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The Sendai and Fukuoka consensus criteria for the management of branch duct IPMN - A meta-analysis on their accuracy

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ABSTRACT

Introduction: The risk of malignancy in branch duct intraductal papillary mucinous neoplasia of the pancreas (BD-IPMN) is controversially debated. An increasing number of studies report on outcomes using the Sendai or Fukuoka consensus criteria for treatment decision-making.
The objective of this work was to evaluate the diagnostic accuracy of the Sendai and Fukuoka criteria.
Methods: We systematically reviewed studies on Sendai or Fukuoka criteria-guided management of BD-IPMN. Pooled sensitivity, specificity and diagnostic odds ratios as compound measures of diagnostic accuracy were calculated from studies matching the inclusion criteria. The meta-analysis was performed using a random effects model.
Results: Fifteen studies with a total of 2710 patients were included. Twelve of these used the Sendai criteria. In these studies, 23% of Sendai-negative patients had a high grade dysplastic lesion or an invasive carcinoma in final histology. Pooled sensitivity was 56%, specificity was 74% and the diagnostic odds ratio for malignancy in Sendai-positive lesions was 7.45. When the results of follow-up examinations were included, diagnostic accuracy improved significantly (14.66, $p < 0.001$). Three studies were identified that used the Fukuoka criteria for decision making. Of 200 patients with Fukuoka-negative lesions who underwent surgery, 22 had a malignant lesion in final histology (11%). Pooled sensitivity was 83%, specificity was 53% and the diagnostic odds ratio was 8.76.
Conclusion: The Fukuoka criteria have considerably improved sensitivity but still lack adequate specificity. For further reduction of a potential surgical overtreatment of BD-IPMN, the development of criteria with an increased specificity is required.

1. Introduction

Intraductal papillary mucinous neoplasms of the pancreas (IPMN) are the most common cystic tumors of the pancreas. They are classified into main duct, branch duct and mixed type IPMN. Main duct and mixed type IPMN harbor a high risk of malignant transformation and resection is therefore generally recommended. Treatment of BD-IPMN is controversially discussed because the risk of malignancy is not completely clear.

Consensus conferences in Sendai (2006) and in Fukuoka (2012) defined algorithms for clinical management of BD-IPMN:

The Sendai-consensus (SC) [1] suggests resection when one or more of the following features are present: cyst size > 3 cm, presence of mural nodules, positive cytology, clinical symptoms and dilation of the main pancreatic duct (MPD).

In the updated Fukuoka-consensus (FC) [2] morphological and clinical features are further categorized into high risk stigmata (resection recommended) and worrisome features (surveillance recommended, Table 1).

In addition, the American Gastroenterology Association (AGA) published their guidelines [3] on the treatment of asymptomatic pancreatic cysts recently. These guidelines take a more conservative approach towards management of IPMN. Surgery is only recommended if two or more suspicious imaging features are present in MRI and endoscopic ultrasound (EUS), surveillance intervals are prolonged to 2 years and surveillance should be stopped after 5 years.

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Table 1
Worrisome features (WF) and high risk stigmata (HR) as displayed in the Fukuoka consensus (FC).

Worrisome features (WF)	High risk stigmata (HR)
history of pancreatitis	jaundice
dilation of MPD 5–9 mm	dilation of MPD > 10 mm
enhanced and thickened cyst wall	enhanced solid component (MN)
size > 3 cm	
change in MPD caliper and distal atrophy	
non-enhanced MN	
lymphadenopathy	

A shift of paradigm from an aggressive surgical approach in the early 2000s to a more and more conservative strategy in recent years becomes apparent. Currently relatively complex diagnostic algorithms are being used for decision making and changes in the weighing of features suggesting malignancy illustrate the dynamics in the field. In the context of an increasing incidence of BD-IPMN, mainly due to improved cross-sectional imaging, the AGA advocates a reluctant approach (as described above) with emphasis on costs of health care delivery.

This, one of the major questions is the diagnostic accuracy of the currently used consensus criteria, especially how safely these criteria allow a differentiation between benign and (pre-) malignant lesions.

In recently conducted meta-analyses, Kim and co-workers [4] identified mural nodules as the feature with the strongest correlation to malignancy, whereas Anand and co-workers [5] showed that cyst size greater than 3 cm was strongly associated with malignant histopathology. However so far, there is no systematic comparison of the diagnostic accuracy of the SC and FC. In particular, the overall scope (in contrast to the evaluation of only single features) of the guidelines has not been compared to date.

We therefore reached out to meta-validate the overall diagnostic efficacy of the Sendai and the Fukuoka consensus criteria.

2. Patients and methods

Retrospective and prospective studies that used one or more criteria for BD-IPMN evaluation as mentioned in the consensus guidelines [1,2] and that reported on more than 40 patients were included. Pathological confirmation of invasive carcinoma, carcinoma *in situ* and high-grade dysplasia was defined as presence of malignancy. Adenoma/low-grade dysplasia and borderline/intermediate dysplasia were defined as benign lesions.

2.1. Search strategy

A computerized literature search of Embase and PubMed including studies published from January 1, 2006 (as the International Consensus Guidelines were published in 2006) was performed, the last search being performed on January 1st, 2015. The following search terms were used: "Pancrea* and (IPMN or "intraductal papillary mucinous")". Only studies restricted to humans and for which an abstract was available were included. In addition, reference lists of each selected article were screened for further studies matching the criteria for inclusion.

Headings and abstracts of articles obtained by the literature search were then analysed. Articles deemed to be potentially useful for analysis were obtained in full text and scrutinized for their utility. This approach yielded 2169 abstracts, 137 studies were analysed of which 15 were included in the final analysis (Fig. 1).

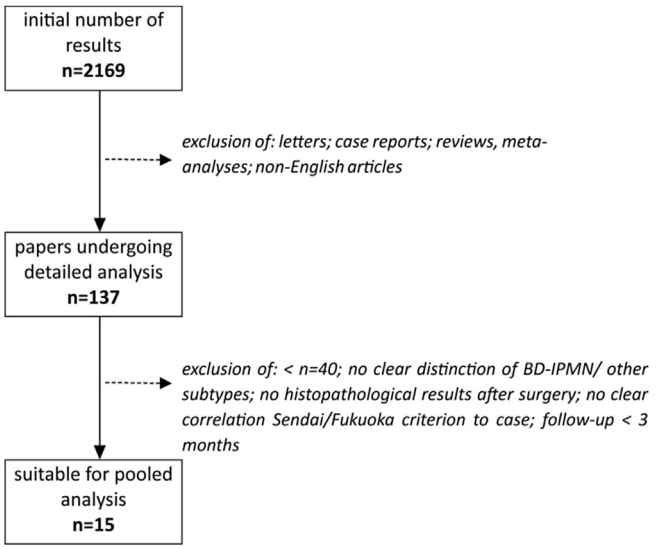

Fig. 1. Flowchart describing the selection process for study inclusion.

2.2. Definitions

Studies including mixed-type IPMN were excluded. Studies that stratified IPMNs into only two groups (main-, branch-duct) were included. Finally, only studies that allowed for clear correlation of preoperative risk assessment to histopathological outcome were included, if surgery was performed.

2.3. Meta-analysis

To quantify the impact of the consensus guidelines, different parameters were assessed statistically: sensitivity and specificity of the criteria were calculated for each study using the open source software R V.3.3 and the metafor-package V1.9-8. Calculation of the diagnostic odds ratio (DOR) derived from the odds of malignant outcome versus benign outcome in Sendai/Fukuoka positive and negative lesions was performed to evaluate the efficacy of the Sendai/Fukuoka criteria, using R: DOR $= \frac{TP*TN}{FN*FP}$. TP and TN represent the true positive and true negative results (malignant histology in Sendai positive lesions and benign histology in Sendai negative lesions), whereas FP and FN represent false positivity and false negativity. All of the included studies used at least one criterion of the consensus guidelines. We thus pooled the collected data and calculated overall rates of malignancy in the different subgroups. Firstly, patients were divided into primarily resected (PR) and primarily conservatively treated (PC groups. These groups were further divided into Sendai-positive and Sendai-negative subgroups. Malignancy rates (high grade dysplasia and invasive carcinoma) were then calculated for the subgroups. In the PC groups, malignancy was calculated for patients who proceeded to resection with consecutive histopathology.

3. Results

Of 137 papers that qualified for detailed analysis, 15 studies were included; of these, 12 used at least one criterion of the Sendai consensus and 3 used the Fukuoka criteria (Fig. 1). These studies comprised a total of 2710 patients.

3.1. Systematic review – characteristics of included studies

The number of included patients ranged from 49[6] to 563[7]. The median/mean age of patients was 63–68 years and in total, 50.9% of the patients were males. Imaging modalities used for preoperative assessment of cystic lesions included computed tomography (CT), magnetic resonance imaging (MRI/MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS). EUS was used as the primary imaging modality in two studies [8,9]. All studies used more than one imaging modality. Among the included studies, one was a multi-center study [8]. The remaining studies represent single-center retrospective analyses. Detailed information on characteristics of each study are described in Table 2. The number of Sendai/Fukuoka-positive lesions in preoperative imaging, time to surgery as well as the final histopathology is summarized in Table 3. Three papers [6,10,11] represent a primarily conservative approach. Patients with Sendai-negative lesions were followed 27.8–77 months and were resected after 20–24 months, when malignancy was suspected. A total of 12 malignant lesions were found during follow-up. A cystic growth rate of >2 mm/year was identified as an independent risk factor for malignancy by Kang et al. [11]. This is in line with the results of Rautou at al [10]. who also identified cystic growth rate (11.3 mm/y) as a sign of malignancy. All three studies conclude that careful observation (e.g. biannually) is a legitimate option in the treatment of unsuspicious BD-IPMN.

A total of seven studies [9,12–17] retrospectively analysed histopathological outcomes after resection of Sendai/Fukuoka (S/F) positive and S/F-negative BD-IPMN. Among the 904 patients that were included, 321 qualified as S/F-negative. Of those patients 76 had a malignant histological result (23.7%).

It is important to mention that Sadakari and colleagues found 11 concomitant PDAC in their series of patients without mural nodules. Five of those PDAC were found in patients with BD-IPMN smaller than 3 cm [17]. In the study by Wong et al. with a high incidence of malignant lesions among patients with BD-IPMN < 3 cm, most patients were considered symptomatic. However, out of 10 asymptomatic patients, 3 had invasive carcinoma and 1 had high-grade dysplasia. The authors point out that a high amount of BD-IPMN below 30 mm but >20 mm harbors malignancy and therefore suggest modification of the guidelines [9].

The studies of Bae et al. [18], Pelaez-Luna et al. [19] and Woo et al. [20] compared resection and conservative follow-up retrospectively. There were no malignant lesions after initial resection of Sendai-negative BD-IPMN, compared to 22 malignant lesions in 120 primarily resected Sendai-positive patients. Initially non-suspicious lesions (n = 48) that were resected during follow-up (mean time to resection 12.7–41 months) due to signs of progression or patient's request, revealed malignancy in 7 cases.

A large cohort of 563 patients with BD-IPMN (included from 1995 to 2012) was retrospectively analysed by Sahora and co-workers [7]. In total, 152 were primarily resected and 411 were followed. Of these, 88 underwent resection after a median of 26 months. Thus, a total of 240 patients were treated surgically. Seventy-six of these were Sendai-negative prior to surgery; final histopathology revealed malignancy in 7 cases (1 carcinoma, 6 high-grade dysplasias). Of 141 patients with worrisome or high-risk features before surgery, 41 had invasive cancer or high-grade dysplasia on final analysis. A subset of 23 patients was resected for pancreatic malignancy (18 PDAC) and had concomitant BD-IPMN. It is important to mention that the authors pooled the worrisome feature and high-risk feature group and classified these patients as Fukuoka-positive. This is in contrast to the study of Aso and co-workers [12], where the authors focused on the high-risk feature population.

In the only included multi-center study, Maguchi and colleagues [8] monitored 349 patients with BD-IPMN without mural nodules (mean follow-up 44.4 months) using EUS. During follow-up, radiological signs of progression occurred in 62 patients. Of those, 22 patients were resected as well as 7 who showed no progression.

Table 2
Basic characteristics of the included studies.

Study	No. of patients	Male	Age (years)	Mean/median follow up (month)	Imaging	Criteria
Arlix 2012	49	21	63	77	CT/MRI/EUS	size, mural nodule, mpd, lymphnodes
Aso 2014	70	unclear	unclear	0	CT/MRI/EUS/ERCP	size, mural nodule, mpd, jaundice
Bae 2011	194	116	63	31	CT/MRI/EUS/ERCP	size, mural nodule, mpd
Fritz 2012	123	64	64	0	CT/MRI/EUS/ERCP	size, mural nodules, mpd, thickened wall, jaundice, elevated Ca 19-9
Jang 2014	350	216	64	0	CT/MRI/EUS/ERCP	size, mural nodule, mpd, jaundice
Kang 2011	201	111	63	28	CT/MRI/ERCP	size, mural nodules, mpd
Maguchi 2011	349	179	66	44	EUS	absence of mn, size, mpd
Nagai 2009	84	48	63	0	CT/MRI/EUS/ERCP	size, mural nodule, mdp
Ohtsuka 2012	99	60	n = 41 < 65	0	CT/MRI/EUS/ERCP	size, mural nodules, acute pancreatitis, pancreatic juice cytology
Pelaez-Luna 2007	147	63	65	15	CT/MRI/EUS/ERCP	size, mural nodule, mpd
Rautou 2008	121	31	63	33	CT/MRI/EUS/ERCP	size, mural nodule, thickened wall, mpd involvement
Sadakari 2010	73	48	66	0	CT/MRI/EUS/ERCP	absence of mural nodules, size, mdp
Sahora 2013	563	232	67	60	CT/MRI/EUS/ERCP	size, mural nodule, mpd, jaundice
Wong 2012	105	47	68	0	EUS/CT/MRI	size
Woo 2009	190	111	63	25	CT/MRI/EUS/ERCP	size, mural nodules, mpd, thickened wall, jaundice, elevated Ca 19-9

Abbreviations: CT: computer tomography, MRI: magnet resonance imaging, EUS: endoscopic ultrasound, ERCP: endoscopic retrograde cholangio-pancreatography, mpd: main pancreatic duct, Ca 19-9: carbohydrate antigen 19-9.

Table 3
Study characteristics including initial Sendai/Fukuoka status and histopathological outcome. *malignant* = invasive carcinoma and high-grade dysplasia/carcinoma *in situ*.

Study	Initally S+/F+	Initial surgery	Surger during f.u.	Mean/median time to surgery (month)	Malignant	Invasive	Concomitant PDAC
Arlix 2012	0	0	5	20	0	0	0
Aso 2014	20 (hr)	70	0	0	28	16	0
Bae 2011	34	34	18	13	11	8	0
Fritz 2012	54	123	0	0	33	23	0
Jang 2014	276	350	0	0	97	57	0
Kang 2011	0	0	35	23	8	5	0
Maguchi 2011	82	0	29	unclear	9	1	7
Nagai 2009	69	84	0	0	36	20	0
Ohtsuka 2012	82	99	0	0	22	13	0
Pelaez-Luna 2007	79	66	11	41	9	5	0
Rautou 2008	0	0	8	24	4	0	0
Sadakari 2010	47	73	0	0	5	1	11
Sahora 2013	141 (ws/hr)	152	88	26	48	23	21
Wong 2012	35	105	0	0	62	39	0
Woo 2009	54	66	19	41	8	3	0

Histopathology showed 20 adenomas, 8 carcinomas *in situ* and one invasive carcinoma. Another 20 patients were diagnosed with a neoplasm (13 BD-IPMN, 7 PDAC) distant from the primary BD-IPMN lesion. Those 'new' neoplasms had developed in patients with and without signs of progression.

3.2. Meta-analysis – Sendai criteria

1727 patients (650 primarily resected, 1077 primarily conservative treatment) were included in the analysis. Median follow-up was 25–77 months. In the primary resection group, 23% of the patients without any feature predicting malignancy (according to the guidelines) had a malignant lesion in histopathology; compared to 34% of patients who were Sendai-positive before surgery. A total of 607 patients with BD-IPMN without features suggesting malignancy were initially followed conservatively. During follow-up, resection was performed in 122 patients after a median time of 12.7–41 months. Of these patients 21 (17%), had a malignant lesion in histopathological analysis (Fig. 2).

To account for the different follow-up periods in the included studies, sensitivity/specificity and the pooled diagnostic odds ratios were evaluated as follows: to address the issue of subsequent imaging with a change of cyst morphology/size and therefore change of Sendai status in some studies, patients that were labelled Sendai-negative initially but who progressed to Sendai-positive were counted as Sendai-negative to investigate the accuracy of only the initial examination. Those patients (initially Sendai negative, progression during follow-up) were then labelled as Sendai-positive for further analysis.

When only the initial imaging was used for calculations, sensitivity was low (only 4 of 12 studies with more than 90% sensitivity, pooled sensitivity 56%; Fig. 3 a). Pooled specificity was 74% (Fig. 3 a). The pooled DOR derived from the odds of malignant outcome versus benign outcome in lesions with at least one sign suggesting

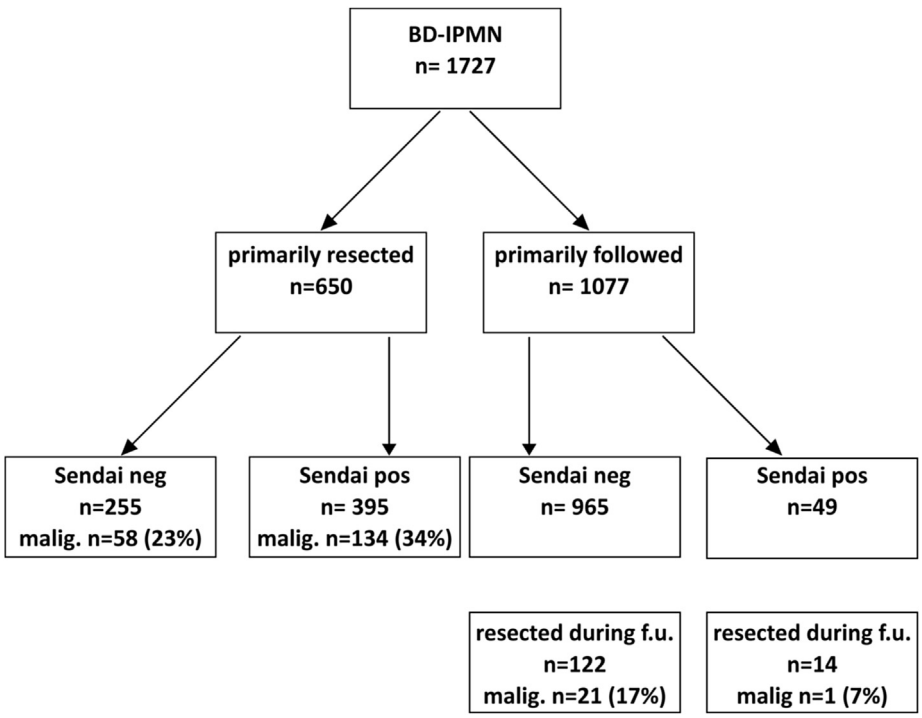

Fig. 2. Pooled rate of malignancy in Sendai-positive and Sendai-negative BD-IPMN. The total number of identified BD-IPMN (n = 1727) patients was divided into a primarily resected and a primarily followed group.

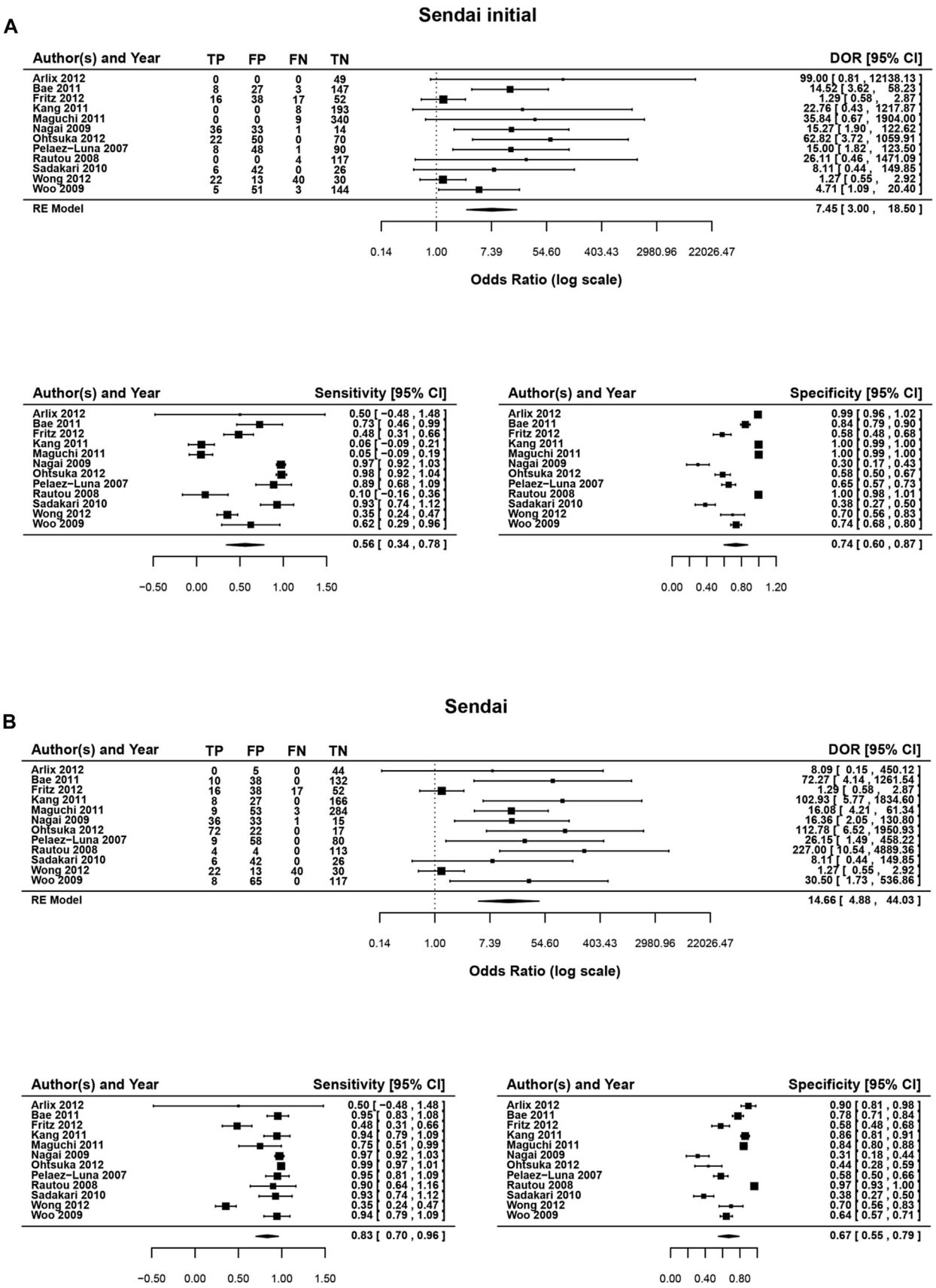

Fig. 3. a: Diagnostic odds ratio (DOR), sensitivity and specificity of included studies (Sendai consensus). This figure shows only the results of the initial examination. **b: Diagnostic odds ratio (DOR), sensitivity and specificity of included studies (Sendai consensus)**. Results of all follow-up examinations included.

malignancy was 7.45 (random effects, $p < 0.001$, heterogeneity was considerable, with an I^2 of 62.85%; Fig. 3 a).

Upon inclusion of the follow-up examinations diagnostic accuracy improved: 8 of 12 studies had a sensitivity of over 90%. Pooled sensitivity was 83% (Fig. 3 b). Specificity was heterogeneous, ranging from 30% to 100%; pooled specificity was 67% (Fig. 3 b). Calculation of the pooled DOR revealed a result of 14.66 (random effects) for the Sendai criteria, including follow-up imaging ($p < 0.001$). However, considerable heterogeneity with an I^2 level of 74.4% was found (Fig. 3 b).

3.3. *Meta-analysis – Fukuoka criteria*

The analysis of data from studies that explicitly refer to the revised guidelines (Fukuoka) [7,12,14] retrieved three studies with a total of 660 resected patients. 437 patients had features arguing for resection according to the consensus guidelines while 200 Fukuoka-negative lesions were resected (Fig. 4 a). Twenty-three patients were operated on because of another pancreatic malignancy and had a concomitant BD-IPMN. Out of 437 Fukuoka-positive patients, 151 (28%) had a malignant tumour in histopathological analysis (carcinoma or carcinoma *in situ*/high-grade dysplasia). Among the 200 Fukuoka-negative patients, 22 (11%) had a malignant lesion. A total of 323 patients who were followed up postoperatively for a median of 60 months showed no signs of malignancy. Sensitivity in two of the assessed studies [7,14] was high (90% and 97%), while in the third study, sensitivity was only 57%[14]. Pooled sensitivity was 83% (Fig. 4 b). Specificity was highest in the study by Aso and colleagues (90%) [12]. Pooled specificity was 53% (Fig. 4 b). The pooled DOR was 8.76 for the Fukuoka criteria (random effects, $p < 0.001$). The calculated inconsistency I^2 was 0%, indicating low heterogeneity (Fig. 4 b).

4. Discussion

In this systematic review, we compared the rate of malignancy in BD-IPMN with and without clinical symptoms and/or suspicious morphological features in imaging. All of the studies were retrospective (some with prospectively maintained databases). Different imaging modalities including CT, MRI and EUS were used. Not all studies explicitly reported on all criteria according to the Sendai/Fukuoka consensus [1,2], but rather on one criterion such as cyst size or mural nodules, whereas other criteria were not mentioned. Those factors contribute to the heterogeneity of the results and must certainly be considered as a source of bias.

We found that a relatively high percentage (23% after primary resection and 17% after resection during follow-up) of patients that had unsuspicious imaging results were diagnosed with cancerous/precancerous lesions in final histopathology, particularly when using the criteria according to the 2006 Sendai consensus. In our pooled analysis of the FC, 11% of Fukuoka negative patients had a malignant lesion, compared to 28% in the Fukuoka-positive group, suggesting an improved detection capacity compared to the SC. The DOR of the criteria (Sendai only initial examination vs Fukuoka) however is relatively comparable. When including the follow-up examinations DOR improves, supporting the theory of a malignant dynamic, even in initially unsuspicious cysts.

Only 3 studies [7,12,14] evaluating the FC, with a total of 983 patients could be included due to strict inclusion criteria, underlining the need for further studies. Although the revised criteria seem to represent an improvement, there are still open questions concerning the inclusion of different factors and the weighting of the included factors. A considerable source of bias is that in many cases it remains unclear why/how a decision to surgically resect the cyst has been reached. This is especially true for the cohort of patients labeled as Sendai/Fukuoka-negative that are initially being followed, but receive surgery in the further course. Many studies fail to explain what factors ultimately lead to resection in those patients.

From an epidemiological point of view, cystic lesions of the pancreas in general and IPMN in particular are relatively common entities, as shown in a large autopsy cohort [21]. Prevalence of cysts in this study was 24.3%, increasing with age. Beyond autopsy findings, the radiological prevalence of cystic lesions of the pancreas is also considerable, with 19.6% in a cohort of over 1400 patients who received MRI scanning mainly without any clinical pathology related to the pancreas or the hepatobiliary system [22]. Compared to these high prevalence rates of cystic findings, PDAC is a rare disease with a prevalence of only approximately 45 000 (SEER database, annual incidence 10.9/100 000[23]) in the US, and only a subset of PDAC arises from cystic lesions. This underlines the urgent need for improvements in stratification of BD-IPMN to achieve reliable criteria to extract those that will progress to invasive cancer among the huge amount of (mainly incidental) cystic findings.

Another possible source of bias is the classification of high grade dysplasia as either malignant or non-malignant entity. A recent publication by Rezaee et al. [24] suggests to label high grade dysplasia as non-malignant due to a better survival compared to invasive carcinoma. While the authors present a very convincing dataset we do not share this view. High grade dysplasia may mark an earlier stage in the disease compared to invasive carcinoma. This is illustrated by survival curves of high-grade dysplasia IPMN ranging between those of low grade lesions and of invasive carcinoma. However, as it remains unclear how long it takes in an individual patient for the progression from high-grade dysplasia to invasive cancer, we regard high-grade dysplasia as a malignant lesion and therefore classified it accordingly.

Clinical symptoms and imaging criteria are the basis of the current guidelines. Additional diagnostic approaches are not yet included: some diagnostic serum markers that are useful tools in the diagnosis and follow-up of pancreatic malignancy, such as CA19-9, are not considered in the Fukuoka consensus. Wang et al. showed in their meta-analysis of 15 studies that serum CEA and serum CA19-9 can help to distinguish between invasive and non-invasive BD-IPMN [25]. This is in line with data from our institution where there was a significant correlation between elevated CA19-9 levels and the risk of malignancy in MD-IPMN and BD-IPMN [26]. The revised consensus guidelines established a first step in differently weighing diagnostic findings by distinguishing between high-risk and worrisome features. The study by Ohtsuka and colleagues [16] extends this concept by describing an algorithm with direct therapeutic implications in correlation to the number of features suggesting malignancy. The authors even propose performing or avoiding lymphadenectomy according to the total number of those features. Hwang et al. developed a scoring formula including different factors, such as mural nodules and serum CEA, to estimate the risk of invasiveness [27]. These examples illustrate possible modifications of the guidelines on BD-IPMN diagnosis and treatment.

In conclusion, the current consensus guidelines for the management of BD-IPMN are useful in clinical practice, but many areas of uncertainty remain: while specificity of imaging is low and many lesions with worrisome features are benign on final analysis; sensitivity is high but a considerable number of lesions that are initially considered low risk exhibit high-risk features during follow-up. Considering the relatively high rate of malignancy in initially Sendai-negative lesions as well as the rate of concomitant malignant lesions of the pancreas in BD-IPMN patients, more accurate criteria for clinical decision-making are warranted to

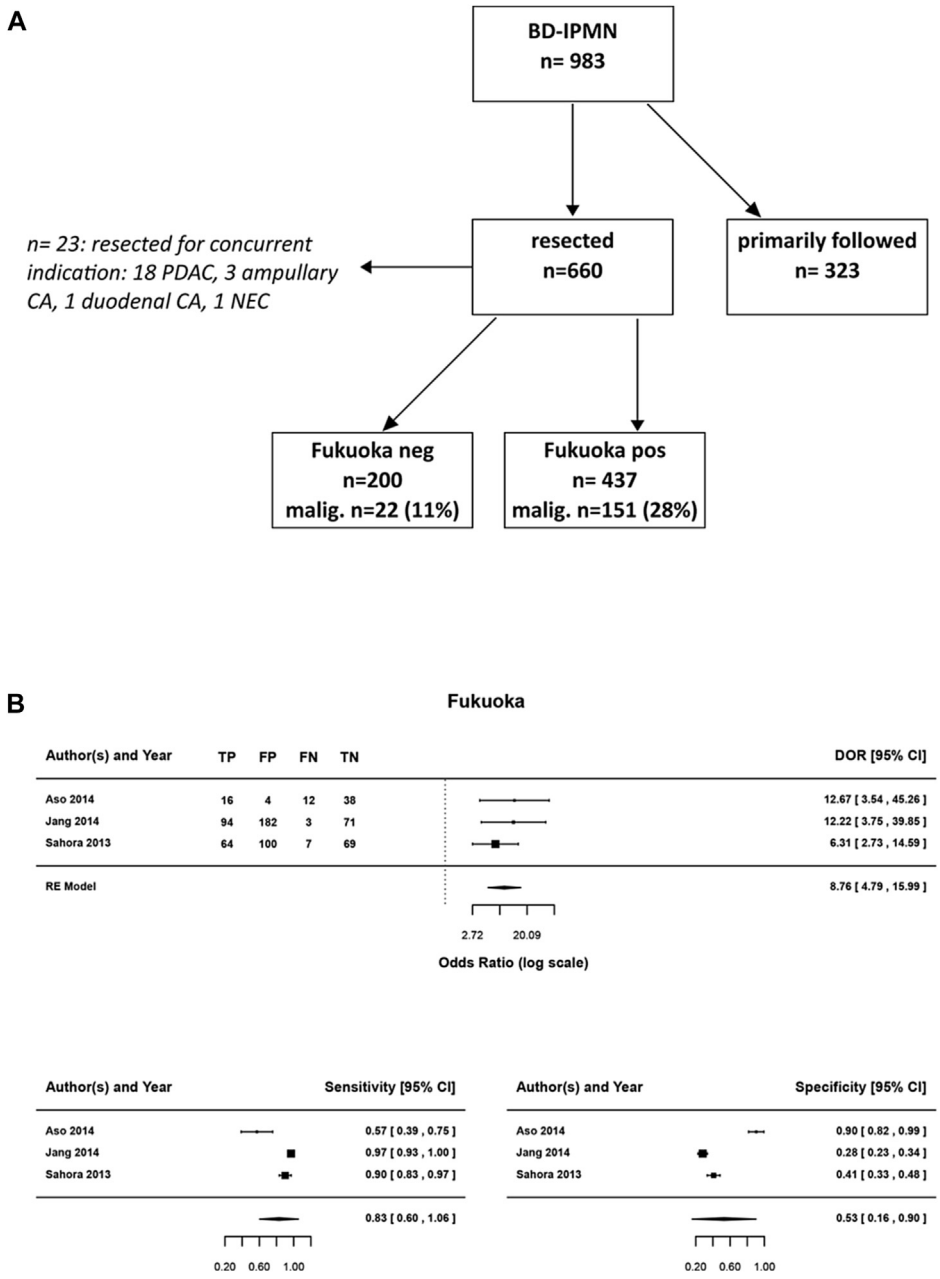

Fig. 4. a. Pooled rate of malignancy in Fukuoka positive and Fukuoka negative BD-IPMN. A total of 983 BD-IPMN patients were included. Final histopathology was available for 660 resected patients. *PDAC* = pancreatic ductal adenocarcinoma, *CA* = carcinoma, *NEC* = neuroendocrine carcinoma **b: Diagnostic odds ratio (DOR), sensitivity and specificity of included studies (Fukuoka consensus)**.

distinguish between patients who benefit from an aggressive surgical approach and those who qualify for observation without the risk of missing malignant transformation.

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