SYSTEMATIC REVIEW AND META-ANALYSIS

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Optimization of ERCP Technique to Improve the Sensitivity of Biliary Brushing: A Systematic Review and Meta-analysis

Robert C. Verdonk[1], Roeland Zoutendijk[1], Peter J. van der Schaar[1], Paul Didden[2], Hans Kelder[3], Lodewijk A.A. Brosens[4], Hjalmar C. van Santvoort[5], Mihaela G. Raicu[6], Frank P. Vleggaar[2]

1) St. Antonius Hospital Nieuwegein, Department of Gastroenterology and Hepatology, Nieuwegein, the Netherlands and University Medical Center Utrecht, Regional Academic Cancer Center, Utrecht;
2) University Medical Center Utrecht, Department of Gastroenterology and Hepatology, Utrecht;
3) St. Antonius Hospital, Nieuwegein, Department of Cardiology, Nieuwegein;
4) University Medical Center Utrecht, Department of Pathology, Utrecht;
5) Regional Academic Cancer Center Utrecht, University Medical Center Utrecht/ St. Antonius Hospital Nieuwegein, Department of Surgery, Nieuwegein;
6) St. Antonius Hospital Nieuwegein, Department of Pathology, Nieuwegein, the Netherlands

Address for correspondence:
Robert C. Verdonk, MD PhD
St. Antonius Hospital Nieuwegein, department of Gastroenterology and Hepatology, Koekoekslaan 1, 3435CM Nieuwegein
r.verdonk@antoniusziekenhuis.nl

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ABSTRACT

Background & Aims: Endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology is an important tool in the diagnosis of hepatobiliary malignancies. However, reported sensitivity of brush cytology is suboptimal and differs markedly per study. The aim of this study is to analyze the optimal technique of endobiliary brushing during ERCP.

Methods: A systematic review and meta-analysis according was performed using Pubmed, Embase and Cochrane library, and reported reported according to the PRISMA guidelines. The intervention reported should involve ERCP, performed by the endoscopist with a comparison of different brushing techniques. The primary outcome was sensitivity for malignancy. Studies published up to December 2022 were included. Percutaneous techniques and cytological or laboratory techniques for processing of material were excluded. Bias was assessed using the Quadas-2 tool. Pooled sensitivity rates and Forest plots were analyzed for the primary outcome.

Results: A total of 16 studies were included. Three studies reported on brushing before or after dilation of a biliary stricture. No improvement in sensitivity was found. Five studies reported on alternative brush designs. This did not lead to improved sensitivity. Seven studies reported on the aspiration and analysis of bile fluid, which resulted in a 16% increase in sensitivity (95% CI 4-29%). One study reported an increased in the number of brush passes to the stricture, providing an increase in sensitivity of 20%. Substantial heterogeneity between studies was found, both methodological and statistical.

Conclusions: Increasing the number of brush-passes and sending bile fluid for cytology increases the sensitivity of biliary brushings during ERCP. Dilation before brushing or alternative brush designs did not increase sensitivity.

Key words: ERCP – biliary brushing – malignancy – citology – meta-analysis – systematic review.

Abbreviations: ERCP: endoscopic retrograde cholangiopancreatography. EUS: endoscopic ultrasonography.

INTRODUCTION

Biliary strictures due to malignant or benign disorders are frequently encountered in the clinical practice. For many decades, endoscopic retrograde cholangiopancreatography (ERCP) with cytological sampling has been the cornerstone for obtaining a definite diagnosis. To obtain a timely diagnosis is of utmost importance, considering the aggressive nature of pancreaticobiliary malignancies, as well as the invasiveness of potential surgery. The relevance of obtaining an adequate diagnosis prior to further therapy is ever growing with the increasing use of neo-adjuvant therapies in pancreaticobiliary malignancies [1]. The specificity for malignancy of cytological samples obtained by brush cytology during ERCP is close to 100% [2]. Unfortunately, the sensitivity is far from optimal. Several (systematic) reviews reported a sensitivity of 30-57% [2, 3]. This relatively low sensitivity has been frustrating clinicians for many years. To improve diagnostic accuracy of intraductal brushing numerous measures have been investigated. Firstly, methods to optimize the endoscopic procedure [2-4] such as dilating the biliary stricture prior to brushing to increase cellular yield, aspirating bile to obtain malignant cells, improved brush designs, or, more recently, increasing the amount of brush passes through the stricture. Secondly, improvement

in handing and preparation of the specimen such as different staining methods or liquid based cytology have been shown to impact diagnostic sensitivity. Third, more advanced molecular techniques are suggested, such as FISH or next-generation sequencing. Finally, different approaches towards obtaining cytological or histological material through intraductal biopsy, cholangioscopy or endoscopic ultrasonography (EUS) -based techniques have been the focus of intense research effort.

However, even in the current day and age, brush cytology remains the most used technique for intraductal sampling for several reasons. It is widely available, does not require an advanced molecular analysis facility, or use of more complex, expensive, or less available devices. Also, not all strictures can be reached using a biopsy forceps, EUS or cholangioscopy. Additionally, even when molecular techniques are used, obtaining more cellular material will improve diagnostic accuracy and diagnostic possibilities.

The importance of obtaining an adequate diagnostic sample during the first procedure, was further highlighted by a study demonstrating a prolonged diagnostic trajectory with repeat investigations after a negative brush finding during the index procedure [5]. However, the best way to obtain such an adequate sample is unclear from the present literature.

Therefore, the aim of the present review was to analyze the optimal technique of endobiliary brushing during ERCP. To this end, we performed a systematic review of comparative studies using different techniques to optimize diagnostic sensitivity of endobiliary brushing.

METHODS

Systematic Literature Search

We performed a systematic search of the literature. Findings were reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. PubMed, Embase and Cochrane library were reviewed starting with title and abstract by 2 authors (R.C.V., R.Z.) for relevant papers published up to December 8, 2022. Papers deemed relevant and consistent with the inclusion and exclusion criteria were further studies after obtaining full text. References were manually checked for relevant papers. When the results of a single study were reported in more than 1 publication, only the most recent and complete data were included in the meta-analysis. Studies published in English, Dutch, German, French of Spanish were included. Disagreements were solved by discussion between the two mentioned reviewers. If no conclusion could be reached, disagreements were solved after discussion with a third co-author, selected based on specific expertise depending on the subject. Duplications of the different search engines were removed using EndNote software. The protocol for this review was previously submitted to the PROSPERO registration [CRD42022332214]. A detailed description of the literature search including search terms is provided in appendix 1.

Eligibility Criteria

Studies were eligible for inclusion if they concerned human subjects, aged 18 year or older. The intervention reported on should involve ERCP, with the intervention done by the endoscopist performing the procedure. The primary outcome measure that should be retrievable in the data section was sensitivity for malignancy. Since the reported sensitivity of endobiliary brushing varies widely per center (33-78%) [2], only comparative studies were included. This includes cohort studies comparing different techniques, retrospective analyses of different techniques, and randomized trials. Studies reporting on less than 10 subjects were excluded. Also, studies reporting on alternative devices to the brush (i.e. endoscopic scrapers, cholangioscopes, baskets etc) were excluded. Other exclusion criteria were studies reporting on percutaneous techniques, molecular analyses, use of EUS compared to ERCP. When more than one reason for exclusion was present (i.e., both lack of comparative group and use of new device) the main reason for exclusion was noted. Conference abstracts, review papers, guidelines were excluded. Studies reporting on several techniques in the same paper could be included provided relevant data could be extracted.

Data Extraction

A predefined data extraction sheet was used, including: year of study, continent of study, study design, type of intervention, number of patients, proportion of patients with malignancy, type of malignancy, number of patients per intervention, sensitivity of brushing in the intervention and control group, inclusion of cellular yield as secondary outcome measure. The data extraction was independently performed by 2 authors blinded to each other's findings (R.C.V. and R.Z.). Both authors independently filled in the predefined data-extraction sheet. Differences were solved in consensus after discussion of the primary data. To solve disagreements a third author was available, but no consultation was needed.

Risk of Bias Assessment

Risk of bias was assessed per study by 2 independent reviewers (R.C.V. and R.Z.) using the QUADAS-2 tool for diagnostic studies [6]. Differences were solved in consensus after discussion of the primary data.

Statistical Analysis

Meta-analyses were performed in R (R version 4.2.1, RStudio Version 2022.12.1) using the metabin function in the meta package [7]. Forest plots were generated using the forest function in meta. For the diagnostic test sensitivity we calculated the pooled sensitivity (rate) differences with 95% confidence intervals for each of the three new diagnostic interventions in comparisons to controls.

We assessed and report heterogeneity quantitatively using the Tau2 and I^2 statistic and performed a χ^2 test. We chose to report both the common and random effect measures in the forest plots to provide some visual aid in assessing heterogeneity.

RESULTS

After exclusion of duplicates, a total of 782 studies were screened using title and abstract. After applying inclusion and exclusion criteria, 16 full papers were included in the present study. Main reasons for exclusion in the final round of paper selection were use of percutaneous techniques [8], overlap

with a more recent study [9], no comparison between different modalities [10, 11] and focus on cytological processing [12] (Fig. 1).

Three studies provided data on balloon dilation prior to brushing, 5 studies on an alternative brush design, 7 studies on the added value of bile aspiration, and 1 study on the number of passes with the cytological brush. For the three interventions for which meta-analysis was possible, there was an important degree of clinical heterogeneity regarding the ERCP procedure, number of brush passes, study protocol and sample handling.

Dilation prior to Brushing

Three studies reported on the impact of balloon dilation before brushing [13-15]. Two studies reported increased sensitivity, one study decreased sensitivity. In none of the studies the difference between brushing before or after dilation reached statistical significance. In the study by de Bellis et al. [13], when combining pre- and postbrushing results, sensitivity increased compared to only pre-brushing. It is unclear, however, whether this was due to the dilation, or merely to the increase in the number of brush passes. The study by Dumonceau et al. [15] had a more complex design, including in addition to the effect of dilatation also the comparison of brush catheters compared to retrieval baskets. Only the effect of the dilation was analyzed in the current analysis. There was no net effect found in meta-analysis as shown in Fig 2A.

Alternative Brush Design

In 5 studies, the diagnostic yield of an alternative brush design as compared to the standard biliary brush were described. Three of these studies [16-18] described the results of brushing using the Infinity® brush. In one study a spiral type brush [19] and one study the Cytolong® brush with longer and stiffer bristles [20] were used. Only one retrospective case control study [18] found a significant increase in sensitivity. One other study [16] reported an increase in cellular yield, but no increase in diagnostic sensitivity. When combined in meta-analysis no effect on sensitivity for malignancy was found as can be seen in Fig. 2B.

Bile Aspirate

Seven studies reported on the additional value of sending a bile aspirate for cytology [21-27]. The amount of bile and the means to sample bile differed per study. In 6 of the 7 studies, an improvement in sensitivity was found when adding an analysis of bile sample to standard brushing, reaching statistical significance in 4 of these 6 studies. The largest increase in sensitivity was noted in the study by Sugimoto et al. [25]. This may be related to the large volume of fluid collected after brushing, where 15 ml of saline was introduced into the bile duct prior to bile aspiration, potentially leading to increased cellular yield. Additional analysis in this paper suggest an amount of at least 10 ml of bile provided highest sensitivity. In the meta-analysis, adding bile aspirate for cytological

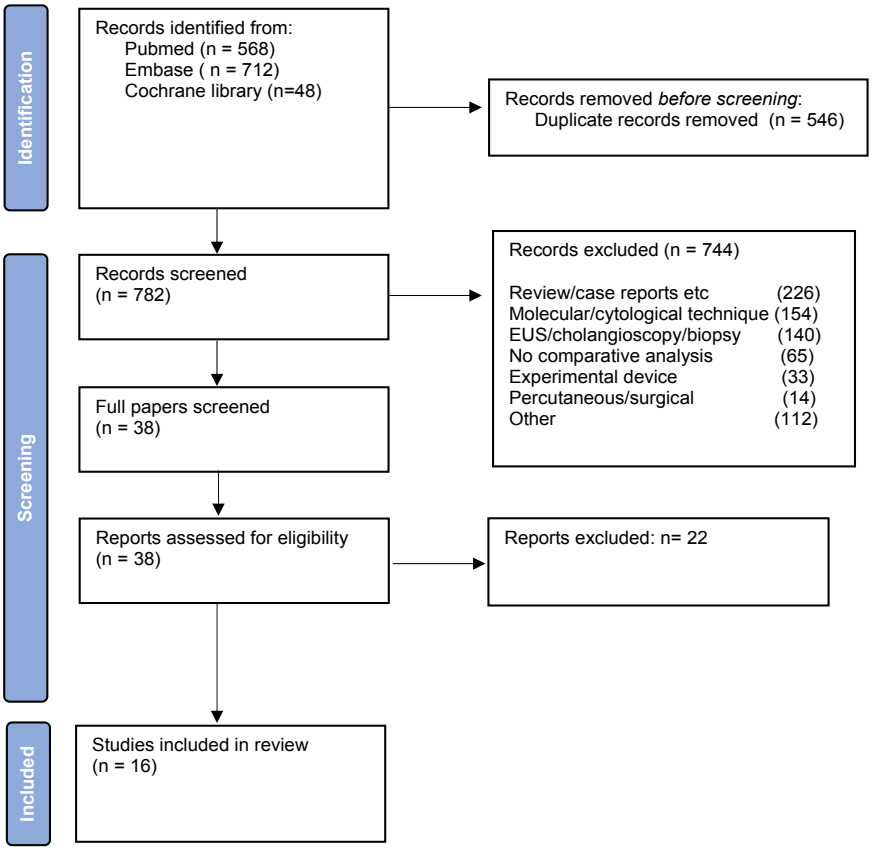

Fig. 1. PRISMA flow chart of the included papers.

examination besides the brush-material led to an in increase in sensitivity of 16% as can be seen in Fig 2C.

Number of Passes

One study on the number of brush passes was identified fulfilling inclusion and exclusion criteria [28]. In this large, recent randomized study from China the sensitivity of bile duct brushing was compared after 10, 20 and 30 brush passes. Increasing the number of brush passes from 10 to 30 provided a 20% increase in sensitivity. However, even in the 30-passes group, sensitivity was still moderate at 57%. Sensitivity of brush results was also impacted by stricture length. Increasing the number of brush passes did not lead to more complications.

Heterogeneity and Risk of Bias

For all three interventions where a meta-analysis was possible, substantial clinical and statistical heterogeneity was found as represented by I2 of 88%, 60% and 84%, respectively. Additionally, a substantial risk of bias was found as depicted in Supplementary file (Table I) representing the results of the Quadas-2 tool. High risk of bias was noted in all domains of the tool, except for the applicability of the reference standard, which was low risk in all studies reported on. Additionally, in most of the domains, unclear risk of bias was identified in at least one of the included studies. The study domain most vulnerable to risk of bias was patient selection (50% low risk). For example, in several studies only patients with a proven malignancy were retrospectively included, limiting the external validity of study results. The studies by Dumonceau [15], Rosch [19], Sasaki [21] and Sugimoto [25] scored high or unclear risk of bias in at least four of the domains reported on. Low risk of bias was found regarding index test in 10 of 16 (63%) studies, regarding reference standard in 9 of 16 (56%) studies, and flow and timing in 1 of 16 (6%) studies.

DISCUSSION

The present study investigated an evidence based strategy to improve the yield of cytological brushing for bile duct stenosis. It is the first study to systematically report on measures that are already available to optimize sensitivity of brushing. Increasing the amount of passes to 30 and providing the pathologist with a bile sample improved sensitivity of 'regular' biliary brushings by 20% and 16%, respectively. Although it makes sense intuitively, dilating a stricture prior to brushing to 'disrupt' a tumour and increase cellular load is of no advantage. The same conclusion can be drawn for alternative brush designs, although the type of design modification differed per study.

Even in the era of advanced endoscopy with new emerging techniques, cytological brushing will probably be here to stay. A cytological brush can reach virtually all segments of the bile duct, is very cheap, widely available in high and low resource settings, does not require additional endoscopic expertise (cholangioscopy, EUS) and has the potential to save significant

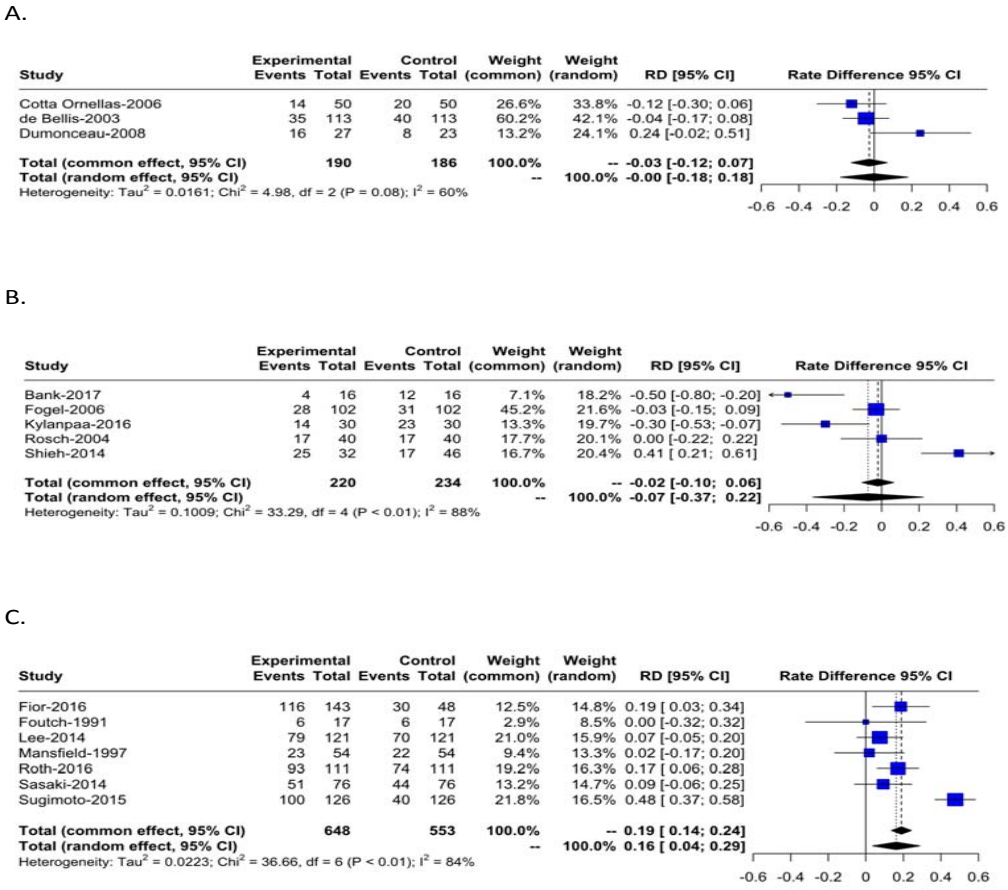

Fig. 2. Results of meta-analysis. A) impact of dilating before brushing; B) impact of alternative brush design; C) impact of sending bile aspirate for cytology.

Table I.

Intervention	Author	Year	Design	Timing	Randomisation	Patient nr	Malignancy nr	pancreas	cholangio	Reference test	New intervention	Both tests	Sensitivity reference	Sensitivity intervention	p-value
Dilation before brush	de Bellis	2003	cohort	prospective	no	139	113	74	20	0	0	113	35	31	NS
	Cotta Ornellas	2006	cohort	prospective	no	50	40	18	17	0	0	50	40	28	0.18
	Dumonceau	2008	cohort	prospective	no	50	50	29	13	23	27	0	35	59	0.084
Different brush design	Fogel	2006	RCT	prospective	yes	102	94	44	18	0	0	102	30	27	NS
	Shieh	2014	case control	retrospective	no	78	78	43	29	46	32	0	37	78	0.0003
	Bank	2017	case control	retrospective	no	32	20	18	2	16	16	0	75	25	0.07
	Kylanpaa	2016	RCT	prospective	yes	60	60	56	4	30	30	0	77	47	0.017
	Rosch	2004	cohort	prospective	no	50	28	16	12	0	0	40	43	43	NS
Bile aspirate	Sasaki	2014	cohort	prospective	no	76	76	0	76	0	0	76	58	67	0.0031
	Lee	2014	cohort	retrospective	no	121	77	18	49	0	0	121	58	65	NS
	Fior	2016	cohort	retrospective	no	218	142	72	33	48	143	0	63	81	
	Sugimoto	2015	cohort	retrospective	no	126	76	76	0	0	0	126	32	79	0.001
	Roth	2016	cohort	prospective	no	111	51	7	43	0	0	111	67	84	0.004
	Mansfield	1997	cohort	prospective	no	54	52	28	10	0	0	54	41	43	NS
	Foutch	1991	cohort	prospective	no	30	17	5	5	0	0	17	29	29	NS
Increased number of passes	Wang	2022	RCT	prospective	yes	443	417	127	231	147	148	0	38	57	0.001

costs and patient burden when a definitive malignant diagnosis makes additional procedures unnecessary. A recent study demonstrated that although same-session ERCP and EUS may be beneficial from an efficacy point of view, this may lead to an increase in complications [29]. These factors should stimulate endoscopists to optimize brushing technique and its diagnostic potential.

A crucial part of optimization of cytological brushing is the handling of the specimen once it has been obtained. There is a wide variation in this practice worldwide. A recent study by Archibugi et al. [30] reported on the value of ROSE (rapid on site evaluation) of the cytological specimen, and describes a 99% adequate sample rate, and an impressive 75% sensitivity rate. This highlights the large potential to improve diagnostic characteristics of cytological brushing. At the same time, this provides a logistical challenge, well known for those performing EUS guided cytology. Other than ROSE, a very important step is providing the cytologist with an optimal specimen, using both glass slides and liquid based cytology. Numerous studies have shown the potential of optimal preparation with an increase in sensitivity of 10-30% using techniques such as ThinPrep, CellPrepPlus, Cytospin or CytoRich [31-34]. Although not included in the current meta-analysis, since the focus of this study was not on cytological processing, also analysis of the brush itself can be of value. Several centers include the bristle in the medium provided to the pathologists. At least one study has shown that studying sections of the bristle can increase diagnostic yield [12].

Another highly promising technique is next-generation sequencing (NGS) of bile. A very recent study in 68 patients with both benign and malignant bile duct stenoses describes an accurate diagnosis of malignancy of 100% using a commercially available panel called Bilemut [35]. If these finding are robust, they have the potential to drastically improve the diagnostic yield in patients with pancreaticobiliary malignant stenoses. These results, however, do require further external validation in other patient cohorts. In addition, these advanced molecular techniques will likely not be universally available, especially in a more low-resource setting.

An additional interesting approach to optimize diagnostic yield from brush samples is to evaluate the specimens using a computer aided prediction tool. In a very recent study, Marya et al. [36] reported the use of artificial intelligence on a large number of existing cytological whole slide images. This resulted in both an increase in sensitivity and a more efficient workflow.

A potentially valuable next step with the results obtained by this systematic review, could be for endoscopic and pathologic societies to provide a path towards optimal biliary diagnostics. Ideally this should include guidelines on optimal and cost effective use of endoscopic (cholangioscopy, EUS, biopsy forceps), cytological and molecular techniques, including the appropriateness of individual techniques in different clinical scenario's. Currently, there is a wide variation in local protocols and the positioning of these techniques.

The present meta-analysis provides two clear, easy, and cheap interventions readily implementable to the endoscopist: when making optimal use of bile duct brushings, at least 30 passes of the brush should be made, and a bile aspirate should be sent for cytological examination as well. The specific amount of bile, the best way to obtain it and optimal medium to preserve it deserve further assessment. Regarding the number of passes, it should be noted that only one study could be included in the analysis. Ideally future multicenter studies would confirm these findings. Also, it remains to be seen whether combining several improvements in technique lead to a cumulative increase in sensitivity, or whether there is a certain ceiling in sensitivity due to the inherent limitations of brush cytology.

Our study has several strengths. A spectrum of endoscopic techniques was evaluated, including a range of recent papers providing insights that can directly be used in the endoscopy suite worldwide. All interventions that were studied have the potential of direct implementation. A potential limitation is the exclusion of other potentially valuable techniques, such as the cytological techniques described above. Importantly, the quality of the data analyzed in this meta-analysis should be interpreted in the right context. There is as stated in the results section and can be seen in supplemental table 1, a substantial risk of bias. For example, techniques used vary widely per study (use of glass slides and/or liquid medium, volume of bile analyzed, number of passes per brush etc). Also, in several studies, the intervention that was analyzed, was part of a larger study, for example including multiple interventions, parallel study of biopsy forceps or FNA This shows that there is indeed a lack of high quality data concerning brush cytology obtained during ERCP, and this should be a call to action to improve the methodological quality of future studies. A potential way forward would be to perform a prospective 'bundle' intervention study. This could include optimizing the yield of brush cytology by increasing the number of passes, providing

bile and bristle to the pathologist and use of liquid based cytology additional to glass slides. This bundle intervention could be compared to the current standard of care.

In addition to the clinical heterogeneity discussed above, substantial statistical heterogeneity was found when combining study results. This also calls for restraint when drawing conclusions from the present meta-analysis.

CONCLUSIONS

Endoscopic bile duct brushing provides a highly specific method for the diagnosis of biliopancreatic cancer, and there is potential for improvement of the currently low sensitivity of conventional brushing. Several studies reporting on the added value of interventions to improve sensitivity are hampered by limited patient numbers, methodological concerns and substantial heterogeneity in the techniques used. Evidence based measures that can be instantly implemented are passing the brush 30 times through the stricture and sending a bile aspirate for cytological analysis. Use of an alternative brush design or dilating a stricture before brushing was of no diagnostic advantage.

Conflicts of interest: None to declare.

Authors' contribution: R.C.V. conceived and designed the methodology of the study. R.C.V. and R.Z. and H.K. collected data, performed the formal analysis. R.C.V and R.Z drafted the manuscriprt, revised and edited the paper. P.S., P.D., L.B., H.S., M.R., F.V. interpreted data and revised the manuscript. All the authors read and approved the final version of the manuscript.

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