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SYSTEMATIC REVIEW

Diagnostic accuracy of ^{18}F -FDG PET/CT for detection of peritoneal carcinomatosis; a systematic review and meta-analysis

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Objective: The current review aimed to investigate the performance of the diagnostic accuracy of ^{18}F -fludeoxyglucose positron emission tomography/CT (PET/CT) in detecting peritoneal carcinomatosis (PC) through a systematic review and meta-analysis.

Methods: The MEDLINE via PubMed and EMBASE from the earliest available date of indexing to 31 March 2017, were searched for studies evaluating the diagnostic performance of ^{18}F -FDG PET/CT in detecting PC. We evaluated the pooled sensitivities and specificities across included studies, calculated positive and negative likelihood ratios (LR+ and LR-), and plotted summary receiver operating characteristic curves. Deek's funnel plot asymmetry tests were used to assess the possible underlying publication bias.

Results: The current meta-analysis demonstrated no significant publication bias ($p = 0.21$). Across 14 studies (671 patients), the overall sensitivity of ^{18}F -FDG PET/CT was 0.87 [95% CI (0.77–0.93)] with heterogeneity

($\chi^2 = 94.2$, $p = 0.00$) and a pooled specificity of 0.92 [95% CI; (0.89–0.94)] with heterogeneity ($\chi^2 = 20.6$, $p = 0.08$). LR syntheses gave an overall LR+ of 10.4 [95% CI (7.5–14.5)] and LR- of 0.14 [95% CI (0.08–0.26)]. The pooled diagnostic odds ratio was 73 [95% CI (34–159)]. In univariate meta-regression analysis, publication year and cohort homogeneity were the potent sources of heterogeneity. However, in multivariate meta-regression, no definite variable was the source of the study heterogeneity.

Conclusion: ^{18}F -FDG PET/CT demonstrated good sensitivity and specificity for the detection of PC. Further large multicentre studies would be necessary to substantiate the diagnostic accuracy of ^{18}F -FDG PET/CT for the diagnosis of PC in various cancers.

Advances in knowledge: ^{18}F -FDG PET/CT showed good diagnostic performance in the evaluation of PC and could provide additional information for that purpose in various cancers.

INTRODUCTION

Peritoneal carcinomatosis (PC) is a common evolution of many abdominal or extra-abdominal malignancies and considered as a terminal condition with a poor outcome, as most patients die within 6 months.¹ The primary treatment of PC include total peritonectomy and resection of involved tissue with intraperitoneal chemotherapy as an approach with curative intention.^{2–4} The development of locoregional therapy has changed dramatically the approach to some clinical entities that evolve with peritoneal diffusion, namely pseudomyxoma peritonei, colon cancer and peritoneal mesothelioma, according to Phase II and III clinical trials.^{5,6} The extent and volume of the PC is one of the most important prognostic factors and the pre-operative detection and quantification of PC is essential for the planning

the treatment algorithm, especially for the design of the surgical approach. The gold standard for quantification of the PC is surgical exploration and the laparoscopy is a less invasive procedure than laparotomy.⁷

Many imaging techniques have been used for the detection of and pre-operative evaluation of patients with PC, including CT, MRI and ^{18}F -fludeoxyglucose (FDG) positron emission tomography/CT (PET/CT).^{8–12} Recently, the diagnostic accuracy of CT for the detection of PC and the detection of peritoneal implants has improved owing to the introduction of multidetector row CT.^{12–14} However, the efficacy of CT for the detection of PC could be compromised by the small size of tumour implants. PET with ^{18}F -FDG PET/CT has remarkably improved the management

of cancer patients and is increasingly applied in the staging and restaging of various cancers.^{15,16} The combination of ¹⁸F-FDG PET/CT allows an improvement in the anatomical localization of intra- and extrapelvic structures and their relationship with ¹⁸F-FDG uptake can provide more reliable data regarding the nature of the pathological findings.

Some previous studies have evaluated the diagnostic performance of ¹⁸F-FDG PET/CT in the evaluation of PC, reporting different values of sensitivity and specificity. The purpose of our study is to meta-analyse the published data on the diagnostic performance of ¹⁸F-FDG PET/CT in the evaluation of PC, in order to provide more evidence-based data and to address further studies in PC.

METHODS AND MATERIALS

Data sources and search strategy

This systematic review and meta-analysis was carried out using the PRISMA 2009 guidelines¹⁷ and we conducted electronic English-language literature searches of MEDLINE via PubMed and Embase from the earliest available date of indexing to 31 March 2017. 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”; and (2) “peritoneum” OR “peritoneal” AND “carcinoma” OR “carcinomatosis”.

The study protocol was prepared and followed to conduct this project and provided to give readers additional information about the current work (, Supplementary material available online)

Study selection

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

Studies were excluded if ¹⁸F-FDG PET/CT had been used for prediction of prognosis or if fewer than five patients had been included. In addition, duplicate studies were excluded. Also the publications such as review articles, case reports, conference abstracts and letters were excluded because of the lack of original data for calculation of sensitivity and specificity. Two researchers (Kim SJ, Lee SW) 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, publication year, country of study conducted), study design (prospective or retrospective), patients' characteristics (number of patients,

mean age, gender) and technical aspects (injected dose of ¹⁸FDG etc) were collected.

Each study was analysed to calculate the number of TP, TN, FP and FN findings of ¹⁸F-FDG PET/CT in patients with PC or suspicious PC, 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.¹⁸ Disagreement between the two authors was resolved by discussion.

Data synthesis and analysis

All data from each eligible study were extracted. The pooled sensitivity and specificity, and diagnostic odds ratios (DORs), are reported as 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.¹⁹ The statistical heterogeneity between studies for sensitivity and specificity was assessed using I^2 and the Cochrane Q test in terms of the random-effects analysis.²⁰ Possible publication bias was investigated using the effective sample size funnel plot and associated regression test of asymmetry described by Deeks and colleagues.²¹ We used the bivariate random-effects model for analysis and pooling of the diagnostic performance measures across studies.^{22,23} 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.²⁴ Also we performed meta-regression to identify potential sources of bias.²⁵ Pooled estimates were also calculated for subgroups of studies that were defined according to specific study designs. Two-sided $p \leq 0.05$ was considered statistically significant. Statistical analyses were performed with commercial software programs (STATA, v. 13.1; StataCorp LP, College Station, TX).

RESULTS

Literature search and selection of studies

After the comprehensive computerized search was performed and references lists were extensively cross-checked, we identified 168 articles from PubMed, 130 articles from Embase. Of which, 157 articles (non-English article 19, Conference abstract 44, not in the field of interest of this review 94) were excluded after reviewing the title and abstract. Remaining 50 full text articles were assessed for eligibility and 36 articles were excluded owing to insufficient data for the calculation of sensitivity and specificity of ¹⁸F-FDG PET/CT for the detection of PC. Finally, 14 articles^{26–39} were selected and were eligible for the systematic review and meta-analysis. The characteristics of the included studies are presented in Table 1. The flow of study selection in the systematic review is shown in Figure 1.

Table 1. Characteristics of the included studies

Authors	Year	Country	Imaging device	Image analysis	Patient number	Age	Male/female	^{18}F -FDG dose	Primary cancer	Study design
Pfannenbergh C	2009	Germany	PET/CT	PB	22	58	8/14	350 ~ 450 MBq	GIC (13), OC (8), MST (1)	R
Suzuki A	2004	Japan	PET + CT	PB	35	NR	NR	200 ~ 370 MBq	OC (9), CC (5), EC (6), CeC (4), PC (3), BDC (3), SC (3), HCC (1)	R
Dirisamer A	2009	Austria	PET/CT	PB	62	62	13/49	370 MBq	OC (32), CRC (16), EC (9), SC (4), CeC (1)	R
Satoh Y	2011	Japan	PET/CT	PB	107	61.1	51/56	3 MBq kg ⁻¹	GIC (45), GUC (23)	R
Berthelot C	2011	France	PET/CT	PB	28	59	7/21	5 MBq kg ⁻¹	CRC (17), OC (9), SC (1), P-MST (1)	R
Panagiotidis E	2012	Greece	PET/CT	PB	73	62	30/43	5 MBq kg ⁻¹	CRC (32), OC (18), SC (7), PC (7), CeC (4), EC (3), DC (1), SBC (1)	P
Soussan M (a)	2012	France	PET/CT	PB	30	63	19/11	3 ~ 3.5 MBq kg ⁻¹	CRC (12), PC (8), SC (5), ESC (3), SBC (2)	R
Klumpp BD	2012	Germany	PET/CT	LB	15	57.9	4/11	350 MBq	OC (6), CRC (3), AC (5), MST (1)	R
Sanli Y	2012	Turkey	PET/CT	PB	47	57.5	0/47	370 ~ 550 MBq	OC (47)	R
Filippi L	2013	Italy	PET/CT	PB	15	64.2	10/5	3.7 MBq kg ⁻¹	CRC (15)	R
Kim HW	2013	Korea	PET/CT	PB	46	54	0/46	350 MBq	OC (46)	R
Rubini G	2014	Italy	PET/CT	PB	79	59.8	0/79	4.6 MBq kg ⁻¹	OC (79)	R
Liberale G	2017	Belgium	PET/CT	PB	52	57.7	23/29	250 ~ 350 MBq	CRC (52)	R
Lopez-Lopez V	2016	Spain	PET/CT	PB	59	54	0/59	370 MBq	OC (59)	R

AC, appendix cancer; BDC, bile duct cancer; CC, colon cancer; CeC, cervical cancer; CRC, colorectal cancer; DC, duodenal cancer; EC, endometrial cancer; ESC, oesophageal cancer; GIC, gastrointestinal cancer; GUC, genitourinary cancer; HCC, hepatocellular cancer; LB, lesion-based; MST, mesothelioma; NR, not reported; OC, ovarian cancer; P, prospective; PB, patient-based; PC, pancreatic cancer; PET, positron emission tomography; P-MST, peritoneal mesothelioma; R, retrospective; SBC, small bowel cancer; SC, stomach cancer.

Study description, quality, publication bias

We conducted all analyses based on per-patient and per-lesion data analysis. Among those 14 studies included in the current review, one study conducted both of lesion-based and patient-based analysis of ^{18}F -FDG PET/CT.³² One study conducted only lesion-based analysis.³³ There was a total of 671 patients in the included studies, and the age ranged from 16 to 95 years. A total of 165 patients were male, and 506 patients were female. The one study did not report the number of male and female patients in their population.²⁷ Of all 14

studies, 13 studies^{26–30,32–39} enrolled patients retrospectively; 1 study³¹ enrolled patients prospectively. The study cohort was homogenous in seven studies^{32,34–39} and heterogeneous in seven studies.^{26–31,33} One study assessed the diagnostic performance of delayed ^{18}F -FDG PET/CT image.³⁵ The principal characteristics of the 14 studies included in the meta-analysis are included in Table 1. To assess a possible publication bias, Deeks's funnel plot asymmetry tests (Figure 2) were designed. The non-significant slope indicates that no significant bias was found. The *p* value was 0.21.

Figure 1. Flow chart of the search for eligible studies on the diagnostic performance of ^{18}F -FDG PET/CT for detection of PC. ^{18}F -FDG, fludeoxyglucose; PC, peritoneal carcinomatosis; PET, positron emission tomography.

Methodological quality assessment

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

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

deemed satisfactory.

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

The diagnostic performance results of ^{18}F -FDG PET/CT in the 14 included studies in the meta-analysis are presented in Figures 4 and 5. The pooled sensitivity for ^{18}F -FDG PET/CT was 0.87 [95% CI (0.77–0.93)] with heterogeneity ($\chi^2 = 94.2$, $p = 0.00$) and a

Figure 3. Risk of bias and applicability concerns summary.

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Berthelot 2011	?	?	+	?	+	+	+
Dirisamer 2009	-	?	-	-	?	+	?
Filippi 2013	-	?	+	+	-	?	+
Kim 2013	-	-	+	+	?	?	+
Klump 2013	-	?	?	+	+	?	+
Liberale 2017	-	-	+	?	-	?	?
Lopez-Lopez 2016	?	?	+	+	+	+	+
Panagiotidis 2012	+	+	+	+	+	+	?
Pfannenberger 2009	?	+	+	+	+	+	+
Rubini 2014	-	?	+	+	?	+	+
Sanli 2012	-	?	+	+	?	?	+
Satoh 2011	+	+	?	+	+	+	+
Soussan 2012	?	+	+	+	+	?	+
Suzuki 2004	?	?	+	+	?	+	+

● High ? Unclear + Low

Figure 4. Forest plot of pooled sensitivity and specificity of ^{18}F -FDG PET/CT in the detection of PC. Summary of sensitivity and specificity of ^{18}F -FDG PET/CT was 0.87 [95% CI (0.77–0.93)] and 0.92 [95% CI (0.89–0.94)], respectively. ^{18}F -FDG, fludeoxyglucose; PC, peritoneal carcinomatosis; PET, positron emission tomography.

pooled specificity of 0.92 [95% CI (0.89–0.95)] without heterogeneity ($\chi^2 = 20.6$, $p = 0.08$). LR syntheses gave an overall LR+ of 10.4 [95% CI (7.5–14.5)] and LR- of 0.14 (95% CI; 0.08–0.26). The pooled DOR was 73 [95% CI; (34–159)]. Forest plots of the sensitivity and specificity of ^{18}F -FDG PET/CT in the detection of PC are shown in Figure 4. Figure 5 shows hierarchical summary receiver operating characteristic curve and indicates that the areas under the curve was 0.92 [95% CI (0.89–0.94)], indicating good diagnostic accuracy.

Heterogeneity evaluation and meta-regression analysis

Between-study heterogeneity was present for sensitivity among studies of ^{18}F -FDG PET/CT for the detection of PC. A meta-regression analysis was performed to explore other sources of heterogeneity in the studies of ^{18}F -FDG PET/CT. Table 2 lists the results of meta-regression analysis for identifying potential sources of heterogeneity. In univariate meta-regression analysis, publication year and cohort homogeneity were the potent sources of heterogeneity. However, in multivariate meta-regression, no definite variable was the source of the study heterogeneity.

DISCUSSION

PC has been considered to be a terminal stage of disease with a poor survival rate in the past and was treated only with palliative intention.⁴⁰ Various imaging modalities have been used in the pre-operative assessment of tumour extent including CT, MRI as well as ^{18}F -FDG PET/CT.^{33,41} Several previous studies showed good results of MRI and PET/CT with advantages of functional and morphological tissue characterization.³⁴ However, there is no universally accepted reference standard for imaging of PC.²⁸

In this meta-analysis, the results reported that ^{18}F -FDG PET/CT has excellent diagnostic accuracy in the detection of PC in various cancers, with an area under the ROC curve of 0.92 (95% CI; 0.89–0.94). ^{18}F -FDG PET/CT demonstrated a sensitivity of 0.87 (95% CI; 0.77–0.93) and a specificity of 0.92 (95% CI; 0.89–0.94). Panagiotidis E investigated the diagnostic accuracy of ^{18}F -FDG PET/CT for detection of PC.³¹ The sensitivity, specificity, positive-predictive value, negative-predictive value and

Figure 5. Hierarchical summary ROC curves for the detection of peritoneal carcinomatosis of ^{18}F -FDG PET/CT.

Table 2. Meta-regression analysis for identifying potential sources of heterogeneity in the diagnostic performance of ^{18}F -FDG PET/CT for the detection of peritoneal carcinomatosis

Variables	No of studies	Univariate analysis				Multivariate analysis	
		Sensitivity	<i>p</i> -value	Specificity	<i>p</i> -value	LRT χ^2	<i>p</i> -value
Study location							
Western countries	11	0.86 (0.76–0.95)	0.40	0.91 (0.88–0.94)	0.10	0.99	0.61
others	3	0.91 (0.79–1.00)		0.93 (0.89–0.98)			
Study year							
Before 2010	3	0.88 (0.72–1.00)	0.69	0.91 (0.88–0.94)	0.03	0.78	0.68
After or during 2010	11	0.87 (0.78–0.96)		0.95 (0.89–1.00)			
Study design							
Prospective	1	0.93 (0.78–1.00)	0.86	0.85 (0.69–1.00)	0.06	1.42	0.49
Retrospective	13	0.86 (0.78–0.94)		0.92 (0.89–0.95)			
Image analysis							
PB	12	0.87 (0.79–0.96)	0.21	0.91 (0.88–0.94)	0.10	0.43	0.81
LB	2	0.84 (0.61–1.00)		0.93 (0.88–0.98)			
Cohort homogeneity							
Homogenous	6	0.84 (0.70–0.98)	0.21	0.89 (0.84–0.94)	0.00	2.31	0.31
Heterogeneous	8	0.89 (0.80–0.98)		0.93 (0.90–0.96)			

^{18}F -FDG, fludeoxyglucose; LRT, likelihood ratio test; PET, positron emission tomography; LB, lesion-based analysis; PB, patient-based analysis.

accuracy for diagnosing PC on a per-patient basis were 92.4, 85, 94.2, 81 and 91%, respectively. Kim HW et al performed a retrospective analysis of 46 patients who underwent ^{18}F -FDG PET/CT for the post-treatment surveillance of ovarian cancer. They demonstrated the sensitivity, specificity, positive-predictive value, negative-predictive value and accuracy of ^{18}F -FDG PET/CT for PC to be 96.2, 90, 92.6, 94.7 and 93.5%, respectively.³⁶

However, some studies included in the current review reported low sensitivity of ^{18}F -FDG PET/CT for the detection of PC. Lopez-Lopez et al³⁹ evaluated the clinical usefulness of the results obtained with ^{18}F -FDG PET/CT in relation to CT in the pre-operative staging of patients with PC secondary to primary or recurrent ovarian cancer candidates to cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy. They demonstrated the sensitivity, specificity, positive-predictive value and negative-predictive value of ^{18}F -FDG PET/CT for PC to be 24, 93, 66 and 68%.

Heterogeneity between studies could be an important source of bias. The included studies showed statistically significant heterogeneity in their estimates of sensitivity and specificity.

Possible explanation of this heterogeneity may be due to the diversity in methodological aspects between different studies and the basic clinical differences among the patients in the included studies (Table 1). However, according to the multivariate meta-regression analysis of the current study, no definite potent source of heterogeneity of this study was exist (Table 2).

CONCLUSION

^{18}F -FDG PET/CT demonstrated good sensitivity and specificity for the detection of PC. Further large multicentre studies would be necessary to substantiate the diagnostic accuracy of ^{18}F -FDG PET/CT for the diagnosis of PC in various cancers.

INFORMED CONSENT

This study is meta-analysis of published articles; therefore IRB approval was waived and informed consent was also waived.

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