Preoperative staging of cholangiocarcinoma and biliary carcinoma using 18F-fluorodeoxyglucose positron emission tomography: a meta-analysis

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ABSTRACT

This meta-analysis was performed to determine the diagnostic accuracy of 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) in assessing primary cholangiocarcinoma (CCA) and CCA with lymph node and distant metastasis. A literature search for studies reporting the use of 18F-FDG-PET for preoperative work-up/staging in patients with CCA was performed. Diagnostic OR (DOR) was used as an index of diagnostic performance of FDG-PET/CT in predicting primary CCA, lymph node metastases, and distant metastases. The pooled DOR was 9.34 (95% CI 4.27 to 20.42) and the area under the summary receiver operating characteristic (SROC) curve was 0.8643 (SE=0.0362), indicating overall good discriminatory test performance in predicting primary CCA. Subgroup analyses based on the primary tumor site showed better diagnostic performance for intrahepatic CCA (DOR=54.44, 95% CI 13.44 to 220.49), both intrahepatic and extrahepatic CCA (DOR=32.96, 95% CI 1.41 to 768.80) and gallbladder cancer (DOR=12.93, 95% CI 1.97 to 84.80), than for extrahepatic CCA (DOR=2.55, 95% CI 0.71 to 9.20) and hilar CCA (DOR=2.75, 95% CI 0.17 to 43.72). The pooled DOR for the prediction of lymph nodes metastases in 10 studies was 11.34 (95% CI 4.79 to 26.80), with moderate heterogeneity (Cochran Q=15.14, p=0.0872, I^2=40.5%). The area under the SROC curve was 0.8584 (SE=0.0729). In conclusion, 18F-FDG-PET and PET/CT were found to be accurate in the evaluation of primary tumors, lymph node metastasis, and distant metastasis in patients with CCA.

Significance of this study

What is already known about this subject?

- No one imaging modality can accurately diagnose, stage, and monitor therapy in patients with cholangiocarcinoma (CCA).
- Positron emission tomography (PET) was shown to be superior to CT in detecting distant metastases.
- PET also exhibited a higher diagnostic accuracy for detecting CCA recurrence compared with CT.

What are the new findings?

- 18F-fluorodeoxyglucose18F-FDG)-PET displayed good diagnostic accuracy in the evaluation of primary tumors.
- 18F-FDG-PET displayed good diagnostic accuracy in the evaluation of metastasis.
- 18F-FDG-PET had better diagnostic accuracy in the evaluation of intrahepatic CCA compared with other subtypes of CCA, that is, extrahepatic or hilar CCA.

How might these results change the focus of research or clinical practice?

- This study provided evidence of the diagnostic accuracy of 18F-FDG-PET in patients with primary CCA and CCA with lymph node metastasis and/or distant metastasis. Thus, it may help physicians in selecting imaging modalities, as well as in monitoring therapy patients with CCA.

INTRODUCTION

Cholangiocarcinoma (CCA) is the most common biliary malignancy and is the second most common hepatic malignancy after hepatocellular carcinoma.[1 2] CCAs are divided into three types based on anatomic location, and include intrahepatic, extrahepatic (or perihilar), and distal extrahepatic. Intrahepatic CCA typically presents as more advanced disease, usually with a palpable mass. Perihilar and extrahepatic CCAs are more common and present with obstructive jaundice.[3] Perihilar tumors, the most common type of CCA, are also known as Klatskin tumors.[4 5] More than 95% of CCAs are ductal adenocarcinomas that arise from the epithelial lining of the biliary tree,[4] and patients often present with unresectable or metastatic disease.[6]

Development of CCA is associated with several risk factors, including parasitic infections, toxins, and hepatitis B and C infections.[4] Liver flukes and hepatolithiasis are important risk factors for CCA in areas where they are endemic. Bile duct cysts and primary sclerosing cholangitis (PSC) are associated with very high risk of CCA in Western countries.[4] Biliary ductal calculi occur in 20%–50% of patients with CCA; however, the association with gallstones is less marked with CCA than it is with gallbladder carcinoma. Similar to CCA,

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adenocarcinoma is the most common histological type of gallbladder carcinoma.[7]

Currently, no one imaging modality can accurately diagnose, stage, and monitor therapy in patients with CCA.[3] The best radiological method appears to be a combination of MRI and magnetic resonance cholangiopancreatography (MRCP), which has a sensitivity of 89% and specificity of 75%.[4 8] Even higher sensitivity and specificity can be achieved with MRCP using a heavily T2-weighted turbo spine echo MR sequence.[9] However, MRI is inferior to CT for detecting distant metastases, particularly in the lungs and bone.[6 10 11] Ultrasound, which is less expensive and more readily available than MRI, may miss small tumors and cannot accurately define tumor extent.[6 10 12 13] Contrast-enhanced CT has higher sensitivity for detecting CCA than ultrasound (up to 80%); however, often the extent of CCA is not well-defined.[6 10 12 13]

The role of positron emission tomography (PET) in the management of CCA is unclear. Although it does not seem useful for the detection of premalignant or early cancers, it can be useful in staging of CCA once it has been identified.[4] The infiltrating tumor type and lesions smaller than 1 cm are difficult to detect using PET.[14–16] Recent studies, however, have demonstrated a role for PET in diagnosing CCA associated with PSC.[17] Retrospective studies have also indicated that PET is superior to CT for detecting distant metastases. Thus, PET may have a role in detection of distant lesions, differentiation of benign from malignant strictures, and in the diagnosis of recurrent disease.[14] In addition, PET/CT has been shown useful in the setting of elevated tumor markers and negative or equivocal CT findings.[14 18] Furthermore, Corvera *et al*[19] identified recurrent CCA with PET in 76% of patients, and in two patients recurrence was identified on PET but not seen on other imaging studies.[19] Jadvar *et al*[20] reported that PET was also 94% sensitive and 100% specific for detecting CCA recurrence, while the sensitivity and specificity for CT were only 82% and 43%, respectively.

The objective of this study was to perform a meta-analysis to determine the diagnostic accuracy of 18F-fluorodeoxyglucose PET (18F-FDG-PET) and PET/CT in patients with primary CCA and CCA with lymph node metastasis and/or distant metastasis.

METHODS

Study selection criteria

We included prospective and retrospective studies in which 18F-FDG-PET or PET/CT was performed for preoperative work-up and staging in patients with CCA. Only studies of patients with CCA where quantitative diagnostic outcomes were available were included. Reviews, letters, comments, editorials, case reports, proceedings, personal communications, or non-English publications were excluded. In addition, any study that had no quantitative outcome was also excluded. Two independent reviewers identified studies using the search strategy, and a third reviewer was consulted when there was uncertainty regarding eligibility and a consensus was reached.

Search strategy

PubMed, CENTRAL, Embase, and ISI Web of Knowledge databases were searched until January 2015. The reference lists of relevant studies were hand-searched. Keywords used for the search included the following: (positron emission tomography) AND (18 F) AND (hilar cholangiocarcinoma OR biliary carcinoma); ((hilar cholangiocarcinoma OR cholangiocarcinoma) AND (biliary carcinoma OR bile duct cancer)) AND (positron emission tomography OR PET).

Data extraction

The following data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of subjects, subjects' age and gender, site of primary tumor, classification system used, tumor stage, PET device used, mean injected dose of 18F-FDG, and time between 18F-FDG injection and image acquisition (min).

Quality assessment

The quality of the included studies was assessed with the QUality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist.[21] The QUADAS-2 checklist consists of four domains relating to patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first three domains are also assessed in terms of applicability. The quality of included studies was independently appraised by two reviewers. Disagreements were resolved by a third reviewer.

Statistical analysis

Diagnostic ORs (DORs) were used as an index of diagnostic performance of FDG-PET/CT in predicting primary CCA, lymph nodes metastases, and distant metastases. DOR is defined as the ratio of odds of being tested positive in those who have a disease to odds of being tested positive in those who do not have a disease, and therefore it is a single index that summarizes statistics for the accuracy of a diagnostic test (ie, sensitivity and specificity). A DOR >1 indicated good diagnostic performance in distinguishing primary tumor, lymph nodes metastases, and distant metastases. Summary receiver operating characteristic (SROC) curves were also plotted for the overall testing accuracy. A larger area under the SROC curve, ranging from 0.5 to 1.0, indicates good diagnostic performance.

Pooled estimates of the DORs were calculated using the DerSimonian and Laird random-effects model, and a two-sided p value <0.05 was considered statistically significant. Heterogeneity was assessed using the Cochran's Q and the I^2 statistic. For the Q statistic, $p<0.10$ was considered statistically significant for heterogeneity. The I^2 statistic indicates the percentage of the observed between-study variability due to heterogeneity, and a value $\geq 50\%$ is considered to indicate large to extreme heterogeneity. In the current analysis, the random-effects model of analysis was used when large to extreme heterogeneity between studies was present.

Subgroup analysis was performed according to the site of primary tumor (eg, intrahepatic, extrahepatic, or hilar CCA). All statistical analyses were performed using the statistical software Meta-DiSc V.1.4 (XI Cochrane Colloquium, Barcelona, Spain).

Table 1 Characteristics of 18 selected studies

Study	Study design	Patients (n)	Age*	Male (%)	Site of primary tumor	Classification system used	Tumor stage	PET device used	Mean injected dose of 18F-FDG	Time between 18F-FDG injection and image acquisition (min)
Park *et al*[22]	Retrospective	18	62.4	28	Intrahepatic cholangiocarcinoma	Standard TNM classification	T1: 72% T2: 11% T3: 17%	PET/CT	370–480 MBq	45
Albazaz *et al*[23]	Retrospective	111	65 (24–87)†	41	Intrahepatic: 42% Extrahepatic: 31%			PET/CT	400 MBq	60
Choi *et al*[24]	Retrospective	39	64 (9)	72	Cholangiocarcinoma: 87%			PET/CT	370–555	60
Yamada *et al*[34]	Retrospective	73	68 (10.5)	63	Intrahepatic cholangiocarcinoma: 22% Hilar cholangiocarcinoma: 25% Extrahepatic bile duct cancer: 27% Gallbladder cancer: 19% Ampullary cancer: 7%	AJCC	I: 5.5% II: 11% III: 8% IV: 68%	PET	4.5 MBq/kg	50
Gu *et al*[36]	Retrospective	32	56	56	Hilar cholangiocarcinoma	Bismuth-Corlette	I: 9% II: 6% III: 38% IV: 47%	PET/CT	5.55 MBq/kg	60
Ruys *et al*[25]	Retrospective	30	62 (39–75)‡	47	Hilar cholangiocarcinoma: 87%	AJCCa staging	Stages 1–2: 22% Stages 3–4: 78%	PET/CT	250	60
Lee *et al*[26]	Retrospective	99	67 (35–91)‡	58.6	Gallbladder cancer: 16.2% Intrahepatic cholangiocarcinoma: 17.2% Extrahepatic cholangiocarcinoma: 49.5%			PET-CT	370–555	60
Li *et al*[27]	Retrospective	17	62‡	65	Hilar cholangiocarcinoma	UICC 6th edition		PET/CT	350	60
Seo *et al*[28]	Prospective	27	64 (41–78)†	56	Intrahepatic cholangiocarcinoma	UICC stage	I: 34% II: 37% III: 18% IV:1 1%	PET	296 (74)	50
Kim *et al*[29]	Prospective	123	60 (28–78)‡	65	Intrahepatic: 29.3% Extrahepatic: 70.7%			PET/CT	370	60
Moon *et al*[30]	Retrospective	54	59.2 (8.7)	63	Intrahepatic bile duct: 42.6% Perihilar cancer: 22.2% Common bile duct: 20.4%			PET	370	60
Furukawa *et al*[37]	Prospective	72	69 (28–84)‡	57	Extrahepatic: 89%		pT1: 8% pT2: 42% pT3: 18% pT4: 3%	PET	200–250	60
Corvera *et al*[19]	Retrospective	126	62 (23–84)‡	52	Extrahepatic: 32% Intrahepatic: 17%			PET	10–15 mCi	
Petrowsky *et al*[31]	Prospective	61	64 (35–81)‡	51	Gallbladder cancer: 23% Intrahepatic cholangiocarcinoma: 23% Extrahepatic cholangiocarcinoma: 54%			PET/CT	370 MBq	45
Anderson *et al*[16]	Retrospective	50	64	56	Gallbladder cancer: 23% Cholangiocarcinoma: 77%			PET	10 mCi	60
Kim *et al*[32]	Retrospective	21	57 (34–74)†	52	Hilar cholangiocarcinoma: 47.6% Peripheral cholangiocarcinoma: 52.4%			PET	370–555	60
Kato *et al*[35]		30	68 (32–82)†	70	Extrahepatic	TNM classification	pT1: 10% pT2: 37% pT3: 33%	PET		60
Kluge *et al*[33]	Prospective	54		54	Cholangiocarcinoma	UICC	II: 7.4% III: 1.9% IV: 38.9%	PET	370	50

*mean (SD).
†mean (range).
‡median (range).
18F-FDG, 18F-fluorodeoxyglucose; AJCC, American Joint Commission of Cancer; PET, positron emission tomography; TNM, Tumor Node Metastasis classification; UICC, Union for International Cancer Control.

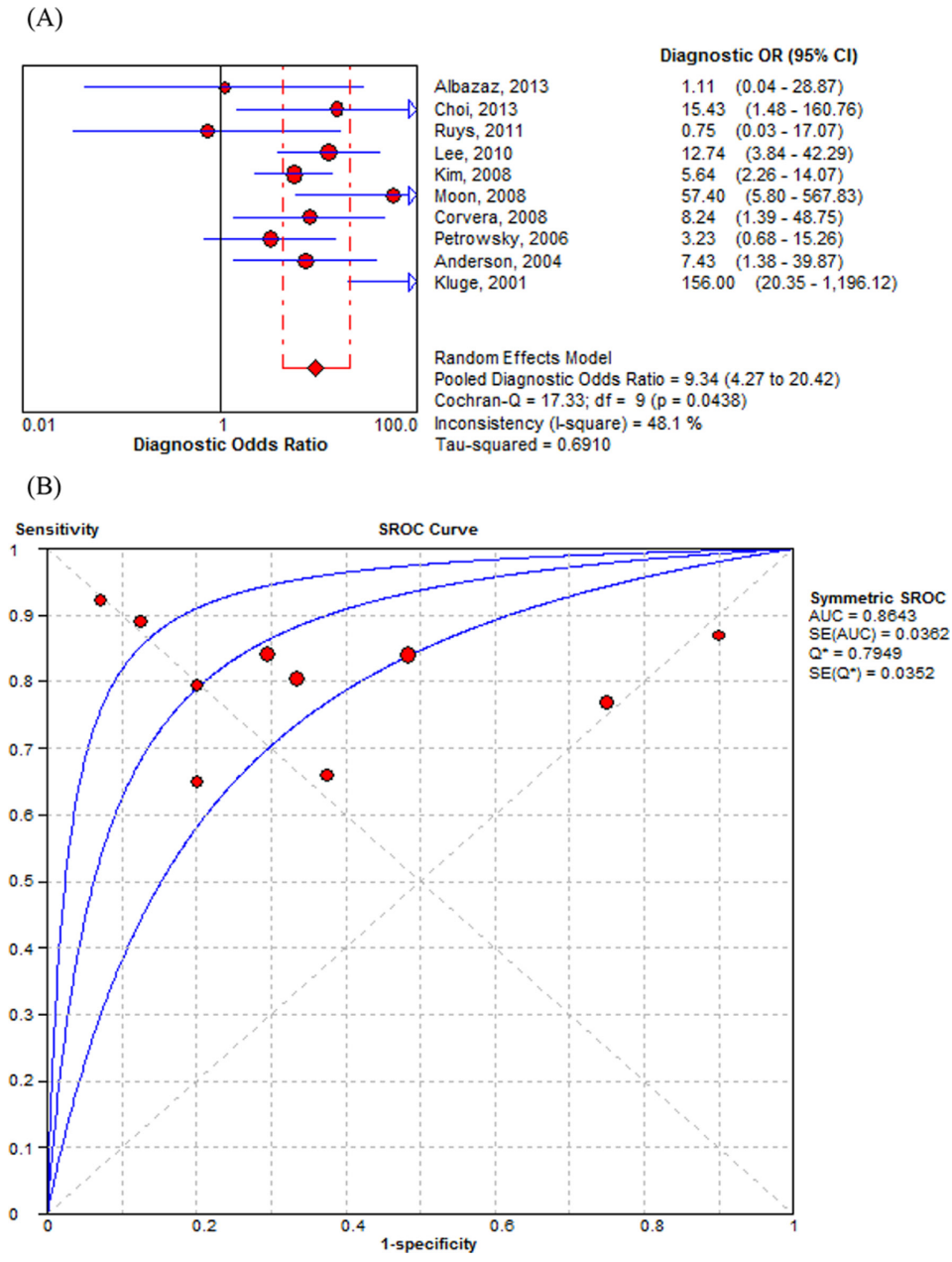

Figure 1 Forest plot of (A) diagnostic OR and (B) SROC curve for FDG-PET/CT in diagnosing primary cholangiocarcinoma. AUC, area under the curve; FDG-PET, fluorodeoxyglucose positron emission tomography; SROC, summary receiver operating characteristic.

RESULTS

Literature search

Of the initial 116 records identified through the database searches, 26 studies were assessed for eligibility. Once the full text of each of the 26 studies was reviewed, eight studies were excluded for the following reasons: (1) no diagnostic outcome (n=6), (2) recurrent and metastatic CCA (n=1), and (3) review study (n=1). Thus, a total of 18 studies[16 19 22–37] were included in the analysis.

Study characteristics

Of the 18 included studies, five[28 29 31 33 37] were prospective studies. The number of subjects across all 18 studies ranged from 17 to 126, with 28%–70% men. The mean or median age of subjects ranged from 57 to 68 years (table 1).

The characteristics of the primary tumors and imaging protocols are also summarized in table 1. Specific sites of the primary tumor were identified in most studies, and included intrahepatic, extrahepatic, and hilar CCA. In addition, four studies[16 26 31 34] included patients with gallbladder cancer. Eight studies[22 25 27 28 33–36] provided data on tumor stage according to various staging systems, such as the American Joint Commission of Cancer, Union for International Cancer Control, and Tumor Node Metastasis staging systems. For imaging protocols, nine studies[22–27 29 31 36] used a combined PET-CT system, while the remaining nine studies used PET. The duration from

Figure 2 Subgroup analysis for the diagnostic performance of FDG-PET/CT according to site of primary cholangiocarcinoma: (A) intrahepatic cholangiocarcinoma, (B) extrahepatic cholangiocarcinoma, (C) both intrahepatic and extrahepatic cholangiocarcinoma, (D) hilar cholangiocarcinoma and (E) gallbladder cancer. FDG-PET, fluorodeoxyglucose positron emission tomography.

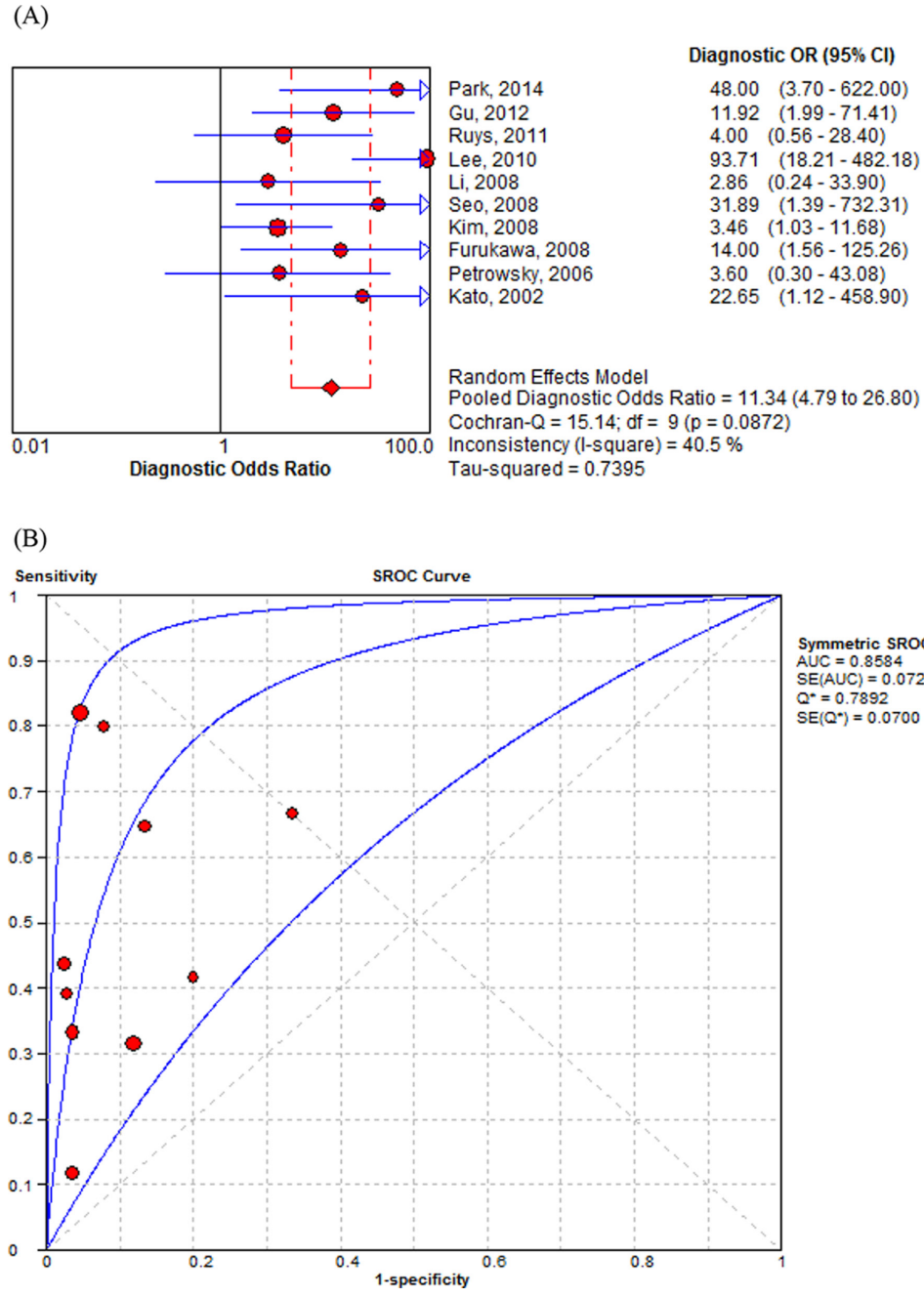

Figure 3 Forest plot of (A) diagnostic OR and (B) SORC curve for FDG-PET/CT in diagnosing lymph nodes metastases. AUC, area under the curve; FDG-PET, fluorodeoxyglucose positron emission tomography; SROC, summary receiver operating characteristic.

18F-FDG injection to image acquisition ranged from 45 to 60 min (table 1).

Diagnostic performance of FDG-PET/CT for primary CCA

There was significant heterogeneity across the 10 included studies (Cochran Q=17.33, p=0.0438, I^2=48.1%). Although the DOR was less than 1 in one study, the pooled DOR was 9.34 (95% CI 4.27 to 20.42; figure 1A) and the area under the SROC curve was 0.8643 (SE=0.0362; figure 1B), indicating overall good diagnostic performance. The pooled sensitivity and specificity were 0.805 (95% CI 0.769 to 0.838) and 0.698 (95% CI 0.606 to 0.780), respectively.

Subgroup analyses were further performed according to the primary tumor site. FDG-PET/CT exhibited significantly better test performance for diagnosing intrahepatic CCA (DOR=54.44, 95% CI 13.44 to 220.49; figure 2A), both intrahepatic and extrahepatic CCA (DOR=32.96, 95% CI 1.41 to 768.80; figure 2C), and gallbladder cancer (DOR=12.93, 95% CI 1.97 to 84.80; figure 2E), than for extrahepatic CCA (DOR=2.55, 95% CI 0.71 to 9.20, figure 2B) and hilar CCA (DOR=2.75, 95% CI 0.17 to 43.72; figure 2D).

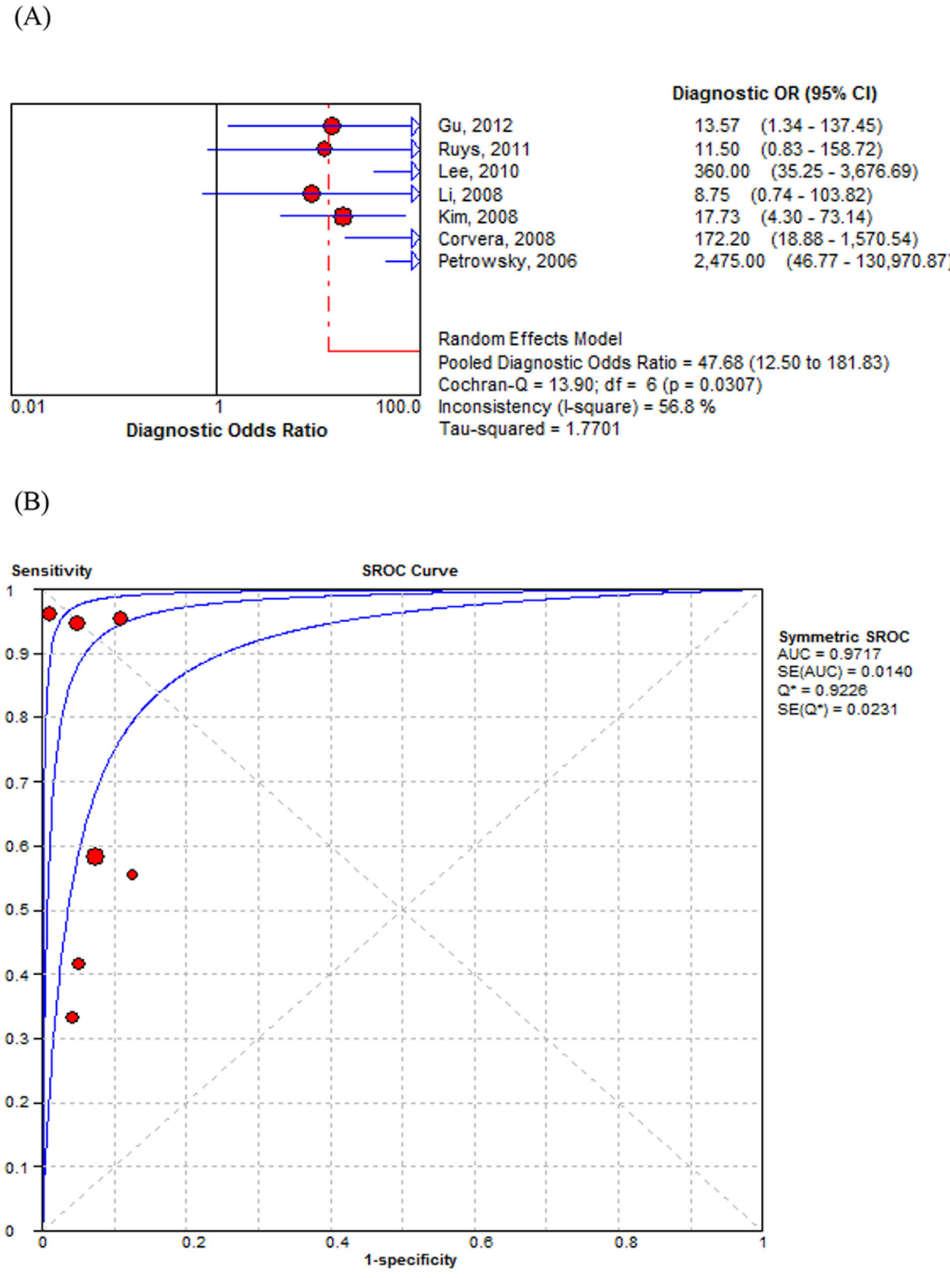

Figure 4 Forest plot of (A) diagnostic OR and (B) SROC curve for FDG-PET/CT in diagnosing distant metastasis. AUC, area under the curve; FDG-PET, fluorodeoxyglucose positron emission tomography; SROC, summary receiver operating characteristic.

Diagnostic performance of FDG-PET/CT for lymph node and distant metastases

The pooled DOR of 10 studies for the diagnosis of lymph node metastases was 11.34 (95% CI 4.79 to 26.80), with moderate heterogeneity (Cochran Q=15.14, p=0.0872, I^2=40.5%) (figure 3A). The area under the SROC curve was 0.8584 (SE=0.0729) (figure 3B). The summary sensitivity and specificity were 0.516 (95% CI 0.436 to 0.595) and 0.914 (95% CI 0.873 to 0.945), respectively.

Five out of seven studies that provided information on the diagnostic performance for distant metastases had a significant DOR. Large heterogeneity, however, was noted among the seven studies (Cochran Q=13.90, p=0.0307, I^2=56.8%). The pooled DOR was 47.68 (95% CI 12.50 to 181.83), and the area under the SROC curve was 0.9717 (SE=0.0140) (figure 4A,B).

Quality assessment

In general, the quality of included studies was good (figure 5). Risk of bias was high or unclear with regard to the index test for two studies, for the reference standard in two studies, and for flow and timing in four studies.

DISCUSSION

This meta-analysis showed that 18F-FDG-PET has good diagnostic accuracy for the evaluation of CAA and

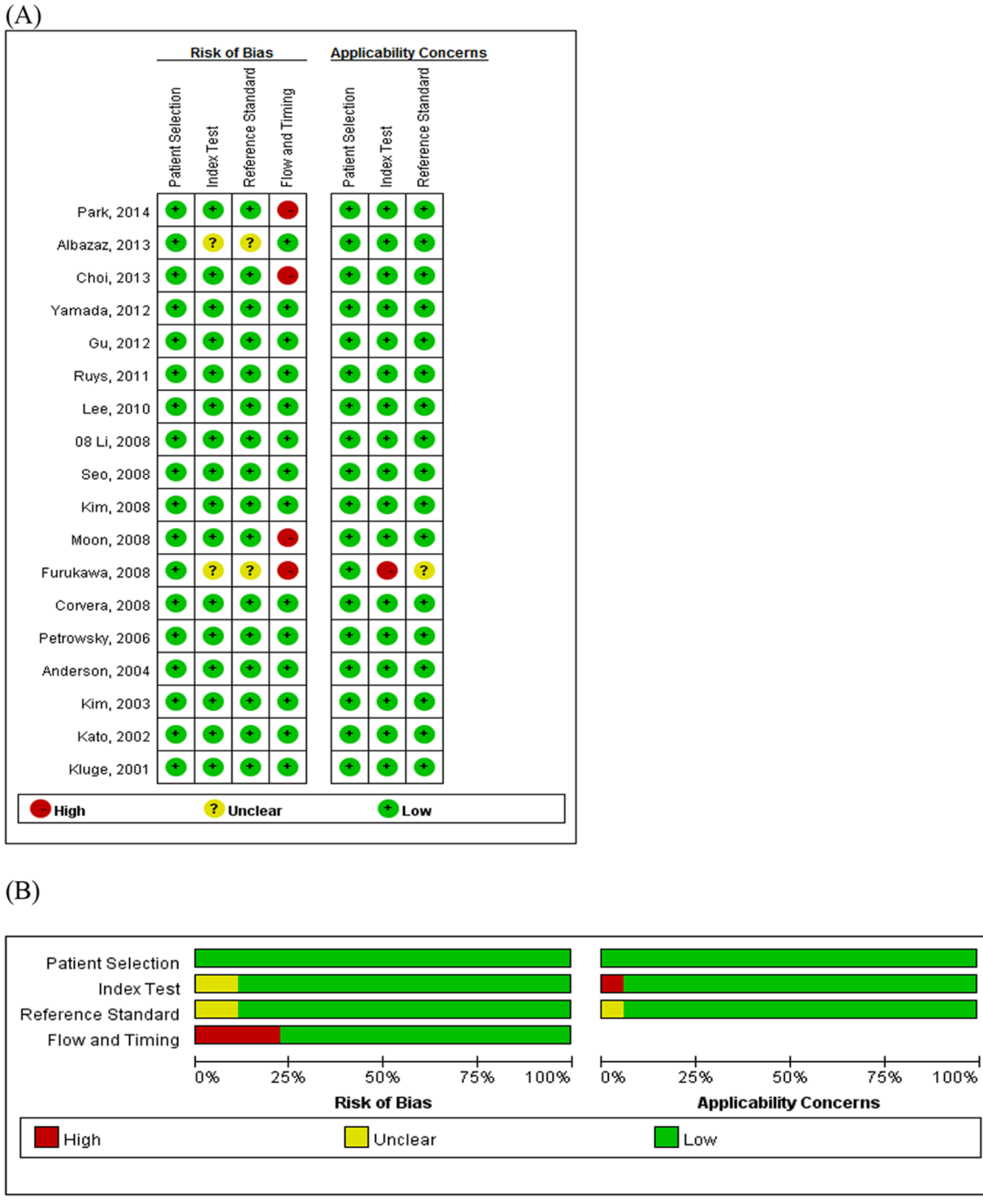

Figure 5 Quality assessment of (A) included studies and (B) proportion of studies with low, high, or unclear risk of bias.

metastasis, particularly distant metastasis. In subgroup analysis, 18F-FDG-PET exhibited better diagnostic accuracy in the evaluation of intrahepatic CCA compared with other subtypes of CCA, that is, extrahepatic or hilar CCA.

The variation in diagnostic accuracy among subgroups was evaluated by Kluge *et al*[33] who found that the reduced detection rate of extrahepatic tumors was dependent on the shape of the tumor. Corvera *et al*[19] analyzed intrahepatic versus extrahepatic CCA based on tumor size, and related the discrepancy in diagnosis among subgroups to differences in tumor size, as intrahepatic CCAs were larger and thus had a better chance of detection as compared with other types of CCA. Lan *et al*[3] also pointed out that varying detection rates may be the result of different clinical presentations between intrahepatic and extrahepatic CCA.

The variation in diagnostic accuracy among subgroups in our analysis may also have been due to the small number of studies included or the varied DOR among the included studies. The variation in DOR among studies evaluating extrahepatic CCA may have been related to the growth pattern of extrahepatic CCA compared with intrahepatic CCA. Extrahepatic CCA often presents as an infiltrating tumor without an evident tumor mass. It is therefore possible that this growth pattern does not reach the tumor

cell mass necessary to produce an identifiable positron emission signal.[31] A similar explanation was postulated by Anderson *et al*,[16] who found that PET was more sensitive for nodular-type CCA compared with infiltrating-type CCA (85% vs 18%). Choi *et al*[24] also concluded that the proportion of infiltrative-type tumors may cause a discrepancy in the diagnostic performance of PET or PET/CT. Infiltrating-type tumors are difficult to detect by PET because the resolution is limited, and normal liver parenchyma has a relatively high background uptake.[14–16] Infiltrating tumors have also been associated with false-negative results because of low FDG accumulation.[14 32]

It has been commonly accepted that PET/CT offers no real advantages for the detection and diagnosis of primary CCA as compared with other imaging methods.[14 15 31] However, one recent study showed PET/CT to be accurate in primary CCA evaluation, especially for intrahepatic compared with extrahepatic CCA,[38] a finding that is similar to that of the current study.

The current results showed that 18F-FDG-PET was especially accurate in the evaluation of distant CCA metastasis. Other studies have reported that PET/CT exhibited higher accuracy for detecting regional lymph node and distant metastases.[6 33] Several retrospective studies have shown PET to be superior to CT in detecting distant metastases. A prospective study by Kim *et al*[29] showed that PET was significantly more accurate for identifying distant metastasis compared with CT (58% vs 0%). Other studies have confirmed that PET is able to detect metastases that are not detected by other imaging methods,[3 30] and influences the management of up to 25% of patients.[3 19]

Compared with other meta-analysis,[38 39] our study is unique in that we used DOR[40] and SROC (combined sensitivity and specificity) to examine the diagnostic performance of 18F-FDG-PET. We also performed subgroup analysis of different locations of the primary tumor, lymph node metastasis, and distant metastasis. In addition, we also performed a subgroup analysis for gallbladder cancer. The rate of peritoneal metastasis in patients with gallbladder cancer ranges from 30% to 75%, and metastasis risk is strongly correlated with the presenting T stage.[41] We also tested for homogeneity as part of our study. A χ^2-based test of homogeneity was performed using Cochran's Q statistic and I^2. The diagnostic performance of FDG-PET/CT in predicting lymph node and distant metastases showed moderate heterogeneity, although the diagnostic performance of FDG-PET/CT in predicting primary CCA showed significant heterogeneity. The quality of each included study was also assessed using the QUADAS-2 checklist,[21] and in general the quality of the included studies was good.

Our study had several limitations. Most of the included studies were retrospective, and this may affect the robustness and reliability of the conclusions. In addition, we did not compare PET with other imaging modalities such as MRI or CT. Image interpretation was subjective, even though reviewed by two experienced reviewers, and the quantification scales were also inconsistent among studies, which may have led to heterogeneity among included studies.

In conclusion, despite the limitations of the analysis, 18F-FDG-PET and PET/CT were found to be accurate in the diagnosis of primary CCA, particularly intrahepatic CCA, as well as lymph node metastasis and distant metastasis. To confirm our conclusions, further high-quality randomized controlled trials comparing PET with other imaging modalities are warranted.

Contributors J-HH: study concepts, study design, definition of intellectual content, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis and manuscript preparation. J-T: definition of intellectual content, literature research, data acquisition, data analysis and statistical analysis. C-HL: literature research and manuscript editing. Y-YC: study design and clinical studies. N-JL: guarantor of integrity of the entire study, manuscript editing and manuscript review. All authors have read and approved the final version to be submitted.

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