratification [7].

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Incidental focal uptake of F-18 FDG is frequently encountered in about 1.3–3% of patients who undergo PET/CT scan [8]. The exact mechanisms of colonic FDG uptake are unclear but may be the result of a physiologic, inflammatory bowel disease, benign polyp, or malignant lesion [9–11]. These incidental colonic FDG uptake could be diffuse, segment, or focal and physiologic uptake or uptake related with benign condition could be diffuse pattern [12]. However, intense focal colonic FDG uptake might result from malignant or premalignant lesions such as adenoma [13–17]. Therefore, it is essential to differentiate whether the colonic focal FDG uptake was by benign lesion or by malignant lesion. Previously, the role of F-18 FDG PET and/or PET/CT for incidental premalignant colonic lesion detection has been investigated [17–20]. Recent systemic review articles showed that the incidental colorectal FDG uptake, as evaluated by subsequent colonoscopy, often reveals neoplastic lesions and have a high risk of malignant or premalignant lesions [21, 22].

The purpose of our study is to meta-analyze published data on the diagnostic performance of F-18 FDG PET/CT for characterization of incidental colorectal focal FDG uptake, in order to provide more evidence-based data and to address further studies in the evaluation of colorectal FDG uptake.

Methods

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 April 30, 2018. We also hand-searched 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) "Colon*" OR "Incidental."

Study selection

The inclusion criteria for relevant studies were as follows: whole-body F-18 FDG PET/CT had been used to identify and to for characterize the incidental colorectal focal FDG uptake; sufficient data to reassess sensitivity and specificity of F-18 FDG PET/CT in predicting malignant or premalignant lesions of incidental focal colorectal FDG uptake or absolute numbers of true-positive, true-negative, false-positive, and false-negative data had been presented; and no data overlap. Studies were excluded if fewer than ten 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 (Kim SJ, Son GM) independently reviewed titles and abstracts of the retrieved articles, applying the above mentioned selection criteria. Articles were rejected if clearly ineligible. The same two researchers then independently evaluated the full-text version of the included articles to determine their eligibility for inclusion.

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 analyzed to retrieve the number of true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) findings of F-18 FDG PET/CT for predicting malignant or premalignant lesions of incidental focal colorectal FDG uptake, according to the reference standard. Only studies providing such complete information were finally included in the meta-analysis.

The F-18 FDG PET/CT results were evaluated and considered to be TP, TN, FP, and FN by following criteria in each study;

TP—a location of a focal FDG uptake corresponded to that of pre-malignant/malignant lesion found by colonoscopy.
TN—a negative PET/CT correlated with a negative colonoscopy.
FP—a focal FDG uptake without a correlative finding by colonoscopy.
FN—no focal FDG uptake seen by PET/CT at a given location, yet pathology was observed at that location by colonoscopy.

Quality of the included studies was assessed based on 15-item modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS2) [23]. Two reviewers (Kim SJ, Son GM) independently assessed each potentially eligible study and assigned them as a quality rating of "good," "fair," or "poor." Quality assessment was conducted based on following criteria: study design and presence of bias including selection, performance, recording, and reporting bias. Studies with high risk of bias were defined as poor quality, presence of moderate risk (did not affect the results) as fair quality, and those with minimal risk as good quality. Disagreements were settled with consensus decision. Disagreement between the two authors was resolved by discussion.

Data synthesis and analysis

All data from each eligible study were extracted. Categorical variables are presented as frequencies or percentages, and continuous variables are presented as mean values unless stated otherwise. Measures of the diagnostic performance, including sensitivity, specificity, and diagnostic odds ratios (DORs), are reported as point estimates with 95% confidence intervals (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 [24]. Between-study statistical heterogeneity was assessed using I^2 and the Cochrane Q test on the basis of the random-effects analysis [25]. Publication bias was examined using the effective sample size funnel plot and associated regression test of asymmetry described by Deeks et al. [26]. 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 [27, 28]. The bivariate model estimates pairs of logit transformed sensitivity and specificity from studies, incorporating the correlation that might exist between sensitivity and specificity. We also used the model to create hierarchical summary receiver operating characteristic curves and to estimate the area under the curve [29]. When statistical heterogeneity was substantial, we performed meta-regression to identify potential sources of bias [30]. 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, version 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 1670 records after removing 263 duplicated studies, of which 1634 records (non-relevant studies 677, Case report 685, Review article 272) were excluded after reviewing the title and abstract. Remaining 36 full-text articles were assessed for eligibility and 28 articles were excluded due to insufficient data for the calculation of sensitivity and specificity of F-18 FDG PET/CT for the predicting malignant or premalignant lesions of incidental focal colorectal FDG uptake. Finally, 8 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 [31–38]. The characteristics of the included studies are presented in Table 1. The detailed procedure of study selection in the meta-analysis is shown in Fig. 1.

Study description, quality, publication bias

We conducted all analyses based on per-patient data and/or per-lesion data analysis. Among those 8 studies included in the current review, seven studies conducted patient-based analysis of F-18 FDG PET/CT [31–34, 36–38]. Remaining one study conducted lesion-based analysis [35]. There was a total of 1451 patients in the included studies, and the age ranged from 10 to 90 years. One study investigated 241 focal colorectal FDG uptake foci in their study [35]. A total 376 patients were male, and 280 patients were female. The two studies did not report the number of male and female patients in their population [34, 35]. All of 8 studies enrolled patients retrospectively. One study [38] used PET and other studies used PET/CT as imaging device in their studies. Of 8 studies, three studies used CRC as reference standard for the evaluation of diagnostic performance of F-18 FDG PET/CT images for predicting malignant or premalignant lesions of incidental focal colorectal FDG uptake [32, 36, 37]. Two studies aimed to detect colorectal neoplasm (CRN) to calculate TP, FP, FN, and TN of F-18 FDG PET/CT [33, 38]. Other three studies used both of CRC and CRN as reference standard to estimate the diagnostic accuracy of F-18 FDG PET/CT [31, 34, 35]. The principal characteristics of the 8 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 0.53 (Fig. 2).

Methodological quality assessment

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

Diagnostic accuracy of F-18 FDG PET or PET/CT

The diagnostic performance results of F-18 FDG PET/CT for characterization of incidental colorectal focal FDG uptake of the 8 included studies in the meta-analysis are presented in Fig. 3. The pooled sensitivity for F-18 FDG PET/CT was 0.87 (95% CI 0.82–0.90) without heterogeneity (χ^2 = 10.84, p = 0.37) and a pooled specificity of 0.83 (95% CI 0.76–0.89) with heterogeneity (χ^2 = 130.1, p = 0.00). Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 5.2 (95% CI 3.6–7.4) and negative likelihood ratio (LR−) of 0.16 (95% CI 0.12–0.22). The pooled DOR was 32 (95% CI 20–51). Forest plots of the sensitivity and specificity of F-18 FDG PET/CT for the differentiation of CRC

Table 1. Characteristics of the included studies

Authors	Year	Country	Device	Analysis	Patient number	Lesion number	Age (range)	Male/ Female	F-18 FDG dose (MBq)	Reference standard	Study design
Choi BW	2016	Korea	PET/ CT	PB	256		62.8 (29–86)	165/91	4–7 MBq/kg	CRC	R
Soltau SR	2016	Denmark	PET/ CT	PB	25		71 (33–90)	12/13	4 MBq/kg	CRC	R
van Hoeij FB	2015	Germany	PET/ CT	PB	242		66	116/87	2.5 MBq/kg	CRN	R
Na SY	2015	Korea	PET/ CT	PB			NA	NA	370–555	CRC	R
Cho SH	2013	Korea	PET/ CT	LB		241	62 (29–86)		370–570	CRN	R
Liu T	2015	USA	PET/ CT	PB	133		58 (10–87)	57/76	370	CRC	R
Lee CH	2013	Korea	PET/ CT	PB	756		61 (23–89)		5.2 MBq/kg	CRC	R
Drenth JPH	2001	Netherlands	PET	PB	39		62.3	26/13	200	CRN	R
Huang SW	2013	Taiwan	PET/ CT	LB	1109		53.2(20–81)	661/448	370	CRC	R

Analysis: LB, lesion bases; PB, patient based. NA, not available. Study design: R, retrospective; P, prospective. CRN, colorectal neoplasia; CRC, colorectal cancer

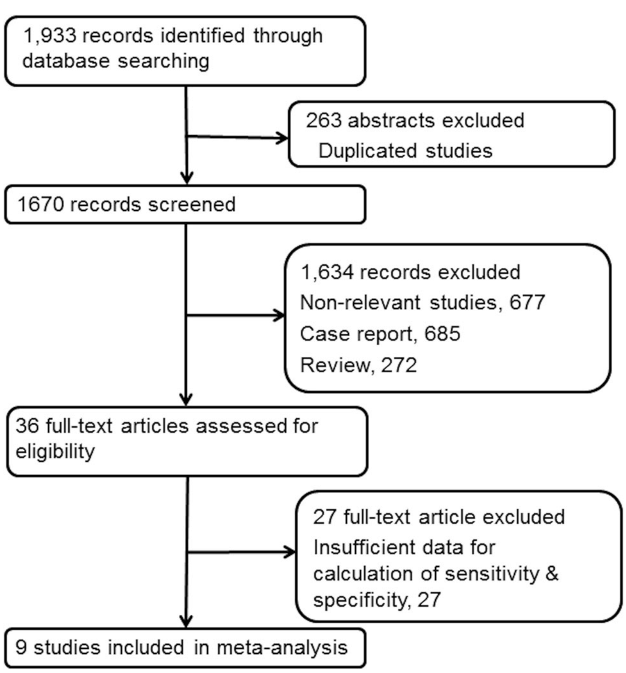

Fig. 1. Flow chart of the search for eligible studies on the diagnostic performance of F-18 FDG PET/CT for characterization of incidental colorectal focal FDG uptake.

and/or CRN of incidental colorectal focal FDG uptake are shown in Fig. 4. Figure 5 shows hierarchical summary receiver operating characteristic (ROC) curve and indicates that the areas under the curve were 0.91 (95% CI 0.88–0.93), indicating good diagnostic accuracy.

Heterogeneity evaluation and meta-regression analysis

Between-study heterogeneity was present for specificity among studies of F-18 FDG PET/CT for the detection of CRC and/or CRN of incidental colorectal focal FDG uptake. A meta-regression analysis was performed to explore other sources of heterogeneity in the studies. Table 2 lists the results of meta-regression analysis for identifying potential sources of heterogeneity. In univariate meta-regression analysis, the used reference standard (CRC vs. CRN) was the potent source of heterogeneity of specificity of F-18 FDG PET/CT. However, in multivariate meta-regression, no definite variable was the source of the study heterogeneity.

Discussion

With wide use of F-18 FDG PET/CT technique in oncologic patients, incidental focal colorectal FDG uptake is found frequently and often related to physiologic uptake. The exact mechanisms of the physiologic activity are unclear, however, peristaltic activity of intestinal wall, presence of reactive lymphocytes in the terminal ileum and cecum, and the presence of FDG secreting cells are presumed [39, 40]. Benign conditions such as adenoma and inflammatory bowel diseases might be associated with FDG uptake [9]. The pattern of colonic FDG uptake was investigated and diffuse FDG uptake is more frequently associated with physiological uptake, while focal uptake may be associated with malignant and pre-malignant lesion [19].

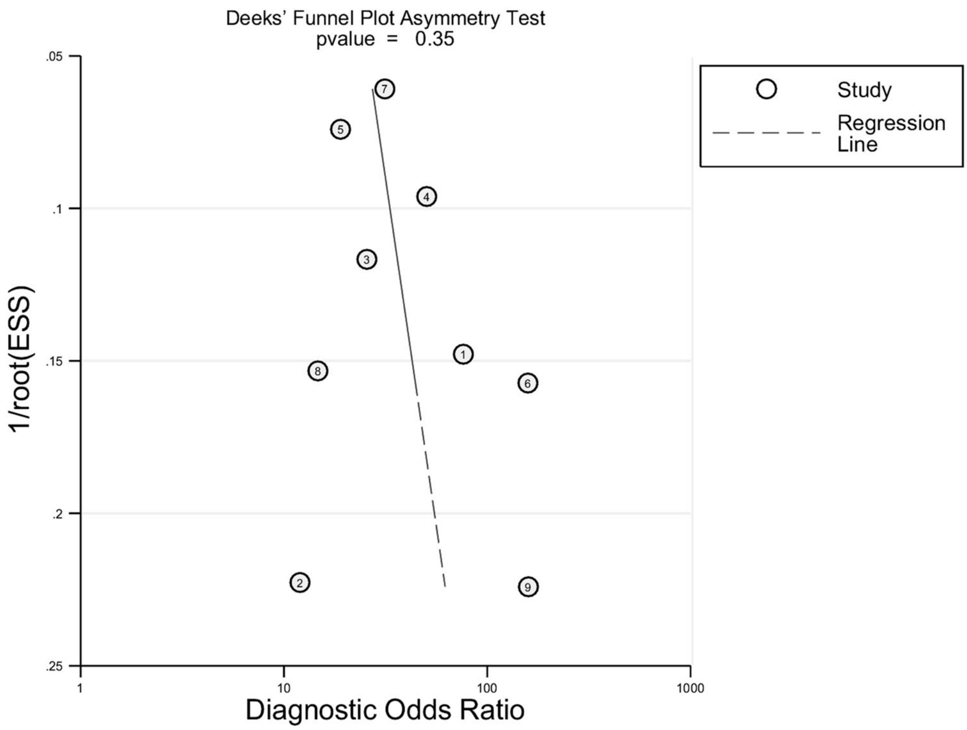

Fig. 2. Results of Deeks's funnel plot of asymmetry test for publication bias. Non-significant slope indicates that no significant bias was found. ESS, effective sample size.

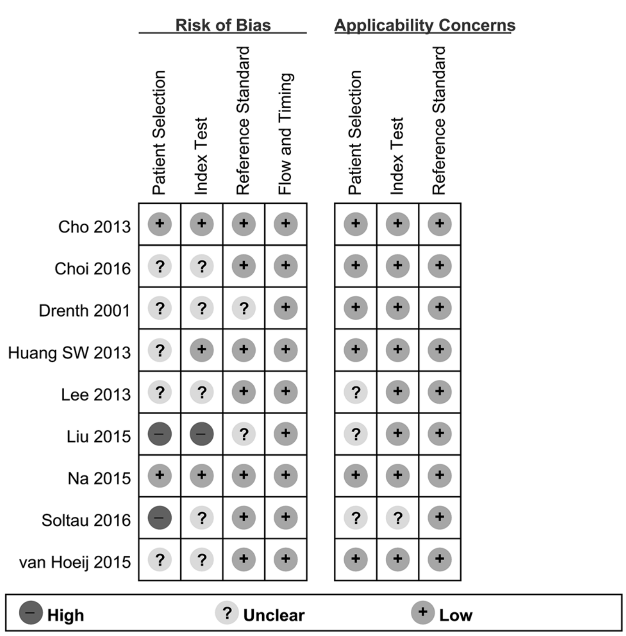

Fig. 3. Risk of bias and applicability concerns summary.

Several previous studies have shown that incidental colorectal F-18 FDG uptake may predict the presence of premalignant or malignant lesions, unrelated to the primary cancer [41]. In a retrospective study, Gutman et al. observed focal colonic F-18 FDG uptake in 45 patients, of whom 20 underwent a colonoscopy. There were 21 foci in 20 patients, and 18 foci were associated with abnormal colonoscopy findings. Although 13 lesions were of a premalignant nature, three were malignant, and five patients had normal colonoscopy finding [42]. Other study included 1000 patients who had been diagnosed as malignancy and received FDG-PET, 20 FDG focal uptakes were detected in 16 patients; 2 lesions were diagnosed as adenocarcinoma, 6 as villotubular adenoma and 1 as tubular adenoma, among 14 lesions of 10 patients who were available for pathological examinations by surgery or endoscopy [43]. Özkol et al. investigated the clinical value of incidental FDG uptake in a sample of 2370 PET/CT images and found 116 incidental FDG uptake lesions, of which 74 were investigated, 59 FDG deposits by biopsy and 15 using other imaging methods. They detected 36 FDG deposits that corresponded to malignant or premalignant lesions (49%): 19 synchronous carcinomas, 14 secondary metastasis of a primary tumor in an unusual location and 3 premalignant adenomas; 33 lesions were benign (44%) and 5 lesions were false positives (7%) [44].

In our meta-analysis, the results reported show that F-18 FDG PET/CT has good diagnostic accuracy for characterization of incidental colorectal focal FDG uptake, with an area under the ROC curve of 0.91 (95% CI 0.88–0.93). F-18 FDG PET/CT demonstrated a sensitivity of 0.87 (95% CI 0.82–0.90) and a specificity of 0.83 (95% CI 0.76–0.89). This result was also consistent with the results of other well-designed studies. Choi et al. investigated the diagnostic accuracy of F-18 FDG PET/

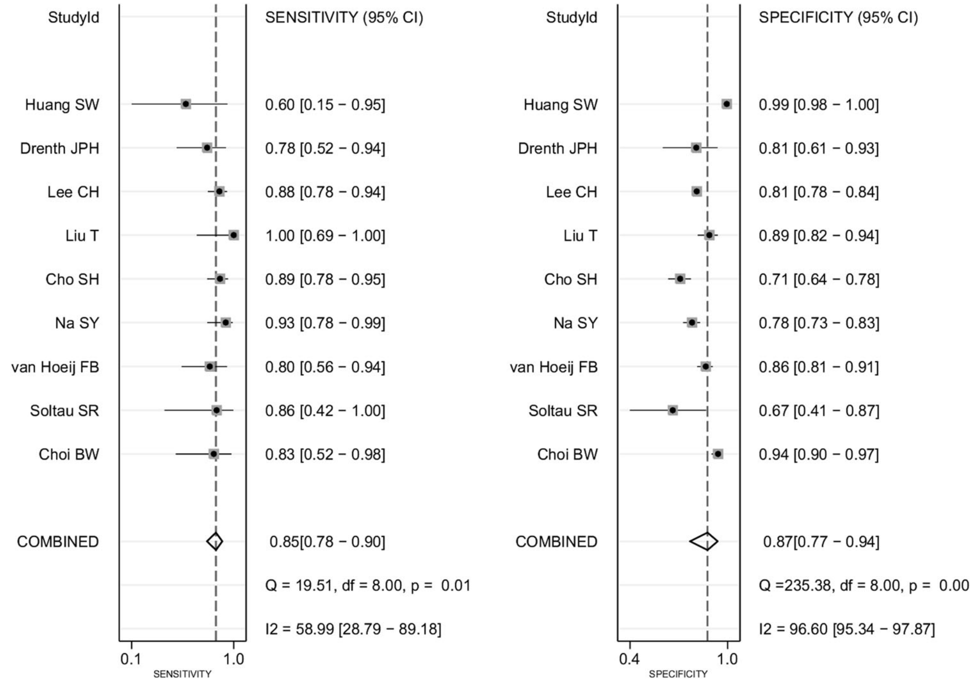

Fig. 4. Forest plot of pooled sensitivity and specificity of F-18 FDG PET/CT for characterization of incidental colorectal focal FDG uptake. Summary of sensitivity and specificity of F-18 FDG PET/CT was 0.87 (95% confidence interval [CI] 0.82–0.90) and 0.83 (95% CI 0.76–0.89), respectively.

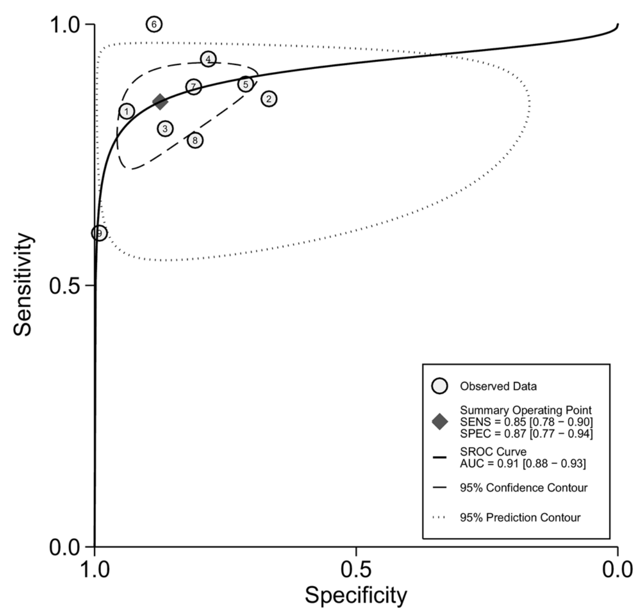

Fig. 5. Hierarchical summary receiver operating characteristic (HSROC) curves for characterization of incidental colorectal focal FDG uptake of F-18 FDG PET/CT.

CT for detecting synchronous advanced CRN in patients with gastric cancer [31]. They found the synchronous advanced CRN in 21 of the 256 patients (4.7%). The sensitivity, specificity, and accuracy of F-18 FDG PET/CT were 76.2, 96.2, and 94.5%. They noted that F-18 FDG PET/CT demonstrated high diagnostic accuracy for detecting synchronous advanced CRN in patients with gastric cancer. Therefore, they concluded that the colonoscopy is recommended as the next diagnostic step for further evaluation of a positive F-18 FDG PET/CT result in patients with gastric cancer. van Hoeij et al. performed a retrospective review of 7318 patients who received F-18 FDG PET/CT images [33]. Of 7318 patients analyzed, 359 (5%) had 404 foci of unexpected colonic FDG uptake. In 242 of these 404 lesions (60%), colonoscopy follow-up data were available. Final diagnoses were as follows: adenocarcinoma in 25 (10%), adenoma in 90 (37%), and benign in 127 (53%). When the cut-off value of 11.4 of SUV_{max} for differentiation of malignant versus non-malignant lesions, the ROC curve showed sensitivity 80%, specificity 82%, positive predictive value (PPV) 34%, negative predictive value (NPV) 98%.

However, some studies included in the current review reported low sensitivity of F-18 FDG PET/CT for characterization of incidental colorectal focal FDG uptake. Lee C et al. showed that the sensitivity, specificity, PPV, and NPV of PET/CT were 54.4, 82.4, 46.9, and 86.3%, respectively, in the detection of advanced CRNs [37]. Drenth et al. compared the diagnostic accuracy of F-18 FDG PET for the detection of pre-malignant lesions of the colon was compared with that of endoscopy. Compared with colonoscopy, F-18 FDG PET had a sensitivity of 74%, specificity of 84%, and the PPV of 78% [38].

Table 2. Effects of moderators

Variables	Coefficient*	SE	DOR	95% CI of DOR		p**
Number of patient (> 150 vs. ≤ 150)	− 0.084	1.1646	0.92	0.01	137.91	0.9489
Reference standard (CRC vs. CRN)	0.651	1.3723	1.92	0.01	703.53	0.6818
Analysis (patient-based vs. lesion-based)	0.419	1.1947	1.52	0.01	259.59	0.7594
Publication year (after 2014 vs. before 2014)	0.550	0.6531	1.73	0.10	28.8	0.4881
Study site (western vs. other countries)	− 0.432	1.7652	0.65	0.00	1290.75	0.8295

Number of patient (1, > 150 vs. 0, ≤ 150); Analysis (1, patient-based vs. 0, lesion-based); publication year (1, after 2014 vs. 0, before 2014); study site (1, western vs. 0, other countries); reference standard (1, CRC vs. 0, CRN)

DOR, diagnostic odds ratio; SE, standard error; CI, confidence interval; CRC, colorectal cancer; CRN, colorectal neoplasia

*Regression coefficient

**p value of random effect meta-regression using maximum likelihood estimation (ML) between study variances and the weighted least squares of study size for regression model estimation

The most important drawback of the current study is heterogeneity. The heterogeneity between studies may represent a potential source of bias. The included studies were statistically heterogeneous in their estimates of specificity. This heterogeneity is likely to arise through diversity in the used standard reference (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. However, according to the multivariate meta-regression analysis of the current study, none of the variables was the source of the study heterogeneity. Also, in sub-group analysis of the current review, the standard reference of CRC provided 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 some asymmetry ($p = 0.53$).

Conclusion

F-18 FDG PET/CT demonstrated good sensitivity and specificity for characterization of incidental colorectal focal FDG uptake. At present, the literature regarding the use of F-18 FDG PET/CT for characterization of incidental colorectal focal FDG uptake remains still limited; thus, further large multicenter studies would be necessary to substantiate the diagnostic accuracy of F-18 FDG PET/CT for characterization of incidental colorectal focal FDG uptake.

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Compliance with ethical standards

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

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

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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