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Comparison of magnetic resonance imaging and 18-fludeoxyglucose positron emission tomography/computed tomography in the diagnostic accuracy of staging in patients with cholangiocarcinoma

A meta-analysis

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Abstract

Background: Accurate clinical staging of patients with cholangiocarcinoma (CCA) has a significant impact on treatment decisions. In this study, we aimed to compare the diagnostic value of magnetic resonance imaging (MRI) and 18-fludeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) for staging of CCA.

Methods: We performed comprehensive systematic search in Web of Science (including MEDLINE) and Excerpta Medica Database for relevant diagnostic studies in accordance with the preferred reporting items for systematic reviews and meta-analysis statement. Based on data extracted from patient-based analysis, we calculated the pooled sensitivity and specificity with the 95% confidence intervals (CIs). In addition, the publication bias was assessed by Deek funnel plot of the asymmetry test. The potential heterogeneity was explored by threshold effect analysis and subgroup analyses.

Results: Thirty-two studies with 1626 patients were included in present analysis. In T stage, the pooled sensitivity and specificity of MRI were 0.90 (95% CI 0.86–0.93), 0.84 (95% CI 0.73–0.91) respectively. The pooled sensitivity and specificity of ^{18}F-FDG PET/CT were 0.91 (95% CI 0.83–0.95) and 0.85 (0.64–0.95) respectively. In N stage, the pooled sensitivity and specificity of MRI were 0.64 (95% CI 0.52–0.74) and 0.69 (95% CI 0.51–0.87) respectively. The pooled sensitivity and specificity of PET/CT were 0.52 (95% CI 0.37–0.66) and 0.92 (95% CI 0.79–0.97) respectively. In M stage, the pooled sensitivity and specificity of ^{18}F-FDG PET/CT were 0.56 (95% CI, 0.42–0.69) and 0.95 (95% CI, 0.91–0.97) respectively. The Deek test revealed no significant publication bias. No threshold effect was identified. The subgroup analyses showed that pathological type (extrahepatic cholangiocarcinoma vs hilar cholangiocarcinoma/intrahepatic cholangiocarcinoma), country (Asia vs non-Asia) and type of MRI (1.5T vs. 3.0T) were potential causes for the heterogeneity of MRI studies and country (Asia vs non-Asia) was a potential source for ^{18}F-FDG PET/CT studies.

Conclusion: The analysis suggested that both modalities provide reasonable diagnostic accuracy in T stage without significant differences between them. We recommend that both modalities be considered based on local availability and practice for the diagnosis of primary CCA tumors. In N stage, the diagnosis of lymph node metastasis (N) of CCA is still limited by MRI and ^{18}F-FDG PET/CT, due to unsatisfactory diagnostic accuracy of both. Nevertheless, ^{18}F-FDG PET/CT can be used to confirm lymph node metastasis while a negative result may not rule out metastasis. Furthermore, ^{18}F-FDG PET/CT have a low sensitivity and a high specificity for detection of distant metastasis.

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XH and JY contributed equally to this work.

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Abbreviations: ^{18}F-FDG PET/CT = 18-fludeoxyglucose positron emission tomography/computed tomography, CCA = cholangiocarcinoma, CI = confidence interval, MRI = magnetic resonance imaging, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SROC = receiver-operating characteristic curves, TNM = Tumor-Node-Metastasis.

Keywords: 18-fludeoxyglucose positron emission tomography/computed tomography, cholangiocarcinoma, meta-analysis, magnetic resonance imaging, TNM staging

1. Introduction

Cholangiocarcinoma (CCA) is an exceptionally aggressive cancer arising from the biliary duct epithelium and CCA represent approximately 3% to 5% of all malignancies of the gastrointestinal system.[1] Importantly, data from the past 25 years indicate an increase in morbidity and mortality, largely due to increased diagnosis of intrahepatic CCA.[2,3] The only potentially curative treatment option for patients with CCA is surgical resection.[4–6] Unfortunately, patients with CCA usually appear in advanced stages when curative resection is impossible, and the vast majority of unresectable patients die within 6 months to 1 year of diagnosis.[7] Meanwhile, radiotherapy and chemotherapy are also recommended to improve survival of patients with CCA. The selected treatment, such as surgery, radiotherapy, and chemotherapy, depends primarily on the TNM staging.[8] Therefore, accurate diagnosis and staging of CCA is necessary for making the optimal treatment planning.

Currently, magnetic resonance imaging (MRI), combined 2-[18 F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) are available for noninvasive CCA staging. MRI with magnetic resonance cholangiopancreatography, contrast-enhanced and diffusion-weighted imaging are generally considered as the best diagnostic tool in the diagnosis of CCA due to its high contrast, multiplanar nature, and ability to characterize parenchyma and biliary tract.[9–12] PET/CT, which combines the anatomical detail and functional statue, has a significant impact on the clinical management decisions of CCA by detecting potential tumor activity and allowing early identification of occult metastases.[13–16] Although PET/CT is less available than MRI, it is increasingly used in clinical practice due to the suspected superior diagnostic performance in detecting distant metastases. In present study, a meta-analysis of published studies was performed to evaluate the diagnostic performance of MRI and ^{18}F-FDG PET/CT in patients with CCA.

2. Methods

This meta-analysis was conducted based on the checklists of the preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies statement.[17] Ethical approval and patient consent were not necessary, as the analysis was performed based on data available in published articles.

2.1. Search strategy

Two reviewers independently searched for relevant studies published in Web of Science (including MEDLINE) and Excerpta Medica Database between January 2000 and September 2019. The following medical subject heading terms and keywords were used to identify related studies: ("cholangiocarcinoma" OR "cholangiocellular carcinoma" OR "carcinoma, cholangiocellular" OR "extrahepatic cholangiocarcinoma" OR "intrahepatic cholangiocarcinoma") AND ("magnetic resonance imaging" OR "magnetic resonance cholangiopancreatography" OR "MRI" OR "positron emission tomography/computed tomography" OR "positron emission tomography-computed tomography" OR "PET-CT" OR "PET/CT" OR "18F-FDG") AND ("Neoplasm Staging" OR "Staging" OR "diagnosis" OR "detection").

2.2. Eligibility criteria

The inclusion criteria were as follows:

(1) studies were published in the English language;
(2) the diagnostic role of MRI or ^{18}F-FDG PET/CT in the CCA Tumor-Node-Metastasis (TNM) staging has been identified in the literature;
(3) the reference standard included surgical or pathological confirmation;
(4) the studies had 2×2 contingency tables or the reported data was sufficient to form a 2×2 contingency table for true-positive, true-negative, false-positive, and false negative values;
(5) the study population (CCA patients with reference standard) included at least 10 patients; and
(6) the studies were based on per-patient statistics.

The exclusion criteria were as follows:

(1) combining patients with gallbladder cancer or hepatocellular carcinoma, and specific information on patients with CCA could not be retrieved;
(2) studies with duplicated or unqualified data, or included animals as research objects,
(3) case reports, meeting abstracts, reviews.

2.3. Data extraction

Two reviewers independently extracted data from each eligible study, and any disagreement can be resolved through discussion or appeal to a third reviewer. The following information was extracted from the included studies: first author, year of publication, study design (prospective or retrospective), country of the study, study population characteristics, diagnostic imaging techniques, and reference standards. Data on true-positive, false-positive, true-negative, and false-negative were also extracted.

2.4. Statistical analysis

We obtained the pooled sensitivities and specificities of ^{18}F-FDG PET/CT and MRI, as well as their 95% confidence intervals (CIs) using the weighted average method. We also calculated the pooled positive and negative likelihood ratios (PLR and NLR) with their 95% CIs. Finally, the data were summarized in receiver-operating characteristic curves (SROC), with the area under the curve (AUC) obtained.

We used the I^2 index to assess the heterogeneity between studies in terms of the sensitivity and specificity. $I^2 > 50\%$ represented substantial heterogeneity, in which case we used the random effect model. When heterogeneity was noted, subgroup analysis was conducted according to pathological type (extrahepatic cholangiocarcinoma vs hilar cholangiocarcinoma/intrahepatic cholangiocarcinoma), sample size (≥50 vs <50), type of MRI (1.5T vs 3.0T) and country (Asia vs non-Asia) to explore the sources of heterogeneity. However, we did not conduct a meta-regression because the number of included studies was small. The publication bias was examined by Deek funnel plot.

The statistical computations were performed using Stata software version 14.0 and Revman 5.3. For *P*-value, the level of statistical significance was set to 5%.

3. Results

3.1. Study characteristics

We selected 32 eligible studies with a total of 1626 patients and the flowchart describing the study selection is shown in Figure 1. Twenty-two studies involving T stage (primary tumor) included 14 studies with MRI and 9 studies with ^{18}F-FDG PET/CT. N stage (lymph node metastasis) analysis included 15 studies, of which 5 were performed by MRI and 11 by ^{18}F-FDG PET/CT. Five studies were analyzed in M stage (distant metastasis), all of which were ^{18}F-FDG PET/CT, but no MRI related studies.

The principal characteristics of the 32 eligible studies[13,14,16,18–44] are summarized in Table 1. All of these studies reported the results on a per-patient basis. The studies were published between 2001 and 2019 from China, Korea, Japan, Austria, Thailand, Netherlands, Germany, Canada, Italy, Switzerland, and India. The sample size ranged from 15 to 131 patients, and the median sample size was 50 patients, of which 16 articles had a sample size of more than 50, while 16 articles had a sample size of less than 50.

3.2. Quality assessment

Using the revised tool for Quality Assessment of Diagnostic Accuracy-2 to analyze the quality of the studies[45] The

Figure 1. Flowchart of study selection process.

Table 1

The principal characteristics of eligible studies.

Study	Year	Country	No. of patients	Female/male	Median age	Study design	Examination	Reference standard
Zou	2019	China	131	29/102	NA	R	MRI	HP
Li	2018	China	53	17/36	68	R	PET/CT	HP
Ma	2018	China	28	NA	63.1	R	PET/CT	HP
Han	2017	Korea	54	24/30	67	R	MRI	HP
Lee	2017	Korea	65	27/38	NA	R	PET/CT	HP
Songthamwat	2017	Thailand	51	18/33	61.5	R	MRI	HP
Wengert	2017	Austria	64	NA	NA	R	MRI	HP
Joo	2016	Korea	106	22/84	58.4	R	MRI	HP
Jiang	2016	China	65	NA	69.2	NA	MRI,PET/CT	HP
Adachi	2015	Japan	67	NA	71	R	PET/CT	HP
Choi	2015	Korea	81	22/59	67.3	R	MRI	HP
Yoo	2014	Korea	60	22/38	NA	R	MRI	HP
Choi	2013	Korea	39	NA	NA	R	PET/CT	HP
Sun	2013	Korea	69	17/52	65.4	R	MRI	HP
Alkhawaldeh	2011	Germany	65	26/39	63	R	PET/CT	HP
Ruys	2011	Netherlands	30	16/14	62	R	PET/CT	HP
Cui	2010	China	56	22/34	61	P	MRI	HP
Kim	2010	Korea	20	9/11	63.8	R	MRI	HP
Albiin	2008	Canada	45	NA	57	NA	MRI	HP
Masselli	2008	Italy	15	4/11	58	R	MRI	HP
Seo	2008	Japan	35	NA	NA	R	PET/CT	HP
Kim	2008	Korea	123	43/80	60	P	MRI,PET/CT	HP
Li	2008	Germany	17	6/11	62	R	PET/CT	HP
Vogl	2006	Germany	33	NA	66	P	MRI	HP
Petrowsky	2006	Switzerland	47	NA	NA	P	PET/CT	HP
Hanninen	2005	Germany	30	14/16	59	P	MRI	HP
Krasnova	2005	Germany	30	13/17	59	R	MRI	HP
Reinhardt	2005	Germany	20	10/10	63	R	MRI	HP
Vaishali	2004	India	30	11/19	48.9	P	MRI	HP
Kim	2003	Korea	21	10/11	57	R	PET/CT	HP
Kato	2002	Japan	30	9/21	68	NA	PET/CT	HP
Kluge	2001	Germany	46	21/25	63	R	PET/CT	HP

HP = histopathology, NA = not available, No. = number, P = prospective, R = retrospective.

methodological results are shown in Figure 2. Patient selection was judged to be at low risk of bias in 15 of the studies and at high or unclear risk of bias in the remaining 17 studies. The majority of studies that were judged to have a high or unclear risk of bias did not provide information on consecutive or random enrollment, nor did they avoid case-control designs. For the index tests and reference standards, common deficiencies focused on failing to provide blinding method or not using it in interpreting the results. In terms of the flow and timing, 13 articles showed unclear or high risk due to the lack of an explicit description of the time interval between the index test and reference standard, and the failure to include all patients in the analysis.

3.3. Diagnostic accuracy: diagnosis of primary tumor (T)

The pooled results are shown in Figures 3 and 4. In MRI, combined with data from 14 eligible studies, the sensitivity was 0.90 (95% CI 0.86–0.93) and the specificity was 0.84 (95% CI

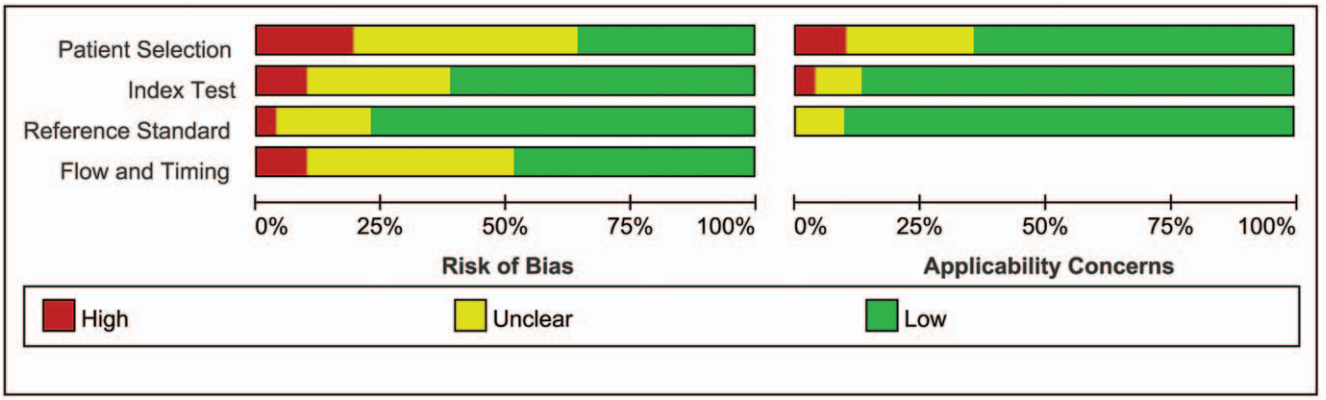

Figure 2. Quality analysis of the included studies based on QUADAS-2. QUADAS-2 = the revised tool for Quality Assessment of Diagnostic Accuracy.

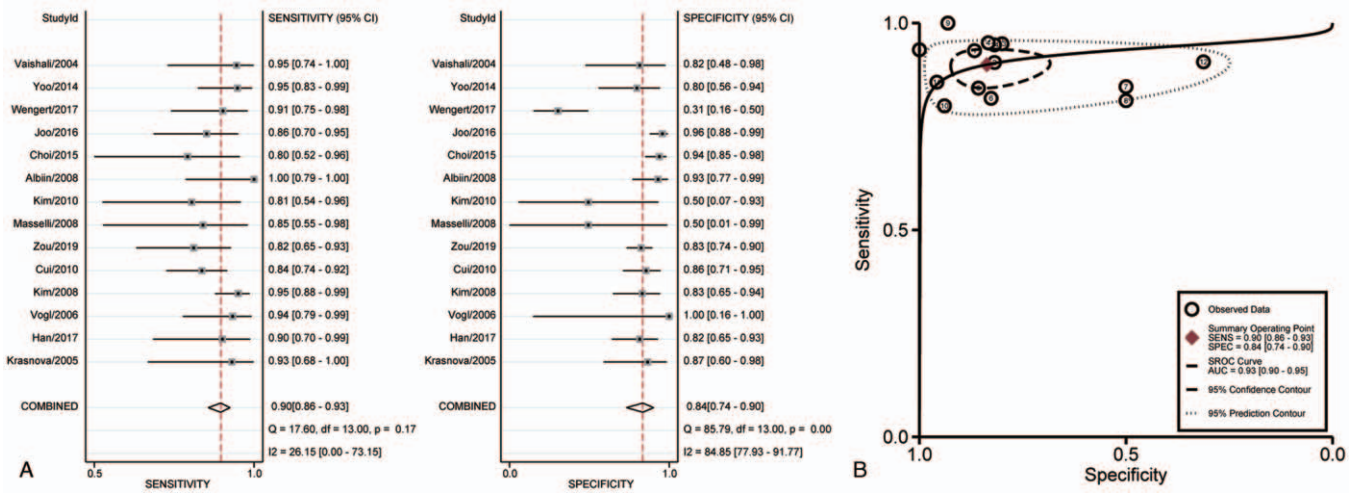

Figure 3. Diagnosis of primary tumor (T) by MRI. (A) Forest plot for pooled sensitivity and specificity. (B) SROC curve. MRI = magnetic resonance imaging, SROC = receiver-operating characteristic curve.

0.73–0.91). As for ^{18}F-FDG PET/CT, the pooled sensitivity and specificity of 9 studies included were 0.91 (95% CI 0.83–0.95) and 0.85 (95% CI 0.64–0.95), respectively. The overall PLR and NLR were 5.51 (95% CI 3.21–9.47) and 0.12 (95% CI3.21–9.47) for MRI respectively. For ^{18}F-FDG PET/CT, the overall PLR was5.88 (3.17–8.93), and the NLR was 0.11 (0.05–0.23). The diagnostic odds ratio was 44.79 (21.72–92.37) for MRI and 53.04 (11.26–149.83) for ^{18}F-FDG PET/CT. SROC curve showed AUC of 0.93 and 0.94 for MRI (Fig. 3B) and ^{18}F-FDG PET/CT (Fig. 4B), respectively. There were no difference in specificity, sensitivity, PLR, and NLR between MRI and ^{18}F-FDG PET/CT ($P > .05$), and both of them had ideal diagnostic value for primary tumor.

As shown in Figures 3 and 4, strong heterogeneity in sensitivity and specificity was found in these studies ($I^2 > 80\%$). Only MRI related studies showed low heterogeneity ($I^2 = 27.95$). The Spearman rank correlation test indicated threshold effect did not occur in either MRI or ^{18}F-FDG PET/CT studies (coefficient = 0.037 and coefficient = 0.311, respectively). The results of the subgroup analyses are provided in Table 2. For MRI, data from 8 studies showed that 3.0T MRI have higher specificity (0.91 vs 0.72, $P < .05$), and non-Asia group based on 6 studies indicated higher specificity for T staging (0.93 vs 0.79, $P < .05$). With regard to ^{18}F-FDG PET/CT studies, all the factors included in subgroup analyses could not explain its heterogeneity ($P > .05$).

3.4. Diagnostic accuracy: diagnosis of lymph node metastases (N)

The pooled sensitivity and specificity of MRI from 5 studies was 0.64 (95% CI, 0.52–0.74) and 0.69 (95% CI, 0.51–0.82), Figure 5A. Based on 11 studies, the sensitivity of ^{18}F-FDG PET/CT was 0.52 (95% CI, 0.37–0.66) and the specificity was 0.92 (95% CI, 0.79–0.97), Figure 6A. The overall PLR and NLR were 2.03 (95% CI, 1.15–3.59) and 0.53 (95% CI, 0.35–0.80) for MRI respectively. For ^{18}F-FDG PET/CT, the overall PLR was

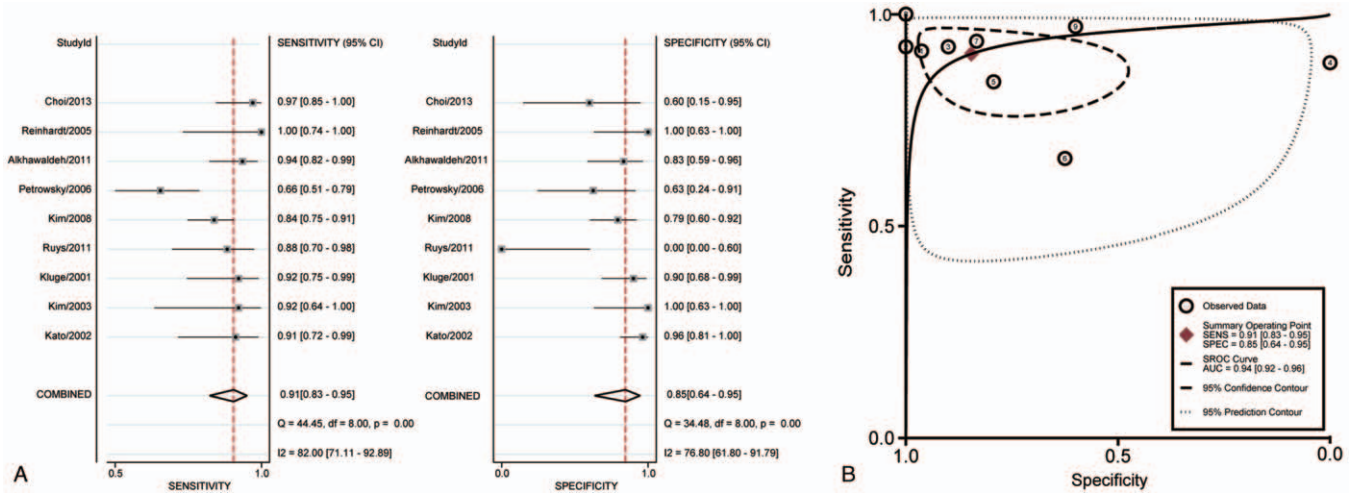

Figure 4. Diagnosis of primary tumor (T) by PET/CT. (A) Forest plot for pooled sensitivity and specificity. (B) SROC curve. PET/CT = positron emission tomography/computed tomography, SROC = receiver-operating characteristic curve.

Table 2

The results of subgroup analysis for primary tumor (T).

Factors	NO. of studies	NO. of patients	Sensitivity, % (95% CI)	Specificity, % (95% CI)
MRI				
Pathological type				
eCCA	4	304	0.88 (0.81–0.92)	0.85 (0.74–0.92)
hCCA/iCCA	9	496	0.87 (0.82–0.91)	0.88 (0.80–0.93)
Sample size				
<50	6	173	0.90 (0.82–0.95)	0.79 (0.61–0.90)
≥50	8	722	0.89 (0.84–0.93)	0.83 (0.70–0.92)
Type of MRI				
1.5T	4	190	0.88 (0.81–0.92)	0.72 (0.61–0.83)
3.0T	8	540	0.91 (0.86–0.95)	0.91 (0.82–0.94)
Country				
Asia	8	678	0.90 (0.83–0.94)	0.79 (0.74–0.85)
non-Asia	6	217	0.92 (0.85–0.96)	0.93 (0.87–0.98)
PET/CT				
Pathological type				
eCCA	4	182	0.90 (0.77–0.98)	0.79 (0.65–0.94)
hCCA/iCCA	4	106	0.92 (0.83–0.97)	0.74 (0.54–0.88)
Sample size				
<50	5	156	0.94 (0.87–0.98)	0.87 (0.74–0.97)
≥50	4	294	0.86 (0.72–0.94)	0.83 (0.76–0.91)
Country				
Asia	4	233	0.93 (0.84–0.97)	0.88 (0.77–0.93)
Non-Asia	5	216	0.90 (0.78–0.97)	0.81 (0.76–0.85)

eCCA = extrahepatic cholangiocarcinoma, hCCA/iCCA = hilar cholangiocarcinoma/ intrahepatic cholangiocarcinoma, NA = not available, No. = number.

10.22 (6.50–22.52), and the NLR was 0.52 (0.39–0.70). The diagnostic odds ratio was 3.83 (1.47–10.00) for MRI and 11.90 (4.38–32.32) for ^{18}F-FDG PET/CT. SROC curve showed AUC of 0.69 and 0.77 for MRI (Fig. 5B) and ^{18}F-FDG PET/CT (Fig. 6B), respectively. Overall, there was no significant difference between MRI and PET in sensitivity. Whereas, the specificity of ^{18}F-FDG PET/CT was significantly higher than that of MRI, (0.92 vs 0.52, $P < .05$). Based on the above-mentioned results, ^{18}F-FDG PET/CT positive findings can diagnose lymph node metastases while negative findings might not exclude the metastases. As for MRI, it can neither rule in nor rule out the disease.

There was also significant heterogeneity in sensitivity and specificity between studies (Figs. 5A and 6A). According to the Spearman rank correlation test, there was no threshold effect in both MRI and ^{18}F-FDG PET/CT studies (coefficient = 0.244 and coefficient = 0.357, respectively). Limited by the small sample of included MRI studies, we only performed a subgroup analyses of ^{18}F-FDG PET/CT based on pathological type, sample size, and country. The analysis results suggested Asia-group has higher sensitivity than non-Asia group (0.63 vs 0.35, $P < .05$), Table 3.

3.5. Diagnostic accuracy: diagnosis of distant metastases (M)

Data from 5 studies demonstrated that the pooled sensitivity and specificity of ^{18}F-FDG PET/CT were 0.56 (95% CI, 0.42–0.69) and 0.95 (95% CI, 0.91–0.97) respectively, Figure 7A. In addition, the overall PLR was 11.53 (5.83–22.79), NLR was 0.48 (0.34–0.63), and the overall AUC was 0.90, Figure 7B. No studies using MRI to detect distant metastasis were found. There was no strong heterogeneity in sensitivity and specificity between studies. According to the pooled sensitivity and specificity, as well as PLR and NLR, the positive findings of ^{18}F-FDG PET/CT can diagnose distant metastases while negative findings alone may not exclude distant metastases.

3.6. Publication bias

As shown in Figure 8, there were no significant publication biases by Deek funnel plot asymmetry tests.

4. Discussion

This meta-analysis aims to evaluate the role of MRI and ^{18}F-FDG PET/CT in the staging of CCA. To the best of our knowledge, this is the first meta-analysis of the accuracy of diagnostic test for comparing MRI and ^{18}F-FDG PET/CT in staging CCA. In this analysis, both MRI and ^{18}F-FDG PET/CT are beneficial to the detection of primary tumor in CCA without significant statistical differences in diagnostic capacity. This result is consistent with Annunziata study,[46] and supports the use of ^{18}F-FDG PET/CT in the diagnosis of primary tumor in CCA.

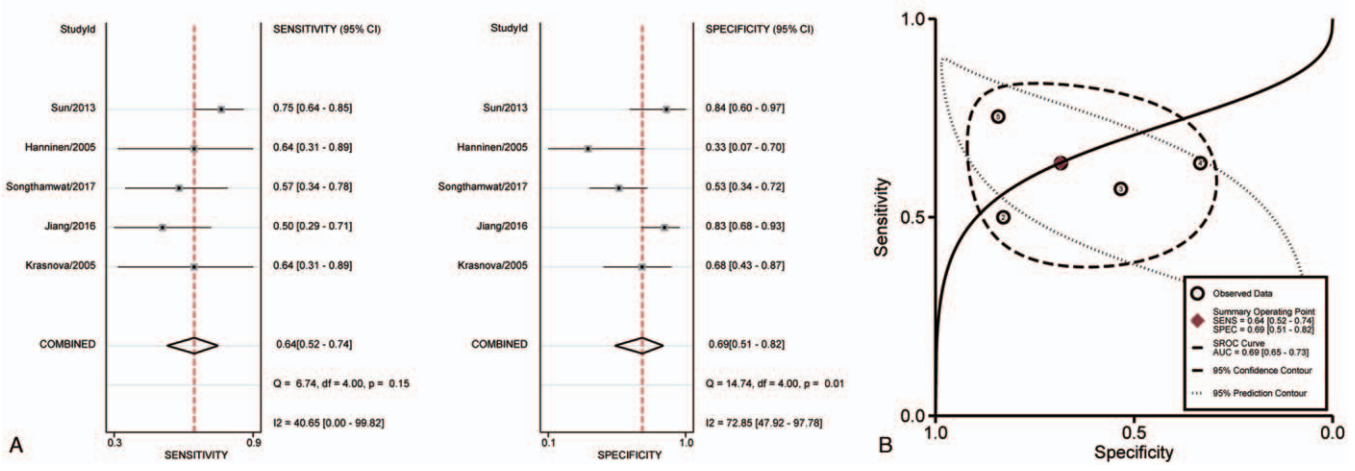

Figure 5. Diagnosis of lymph node metastases (N) by MRI. (A) Forest plot for pooled sensitivity and specificity. (B) SROC curve. MRI = magnetic resonance imaging, SROC = receiver-operating characteristic curve.

Table 3

The results of subgroup analysis for lymph node metastases (N).

Factors	No. of studies	No. of patients	Sensitivity, % (95% CI)	Specificity, % (95% CI)
PET/CT				
Pathological type				
eCCA	1	87	NA	NA
hCCA/iCCA	7	330	0.62 (0.48–0.74)	0.89 (0.78–0.97)
Sample size				
<50	6	180	0.46 (0.38–0.57)	0.96 (0.91–1.00)
≥50	5	337	0.57 (0.39–0.73)	0.91 (0.85–0.94)
Country				
Asia	6	328	0.63 (0.46–0.77)	0.88 (0.82–0.92)
non-Asia	5	187	0.35 (0.21–0.52)	0.94 (0.46–0.98)

eCCA = extrahepatic cholangiocarcinoma, hCCA/iCCA = hilar cholangiocarcinoma/ intrahepatic cholangiocarcinoma, NA = not available, No. = number.

Some studies have suggested that nodal status is an important prognostic factor for the survival of patients diagnosed with CCA, and the identification of nodal status has a significant impact on treatment management.[47–49] Our analysis indicates the role of MRI for diagnosis of lymph node metastases (N) is poor because of its limited sensitivity, specificity, PLR, and NLR. While, based on the pooled sensitivity and NLR, ^{18}F-FDG PET/CT findings could be only helpful in diagnosing metastatic lymph nodes, not useful to exclude metastatic lesions. Overall, compared with MRI, ^{18}F-FDG PET/CT seems to be more effective in assessing metastatic lymph nodes in patients with CCA, but negative results should not be used as a basis for exclusion of lymph node dissection.

The incidence of distant metastasis of CCA is relatively high, and the common sites of distant metastasis include liver, lung, bone, and brain.[50] The diagnosis and surgery at distant metastatic sites are helpful to improve cancer-specific survival.[6] Previous studies have shown that PET/CT is particularly valuable in detecting unsuspected distant metastases.[24] Our analysis shows that ^{18}F-FDG PET/CT is beneficial to diagnose distant metastases, but not useful to exclude metastatic lesions, which means that some patients with distant metastases may be misdiagnosed as negative.

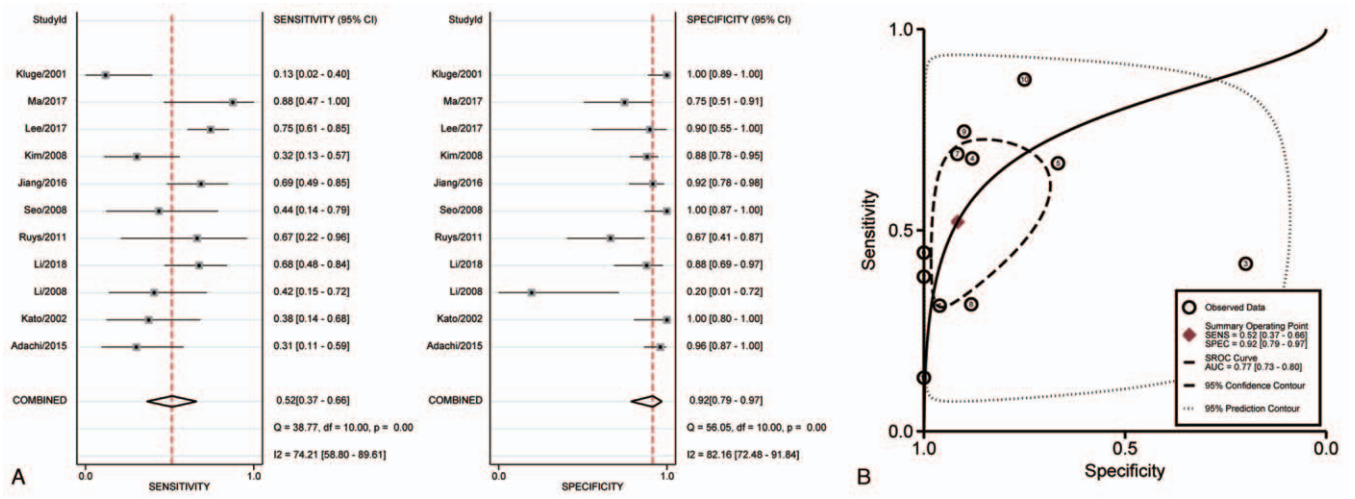

Figure 6. Diagnosis of lymph node metastases (N) by PET/CT. (A) Forest plot for pooled sensitivity and specificity. (B) SROC curve. PET/CT = positron emission tomography/computed tomography, SROC = receiver-operating characteristic curve.

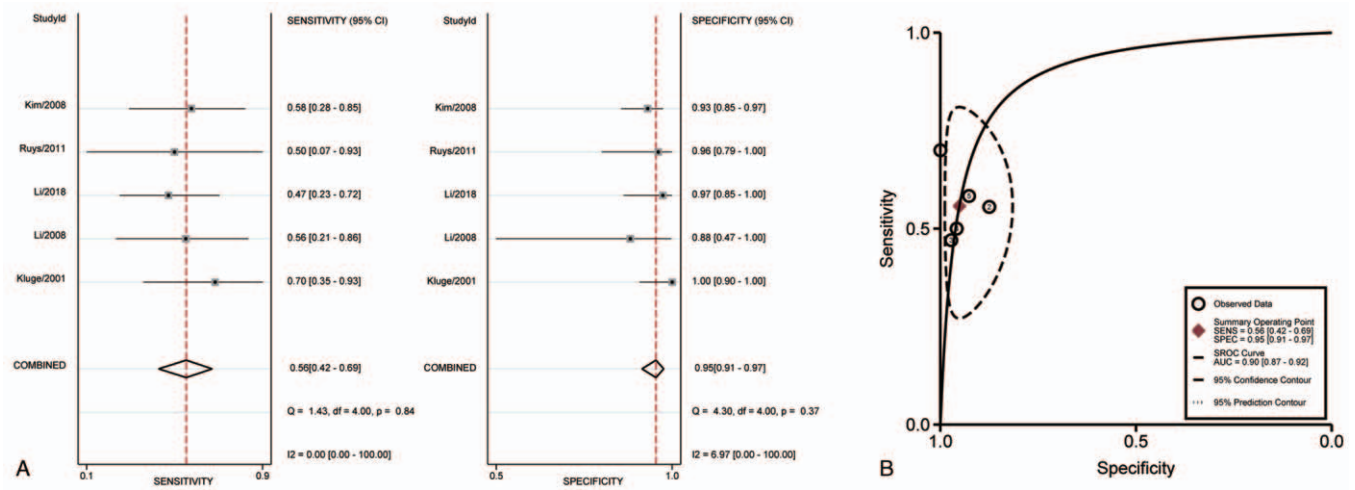

Figure 7. Diagnosis of distant metastases (M) by PET/CT. (A) Forest plot for pooled sensitivity and specificity. (B) SROC curve. PET/CT = positron emission tomography/computed tomography, SROC = receiver-operating characteristic curve.

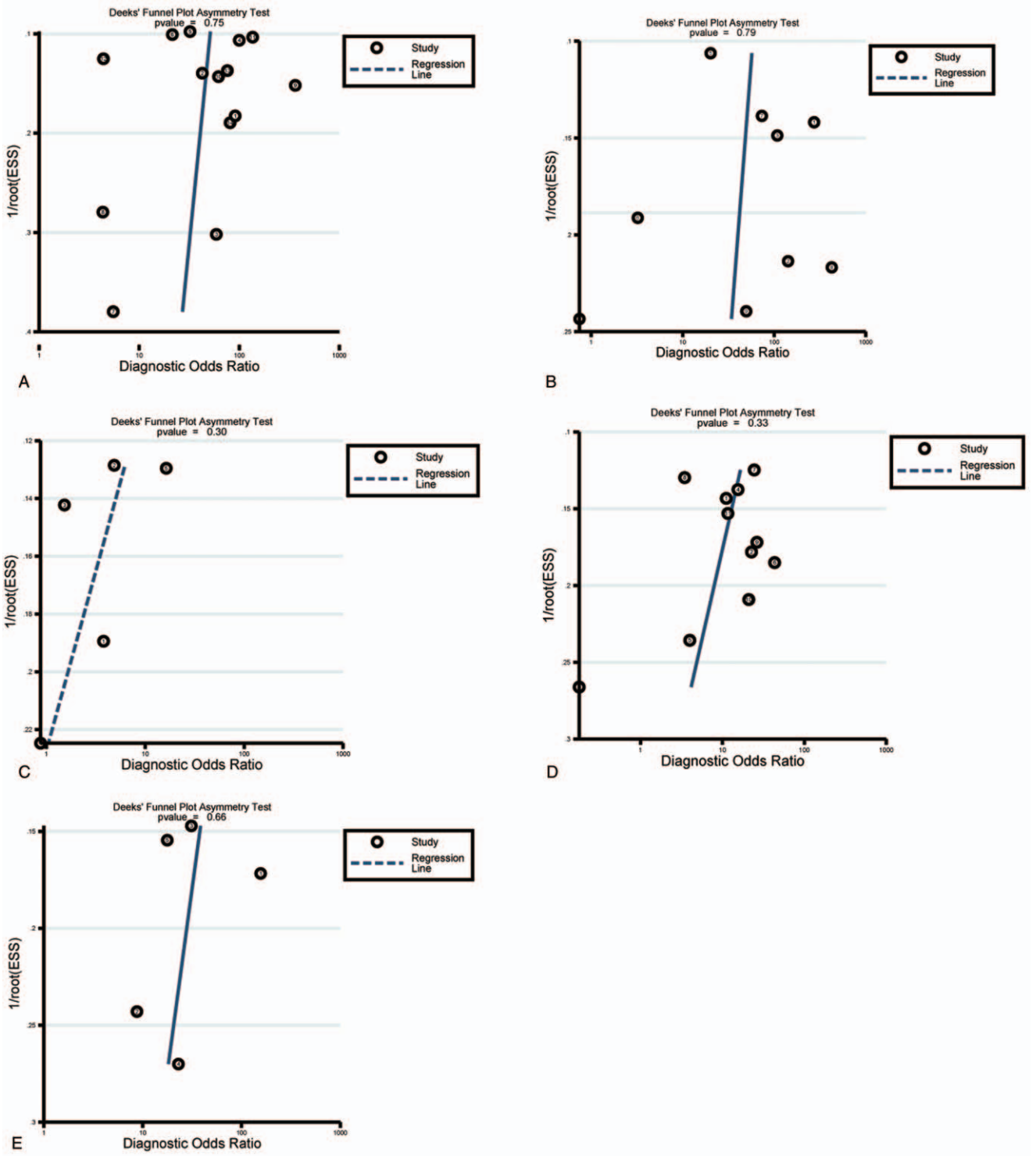

Figure 8. Funnel plot of publication bias. (A) MRI for primary tumor; (B) PET/CT for primary tumor; (C) MRI for lymph node metastases; (D) PET/CT for lymph node metastases; (E) PET/CT for distant metastases. MRI = magnetic resonance imaging, PET/CT = positron emission tomography/computed tomography.

4.1. Limitations

The present analysis has several limitations. First, no studies were found to detect distant metastases using MRI, which made it impossible to compare MRI and ^{18}F-FDG PET/CT for distant metastasis. Second, the heterogeneity within studies is considerable. Although we investigated possible sources of heterogeneity by subgroup analysis, the exploration of heterogeneity may still have been inadequate since the variables collected from the included studies were limited. Third, the reference standard strategy (biopsy, surgery, or both) for histopathologic analyses is difficult to classify, so no subgroup analysis was performed.

Finally, a majority of the included studies were retrospectively designed and used multiple reference standards, which can be considered limitations and potentially bias the results.

5. Conclusion

This meta-analysis is the first to evaluate the diagnostic performance of ^{18}F-FDG PET/CT versus MRI for staging in patients with CCA. Our meta-analysis indicates that both MRI and ^{18}F-FDG PET/CT can provide reasonable diagnostic accuracy for primary tumor of CCA. According to our study, ^{18}F-FDG PET/CT positive findings can diagnose lymph node metastases while negative findings might not exclude the metastases. As for MRI, it can neither rule in nor rule out the disease. Therefore, in the diagnosis of lymph node metastasis of CCA, ^{18}F-FDG PET/CT may be a better choice. It is worth noting that clinicians should be cautious about the negative diagnosis of ^{18}F-FDG PET/CT for lymph node metastasis of CCA. More advanced imaging techniques and a better knowledge of imaging characteristics of metastatic lymph node and distant metastasis are needed to improve the accuracy of CCA staging and the quality of life of patients with CCA.

Author contributions

Data curation: Xujian Huang, Jialin Yang.
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References

[1] Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology 2013;145:1215–29.
[2] Saha SK, Zhu AX, Fuchs CS, et al. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. Oncologist 2016;21:594–9.
[3] Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33:1353–7.
[4] Murakami Y, Uemura K, Sudo T, et al. Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma. Ann Surg Oncol 2011;18:651–8.
[5] Lang H, Sotiropoulos GC, Sgourakis G, et al. Operations for intrahepatic cholangiocarcinoma: single-institution experience of 158 patients. J Am Coll Surg 2009;208:218–28.
[6] Matull WR, Dhar DK, Ayaru L, et al. R0 but not R1/R2 resection is associated with better survival than palliative photodynamic therapy in biliary tract cancer. Liver Int 2011;31:99–107.
[7] Burke EC, Jarnagin WR, Hochwald SN, et al. Hilar cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. Ann Surg 1998;228:385–94.
[8] Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67:93–9.
[9] Malhi H, Gores GJ. Cholangiocarcinoma: modern advances in understanding a deadly old disease. J Hepatol 2006;45:856–67.
[10] Jhaveri KS, Hosseini-Nik H. MRI of cholangiocarcinoma. J Magn Reson Imaging 2015;42:1165–79.
[11] Angulo P, Pearce DH, Johnson CD, et al. Magnetic resonance cholangiography in patients with biliary disease: its role in primary sclerosing cholangitis. J Hepatol 2000;33:520–7.
[12] Park MJ, Kim YK, Lim S, et al. Hilar cholangiocarcinoma: value of adding DW imaging to gadoxetic acid-enhanced MR imaging with MR cholangiopancreatography for preoperative evaluation. Radiology 2014;270:768–76.
[13] Kim JY, Kim MH, Lee TY, et al. Clinical role of 18F-FDG PET-CT in suspected and potentially operable cholangiocarcinoma: a prospective study compared with conventional imaging. Am J Gastroenterol 2008;103:1145–51.
[14] Lee Y, Yoo IR, Boo SH, et al. The role of F-18 FDG PET/CT in intrahepatic cholangiocarcinoma. Nucl Med Mol Imaging 2017;51:69–78.
[15] Albazaz R, Patel CN, Chowdhury FU, et al. Clinical impact of FDG PET-CT on management decisions for patients with primary biliary tumours. Insights Imaging 2013;4:691–700.
[16] Jiang L, Tan H, Panje CM, et al. Role of 18F-FDG PET/CT imaging in intrahepatic cholangiocarcinoma. Clin Nucl Med 2016;41:1–7.
[17] McInnes MDF, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. JAMA 2018;319:388–96.
[18] Wengert GJ, Baltzer PAT, Bickel H, et al. Differentiation of intrahepatic cholangiocellular carcinoma from hepatocellular carcinoma in the cirrhotic liver using contrast-enhanced MR imaging. Acad Radiol 2017;24:1491–500.
[19] Zou X, Luo Y, Li Z, et al. Volumetric apparent diffusion coefficient histogram analysis in differentiating intrahepatic mass-forming cholangiocarcinoma from hepatocellular carcinoma. J Magn Reson Imaging 2019;49:975–83.
[20] Yoo R-E, Lee JM, Yoon JH, et al. Differential diagnosis of benign and malignant distal biliary strictures: value of adding diffusion-weighted imaging to conventional magnetic resonance cholangiopancreatography. J Magn Reson Imaging 2014;39:1509–17.
[21] Vogl TJ, Schwarz WO, Heller M, et al. Staging of Klatskin tumours (hilar cholangiocarcinomas): comparison of MR cholangiography, MR imaging, and endoscopic retrograde cholangiography. Eur Radiol 2006;16:2317–25.
[22] Vaishali MD, Agarwal AK, Upadhyaya DN, et al. Magnetic resonance cholangiopancreatography in obstructive jaundice. J Clin Gastroenterol 2004;38:887–90.
[23] Sun HY, Lee JM, Park HS, et al. Gadoxetic acid-enhanced MRI with MR cholangiography for the preoperative evaluation of bile duct cancer. J Magn Reson Imaging 2013;38:138–47.
[24] Songthamwat M, Chamadol N, Khuntikeo N, et al. Evaluating a preoperative protocol that includes magnetic resonance imaging for lymph node metastasis in the cholangiocarcinoma screening and care program (CASCAP) in Thailand. World J Surg Oncol 2017;15:176.
[25] Seo S, Hatano E, Higashi T, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography predicts lymph node metastasis, P-glycoprotein expression, and recurrence after resection in mass-forming intrahepatic cholangiocarcinoma. Surgery 2008;143:769–77.
[26] Ruys AT, Bennink RJ, van Westreenen HL, et al. FDG-positron emission tomography/computed tomography and standardized uptake value in the primary diagnosis and staging of hilar cholangiocarcinoma. HPB (Oxford) 2011;13:256–62.
[27] Petrowsky H, Wildbrett P, Husarik DB, et al. Impact of integrated positron emission tomography and computed tomography on staging and management of gallbladder cancer and cholangiocarcinoma. J Hepatol 2006;45:43–50.
[28] Masselli G, Manfredi R, Vecchioli A, et al. MR imaging and MR cholangiopancreatography in the preoperative evaluation of hilar cholangiocarcinoma: correlation with surgical and pathologic findings. Eur Radiol 2008;18:2213–21.
[29] Ma KW, Cheung TT, She WH, et al. Diagnostic and prognostic role of 18-FDG PET/CT in the management of resectable biliary tract cancer. World J Surg 2018;42:823–34.
[30] Li X, Zhang Y, Zhang Y. (18)F-FDG PET/CT may be a suitable method for preoperative diagnosis and evaluation of Chinese older patients with hilar cholangiocarcinoma. BMC Geriatr 2018;18:150.
[31] Li J, Kuehl H, Grabellus F, et al. Preoperative assessment of hilar cholangiocarcinoma by dual-modality PET/CT. J Surg Oncol 2008;98:438–43.
[32] Kluge R, Schmidt F, Caca K, et al. Positron emission tomography with [(18)F]fluoro-2-deoxy-D-glucose for diagnosis and staging of bile duct cancer. Hepatology 2001;33:1029–35.
[33] Kim YJ, Yun M, Lee WJ, et al. Usefulness of 18F-FDG PET in intrahepatic cholangiocarcinoma. Eur J Nucl Med Mol Imaging 2003;30:1467–72.

[34] Kim HM, Park JY, Kim KS, et al. Intraductal ultrasonography combined with percutaneous transhepatic cholangioscopy for the preoperative evaluation of longitudinal tumor extent in hilar cholangiocarcinoma. J Gastroenterol Hepatol 2010;25:286–92.
[35] Kato T, Tsukamoto E, Kuge Y, et al. Clinical role of (18)F-FDG PET for initial staging of patients with extrahepatic bile duct cancer. Eur J Nucl Med Mol Imaging 2002;29:1047–54.
[36] Hanninen EL, Pech M, Jonas S, et al. Magnetic resonance imaging including magnetic resonance cholangiopancreatography for tumor localization and therapy planning in malignant hilar obstructions. Acta Radiol 2005;46:462–70.
[37] Cui XY, Chen HW. Role of diffusion-weighted magnetic resonance imaging in the diagnosis of extrahepatic cholangiocarcinoma. World J Gastroenterol 2010;16:3196–201.
[38] Choi EK, Yoo Ie R, Kim SH, et al. The clinical value of dual-time point 18F-FDG PET/CT for differentiating extrahepatic cholangiocarcinoma from benign disease. Clin Nucl Med 2013;38:e106–11.
[39] Alkhawaldeh K, Faltten S, Biersack H-J, et al. The value of F-18 FDG PET in patients with primary sclerosing cholangitis and cholangiocarcinoma using visual and semiquantitative analysis. Clin Nucl Med 2011;36:879–83.
[40] Albiin N, Smith ICP, Arnelo U, et al. Detection of cholangiocarcinoma with magnetic resonance spectroscopy of bile in patients with and without primary sclerosing cholangitis. Acta Radiol 2008;49:855–62.
[41] Adachi T, Eguchi S, Beppu T, et al. Prognostic impact of preoperative lymph node enlargement in intrahepatic cholangiocarcinoma: a multi-institutional study by the Kyushu study group of liver surgery. Ann Surg Oncol 2015;22:2269–78.
[42] Han NY, Kim JY, Kim MJ, et al. Validation of feasibility of magnetic resonance imaging for the measurement of depth of tumor invasion in distal bile duct cancer according to the new American Joint Committee on Cancer Staging System. Acad Radiol 2017;24:1526–34.
[43] Choi KS, Lee JM, Joo I, et al. Evaluation of perihilar biliary strictures: does DWI provide additional value to conventional MRI? Am J Roentgenol 2015;205:789–96.
[44] Joo I, Lee JM, Lee SM, et al. Diagnostic accuracy of liver imaging reporting and data system (LI-RADS) v2014 for intrahepatic mass-forming cholangiocarcinomas in patients with chronic liver disease on gadoxetic acid-enhanced MRI. J Magn Reson Imaging 2016;44:1330–8.
[45] Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
[46] Annunziata S, Caldarella C, Pizzuto DA, et al. Diagnostic accuracy of fluorine-18-fluorodeoxyglucose positron emission tomography in the evaluation of the primary tumor in patients with cholangiocarcinoma: a meta-analysis. Biomed Res Int 2014;2014:247693.
[47] de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol 2011;29:3140–5.
[48] Saxena A, Chua TC, Sarkar A, et al. Clinicopathologic and treatment-related factors influencing recurrence and survival after hepatic resection of intrahepatic cholangiocarcinoma: a 19-year experience from an established Australian hepatobiliary unit. J Gastrointest Surg 2010;14:1128–38.
[49] Clark CJ, Wood-Wentz CM, Reid-Lombardo KM, et al. Lymphadenectomy in the staging and treatment of intrahepatic cholangiocarcinoma: a population-based study using the National Cancer Institute SEER database. HPB (Oxford) 2011;13:612–20.
[50] Wang X, Yu GY, Chen M, et al. Pattern of distant metastases in primary extrahepatic bile-duct cancer: a SEER-based study. Cancer Med 2018;7:5006–14.