



Pancreas

Systematic review of the utility of 18-FDG PET in the preoperative evaluation of IPMNs and cystic lesions of the pancreas



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ABSTRACT

Background: The aim of this systematic review is to assess the role of 18-fluorodeoxyglucose positron emission tomography in the preoperative evaluation of intraductal papillary mucinous neoplasms and cystic lesions of the pancreas.

Methods: A computerized PubMed search was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to identify studies evaluating positron emission tomography in the preoperative evaluation of pancreatic cystic lesions.

Results: A total of 14 studies evaluated the role of 18-fluorodeoxyglucose positron emission tomography/positron emission tomography-computed tomography, 9 of which evaluated only intraductal papillary mucinous neoplasms and 5 evaluated all pancreatic cystic lesions, including intraductal papillary mucinous neoplasms. Pooled analysis was carried out for studies evaluating intraductal papillary mucinous neoplasms only and studies evaluating all cystic lesions. Imaging with 18-fluorodeoxyglucose positron emission tomography had a positive predictive value, negative predictive value, sensitivity, specificity, and accuracy of 90%, 91%, 85%, 95%, and 91% in identifying malignancy (defined as either invasive and/or high-grade dysplasia) in intraductal papillary mucinous neoplasms and a positive predictive value, negative predictive value, sensitivity, specificity, and accuracy of 85%, 81%, 79%, 86%, and 88% in identifying malignancy in other cystic lesions. Pooled analysis reported the positive predictive value, negative predictive value, sensitivity, specificity, and accuracy of Sendai consensus guidelines (SCG) criteria as 69%, 69%, 68%, 55%, and 58%. The Fukuoka consensus guidelines (FCG) only had sensitivity, specificity, and accuracy reported as 61%, 52%, and 52%, respectively.

Conclusion: The 18-fluorodeoxyglucose positron emission tomography had a high degree of accuracy of detecting malignancy in intraductal papillary mucinous neoplasm and cystic lesion of the pancreas. Comparison of the utility of positron emission tomography with the Fukuoka consensus guidelines and the Sendai consensus guidelines suggest that positron emission tomography is superior to present guidelines in detecting malignant intraductal papillary mucinous neoplasm and cystic lesion of the pancreas. Further studies in larger patient cohorts may be required to corroborate these findings and to determine the place of positron emission tomography in the management of intraductal papillary mucinous neoplasm and cystic lesions of the pancreas.

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Introduction

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are potentially malignant or overt malignant mucinous

cystic lesions.^{1–3} These can be classified into main-duct IPMNs, branch-duct IPMNs, and mixed-duct IPMNs, depending on the site of involvement. The Sendai and Fukuoka classification systems were developed in 2006 and 2012, respectively to guide the management of IPMNs.^{4,5} The Sendai consensus guidelines (SCG) proposed that all main-duct IPMNs with a main-duct diameter ≥ 10 mm should be resected, and all branch-duct IPMNs with a size ≥ 3 cm (or if ≤ 3 cm but with symptoms), mural nodules of main duct dilation ≥ 6 mm or positive cytology should be

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resected.^{6,7} Subsequent studies, however, indicated that numerous unnecessary resections were carried out because of this aggressive approach. Subsequently, the SCG guidelines were re-evaluated, and the Fukuoka consensus guidelines (FCG) were then proposed, which classified IPMNs into the following 3 groups: low risk, worrisome risk, and high risk in order to decrease the number of unnecessary resections for benign, branch duct IPMNs.⁸ Minor revisions were further made to the FCG most recently in 2017.⁹

Positron emission tomography (PET) with F-18 fluorodeoxyglucose (18-FDG) has been reported to being used increasingly in preoperative imaging of IPMNs and other cystic lesions of the pancreas (CLP). A radioactive glucose analog, 18-FDG helps detect abnormal glucose metabolism between normal tissue and tumor tissue because tumor tissue has a greater metabolic activity. A handful of articles have compared the roles of the SCG and PET in the preoperative imaging of IPMNs. These demonstrated that the PET was superior to the SCG in detecting malignant IPMNs. PET has also been found to be useful in differentiating pancreatic carcinoma from pancreatitis, detection of liver metastases, tumor viability, and the response of the tumor to treatment.

Presently, few articles have been published that study the utility of PET for the evaluation of IPMN and CLP. Hence, we performed this systematic review with the primary objective of summarizing the current literature to assess the clinical utility and validity of 18-FDG PET in the assessment of IPMNs and all CLP.

Methods

Inclusion and exclusion criteria

A PubMed search was conducted, using the key words “IPMN and PET” up to March 2018, with no beginning date limit. Inclusion criteria were as follows: (1) English language articles, (2) full text articles, (3) articles evaluating cystic lesions with PET, (4) having a study sample size of a minimum of 10 patients. Exclusion criteria were as follows: (1) case reports, abstracts, expert opinions, other systematic reviews or editorials and (2) articles not evaluating cystic lesions with PET. The selection of studies was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure). The search was performed by N.S. and Y.X.K., and final inclusion was discussed with B.K.P.G.

Definitions

Positive predictive value (PPV) was defined as true positive/(true positive + false positive). Negative predictive value (NPV) was defined as true negative/(true negative + false negative). Sensitivity was defined as true positive/(false negative + true positive). Specificity was defined as true negative/(false positive + true negative). Accuracy was defined as (true positive + true negative)/(true positive + false positive + true negative + false negative). Specifically for IPMNs, histologic classification was done according to the World Health Organization (WHO) classification into low-grade, intermediate-grade, high-grade dysplasia, or invasive disease. In this study low-grade and intermediate-grade dysplasia IPMNs were defined as benign and high-grade dysplasia, and invasive IPMNs were defined as malignant.¹⁰

Data extraction and quality assessment

Two investigators (N.S. and Y.X.K.) independently performed data extraction and quality assessment. Discrepancies were resolved by consensus after consultation with B.K.P.G. Data were extracted on the following demographic parameters: study sample size, patient cohort, country of study, mean/median age, proportion of males, mean/median cyst size, presence of symptoms,

standardized uptake value (SUV) maximum cutoff, and proportion of patients managed with operative intervention or surveillance (Table 1). Outcome measurements were as follows: PPV, NPV, sensitivity, specificity, and accuracy of PET and International Consensus Guidelines (ICG) criteria in detecting a malignant lesion preoperatively.

Quality of studies were appraised using the QUADAS-2 assessment tool.¹¹ This tool assessed the risk of bias and applicability of studies based on four domains, including patient selection, index test, reference standard, and flow and timing. A judgment of low, high, or unclear rating was given, based on the signalling questions of the QUADAS-2 tool.

Results

The PubMed search yielded a total of 23 articles.^{12–34} All 23 abstracts^{12–34} were analyzed and 10 eligible studies^{12,15,23–25,28,29,31–33} that fulfilled our inclusion criteria were included in this systematic review. As a result of the PubMed search, we found that 3 studies^{12,13,34} were from the same institution. Of the 3 studies, 2^{12,13} were retrospective studies and 1³⁴ was a literature review. Because there was an overlap of patient cohort, the more updated retrospective study¹² was included in this systematic review. The list of references in the selected studies were analyzed, and a further 4 studies,^{35–38} which fulfilled our inclusion criteria, were included. In total, 14 studies^{12,15,23–25,28,29,31–33,35–38} were included in this systematic review. All 14 studies were retrospective studies. Of the 14 studies, 9 studied only IPMNs^{12,15,23–25,28,29,32,33} and 5^{31,35–38} studied all cystic lesions of the pancreas, including IPMNs. A total of 7 studies^{12,23–25,29,32} compared the role of PET with the ICG in the clinical management of IPMNs. The clinical outcomes of the studies are summarized in Tables 2–4. We observed that 18-FDG PET was used in all 14 included studies.

Study and patient characteristics

A total of 14 studies were included in this systematic review (Table 1). We found that 6^{15,23,25,28,29,31} of the studies were from Asia (Japan and Korea), 5^{12,24,32,33,38} of the studies were from Europe, and 3^{35–37} from the United States (Table 1). A total of 726 patients were included in the 14 studies. All 14 reports evaluated the role of 18-FDG PET in the preoperative evaluation of pancreatic lesions; whereas 6^{12,23–25,29,32} studied the concomitant role of the ICG (Sendai or Fukuoka criteria) in the preoperative evaluation of IPMNs. The mean or median age of the patients ranged from 57 years to 69 years. The proportion of males ranged from 30% to 81%. Median cyst size was reported in 7 studies and ranged from 2 cm to 8 cm. The SUV_{max} cutoff was only available in 11 studies,^{12,15,24,25,28,29,31–33,37,38} with 7 studies^{12,15,29,31–33,37} setting 2.5 as the cutoff for differentiating a benign from a malignant lesion.

Quality assessment of studies

Quality assessment of the included studies is summarized in Table 5. In the index test domain, 5 studies^{12,25,29,31,35} had an unclear risk of bias, because they did not specify whether the nuclear medicine physicians interpreting 18-FDG-PET results were blinded to the findings on computed tomography (CT). We found that 3 studies^{28,36,38} had a high risk of bias, because they did not report a prespecified SUV_{max} to determine malignancy in a lesion detected on 18-FDG-PET, and 1 study²³ had a high risk of bias and a high applicability concern, because it used the presence or absence of 18-FDG uptake as a determinant of malignancy as compared with the other studies, which used an SUV_{max} cutoff value to classify a detected lesion as benign or malignant.

Table 1
Summary of clinicopathologic features of all studies in this systematic review.

Number	Author	Type of lesions included	Total Number of patients	Year, cohort	Country	Median/mean age (years)	Male, n %	Median cyst size (cm) ± SD or mean size cyst (cm) with range	Symptoms	SUV max cut-off	Operative procedure
1.	Saito et al. ²⁵	IPMN only	48 IPMN MD IPMN 16 BD IPMN 32	2004–2012	Japan	69 ± 7	32 (67)	Mal: 8 ± 4 Ben: 5 ± 2	NA	2.	Surg: 48 PD: 23 DP: 23 P: 2
2.	Sperti et al. ³³	IPMN only	64 IPMN MD IPMN 28 BD IPMN 36	1998–2004	Italy	64 (37–84)	33 (52)	Mean: 3	27 (42)	2.5	Surg: 42 Bypass: 2 Obs: 20
3.	Hong et al. ¹⁵	IPMN only	31 IPMN	2005–2009	Korea	65 (50–78)	15 (48)	NA	Abdo pain: 10 Indigestion: 6 Jaundice: 4 Low: 1 Incidental: 9 Raised CA 19-9: 1	2.5	Surg: 27 Obs: 4 Mal: 7+/-4 Ben 2+/-1
4.	Takanami et al. ²⁸	IPMN only	16 IPMN MD IPMN 4 BD IPMN 7 Mixed 5	2006–2010	Japan	66 (52–75)	13 (81)	NA	NA	2.4	NA Mal: 3+/-1 Ben: 2+
5.	Baiocchi et al. ¹²	IPMN only	44 IPMN MD IPMN 17 BD IPMN 20 Mixed 7	2000–2010	Italy	69 (38–86)	NA	2 (1–far8)	Jaundice: 2 Low: 3 Back pain: 5 Increased CA 19-9: 9	2.5	Surg: 13 PD 4 DP: 6 TP 3
6.	Roch et al. ²⁴	IPMN only	50 IPMN MD IPMN 2 BD IPMN 18 Mixed 30	2009–2013	Italy	69 (28–5)	27 (54)	NA	11 (22)	3.0	Obs 31 PD 25 DP 21 TP 4
7.	Ohta et al. ²³	IPMN only	29 IPMN	NA	Japan	NA	11 (38)	NA	NA	NA	NA
8.	Pedrazzoli et al. ³²	IPMN only	Total 162 IPMN MD IPMN/Mixed: 61 BD IPMN: 101 PET-CT: 145 Histo known: 68	1989–2010	Italy	65 (36–87)	NA	NA	NA	2.5	Pppd: 28 DP 14 SPDP 8 TP 4 DPPHR 6 DPSP 2 CP 3 Others: 6 DP 14
9.	Tomimaru et al. ²⁹	IPMN only	29 IPMN MD IPMN 3 BD IPMN 13 Mixed 13	2006–2008	Japan	65 (48–82)	16 (55)	4 ± 2 (1–8)	11 (38)	2.5	PD 14 CP 1
10.	Kauhanen et al. ³⁸	All cystic lesions	Total: 31 6 IPMN 5 SCN 2 MCN 1 NET 3 PDAC 1 SPT 5 PC 1 GCT 1 mesentric cyst 1 lymphangioma 5 unknown	2011–2013	Finland	57 (28–74)	12/31 (39)	5 ± 4 (1–2)	19/31 (61)	3.6	NA Mal: 7+/- 3 Ben: 2 +/- 1
11.	Mansour et al. ³⁶	All cystic lesions	Total: 68 5 IPMN 5 adenocarcinoma 5 SCN 2 MCN 4 PC 47 unknown	1997–2005	USA	66 (39–84)	23 (34)	3(1–9)	34 (50)	NA	Surg: 21 (31) Obs: 47 (69)

(continued on next page)

Table 1 (continued)

Number	Author	Type of lesions included	Total Number of patients	Year, cohort	Country	Median/mean age (years)	Male, n %	Median cyst size (cm) ± SD or mean size cyst (cm) with range	Symptoms	SUV max cut-off	Operative procedure
12.	Tann et al. ³⁷	All cystic lesions	Total: 30 21 IPMN 2 MCN 1 MCA 5 PC 1 GCT	2002–2004	USA	63 (34–88)	16 (30)	Ben: 2 (1–5) Mal: 4 (2–6)	NA	2.5	NA
13.	Farma et al. ³⁵	All cystic lesions	Total: 82	2006–2007	USA	69 (24–88)	43 (52)	NA	NA	NA	NA
14.	Yoshioka et al. ³¹	All cystic lesions	Total: 136 80 ductal cancer 10 mass forming pancreatitis 30 IPMN 16 NET	2001–2014	Japan	66 (26–88)	76%	NA	NA	2.5	NA
										Mal: 6+/-4 Ben: 2	

Mal, malignant; Ben, benign; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; CP, complete pancreatectomy; Obs, observation; PPPD, pylorus preserving pancreaticoduodenectomy; SPDP, spleen preserving distal pancreatectomy; DPPHR, duodenum-preserving pancreatic head resection; DPSP, duodenum-preserving subtotal pancreatectomy; SCN, serous cystic neoplasm; MCN, mucinous cystic neoplasm; MCA, mucinous cystadenocarcinoma; NET, neuroendocrine tumor; PDAC, pancreatic ductal adenocarcinoma; SPT, solid pseudopapillary tumor; PC, pseudocyst; GCT, giant cell tumor.

In the reference standard domain, 7 studies^{12,23–25,29,31,35} had an unclear risk of bias because they did not specify whether the radiologists interpreting the CT results were blinded to the 18-FDG-PET findings. In the flow and timing domain, 1 study³² had a high risk of bias because only 145 patients of

a total 162 patients received 18-FDG-PET, and the remaining 17 patients were excluded from the analysis. In general, the overall quality of the included studies was reasonable, with all 14 studies fulfilling at least 4 out of the 7 QUADAS-2 domains.

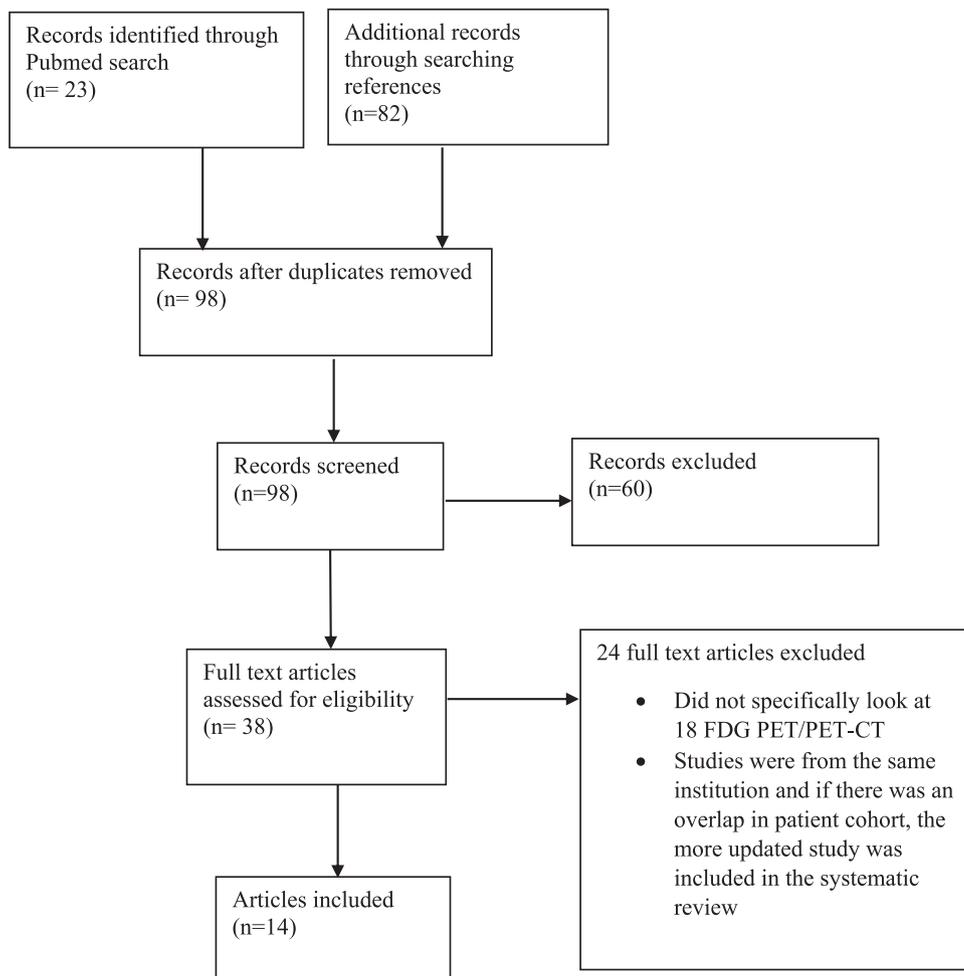


Fig. PRISMA flow diagram of the results of the literature search.

Table 2
Studies evaluating the utility of the PET and ICG for IPMNs of the pancreas*.

Author	Total number of patients (n)	Histologic grade	PET results	PPV of PET, %	NPV of PET	Sensitivity of PET	Specificity of PET	Accuracy of PET	ICG evaluated	ICG +ve	ICG-ve	PPV of ICG	NPV of ICG	Sensitivity of ICG (%)	Specificity of ICG (%)	Accuracy of ICG (%)
Saito et al ²⁵	32 (the remaining 16 did not undergo PET-CT)	Ben 13 HGD 12 Invas 7	1+ve 12-ve 8+ve 4-ve 7+ve	15/19 (79)	12/13 (92)	79	92	84	SCG	*Cyst size ≥30mm: 9 Ben 15 Mal *MPD Diameter ≥7mm 0 Ben 9 Mal *Intramural nodules 8 Ben 16 Mal *Positive cytology(N=26) 0 Ben 2 Mal	*Cyst size ≤30mm: 4 Ben 4 Mal *MPD Diameter ≤7mm 13 ben 10 Mal *Intramural nodules 5 Ben 3 Mal *Negative cytology (N=26) 10 Ben 14 Mal	15/19 (79) 9/19 (47) 16/19 (84) 14/16 (88)	9/13 (69) 13/13 (100) 5/13(38) 10/10 (100)	79 47 84 13	31 100 38 100	59 69 66 46
Sperti et al ³³	64	Ben 21 Mal 26 UD 17	1+ve 20-ve 24+ve 2-ve	24/25 (96)	20/22 (91)	92	95	94	NA	NA	NA	NA	NA	NA	NA	
Hong et al ¹⁵	31	Lgd 3 Hgd 12 Invas 14	Ben: 2+ve 13-ve Mal 16+ve 0-ve	16/18 (78)	13/13 (100)	16/18 (78)	13/13 (100)	29/31 (94)	FCG	39/50	11/50	NA	NA	92	23	NA
Takanami et al ²⁸	16	LGD 1 IGD 6 HGD 8 Invas 1	NA	100	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Baiocchi et al ¹²	44	Ben 32 Mal 12	32-ve 10+ve 2-ve	100	32/34 (94)	83	100	96	SCG	NA	NA	32	100	100	22	43
Roch et al ²⁴	50	Ben 37 Hgd 8 Invas 5	2+ve 35-ve 4+ve 4-ve 4+ve 1-ve	8/10 (80)	35/40 (88)	8/10 (80)	35/37(95)	43/50 (86)	SCG	*Cyst size ≥ 30mm 12 Ben 7 Mal *MPD diameter ≥ 7mm 3 Ben 6 Mal *Mural nodule + 3 Ben 13 Mal	*Cyst size ≤30mm 2 Ben 5 Mal *MPD diameter ≤ 7mm 4 Ben 3 Mal *Mural nodule - 12 Ben 1 Mal	7/12 (58) 6/9 (67) 13/14 (93)	2/14 (14) 4/7 (57) 12/15 (75)	58 67 93	14 57 80	35 63 86
Ohta et al ²³	29	Lgd 9 Hgd 9 Invas 11	2+ve 7-ve 18+ve 2-ve	18/20 (90)	7/9 (78)	90	78	86	FCG	*Mural nodule 10 Mal 3 Ben *MPD Diameter ≥5mm 8 Mal 3 Ben	*Mural nodule 10 Mal 6 Ben *MPD Diameter <5mm 12 Mal 6 Ben	NA NA	NA NA	50 40	67 67	55 48
Pedrazzoli et al ³²	Total 162 PET: 145 Histo known: 68	LGD 17 IGD 12 HGD 6 Invas 18 Others 15	17-ve 12-ve 3-ve 3+ve 18+ve	21/24 (88)	17/17 (100)	21/24 (88)	29/32 (91)	50/53 (94)	SCG	NA	NA	53	80	93	22	57
Tomimaru et al ²⁹	29	LGD 14 IGD1 HGD 3 Invas 11 Note: one patient was excluded in PET-CT due to hyperglycemia	0+ve 13-ve 0+ve 1-ve 2+ve 1-ve 11+ve 0-ve	13/14 (93)	14/14 (100)	93	100	96	SCG	*Cyst size ≥ 30mm 12 Ben 7 Mal *MPD diameter ≥ 7mm 3 Ben 6 Mal *Mural nodule + 3 Ben 13 Mal	*Cyst size ≤30mm 2 Ben 5 Mal *MPD diameter ≤ 7mm 4 Ben 3 Mal *Mural nodule - 12 Ben 1 Mal	7/12 (58) 6/9 (67) 13/14 (93)	2/14 (14) 4/7 (57) 12/15 (75)	58 67 93	14 57 80	35 63 86
Yoshioka et al ³¹	Total: 136 Only IPMN: 30	Ben 12 Mal 18	NA	100	75	78	100	87	NA	NA	NA	NA	NA	NA	NA	NA
Total	393	Ben 190 Mal 170 Histology unreported 32 PET-CT excluded 1	NA	90	91	85	95	91	NA	NA	NA	68	64	69	51	58

* The studies by Saito et al.,²⁵ Ohta et al.,²³ and Tomimaru et al.²⁹ only reported the number of patients who were positive or negative for each of the features in the SCG but not the overall number of patients who were SCG+ or SCG-ve. Thus, the PPV, NPV, sensitivity, specificity, and accuracy have been calculated separately for each of the features in the SCG, as reported by the studies.

Table 3
Studies evaluating the utility of PET for all cystic lesions of the pancreas.

Study	Total number of patients (n)	Histologic grade	PET results	PPV of PET, (%)	NPV of PET (%)	Sensitivity of PET (%)	Specificity of PET (%)	Accuracy of PET (%)
Kauhanen et al. ³⁸	31	Ben 25	2+ve 23-ve	6/8 (75)	23/23 (100)	6/6 (100)	23/25 (92)	29/31 (94)
Mansour et al. ³⁶	21	Mal 6 Ben 14	6+ve 2+ve 12-ve	4/6 (67)	12/15 (75)	4/7 (57)	12/14 (86)	16/21 (76)
Tann et al. ³⁷	30	Mal: 7 HGD: 5 Invas: 2 Ben 23	4 +ve 3-ve	NA	NA	57%	65%	NA
Farma et al. ³⁵	82	Mal 7 Adeno CA: 65	58+ve 7-ve	58/60 (97)	15/22 (68)	58/65 (89)	15/17 (88)	73/82 (89)
Yoshioka et al. ³¹	136	Histo unknown: 17 Ben 22	2+ve 15-ve NA	99	80	92	97	93
Total	270 Excluding IPMN: 106	Mal 84 Ben 84 Mal 169 Histology unreported 17	NA	85	81	79	86	88

Table 4
Pooled Analysis for studies evaluating IPMNs only.

	PET	SCG	FCG
No of studies (n)	10	4	2
Total number of patients (n)	392 (32 unknown histo)	190 (32 unknown histo)	79 (2 studies only)
Benign, n (%)	190 (53)	89 (56)	46 (58)
Malignant, n (%)	170 (47)	69 (44)	33 (42)
Positive predictive value (%)	90 (153/170)	69	NA
Negative Predictive Value (%)	91	69	NA
Sensitivity (%)	85	68	61
Specificity (%)	95	55	52
Accuracy (%)	91	58	52 (1 study only)

Table 5
QUADAS 2 TOOL to assess risk of bias and applicability concerns of included studies.

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Saito et al. ²⁵	Low	Unclear	Unclear	Low	Low	Low	Low
Sperti et al. ³³	Low	Low	Low	Low	Low	Low	Low
Hong et al. ¹⁵	Low	Low	Low	Low	Low	Low	Low
Takanami et al. ²⁸	Low	High	Low	Low	Low	Low	Low
Baiocchi et al. ¹²	Low	Unclear	Unclear	Low	Low	Low	Low
Roch et al. ²⁴	Low	Low	Unclear	Low	Low	Low	Low
Ohta et al. ²³	Low	High	Unclear	Low	Low	High	Low
Pedrazzoli et al. ³²	Low	Low	Low	High	Low	Low	Low
Tomimaru et al. ²⁹	Low	Unclear	Unclear	Low	Low	Low	Low
Kauhanen et al. ³⁸	Low	High	Low	Low	Low	Low	Low
Mansour et al. ³⁶	Low	High	Low	Low	Low	Low	Low
Tann et al. ³⁷	Low	Low	Low	Low	Low	Low	Low
Farma et al. ³⁵	Low	Unclear	Unclear	Low	Low	Low	Low
Yoshioka et al. ³¹	Low	Unclear	Unclear	Low	Low	Low	Low

Studies evaluating the utility of 18-FDG-PET for the preoperative evaluation of IPMNs

Of the 14 studies, 9 studied only IPMNs^{12,15,23–25,28,29,32,33} and 5 included all CLP,^{31,35–38} including IPMNs (Table 1). We found that 1 study³¹ reported the clinical outcomes of 18-FDG-PET for IPMNs and all CLP separately and thus enabled it to be included in both analyses of IPMNs alone and all CLP (Tables 2 and 3). A total of 392

patients with IPMNs underwent 18-FDG-PET from these 10 studies (Table 4), 190 of whom had benign IPMNs (53%) and 170 of them had malignant IPMNs (47%). The remaining 32 did not report the histology of the IPMN. Pooled analysis revealed a PPV, NPV, sensitivity, specificity, and accuracy of 90%, 91%, 85%, 95%, and 91%, respectively (Table 4).

Table 6
Studies evaluating utility of PET for Invasive IPMNS.

Study	Number of Invasive IPMN (n)	18 FDG PET	
		Sensitivity (%)	Specificity (%)
Saito et al. ²⁵	15	100	88
Takanami et al. ²⁸	1	100	NA
Tomimaru et al. ²⁹	11	100	100
Baiocchi et al. ¹²	NA	NA	NA
Roch et al. ²⁴	5	80	95
Ohta et al. ²³	11	100	78
Pedrazzoli et al. ³²	25	87	100
Total	68	95	92

Table 7

Pooled analysis for studies evaluating the utility of FDG-PET for detecting benign or malignant tumors for all cystic lesions.

No of studies (n)	5
Total Number of patients (n)	270 (17 unknown histo)
Benign, n (%)	84 (33)
Malignant, n (%)	169 (67)
Positive predictive value (%)	85
Negative predictive value (%)	81
Sensitivity (%)	79
Specificity (%)	86
Accuracy (%)	88

Studies evaluating the utility of 18 FDG-PET for invasive IPMNs

Of the 14 studies, 7^{12,23–25,28,29,32} evaluated the clinical utility of 18-FDG-PET and the ICG criteria in detecting invasive IPMNs (Table 6). A total of 68 invasive IPMNs were reported from 6 studies^{23–25,28,29,32} with 1 study¹² not reporting the number of invasive IPMNs. The 18-FDG-PET had a sensitivity of 95% and specificity of 92%, and the ICG criteria had a sensitivity of 61% and specificity of 58% in detecting an invasive IPMN.

Studies evaluating the utility of 18-FDG-PET for the preoperative evaluation of all CLP

A total of 5 articles^{31,35–38} studied the utility of PET for all CLP (Table 4). A total of 270 patients were reported from these 5 studies, with 84 (33%) having benign lesions, 169 (67%) having malignant lesions, and the remaining 17 with no histology reported. Pooled analysis revealed PPV, NPV, sensitivity, specificity, and accuracy of 85%, 81%, 79%, 86%, and 88%, respectively (Table 7). The studies did not further stratify malignant lesions into those with high-grade dysplasia and invasive features.

Studies comparing the utility of 18-FDG-PET versus the FCG/SCG in IPMNs

Only 6 of the studies^{12,23–25,29,32} evaluated both the role of 18-FDG-PET and FCG/SCG in the preoperative evaluation of IPMNs. The findings are summarized in Table 5. We found that 4 of the studies^{12,25,29,32} evaluated the role of SCG, and 2 studies^{23,24} evaluated the role of FCG. For the studies evaluating the Sendai criteria, the main features they evaluated were cyst size ≥ 3 cm, main pancreatic duct dilation ≥ 7 mm, and the presence of mural nodules. The study by Roch et al.²⁴ also evaluated positive cytology as one of the features under the Sendai criteria.

A total of 190 patients were reported in the 4 studies^{12,25,29,32} that evaluated the SCG, with 89 (56%) having benign IPMNs, 69 (44%) having malignant IPMNs, and the remaining 32 having no reported histology. Pooled analysis demonstrated that the SCG had PPV, NPV, sensitivity, specificity, and accuracy of 69%, 69%, 69%,

55%, and 58%, respectively. Of note, the study by Baiocchi et al.¹² reported the outcomes of a combined triad of the SCG, presence of symptoms, and CA-19 9 levels, and thus their results may not be fully representative of the clinical utility and validity of the SCG alone

A total of 79 patients were reported in the 2 studies^{23,24} that evaluated the FCG, with 46 (58%) having benign IPMNs and 33 (42%) having malignant IPMNs. Pooled analysis only reported sensitivity, specificity, and accuracy of the FCG to be 61%, 52%, and 52%, respectively, because PPV and NPV were not reported by these 2 studies.

In 6 studies, the overall pooled PPV, NPV, sensitivity, specificity, and accuracy of 18-FDG-PET in detecting malignancy in IPMNs was 88%, 92%, 86%, 93%, and 90%. Hence, 18-FDG-PET seemed to achieve a better utility and accuracy in distinguishing benign from malignant IPMNs compared with the ICG. This is vital because preoperative imaging with a high specificity can decrease unnecessary resections of lesions with little or no potential of malignancy given the morbidity and mortality of pancreatic resections. In addition, the study by Saito et al.²⁵ reported that 18-FDG-PET/CT had a sensitivity, specificity, and accuracy of 79%, 82%, and 94% in detecting malignancy in branch-duct IPMN. This finding is important because the current FCG manages branch-duct IPMN conservatively, and some groups believe it to be very important to detect malignant potential in these lesions.

Discussion

The management of IPMN should be guided by the following two issues: (1) whether the IPMN is malignant and (2) whether the IPMN will become malignant during a patient's lifetime. Presently, it still remains challenging for clinicians to determine the presence of a malignancy in IPMN and even more so to determine its future malignant potential.³⁴ Currently, the updated FCG recommends operative resection for most clinically fit patients with at least one high-risk feature. For patients with at least one worrisome-risk feature, resection is recommended for selected patients with a long life expectancy and endoscopic ultrasonographic fine-needle aspiration (EUS-FNA) is recommended for patients with worrisome-risk features before undergoing close surveillance. Limitations remain with the present FCG criteria. Indeed, a recent systematic review reported that up to 14% of IPMNs without worrisome-risk or high-risk features ultimately proved to harbor high-grade dysplasia or malignancy on final histology.⁸ Minor revisions were made to the FCG in 2017, although it remains to be determined whether these revisions will improve the accuracy of the guidelines.⁹ Most recently, the European Study Group on Cystic Tumours of the Pancreas also published evidence-based guidelines to improve the diagnosis and management of IPMN and cystic neoplasms, which similarly requires further evaluation to determine its clinical utility.²

The 18-FDG-PET is a noninvasive scintigraphic technique that works on the principle of the metabolism of intracellular glucose. Glucose metabolism occurs at a greater rate in malignant cells because of the increased activity of glycolytic enzymes and membrane transportation of glucose. The 18-FDG is a radioactive glucose analog taken up by malignant cells and hence is detected on PET. PET can be used to address the presence of a tumor, a qualitative diagnosis, and the presence of local occurrence, or distant metastases²³ noninvasively as compared with other modalities, such as EUS-FNA, if combined with CT. Ohta et al.²³ explained that a PET-CT evaluates a lesion in 2 stages. The CT portion helps to identify the enhancement of mural nodules, main pancreatic duct dilation, and size of the cystic lesion, and the PET portion evaluates the 18-FDG uptake of the lesion, which suggests whether it is malignant or benign. In the present systematic review, we found 18-FDG-PET to be extremely useful in detecting malignant (high-grade dysplasia or invasive) IPMN with a high degree of accuracy.

To date, several studies have compared the role of CT and 18-FDG-PET in the evaluation of pancreatic cystic lesions. Hong et al.¹⁵ reported a sensitivity, specificity, and accuracy of 100%, 87%, and 94% for 18-FDG-PET vs 94%, 60%, and 77% for CT. Sperti et al.³³ reported on sensitivity, specificity, and accuracy of 92%, 97%, and 95% for 18-FDG PET and 58%, 82%, and 72% for CT. They also reported that 18-FDG-PET was able to detect 24 of the 25 malignant IPMNs, with 4 patients having carcinoma in situ in which the CT/MRI did not suggest malignancy in 3 of the 4, suggesting that CT has limited ability to differentiate carcinoma in situ from invasive carcinoma. In contrast, the 18-FDG-PET suggested the need for resection in 7 patients who had no features of malignancy on conventional CT/MRI imaging, 3 patients with positive CT findings to be put on active surveillance, and a more conservative resection in 15 patients.

Presently, the FCG is probably the most commonly utilized guideline to assist clinicians in the management of IPMN⁸ and can probably be regarded as the current gold standard. Hence, any potentially new modality for the evaluation of IPMN should ideally be compared with the accuracy of the current FCG. In the current systematic review, the pooled sensitivity and specificity of PET was 85% and 95%, respectively. In comparison, the overall sensitivity and specificity for SCG was 68% and 55% and for FCG was 61% and 52%. These findings suggest that PET may be superior to both the SCG and FCG for the stratification of IPMN. It is imperative, however, to emphasize that only 2 studies compared the utility of PET with the FCG in only 79 patients. The accuracy of the FCG in these studies also seemed less than that published by other authors.⁸

A major advantage of PET is that the 18-FDG uptake (expressed as the SUV_{max}) is an objective value and is subjected to less operator error compared with a qualitative analysis of CT images. The SUV_{max} cutoff has been set as 2.5 by several studies, where lesions with SUV_{max} > 2.5 are deemed malignant. Sperti et al.³³ reported the greatest sensitivity, specificity, and accuracy of 93%, 100%, and 96% when the SUV_{max} cutoff was set at 2.5; whereas the sensitivity, specificity, and accuracy was 71%, 100%, and 86% when the SUV_{max} was set at 3.0 and 93%, 86%, and 89% when the SUV_{max} was set at 2.0. Similarly, Tomimaru et al.²⁹ reported a sensitivity and specificity of 93% and 100% respectively, and Baiocchi et al.¹² reported a sensitivity and specificity of 100% when the SUV_{max} cutoff was set at 2.5. We want to emphasize that SUV_{max} values are set arbitrarily and may possibly vary from institution to institution, depending on the software and technology used in the PET. Also, SUV_{max} can be influenced by factors such as tumor size, weight, and height of the patient. Moreover, 18-FDG accumulates in inflammatory lesions, such as pancreatitis, or may be falsely increased in patients with impaired glucose tolerance or diabetes mellitus. To overcome this, Saito et al.²⁵ suggested the use of dual phase PET-CT, where 18-FDG levels take a greater time to plateau

compared with inflammatory lesions because of greater metabolic activity.

Based on the present findings, we propose that PET may have a potentially important role in the management of patients with IPMN and CLP. First, the addition of a PET scan may decrease the incidence of high-grade or malignant lesions being missed and managed conservatively. This possibility has been reported to be up to 14% based on the FCG in a recent systematic review⁸ Furthermore, the use of PET may also be useful in higher-risk patients, such as in the elderly, where the need for pre-emptive resection or the diagnosis of malignancy is not as clear-cut. In such patients, unless conventional imaging, such as CT/MRI, shows clear-cut high-risk features, with no distant metastases, a PET-CT can be performed to offer a much greater estimation of the presence of malignancy. Given the high morbidity and mortality of pancreatic resections, which are often the only curative management of pancreatic neoplasms, PET can prevent unnecessary resections and improve postoperative quality of life in these cases.

This systematic review is associated with several limitations. Because all the studies included were retrospective studies, the results could be affected by numerous biases and confounding factors. In addition, not all the studies attempted to evaluate and compare the utility of PET with the FCG or SCG, resulting in only a small number of patients in the comparison analysis. Finally, the protocol for a PET scan was not standardized, and thus the technique differed with the various institutions using different PET technology and software, which may influence the SUV_{max} values, making it difficult to decide on a single cutoff value for determining malignancy. Finally, the definition we used for malignancy was either the presence of invasive disease or high-grade lesions.

In conclusion, the results of this systematic review suggest that 18-FDG PET has a high degree of accuracy in detecting malignancy (invasive disease and/or high-grade changes in IPMN and CLP). Comparison of the utility of PET with the FCG and SCG suggest that PET is superior to present guidelines in detecting malignant IPMN and CLP. Further studies in larger patient cohorts will be required to corroborate these findings and to determine the place of PET in the management of IPMN and CLP.

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