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Diagnostic performance of F-18 FDG PET/CT for prediction of KRAS mutation in colorectal cancer patients: a systematic review and meta-analysis

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Abstract

Objective The purpose of the current study was to investigate the diagnostic performance of F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for the prediction of v-Ki-ras-2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation in colorectal cancer (CRC) patients through a systematic review and meta-analysis.

Methods The PubMed and EMBASE 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 prediction of KRAS mutation in CRC patients.

Results Across 9 studies (804 patients), the pooled sensitivity for F-18 FDG PET/CT was 0.66 (95% CI 0.60–0.73) without heterogeneity ($I^2 = 34.1$, $p = 0.14$) and a pooled specificity of 0.67 (95% CI 0.62–0.72) without heterogeneity ($I^2 = 1.63$, $p = 0.42$). Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 2.0 (95% CI 1.7–2.4) and negative likelihood ratio (LR−) of 0.5 (95% CI 0.41–0.61). The pooled diagnostic odds ratio (DOR) was 4 (95% CI 3–6). Hierarchical summary receiver operating characteristic (ROC) curve indicates that the areas under the curve were 0.69 (95% CI 0.65–0.73).

Conclusion The current meta-analysis showed the low sensitivity and specificity of F-18 FDG PET/CT for prediction of KRAS mutation in CRC patients. The DOR was very low and the likelihood ratio scatter-gram indicated that F-18 FDG PET/CT might not be useful for prediction of KRAS mutation and not for its exclusion. Therefore, cautious application and interpretation should be paid to the F-18 FDG PET/CT for prediction of KRAS mutation in CRC patients.

Keywords F-18 FDG · Colon cancer · Rectal cancer · PET/CT · KRAS

Introduction

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 2018, an estimated 75,610 men and 64,640 women will be diagnosed with CRC and 27,390 men and 23,240 women will die of the disease [1].

The mutations of the v-Ki-ras-2 Kirsten rat sarcoma viral oncogene homolog (KRAS), which encodes a GTPase downstream of epidermal growth factor receptor (EGFR), are known to be associated with resistance to tyrosine kinase inhibitor (TKI) [2]. Thus, KRAS mutations are a useful biomarker of EGFR-TKI resistance [3]. KRAS mutations occur in approximately 40% of CRCs and known to be crucial because they can predict a lack of responses to therapies with antibodies targeted to EGFR [4–7]. In addition, the mutation of KRAS genome has been indicated as prognostic factors or therapeutic responder in CRC [5, 6, 8]. Therefore, optimal assessment of KRAS mutation status might be helpful for establishment of treatment strategies such as anti-EGFR antibody treatment. A surrogate biomarker for KRAS mutation status would provide genomic information without

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the need for biopsy or surgery. To identify this surrogate marker, it may be helpful to assess the biological effects of KRAS mutation.

F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has been reported to be an functional and useful imaging modality for tumor staging in different cancers [9, 10]. Also, F-18 FDG PET/CT had an improved diagnostic accuracy and is now considered an important technique in cancer imaging [11]. 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 [12]. Moreover, F-18 FDG PET/CT has new potential indications, such as initial pre-therapeutic staging and risk stratification [12].

A recent study reported that in CRC cell lines, under normoxic conditions, the increase in glucose transporter-1 (GLUT1) expression and glucose uptake is critically dependent on KRAS mutations [13]. Also, some studies demonstrated that F-18 FDG PET/CT-derived parameters were associated in CRC tumors with TP53 and KRAS mutations [14]. On the contrary, in other study, they could not predict KRAS gene mutations using PET/CT parameters in patients with CRC [15].

The purpose of our study is to meta-analyze published data on the diagnostic performance of F-18 FDG PET/CT for the prediction of KRAS mutation in CRC patients, in order to provide more evidence-based data and to address further studies in the prediction of KRAS mutation in CRC patients.

Methods

Data sources and search strategy

We conducted electronic English-language literature searches of MEDLINE/PubMed and Embase 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" OR "positron emission tomography-computed tomography" OR "PET-CT" OR "FDG" OR "Fluorodeoxyglucose" and (2) "colon cancer" OR "rectal cancer" OR "colorectal cancer" and (3) "KRAS."

Study selection

The inclusion criteria for relevant studies were as follows: F-18 FDG PET/CT had been used to predict the KRAS mutation in CRC patients; sufficient data to reassess sensitivity and specificity of F-18 FDG PET/CT for the prediction of KRAS mutation in CRC patients or absolute numbers of true-positive, true-negative, false-positive, and false-negative data had been presented; and no data overlap. The duplicated 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 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 the prediction of KRAS mutation in CRC patients, 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) [16]. 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 ratio (DOR) with 95% confidence interval (CI). 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 [17]. Between-study statistical heterogeneity was assessed using I^2 and the Cochrane Q test on the basis of the random-effects analysis [18]. Publication bias was examined using the effective sample size funnel plot and associated regression test of asymmetry described by Deeks et al. [19]. 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 [20, 21]. 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 [22]. When statistical heterogeneity was substantial, we performed meta-regression to identify potential sources of bias [23]. Pooled estimates were also calculated for subgroups of studies that were defined according to specific study designs. Informativeness was represented graphically by a likelihood ratio scatter-gram or matrix [24]. The likelihood ratio scatter-gram shows summary point of likelihood ratios obtained as functions of mean sensitivity and specificity [25]. 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 124 records, of which 19 records of duplicated abstracts were excluded after reviewing the title and abstract. Also, non-relevant 39 studies, 46 conference abstracts, 1 letter, and 7 review articles were excluded. Remaining 12 full-text articles were assessed for eligibility and 3 articles were excluded due to insufficient data for the calculation of sensitivity and specificity of F-18 FDG PET/CT for the prediction of KRAS mutation in CRC patients. Finally, 9 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 [26–34]. The characteristics of the included studies are presented in Table 1. The detailed procedure of study selection in the current meta-analysis is shown in Fig. 1.

Study description, quality, publication bias

We conducted all analyses based on per-patient data. There was a total of 804 patients in the included studies, and the age ranged from 26 to 90 years. A total 488 patients were male, and 316 patients were female. All of the 9 studies enrolled patients retrospectively. The mean prevalence of KRAS mutation was 43.5% with a range of 28.5–61.3%. All included studies used quantitative method for interpretation of F-18 FDG PET/CT. Six studies used SUV values for interpretation of F-18 FDG PET/CT for prediction of KRAS mutation status in CRC patients [28, 30–34]. One study used tumor width of 40% of SUV_{max} [26] and one study used practile 25 [27], and the other study used tumor-to-normal

Table 1 Characteristics of the included studies

Authors	Year	Country	Study design	CEA (range)	KRAS analysis	Patient number	M/F	Age (range)	F-18 FDG dose (MBq)	Interpretation criteria of PET	KRAS mutant (%)	Cutoff value
Chen et al. [26]	2014	Taiwan	R	NR	PCR	121	72/49	59 (26–86)	370	QA, TW40%	40.4	2.6
Chen et al. [27]	2018	Taiwan	R	38.5 (0.5–959.5)	PCR	74	46/28	58 (26–85)	370	QA, Practile25	28.3	7.5
Cho et al. [28]	2017	Korea	R	34.9 (0.6–20,000)	PCR	93	47/46	60 (32–86)	550	QA, SUV_{max}	43	12.3
Kawada et al. [29]	2012	Japan	R	NR	PCR	51	30/21	68 (36–90)	370	QA, TLR	43.1	7
Kawada et al. [30]	2015	Japan	R	NR	PCR	42	33/9	64.5 (NR)	370	QA, SUV_{max}	45.2	6.0
Krikelis et al. [31]	2014	Greece	R	3.4 (0.6–308)	PCR	44	28/16	60 (39–79)	5 MBq/kg	QA, SUV_{max}	61.3	8.6
Lee et al. [32]	2016	Korea	R	10.4 (NR)	PCR	179	101/78	64 (25–72)	5.5 MBq/kg	QA, SUV_{peak}	33.5	7.4
Lovinfosse et al. [33]	2016	Belgium	R	NR	PCR	151	95/56	65.8 (19–67)	282	QA, SUV_{cov}	55	0.25
Mao et al. [34]	2018	China	R	NR	PCR	49	36/13	NR	5.1 MBq/kg	QA, SUV_{delayd}	42.5	11.8

NR not reported

Study design: *R* retrospective, *QA* quantitative analysis, SUV_{max} maximal standardized uptake value, SUV_{peak} peak standardized uptake value, SUV_{cov} standardized uptake value of coefficient of variation, *TW40%* tumor width of 40% of SUV_{max}, *TLR* tumor-to-normal tissue ratio, *PCR* polymerase chain reaction

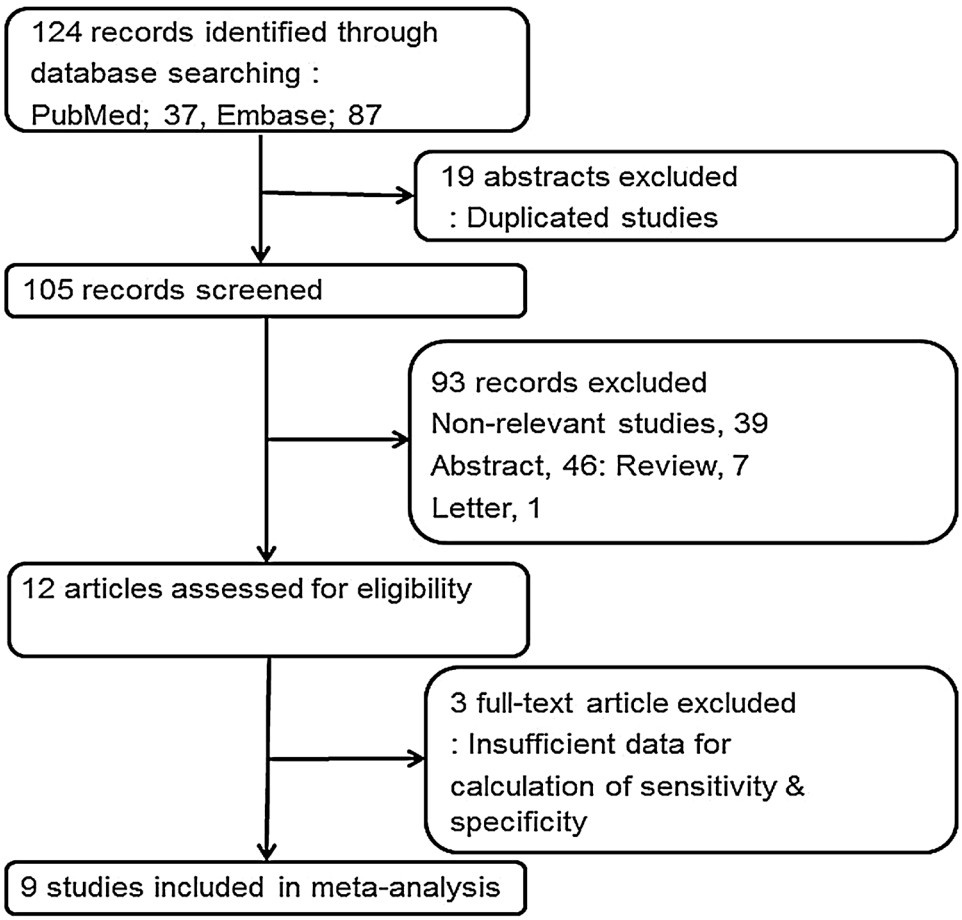

Fig. 1 Flow chart of the search for eligible studies on the diagnostic performance of F-18 FDG PET/CT for prediction of KRAS mutation in CRC patients

ratio as quantitative index [29]. The principal characteristics of the nine 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 0.12 (Fig. 2).

Methodological quality assessment

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

Diagnostic accuracy of F-18 FDG PET/CT

The diagnostic performance results of F-18 FDG PET/CT for the prediction of KRAS mutation in CRC patients in the nine included studies in the meta-analysis are presented in Fig. 4. The pooled sensitivity for F-18 FDG PET/CT was 0.66 (95% CI 0.60–0.73) without heterogeneity ($I^2 = 34.1$, 95% CI 0–85.2, $p = 0.14$) and a pooled specificity of 0.67 (95% CI 0.62–0.72) without heterogeneity ($I^2 = 1.63$, 95% CI 0–100, $p = 0.42$). Likelihood ratio (LR) syntheses gave an overall positive likelihood ratio (LR+) of 2.0 (95% CI 1.7–2.4) and negative likelihood ratio (LR−) of 0.5 (95% CI 0.41–0.61). The pooled diagnostic odds ratio (DOR) was 4 (95% CI 3–6). Forest plots of the sensitivity and specificity F-18 FDG PET/CT for the prediction of KRAS mutation in CRC patients are shown in Fig. 4. Figure 5 shows hierarchical summary receiver operating characteristic (ROC) curve and indicates that the areas under the curve were 0.69 (95% CI 0.65–0.73).

Likelihood ratio scatter-gram

Figure 6 shows the likelihood ratio scatter-gram which displays the summary point of likelihood ratios obtained as functions of mean sensitivity and specificity in the right lower quadrant suggesting that F-18 FDG PET/CT might not be useful for prediction of the presence of KRAS mutation (when positive) and not for its exclusion (when negative).

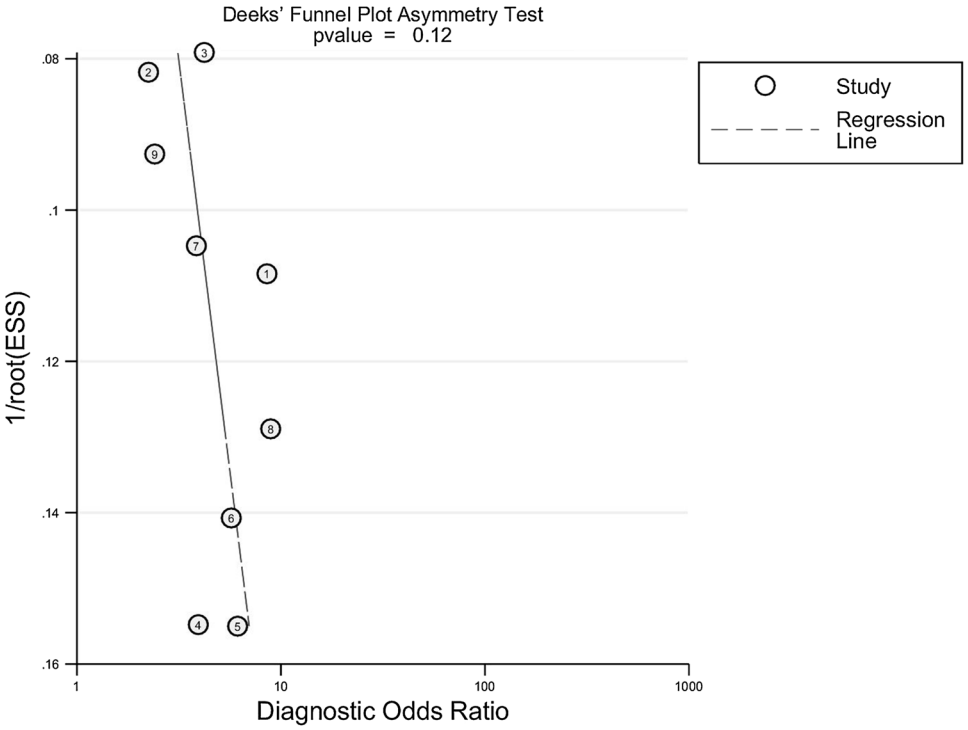

Fig. 2 Results of Deeks's funnel plot of asymmetry test for publication bias. Non-significant slope indicates that no significant bias was found. *ESS* effective sample size

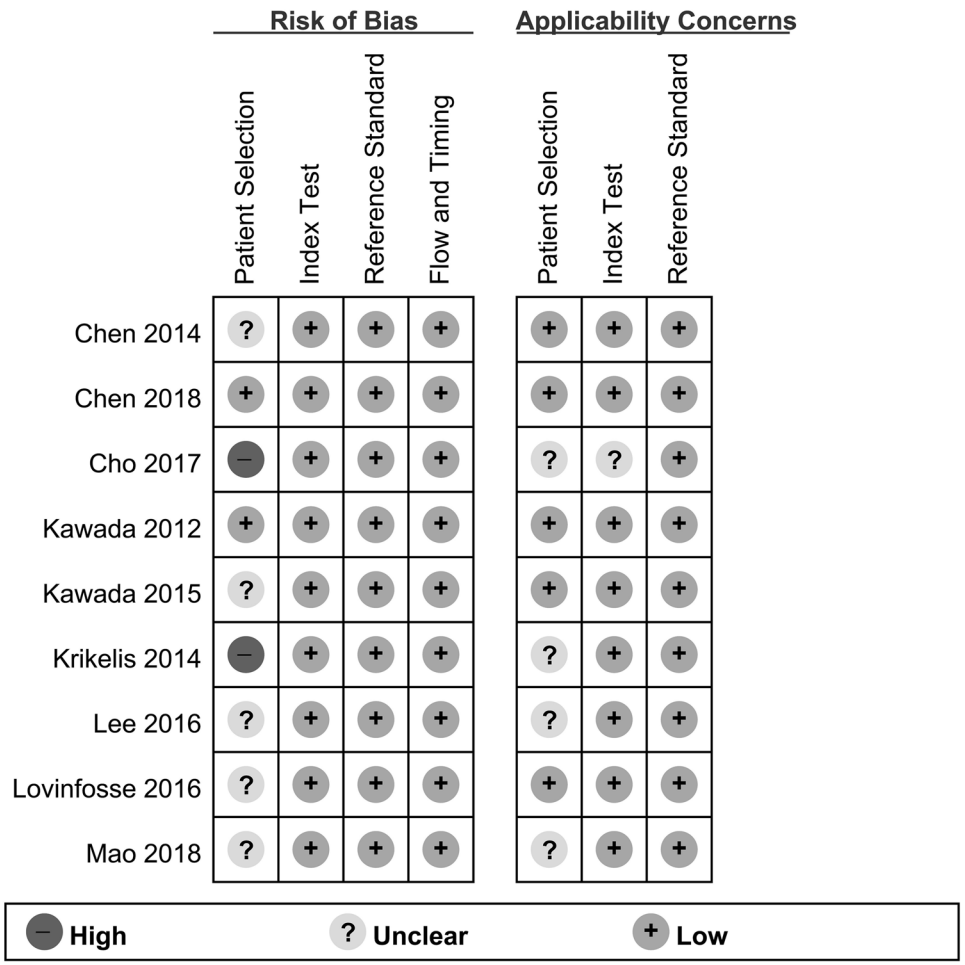

Fig. 3 Risk of bias and applicability concerns summary

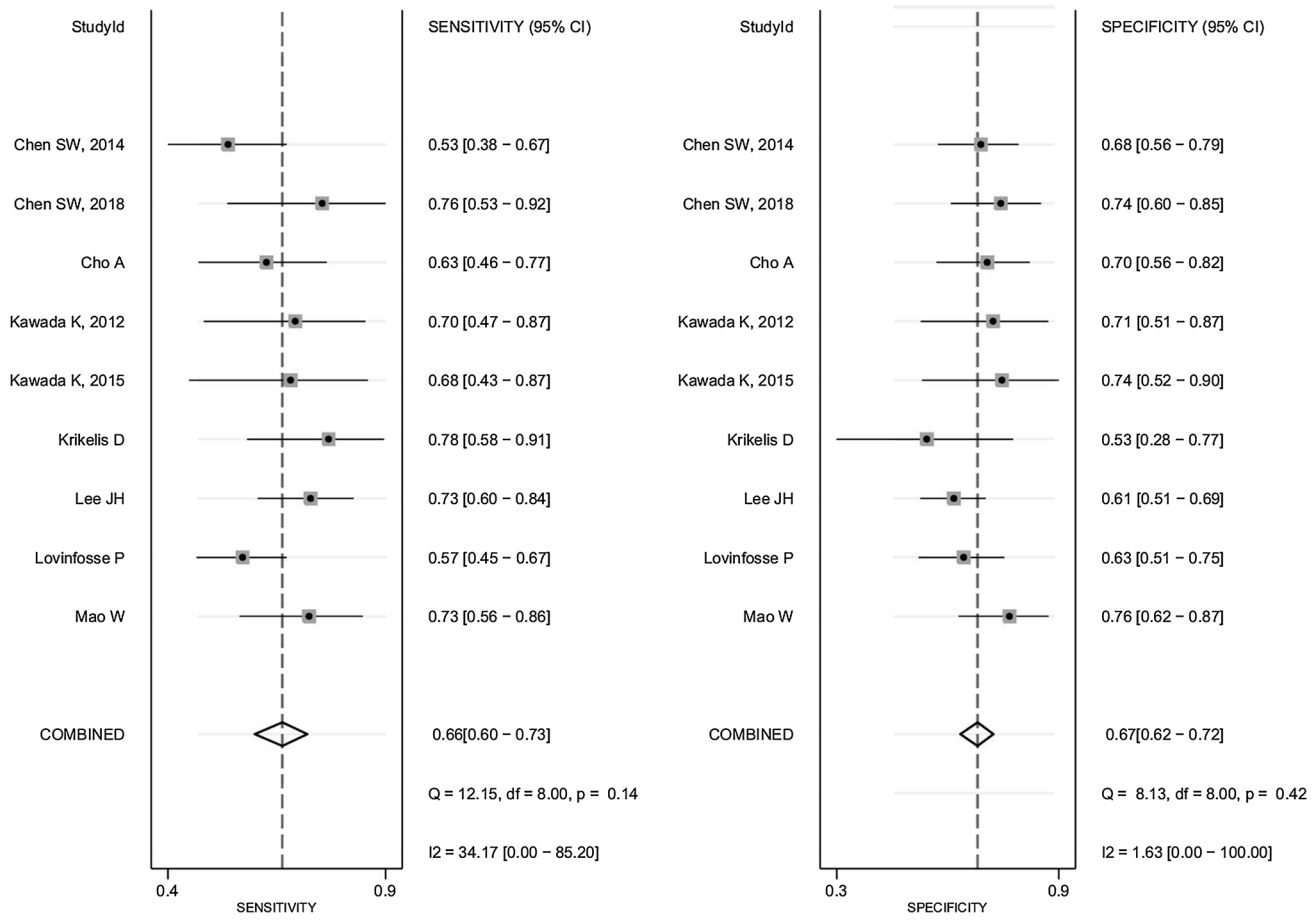

Fig. 4 Forest plot of pooled sensitivity and specificity of F-18 FDG PET/CT for prediction of KRAS mutation in CRC patients

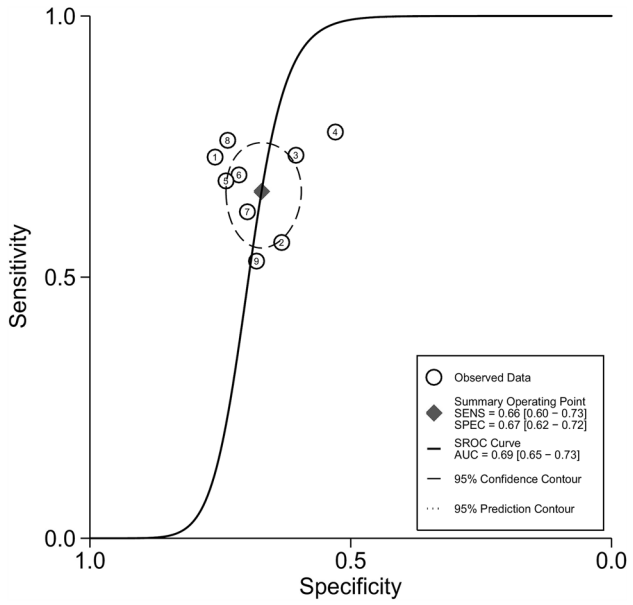

Fig. 5 Hierarchical summary receiver operating characteristic (HSROC) curves of F-18 FDG PET/CT for prediction of KRAS mutation in CRC patients

Discussion

The current meta-analysis showed the low sensitivity and specificity of F-18 FDG PET/CT for the prediction of KRAS mutation in CRC patients. Furthermore, the DOR was low and the likelihood ratio scatter-gram indicated that F-18 FDG PET/CT might not be useful for the prediction of KRAS mutation in CRC patients and not for its exclusion.

Oncogenic activation of KRAS can influence several cellular processes that regulate biological courses such as morphology, proliferation, and motility [35]. KRAS mutations occur in a variety of human malignancies, most frequently in pancreatic cancer, non-small cell lung carcinoma, and colon cancer. It has been reported that F-18 FDG uptake reflects the KRAS mutational status of cancers [28, 36, 37]. However, F-18 FDG PET/CT has been rarely used in the assessment of gene expression status. Few studies have evaluated the association between F-18 FDG accumulation and KRAS mutational status. F-18 FDG accumulation was shown to be higher in CRC with KRAS mutations and F-18 FDG PET/CT scans may be useful for predicting the KRAS status of patients with CRC [29]. Another study showed that SUV_{max}

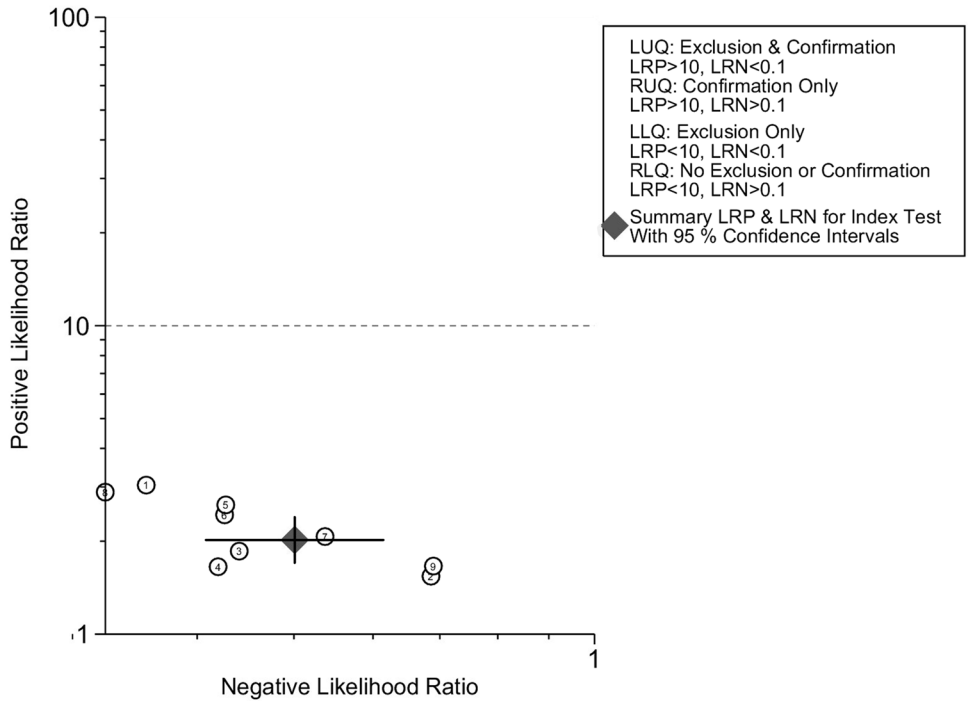

Fig. 6 Likelihood ratio scatter-gram of F-18 FDG PET/CT for prediction of KRAS mutation in CRC patients

and TW40% were associated in CRC with KRAS mutations [26]. However, a recent study could not find significant correlation between F-18 FDG PET/CT SUV_{max} values and KRAS mutation status in metastatic CRC patients [31].

Several studies investigated the diagnostic role of F-18 FDG PET/CT for prediction of KRAS mutation in CRC patients [26, 28–33]. Chen et al. reported that using SUV_{max} cutoff value of 11, the sensitivity and specificity for predicting the KRAS mutant were 52.4% and 71.7%, respectively, and using the median value of TW40% as a cutoff (2.6 cm), the sensitivity, specificity, and accuracy were 53.2%, 67.6%, and 62%, respectively [26]. Cho et al. demonstrated that using SUV_{max} cutoff of 12.3, F-18 FDG PET/CT showed sensitivity of 62.5% (25/40), specificity of 69.8% (37/53), and accuracy of 66.7% (62/93) in predicting KRAS mutation in CRC patients [28]. Using TLR instead of SUV_{max} value, Kawada et al. showed that sensitivity and specificity were 70% (16 of 23) and 71% (20 of 28), respectively (PPV, 67%, 16 of 24; NPV, 74%, 20 of 27; accuracy, 71%, 36 of 51) [29]. They concluded that F-18 FDG PET/CT scans can be predictive of KRAS and BRAF status of primary CRC [29]. However, Krikelis et al. revealed that SUV_{max} values did not differ in a statistically significant manner between KRAS wild-type and KRAS-mutated CRC [31].

Recent several studies investigated the predictive value of F-18 FDG PET/CT for the prediction of KRAS mutation in different cancers [36, 38–40]. In patient with advanced non-small cell lung cancer (NSCLC), Caicedo et al. showed that NSCLC patients with tumors harboring KRAS mutations showed significantly higher F-18 FDG uptake than wild-type patients, as assessed in terms of SUV_{peak}, SUV_{max}, and SUV_{mean} [36]. Lee et al. demonstrated different SUV-derived variables separately, and none of these variables revealed FDG avidity to be an independent predictor of EGFR or KRAS mutation status in patients with NSCLC [38]. A large population-based study showed that the probability of EGFR mutation was inversely correlated with SUV_{max} but the probability of KRAS mutation was not correlated with SUV_{max} in lung adenocarcinoma (ICC) patients [39]. According to a study conducted in patients with intrahepatic cholangiocarcinoma, among the F-18 FDG PET parameters, metabolic tumor volume (MTV) using cutoff value of 38 showed 77.8% sensitivity, 67.9% specificity, and 68% accuracy for predicting KRAS mutation status [40]. They concluded that high MTV is associated with KRAS mutation and poor postoperative outcomes in patients with ICC, suggesting that the MTV of ICC measured by F-18 FDG PET may provide useful information for tumor molecular profiles and prognosis [40].

Conclusion

The current meta-analysis showed the low sensitivity and specificity of F-18 FDG PET/CT for the prediction of KRAS mutation in CRC patients. The DOR was very low and the likelihood ratio scatter-gram indicated that F-18 FDG PET/CT might not be useful for the prediction of KRAS mutation in CRC patients and not for its exclusion. Therefore, cautious application and interpretation should be paid to the

F-18 FDG PET/CT for the prediction of KRAS mutation in CRC patients.

Author contribution Kim SJ and Pak K contributed in protocol/project development. Kim SJ, Kim K, and Pak K contributed in data collection or management. Kim SJ and Kim K contributed in data analysis. Kim SJ, Pak K, and Kim K contributed in manuscript writing/editing.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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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